22 June 2017
EMA/772719/2017

Withdrawal Assessment Report

Invented name: OPDIVO

International non-proprietary name/Common name: nivolumab

Procedure No. EMEA/H/C/003985/II/0029

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Marketing authorisation holder (MAH): Bristol-Myers Squibb Pharma EEIG

Rapporteur(s) and type of application	
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Assessment Timetable

Timetable	Planned dates
Start of procedure:	24 December 2016
CHMP Rapporteur Assessment Report	17 February 2017
CHMP Co-Rapporteur Assessment Report	17 February 2017
Similarity Assessment Report	17 February 2017
PRAC Rapporteur Assessment Report	24 February 2017
PRAC members comments	1 March 2017
Updated PRAC Rapporteur Assessment Report	2 March 2017
PRAC Outcome	9 March 2017
CHMP members comments	13 March 2017
Updated Similarity Assessment Report	16 March 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 March 2017
Request for Supplementary information	23 March 2017
Submission of MAH's responses	21 April 2017
Restart of the procedure	24 April 2017
CHMP Rapporteur Assessment Report	23 May 2017
PRAC Rapporteur Assessment Report	26 May 2017
PRAC members comments	31 May 2017
Updated PRAC Rapporteur Assessment Report	1 June 2017
PRAC Outcome	9 June 2017
CHMP members comments	12 June 2017
Updated CHMP Rapporteur Assessment Report	15 June 2017
Request for Supplementary information	22 June 2017
Submission of MAH's responses	27 June 2017
CHMP Rapporteur Assessment Report	05 July 2017
CHMP members comments	10 July 2017
Updated CHMP Rapporteur Assessment Report	13 July 2017
Opinion	20 July 2017

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1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 30 November 2016 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the treatment of hepatocellular carcinoma after prior sorafenib therapy in adults for OPDIVO.
As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated in order to add the new indication and update the safety information. The Package Leaflet is updated in accordance.
Moreover, the updated RMP version 8.0 has been submitted.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0064/2014 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP for this indication. On 26-Oct-2016 a pre-submission meeting was held with the CHMP Rapporteurs.

2. Scientific discussion

2.1. Introduction

Nivolumab (Opdivo, BMS-936558, MDX-1106, ONO-4538) is a human immunoglobulin G4 monoclonal antibody that binds to the programmed death-1 (PD-1) T-cell membrane receptor and thereby blocks its interaction with PD-1 ligand 1 (PD-L1 or B7-H1) and PD-1 ligand 2 (PD-L2). PD-1 functions as an immune checkpoint and is a negative regulator of T cell activity which has been shown to control T cell immune response. Engagement of PD-1 with its ligands PD-L1 and PD-L2, which are expressed by antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T cell proliferation and cytokine secretion. Nivolumab, by blocking binding of PD-L1 and

PD-L2 ligands to PD-1 receptor, potentiates T cell responses, including anti-tumour response, in a proportion of patients (Figure 1

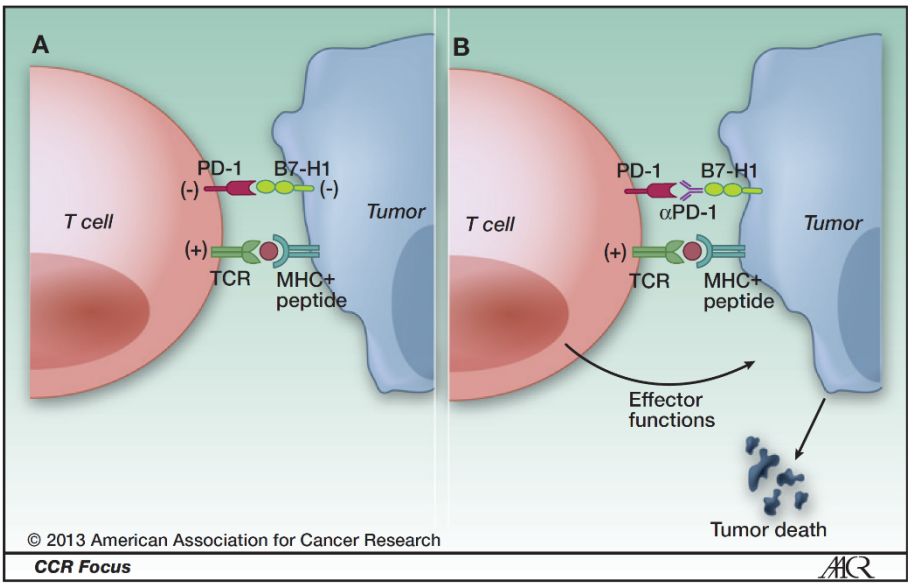


Figure 1. PD-1 and cancer. A, ligation of T-cell PD-1 by tumor B7-H1 results in the downregulation of T-cell effector functions that destroy tumor tissue. B, blockade of this pathway by anti-PD-1 antibodies prevents this downregulation, and allows T cells to maintain their antitumor functionality and ability to mediate tumor cell death.

B7-H1 = PD-L1

Figure 1 PD-1 Mechanism of action and cancer

Hepatocellular carcinoma (HCC)

Liver cancer is largely a problem of the less developed regions where 83% of the estimated 782,000 new cancer cases worldwide occurred in 2012 (Figure 2). In this year, there were 52,000 new cases diagnosed in the European Union (EU-28). It is the fifth most common cancer in men and the ninth in women. Liver cancer is the second most common cause of death from cancer worldwide, estimated to be responsible for nearly 746,000 deaths in 2012. The prognosis for liver cancer is in general very poor with an overall ratio of mortality to incidence of 0.95 (Ferlay et al. 2013. Available from: http://globocan.iarc.fr, accessed on 08/11/2016).

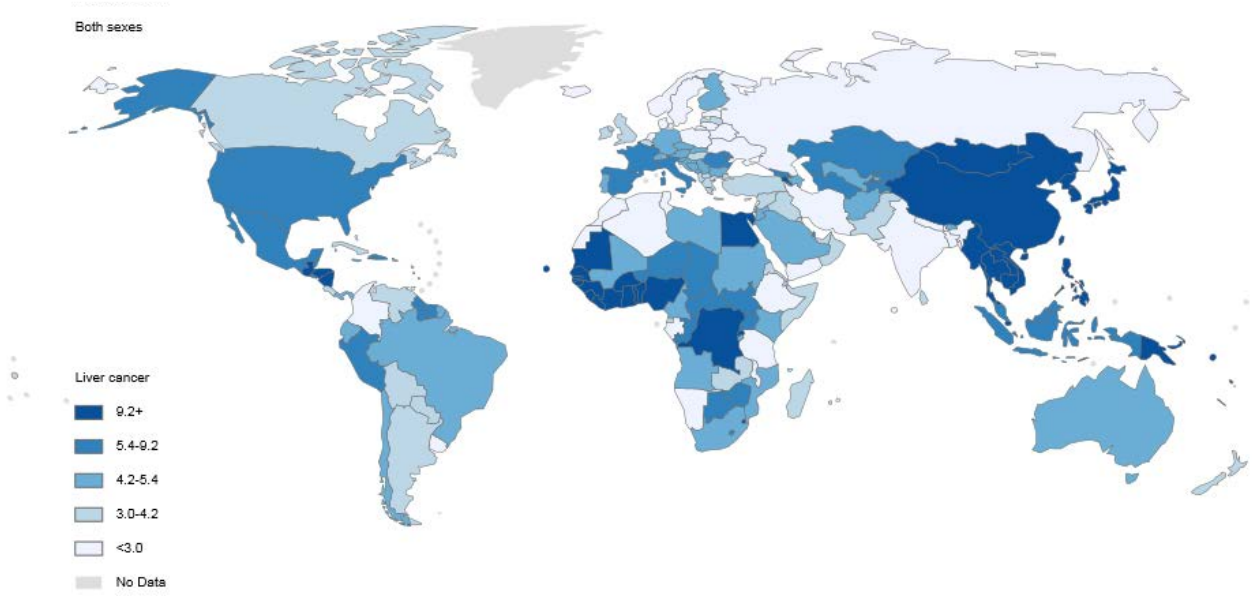


Figure 2 Worldwide estimated age-standardised liver cancer incidence rates (per 100,000) (Ferlay et al. 2013. Available from: http://globocan.iarc.fr, accessed on 08/11/2016).

Hepatocellular carcinoma (HCC) accounts for >90% of the cases of primary liver cancer. Most cases of hepatocellular carcinoma (80%) arise in eastern Asia and sub-Saharan Africa, where the dominant risk factor is chronic infection with hepatitis B virus (HBV), together with exposure to aflatoxin B1. By contrast, in North America, Europe, and Japan, infection with hepatitis C virus (HCV) is the main risk factor, together with alcohol use (Forner et al. Lancet. 2012 Mar 31;379(9822):1245-55).
The overall 5-year survival rate for HCC patients is only approximately 5-6% (Buonaguro et al. J Hepatol. 2013 Oct;59(4):897-903).

Staging of HCC

The standard classification strategy that stratifies HCC patients according to outcome and simultaneously links it with treatment indication is the Barcelona Clinic Liver Cancer (BCLC) strategy (Figure 3).

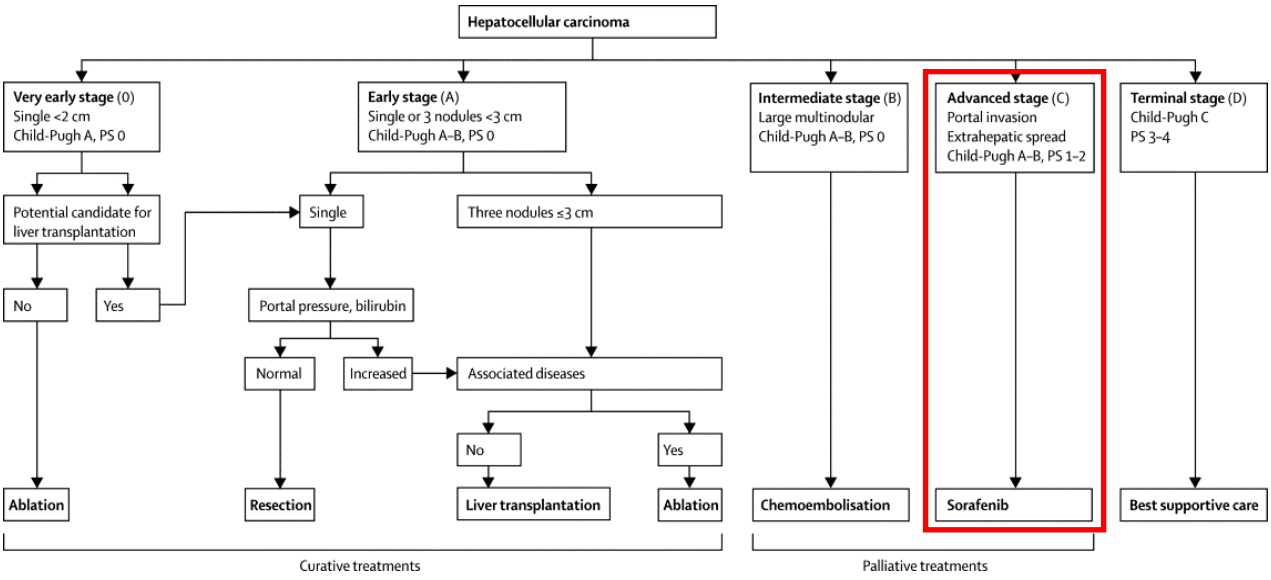


Figure 3 BCLC staging and treatment strategy.

BCLC stage C comprises patients with advanced HCC and includes patients with extrahepatic spread (Verslype et al. Ann Oncol. 2012 Oct;23 Suppl 7:vii41-8).

The Child-Pugh (CP) scoring system is used to assess the prognosis of chronic liver disease, mainly cirrhosis. There are three CP classes, i.e. A, B and C, with A representing the best and C representing the worst prognosis.

Systemic treatment for advanced HCC: palliative treatment

For patients with localized, non-advanced, disease radical, curative treatment is recommended, including surgical resection, liver transplantation and local destruction methods. Unfortunately, at 5 years following surgery tumour recurrence is between 50% and 70% (Verslype et al. Ann Oncol. 2012 Oct;23 Suppl 7:vii41-8).

Moreover, HCC is diagnosed at an advanced stage in more than 80% of patients thereby precluding potentially curative treatment approaches (Hung Curr Cancer Drug Targets. 2005 Mar;5(2):131-8).

For patients with advanced HCC (BCLC stage C) the median survival without therapy is 4-8 months (Verslype et al. Ann Oncol. 2012 Oct;23 Suppl 7:vii41-8).

First-line (1L) treatment

Sorafenib, an oral multikinase inhibitor, is the standard systemic therapy for patients with advanced (BCLC stage C) HCC and well-preserved liver function (Verslype et al. Ann Oncol. 2012 Oct;23 Suppl 7:vii41-8). It was authorized for this indication in the EU in 2007 based on the results of a randomized, placebo-controlled, double-blind phase 3 study. Six hundred and two patients with advanced HCC, no prior systemic treatment and CP liver function class A were randomized between sorafenib 400 mg twice daily or placebo. Sorafenib increased median overall survival (OS) from 7.9 to 10.7 months (HR 0.69, 95% CI 0.55-0.87). The most common grade ≥3 drug-related adverse events occurring more frequently in the sorafenib group included diarrhoea and hand–foot skin reaction (Llovet et al. N Engl J Med. 2008 Jul 24;359(4):378-90).

A similar benefit was demonstrated in a subsequent Asian-Pacific randomized, placebo-controlled trial in which sorafenib increased median OS from 4.2 to 6.5 months (HR 0.68, 95% CI 0.50-0.93) (Cheng et al. Lancet Oncol. 2009 Jan;10(1):25-34).

Systemic therapy with cytotoxic drugs, e.g. doxorubicin or cisplatin, yields low objective response rates (<10%) and is without a proven survival benefit. In addition, chemotherapy is poorly tolerated, due to underlying cirrhosis, coexisting cytopenias and unpredictable pharmacokinetics (altered activity of drug metabolizing enzymes, fluid retention). Chemotherapy is therefore not recommended (Verslype et al. Ann Oncol. 2012 Oct;23 Suppl 7:vii41-8).

For patients with end-stage disease with heavily impaired liver function or a poor performance status (both due to the tumour involvement of the liver) only symptomatic treatment is advocated (Verslype et al. Ann Oncol. 2012 Oct;23 Suppl 7:vii41-8).

Second line (2L) treatment

It is stated in the 2012 clinical practice guidelines on HCC of the European society for medical oncology that in case of progression or intolerance to sorafenib, best supportive care is preferred or patients should be included in clinical trials. Systemic chemotherapy, tamoxifen, immunotherapy, anti-androgen or somatostatin analogues are not recommended (Verslype et al. Ann Oncol. 2012 Oct;23 Suppl 7:vii41-8).

Very recently, the results from a randomized phase 3 trial with another oral multikinase inhibitor, regorafenib, in patients progressing after first-line treatment with sorafenib were published. Five hundred

and seventy three patients were randomized to regorafenib 160 mg once daily or placebo. Regorafenib improved median OS from 7.8 to 10.6 months (HR 0.62; 95% CI 0.50-0.78). The most common grade ≥3 adverse events occurring more frequently in the regorafenib group included hypertension, hand-foot skin reaction, fatigue, and diarrhoea (Bruix et al. Lancet. 2017 Jan 7;389(10064):56–66).

At the time of submission of this application, multiple second line Phase 3 RCTs were ongoing or had recently been completed, but the results had not been presented yet, for instance with:

- Pembrolizumab, a humanized monoclonal antibody targeting PD-1 (ClinicalTrials.gov identifier: NCT02702401)
- Cabozantinib , a multikinase inhibitor (ClinicalTrials.gov identifier: NCT01908426)
- Tivantinib, a c-MET kinase inhibitor, in a selected patient population with tumours with high c-Met expression (ClinicalTrials.gov identifiers: NCT01755767 and NCT02029157) (as in a phase 2 trial the most clinically significant treatment effect - in terms of both time to progression and OS - was noted in the subgroup of patients with tumours with high c-Met expression (Santoro 2013 et al. Lancet Oncol. 2013 Jan;14(1):55-63)
- Ramucirumab, a human monoclonal antibody targeting the vascular endothelial growth factor receptor 2, in a selected patient population with elevated baseline alpha-fetoprotein (AFP ≥400 ng/mL) (as a phase 3 trial in an unselected patient population failed to show a benefit in OS (Zhu et al. Lancet Oncol. 2015 Jul;16(7):859-70)) (ClinicalTrials.gov identifier: NCT02435433)
- Pegylated arginine deiminase (ADI-PEG 20), an arginine-degrading enzyme (ClinicalTrials.gov identifier: NCT01287585)

Response evaluation should be based on dynamic CT or MRI studies and the modified response evaluation criteria in solid tumours (mRECIST) criteria. Patients with advanced HCC receiving systemic treatment should be evaluated clinically for signs of liver decompensation and by dynamic CT or MRI for tumour progression every 2 months to guide therapy decisions (Verslype et al. Ann Oncol. 2012 Oct;23 Suppl 7:vii41-8).

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity / environmental risk assessment

The active substance, nivolumab is a protein and therefore no environmental risk assessment studies have been submitted, in line with guidelines.

2.2.2. Discussion on non-clinical aspects

NA

2.2.3. Conclusion on the non-clinical aspects

NA

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies ()

Table 1. Overview of study CA209040 a phase 1/2, dose escalation, open-label, non-comparative study of nivolumab in advanced hepatocellular carcinoma patients after prior sorafenib treatment with or without chronic viral hepatitis.

Study design	No. of study centres/ locations	Duration	Diagnosis/ inclusion criteria	Study population	Total no. of nivolumab-treated patients	Gender M/F Median Age	Treatment cohorts	Study objective	Primary Endpoint
Phase 1/2, dose-escalation, open-label, non-comparative study	39 sites/11 countries	Approximately 45 months Study initiation date: 30-Oct-2012 Study completion date (i.e.): 08-Aug-2016 clinical database lock (24-Jun-2016 last patient, last visit)	Adults with histologically confirmed, advanced HCC, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1, and progressive disease following sorafenib treatment (2L), or refusal of or intolerance to sorafenib treatment	**Dose escalation (ESC) cohort:** 48 of whom 37 2L **Expansion (EXP) cohort:** 214 of whom 145 2L	262 of whom 182 2L	M 79%/F 21% 63 years	**ESC cohort:** patients were assigned sequentially into treatment groups of ascending dose by 3+3 design; 0.1, 0.3, 1, 3, and 10 mg/kg nivolumab Q2W **EXP cohort:** 3 mg/kg nivolumab Q2W	**ESC cohort:** establish the safety, tolerability, dose limiting toxicities (DLT) and maximum tolerated dose (MTD) of nivolumab Q2W **EXP cohort:** estimate the objective response rate (ORR) and duration of response (DOR) of nivolumab monotherapy	**ESC cohort:** safety, tolerability, DLT and MTD **EXP cohort:** ORR determined by blinded independent central review (BICR) assessed tumour response based on RECIST 1.1)

2.3.2. Pharmacokinetics

Nivolumab clinical pharmacology profile, including single- and multiple-dose pharmacokinetics (PK), drug-drug interaction potential, effect of renal and hepatic impairment, QT prolongation potential, dose selection for phase 2/3 studies, and exposure-response (E-R) relationships with safety and efficacy across multiple tumor types have been well characterized and described in previously submitted clinical pharmacology package.

The current submission concerns the extension of the indication for nivolumab monotherapy for the treatment of hepatocellular carcinoma (HCC) after prior sorafenib therapy. The recommended nivolumab dose and schedule for HCC is the same as that initially as that initially approved for non-small cell lung carcinoma (NSCLC), renal cell carcinoma (RCC), melanoma, and classical Hodgkin's lymphoma (cHL): 3 mg/kg IV infusion over 60 minutes Q2W.

PPK analyses have previously been performed using serum concentration data from several Phase 1, 2, and 3 studies evaluating nivolumab treatment in solid tumors, including NSCLC, melanoma, and RCC. Collectively, these analyses indicated that age, gender, race, baseline lactate dehydrogenase (LDH), hepatic impairment, PD-L1 expression, immunogenicity, manufacturing process, and tumor type had no effect on nivolumab clearance. Baseline glomerular filtration rate, ECOG performance status, and body weight had minor, non-clinically meaningful effects on nivolumab clearance. Results of a post hoc analysis indicated that baseline serum albumin appeared to have an effect on nivolumab clearance, although the effect was not considered to be clinically meaningful because the E-R relationships for both efficacy and safety were relatively flat in the NSCLC population.

The basis of this submission is Phase 1/2 Study CA209040. An updated popPK analysis is presented and immunogenicity of nivolumab assessed from Study CA209040 was integrated with the overall immunogenicity summary across tumour types.

The E-R relationship for efficacy was assessed in advanced HCC subjects with prior sorafenib treatment with BICR-assessed objective response (OR) as the efficacy endpoint. The E-R safety relationship was assessed in all HCC subjects including both sorafenib naive and sorafenib treated subjects who had been treated with nivolumab monotherapy with Grade 3 and above drug-related adverse events (G3+ DR-AEs) as the safety endpoint. Additionally, the incidence and effect of immunogenicity on the safety and efficacy of nivolumab was assessed in CA209040.The effect of anti-drug antibodies on nivolumab CL was previously assessed in a previous PPK analysis and was not clinically relevant.

Special populations

Pharmacokinetics in HCC - Population Pharmacokinetic Analysis

Current PPK analysis serves to characterize nivolumab PK in subjects with advanced HCC, based on a previously established nivolumab PPK model using time-varying CL.

The objective of the present analysis was to characterize the PK of nivolumab in subjects with advanced HCC, and to determine the effect of key covariates (in particular, tumor type, etiology, and hepatic function) on nivolumab PK and exposure. In addition, nivolumab exposure estimates in HCC subjects were provided and used in the E-R analyses. The effect of tumor type on nivolumab CL was assessed relative to NSCLC 2L+ subjects in the full model along with several other covariates.

The PPK analysis was performed using data from 1117 subjects with multiple tumor types including HCC. The analysis population consisted of all subjects enrolled who received nivolumab, and for whom nivolumab concentration values were available following nivolumab monotherapy from: 2 Phase 1 studies (MDX-1106-01 and MDX-1106-03), 1 Phase 1/2 study (CA209040), 1 Phase 2 study (CA209063), and 2 Phase 3 studies (CA209017 and CA209057).

These studies were selected either because they had intensive PK samples collected to allow characterization of nivolumab PK (MDX-1106-01 and MDX-1106-03) or because they were used as a reference tumor in the PPK analysis (NSCLC 2L+ subjects from studies CA209063, CA209017, and CA209057). Data from study CA209040 allowed assessment of nivolumab PK in subjects with advanced HCC.

The PPK model was developed using a previously developed final model and included the effect of tumor type (HCC, NSCLC, or Other) and albumin on CL, and tumor type on Emax and T50.

The effect of tumor burden on nivolumab CL and VC was estimated with a subset of the PPK analysis dataset, as values of this covariate were not available for all subjects in the analysis dataset (specifically subjects in CA209040). The final model was a 2-compartment model with zero-order IV infusion input and time-varying CL. The final PPK model included effects of baseline WT, eGFR, PS, ALB, tumor type, gender, and race (Asian) on CL, baseline WT and sex on VC, and HCC tumor type on T50.

The PPK model parameters were estimated with good precision and the model evaluation demonstrated that there was good agreement between model predictions and observations.

Table 2 Parameter estimates of the final PPK model

Parameter	Final Parameter Estimate		Interindividual Variability[a] / Residual Variability	
	Estimate	%RSE	Estimate	%RSE
CL: Clearance (mL/h)[b]	11.6	4.36		
CL: Power of BBWT on CL[c]	0.529	11.4		
CL: Power of GFR on CL[c]	0.158	29.9		
CL: Sex Effect on CL[d]	-0.208	14.8		
CL: PS Effect on CL[d]	0.0747	33.3	0.103	8.95
CL: Tumor Type (OTHER) Effect on CL[d]	0.0642	49.0		
CL: Race (Asian) Effect on CL[d]	-0.0630	60.2		
CL: Tumor Type (HCC) Effect on CL[d]	-0.0211	203		
CL: Baseline Albumin Effect on CL[c]	-0.800	11.9		
VC: Central Volume (L)[b]	4.27	1.36		
VC: Power of BBWT on VC[c]	0.734	6.63	0.0938	18.1
VC: Sex Effect on VC[d]	-0.142	19.1		
Q: Intercompartmental CL (mL/h)	33.1	8.96	NE	NA
VP: Peripheral Volume (L)	3.06	4.10	0.193	14.9
EMAX: Time-varying CL	-0.302	21.1	0.165	26.6
T50: Time-varying CL (h)	1530	17.9	NE	NA
T50: Tumor Type (HCC) Effect on T50[d]	1.38	22.2		
HILL: Coefficient for Time-varying CL	1.63	17.8	NE	NA
cov(IIV in VC, IIV in CL)[e]	0.0476	15.0	NA	NA
RV: Residual Error (Proportional)	NE	NA	0.0529	4.07
Minimum value of the objective function = 43638.77				

Source: KIWI Run ID 165678

[a] Eta shrinkage: ETA_CL: 16.7%, ETA_VC: 19.8%, ETA_VP: 43.6%; ETA_EMAX; 47.1%; Epsilon shrinkage: 12.9%

[b] CL_{REF} and VC_{REF} are typical values of CL and VC at the reference covariate values. Covariate effects were estimated relative to a reference subject who is a male, weighing 80 kg, estimated GFR of 90 mL/min/1.73 m^2, serum albumin of 4 g/dL, PS of 0, tumor type of NSCLC 2L+, and race = white or other, defined as not African American

and not Asian. The reference values for continuous valued covariates were selected to be approximately the median of the covariate values in the analysis dataset.

[c] The typical value of CL and VC corresponding to continuous valued covariates of subject i are modeled as:

$$CL_{TV,i} = CL_{REF} \times \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{CL_{BBWT}} \times \left(\frac{BGFR_i}{BGFR_{REF}}\right)^{CL_{BGFR}} \left(\frac{BALB_i}{BALB_{REF}}\right)^{CL_{BALB}}$$

$$VC_{TV,i} = VC_{REF} \times \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{VC_{BBWT}}$$

[d] The typical value of CL, VC, and T50 corresponding to categorical valued covariates of subject i are modeled as:

$$CL_{TV,i} = CL_{REF} \times \left(e^{CL_{PS}}\right)^{PS_i} \times \left(e^{CL_{HCC}}\right)^{HCC_i} \times \left(e^{CL_{OTHER}}\right)^{OTHER_i} \times \left(e^{CL_{SEX}}\right)^{SEX_i} \times \left(e^{CL_{RAAS}}\right)^{RAAS_i}$$

$$VC_{TV,i} = VC_{REF} \times \left(e^{VC_{SEX}}\right)^{SEX_i}$$

$$T50_{TV,i} = T50_{REF} \times \left(e^{T50_{HCC}}\right)^{HCC_i}$$

[e] The calculated correlation coefficient (r^2) of the off-diagonal omegas was 0.235 for cov(IIV in VC, IIV in CL); the highest correlation between parameters was 0.405

Note: The condition number for the final model was 108.3, indicating there was no evidence for ill-conditioning.

The PPK model was used to obtain summary measures of exposure for each subject in the analysis dataset. In addition, a graphical assessment of the effect of tumor type on nivolumab exposure was conducted.

Analysis of Covariate Effects

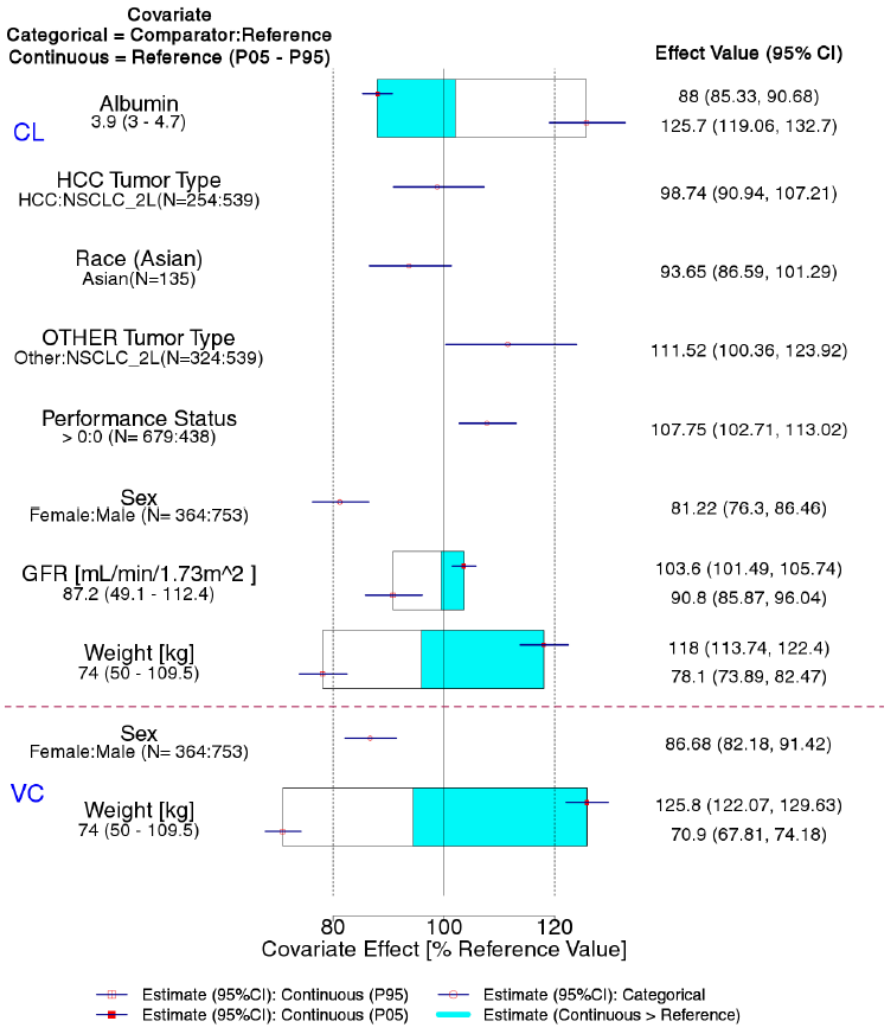
The effect of categorical and continuous covariates on the typical value of the structural model parameters of CL and VC and the estimated covariate effects (and 95% confidence intervals) are presented in Figure 4.

The magnitude of the effect of covariates on CL, accounting for uncertainty, was within the ± 20% boundaries for HCC tumor type, race (Asian), PS, and GFR, but outside the ± 20% boundaries for body weight (BW), sex, serum ALB, and OTHER tumor type. Body weight was associated with an 18% increase in CL with an increase in weight from the median to 95th percentile value.

Nivolumab CL increased approximately 26% with a reduction in serum ALB from the median to 5th percentile value. For sex, the lower bound of the confidence interval around the effect exceeded the ± 20% boundary for CL, however the point estimate was within the ± 20% boundaries, suggesting a lack of clinical relevance of this effect on nivolumab PK. Similarly, the upper bound of the 95% confidence interval around the effect of OTHER tumor type marginally exceeded the ± 20% boundary for CL while the point estimate was within the ±20% boundaries, also suggesting a lack of clinical relevance for this effect on nivolumab PK.

The effect of sex was within the ± 20% boundaries for VC. The magnitude of the effect of baseline BW exceeded the ± 20% boundaries for VC. The VC was higher with higher baseline body weight (approximately 26%, between the median and 95th percentile values for body weight).

Overall, the effects of covariates including baseline body weight, baseline ALB, baseline GFR, PS, sex, and race were consistent with previous analyses.



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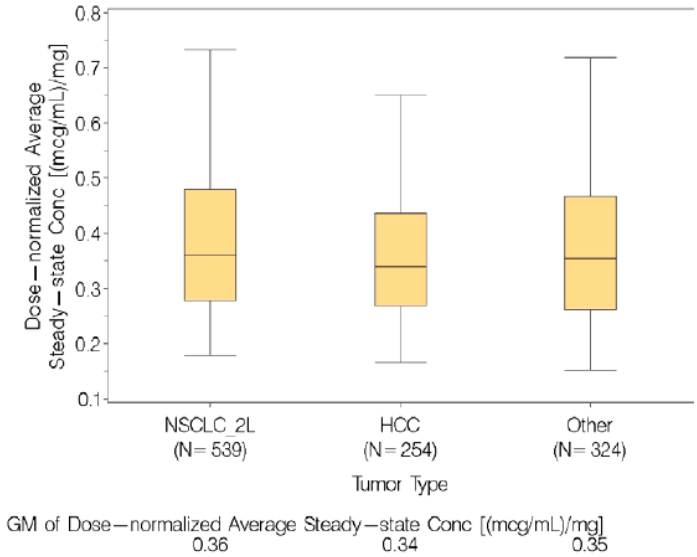
Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).
Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.

Note 3: Reference subject is male, PS = 0, estimated GFR = 87.2 mL/min/1.73m^2, body weight = 74 kg, albumin = 3.9 g/dL, NSCLC 2L+ tumor type, and race = white or other, defined as not African American and not Asian. Parameter estimate in reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.
Note 4: Due to the wide 95% CIs, results for tumor type OTHER and tumor type HCC effects on EMAX and T50 are not shown. The estimate (95% CI) of effect of tumor type OTHER and HCC on Emax (expressed as a % of the reference value) are 86.33 (33.98, 219.32), and 159.36 (99.54, 255.13), respectively; and the corresponding values for the effect on T50 are 385.74 (204.53, 727.51), and 99.92 (40.37, 247.31), respectively.

Figure 4: Covariate effects on PK model parameters (full PPK model)

Effect of Tumor Type on Nivolumab PK

Nivolumab exposure (measured as dose-normalized Cavgss, other exposure measurements were highly correlated with Cavgss) appeared to be similar across the NSCLC, HCC, and Other tumor types as shown in Figure 5, suggesting that nivolumab PK was independent of these tumor types. Nivolumab CL in HCC is similar to CL in subjects with NSCLC 2L+ (Figure 3.1.2.1-1 and was consistent with previous results in the nivolumab development program in CL for other tumor types.



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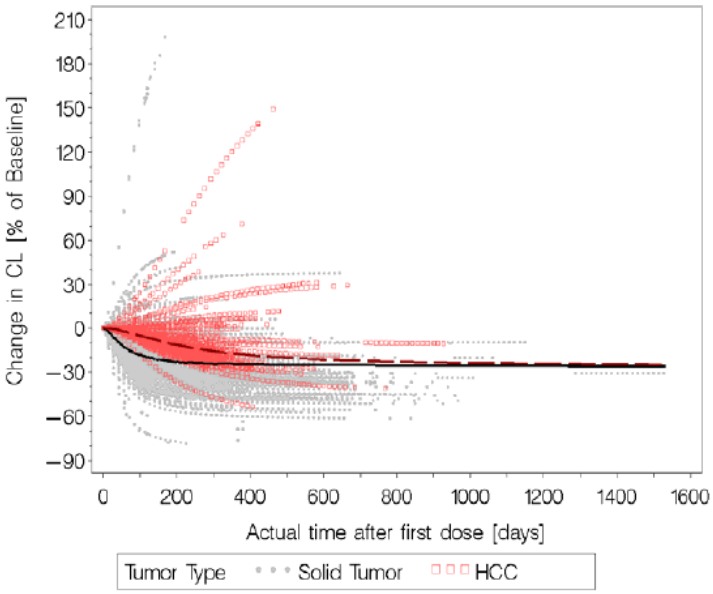
Note: The boxes represent the 25th, 50th, and 75th percentiles of the distribution. The whiskers extend from the 5th to 95th percentiles. The predicted geometric mean is shown at the bottom of each boxplot for the various tumor type groups.

Figure 5: Distribution of nivolumab Cavgss estimates between tumour types

The model estimated (typical value) of Emax (-0.302) indicated that nivolumab CL decreased with time, and that the maximal decrease was approximately 26% [calculated as: 1 −exp(Emax)]. The change in CL was estimated to occur relatively slowly compared to other solid tumors (T50 = approximately 8 months in patients with HCC versus 2 months forother solid tumor types). Although the time to steady state CL was slower in HCC, steady state CL was expected to be similar in both groups since there was no effect of tumor type on EMAX, the maximum reduction in CL. The results showed that the HCC tumor type was associated with an increase in T50 in the time-varying CL of nivolumab, but estimated Emax in HCC was similar to the NSCLC 2L+ reference group.



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Note: % change in CL was calculated using formula below:

%Difference in CL = $100 \times ((CL_t - CL_{t=0})/CL_{t=0})$

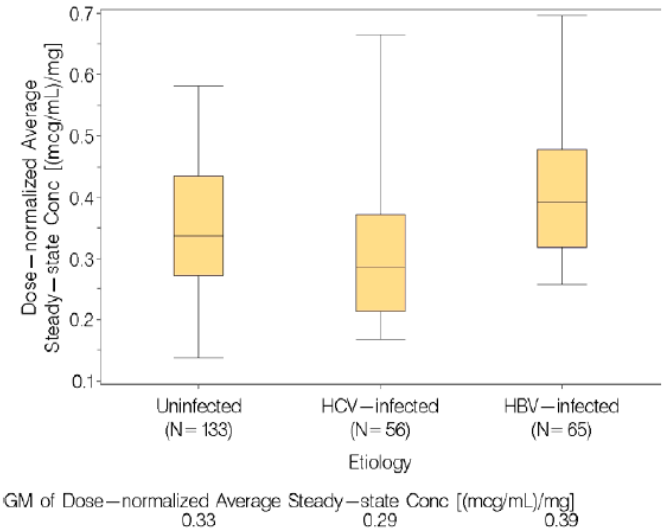
The red dashed line represents the CL-Time profile for a typical subject with HCC.

The black solid line represents the CL-Time profile for a typical subject with a solid tumor type other than HCC.

Figure 6: Model estimated change in clearance versus time from the final model

Evaluation of Effect of Etiology of Nivolumab Clearance and Exposure

HCC etiology does not have a clinically relevant effect on nivolumab exposure as shown in Figure 7, with dose-normalized average steady-state concentration values being generally similar between uninfected subjects and those with HCV or HBV. The CL (expressed as a % typical value) was also similar for uninfected subjects and those with HBV, but slightly higher (~10%) for those with HCV (Figure 8). Overall, this slight difference was not considered to be clinically meaningful.



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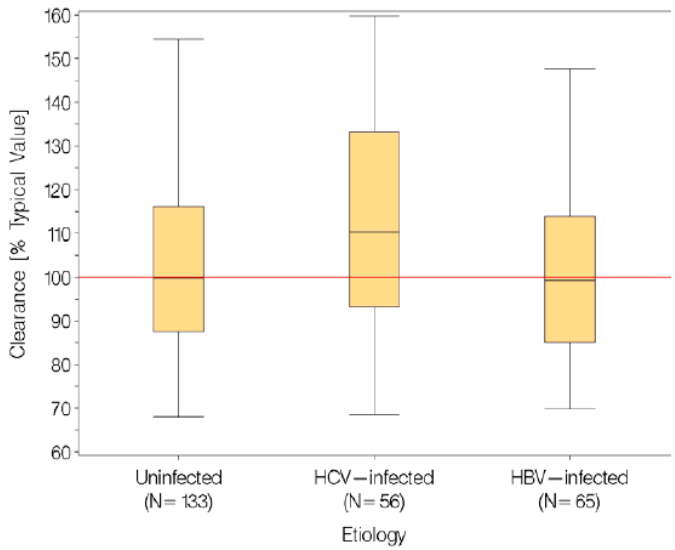
Note: The box plots represent median (bold line), 25th, and 75th percentiles of the distribution. The whiskers represent 5th and 95th percentiles of the distribution

Figure 7: Nivolumab dose-normalised Cavgss versus etiology



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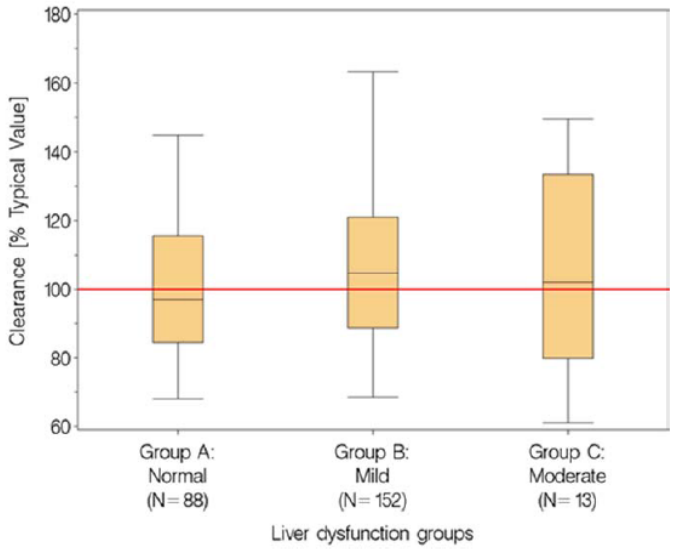
Note: The box plots represent median (bold line), 25th, and 75th percentiles of the distribution. The whiskers represent 5th and 95th percentiles of the distribution. The solid red line represents the 100% reference value.

Figure 8: Distribution of clearance estimates between uninfected subjects and subjects with HCV or HBV

Evaluation of Effect of Hepatic Function on Nivolumab Clearance and Exposure

The CL (expressed as a % typical value) was similar for subjects with normal, mild, or moderate liver dysfunction, as assessed by NCI criteria (Figure 9). The Cavgss was also comparable among different liver function groups (Figure 10). For subjects who had HCC in CA209040, geometric mean exposures of nivolumab in subjects with mild (n=152) and moderate (n=13) hepatic dysfunction were approximately 14% and 19% lower, respectively, compared to subjects with normal hepatic function (n=88) and these differences were not considered to be clinically meaningful.



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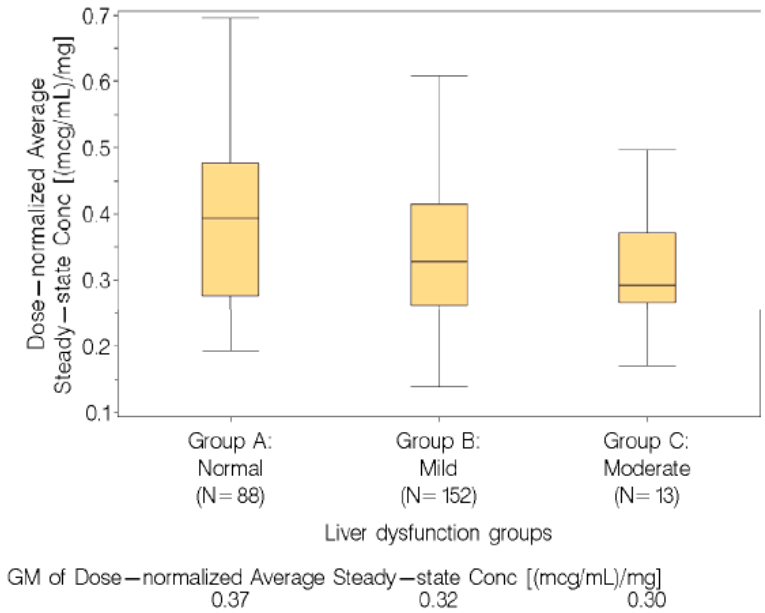
Note: The box plots represent median (bold line), 25th, and 75th percentiles of the distribution. The whiskers represent 5th and 95th percentiles of the distribution.

Figure 9: Distribution of CL estimates versus NCI criteria for hepatic dysfunction



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Note: The box plots represent median (bold line), 25th, and 75th percentiles of the distribution. The whiskers represent 5th and 95th percentiles of the distribution.

Figure 10: Nivolumab dose-normalised Cavgss versus NCI criteria for hepatic dysfunction

Evaluation of Tumour Burden

Tumour burden in HCC subjects with prior sorafenib treatment did not appear to be a clinically relevant covariate on nivolumab PK as the magnitude of this effect was within ± 20% boundary based on the sensitivity analysis using available data from HCC subjects in study CA209040. The effect of tumour burden on CL at a tumour burden of 22.5 cm (95th percentile value in this population) corresponds to an approximate 15% increase in CL relative to the median value (reference) of 6.8 cm and an approximate 18% decrease in CL for baseline tumour burden of 2.2 cm (5th percentile value). The effect of tumour burden on VC was smaller and also within ± 20% of the reference value.

Estimates of Individual Exposure

A summary of the individual PK parameter estimates obtained from the final PPK model for subjects with other solid tumours and HCC is provided in Table 3 and Table 4, respectively. A separate table summarizing the individual measures of exposure for only the HCC subjects enrolled in CA209040 (receiving 3 mg/kg Q2W) is provided in Table 5.

Table 3: Summary of statistics of individual PK parameter values for subjects with other solid tumours (N=863)

Parameter	Mean (SD)	Geometric Mean (%CV)	Median (Min, Max)
Baseline Clearance [mL/h]	12.1 (5.14)	11.2 (42.5)	11.2 (2.47, 46.9)
Clearance,ss [mL/h]	9.46 (6.68)	8.35 (70.7)	8.35 (0.414, 142)
Volume of the Central Cmt [L]	4 (1.3)	3.79 (32.4)	3.83 (0.221, 9.97)
Volume of the Peripheral Cmt [L]	3.19 (0.905)	3.08 (28.4)	3.1 (0.935, 12.3)
Volume of Distribution [L][a]	7.19 (1.72)	6.99 (23.9)	7 (2.59, 15.5)
Alpha half-life [h]	34.3 (7.73)	33.3 (22.6)	33.9 (4.31, 73.6)
Beta half-life [d]	28.4 (21.9)	25.6 (77.2)	25.2 (2.95, 412)

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[a] Volume of Distribution (L) at steady-state = Volume of the Central Compartment (L) + Volume of the Peripheral Compartment (L)

%CV: coefficient of variation expressed as a percentage; Cmt: compartment; Min: minimum; Max: maximum; n: number of subjects; SD: standard deviation.

Table 4: Summary statistics of individual PK parameters for subjects with HCC (N=254)

Parameter	Mean (SD)	Geometric Mean (%CV)	Median (Min, Max)
Baseline Clearance [mL/h]	11.3 (4.46)	10.6 (39.3)	10.7 (2.85, 33.9)
Clearance,ss [mL/h]	9.74 (4.77)	8.88 (49)	8.77 (2.23, 41.5)
Volume of the Central Cmt [L]	4.04 (1.03)	3.91 (25.6)	3.91 (1.95, 7.42)
Volume of the Peripheral Cmt [L]	3.2 (0.681)	3.13 (21.3)	3.12 (1.08, 6.42)
Volume of Distribution [L][a]	7.23 (1.35)	7.11 (18.6)	7.13 (3.49, 11.1)
Alpha half-life [h]	34.8 (5.89)	34.3 (16.9)	34.6 (15.4, 52.9)
Beta half-life [d]	26.1 (9.66)	24.5 (37)	24.7 (6.33, 76.1)

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[a] Volume of Distribution (L) at steady-state = Volume of the Central Compartment (L) + Volume of the Peripheral Compartment (L)

%CV: coefficient of variation expressed as a percentage; Cmt: compartment; Min: minimum; Max: maximum; n: number of subjects; SD: standard deviation.

Table 5: Summary statistics of individual measures of nivolumab exposure for subjects with HCC enrolled in CA2090040 (3 mg/ml Q2W; n=216)

Parameter	Mean (SD)	Geometric Mean (%CV)	Median (Min, Max)
C_{min1} (µg/mL)	16.5 (4.09)	16.1 (24.7)	16.4 (8.48, 31.6)
C_{max1} (µg/mL)	54.8 (8.45)	54.1 (15.4)	53.8 (34.6, 88.2)
C_{avg1} (µg/mL)	25.2 (4.82)	24.8 (19.1)	24.6 (16, 44.2)
C_{minss} (µg/mL)	62 (28)	56.1 (45.2)	59.5 (8.61, 177)
C_{maxss} (µg/mL)	117 (33.8)	112 (29)	112 (55.4, 251)
C_{avgss} (µg/mL)	78.7 (29.8)	73.5 (37.9)	75.7 (22.8, 199)

Source: M:\bms\nivolumab\010027\d1pk\tables\rtf\hcc-q2wk-sumstat-exps.rtf

%CV: coefficient of variation expressed as a percentage; Min: minimum; Max: maximum; n: number of subjects; SD: standard deviation.

2.3.3. Pharmacodynamics

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response.

The recommended dose for nivolumab monotherapy is 3 mg/kg every 2 weeks which has been investigated across melanoma, NSCLC, RCC, cHL, and head and neck indications.

Exposure-Response: Efficacy

The exposure-response relationship was characterized for nivolumab exposure (Cavg1) and BICR-assessed OR using 174 HCC subjects from study CA209040 who had been previously treated with sorafenib and who had nivolumab exposure data available. The relationship between the nivolumab exposure and OR was characterized using a logistic regression model that incorporated the effects of covariates that may modulate the E-R relationship. The covariate variables investigated in the E-R analysis of OR included etiology, EHS/VI, AFP, baseline CL, and nivolumab Cavg1. PPK model predicted Cavg1 was used as the measure of nivolumab exposure for the characterization of the E-R of efficacy, as Cavg1 was not confounded by CL.

Furthermore, other measures of exposure (such as Cminss, Cmaxss, Cavgss and Cmin1) were highly correlated with Cavg1. Cavg1 was not found to be a significant predictor of Pr(OR) in the full model (95% CI included 1), similar to the finding of the base model. The 95% CI of all other predictor variables evaluated (EHS/VI, etiology, baseline AFP, baseline clearance) also included unity, indicating a lack of evidence for the effect of these variables on Pr(OR). The estimated covariate effects are shown in Figure 11.

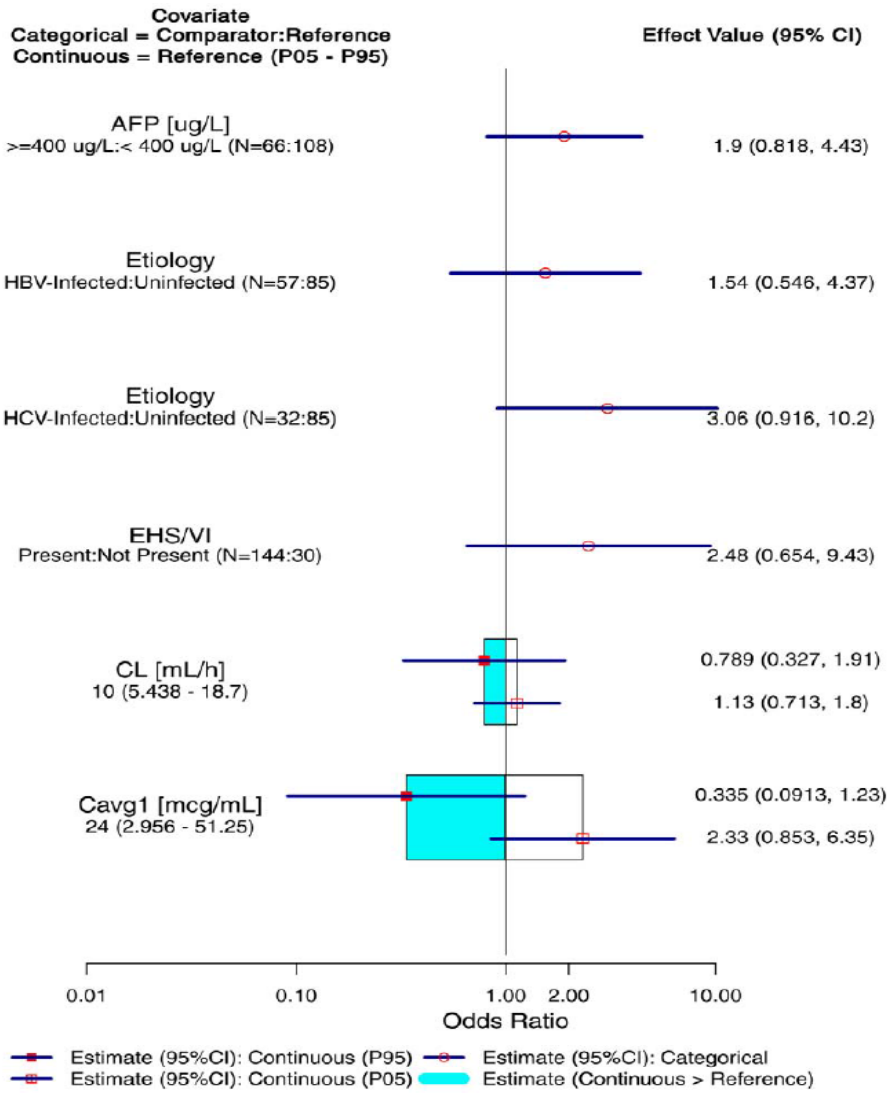

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Figure 11: Estimated covariate effects on the odds of OR (full model)

Exposure-Response: Safety

The E-R relationship for safety was characterized for nivolumab exposure (Cavg1) and G3+ DR-AEs in 254 HCC subjects who had nivolumab exposure estimates available in CA209040.

Time to first G3+ DR-AEs was used as the safety endpoint. The E-R relationship was characterized by a semi-parametric CPH model, and included assessments of the modulatory effect of covariates (etiology, EHS/VI, and AFP) on the E-R relationship.

Figure 3.3-1 presents the estimated effects of all of the predictor variables on the hazard of Grade 3+ DR-AEs in the Full Model. There was no evidence that the risk of Grade 3 or greater drug related DR-AEs increased with increasing nivolumab exposure (Cavg1). In fact, the estimated effect of Cavg1 in the final CPH model suggested a trend towards a decrease in the risk of Grade 3+ DR-AEs with increasing nivolumab exposure. This inverse relationship between exposure and risk of Grade 3+ DR-AEs may be due to several reasons. One potential confounding effect is that there were no Grade 3+ DR-AEs in the highest dose group (10 mg/kg), while the incidence of Grade 3+ DR-AEs was higher in the lower dose groups. While the highest and lowest dose groups (0.1, 0.3 and 1 mg/kg) had smaller sample sizes

relative to the nivolumab 3 mg/kg group (n = 13 and n = 25 for the highest and lowest groups relative to n = 216 for the 3 mg/kg group), the differing Grade 3+ AE rates in these groups could have influenced the E-R analyses at the extreme dose ranges. Another potentially confounding effect may be due to an association between CL and safety. In particular, the exposure of mAb drugs in cachexic subjects may be lower due to higher CL of these drugs as a result of the elevated whole body protein turnover in these subjects.

This may manifest as an apparent inverse exposure response for Grade 3+ AEs. EHS/VI and AFP were not significant predictors of the risk of Grade 3+ DR-AEs in patients with HCC. The effect of etiology of HBV-infected subjects was not a significant predictor of experiencing a Grade 3+ DR-AE. The effect of etiology in HCV-infected subjects was a significant predictor of experiencing a Grade 3+ DR-AE, relative to uninfected subjects. This difference could be due to asymptomatic increases in AST/ALT (more common in HCV). Overall, these results were consistent with the observed data.

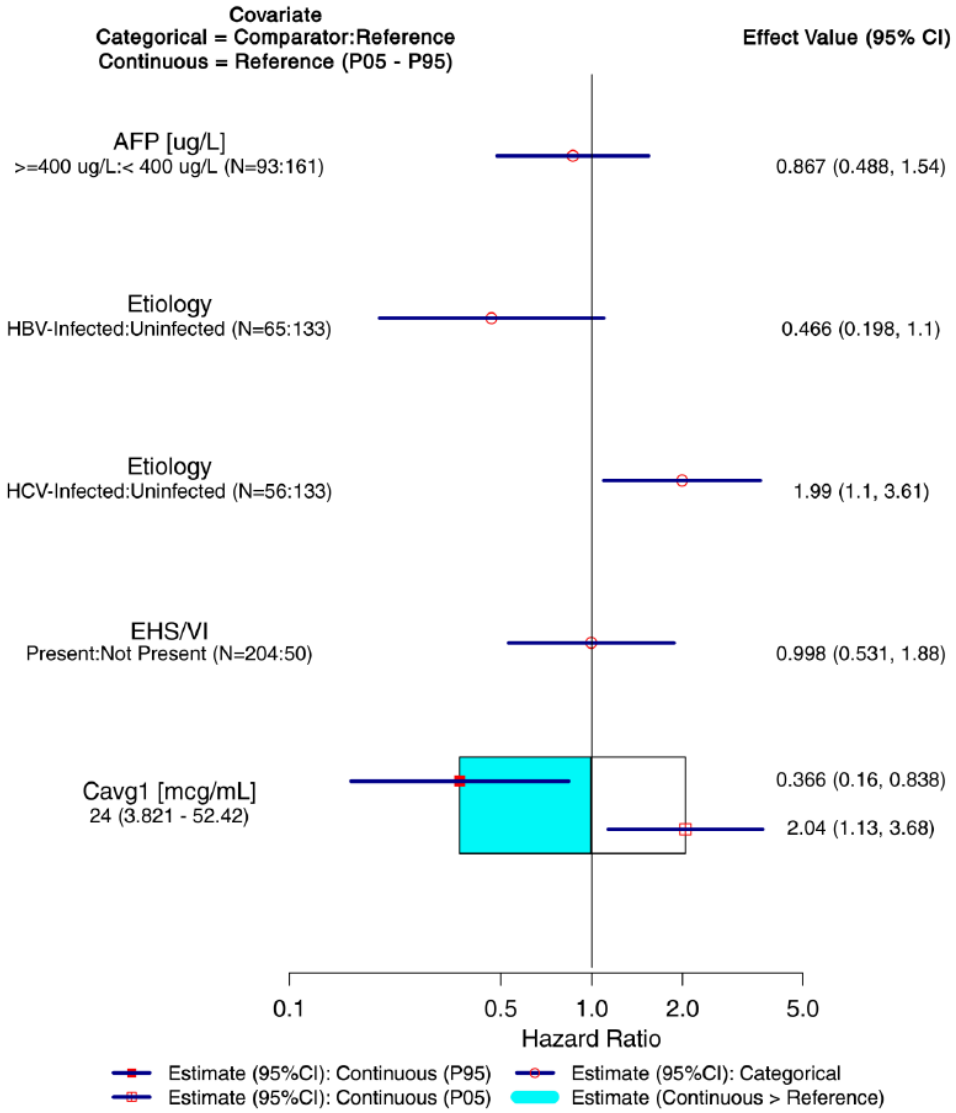

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Figure 12: Estimated covariate effects of E-R grade 3+ DR-AEs (full model)

Immunogenicity

The immunogenicity following the administration of nivolumab 3 mg/kg Q2W monotherapy has been well characterized in the nivolumab development program across multiple tumor types. This section provides updated immunogenicity analysis integrated with data from Study CA209040.

A summary of the ADA assessments for subjects on Study CA209040 who had evaluable ADA data at baseline and on treatment is presented in Table 6.

Table 6: Summary of ADA assessments in study CA209040 – Nivolumab treated subjects with baseline and at least one post-baseline assessment

	Number of Subjects (%)
	CA209040 3 mg/kg ESC + EXP (N=210)
Baseline ADA Positive	20 (9.5)
ADA Positive	56 (26.7)
Persistent Positive	6 (2.9)
Not PP - Last Sample Positive	14 (6.7)
Other Positive	36 (17.1)
Neutralizing ADA Positive[a]	1 (0.5)
ADA Negative	154 (73.3)

The highest titer value observed in ADA positive subjects was 256, which occurred in 1 subject in the 3 mg/kg Q2W dose regimen who was persistent positive for ADA and NAb negative. All other ADA positive subjects had titer values of 128 or less.

Of all subjects who were evaluable for ADA across all doses (ESC + EXP), 3/67 subjects (4.5%) who were ADA positive and 8/180 subjects (4.4%) who were ADA negative had a hypersensitivity/infusion reaction category event after nivolumab treatment suggesting a lack of effect of ADA on safety.

Among the 42 ADA positive subjects with prior sorafenib treatment across the ESC + EXP cohorts, 7 subjects had a PR per BICR assessment. The ORR (16.7%) in ADA positive subjects was similar to the overall 2L population (14.5%-18.9%) in study CA209040. Additionally, there did not appear to be a causal relationship between the onset of ADA and efficacy. Out of the 36 ADA positive subjects treated with 3 mg/kg Q2W, 22 (61.1%) subjects achieved PR or SD with PFS ranging from 2.6-11.1 months. Thus, the incidence of ADA did not appear to have an effect on efficacy of nivolumab.

Overall, based on the above data, the incidence of nivolumab ADA at 3 mg/kg Q2W dose regimen did not appear to have an effect on the safety and efficacy of nivolumab in the HCC subjects in study CA209040.

A pooled analysis of nivolumab ADA assessments was performed with data available from the following BMS-sponsored studies in which ADA was assessed by the current sensitive and drug tolerant assay (ICDIM 140 V1.00/V2.02): CA209037 (interim CSR), CA209063, CA209066, CA209017, CA209057, CA209067 (nivolumab monotherapy arm), CA209025, CA209039, CA209205, CA209141, CA209032 (UC subjects only), CA209275 and CA209040 (3 mg/kg Q2W only) (see Table 7).

Table 7: Summary of nivolumab antibody assessments using method ICDIM 140 following nivolumab 3 mg/kg Q2W

	Number of Subjects (%)		
Study Number	Summary of Previous Studies[a] (N = 2022)	CA209040 3 mg/kg ESC + EXP (N=210)	Pooled Summary (N=2232)
Baseline ADA Positive	107 (5.3)	20 (9.5)	127 (5.7)
ADA Positive	231 (11.4)	56 (26.7)	287 (12.9)
Persistent Positive[b]	2 (0.1)	6 (2.9)	8 (0.4)
Not PP - Last Sample Positive	88 (4.4)	14 (6.7)	102 (4.6)
Other Positive	141 (7.0)	36 (17.1)	177 (7.9)
Neutralizing ADA Positive	15 (0.7)	1 (0.5)	16 (0.7)
ADA Negative	1791 (88.6)	154 (73.3)	1945 (87.1)

Source: See note a and Table 8.14.1-1 of the CA209040 CSR

To further explore the relationship between immunogenicity and safety, an integrated assessment of the potential impact of nivolumab ADA on immunogenicity-related effects was performed by summarizing the select adverse events in the hypersensitivity/infusion reaction category by ADA Status (positive or negative) for those subjects who were treated with nivolumab monotherapy.

Of the 2318 subjects evaluable for the presence of ADA and hypersensitivity/infusion reactions, a total of 127 experienced hypersensitivity/infusion reactions. Of these 127 subjects who experienced hypersensitivity/infusion reactions, 8 were positive for nivolumab ADA and 119 were negative for nivolumab ADA. A total of 8/308 (2.6%) ADA positive subjects experienced adverse events in the hypersensitivity/infusion reaction category. These findings are consistent with the results previously reported.

Overall, an association was not established between the presence of ADA and hypersensitivity or infusion reactions, suggesting that ADA does not alter the safety profile of nivolumab.

Table 8: Summary of hypersensitivity/infusion reactions by nivolumab ADA status across studies – All treated subjects receiving nivolumab monotherapy with ADA positive or ADA negative

Select AE Category: Hypersensitivity/Infusion Reaction	Number of Subjects (%)	
	Nivolumab ADA Positive (N = 308)	Nivolumab ADA Negative (N = 2010)
Total Subjects with an Event	8 (2.6)	119 (5.9)
Anaphylactic Shock	0	1 (0.05)
Bronchospasm	1 (0.32)	10 (0.50)
Hypersensitivity	5 (1.62)	44 (2.19)
Infusion Related Reaction	2 (0.65)	71 (3.53)

Note: Integrated data from studies CA209063, CA209037, CA209066, CA209017, CA209057, CA209067 (monotherapy arm), CA209025, CA209039 (all cHL), CA209205, CA209141, CA209032 (UC cohort), and CA209275, and CA209040 (ESC + EXP ALL)

2.3.4. Discussion on clinical pharmacology

The recommended dose and schedule of nivolumab monotherapy for treatment of HCC is the same as that approved for other indications: 3 mg/kg IV infusion over 60 minutes Q2W. This is considered acceptable.

Pharmacokinetic data were collected in the Phase I/II study CA209040. An updated popPK analysis was presented. PK was described by a 2-compartment model with time-varying CL (CL decreased with time ~26%).

Overall, the popPK analysis indicated that there are no major differences in pharmacokinetics of nivolumab in HCC compared to NSCLC 2L+ tumour type. Similar CL in steady state was observed, however the change in CL over time was slower in HCC patients compared to other solid tumour indications.

The effects of covariates (body weight, ALB, baseline GFR, PS, sex, race) were consistent with previous analyses. HCC Etiology did not have a clinically relevant effect on nivolumab exposure as dose-normalized average steady-state concentration values were generally similar among three etiology groups: uninfected subjects, those with HCV, or those with HBV. Baseline hepatic function status did not either appear to affect nivolumab exposure.

E-R analysis for efficacy was conducted for 174 patients with HCC from study CA20040 who had previously been treated with sorafenib and who had nivolumab data available. Cavg1 was not found to be a predictor of OR in the model. No effect of other predictor covariates (EHS/VI, baseline AFP, baseline Cl or etiology) was observed.

There was no evidence that the risk of Grade 3 or greater drug related drug related-AEs increased with increasing nivolumab exposure. In fact, a trend towards an inverse relationship between exposure and risk of Grade 3+ drug related-AEs was observed. This effect might be driven by a small number of subjects in the highest and lowest dose groups: there were no Grade 3+ drug related-AEs in the highest dose group (10 mg/kg), while the incidence of Grade 3+ DR-AEs was higher in the lower dose groups. Another potentially confounding effect may be that exposure of nivolumab is in general lower in patients with poor health status; low performance status, high tumour burden and low serum albumin increase the clearance of nivolumab. This may manifest as an apparent inverse exposure-response for Grade 3+ AEs. Such an apparent inverse relationship was also observed for RCC.

Nivolumab has low immunogenic potential. Nevertheless, the incidence of ADA in HCC population is slightly higher than in the pool of previous trials.

The rate of ADA positive patients (56 out of 210 subjects (26.7%) HCC tested positive for treatment-emergent anti-nivolumab antibody) is one of the highest observed throughout the nivolumab clinical development across different indications. Of those who were anti-nivolumab antibody positive, 6 subjects (2.9% of the total) were persistent positive, and neutralizing antibodies were only detected in 1 subject (0.5% of the total). The safety profiles of persistent positive or neutralizing positive subjects were no different than those in other subjects. There was no evidence of loss of efficacy in subjects with neutralizing antibodies.

2.3.5. Conclusions on clinical pharmacology

New analyses presented do not change current knowledge on PK/PD and immunogenicity for Opdivo.

2.4. Clinical efficacy

There are 2 ongoing studies of nivolumab monotherapy in HCC: 1 Phase 1/2 non-comparative study of nivolumab monotherapy or in combination with ipilimumab in subjects with advanced HCC with or without chronic viral hepatitis (**CA209040**); and one Phase 3 randomized study of nivolumab versus sorafenib as first-line treatment in patients with advanced HCC (**CA209459**).

Table 9: Design of the main studies

Trial	Phase	Size	Trial Design
CA209040 NCT01658878	I/II	600	**5 Cohorts:** 1) Phase 1 dose escalation in advanced HCC patients 2) Phase 1b expansion in advanced HCC patients 3) Phase 2 non-comparative randomized study of nivolumab vs sorafenib in advanced 1L patients 4) Phase 1b to evaluate 3 different dose/schedules of the combination of nivolumab/ipilimumab in advanced 2L HCC patients 5) Phase 1b to evaluate safety/efficacy in Child-Pugh B HCC patients
CA209459 NCT02576509	III	726	A Randomized, Multi-center Phase III Study of Nivolumab Versus Sorafenib as 1L Treatment in Patients With Advanced HCC

The current submission for 2L (post sorafenib) HCC is based on interim data from the dose escalation phase (ESC) and the expansion phase (EXP) cohorts from **CA209040 (262 treated subjects, monotherapy)**.

2.4.1. Dose response studies

Dose response studies were not performed specifically for the indication in HCC. The dose is the same as the one used in the already approved indications.

2.4.2. Main study:

CA209040: A Phase 1/2, Dose-escalation, Open-label, Non-comparative Study of Nivolumab or Nivolumab in Combination with Ipilimumab in Advanced HCC Subjects with or without Chronic Viral Hepatitis; and a Randomized, Open-label Study of Nivolumab vs Sorafenib in Advanced Hepatocellular Carcinoma Subjects who are Naive to Systemic Therapy.

The primary evidence of efficacy of nivolumab monotherapy presented in this application focuses on 2L post sorafenib population.

Study design

At the time of submission, the full study was comprised of five cohorts:

1. Phase 1 dose escalation in advanced HCC patients (ESC)
2. Phase 1b expansion in advanced HCC patients (EXP)
3. Phase 2 non-comparative randomized study of nivolumab vs sorafenib in advanced 1L patients
4. Phase 1b to evaluate 3 different dose/schedules of the combination of nivolumab/ipilimumab in advanced 2L HCC patients
5. Phase 1b to evaluate safety/efficacy in CP B HCC patients

However, the current application for post sorafenib (2L) treatment of advanced HCC is based solely on interim data from the first two cohorts, i.e. ESC and EXP. Data from the other three cohorts is not provided by the applicant and therefore the combination with ipilimumab is not discussed.

Study design rationale for ESC

Prior available pharmacokinetic (PK) data from patients with normal hepatic function (804 patients) and those with mild hepatic impairment (92 patients), indicate that nivolumab clearance is not affected by mild hepatic impairment (< 20% effect on clearance). Exposures in mild hepatic impairment patients that received nivolumab Q2W were comparable with normal patients. Thus, mild hepatic impairment had no effect on nivolumab clearance and exposure, suggesting that no dose adjustment is needed for patients with mild hepatic impairment. However, PK data were not available for patients with moderate and severe hepatic impairment. HCC generally occurs in the setting of an underlying cirrhosis and impaired liver function. In addition, nivolumab is known to have potential hepatic adverse events. For this reason, this study was initially designed to specifically assess the safety and tolerability of multiple doses of nivolumab in patients with HCC.

Furthermore, there were additional concerns for HCC patients with ongoing active hepatitis virus infections. Stimulation of the immune system could potentially result in immune related viral clearance due to a cytolytic viral-specific response and additional hepatic toxicity. This was of particular concern in patients with chronic HBV infection who tend to have a higher number of infected hepatocytes expressing viral-specific antigens than patients with chronic HCV infection. In addition, the potential for ALT flares due to complex and poorly characterized changes in viral-host interactions is a well-described phenomenon in patients with chronic HBV infection which can result in significant morbidity and mortality. Therefore, there was a significant concern that the immuno-stimulatory effect of nivolumab could result in a greater frequency of hepatic adverse events in virally-infected HCC patients, with HBV-infected patients perceived to have the greatest risk.

Study design ESC

The ESC was an open label, multi-dose, sequential 3-arm phase I study using a traditional 3+3 design with escalating doses (Figure 13). Patients with differing underlying risk factors for the development of HCC were evaluated in three separate dose escalation cohorts; HCC patients with no active hepatitis virus infection (uninfected HCC), patients with HCC due to chronic HCV infection, and patients with HCC due to chronic HBV infection. Within each independent ESC study arm, 3-6 patients were assigned to a dose level in the order of study entry and starting at the lowest dose. There was no intra-patient dose escalation. Dose escalation was performed independently in each group because of the concern that virally infected patients might have a toxicity profile that is more severe. The study opened with patients with non-viral and HCV HCC treated in parallel dose cohorts simultaneously and starting at a dose of 0.3 mg/kg. The 0.1 mg/kg starting dose employed in the HBV HCC cohort was lower than that employed in the other two cohorts for the above mentioned reason.

Study design rationale for EXP

Preliminary data from the ESC demonstrated the safety and tolerability of nivolumab in uninfected HCC up to 10 mg/kg Q2W. Based on the observed safety and efficacy of nivolumab in other tumour types and from the ESC, in conjunction with clinical pharmacology profiles, 3 mg/kg IV Q2W was selected as the nivolumab monotherapy dose and schedule for expansion, thereby providing unified monotherapy dosing across all indications. As tumour immuno-biology might be different between uninfected HCC patients who fail sorafenib and those with inadequate or no exposure to sorafenib, two separate expansion cohorts were added, i.e. one with patients who failed sorafenib and one with patients who refused or were intolerant to sorafenib.

In addition, preliminary data from ESC indicated anti-tumour as well as anti-viral effects in HCC patients with viral hepatitis with an acceptable safety profile. Thus, both the HCV and HBV cohorts were expanded to further characterize the safety, anti-tumour, and anti-viral properties of nivolumab. As the 3 mg/kg dose level was already selected, the HCV and HBV cohorts were no longer dose escalated to the 10 mg/kg dose level.

Study design EXP

Further characterization of nivolumab safety and activity in both uninfected and hepatitis virus infected HCC patients in four cohorts of approximately 50 patients (Figure 13):

- uninfected patients who refused or were intolerant to sorafenib
- uninfected patients who progressed during or after sorafenib
- HBV-infected patients
- HCV-infected patients

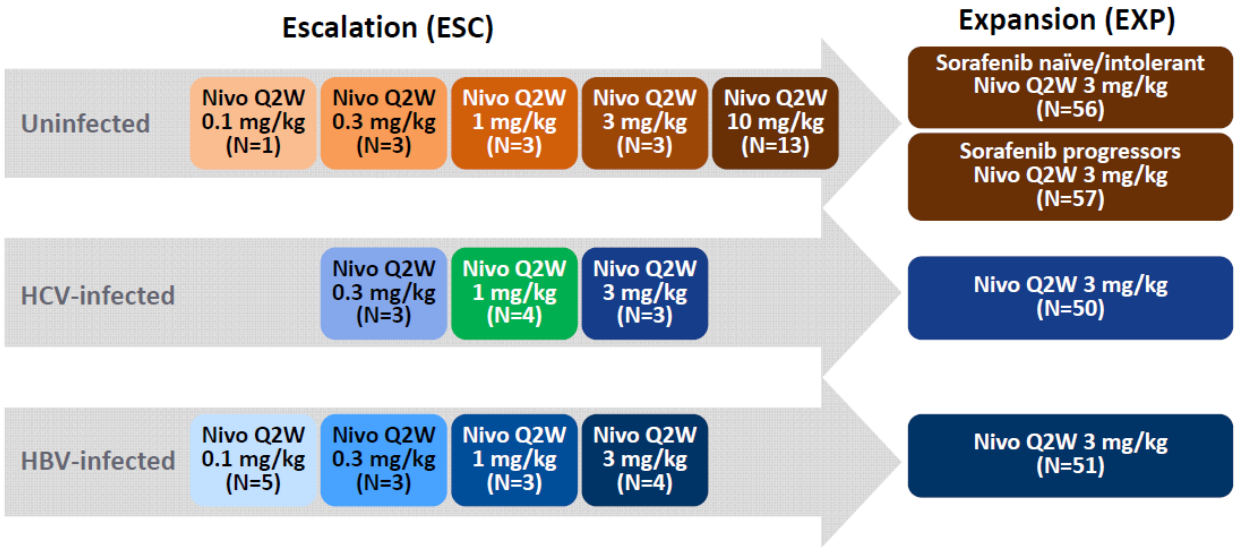


Figure 13 Study design of CA209040 ESC and EXP cohorts (Nivo = nivolumab).

As stated earlier, the current application is for post sorafenib (2L) treatment of advanced HCC and is based on interim data. Thus, the dataset submitted consisted of:

- **2L ESC** population: n=37 sorafenib-treated patients administered 0.1 to 10 mg/kg nivolumab Q2W in the dose escalation phase
- **2L EXP** population: n=145 sorafenib-treated patients administered 3 mg/kg nivolumab Q2W in the expansion phase

Furthermore, in

Figure 14: - it is clarified that the:

- **ESC + EXP** cohort: n=262 total treated patients, is composed of both sorafenib-naive and sorafenib prior treated and includes the:

    1. ESC cohort: n=48 patients (i.e. 11 sorafenib-naive and 37 sorafenib treated) administered 0.1-10 mg/kg nivolumab monotherapy Q2W in the dose escalation phase
    2. EXP cohort: n=214 patients (i.e. 69 sorafenib-naive and 145 sorafenib-treated) administered 3 mg/kg nivolumab Q2W in the expansion phase

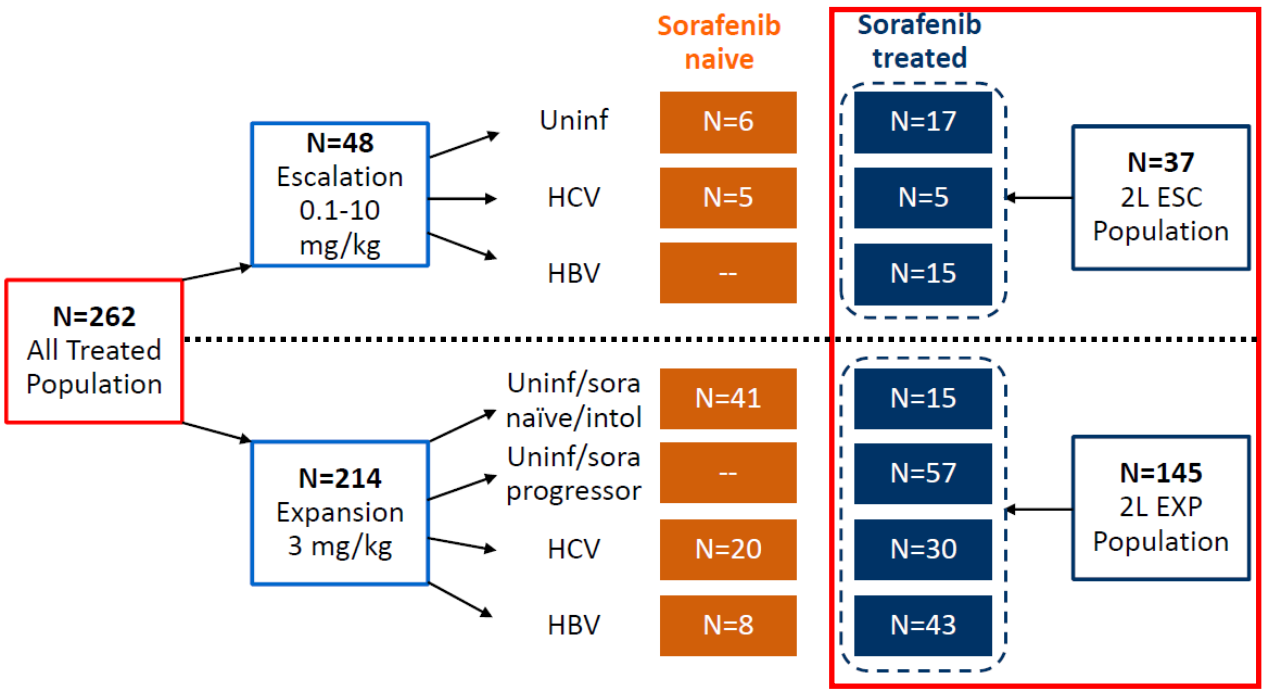


Figure 14: Schematic breakdown of the all treated population and illustration of the dataset supporting the current application for post sorafenib (2L) treatment of advanced HCC (in the red box) (intol = intolerant; sora = sorafenib; Uninf = uninfected).

Study participants

Main inclusion criteria

The study population included adults (⩾ 18 years) with histologically confirmed HCC, not amenable for management with curative intent by surgery or local therapeutic measures, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1. All subjects must had at least one measurable lesion at baseline.

Subjects were to fulfill the following criteria for prior therapy:

For the **ESC** Cohort:

- Subjects were Child-Pugh A (5 or 6 points) or Child-Pugh B7
- Uninfected, HCV-infected, and HBV-infected subjects must have had progressive disease following or be intolerant of at least one line of systemic therapy or refuse sorafenib treatment (refusal must be documented); subjects cannot be on active cancer therapy during the screening period.

For the **EXP** Cohort:

- Subjects were Child-Pugh A
- Uninfected sorafenib progressors must have had documented radiographic or symptomatic progression during or after sorafenib therapy
- Uninfected sorafenib naive or intolerant subjects must either have never received sorafenib treatment or were intolerant to sorafenib therapy as defined in Section 1.4.9 of the protocol

(see Appendix 1.1 of the Study CA209040 Interim CSR).

- Per Amendment 4, HCV- and HBV-infected subjects must have progressive disease (PD) following, or be intolerant of, at least one line of systemic therapy or refuse sorafenib treatment (refusal must be documented); subjects could not have been on active cancer therapy during the screening period (see Appendix 1.1 of the Study CA209040 Interim CSR).

- Following Amendment 8, HCV and HBV subjects must have received sorafenib treatment and were either intolerant to or have had documented radiographic or symptomatic progression during or after sorafenib therapy as defined in protocol.

In addition, subjects in the non-infected HCC arm were to include those with prior HCV or HBV infection with no active viral replication (ie, negative for HBV deoxyribonucleic acid [DNA] and/or HBV surface antigen and HCV ribonucleic acid [RNA]). Subjects in the HCV-infected arms were to have evidence of HCV RNA and those in the HBV-infected arm must have evidence of ongoing viral replication (detectable hepatitis B surface antigen [HBsAg], hepatitis B e antigen [HBeAg], or HBV DNA). Tumor tissue was to be available for biomarker evaluation.

- 'Sorafenib intolerance' is defined as experiencing:
  - CTCAE Grade 2 drug-related adverse event which persisted in spite of comprehensive supportive therapy according to institutional standards AND persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (to 400 mg once daily)
  - CTCAE Grade 3 drug-related adverse event which persisted in spite of comprehensive supportive therapy according to institutional standards OR persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (to 400 mg once daily).
- 'Sorafenib progressors' are defined as:
  - Documented symptomatic OR radiographic progression during or after sorafenib therapy

Main exclusion criteria

Patients with active autoimmune disease, brain metastasis, a history of hepatic encephalopathy, clinically significant ascites on physical exam, infection with HIV, or active coinfection with HBV/HCV or HBV/HDV were excluded from the study.

Treatments

In the Dose Escalation Phase, subjects entered sequentially into the dose level (ranging from 0.1 mg/kg to 10 mg/kg Q2W) accruing up to a maximum of 6 subjects at 0.1 to 3 mg/kg dose arms, and a maximum of 13 subjects at 10 mg/kg.

Once the determination that the dose level was safe had been made, the next dose level could begin accrual. No intrasubject nivolumab dose escalation was allowed.

Nivolumab was administered as an IV infusion on treatment every two weeks until either RECIST 1.1 progression or toxicity. Prior to activation of amendment 8, subjects in the ESC Cohort were treated until either a confirmed CR, completion of 2 years of therapy, toxicity, or disease progression. The maximum dose level in this phase was 10 mg/kg in uninfected HCC subjects and 3 mg/kg in HCV and HBV infected HCC subjects, respectively.

In the Expansion Phase, subjects were administered a dose of 3 mg/kg nivolumab Q2W in the uninfected sorafenib-naive, uninfected sorafenib progressor, HCV-infected subjects, and HBV-infected subjects until toxicity or RECIST 1.1 progression.

Dose modifications of nivolumab were not allowed during the Dose Escalation and Expansion Phases, except to adjust for weight changes (± 10%). Nivolumab dose reductions were not permitted in this study.

Dose delays were permitted in all treatment groups.

Nivolumab was supplied as a solution for injection in 10-mL vials. Each vial contained a concentrated solution with the equivalent of 100 mg of nivolumab (10 mg/mL). The following nivolumab batches were administered to subjects: 2E71978, 2A73820, 3C83433, 2M50921, 4M56971, AAC5734, 4C88648, AAD8587, AAA6619, AAD6706, AAE1304.

Prohibited prior therapies include: anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways), systemic corticosteroids or other immunosuppressive medications within 14 days of study drug administration, and other investigational drugs within 28 days or at least 5 half-lives (whichever is longer) before study drug administration.

Objectives

The study was initially designed as a Phase 1 dose escalation study to investigate safety, immuno-regulatory activity, PK, and preliminary anti-tumor activity of nivolumab in advanced HCC subjects with or without chronic viral hepatitis. Following a protocol amendment (Protocol Amendment 4) 4 cohorts were added in order to expand the study to confirm the preliminary safety and efficacy of nivolumab in a diverse group of subjects with advanced HCC.

The purposes of Study CA209040 were:

- **ESC Cohort:** to establish safety, tolerability, dose limiting toxicities (DLTs) and MTD for nivolumab administered every 14 days to subjects with advanced HCC.
- **EXP Cohort:** to estimate ORR and DOR of nivolumab monotherapy (3 mg/kg) in adults with advanced HCC with or without chronic viral hepatitis (HCV or HBV) who are naive to sorafenib or have been previously treated with sorafenib. ORR will be determined with a blinded independent central review (BICR)-assessed tumor response based on RECIST 1.1.

Key secondary endpoints for both ESC and EXP Cohorts included time to progression (TTP), progression-free survival (PFS), OS, and DOR. The association between programmed death ligand 1 (PD-L1) expression and clinical efficacy measures was also evaluated.

The interim analysis of the ESC and EXP Cohorts is based on data from the **08-Aug-2016** clinical database lock (DBL) and **10-Aug-2016** BICR DBL.

Outcomes/endpoints

Primary endpoint:

- ESC: safety and tolerability of nivolumab as evaluated by:
    1. Incidence of adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, and deaths
    2. Incidence of clinical laboratory test abnormalities
- EXP: ORR determined by BICR assessed tumour response based on RECIST 1.1

Of note, ORR is defined as the proportion of all treated patients whose best overall response (BOR) is CR or PR. BOR is determined by the best response designation recorded between the date of first dose of study medication and the date of first objectively documented progression or the date of subsequent anticancer therapy, whichever occurs first. Responders are the patients with BOR of CR or PR.

Secondary endpoints:

- ESC only: maximum observed serum concentration (Cmax), time of maximum observed serum concentration (Tmax), area under the serum concentration time curve in the dosing interval (AUC(TAU)), serum concentration achieved at the end of dosing interval (trough concentration, Ctrough), serum concentration achieved at the end of the infusion (Ceoinf), Cmax at Cycle 3/ Cmax at Cycle 1 (AI_Cmax), AUC(TAU) at Cycle 3/ AUC(TAU) at Cycle 1 (AI_AUC), and effective T-Half
- ESC only: incidence of patient anti-drug antibody (ADA) status, which include baseline ADA-positive, ADA-positive and ADA-negative
- ESC only: ORR determined by BICR assessed tumour response based on RECIST 1.1
- Both ESC and EXP: CR rate, disease control rate (DCR), DOR, TTR (time to response), TTP, TTP rate, and PFS, all determined by BICR or investigator assessed tumour response based on RECIST 1.1
- Both ESC and EXP: OS and OS rate (OSR)
- Both ESC and EXP: ORR, PFS, and OS per baseline PD-L1 expression

Exploratory endpoints (include but are not limited to):

- Both ESC and EXP: BOR and ORR determined by BICR assessed tumour response based on mRECIST
- EXP only: incidence of patient ADA status, which include baseline ADA-positive, ADA-positive and ADA-negative
- EXP only: summary of EQ-5D-3L and VAS scores

Sample size

For the ESC cohort, the sample size at each dose level depends on the observed toxicity and is not based on statistical considerations. Three to 6 patients will be evaluated at each dose level from 0.1 mg/kg to 3 mg/kg, and 13 patients at 10 mg/kg in the uninfected arm only.

For the EXP cohort, in order to better estimate efficacy of nivolumab, approximately an additional 100 uninfected patients (50 sorafenib progressors and 50 sorafenib naive or intolerant), 50 HCV-infected patients, and 50 HBV-infected patients will be included. If 50 patients are treated at 3 mg/kg dose level in any of the four additional expansion arms and 10 of 50 patients (20%) are responders (BOR of PR or CR), the lower bound of 95% confidence interval of the response rate is 10% using the Clopper-Pearson method.

Randomisation

Not applicable as this was a non-randomised, non-comparative study.

Blinding (masking)

Not applicable; this was an open-label study.

Statistical methods

Continuous variables were summarized using descriptive statistics; ie, number of non-missing observations (n), mean, standard deviation, median, minimum, maximum, and quartiles. Categorical variables were summarized by frequencies and percentages.

Efficacy endpoints based on tumor response evaluations will be analyzed for both BICR assessments per RECIST 1.1 and investigator assessment per RECIST 1.1. For ORR analysis, BICR assessments per RECIST 1.1 will serve for the purpose of primary analysis, while investigator assessments per RECIST 1.1 will serve for sensitivity analysis.

Time to event distribution (eg, TTP, OS, and DOR) were estimated using Kaplan-Meier techniques. Median survival time along with 95% CI were constructed based on Brookmeyer and Crowley method using log-log transformation7. Rates at fixed timepoints (eg, OS at 6 months) were derived from the Kaplan-Meier estimate and corresponding CI were derived based on Greenwood formula8 for variance derivation and on log-log transformation applied on the survival function.

Populations for analyses

- All Enrolled Subjects: All subjects who sign an informed consent form.
- All Treated Subjects: All enrolled subjects who receive at least one dose of study medication.
- Pharmacokinetic Subjects: All treated subjects who receive at least one dose of study medication and have available serum concentration data.
- Immunogenicity Subjects: All treated subjects who receive at least one dose of study medication and have pre- and on-treatment ADA data.
- Biomarker Subjects: All treated subjects who receive at least one dose of study medication and have available biomarker data.
- Expansion Post Sorafenib Subjects: All treated subjects who are post sorafenib in the expansion cohort.
- Escalation Post Sorafenib Subject: All treated subjects who are post sorafenib in the escalation cohort.
- Expansion Sorafenib Naive Subjects: All treated subjects who are sorafenib naive in the expansion cohort
- Escalation Sorafenib Naive Subjects: All treated subjects who are sorafenib naive in the escalation cohort

Results

Participant flow

In Figure 15 - the participant flow is shown.

Not treated n=114
ESC cohort n=27
No longer meets study criteria n= 1
Other n=1
EXP cohort n=87
No longer meets study criteria n= 75
Withdrew consent n=10
Administrative reason sponsor n=1
Other n=1

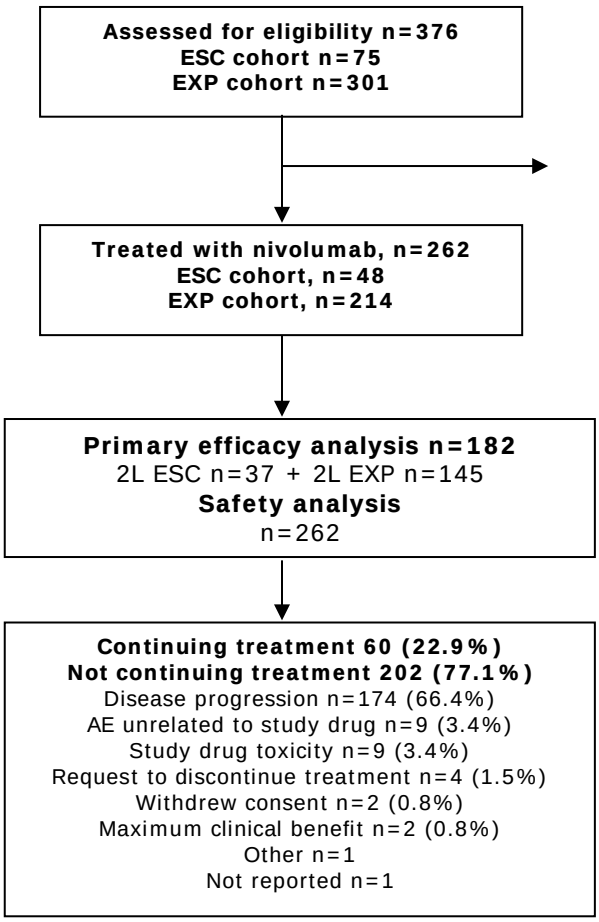


Figure 15 Participant flow.

Recruitment

262 subjects were treated at 39 sites in 11 countries (Canada, Germany, Hong Kong, Italy, Japan, Republic of Korea, Singapore, Spain, Taiwan, United Kingdom and United States).

Of the 262 treated subjects in ESC+EXP Cohort, 62 (23.7%) were in the US, 32 (12.2%) were in Japan, and 31 (11.8%) were in Spain and the United Kingdom.

In the ESC Cohort, the enrollment period lasted for approximately 9 months. The first patient first visit date (FPFV) was 30-Oct-2012 and the last patient first treatment (LPFT) date was 08-Jul-2015. In the EXP Cohort, the FPFV was 27-Jan-2015 and the LPFT was 28-Oct-2015. This study is ongoing, and the last patient last visit date (LPLV) for this CSR was 24-Jun-2016.

The clinical DBL for this CSR occurred on 08-Aug-2016 and the BICR assessment DBL occurred on 10-Aug-2016, leading to a minimum follow-up of approximately 7 months and study duration of 16 months for this DBL.

Conduct of the study

Protocol deviations:

Significant protocol deviations, i.e. study conduct that differed significantly from the protocol, including GCP noncompliance, mostly concerned delayed reporting of an SAE by a site.

Relevant protocol deviations, i.e. significant protocol deviations that were programmable and could potentially affect the interpretability of study results, were reported in 12 patients (4.6%) in the all treated population. At study entry one patient in the 2L EXP cohort did not have evaluable disease at

baseline and on treatment deviations were reported for 11 patients (4.2%) as they had received concurrent anticancer therapy:

- in the uninfected 2L ESC cohort one patient received both surgery and radiotherapy
- in the HBV-infected 2L ESC cohort one patient received radiotherapy alone
- in the uninfected 1L EXP cohort three patients received radiotherapy
- in the uninfected 2L EXP cohort four patients received radiotherapy and one received surgery
- in the HCV-infected 2L EXP cohort one patient received radiotherapy

However, the applicant did not consider these 11 true relevant protocol deviations because all had documented radiographic progression. Moreover, 3 patients started radiotherapy after last dose of study and 2 patients received palliative radiotherapy, as was allowed per protocol.

Palliative local therapy for clinically symptomatic tumour sites was permitted per protocol provided the lesion for palliative local therapy was a non-target lesion, and only for patients who were considered to already have progressed at the time of palliative therapy and who in addition met criteria to continue study treatment beyond progression as in e.g. investigator-assessed clinical benefit.

Table 10 Relevant protocol deviations for the all treated population (percentages in brackets).

	ESC + EXP Cohort N = 262
SUBJECTS WITH AT LEAST ONE DEVIATION	12 (4.6)
AT ENTRANCE	
SUBJECTS WITH ECOG PS > 1	0
SUBJECTS WITHOUT EVALUABLE DISEASE AT BASELINE	1 (0.4)
SUBJECTS WITH SERUM ALBUMIN < 2.8 G/DL	0
SUBJECTS WITH TOTAL BILIRUBIN > 3 MG/DL	0
SUBJECTS WITH AST > 5 TIMES THE INSTITUTIONAL UPPER LIMITS OF NORMAL	0
SUBJECTS WITH ALT > 5 TIMES THE INSTITUTIONAL UPPER LIMITS OF NORMAL	0
CHILD-PUGH SCORE OF B8 OR GREATER	0
CHILD-PUGH SCORE OF B OR HIGHER FOR EXPANSION PHASE	0
ON TREATMENT DEVIATIONS	
SUBJECTS RECEIVING CONCURRENT ANTI-CANCER THERAPY	11 (4.2)

Amendments:

The full study was amended 13 times, but only four of these amendments concerned the ESC and EXP cohorts

Table 11: List of protocol amendments concerning ESC and EXP cohorts.

Amendment number	Date	Summaries
2	18-Mar-2013	Updated text for pre-clinical toxicology finding
3	06-Sept-2013	Added a 10mg/kg dose group to all disease types
4	29-Oct-2014	Added the expansion cohort of 4 arms - uninfected sorafenib progressor 3 mg/kg, uninfected sorafenib naïve or intolerant 3 mg/kg, HBV infected at MTD or 3 mg/kg, and HCV infected 3 mg/kg. Switch of tumor evaluation criteria from mRECIST to RECIST 1.1. mRECIST remains for exploratory analysis. Added retreatment period Added EQ-5D-3L as exploratory objective Removed HBV infected 10 mg/kg cohort and HCV infected 10 mg/kg cohort
8	31-Jul-2015	Changed the criteria of stopping treatment.

Of note, following amendment 4 patients that had entered the follow-up period with confirmed CR and had discontinued nivolumab treatment were permitted to reinitiate treatment upon disease progression in certain conditions. However, following amendment 8 this was once again not allowed.

In addition, following amendment 8 HBV and HCV patients were required to have progression following or intolerance to sorafenib treatment and thus were not allowed to be sorafenib naïve.

Lastly, prior to amendment 8, patients in the ESC cohort were treated until either a confirmed CR, completion of 2 years of therapy, toxicity, or disease progression. Following amendment 8 all patients were treated until RECIST 1.1 defined progression, unacceptable toxicity, or study discontinuation for any other reason.

Baseline data

Table 12: Baseline Demographic Characteristics - All Treated Subjects in the 2L EXP, 2L ESC, and ESC + EXP Cohorts

	2L EXP Cohort N = 145	2L ESC Cohort N = 37	ESC + EXP Cohort N = 262
AGE (YEARS)			
N	145	37	262
MEAN	61.4	58.5	61.7
MEDIAN	63.0	58.0	63.0
MIN , MAX	19 , 81	22 , 79	19 , 83
Q1 , Q3	56.0 , 70.0	53.0 , 66.0	56.0 , 70.0
STANDARD DEVIATION	12.26	12.73	12.26
AGE CATEGORIZATION (%)			
< 65	81 (55.9)	23 (62.2)	142 (54.2)
>= 65 AND < 75	48 (33.1)	11 (29.7)	89 (34.0)
>= 75 AND < 85	16 (11.0)	3 (8.1)	31 (11.8)
>= 85	0	0	0
GENDER (%)			
MALE	112 (77.2)	27 (73.0)	207 (79.0)
FEMALE	33 (22.8)	10 (27.0)	55 (21.0)
RACE (%)			
WHITE	67 (46.2)	20 (54.1)	133 (50.8)
BLACK OR AFRICAN AMERICAN	3 (2.1)	1 (2.7)	8 (3.1)
ASIAN	75 (51.7)	16 (43.2)	119 (45.4)
ASIAN INDIAN	1 (0.7)	0	4 (1.5)
CHINESE	34 (23.4)	15 (40.5)	65 (24.8)
JAPANESE	25 (17.2)	0	31 (11.8)
KOREAN	13 (9.0)	0	14 (5.3)
ASIAN OTHER	2 (1.4)	1 (2.7)	5 (1.9)
AMERICAN INDIAN OR ALASKA NATIVE	0	0	0
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	1 (0.4)
OTHER	0	0	1 (0.4)
ETHNICITY (%)			
HISPANIC OR LATINO	2 (1.4)	3 (8.1)	13 (5.0)
NOT HISPANIC OR LATINO	59 (40.7)	11 (29.7)	102 (38.9)
NOT REPORTED	84 (57.9)	23 (62.2)	147 (56.1)

Source: Table S.3.1 (ESC + EXP Cohort) and Table S.3.1b (2L ESC and 2L EXP Cohorts)

Table 13: Baseline Demographic Characteristics and Tumour Assessments - All Treated Subjects in the 2L EXP, 2L ESC, and ESC + EXP Cohorts

	2L EXP COHORT N = 145	2L ESC COHORT N = 37	ESC + EXP COHORT N = 262
ECOG PS (%)			
0	93 (64.1)	26 (70.3)	166 (63.4)
1	52 (35.9)	11 (29.7)	96 (36.6)
BCLC STAGE			
0	0	0	1 (0.4)
A	2 (1.4)	1 (2.7)	3 (1.1)
B	14 (9.7)	3 (8.1)	24 (9.2)
C	126 (86.9)	33 (89.2)	230 (87.8)
D	0	0	0
UNKNOWN	3 (2.1)	0	4 (1.5)
OKUDA STAGING			
I	105 (72.4)	28 (75.7)	199 (76.0)
II	37 (25.5)	9 (24.3)	59 (22.5)
III	0	0	0
UNKNOWN	3 (2.1)	0	4 (1.5)
CHILD-PUGH SCORE (%)			
5	98 (67.6)	34 (91.9)	190 (72.5)
6	45 (31.0)	3 (8.1)	68 (26.0)
7	2 (1.4)	0	3 (1.1)
8	0	0	0
9 OR ABOVE	0	0	1 (0.4)
VASCULAR INVASION PRESENT (A)	41 (28.3)	15 (40.5)	82 (31.3)
EXTRAHEPATIC SPREAD PRESENT (A)	102 (70.3)	27 (73.0)	178 (67.9)
VI OR EHS PESENT (A)	118 (81.4)	32 (86.5)	210 (80.2)
AFP CATEGORY (UG/L)			
<400	85 (58.6)	25 (67.6)	158 (60.3)
>=400	55 (37.9)	12 (32.4)	94 (35.9)
AFP (UG/L)			
MEDIAN	84.65	56.00	62.70
MIN - MAX	1.0 - 316946.7	1.1 - 771330.2	1.0 - 771330.2
PRIOR SORAFENIB TREATED (%)	145 (100.0)	37 (100.0)	182 (69.5)
PROGRESSOR	132 (91.0)	33 (89.2)	165 (63.0)
INTOLERANT	12 (8.3)	1 (2.7)	13 (5.0)
NEITHER PROGRESSOR NOR INTOLERANT	1 (0.7)	3 (8.1)	4 (1.5)

	2L EXP COHORT N = 145	2L ESC COHORT N = 37	ESC + EXP COHORT N = 262
SUBJECT HAS HCC RISK FACTOR			
YES	117 (80.7)	23 (62.2)	201 (76.7)
NO	23 (15.9)	14 (37.8)	53 (20.2)
UNKNOWN	5 (3.4)	0	8 (3.1)
RISK FACTOR PRESENT:			
HEPATITIS B	49 (33.8)	15 (40.5)	74 (28.2)
HEPATITIS C	43 (29.7)	6 (16.2)	84 (32.1)
ALCOHOLIC LIVER DISEASE	28 (19.3)	1 (2.7)	38 (14.5)
AFLATOXIN EXPOSURE	0	0	0
HEMOCHROMATOSIS	4 (2.8)	0	7 (2.7)
NON-ALCOHOLIC FATTY LIVER	10 (6.9)	1 (2.7)	19 (7.3)
SUBJECTS WITH >= 1 TARGET LESION	143 (98.6)	35 (94.6)	261 (99.6)
ORGAN OF TARGET LESION (B)			
VISCERAL, LIVER	114 (78.6)	31 (83.8)	211 (80.5)
ALL OTHERS	83 (57.2)	19 (51.4)	156 (59.5)
Subjects with the Following			
Number of Liver Nodule(s)			
0	32 (22.1)	7 (18.9)	56 (21.4)
1 - 3	45 (31.0)	12 (32.4)	83 (31.7)
> 3	65 (44.8)	18 (48.6)	118 (45.0)
Tumor Invasion In Liver Above 50%	22 (15.2)	7 (18.9)	39 (14.9)

(A) Derived Based on Reported CRF Data
(B) Subjects may have lesions at more than one site
Subjects may have more than one risk factor present and particularly both HCV and HBV risk factors may be present
Source: Table S.3.2 (EDOG - ESC+ EXP Cohort), Table S.3.2b (EDOG - 2L ESC, 2L EXP), Table S.3.3 (baseline characteristics - ESC+ EXP Cohort), Table S.3.3b (baseline characteristics - 2L ESC, 2L EXP), Table S.3.4 (time from initial diagnosis - ESC+ EXP Cohort), Table S.3.4b (time from initial diagnosis - 2L ESC, 2L EXP), Table S.3.5.1b (pretreatment assessments - 2L ESC, 2L EXP), Table S.3.5.2 (pretreatment assessments - ESC+ EXP Cohort), Table S.3.11 (HCC risk factors - ESC+ EXP Cohort), and Table S.3.11b (HCC risk factors - 2L ESC, 2L EXP)

Of the prior sorafenib-treated population, 132 patients (91.0%) in the 2L EXP cohort had progressive disease on or after sorafenib and 12 patients (8.3%) were sorafenib intolerant. For the 2L ESC cohort these numbers were 33 patients (89.2%) and 1 patient (2.7%), respectively.

Respectively 58 patients (40%) in the 2L EXP cohort and 10 patients (27%) in the 2L ESC cohort were from Europe, 71 (49%) and 14 (38%) were from Asia, and the rest were from the US or Canada.

Of note, the time from initial diagnosis to first dose of study therapy was ≥5 years for 37.2% of patients in the 2L EXP cohort and for 40.5% of patients in the 2L ESC cohort.

Table 14: Time from initial diagnosis to first dose of study therapy (percentages in brackets).

	Exp Post Sorafenib All N = 145	Esc Post Sorafenib All N = 37
< 1 YEAR	4 (2.8)	2 (5.4)
1- < 2 YEARS	11 (7.6)	5 (13.5)
2- < 3 YEARS	12 (8.3)	1 (2.7)
3- < 4 YEARS	5 (3.4)	1 (2.7)
4- < 5 YEARS	3 (2.1)	0
>= 5 YEARS	54 (37.2)	15 (40.5)
NOT REPORTED	56 (38.6)	13 (35.1)

Medical History

Abnormal physical examination findings were reported at baseline for 39.3% of subjects in the ESC+EXP Cohort.

The most frequent body systems with abnormal physical exam findings at baseline were the abdomen (25.6%) and skin (11.8%). The most frequent pre-treatment events were AST increased (11.8%), ALT increased (9.9%), hypertension (8.8%), and blood alkaline phosphatase increased (8.4%).

Subjects in the HCV-infected cohort had higher frequencies of AST, ALT, and total bilirubin increases at baseline.

The most frequent body systems with abnormal physical exam findings at baseline for the 2L EXP cohort were the abdomen (20.7%) and skin (11.7%). The most frequent pre-treatment events were abdominal pain (6.2%), fatigue (8.3%), decreased appetite, AST increased, and insomnia (each 5.5%), anemia and hypertension (each 4.8%).

Previous Treatments

In the ESC Cohort, all subjects (whether uninfected, HCV-infected, or HBV-infected) were required to have progressive disease following or have been intolerant of at least one line of systemic therapy or have refused sorafenib therapy.

In the EXP Cohort, uninfected naive/intolerant subjects were required to be naive or intolerant to sorafenib; uninfected progressor subjects were required to have progressive disease during or after sorafenib therapy (progressor); HCV and HBV subjects must have had progressive disease following or be intolerant of at least one line of systemic therapy or refuse sorafenib treatment (refusal must be documented). Following Amendment 8, HCV and HBV subjects must have received sorafenib treatment and be either intolerant or have had documented radiographic or symptomatic progression during or after sorafenib therapy.

Table 15: Prior Cancer Therapy Summary - All Treated Subjects in the 2L EXP, 2L ESC, and ESC + EXP cohorts

	Number of Subjects (%)		
	2L EXP COHORT N = 145	2L ESC COHORT N = 37	ESC + EXP COHORT N = 262
NUMBER OF SYSTEMIC REGIMEN RECEIVED			
0	0	0	63 (24.0)
1	118 (81.4)	23 (62.2)	157 (59.9)
2	12 (8.3)	8 (21.6)	21 (8.0)
>=3	15 (10.3)	6 (16.2)	21 (8.0)
SUBJECTS WITH PRIOR SORAFENIB TREATMENT UNDER ALL REGIMENS AND REGIMEN SETTINGS			
N (%)	145 (100.0)	37 (100.0)	182 (69.5)
BEST RESPONSE (A) (B)			
CR	0	0	0
PR	3 (2.1)	0	3 (1.6)
SD	62 (42.8)	16 (43.2)	78 (42.9)
PD	61 (42.1)	15 (40.5)	76 (41.8)
UNABLE TO DETERMINE	10 (6.9)	2 (5.4)	12 (6.6)
NOT APPLICABLE	8 (5.5)	4 (10.8)	12 (6.6)
NOT REPORTED	1 (0.7)	0	1 (0.5)
REASON OF DISCONTINUATION (A) (C)			
DISEASE PROGRESSION	108 (74.5)	27 (73.0)	135 (74.2)
MAXIMUM CLINICAL BENEFIT	1 (0.7)	1 (2.7)	2 (1.1)
TOXICITY	34 (23.4)	5 (13.5)	39 (21.4)
COMPLETED TREATMENT	0	2 (5.4)	2 (1.1)
OTHER	3 (2.1)	3 (8.1)	6 (3.3)
DOCUMENTATION OF PROGRESSION BASED ON (A) (D)			
RADIOGRAPHIC	120 (82.8)	32 (86.5)	152 (83.5)
CLINICAL	30 (20.7)	3 (8.1)	33 (18.1)
NOT REPORTED	1 (0.7)	0	1 (0.5)
TIME FROM COMPLETION OF MOST RECENT PRIOR REGIMEN TO TREATMENT			
< 3 MONTHS	100 (69.0)	25 (67.6)	136 (51.9)
3 - 6 MONTHS	15 (10.3)	7 (18.9)	24 (9.2)
> 6 MONTHS	30 (20.7)	5 (13.5)	39 (14.9)
PRIOR SURGERY RELATED TO CANCER			
YES	95 (65.5)	27 (73.0)	164 (62.6)
NO	50 (34.5)	10 (27.0)	98 (37.4)
PRIOR RADIOTHERAPY			
YES	36 (24.8)	9 (24.3)	51 (19.5)
NO	109 (75.2)	28 (75.7)	211 (80.5)
PRIOR LOCAL TREATMENT FOR HCC			
YES	85 (58.6)	19 (51.4)	141 (53.8)
NO	60 (41.4)	18 (48.6)	121 (46.2)
RFA	30 (20.7)	6 (16.2)	44 (16.8)
TAE	5 (3.4)	2 (5.4)	16 (6.1)
TACE	66 (45.5)	14 (37.8)	106 (40.5)
PEI	5 (3.4)	0	5 (1.9)
CRYOABLATION	0	0	0
Y-90 MICROSPHERES	8 (5.5)	3 (8.1)	16 (6.1)
HAI CHEMOTHERAPY	6 (4.1)	0	7 (2.7)
OTHER	6 (4.1)	1 (2.7)	8 (3.1)

(A) Denominator is the number of subjects with sorafenib prior treatment records under all regimens and regimen settings
(B) Best response is picked when multiple records of prior sorafenib treatment are available
(C) Subject could have multiple off-treatment reasons and was counted under each unique off-treatment reason
(D) Subject could be reported to have progressed based on both radiographic and clinical documentation
Source: Table S.3.8 (ESC + EXP Cohort) and Table S.3.8b (2L ESC and 2L EXP Cohorts)

PD-L1 expression

Tumour tissue samples were tested for PD-L1 expression using the Dako PD-L1 immunohistochemistry (IHC) 28-8 pharmDx test. PD-L1 was not used as a stratification factor in either the EXP cohort or ESC cohort.

In most patients less than 1% of the tumour cells expressed PD-L1, i.e. 99 (68.3%) in the 2L EXP cohort and 26 patients (70.3%) in the 2L ESC cohort. Strong (≥5%) PD-L1 expression was measured in only 9 (6.2%) patients in the 2L EXP cohort and 2 patients (5.4%) in the 2L ESC cohort. Median PD-L1 expression was 0.0% and the interquartile range was 0.0-1.0%.

Table 16: PD-L1 expression at baseline in the 2L EXP and 2L ESC cohorts (percentages in brackets)

	2L EXP Cohort N = 145	2L ESC Cohort N = 37
SUBJECTS WITH QUANTIFIABLE PD-L1 EXPRESSION AT BASELINE (A)	124	35
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1%	25 (17.2)	9 (24.3)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%	99 (68.3)	26 (70.3)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 5%	9 (6.2)	2 (5.4)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 5%	115 (79.3)	33 (89.2)
SUBJECTS WITHOUT PD-L1 QUANTIFIABLE AT BASELINE (B)	21 (14.5)	2 (5.4)

(A) Baseline is defined as the most recent pre-treatment quantifiable PD-L1 IHC expression result. If there are multiple PD-L1 IHC assessments on a same date, the result with largest tumor expression value is considered for baseline selection.
(B) Includes PD-L1 tumor sample not available, PD-L1 not evaluable and indeterminate.

Extent of exposure

Importantly, the (2L) ESC cohort was from the dose escalation phase of the study with dose levels ranging from 0.1 to 10 mg/kg and this cohort was included in the all treated population.

Median duration of therapy was 5.26 months for the 2L EXP cohort, 2.56 months for the ESC cohort, and 4.88 months for the all treated population respectively. Dose reductions were not allowed per protocol.

Subsequent anticancer therapy

Subsequent anticancer therapy was received by 31.0% in the 2L EXP cohort, 45.9% in the 2L ESC cohort, and 35.1% in the all treated population respectively.

Subsequent systemic cancer therapy was received by 15.2% in the 2L EXP cohort, 29.7% in the 2L ESC cohort, and 20.2% in the all treated population were respectively, the most common agents being:

- in the 2L EXP cohort sorafenib (3.4%), herbs (2.8%), doxorubicin (2.1%), and fluorouracil (2.1%)
- in the 2L ESC cohort capecitabine (10.8%), herbs (10.8%), and sorafenib (8.1%)
- in the all treated population sorafenib (6.9%), herbs (3.1%), and oxaliplatin (2.3%)

Subsequent non-systemic cancer therapy included radiotherapy (13.1% for the 2L EXP cohort, 13.5% for the 2L ESC cohort, and 11.8% for the all treated population), locoregional treatment for HCC (12.4%, 8.1%, and 11.5% respectively) and surgery (4.1%, 10.8%, and 4.8% respectively).

Patients treated beyond investigator-assessed progression

Some patients treated with immune system stimulating agents may develop disease progression by conventional response criteria before demonstrating clinical objective responses and/or stable disease. Therefore, patients were allowed to continue study therapy after an initial investigator-assessed RECIST 1.1 defined progression as long as they met specific criteria, e.g. investigator-assessed clinical benefit. Importantly, nivolumab treatment was to be discontinued permanently upon documentation of further progression.

A total of 49.0% (71/145) of treated patients in the 2L EXP cohort, 56.8% (21/37) in the 2L ESC cohort, and 46.2% (121/262) in the all treated population received at least one dose of nivolumab after radiographic progression per investigator-assessed RECIST 1.1 or clinical progression, whichever was earlier.

Concurrent anticancer therapy

As is stated in the section “Conduct of the study” above, concurrent anticancer therapy was received by 11 patients (4.2%) in the all treated population, i.e. 8 patients (4.4%) of the 2L EXP and ESC cohorts (protocol deviations). The applicant did not consider these true relevant protocol deviations because all patients involved had documented radiographic progression.

Numbers analysed

Efficacy analyses were performed on the 145 patients in the 2L EXP cohort and the 37 patients in the 2L ESC cohort. The safety analyses included the 2L EXP cohort, the 2L ESC cohort, and in addition the all treated population (n=262).

Outcomes and estimation

The efficacy results will be described using the pooled data from all cohorts. The protocol had prospectively identified 50 subjects per etiologic subtype in the EXP Cohort to describe the safety and efficacy of nivolumab in HCC. Response rates were 23.2% (95% CI: 13.0, 36.4), 21.1% (95% CI: 11.4, 33.9), 20.0% (95% CI: 10.0, 33.7), and 13.7% (95% CI: 5.7, 26.3) in the uninfected naive/sorafenib-intolerant, uninfected progressor, HCV-infected, and HBV-infected Cohorts, respectively. Given that safety and efficacy were similar across the 4etiologic cohorts in the 214 expansion subjects, a pooled approach was taken to strengthen the estimation of response rates in subjects previously treated with sorafenib who have a high unmet medical need.

Therefore, the focus of the primary analysis for this CSR is on prior sorafenib-treated subjects in the 2L EXP (N = 145) Cohort which is also supported by subjects in the 2L ESC (N = 37) Cohort.

Table 17: Table-Summary of Efficacy Results in CA209040 by BICR and Investigator Assessment- All Treated Post-Sorafenib Subjects (2L EXP and 2L ESC Cohorts)

	BICR ASSESSMENT		INVESTIGATOR ASSESSMENT	
	2L EXP COHORT N = 145	2L ESC COHORT N = 37	2L EXP COHORT N = 145	2L ESC COHORT N = 37
OBJECTIVE RESPONSE RATE (A)	21/145 (14.5%)	7/37 (18.9%)	27/145 (18.6%)	6/37 (16.2%)
(95% CI)	(9.2, 21.3)	(8.0, 35.2)	(12.6, 25.9)	(6.2, 32.0)
BEST OVERALL RESPONSE:				
COMPLETE RESPONSE (CR)	1 (0.7)	1 (2.7)	3 (2.1)	3 (8.1)
(95% CI)	(0.0, 3.8)	(0.1, 14.2)	(0.4, 5.9)	(1.7, 21.9)
PARTIAL RESPONSE (PR)	20 (13.8)	6 (16.2)	24 (16.6)	3 (8.1)
(95% CI)	(8.6, 20.5)	(6.2, 32.0)	(10.9, 23.6)	(1.7, 21.9)
STABLE DISEASE (SD)	59 (40.7)	12 (32.4)	66 (45.5)	16 (43.2)
NON-CR/NON-PD	0	1 (2.7)	0	0
PROGRESSIVE DISEASE (PD)	56 (38.6)	13 (35.1)	46 (31.7)	12 (32.4)
UNABLE TO DETERMINE (UTD)	9 (6.2)	4 (10.8)	6 (4.1)	3 (8.1)
NO BEST OVERALL RESPONSE AVAILABLE	0	0	0	0
NO FOLLOW-UP RADIOLOGICAL IMAGING AVAILABLE FOR ASSESSMENT	4 (2.8)	1 (2.7)	0	0
DEATH PRIOR TO DISEASE ASSESSMENT	0	0	2 (1.4)	1 (2.7)
OTHER	0	0	4 (2.8)	2 (5.4)
NOT REPORTED	5 (3.4)	3 (8.1)	0	0
NUMBER OF RESPONDERS	21	7	27	6
TIME TO RESPONSE (MONTHS)				
MEDIAN	2.76	1.41	2.73	1.87
MIN, MAX	1.2, 7.0	1.3, 6.9	1.2, 9.6	1.4, 5.6
DURATION OF RESPONSE (MONTHS)				
MIN, MAX (B)	1.4+, 9.8+	2.8, 32.5+	1.4+, 9.8+	7.2, 32.5+
MEDIAN (95% CI) (C)	N.A.	19.35 (2.83, N.A.)	N.A. (7.16, N.A.)	17.07 (7.16, N.A.)
SUBJECTS WITH ONGOING RESPONSE (D)	19/21 (90.5)	2/7 (28.6)	19/27 (70.4)	1/6 (16.7)
MEDIAN PFS (MONTHS) (95% CI) (C)	2.79 (2.63, 4.04)	3.45 (1.61, 4.14)	4.04 (2.76, 5.45)	3.12 (1.61, 5.49)
# EVENTS / # SUBJECTS (%)	110/145 (75.9)	31/37 (83.8)	109/145 (75.2)	35/37 (94.6)
TIME TO PROGRESSION (MONTHS) (C)				
MEDIAN	2.79	4.01	4.07	3.40
(95% CI)	(2.66, 4.11)	(1.41, 6.97)	(2.76, 5.52)	(1.41, 5.72)
MEDIAN OS (MONTHS) (95% CI) (C)	13.24 (13.24, N.A.)	14.95 (4.99, 20.21)		
# EVENTS / # SUBJECTS (%)	53/145 (36.6)	23/37 (62.2)		
OS RATE (95% CI)				
6-MONTH	81.8 (74.4, 87.2)	66.7 (48.9, 79.5)		
NO. AT RISK	116	24		
9-MONTH	71.1 (62.9, 77.8)	66.7 (48.9, 79.5)		
NO. AT RISK	95	23		

All confidence intervals are based on the Clopper and Pearson method except as otherwise specified.
(A) CR+PR
(B) Symbol + indicates a censored value.
(C) Median and rates computed using Kaplan-Meier method.
(D) Subjects with Ongoing Response include responders who had neither progressed nor initiated subsequent therapy.
N.A.: Not Available due to insufficient follow up
Source: Table S.5.1b-BICR and Table S.5.1b-INV (ORR); Table S.5.4b-BICR and Table S.5.4b-INV (TTR and DOR); Table S.5.7b-BICR and Table S.5.7b-INV (PFS); Figure S.5.8b-BICR and Figure S.5.8b-INV (TTP); Table S.5.12b (OS)

- **Primary endpoint (ORR per RECIST 1.1)-2L EXP and 2L ESC Cohorts**

The BICR-assessed ORR using RECIST 1.1 as well as disease control rate overall and at 6 months was similar across both Cohorts: 14.5% (95% CI: 9.2, 21.3) in the 2L EXP Cohort and 18.9% (95% CI: 8.0, 35.2) in the 2L ESC Cohort. Minimum follow-up (LPFT to clinical cut-off date) was approximately 11 months for all treated subjects in the ESC Cohort and approximately 7 months in the EXP Cohort.

Table 18: Objective Response Rate, Best Overall Response, Duration of Response, and Time to Response per BICR, RECIST 1.1 – All Treated, Post-Sorafenib Subjects

	Number of Subjects (%)	
	2L EXP COHORT N = 145	2L ESC COHORT N = 37
OBJECTIVE RESPONSE RATE (A)	21/145 (14.5)	7/37 (18.9)
(95% CI)	(9.2, 21.3)	(8.0, 35.2)
DISEASE CONTROL RATE (B)	80/145 (55.2)	20/37 (54.1)
(95% CI)	(46.7, 63.4)	(36.9, 70.5)
DISEASE CONTROL RATE WITH SD AT LEAST 6 MONTHS LONG	38/145 (26.2)	11/37 (29.7)
(95% CI)	(19.3, 34.2)	(15.9, 47.0)
COMPLETE RESPONSE (CR)	1 (0.7)	1 (2.7)
(95% CI)	(0.0, 3.8)	(0.1, 14.2)
PARTIAL RESPONSE (PR)	20 (13.8)	6 (16.2)
(95% CI)	(8.6, 20.5)	(6.2, 32.0)
STABLE DISEASE (SD)	59 (40.7)	12 (32.4)
NON-CR/NON-PD	0	1 (2.7)
PROGRESSIVE DISEASE (PD)	56 (38.6)	13 (35.1)
UNABLE TO DETERMINE (UTD)	9 (6.2)	4 (10.8)
NO BEST OVERALL RESPONSE AVAILABLE	0	0
NO FOLLOW-UP RADIOLOGICAL IMAGING AVAILABLE FOR ASSESSMENT	4 (2.8)	1 (2.7)
SUBJECT DOES NOT HAVE NON-TARGET LESIONS	0	0
SUBJECT DOES NOT HAVE TARGET LESIONS	0	0
NOT REPORTED	5 (3.4)	3 (8.1)
NUMBER OF RESPONDERS	21	7
TIME TO RESPONSE (MONTHS)		
MEAN	3.47	2.49
MEDIAN	2.76	1.41
MIN, MAX	1.2, 7.0	1.3, 6.9
Q1, Q3	1.45, 4.47	1.31, 2.79
STANDARD DEVIATION	1.949	2.042
DURATION OF RESPONSE (MONTHS)		
MIN, MAX (C)	1.4+, 9.8+	2.8, 32.5+
MEDIAN (95% CI) (D)	N.A.	19.35 (2.83, N.A.)
N EVENT/N RESP (%)	2/21 (9.5)	4/7 (57.1)
SUBJECTS WITH ONGOING RESPONSE (E)	19 (90.5)	2 (28.6)
NUMBER OF SUBJECTS WITH DISEASE CONTROL	80	20
DURATION OF DISEASE CONTROL (MONTHS)		
MIN, MAX (C)	2.6+, 12.0+	2.7, 33.9+
MEDIAN (95% CI) (D)	6.90 (4.40, 8.54)	6.97 (4.01, 14.95)
N EVENT/N DISEASE CONTROL (%)	50/80 (62.5)	16/20 (80.0)

All confidence intervals are based on the Clopper and Pearson method except as otherwise specified.
(A) CR+PR.
(B) CR+PR+SD+Non-CR/Non-PD.
(C) Symbol + indicates a censored value.
(D) Median computed using Kaplan-Meier method.
(E) Subjects with Ongoing response include responders who had neither progressed nor initiated subsequent therapy at the time of analysis, and excludes responders censored prior to 14 weeks of the clinical data cutoff date.
Source: Table S.5.1b-BICR (ORR and BOR), Table S.5.4b-BICR (DOR and time to response), Table S.5.9b-BICR (Duration of disease control)

BICR and investigator assessments of ORR in both the 2L EXP and 2L ESC Cohorts were highly concordant (88.3% and 89.2%, respectively).

At the time of DBL, 19/21 (90.5%) subjects in the 2L EXP Cohort and 2/7 (28.6%) subjects in the 2L ESC Cohort had an ongoing response (as of the last available tumor assessment). The lower number of subjects in the 2L ESC Cohort with ongoing response is likely due to the longer extent of follow-up in this cohort at the time of DBL.

The durations of response per BICR in the 2L ESC and 2L EXP Cohorts demonstrated consistency although the ESC Cohort had a longer duration of response due to longer study duration/follow-up.

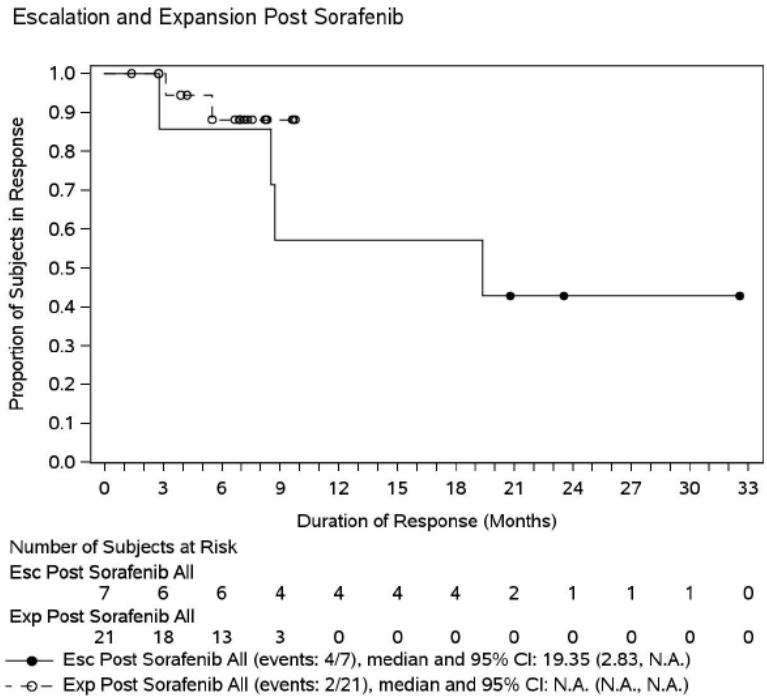
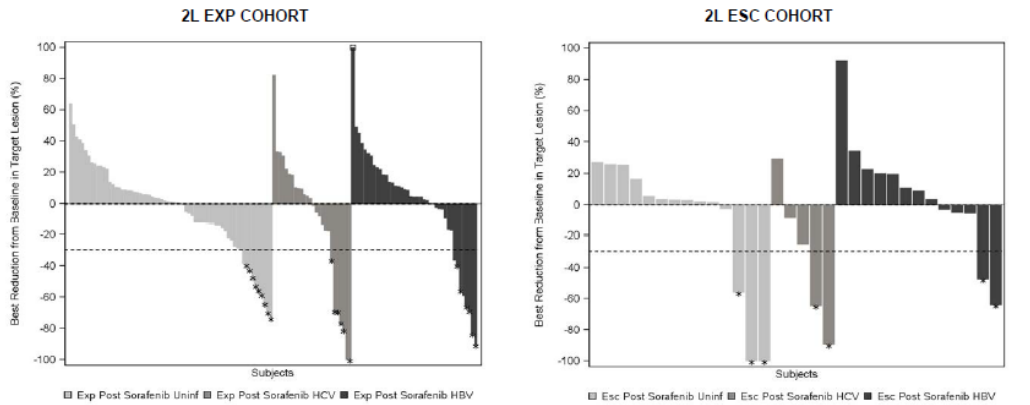


Figure 16: Duration of Response per BICR, RECIST 1.1 - 2L ESC and 2L EXP Cohorts



Response Evaluable: Subjects with i) a BOR of CR, PR, SD, Non-CR/Non-PD or PD, ii) target lesion(s) assessed at baseline, and iii) at least one on-study timepoint with all baseline target lesion(s) assessed.
Negative/positive value means maximum tumor reduction /minimum tumor increase.
Best change is based on evaluable target lesion measurements up to progression or start of subsequent therapy.
Horizontal reference line indicates the 30% reduction consistent with a response per RECIST 1.1.
Asterisk symbol represents responders; Square symbol represents % change truncated to 100%.

Figure 17: Waterfall Plot of Best Change in Target Lesion per BICR RECIST 1.1 - All Response-Evaluable

- **Secondary endpoint (Time to Progression by BICR Assessment)-2L EXP and 2LESC Cohorts.**

Median TTP per BICR assessment was 2.79 months in the 2L EXP Cohort and 4.01 months in the 2L ESC Cohort. A total of 100 (69.0%) and 27 (73.0%) subjects in the 2L EXP and 2L ESC Cohorts progressed, respectively.

45 (31.0%) subjects in the 2L EXP Cohorts and 10 (27.0%) subjects in the 2L ESC Cohort were censored in the time-to-progression analysis.

- 26.9% and 21.6% of treated subjects in the 2L EXP and 2L ESC Cohorts, respectively, had their time-to-progression time censored on either the date of last on-study tumor assessment or date of last assessment prior to subsequent anti-cancer therapy.
- The most common reason for censoring among these subjects was progression-free on-treatment in the 2L EXP Cohort (13.8%) and death (off-study) in the 2L ESC Cohort (8.1%).

- **Secondary endpoint (Progression-free Survival by BICR Assessment)-2L EXP and 2LESC Cohorts.**

The median PFS was 2.79 months in the 2L EXP and 3.45 months in the 2L ESC Cohorts.

PFS rates were similar in the 2L EXP and in the 2L ESC Cohorts at 3, 6, and 9 months (47.7% vs 51.6%, 29.5% vs 31.3%, and 21.9% vs 28.2%, respectively).

Of note, when a new anticancer treatment was started without a prior reported radiographic progression per RECIST 1.1, then a patient was censored for PFS. 35 (24.1%) subjects in the 2L EXP and 6 (16.2%) subjects in the 2L ESC Cohorts were censored in the PFS analysis.

- The most common reason for censoring among these subjects was progression-free on-treatment (13.8%) in the 2L EXP Cohort and lost to follow-up (off study) (5.4%) in the 2L ESC Cohort (Table S.5.8b-BICR).

Table 19: Progression free survival (PFS) and PFS rates (median and rates computed using Kaplan-Meier method)

	Exp Post Sorafenib All N = 145	Esc Post Sorafenib All N = 37
# EVENTS / # SUBJECTS (%)	110/145 (75.9)	31/37 (83.8)
MEDIAN PFS (MONTHS) (95% CI)	2.79 (2.63, 4.04)	3.45 (1.61, 4.14)
PFS RATE (95% CI)		
3-MONTH	47.7 (39.2, 55.7)	51.6 (34.2, 66.5)
NO. AT RISK	64	18
6-MONTH	29.5 (22.0, 37.3)	31.3 (16.9, 46.8)
NO. AT RISK	37	10
9-MONTH	21.9 (15.2, 29.4)	28.2 (14.5, 43.6)
NO. AT RISK	23	9

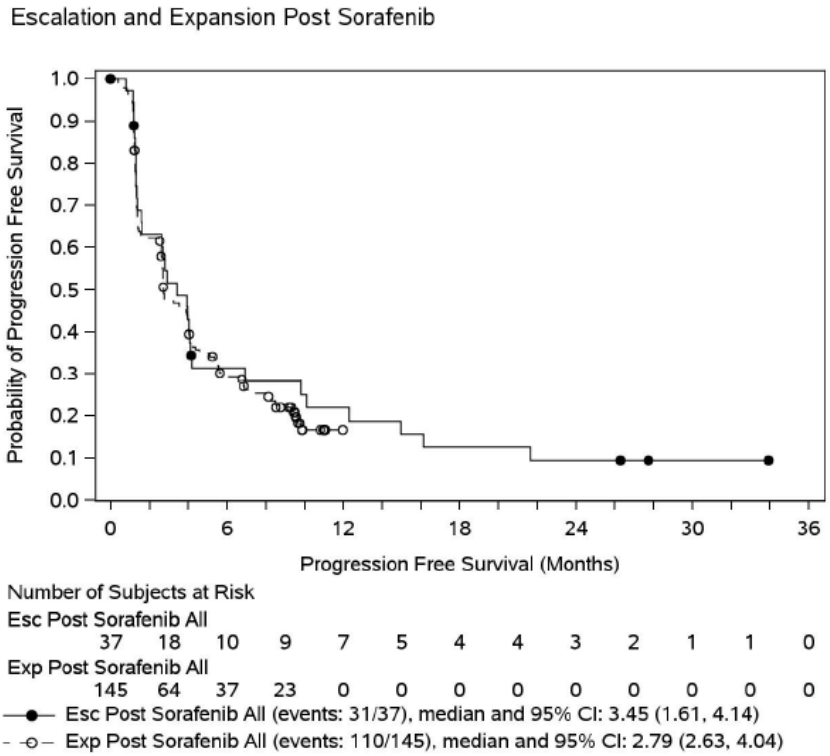


Figure 18: Kaplan-Meier Plot of PFS per BICR, RECIST 1.1 - All Treated, Post-Sorafenib Subjects

- **Secondary endpoint (Overall Survival)-2L EXP and 2LESC Cohorts.**

In all treated subjects in the 2L EXP and 2L ESC Cohorts, nivolumab demonstrated a favorable OS.

Median OS was similar in both Cohorts (13.24 and 14.95 months in the 2L EXP Cohort and 2L ESC Cohort, respectively). OS rates were higher in the 2L EXP Cohort than in the 2L ESC Cohort at 6 months (81.8% vs 66.7%, respectively) and similar at 9 months (71.1% vs 66.7%, respectively). As the median survival follow-up was 10.58 months in the 2L EXP Cohort, OS rates were not calculated beyond 9 months. The OS rate in the 2L ESC Cohort was 58.0 (95% CI: 40.2, 72.2) at 12 months and 46.2 (95% CI: 29.3, 61.6) at 18 months with a median follow-up of 14.32 months.

- At the time of the DBL, 92 (63.4%) subjects in the 2L EXP Cohort and 14 (37.8%) subjects in the 2L ESC Cohort were censored. Among those censored in the 2L EXP Cohort and 2L ESC Cohort, 24.8% and 5.4% of subjects were still on treatment, 34.5% and 27.0% were in follow-up, and 4.1% and 5.4% were off study, respectively.

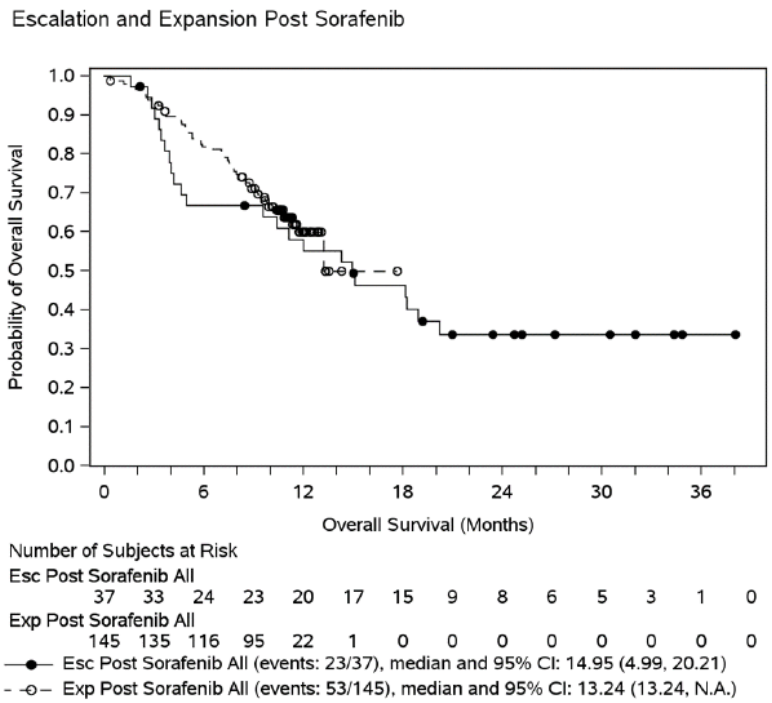


Figure 19: Kaplan-Meier Overall Survival Plot - All Treated, Post-Sorafenib Subjects

Table 20: Overall Survival Rates - All Treated, Post-Sorafenib Subjects

	Exp Post Sorafenib All N = 145	Esc Post Sorafenib All N = 37
# EVENTS / # SUBJECTS (%)	53/145 (36.6)	23/37 (62.2)
MEDIAN OS (MONTHS) (95% CI)	13.24 (13.24, N.A.)	14.95 (4.99, 20.21)
OS RATE (95% CI)		
6-MONTH	81.8 (74.4, 87.2)	66.7 (48.9, 79.5)
NO. AT RISK	116	24
9-MONTH	71.1 (62.9, 77.8)	66.7 (48.9, 79.5)
NO. AT RISK	95	23

Median follow-up for OS (time between date of first dose and last known date alive or death) was 10.58 months (range: 0.4 to 17.7 months) in the 2L EXP Cohort and 14.32 months (range: 1.6 to 38.0 months) in the 2L ESC Cohort.

Follow-up for OS was current for the majority of subjects; 95.2% and 89.2% of subjects in the 2L EXP Cohort and 2L ESC Cohort, respectively, either died or had a last known alive date on or after the last patient last visit date (clinical cut-off date) for the CSR of 24-Jun-2016.

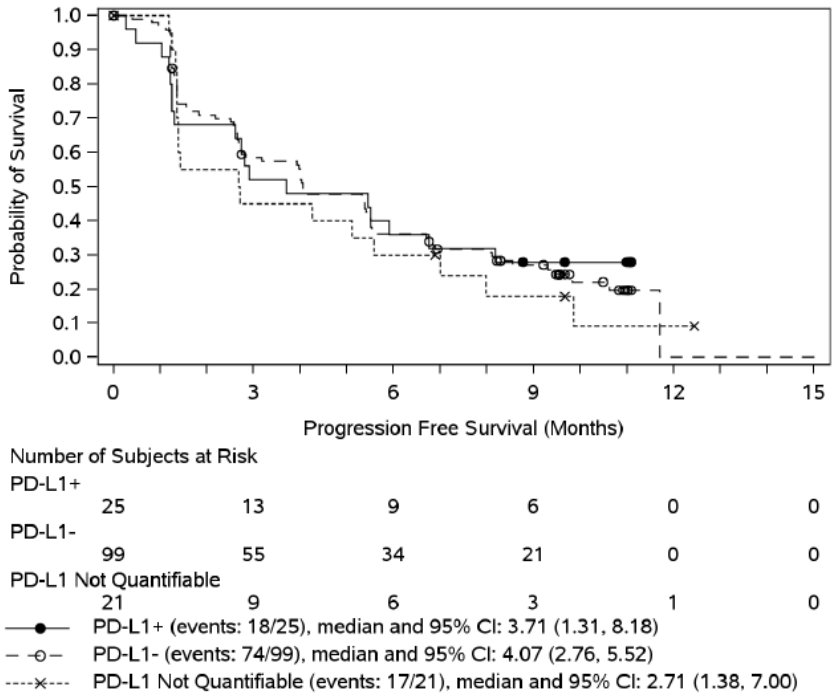
Efficacy endpoints per baseline PD-L1 expression

For efficacy analyses the cohorts with PD-L1 expression were divided as PD-L1 expression ≥1% versus <1%, ≥5% versus <5%, and PD-L1 expression non-quantifiable, respectively. Investigator-assessed ORR using RECIST 1.1 is summarised by baseline PD-L1 expression (**OC**).

Table 21: Investigator-assessed overall response rate (ORR) using RECIST 1.1 (ORR=CR+PR; * includes PD-L1 tumour sample not available, PD-L1 not evaluable and indeterminate).

Baseline PD-L1 expression		2L EXP cohort N=145	2L ESC cohort N=37
≥5%	N	9 (6.2%)	2 (5.4%)
	ORR	**4/9 (44.4%)**	**1/2 (50.0%)**
<5%	N	115 (79.3%)	33 (89.2%)
	ORR	**21/115 (18.3%)**	**5/33 (15.2%)**
≥1%	N	25 (17.2%)	9 (24.3%)
	ORR	**8/25 (32.0%)**	**2/9 (22.2%)**
<1%	N	99 (68.3%)	26 (70.3%)
	ORR	**17/99 (17.2%)**	**4/26 (15.4%)**
Non-quantifiable*	N	21 (14.5%)	2 (5.4%)
	ORR	**2/21 (9.5%)**	**0/2 (0%)**

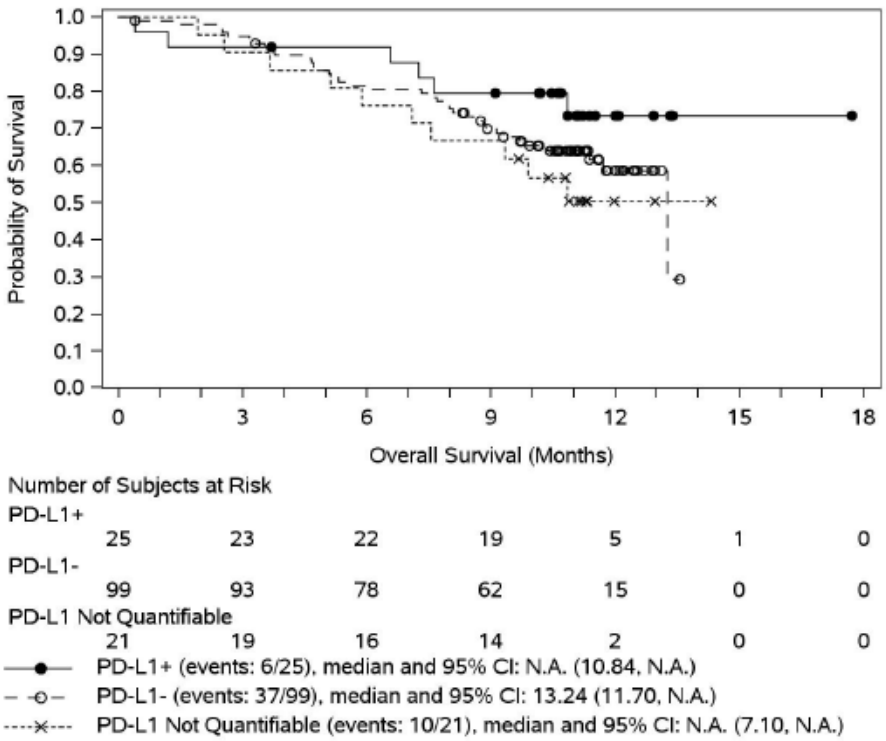
PFS by investigator assessment using RECIST 1.1 per baseline PD-L1 expression for the 2L EXP cohort is shown in Figure.



Symbols represent censored observations.
PD-L1 Not Quantifiable: includes PD-L1 tumor sample not available, PD-L1 not evaluable and indeterminate.

Figure 20: Kaplan-Meier progression free survival plot by investigator assessment using RECIST 1.1 per baseline PD-L1 expression for the 2L EXP cohort (PD-L1+=baseline PD-L1 expression ≥1%).

Median OS in patients in the 2L EXP cohort with baseline PD-L1 expression ⩾1% was not reached (95% CI: 10.84-NA) and was 13.24 months (95% CI: 11.70-NA) in patients with baseline PD-L1 expression <1%. Of note, the information in the study report is somewhat unclear (**OC**). OS per baseline PD-L1 expression is shown in Figure-.



Symbols represent censored observations.
PD-L1 Not Quantifiable: includes PD-L1 tumor sample not available, PD-L1 not evaluable and indeterminate.

Figure 21: Kaplan-Meier overall survival plot per baseline PD-L1 expression for the 2L EXP cohort (PD-L1+=baseline PD-L1 expression ≥1%).

Exploratory efficacy endpoint - ORR by BICR using mRECIST

The ORR by BICR using mRECIST was 18.6% in the 2L EXP cohort and 21.6% in the 2L ESC cohort. See Table 21 for best overall response. The CR rate was 3.4% in the 2L EXP cohort and 5.4% in the 2L ESC cohort.

Table 22: Objective response rate and best overall response by BICR using mRECIST.

	Number of Subjects (%)	
	2L EXP Cohort N = 145	2L ESC Cohort N = 37
OBJECTIVE RESPONSE RATE (A)	27/145 (18.6%)	8/37 (21.6%)
(95% CI)	(12.6, 25.9)	(9.8, 38.2)
DISEASE CONTROL RATE (B)	79/145 (54.5%)	21/37 (56.8%)
(95% CI)	(46.0, 62.8)	(39.5, 72.9)
DISEASE CONTROL RATE WITH SD AT LEAST 6 MONTHS LONG	41/145 (28.3%)	11/37 (29.7%)
(95% CI)	(21.1, 36.3)	(15.9, 47.0)
BEST OVERALL RESPONSE:		
COMPLETE RESPONSE (CR)	5 (3.4)	2 (5.4)
(95% CI)	(1.1, 7.9)	(0.7, 18.2)
PARTIAL RESPONSE (PR)	22 (15.2)	6 (16.2)
(95% CI)	(9.8, 22.1)	(6.2, 32.0)
STABLE DISEASE (SD)	52 (35.9)	12 (32.4)
NON-CR/NON-PD	0	1 (2.7)
PROGRESSIVE DISEASE (PD)	58 (40.0)	12 (32.4)
UNABLE TO DETERMINE (UTD)	8 (5.5)	4 (10.8)
NO BEST OVERALL RESPONSE AVAILABLE	0	0
NO FOLLOW-UP RADIOLOGICAL IMAGING AVAILABLE FOR ASSESSMENT	4 (2.8)	1 (2.7)
SUBJECT DOES NOT HAVE NON-TARGET LESIONS	0	0
SUBJECT DOES NOT HAVE TARGET LESIONS	0	0
NOT REPORTED	4 (2.8)	3 (8.1)

All confidence intervals are based on the Clopper and Pearson method.
(A) CR+PR.
(B) CR+PR+SD+Non-CR/Non-PD.

Ancillary analyses

Primary efficacy endpoint (BICR-assessed ORR per RECIST 1.1) per baseline Subgroup

The BICR-assessed ORR using RECIST 1.1 was comparable across baseline subgroups (age, region, gender, VI/EHS, AFP, and BCLC category) and consistent with overall 2L populations in both the 2L EXP and 2L ESC Cohorts across the majority of baseline subgroups.

Table 23: Best Overall Response per RECIST 1.1 by Subgroup - All Treated, Post-Sorafenib Subjects

	Objective Response Rate (%) (95% CI)	
	2L EXP COHORT N = 145	2L ESC COHORT N = 37
AGE CATEGORIZATION 1		
< 65	11/81 (13.6%) (7.0, 23.0)	5/23 (21.7%) (7.5, 43.7)
>= 65 AND < 75	6/48 (12.5%) (4.7, 25.2)	2/11 (18.2%) (2.3, 51.8)
>= 75 AND < 85	4/16 (25.0%) (7.3, 52.4)	0/3 (0.0, 70.8)
>= 65	10/64 (15.6%) (7.8, 26.9)	2/14 (14.3%) (1.8, 42.8)
>= 75	4/16 (25.0%) (7.3, 52.4)	0/3 (0.0, 70.8)
REGION		
US/CANADA	3/16 (18.8%) (4.0, 45.6)	2/13 (15.4%) (1.9, 45.4)
EUROPE	6/58 (10.3%) (3.9, 21.2)	4/10 (40.0%) (12.2, 73.8)
ASIA	12/71 (16.9%) (9.0, 27.7)	1/14 (7.1%) (0.2, 33.9)
GENDER		
FEMALE	4/33 (12.1%) (3.4, 28.2)	1/10 (10.0%) (0.3, 44.5)
MALE	17/112 (15.2%) (9.1, 23.2)	6/27 (22.2%) (8.6, 42.3)
VI/EHS - CRF		
YES	18/118 (15.3%) (9.3, 23.0)	6/32 (18.8%) (7.2, 36.4)
NO	2/26 (7.7%) (0.9, 25.1)	1/5 (20.0%) (0.5, 71.6)
UNKNOWN	1/1 (100.0%) (2.5, 100.0)	0/0 (N.A., N.A.)
AFP CATEGORY AT BASELINE 2		
<400	10/85 (11.8%) (5.8, 20.6)	3/25 (12.0%) (2.5, 31.2)
>=400	10/55 (18.2%) (9.1, 30.9)	4/12 (33.3%) (9.9, 65.1)
NOT REPORTED	1/5 (20.0%) (0.5, 71.6)	0/0 (N.A., N.A.)
BCLC CATEGORY		
0	0/0 (N.A., N.A.)	0/0 (N.A., N.A.)
A	1/2 (50.0%) (1.3, 98.7)	0/1 (0.0, 97.5)
B	0/14 (0.0, 23.2)	1/3 (33.3%) (0.8, 90.6)
C	19/126 (15.1%) (9.3, 22.5)	6/33 (18.2%) (7.0, 35.5)
D	0/0 (N.A., N.A.)	0/0 (N.A., N.A.)
UNKNOWN	1/3 (33.3%) (0.8, 90.6)	0/0 (N.A., N.A.)

Confidence interval based on the Clopper and Pearson method.
Source: Table S.5.5b-BICR

Efficacy by Etiologic Subtype

ORR by BICR using RECIST 1.1 was 12.5% in the uninfected, 20.0% in the HCV-infected, and 14.0% in the HBV-infected groups in the 2L EXP cohort.

Table 24: Objective response rate and best overall response by BICR using RECIST 1.1 per aetiologic subtype ((A)=CR+PR; (B)=CR+PR+SD+Non-CR/Non-PD)

	Uninfected N = 72	HCV-infected N = 30	HBV-infected N = 43
OBJECTIVE RESPONSE RATE (95% CI) (A)	9/72 (12.5%) (5.9, 22.4)	6/30 (20.0%) (7.7, 38.6)	6/43 (14.0%) (5.3, 27.9)
DISEASE CONTROL RATE (95% CI)	45/72 (62.5%) (B) (50.3, 73.6)	15/30 (50.0%) (B) (31.3, 68.7)	20/43 (46.5%) (B) (31.2, 62.3)
BEST OVERALL RESPONSE:			
COMPLETE RESPONSE (CR) (95% CI)	0 (0.0, 5.0)	1 (3.3) (0.1, 17.2)	0 (0.0, 8.2)
PARTIAL RESPONSE (PR) (95% CI)	9 (12.5) (5.9, 22.4)	5 (16.7) (5.6, 34.7)	6 (14.0) (5.3, 27.9)
STABLE DISEASE (SD)	36 (50.0)	9 (30.0)	14 (32.6)
NON-CR/NON-PD	0	0	0
PROGRESSIVE DISEASE (PD)	23 (31.9)	11 (36.7)	22 (51.2)
UNABLE TO DETERMINE (UTD)	4 (5.6)	4 (13.3)	1 (2.3)
NO FOLLOW-UP RADIOLOGICAL IMAGING AVAILABLE FOR ASSESSMENT	2 (2.8)	2 (6.7)	0
DEATH PRIOR TO DISEASE ASSESSMENT	0	0	0
OTHER	0	0	0
NOT REPORTED	2 (2.8)	2 (6.7)	1 (2.3)
NUMBER OF RESPONDERS	9	6	6

OS data per aetiologic subgroup are immature as the median OS for the HCV- and HBV-infected groups was not reached (Table-).

Table 25: Overall survival per aetiologic subtype ((E)=median computed using Kaplan-Meier method)

	Uninfected N = 72	HCV-infected N = 30	HBV-infected N = 43
MEDIAN OS (MONTHS) (95% CI) (G)	13.24 (10.84, N.A.)	N.A. (11.37, N.A.)	N.A. (9.13, N.A.)
# EVENTS / # SUBJECTS (%)	29/72 (40.3)	8/30 (26.7)	16/43 (37.2)

Efficacy By Etiologic Subtype and Baseline PD-L1 Expression

Tumour Tissue Disposition

As of the DBL, the majority of treated subjects in the 2L EXP Cohort across HCC etiologies had a tumour tissue sample collected at baseline.

- Among all treated subjects, 55/72 (76.4%), 28/30 (93.3%), and 41/43 (95.3%) subjects who were uninfected, HCV-infected, or HBV-infected, respectively, had tumour samples with quantifiable PD-L1 expression at baseline and 17/72, 2/30, and 2/43 who were uninfected, HCV-infected, or HBV-infected, respectively, did not have quantifiable PDL1expression at baseline.

PD-L1 Expression and Efficacy

- Objective responses per RECIST v1.1 were observed across all HCC etiologies in the 2LEXP Cohort regardless of PD-L1 expression.

Table 26: Best Overall Response and Objective Response per Investigator RECIST 1.1 by PD-L1 expression

BASELINE PD-L1 STATUS	Exp Post Sorafenib Uninf N = 72	Exp Post Sorafenib HCV N = 30	Exp Post Sorafenib HBV N = 43
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1%	9 (12.5)	8 (26.7)	8 (18.6)
BEST OVERALL RESPONSE:			
COMPLETE RESPONSE (CR)	0	0	1 (12.5)
PARTIAL RESPONSE (PR)	4 (44.4)	3 (37.5)	0
STABLE DISEASE (SD) OR NON-CR/NON-PD	4 (44.4)	3 (37.5)	2 (25.0)
PROGRESSIVE DISEASE (PD)	1 (11.1)	2 (25.0)	5 (62.5)
UNABLE TO DETERMINE (UTD)	0	0	0
OBJECTIVE RESPONSE RATE (1)	4/9 (44.4%)	3/8 (37.5%)	1/8 (12.5%)
(95% CI)	(13.7, 78.8)	(8.5, 75.5)	(0.3, 52.7)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%	46 (63.9)	20 (66.7)	33 (76.7)
BEST OVERALL RESPONSE:			
COMPLETE RESPONSE (CR)	2 (4.3)	0	0
PARTIAL RESPONSE (PR)	6 (13.0)	4 (20.0)	5 (15.2)
STABLE DISEASE (SD) OR NON-CR/NON-PD	23 (50.0)	10 (50.0)	15 (45.5)
PROGRESSIVE DISEASE (PD)	12 (26.1)	4 (20.0)	13 (39.4)
UNABLE TO DETERMINE (UTD)	3 (6.5)	2 (10.0)	0
OBJECTIVE RESPONSE RATE (1)	8/46 (17.4%)	4/20 (20.0%)	5/33 (15.2%)
(95% CI)	(7.8, 31.4)	(5.7, 43.7)	(5.1, 31.9)
SUBJECTS WITHOUT PD-L1 QUANTIFIABLE AT BASELINE (2)	17 (23.6)	2 (6.7)	2 (4.7)
BEST OVERALL RESPONSE:			
COMPLETE RESPONSE (CR)	0	0	0
PARTIAL RESPONSE (PR)	2 (11.8)	0	0
STABLE DISEASE (SD) OR NON-CR/NON-PD	7 (41.2)	1 (50.0)	1 (50.0)
PROGRESSIVE DISEASE (PD)	7 (41.2)	1 (50.0)	1 (50.0)
UNABLE TO DETERMINE (UTD)	1 (5.9)	0	0
OBJECTIVE RESPONSE RATE (1)	2/17 (11.8%)	0/2	0/2
(95% CI)	(1.5, 36.4)	(0.0, 84.2)	(0.0, 84.2)

- OS rates in the 2L EXP Cohort in subjects with ≥ 1% PD-L1 expression were not achieved for uninfected, HCV-infected, or HBV-infected subtypes; in subjects with < 1% PD-L1expression, the OS rate was 13.24 months in uninfected subtypes, and not achieved in HCV-infected or HBV-infected subtypes.

Exploratory endpoint - patient-reported general health status (EQ-5D-3L)

Of note, this was for the EXP cohort only.

Patient reported general health status was assessed using the EQ-5D-3L following enrolment but prior to first dose, and then at each tumour assessment (every 6 weeks) through week 24.

The EQ-5D-3L is a generic multi-attribute health-state classification system by which health is described in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is evaluated using 3 levels: no problems, some problems, and severe problems.

Questionnaire completion rates were not calculated for the EQ-5D-3L. - summarises the patient reported problems by EQ-5D-3L dimension and level.

Table 27: Patient reported problems by EQ-5D-3L dimension and level per time point for the 2L EXP cohort (Level1=no problems; Level2=some problems; Level3=extreme problems; percentages are based on number of patients assessed at each visit)

EQ-5D: Mobility
Treatment Group: Exp Post Sorafenib All N = 145

		Number of Subjects (%)		
Nominal Timepoint	N	Level1	Level2	Level3
BASELINE	140	122 (87.1)	18 (12.9)	0
ON TREATMENT				
WEEK 7	118	95 (80.5)	23 (19.5)	0
WEEK 13	91	67 (73.6)	24 (26.4)	0
WEEK 19	74	56 (75.7)	18 (24.3)	0
WEEK 25	65	45 (69.2)	20 (30.8)	0

EQ-5D: Self Care
Treatment Group: Exp Post Sorafenib All N = 145

		Number of Subjects (%)		
Nominal Timepoint	N	Level1	Level2	Level3
BASELINE	140	136 (97.1)	4 (2.9)	0
ON TREATMENT				
WEEK 7	117	111 (94.9)	6 (5.1)	0
WEEK 13	91	83 (91.2)	8 (8.8)	0
WEEK 19	74	69 (93.2)	5 (6.8)	0
WEEK 25	65	59 (90.8)	6 (9.2)	0

EQ-5D: Activity
Treatment Group: Exp Post Sorafenib All N = 145

		Number of Subjects (%)		
Nominal Timepoint	N	Level1	Level2	Level3
BASELINE	140	113 (80.7)	24 (17.1)	3 (2.1)
ON TREATMENT				
WEEK 7	118	90 (76.3)	25 (21.2)	3 (2.5)
WEEK 13	91	63 (69.2)	26 (28.6)	2 (2.2)
WEEK 19	74	50 (67.6)	22 (29.7)	2 (2.7)
WEEK 25	65	45 (69.2)	20 (30.8)	0

EQ-5D: Pain
Treatment Group: Exp Post Sorafenib All N = 145

		Number of Subjects (%)		
Nominal Timepoint	N	Level1	Level2	Level3
BASELINE	139	82 (59.0)	52 (37.4)	5 (3.6)
ON TREATMENT				
WEEK 7	118	68 (57.6)	45 (38.1)	5 (4.2)
WEEK 13	91	46 (50.5)	42 (46.2)	3 (3.3)
WEEK 19	74	42 (56.8)	29 (39.2)	3 (4.1)
WEEK 25	65	35 (53.8)	28 (43.1)	2 (3.1)

EQ-5D: Anxiety
Treatment Group: Exp Post Sorafenib All N = 145

		Number of Subjects (%)		
Nominal Timepoint	N	Level1	Level2	Level3
BASELINE	139	103 (74.1)	33 (23.7)	3 (2.2)
ON TREATMENT				
WEEK 7	118	88 (74.6)	28 (23.7)	2 (1.7)
WEEK 13	91	67 (73.6)	23 (25.3)	1 (1.1)
WEEK 19	74	55 (74.3)	17 (23.0)	2 (2.7)
WEEK 25	65	50 (76.9)	15 (23.1)	0

In addition, the EQ-5D-3L includes a VAS allowing a respondent to rate his/her health on a scale ranging from 0-100 with 0 being the worst and 100 being the best health state imaginable, respectively. A 7 point difference in EQ-5D-3L VAS score may be regarded as a clinically meaningful change (Pickard et al. Health Qual Life Outcomes. 2007 Dec 21;5:70) summarises the EQ-5D-3L VAS scores per time point for the 2L EXP cohort.

Overall, questionnaires exhibited generally stable patient-reported outcomes. No major improvements or decreases from baseline were observed during the study.

Table 28: EQ-5D-3L visual analogue scale scores per time point for the 2L EXP cohort

Nominal Timepoint	N	Mean	SD	Median	Q25-Q75
BASELINE	139	71.3	27.72	80.0	65.0-90.0
ON TREATMENT					
WEEK 7	118	74.2	25.57	80.0	70.0-90.0
WEEK 13	90	73.4	25.17	80.0	69.0-90.0
WEEK 19	74	74.3	25.89	82.5	65.0-92.0
WEEK 25	65	75.0	26.77	85.0	65.0-95.0

Updated efficacy analyses (clinical DBL on 29-Nov-2016/BICR DBL on 12-Dec-2016, and a combined clinical and BICR DBL on 17-Mar-2017)

Subsequent to the initial Type II variation for the OPDIVO 2L HCC extension of indication submission on 30-Nov-2016, BMS performed additional database locks (DBLs) to evaluate the efficacy of nivolumab in 2L HCC cohorts of Study CA209040 (clinical DBL on 29-Nov-2016/BICR DBL on 12-Dec-2016, and a combined clinical and BICR DBL on 17-Mar-2017). The results from these additional DBLs confirmed the earlier results of nivolumab in 2L HCC. Additional details are summarized below in the next Section and in Table 28.

Based on the most recent DBL performed on 17-Mar-2017 with a minimum of 15 months follow up, the BICR-confirmed ORR is 14.5%, median DOR is 16.6 months, and median OS is 15.6 months (95% CI: 13.24, 18.89) for 2L EXP subjects.

Table 29: Summary of Updated Efficacy Results Since Initial Submission with Indirect Comparison to Regorafenib or Placebo+BSC RESORCE Data

median (95% CI) unless otherwise noted	2L EXP N = 145		2L ESC N = 37		Regorafenib[3] N = 379		Placebo+BSC[3] N = 194	
	RECIST 1.1	mRECIST	RECIST 1.1	mRECIST	RECIST 1.1	mRECIST	RECIST 1.1	mRECIST
ORR, %[a,c]								
By BICR	14.5% (9.2, 21.3)	18.6% (12.6, 25.9)	18.9% (8.0, 35.2)	21.6% (9.8, 38.2)	-	-	-	-
By Investigator	19.3% (13.2, 26.7)	-	16.2% (6.2, 32.0)	-	6.6%	10.6%	2.6%	4.0%
BOR, n (%)								
By BICR								
CR	2 (1.4%)	4 (2.8%)	1 (2.7%)	2 (5.4%)	-	-	-	-
PR	19 (13.1%)	23 (15.9%)	6 (16.2%)	6 (16.2%)	-	-	-	-
By Investigator								
CR	3 (2.1%)	-	3 (8.1%)	-	0	2 (0.5%)	0	0
PR	25 (17.2%)	-	3 (8.1%)	-	25 (6.6%)	38 (10.1%)	5 (2.6%)	8 (4.1%)
DoR, months[b,c]								
By BICR	N.A. (11.30, N.A.)	N.A. (8.31, N.A.)	19.35 (2.83, N.A.)	8.64 (2.83, N.A.)	-	-	-	-
min, max[d]	3.2, 13.8+	-	2.8, 35.4+	-	-	-	-	-
By Investigator	12.35 (7.71, N.A.)	-	17.07 (7.16, N.A.)	-	-	3.5 (1.9, 4.5)	-	2.7 (1.9, NE)
min, max[d]	2.8, 13.8+	-	7.2, 35.4+	-	-	-	-	-
DoR, months[b,e]								
By BICR	16.59 (9.69, N.A.)	-	19.35 (2.83, N.A.)	-	-	-	-	-
min, max[d]	3.2, 16.8+	-	2.8, 38.2+	-	-	-	-	-
By Investigator	N.A. (9.53, N.A.)	-	17.07 (7.16, N.A.)	-	-	3.5 (1.9, 4.5)	-	2.7 (1.9, NE)
min, max[d]	2.8, 16.8+	-	7.2, 38.2+	-	-	-	-	-
PFS, months[b,c]								
By BICR	2.79 (2.63, 4.04)	-	3.45 (1.61, 4.14)	-	-	-	-	-
By Investigator	4.07 (2.76, 5.52)	-	3.40 (1.41, 5.72)	-	3.4 (2.9, 4.2)	3.1 (2.8, 4.2)	1.5 (1.4, 1.5)	1.5 (1.4, 1.6)
OS, months (based on 29-Nov-2016 clinical DBL)	16.66 (13.24, NA)[c]		14.95 (4.99, 28.06)[c]		10.6 (9.1, 12.1)		7.8 (6.3, 8.8)	
OS, months (based on 17-Mar-2017 clinical DBL)	15.64 (13.24, 18.89)[e]		14.95 (4.99, 28.06)[e]					

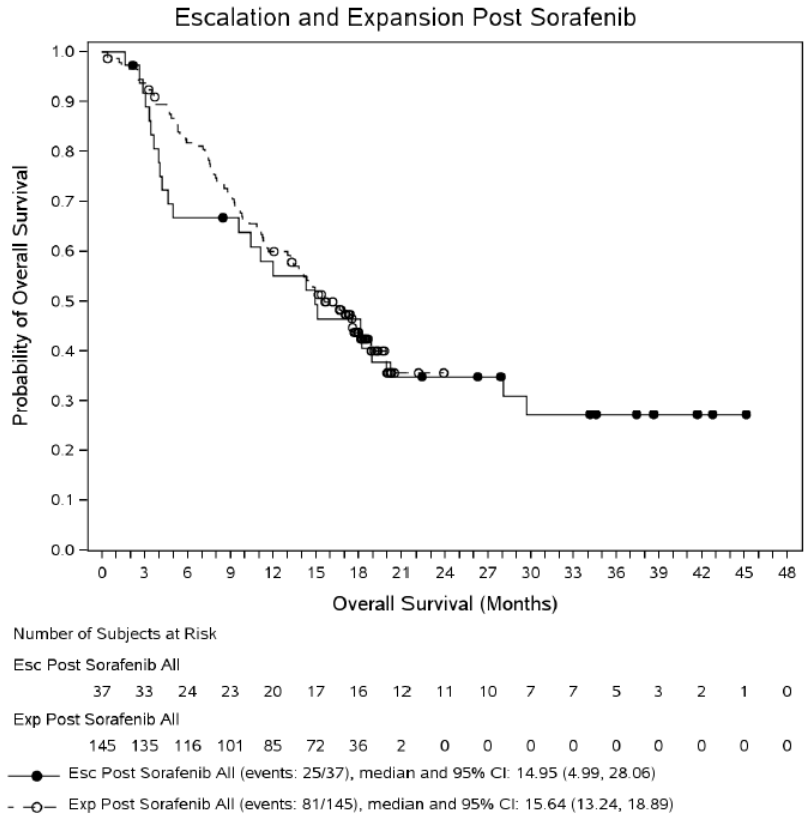
[a] Complete response + Partial response

[b] Median computed using Kaplan-Meier method

[c] Based on 29-Nov-2016 clinical DBL and 12-Dec-2016 BICR DBL

[d] Symbol + indicates a censored value

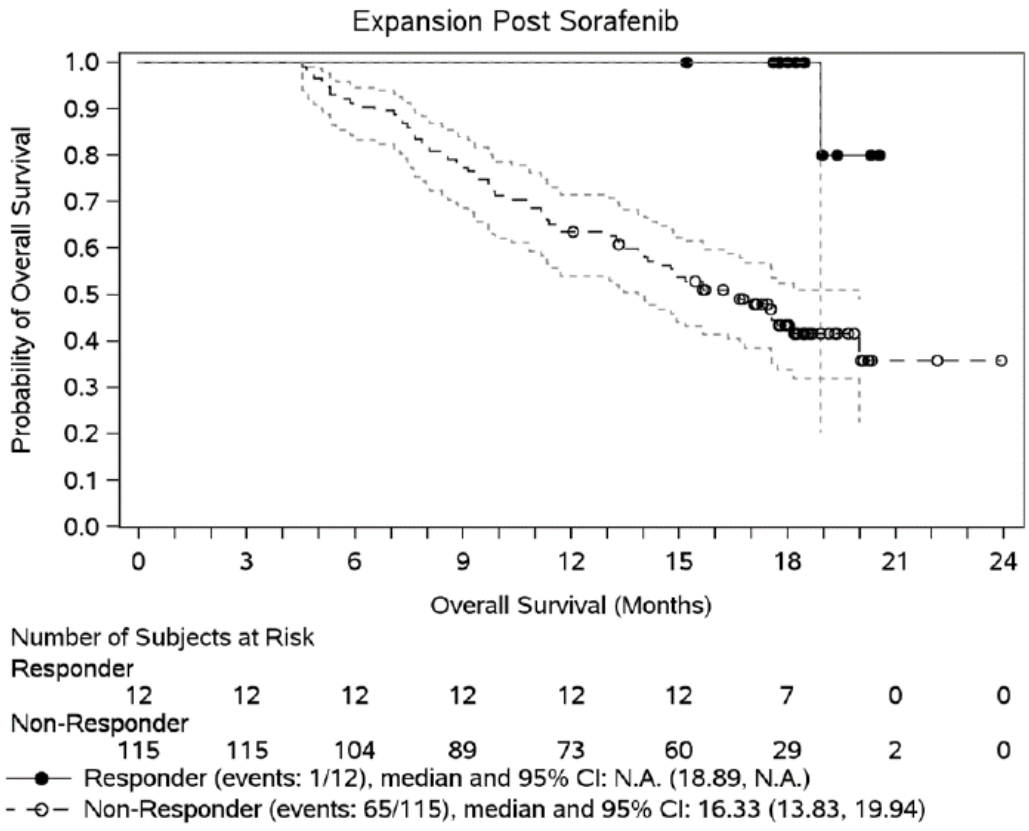
[e] Based on 17-Mar-2017 DBL



Symbols represent censored observations.

Figure 22: Kaplan-Meier Plot of Overall Survival in the 2L ESC and 2L EXP Cohorts

Next, a landmark analysis of OS by responders (n=12) vs. non-responders (n=112) at 4.5 months was conducted. Given that most responses to nivolumab occur within the first 3 months, the 4.5 months landmark was selected to allow up to 3 months (2 scans at Q6 week intervals) for subjects to respond and an additional 1.5 months to allow a follow-up scan to confirm the response. As shown in Figure 23, subjects who were confirmed responders per BICR RECIST 1.1 by 4.5 months had longer survival versus those who were not. The median OS was not reached even after a minimum of 15 months of follow-up in responders. The median OS was 16.3 months (95% CI 13.83, 19.44) for non-responders. Of note, among all responders (n=12) by month 4.5 in the 2L EXP cohort, only one death occurred, with OS close to 19 months. In addition, a survival analysis was performed on all BICR confirmed responders, which showed that all responders in 2L ESC had a minimum OS of ⩾ 18 months, and all responders in 2L EXP had a minimum OS of ⩾ 12 months.



Symbols represent censored observations.

A period of 1.5 months is added to ensure an initial objective response as far as 3 months after study therapy to be confirmed by a subsequent tumour assessment

Responder: Initial response and its subsequent confirming response within 4.5 months after study therapy

Non-Responder: BOR other than PR and CR, or initial response not confirmed within 4.5 months after study therapy

Figure 23: Landmark Analysis of OS by Response Status per BICR RECIST 1.1 - For Subjects Having Survived Beyond and Including 4.5 Months in the 2L EXP Cohort

Table 30: Summary of Efficacy Results by Etiologic Subtype, per RECIST 1.1 (Based on 29-Nov-2016 Clinical DBL and 12-Dec-2016 BICR DBL) - All Treated, Post-sorafenib Subjects in the 2L EXP Cohort

	BICR ASSESSMENT		
	Uninfected N = 72	HCV-infected N = 30	HBV-infected N = 43
OBJECTIVE RESPONSE RATE (95% CI) (A)	9/72 (12.5%) (5.9, 22.4)	6/30 (20.0%) (7.7, 38.6)	6/43 (14.0%) (5.3, 27.9)
DISEASE CONTROL RATE (95% CI)	6/72 (63.9%) (B) (51.7, 74.9)	15/30 (50.0%) (B) (31.3, 68.7)	20/43 (46.5%) (B) (31.2, 62.3)
DCR WITH SD AT LEAST 6 MONTHS LONG (95% CI)	19/72 (26.4%) (16.7, 38.1)	10/30 (33.3%) (17.3, 52.8)	10/43 (23.3%) (11.8, 38.6)
BEST OVERALL RESPONSE:			
COMPLETE RESPONSE (CR) (95% CI)	0 (0.0, 5.0)	1 (3.3) (0.1, 17.2)	1 (2.3) (0.1, 12.3)
PARTIAL RESPONSE (PR) (95% CI)	9 (12.5) (5.9, 22.4)	5 (16.7) (5.6, 34.7)	5 (11.6) (3.9, 25.1)
STABLE DISEASE (SD)	37 (51.4)	9 (30.0)	14 (32.6)
NON-CR/NON-PD	0	0	0
PROGRESSIVE DISEASE (PD)	23 (31.9)	11 (36.7)	22 (51.2)
UNABLE TO DETERMINE (UTD)	3 (4.2)	4 (13.3)	1 (2.3)
NO FOLLOW-UP RADIOLOGICAL IMAGING AVAILABLE FOR ASSESSMENT	2 (2.8)	2 (6.7)	0
DEATH PRIOR TO DISEASE ASSESSMENT	0	0	0
OTHER	0	0	0
NOT REPORTED	1 (1.4)	2 (6.7)	1 (2.3)
NUMBER OF RESPONDERS	9	6	6
TIME TO RESPONSE (MONTHS)			
MEDIAN	4.04	2.10	2.00
MIN, MAX	2.6, 6.8	1.2, 7.0	1.2, 6.8
DURATION OF RESPONSE (MONTHS)			
MIN, MAX (C)	5.6, 13.8+	3.2+, 13.8+	6.9+, 13.7+
MEDIAN (95% CI) (D)	N.A.(5.55, N.A.)	N.A.(3.15, N.A.)	N.A.(8.31, N.A.)
NUMBER OF SUBJECTS WITH DURATION OF RESPONSE OF AT LEAST (%)			
3 MONTHS	9 (100.0)	6 (100.0)	6 (100.0)
6 MONTHS	8 (88.9)	5 (83.3)	6 (100.0)
10 MONTHS	4 (44.4)	3 (50.0)	3 (50.0)
12 MONTHS	2 (22.2)	3 (50.0)	3 (50.0)
SUBJECTS WITH ONGOING RESPONSE (E)	5 (55.6)	5 (83.3)	5 (83.3)
MEDIAN PFS (MONTHS) (F) (95% CI) # EVENTS / # SUBJECTS (%)	3.29 (2.69, 4.60) 58/72 (80.6)	2.83 (1.38, 6.90) 21/30 (70.0)	2.63 (1.35, 4.04) 36/43 (83.7)
TIME TO PROGRESSION (MONTHS)			
NUMBER OF EVENTS (%)	51/72 (70.8)	18/30 (60.0)	35/43 (81.4)
MEDIAN (95% CI) (F)	4.04 (2.73, 5.52)	4.01 (1.38, 7.23)	2.63 (1.35, 4.07)

MEDIAN OS (MONTHS) (95% CI) (F) # EVENTS / # SUBJECTS (%)	16.66 (11.33, N.A.) 34/72 (47.2)	N.A. (11.17, N.A.) 11/30 (26.7)	N.A. (9.30, N.A.) 20/43 (46.5)
OS RATE (95% CI)			
6-MONTH	80.6 (69.4, 88.0)	85.8 (66.3, 94.4)	81.4 (66.2, 90.2)
NO. AT RISK	58	23	35
12-MONTH	59.7 (47.4, 70.0)	67.1 (46.2, 81.4)	55.6 (39.6, 69.0)
NO. AT RISK	42	18	22

All confidence intervals are based on the Clopper and Pearson method except as otherwise specified.
(A) CR+PR
(B) CR+PR+SD+Non-CR/Non-PD
(C) Symbol + indicates a censored value.
(D) Median computed using Kaplan-Meier method.
(E) Subjects with Ongoing Response include responders who had neither progressed nor initiated subsequent therapy.
(F) Median and rates computed using Kaplan-Meier method.
N.A.: Not Available due to insufficient follow up.

Efficacy by Baseline Tumour Cell PD-L1 Expression and Viral Etiology Status

Table 30 summarizes BICR ORR for each viral etiological subgroup by tumour cell PD-L1 status (data based on updated 29-Nov-2016 clinical DBL and 12-Dec-2016 BICR DBL).

There is a trend for higher ORR for tumour cell PD-L1 ≥1% for each viral aetiology, however no definitive conclusion can be drawn from these data since the number of patients per subgroup is too small, and the 95% CIs are broad and overlapping.

Table 31: BOR and ORR by BICR RECIST 1.1 for ≥ 1% and < 1% PD-L1 Expression Status at Baseline by Viral Etiology in the 2L EXP Cohort

BASELINE PD-L1 STATUS	Exp Post Sorafenib Uninf N = 72	Exp Post Sorafenib HCV N = 30	Exp Post Sorafenib HBV N = 43
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1%	9 (12.5)	8 (26.7)	8 (18.6)
BEST OVERALL RESPONSE:			
COMPLETE RESPONSE (CR)	0	0	0
PARTIAL RESPONSE (PR)	2 (22.2)	3 (37.5)	2 (25.0)
STABLE DISEASE (SD) OR NON-CR/NON-PD	4 (44.4)	1 (12.5)	2 (25.0)
PROGRESSIVE DISEASE (PD)	3 (33.3)	3 (37.5)	3 (37.5)
UNABLE TO DETERMINE (UTD)	0	1 (12.5)	1 (12.5)
OBJECTIVE RESPONSE RATE (1)	2/9 (22.2%)	3/8 (37.5%)	2/8 (25.0%)
(95% CI)	(2.8, 60.0)	(8.5, 75.5)	(3.2, 65.1)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%	48 (66.7)	20 (66.7)	33 (76.7)
BEST OVERALL RESPONSE:			
COMPLETE RESPONSE (CR)	0	1 (5.0)	1 (3.0)
PARTIAL RESPONSE (PR)	6 (12.5)	2 (10.0)	3 (9.1)
STABLE DISEASE (SD) OR NON-CR/NON-PD	25 (52.1)	8 (40.0)	11 (33.3)
PROGRESSIVE DISEASE (PD)	15 (31.3)	7 (35.0)	18 (54.5)
UNABLE TO DETERMINE (UTD)	2 (4.2)	2 (10.0)	0
OBJECTIVE RESPONSE RATE (1)	6/48 (12.5%)	3/20 (15.0%)	4/33 (12.1%)
(95% CI)	(4.7, 25.2)	(3.2, 37.9)	(3.4, 28.2)

(1) CR+PR, 95% CI based on Clopper and Pearson method
(2) Includes PD-L1 tumour sample not available, PD-L1 not evaluable and indeterminate.

To investigate further whether there are potential subgroups of patients who may respond better to nivolumab, BMS has performed a preliminary, exploratory analysis of tumour-associated immune cell

(TAIC) PD-L1 expression in baseline tumour samples from CA209040. At the time of tumour cell (TC) PD-L1 tumour assessment, an additional qualitative assessment of PD-L1-expressing tumour TAICs was also reported for each tumour sample; importantly, however this assay was not analytically validated for measurement of TAIC PD-L1 expression. TAIC PD-L1 expression in the tumour microenvironment was qualitatively assessed by pathologist assessments and both TAIC PD-L1 positive and negative groups consisted of combining multiple qualitatively-defined subgroups together.

The efficacy responses per baseline TC and TAIC PD-L1 expression by BICR using RECIST 1.1 from the updated clinical DBL of 29-Nov-2016 and BICR DBL of 12-Dec-2016, are provided in Table 31. Unlike TC PD-L1 expression which has a low prevalence in 2L HCC (17.2% in 2L EXP), TAIC PD-L1 expression was frequently observed (in >75% or 121 out of the 161 cases with TAIC PD-L1 data available). Also, samples that were TC PD-L1 ≥ 1% (N = 34) were generally TAIC PD-L1 positive (N = 30; >88%). The 7 responders with TC PD-L1 ≥ 1% were the same 7 responders who were TC PD-L1 ≥ 1% and TAIC PD-L1 positive. The preliminary conclusion is that TAIC PD-L1 positive is highly correlated with TC PD-L1 ≥ 1% meaning that may increase the possibility to HCC patient subgroups who benefit from nivolumab treatment.

Table 32: Efficacy (ORR) by Tumour Cell and Tumour Associated Immune Cell PD-L1 Expression (CA209040)

Baseline PD-L1 Status (TC = Tumour Cell, TAIC[a] = Tumour Associated Immune Cells)	ORR 2L EXP per BICR (N=145)	ORR 2L ESC per BICR (n=37)
TC PD-L1 ≥1%	7/25 (28.0%) (95% CI: 12.1, 49.4)	2/9 (22.2%) (95% CI: 2.8, 60.0)
TC PD-L1 <1%	13/101 (12.9%) (95% CI: 7.0, 21.0)	5/26 (19.2%) (95% CI: 6.6, 39.4)
TAIC PD-L1 positive	18/94 (19.1%) (95% CI: 11.8, 28.6)	7/27 (25.9%) (95% CI: 11.1, 46.3)
TAIC PD-L1 negative	2/32 (6.3%) (95% CI: 0.8, 20.8)	0/8 (0%) (95% CI: 0.0, 36.9)
TC PD-L1 ≥1% and TAIC PD-L1 positive	7/23 (30.4%) (95% CI: 13.2, 52.9)	2/7 (28.6%) (95% CI: 3.7, 71.0)
TC PD-L1 ≥1% or TAIC PD-L1 positive	18/96 (18.8%) (95% CI: 11.5, 28.0)	7/29 (24.1%) (95% CI: 10.3, 43.5)
TC PD-L1 <1% and TAIC PD-L1 negative	2/30 (6.7%) (95% CI: 0.8, 22.1)	0/6 (0%) (95% CI: 0.0, 45.9)

[a] PD-L1+ TAIC in the tumour microenvironment were qualitatively assessed, and characterised as "Lymphocytes and Macrophages", "Lymphocytes Only", "Macrophages Only", "Neither Lymphocytes or Macrophages" based on PD-L1 Immune Cell Membrane Staining by pathologist assessments. "Lymphocytes and Macrophages", "Lymphocytes Only", and "Macrophages Only" were combined to define the TAIC PD-L1 positive group. "Neither Lymphocytes or macrophages" and tumours without the presence of any tumour associated immune cells were combined to define the TAIC PD-L1 negative group.

The MAH is committed to extend the evaluation of clinical samples collected in CA209040 for biomarker purposes, and proposes to update ANNEX II of the MA accordingly. To support exploratory biomarker endpoints in the CA209040 study, tumour samples were collected at screening from treated patients to identify biomarkers potentially predictive of nivolumab efficacy. These include tumour mutation burden (TMB) and immune cell infiltration within the tumour as measured by IHC and gene expression. These assessments have been prioritized using available tumour samples collected from CA209040.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 33: Summary of Efficacy for trial CA209040

<table>
<tr><td colspan="4">Title: A phase 1/2, dose escalation, open-label, non-comparative study of nivolumab in advanced hepatocellular carcinoma patients with or without chronic viral hepatitis.</td></tr>
<tr><td>Study identifier</td><td colspan="3">CA209040</td></tr>
<tr><td rowspan="2">Design</td><td colspan="3">Phase 1/2, dose escalation, open-label, non-comparative study</td></tr>
<tr><td colspan="2">Duration of main phase:
Duration of extension phase:</td><td>Oct-2012 to Nov-2015 (enrolment)
Not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="3">- For the dose escalation phase the hypothesis is to evaluate the safety profile, tolerability, PK, and PD of nivolumab at doses of 0.1-10 mg/kg in patients with advanced HCC who have been previously treated with sorafenib
- For the expansion phase the hypothesis is that treatment with nivolumab monotherapy will lead to clinical benefit as demonstrated by a clinically meaningful ORR and DOR in patients with advanced HCC who have been previously treated with sorafenib</td></tr>
<tr><td rowspan="2">Treatment groups</td><td colspan="2">2L dose escalation (ESC) cohort</td><td>Nivolumab IV infusion Q2W at ascending dose levels ranging from 0.1 to 10 mg/kg; n=37</td></tr>
<tr><td colspan="2">2L expansion (EXP) cohort</td><td>Nivolumab 3 mg/kg IV infusion Q2W; n=145</td></tr>
<tr><td rowspan="4">Endpoints and definitions</td><td>Primary endpoint</td><td>ORR</td><td>Proportion of patients with best overall response of CR or PR by BICR using RECIST 1.1.</td></tr>
<tr><td>Secondary endpoint</td><td>CR rate</td><td>Proportion of patients with best overall response of CR by BICR using RECIST 1.1.</td></tr>
<tr><td>Secondary endpoint</td><td>DCR</td><td>Proportion of patients with best overall response of CR, PR, or SD (including non-CR/non-PD) by BICR using RECIST 1.1.</td></tr>
<tr><td>Secondary endpoint</td><td>DOR</td><td>Time between date of first radiographic documented objective response (PR or CR) and date of radiographic progression by BICR using RECIST 1.1.
DOR was derived for responders only.</td></tr>
</table>

	Secondary endpoint	TTR	Time from first dosing date to date of first confirmed CR or PR by BICR using RECIST 1.1. TTR was derived for responders only.
	Secondary endpoint	TTP	Time from first dosing date to date of first radiographic progression by BICR using RECIST 1.1.
	Secondary endpoint	PFS	Time from first dosing date to date of first radiographic progression by BICR using RECIST 1.1 or death due to any cause.
	Secondary endpoint	OS	Time from first dosing date to date of death (due to any cause).
	Secondary endpoint	OS rate	Probability that patient is still alive at time T following first dosing date.
	Secondary endpoint	ORR per baseline PD-L1 expression	Tumour tissue samples were tested for PD-L1 expression using the Dako PD-L1 IHC 28-8 pharmDx test and patients were divided in groups with baseline PD-L1 expression ≥5% versus <5%, ≥1% versus <1%, and PD-L1 expression non-quantifiable, respectively. ORR (for definition see above) was calculated per group.
Database lock	17-Mar-2017		

Results and analysis

Analysis description	**Primary analysis**		
Analysis population and time point description	- 2L ESC cohort - 2L EXP cohort		
Descriptive statistics and estimate variability	Treatment group	2L EXP cohort	2L ESC cohort
	Enrolment period:	Jan 2015 to Nov-2015 (10 months)	Oct-2012 to Jul-2015 (32 months)
	Number of patients	145	37
	ORR by BICR using RECIST 1.1 (95% CI)	14.5% (9.2-21.3)	18.9% (8.0-35.2)
	CR rate by BICR using RECIST 1.1 (95% CI)	1.4% (0.2-4.9)	2.7% (0.1-14.2)
	DCR by BICR using RECIST 1.1 (95% CI)	55.9% (47.4-64.1)	54.1% (36.9-70.5)
	Median DOR by BICR using RECIST 1.1 (min, max)	16.6 months (3.2, 16.8+)	19.35 months (2.8, 38.2+)
	Median TTR by BICR using RECIST 1.1 (min, max)	2.76 months (1.2, 7.0)	1.41 months (1.3, 6.9)
	Median TTP by BICR using RECIST 1.1 (95% CI)	2.83 months (2.66-4.11)	4.01 months (1.41-6.97)

	Median PFS by BICR using RECIST 1.1 (95% CI)	2.79 months (2.63-4.04)	3.45 months (1.61-4.14)
	Median OS (95% CI)	15.64 months (13.24-18.89)	14.95 months (4.99-28.06)
	OS rate at 6 months (95% CI) OS rate at 9 months (95% CI) OS rate at 12 months (95% CI)	81.8% (74.4-87.2) 71.2% (63.0-77.9) 59.9% (51.4-67.5)	66.7% (48.9-79.5) 66.7% (48.9-79.5) 58.0% (40.2-72.2)
	Investigator-assessed ORR using RECIST 1.1 per baseline PD-L1 expression		
	Baseline PD-L1 expression ≥5%	n=9 ORR=44.4%	n=2 ORR=50.0%
	Baseline PD-L1 expression <5%	n=118 ORR=19.5%	n=33 ORR=15.2%
	Baseline PD-L1 expression ≥1%	n=25 ORR=32.0%	n=9 ORR=22.2%
	Baseline PD-L1 expression <1%	n=102 ORR=18.6%	n=26 ORR=15.4%
	Baseline PD-L1 expression non-quantifiable	n=18 ORR=5.6%	n=2 ORR=0%
Analysis description	**Exploratory analysis**		
Descriptive statistics and estimate variability	ORR by BICR using mRECIST (95% CI)	18.6% (12.6-25.9)	21.6% (9.8-38.2)
Analysis description	**Sensitivity analysis**		
Descriptive statistics and estimate variability	ORR by investigator assessment using RECIST 1.1 (95% CI)	19.3% (13.2-26.7)	16.2% (6.2-32.0)
	Median PFS by investigator assessment using RECIST 1.1 (95% CI)	4.01 months (2.73-5.42)	3.12 months (1.61-5.49)
Notes	Median follow up for survival was 14.92 months for the 2L EXP cohort and 14.32 months for the 2L ESC cohort.		

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable, considering that only 1 CT from an early phase of development is presented in support of this application.

No additional studies are presented in support of this variation.

Efficacy in special populations - ORR by BICR using RECIST 1.1 in elderly patients

Patients ≥65 years old comprised 44.1% of the 2L EXP cohort and 37.8% of the 2L ESC cohort, whereas patients ≥75 years old comprised 11.0% and 8.1%, respectively. There were no patients ≥85 years old enrolled in study CA209040.

Table 34: Objective response rate by BICR using RECIST 1.1 in elderly patients.

	Age 65-74		Age 75-84	
	2L EXP cohort	2L ESC cohort	2L EXP cohort	2L ESC cohort
Older patients number/total number (%)	48/145 (33.1%)	11/37 (29.7%)	16/145 (11%)	3/37 (8.1%)
ORR by BICR using RECIST 1.1 (95% CI)	12.5% (4.7-25.2)	18.2% (2.3-51.8)	25.0% (7.3-52.4)	0% (0.0-70.8)

2.4.3. Discussion on clinical efficacy

Within this Type II variation, nivolumab, a IgG4 monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, is requested for the treatment of hepatocellular carcinoma after prior sorafenib therapy in adults.

The new claimed indication for OPDIVO® is for a late line setting of HCC in which no treatment options are currently approved. Sorafenib is to date the only therapy approved in the EU for the treatment of advanced HCC for patients no longer candidates for locoregional therapy. Nowadays, there is no second-line treatment for patients progressing on sorafenib treatment and clinical guidelines recommend either BSC or enrolment into experimental clinical trials. In an evolving field such as HCC, large phase III trials are currently or have recently challenged different therapies, importantly some of them failed to demonstrate superiority over placebo in spite of initial promising results. In any case, there is an unmet need for this population with dismal prognosis (OS medians around 6-8 months if left untreated).

Design and conduct of clinical studies

Currently, there are two clinical trials testing nivolumab in HCC population: an uncontrolled Phase I/II trial that has been submitted in support of this late line setting indication and a Phase III trial of nivolumab versus the current standard of care in the first line setting, sorafenib. Results from the latter have not been submitted yet.

Trial CA209040 is a Phase 1/2, open-label, multi-cohort, study in which nivolumab was administered in monotherapy and in combination in both first and second-line settings across 5 different cohorts. Efficacy data in support of this application focus on data from a second-line dose escalation cohort of 37 patients that was subsequently expanded to a second-line expansion cohort of 145 patients (sorafenib progressors or intolerant). In the latter, nivolumab 3 mg/kg was administered as a 60-minute intravenous (IV) infusion every 2 weeks (Q2W) until either RECIST 1.1 progression or unacceptable toxicity. Initial results from an interim analysis of data were subsequently updated. This study design and dosing schedule seem justified for a phase 1/2 study.

The choice for nivolumab, as next line treatment after sorafenib, is an intriguing one. In case of the possibility of relevant PD-L1 expression in cancerous hepatic tissue and failed immune protection in HCC, the investigation of the benefits of this PD-1 directed antibody in HCC can be justified.

Non-comparative phase 1/2 study. This application is based on the data of a non-comparative phase 1/2 study. The interpretation of efficacy results is difficult in non-comparative studies. According to CPMP guidance (*CPMP/ICH/364/96 - ICH E10 Choice of control group in clinical trials*), the use of historical controls should be restricted, but can be justifiable in situations where dramatic treatment effects are

seen and the usual course of the disease is highly predictable. Therefore, some cancer medications have been approved based on the data of single-arm trials in case of rare cancer or compelling evidence of efficacy in exploratory trials. Until now, for HCC treatment no systemic therapy has been approved solely on the data of a non-comparative study, as the only product sorafenib authorized for this disease was approved based on the results of a randomized, placebo-controlled, double-blind phase 3 study. With almost 50,000 new patients with HCC in Europe per year, a comparative clinical study including a sufficient number of patients is feasible. This is illustrated by the fact that multiple randomized, controlled, 2L phase 3 studies have (recently) been completed or are ongoing. Moreover, the applicant is conducting a 1L advanced HCC randomized, phase 3 study comparing nivolumab with sorafenib. Importantly, on 26-Oct-2016 a pre-submission meeting was held with the CHMP Rapporteurs. There the lack of controlled data was acknowledged as a weakness for this application and thus the Rapporteurs requested that the dossier should include appropriate rationale to justify the choice of study design. However, in the dossier the applicant did not provide an explanation why this variation application is based on data from a non-comparative study only.

One pivotal study. This application is based on the data of one pivotal study. In the CPMP "Points to consider on application with 1. Meta-analyses; 2. One pivotal study" (CPMP/EWP/2330/99) are a number of reasons why it is usually prudent to plan for more than one study (in the phase 3 program). These reasons include a therapeutic area with a history of failed studies or failures to confirm seemingly convincing results. In addition, in one pivotal study applications, this single study will have to be exceptionally compelling, and special attention will be paid to e.g. the clinical relevance and external validity of the study.

In the 2L treatment of advanced HCC, there is a history of phase 3 trials with negative results following phase 2 trials with seemingly convincing results. Brivanib showed promising antitumour activity in the 2L treatment of patients with advanced HCC in a single-arm phase 2 study, i.e. median OS was 9.8 months (Finn et al. Clin Cancer Res. 2012 Apr 1;18(7):2090-8). However, in the subsequent phase 3 trial OS was not significantly improved, i.e. median OS in the brivanib group was 9.4 months compared to 8.2 months in the placebo group (Llovet et al. J Clin Oncol. 2013 Oct 1;31(28):3509-16). The same is true for everolimus with preliminary antitumour activity and a median OS of 8.4 months (95% CI, 3.9-21.1) in a single-arm phase 1/2 study (Zhu et al. Cancer. 2011 Nov 15;117(22):5094-102), but no improvement in OS in a subsequent phase 3 trial with a median OS of 7.6 months for everolimus and 7.3 months for placebo (Zhu et al. JAMA. 2014 Jul 2;312(1):57-67). These examples illustrate why in the 2L treatment of advanced HCC it is prudent to plan for more than one study. Moreover, also with nivolumab, promising earlier phase study data do not always give rise to a positive result in a phase 3 study. In a phase 1 study nivolumab showed promising activity as 1L therapy for patients with advanced non-small cell lung cancer (Gettinger et al. J Clin Oncol. 2016 Sep 1;34(25):2980-7), but the phase 3 CheckMate-026 study did not meet its primary endpoint of PFS in 1L patients with advanced non-small cell lung cancer with baseline tumour PD-L1 expression ⩾5% (BMS press release concerning the results of the CheckMate 026 study available from: http://bms.com, accessed on 04/01/2017).

Endpoint. In this application, ORR by independent central radiological review was the primary endpoint and PFS and OS were among the secondary endpoints. Following study amendment 4 there was a change in primary tumour assessment criteria from mRECIST to RECIST 1.1.

Patients with histologic confirmation of HCC, not amenable for management with curative intent by surgery or local therapeutic measures and ECOG-PS 0-1 were enrolled regardless of PD-L1 status or aetiological subtypes (i.e., uninfected, HCV-infected, or HBV-infected).The EXP cohort only enrolled patients with Child-Pugh Class A, whereas Child-Pugh Class B7 patients were also allowed to enter in the ESC cohort. Patients were required to have measurable disease at baseline.

For this second-line setting patients must had shown progression on sorafenib treatment (either

symptomatic or radiographic) or sorafenib-intolerance (due to safety events). On the one hand, two different populations can be anticipated if considering that intolerant patients could be more sensitive to second line treatments, as they had not progressed on any previous systemic treatment. On the other hand, it is not clear whether any difference could be expected according to the two different possible types of progression to sorafenib (symptomatic vs. radiographic). However, and considering the poor prognosis of the target population, no very meaningful differences are expected.

In addition, it should be mentioned that one of the most common adverse events associated with sorafenib treatment, hand-foot skin reactions, which generally occur in the first 4 weeks of therapy, is managed according to a detailed symptom-driven algorithm. Sometimes dose reduction or even hold of sorafenib therapy is needed. Nonetheless, many of these patients could be rechallenged without recurrence of these toxicities. The definition of sorafenib intolerance thus allowed the recruitment of some patients that otherwise would have continued on sorafenib treatment (if possible). Albeit this possibility is expectable, it is also reasonable to offer a new and less toxic treatment to these patients. Provided that the population of intolerant patients is limited, little impact is expected.

The primary objective of the trial was to assess the Objective Response Rate (ORR primary endpoint) according to BIRC-assessed tumour response (RECIST 1.1.) and Duration of Response (DOR) of nivolumab monotherapy in adults with advanced HCC with or without chronic viral hepatitis (HCV or HBV) who have been previously treated with sorafenib. Tumour assessments were performed at baseline and every 6 weeks for 48 weeks and every 12 weeks thereafter until disease progression or treatment discontinuation. Secondary efficacy endpoints include ORR investigator-assessed, Time to tumor progression (TTP), progression-free survival (PFS) based on investigator and IRRC assessments, overall survival (OS). Taking into account that some therapeutic agents have previously failed to demonstrate OS benefit in spite of their initial response rates (brivavinib, BRISK-PS Study), ORR as a marker of anti-tumour activity cannot be considered a surrogate for OS in HCC. The choice for ORR as the primary endpoint does not seem justified, especially as OS is an endpoint that can easily be reached in 2L studies for advanced HCC patients as median survival with best supportive care is only 7-8 months (Bruix et al. Lancet. 2017 Jan 7;389(10064):56–66) . In spite of this fact, the lack of alternatives in the high unmet medical need could make study results acceptable provided that mature long-term data is available.

Subgroup analysis according to biomarkers (PD-L1) as well as according to different etiologic subgroups (Uninfected vs. HCV vs. HBV) were performed. ORR was also assessed according to mRECIST criteria. Evaluation of health related QoL (EQ-5D) was included as an exploratory objective.

39 sites in 11 countries enrolled subjects for trial CA209040. The clinical DBL for this CSR occurred on 08-Aug-2016 and the BICR assessment DBL occurred on 10-Aug-2016. Minimum follow-up (LPFT to clinical cut-off date) was approximately 7 months in the EXP Cohort.

Updated efficacy analyses were submitted as part of the responses to the first request of supplementary information with a minimum of 15 months follow-up on all subjects (clinical DBL on 29-Nov-2016/BICR DBL on 12-Dec-2016, and a combined clinical and BICR DBL on 17-Mar-2017).

Trial population

Regarding characteristics in the 2L-EXP cohort, the median age of patients was 63 years, with an 11% (n=16) of patients being >75. The majority of patients were male (77.2%) and there was a similar representation of White (46.2%) and Asian patients (51.7%). Demographic characteristics can be considered consistent with those of an advanced HCC population.

Most patients (64.1%) had ECOG-PS of 0 and advanced disease stage according to BCLC (C (86.9%), B (9.7%), A (1.4%)). CP score was 5 (67.6%) or 6 (31.0%) for most patients. Regarding one of the most important disease prognostic factors, vascular invasion which is known to adversely affect survival, was

present in 28.3% of patients. Extrahepatic spread was present in 70.3% of patients and either vascular invasion or extrahepatic spread was present in 81.4% of patients. Approximately half of patients had AFP levels below 400 µg/ml, nevertheless the value of AFP as prognostic factor is still questionable. Furthermore in almost 40% of patients in the 2L EXP and 2L ESC cohorts the time from initial diagnosis to first dose of study therapy was ⩾5 years. In contrast, the overall 5-year survival rate for HCC patients is only approximately 5-6% (Buonaguro et al. J Hepatol. 2013 Oct;59(4):897-903), and the median time from initial HCC diagnosis to start of study treatment in the regorafenib arm of the RESORCE study was 21 months (Bruix et al. Lancet. 2017 Jan 7;389(10064):56–66). Based hereon, the conclusion is that there appears to have been a selection bias for relatively indolent tumours. This complicates the interpretation of the clinical relevance of the observed efficacy and limits the external validity of the study.

The MAH explained that the reason for a large number of patients having a time from initial diagnosis to first dose of study therapy of ⩾5 years was that a majority of investigators had reported the time from initial diagnosis for patients with the date of initial viral diagnosis instead of initial HCC diagnosis by mistake. The actual number of patients having a time from initial diagnosis to first dose of study therapy of ⩾5 years is 20% (not 37.2%) and the median time from initial diagnosis to first dose of study therapy is 26.5 months (2.2 years). Importantly, although being more comparable, these numbers clearly still exceed the median time from initial HCC diagnosis to start of study treatment of 21 months for the regorafenib arm in the RESORCE trial, as well as the 5-year survival percentages from EUROCARE-5 (11.7%) and SEER (17.5%), as presented by the MAH.

Overall, although the population enrolled in the 2L-Exp cohort of the trial can be considered representative of the target population, it is expected that in clinical practice not all patients have preserved liver function. There are no data on patients with Child-Plug status B and C or ECOG-PS>1. (OC). These patients were excluded from study CA209040, therefore the SmPC should reflect these restrictions. In addition, the risk management plan should take this information in consideration.

Regarding aetiology, one third of the population presented HVB or HVC (33.8% and 29.7% respectively) and 19.3% had liver alcoholic disease.

65.5% of patients had undergone prior surgery related to cancer, 24.8 has prior radiotherapy and 58.6% had prior local treatment for HCC.

All patients had received at least 1 prior line of systemic cancer treatment and all patients had previously received sorafenib. 81.4% had received one single prior line, 8.3% two prior lines and 10.3% has received 3 or more prior lines.

Regarding prior sorafenib therapy, most patients were progressors (n=132; 91.0%) with a minority of patients being intolerants to sorafenib (n=12; 8.3%). One single patient was neither progressor nor intolerant. As previously anticipated, intolerant patients could be more sensitive to 2L treatment than progressing patients, nevertheless considering the low percentage of intolerant patients, no concerns arise.

'Taking into account that one patient can have reported both clinical (documented symptomatic) and radiographic progression, 82.8% of the progressions were radiographic and 20.7% were clinical.

As of the DBL, 124 subjects in the 2L EXP Cohort had quantifiable PD-L1 expression at baseline. Of these25 (17.2%) had ≥1% baseline PD-L1 expression and 99 (68.3%) had < 1% baseline PD-L1 expression. 9 (6.2%) had ≥5% baseline PD-L1 expression and 115 (79.3) had < 5% baseline PD-L1 expression. 21 subjects had no quantifiable levels at baseline. An exploratory analysis of

Tumour-Associated Immune Cell (TAIC) PD-L1 expression in baseline tumour samples from CA209040 was also performed.

Potential relevant protocol deviations were reported in 14 (5.3%) subjects in the total population. Of the 14 potential protocol deviations, the only actual relevant protocol deviation at study entry was in a subject in the 2L EXP cohort who did not have evaluable disease at baseline. In addition, the other 13 subjects who were listed as a relevant protocol deviation due to receiving "concurrent" anti-cancer therapy were not considered true relevant protocol deviations as palliative therapy after progression was allowed per protocol. Statistical analysis used by the applicant are commonly used and acceptable. However, type I error control, sample size and power calculation was done for ORR in the (2L) EXP cohort only. Therefore, it is difficult to draw definitive conclusions on other endpoints such as PFS and OS. Of note, when a new anticancer treatment was started without a prior reported radiographic progression per RECIST 1.1, then a patient was censored for PFS and TTP.

Efficacy data and additional analyses

The focus of the primary analysis for this application is on prior sorafenib-treated subjects that received nivolumab 3 mg/kg Q2W, i.e. the 2nd line expansion cohort (2L EXP (N = 145)) which is supported by subjects in the 2nd line expansion cohort (2L ESC (N = 37)).

ORR based on BICR assessment and according to RECIST 1.1. criteria was the primary endpoint. Initial response assessment must have been confirmed by a consecutive assessment (no less than 4 weeks later). Results from the 2L-EXP cohort showed an ORR of 14.5% (95% CI 9.2, 21.3), 1 patient (0.7%) reported a complete response, 20 (13.8%) showed partial responses. SD was shown in 40.7% of the population. 19 out of 21 patients had ongoing response at the time of DBL thus median DoR has yet not being reached.

ORR using mRECIST criteria (BICR assessed) was higher than ORR according to RECIST 1.1 criteria with overlapping 95 % CI: 18.6% (95% CI 12.6, 25.9).

For PFS, 110 events in 145 patients (75.9%) have been reported by BIRC assessment, which show a median PFS of 2.76 months (95%CI: 2.63, 4.04). 35 subjects (24.1%) were censored (Most common reason for censoring progression-free on treatment: 13.8%). TTP median was the same, 2.79 months (95%CI: 2.66, 4.11). A total of 100 (69.0%) subjects progressed in the 2L EXP Cohort. 45 (31.0%) subjects in the 2L EXP were censored in the time-to-progression analysis (Most common reason for censoring progression-free on treatment: 13.8%).

With a median follow-up of 10.58 months OS results were still immature with an event rate of 36.6% (53/145) a median OS of 13.24 months was observed. The 9-month OS rate was 71.1%. Taking into account the immaturity of data an update of main efficacy data is guaranteed. ORR BICR-assessed by subgroups appeared consistent across baseline demographic subgroups (age, region, gender, VI/EHS, AFP, and BCLC category) .Particularly high response rates were observed in the subgroup of patients >75 years, greater response rates were observed for the subgroup of patients with baseline AFP $\geqslant$400 UG/L and for those from the US/Canada and Asia compared to patients from Europe. ORR results are also presented by PD-L1 expression, which is based on tumour cell expression. 99 patients were classified as PD-L1<1% vs 25 were PD-L1 ≥1%. A less pronounced effect is observed in patients with low expression and even lesser in patients without quantifiable PD-L1 based on IRRC assessment (32% high vs 17.2% low expression vs 9.5% no quantifiable). This difference was more marked in subjects classified as PD-L1≥5% vs. PD-L1<5% were ORR were 44.4% vs. 18.3% respectively. Intuitively, a trend for greater ORR can be anticipated for higher baseline PD-L1 expression, however this cannot be confirmed.

Updated efficacy data with a minimum 15-months of follow-up was provided as part of the responses to the request for supplementary information and confirmed previous findings in terms of ORR (14.5% 2L-EXP), and PFS (median 2.79 months) for the overall population. Importantly, the company also provided an estimate of median DoR *(*16.3 months (95% CI 13.83, 19.44)) and median OS data (15.6 months (13.2, 18.9) event rate 55.9%; 81/145).

A landmark analysis of OS by responders vs. non-responders at 4.5 months, showed a marked difference between both groups. Whereas OS for the population showing response to nivolumab is considered outstanding (OS median not reached, minimum OS≥12 months), the median OS for the non-responder population is considered remarkably high (16.3 months (95% CI 13.83, 19.44)) as is well-above what could be expected for this setting.

OS was not reached in subjects with ≥1% PD-L1 expression (95% CI: 10.84, NA) and was 13.24 months (95% CI: 11.70, NA) in subjects with <1% PD-L1 expression. In addition, the median OS (using the 29-Nov-2016 clinical and 12-Dec-2016 BICR DBL) was similar and was not reached in subjects with ≥1% PD-L1 expression and was 14.4 months (95% CI: 11.70, 16.66) in subjects with <1% PD-L1 expression.

The limited number of patients in each subgroup analysed may translate minor absolute numerical changes into great changes in relative numbers, precluding from drawing any firm conclusion from the subgroup analysis. Available data do not allow to identify potential subgroups of patients that could be benefitting to a greater or lesser extent from nivolumab therapy. Efficacy analyses according to aetiologic subtype did not show relevant differences across aetiology subgroups. Although the ORR was greater for the HCV subgroup, due to the limited sample these results should be taken cautiously.

Data has been submitted according to of PD-L1 expression subgroups in each of the 3 different aethiologic subgroups, nevertheless the limited sample size hampers reaching any conclusion.

Regarding Quality of life data questionnaires exhibited generally stable patient-reported outcomes. No major improvements or decreases from baseline were observed during the study. The non-comparative nature of study CA209040 hampers further interpretation of the results.

Comparison outcomes nivolumab and other treatment options from literature

According to the 2012 clinical practice guidelines on HCC of the European Society for Medical Oncology, in case of progression or intolerance to sorafenib, best supportive care is preferred or patients should be included in clinical trials. Therefore, there is an unmet medical need for the treatment of patients with advanced HCC who are intolerant of sorafenib or who have progressed following sorafenib therapy.

Very recently, the results from the 2L phase 3 regorafenib RESORCE study were published (Bruix et al. Lancet. 2017 Jan 7;389(10064):56–66). The RESORCE study population seems comparable to the CA209040 study population. The applicant states that the efficacy data compare favourably to those reported with regorafenib. In our opinion only ORR seems greater for nivolumab and DCR, median PFS and median TTP are comparable to regorafenib.

Table 35: Efficacy by investigator assessment using RECIST 1.1 in the RESORCE and the CA209040 study.

Study/investigational product	RESORCE/regorafenib		CA209040/nivolumab	
Treatment arm/cohort	Placebo	Regorafenib	2L EXP cohort	2L ESC cohort
ORR	3%	7%	19.3%	16.2%
DCR	35%	66%	64.1%	56.8%
Median PFS	1.5 months	3.4 months	4.01 months	3.12 months
Median TTP	1.5 months	3.9 months	4.04 months	3.40 months
Median OS	7.8 months	10.6 months	15.64 months	14.95 months

Updated OS findings of trial CA209040 seem to be well-above what can be expected to date for a 2L HCC population that lacks effective therapies. The phase I/II CA209040 trial has methodological limitations such as ORR being the primary endpoint or the absence of comparator. The former, cast doubts with regard to the correlation with OS, even though it would be reasonable to expect that patients experiencing prolonged responses could likely live longer, as previously observed with nivolumab in other tumour types.

Importance of PD-L1 expression

A higher expression of PD-L1 in HCC tumours has been associated with a significantly poorer prognosis (Gao et al. Clin Cancer Res. 2009 Feb 1;15(3):971-9). However, full understanding of PD-L1 is far from complete and much remains unclear on how to properly measure PD-L1 expression, mainly due to the lack of standardization of measurement methods and the dynamic nature of PD-L1 expression during the course of the disease (Fusi et al. Lancet Oncol. 2015 Oct;16(13):1285-7). Moreover, thus far use of PD-L1 IHC alone has not been sufficient for ruling in or ruling out the use of anti-PD-1 (or anti-PD-L1) expression-based therapies (Gibnet et al. Predictive biomarkers for checkpoint inhibitor-based immunotherapy). In conclusion, there is much to be learned on how to use PD-L1 expression to determine which patient population would benefit from the inhibition of PD-(L)1.

Therefore, for all approved indications of nivolumab, a post-approval commitment exist to further investigate the value of biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., other genomic-based methods / assays, and associated cut-offs, that might prove more sensitive and specific in predicting response to treatment based on PD-L1, PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, expression of components of antigen-presentation complexes and/or other inhibitory checkpoint receptors/ligands within tumour, etc.) as predictive of nivolumab therapy efficacy.

The applicant states that no threshold of PD-L1 expression was identified to be required for benefit from nivolumab treatment, as clinically meaningful increases in investigator-assessed ORR were reported in patients regardless of PD-L1 expression levels at baseline. However, baseline tumour PD-L1 expression ≥1% was infrequent in the 2L EXP cohort (17.2%) and nevertheless there was a clear trend for greater ORR with higher baseline PD-L1 expression.

At minimum the post-approval commitment should be extended to include HCC, see comments on Annex II to the SmPC in separate document. However, a confirmatory phase 3 study would have been the best way to select the patient population that could benefit most from nivolumab treatment.

2.4.1. Conclusions on the clinical efficacy

In CA209040, nivolumab showed prolonged antitumour activity evidenced by ORR results (14.5%) with a median DoR (16.6 months) and importantly supported by OS data (median 15.6 months (95%CI: 13.2, 18.9). With a 55.9%

The median OS observed for the overall population of 15.6 months supported by durable responses is considered of clinical relevance in a setting where no treatments are available after progression on sorafenib. Even acknowledging that ORR cannot be considered a valid surrogate for true clinically relevant patient benefit, it would be reasonable to expect that patients experiencing prolonged responses could likely live longer, as previously observed with nivolumab in other tumour types.

Being considered outstanding for the overall population, there is 20% of the population suspected from having better prognosis. This selection bias creates a source of uncertainty and also hampers interpretation of results from any comparison with an external control, and thereby prevents assessment of the actual effect size and clinical relevance of the study results (MO).

The possible impact of selection-bias is supported by results of OS according to subgroups of responders, which showed a remarkably high median OS for the non-responder population of 16.3 months (95% CI 13.83, 19.44)). Although among other possible causes of this unexpected high OS median for the non-responders, are the disease stabilization rate observed (40.7%) for the overall population or due to the possible influence of post-progression therapies. Regarding the former, and despite SD and DCR (by BICR using RECIST 1.1) for nivolumab in study CA209040 (i.e. 41% and 56%, respectively) were lower than that for regorafenib in the RESORCE trial (i.e. 59% and 66%, respectively), the behaviour of immunotherapy within tumour micro environment has not been totally elucidated to date, so there could be some unknown pharmacodynamic effects that could be impacting in long-term benefit of nivolumab. In any case, none of them seem to be solid arguments when it comes to explaining this finding.

Efficacy across different subgroups of study population (PD-L1 expression and aetiology) remains uncertain. Although better results could be intuitively anticipated for the subgroups of patients with higher PD-L1 expression no sound conclusion can be drawn. The exact influence of both baseline tumour PD-L1 expression and HCC aetiology on nivolumab efficacy cannot be elucidated from available data.

In summary, the evidence provided by the exploratory, non-comparative trial CA209040 is considered insufficient to support a positive B/R in the target population applied for. The key issues identified pertain to the non-comparative design of the study and an apparent selection bias for relatively indolent tumours in the study population. This selection bias creates a source of uncertainty regarding the study population with respect to a wide range of known and unknown factors that could affect the outcome, thus making it difficult to infer that a favourable outcome in terms of OS, is from the treatment alone. This uncertainty also hampers interpretation of the results when compared to an external control. In an attempt to assess the actual effect size and clinical relevance of the study results the company is asked to submit some exploratory analyses (MO).

2.5. Clinical safety

Introduction

The focus of the safety data presented in this summary is from 2 key populations in CA209040, as described in the Interim CSR. Safety data from the All Treated population in the EXP + ESC Cohort is presented side-by-side with safety data from the sorafenib-treated 2L EXP Cohort. The 2L EXP Cohort is a subset of the ESC + EXP Cohort treated with the proposed dose of 3 mg/kg nivolumab monotherapy Q2W, and the primary efficacy population for this submission.

- **2L EXP Cohort:** n = 145 prior sorafenib-treated subjects administered 3 mg/kg nivolumabmonotherapy Q2W in the expansion phase
- **ESC + EXP Cohort:** N = 262 total treated subjects administered 0.1 to 10 mg/kg nivolumab monotherapy Q2W in the dose escalation and expansion phases.
  - **ESC Cohort:** 48 subjects (11 sorafenib-naive and 37 sorafenib-treated) received 0.1 to10 mg/kg nivolumab monotherapy Q2W.
  - **EXP Cohort:** 214 subjects (69 sorafenib-naive and 145 sorafenib-treated) received3 mg/kg nivolumab monotherapy Q2W.

As of the clinical database lock (DBL) on 08-Aug-2016, and the blinded independent central review (BICR) DBL on 10-Aug-2016, the majority of treated subjects in the EXP + ESC and 2L EXP Cohorts received the planned dose intensity (with 90% - 110% relative dose intensity): 80.9% in the EXP + ESC Cohort and 77.9% in the 2L EXP Cohort. Dose reductions or intrasubject escalations were not permitted with nivolumab treatment.

Table 36: Summary of Safety Results - All Treated Subjects

	Number (%) Subjects	
	2L Exp Cohort N = 145	Esc + Exp Cohort N = 262
DEATHS	53 (36.6)	101 (38.5)
WITHIN 30 DAYS OF LAST DOSE	8 (5.5)	9 (3.4)
WITHIN 100 DAYS OF LAST DOSE	29 (20.0)	54 (20.6)
DUE TO STUDY DRUG TOXICITY	0	0

	Number (%) Subjects			
	2L Exp Cohort (N=145)		Esc + Exp Cohort (N=262)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
ALL CAUSALITY SAEs	68 (46.9)	40 (27.6)	120 (45.8)	79 (30.2)
DRUG-RELATED SAEs	13 (9.0)	6 (4.1)	19 (7.3)	11 (4.2)
ALL CAUSALITY AEs LEADING TO DC	15 (10.3)	8 (5.5)	27 (10.3)	17 (6.5)
DRUG-RELATED AEs LEADING TO DC	3 (2.1)	2 (1.4)	7 (2.7)	4 (1.5)
ALL-CAUSALITY AEs	144 (99.3)	67 (46.2)	261 (99.6)	135 (51.5)
Most Frequent AEs (≥ 20% of Any Grade in either treatment group)				
DIARRHOEA	38 (26.2)	2 (1.4)	65 (24.8)	4 (1.5)
ABDOMINAL PAIN	33 (22.8)	5 (3.4)	49 (18.7)	6 (2.3)
FATIGUE	50 (34.5)	4 (2.8)	91 (34.7)	5 (1.9)
PRURITUS	39 (26.9)	1 (0.7)	78 (29.8)	1 (0.4)
DECREASED APPETITE	29 (20.0)	2 (1.4)	54 (20.6)	2 (0.8)
COUGH	31 (21.4)	0	55 (21.0)	0
DRUG-RELATED AEs	109 (75.2)	23 (15.9)	199 (76.0)	52 (19.8)
Most Frequent Drug-related AEs (≥15% of Any Grade in either treatment group)				
PRURITUS	27 (18.6)	1 (0.7)	54 (20.6)	1 (0.4)
RASH	23 (15.9)	1 (0.7)	44 (16.8)	2 (0.8)
ALL CAUSALITY SELECT AES, BY CATEGORY				
ENDOCRINE	13 (9.0)	0	25 (9.5)	1 (0.4)
GASTROINTESTINAL	38 (26.2)	2 (1.4)	65 (24.8)	4 (1.5)
HEPATIC	31 (21.4)	22 (15.2)	74 (28.2)	45 (17.2)
PULMONARY	2 (1.4)	1 (0.7)	3 (1.1)	1 (0.4)
RENAL	3 (2.1)	1 (0.7)	9 (3.4)	1 (0.4)
SKIN	59 (40.7)	2 (1.4)	120 (45.8)	5 (1.9)
HYPERSENSITIVITY/INFUSION REACTIONS	5 (3.4)	0	11 (4.2)	0
DRUG-RELATED SELECT AES, BY CATEGORY				
ENDOCRINE	10 (6.9)	0	21 (8.0)	1 (0.4)
GASTROINTESTINAL	20 (13.8)	2 (1.4)	34 (13.0)	3 (1.1)
HEPATIC	13 (9.0)	6 (4.1)	37 (14.1)	17 (6.5)
PULMONARY	2 (1.4)	1 (0.7)	3 (1.1)	1 (0.4)
RENAL	0	0	1 (0.4)	0
SKIN	45 (31.0)	2 (1.4)	91 (34.7)	5 (1.9)
HYPERSENSITIVITY/INFUSION REACTIONS	5 (3.4)	0	11 (4.2)	0

MedDRA version 18.1; CTC version 4.0.
All events are within 30 days of the last dose of study drug, unless otherwise indicated.
Source: Table 8.1-1 of the CA209040 Interim CSR.

Patient exposure

Safety analyses were conducted in all 262 treated subjects who received at least one dose of study drug. Additional analyses were conducted in treated subjects in the 2L EXP Cohort, which was the primary cohort for the efficacy analyses presented in this application.

Safety presentations of AEs, SAEs, AEs leading to discontinuation, laboratory abnormalities, and select AEs for this SCS are based on all treated subjects using a safety window of 30 days after last dose. The 30-day safety window was intended to provide a clean characterization of the safety experience of nivolumab monotherapy without influence of AEs associated with subsequent therapies. Further details

for safety analyses are provided in the Core Safety Statistical Analysis Plan (SAP)

The majority of treated subjects (78.6%) in the 2L EXP Cohort received ≥ 90% of the planned dose intensity, which was similar to that in the total ESC + EXP Cohort (81.7%).

The majority of treated subjects across etiologic subtypes in the ESC and EXP Cohorts received ≥ 90% of the planned dose intensity.

- In the EXP Cohort, 80.4% in the uninfected naive/intolerant, 80.7% in the uninfected progressor, 80.0% in the HCV-infected, and 84.4% in the HBV-infected received ≥ 90% of the planned dose intensity.

- In the ESC Cohort, 87.0% in the uninfected, 80.0% in the HCV-infected, and 80.0% in the HBV-infected received ≥ 90% of the planned dose intensity.

Table 37: Cumulative Dose and Relative Dose Intensity Summary - All Treated Subjects in the 2L EXP Cohort and ESC+EXP Cohort

	2L EXP Cohort N = 145	ESC + EXP Cohort N = 262
NUMBER OF DOSES RECEIVED		
MEAN (SD)	12.8 (8.40)	13.4 (10.05)
MEDIAN (MIN - MAX)	12.0 (1 - 36)	10.0 (1 - 55)
CUMULATIVE DOSE (MG/KG)		
MEAN (SD)	38.40 (25.045)	40.02 (44.416)
MEDIAN (MIN - MAX)	35.62 (3.0 - 107.0)	27.92 (0.2 - 460.6)
RELATIVE DOSE INTENSITY		
>= 110%	1 (0.7)	2 (0.8)
90% TO < 110%	113 (77.9)	212 (80.9)
70% TO < 90%	29 (20.0)	46 (17.6)
50% TO < 70%	1 (0.7)	1 (0.4)
< 50%	1 (0.7)	1 (0.4)

Source: Table S.4.1

Table 38: Duration of Study Therapy Summary - All Treated Subjects in the 2L EXP, 2L ESC, and ESC + EXP Cohorts

	2L EXP Cohort N = 145	2L ESC Cohort N = 37	ESC + EXP Cohort N = 262
DURATION OF THERAPY (MONTHS)			
MIN, MAX (A)	0.0, 17.7+	0.0, 30.5+	0.0, 30.5+
MEDIAN (95% CI) (B)	5.26 (3.71, 6.47)	2.56 (2.33, 6.44)	4.88 (3.71, 5.78)
N OFF TRT/N TREATED (%)	109/145 (75.2)	35/37 (94.6)	202/262 (77.1)
> 3 MONTHS (%)	95 (65.5)	18 (48.6)	162 (61.8)
> 6 MONTHS (%)	67 (46.2)	13 (35.1)	115 (43.9)
> 9 MONTHS (%)	39 (26.9)	10 (27.0)	79 (30.2)
> 12 MONTHS (%)	7 (4.8)	8 (21.6)	23 (8.8)
> 18 MONTHS (%)	0	5 (13.5)	6 (2.3)

(A) Symbol + indicates a censored value
(B) Median computed using Kaplan-Meier method.

Source: Table S.4.8 (ESC + EXP) and Table S.4.8b (2L ESC and 2L EXP)

The median duration of therapy was 2.56 months in the ESC Cohort and 2.56 months in the 2L ESC Cohort. The median duration of therapy in the EXP Cohort was 5.09 months and in the 2L EXP Cohort was 5.26 months.

The median duration of therapy was longer in HCV-infected subjects in the ESC Cohort (14.82 months) than in HCV-infected subjects in the EXP Cohort (4.32 months).

As of the 08-Aug-2016 DBL, 202 of 262 (77.1%) treated subjects in the ESC + EXP Cohort had discontinued study treatment. The most common reason was disease progression.

Table 39: Subject Status Summary - All Treated Subjects in the 2L EXP Cohort and ESC + EXP Cohort

	2L EXP COHORT	ESC + EXP COHORT
SUBJECTS	145	262
SUBJECTS CONTINUING IN THE TREATMENT PERIOD (%) (A)	36 (24.8)	60 (22.9)
SUBJECTS NOT CONTINUING IN THE TREATMENT PERIOD (%) (A)	109 (75.2)	202 (77.1)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD (%) (A)		
DISEASE PROGRESSION	96 (66.2)	174 (66.4)
STUDY DRUG TOXICITY	4 (2.8)	9 (3.4)
ADVERSE EVENT UNRELATED TO STUDY DRUG	4 (2.8)	9 (3.4)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	4 (2.8)	4 (1.5)
SUBJECT WITHDREW CONSENT	1 (0.7)	2 (0.8)
MAXIMUM CLINICAL BENEFIT	0	2 (0.8)
OTHER	0	1 (0.4)
NOT REPORTED	0	1 (0.4)
SUBJECTS CONTINUING IN THE STUDY (%) (A) (B)	130 (89.7)	240 (91.6)
SUBJECTS NOT CONTINUING IN THE STUDY (%) (A)	15 (10.3)	21 (8.0)
REASON FOR NOT CONTINUING IN THE STUDY (%)		
SUBJECT WITHDREW CONSENT	1 (0.7)	2 (0.8)
OTHER	14 (9.7)	19 (7.3)

Percentages based on subjects entering period or continuing study
(A) Subject status at end of treatment if without retreatment and at end of retreatment if retreated
(B) Includes subjects still on treatment and subjects off treatment continuing in the Follow-up period
Source: Table 5.1-1 of CA209040 Interim CSR

A total of 94.6% and 75.2% subjects in the 2L ESC Cohort and 2L EXP Cohort discontinued study treatment, respectively. The most common reason was disease progression in both Cohorts.

Most subjects in the ESC + EXP Cohort received all doses of study medication without an infusion interruption, infusion rate reduction, or dose delay. Reasons for infusion interruption, infusion rate reduction, or dose delay are provided in Table below. Dose reductions or intrasubject escalations were not permitted with nivolumab treatment.

Infusion interruptions: Only 6.5% of subjects in the ESC + EXP Cohort had an infusion interruption. Of the subjects who required an infusion interruption, most had only 1 infusion interrupted. A similar frequency was reported in the 2L EXP Cohort (6.9% subjects) and no differences were noted by HCC etiology. Only 2 subjects in the ESC Cohort experienced infusion interruptions; 1 subject with 1 infusion interruption and 1 subject with 2 infusion interruptions. No subject who had an infusion interruption required permanent discontinuation of study drug for hypersensitivity reaction.

Infusion rate reductions: 4.2% of subjects in the ESC + EXP Cohort had an infusion rate reduction. Of the subjects who required an infusion rate reduction, most had only 1 infusion rate reduced. A lower frequency was reported in the 2L EXP Cohort (2.8% subjects) with no differences noted across HCC etiologies (Table 6.3-1 and Table S.4.5). In the ESC Cohort, 1 subject in the ESC uninfected cohort experienced 3 infusion rate reductions.

Dose delays in the ESC + EXP Cohort were infrequent (43.5%). Most subjects with dose delay only experienced only 1. A similar frequency was reported in the 2L EXP Cohort (43.4% subjects) with no differences noted across HCC etiologies (Table 6.3-1 and Table S.4.2). Dose delays were most frequent in HCV-infected subjects in the ESC Cohort (70% experienced at least 1 dose delay) compared to the overall ESC population [45.8%]).

Table 40: Subjects with dose interruption, reduction or delays - - All Treated Subjects in the 2L EXP Cohort and ESC + EXP Cohort

	2L EXP Cohort N = 145	ESC + EXP Cohort N = 262
SUBJECTS WITH AT LEAST ONE INFUSION INTERRUPTED (%)	10 (6.9)	17 (6.5)
NUMBER OF INFUSIONS INTERRUPTED PER SUBJECT (%)		
0	135 (93.1)	245 (93.5)
1	8 (5.5)	13 (5.0)
2	2 (1.4)	4 (1.5)
3	0	0
>= 4	0	0
TOTAL NUMBER INFUSIONS INTERRUPTED/TOTAL NUMBER INFUSIONS RECEIVED	12/1863 (0.6)	21/3499 (0.6)
REASON FOR INFUSION INTERRUPTION (A)		
HYPERSENSITIVITY REACTION	4 (33.3)	10 (47.6)
INFUSION ADMIN ISSUES	1 (8.3)	4 (19.0)
OTHER	7 (58.3)	7 (33.3)
SUBJECTS WITH AT LEAST ONE INFUSION WITH IV RATE REDUCED (%)	4 (2.8)	11 (4.2)
NUMBER OF INFUSIONS WITH IV RATE REDUCTION PER SUBJECT (%)		
0	141 (97.2)	251 (95.8)
1	3 (2.1)	7 (2.7)
2	1 (0.7)	2 (0.8)
3	0	1 (0.4)
>=4	0	1 (0.4)
TOTAL NUMBER IV RATE REDUCED /TOTAL NUMBER DOSE RECEIVED)	5/1863 (0.3)	25/3499 (0.7)
REASON FOR IV RATE REDUCTION (B)		
HYPERSENSITIVITY REACTION	2 (40.0)	4 (16.0)
INFUSION ADMIN ISSUES	0	1 (4.0)
OTHER	3 (60.0)	20 (80.0)
SUBJECTS WITH AT LEAST ONE DOSES DELAYED (%)	63 (43.4)	114 (43.5)
NUMBER OF DOSES DELAYED PER SUBJECT		
0	82 (56.6)	148 (56.5)
1	39 (26.9)	71 (27.1)
2	14 (9.7)	24 (9.2)
3	6 (4.1)	12 (4.6)
>=4	4 (2.8)	7 (2.7)
TOTAL NUMBER DOSES DELAYED/ TOTAL NUMBER DOSES RECEIVED (%) (C)	101/1718 (5.9)	185/3236 (5.7)
REASON FOR DOSE DELAY (D)		
ADVERSE EVENT	27 (26.7)	68 (36.8)
OTHER	34 (33.7)	56 (30.3)
NOT REPORTED	40 (39.6)	61 (33.0)

	2L EXP Cohort N = 145	ESC + EXP Cohort N = 262
LENGTH OF DELAY (D)		
4 - 7 DAYS	44 (43.6)	87 (47.0)
8 - 14 DAYS	31 (30.7)	51 (27.6)
15 - 42 DAYS	22 (21.8)	43 (23.2)
> 42 DAYS	4 (4.0)	4 (2.2)

(A) Percentages are computed out of the total number of Dose Interrupted.
(B) Percentages are computed out of the total number of infusions with IV rate reduction
(C) Total number doses received is excluding first dose.
(D) Percentages are computed out of the total number of doses delayed.
Source: Table S.4.2 (dose delay), Table S.4.4 (infusion interruption), and Table S.4.5 (infusion rate reduction)

Adverse events

The majority of subjects in the ESC + EXP Cohort experienced at least one AE, regardless of causality (Table below). The overall frequency of any-grade and Grade 3-4 AEs (regardless of causality) and drug-related AEs (any grade and Grade 3-4) was similar between the ESC + EXP and 2L EXP Cohorts.

Adverse Events (Regardless of Causality)

Any-grade AEs (regardless of causality) were reported in 99.6% of subjects in the ESC + EXP Cohort and 99.3% of subjects in the 2L EXP Cohort.

- In the 2L EXP Cohort, the most frequently reported AEs were fatigue (34.5%), pruritus (26.9%), diarrhea (26.2%), abdominal pain (22.8%), cough (21.4%), and decreased appetite (20.0%).

Grade 3-4 AEs (regardless of causality) were reported in 51.5% of subjects in the ESC + EXP Cohort and 46.2% of subjects in the 2L EXP Cohort.

- In the 2L EXP Cohort, the most frequently reported Grade 3-4 AEs were increased AST (9.7%) and increased ALT (6.2%).

Drug-related Adverse Events

Any-grade drug-related AEs were reported in 76.0% of subjects in the ESC + EXP Cohort and 75.2% of subjects in the 2L EXP Cohort.

- In the 2L EXP Cohort, the most frequently reported drug-related AEs were fatigue (23.4%), pruritus (18.6%), and rash (15.9%).

Grade 3-4 drug-related AEs were reported in 19.8% of subjects in the ESC + EXP Cohort and 15.9% of subjects in the 2L EXP Cohort.

- In the 2L EXP Cohort, the most frequently reported Grade 3-4 drug-related AEs were increased AST (3.4%), and increased lipase (3.4%)

Table 41: Adverse Events by Worst CTC Grade Reported in (≥ 10% of Subjects) - All Treated Subjects in the 2L EXP Cohort and ESC + EXP Cohort

System Organ Class (%) Preferred Term (%)	2L EXP Cohort N = 145			ESC + EXP Cohort N = 262		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	144 (99.3)	67 (46.2)	5 (3.4)	261 (99.6)	135 (51.5)	7 (2.7)
GASTROINTESTINAL DISORDERS	101 (69.7)	13 (9.0)	0	176 (67.2)	27 (10.3)	1 (0.4)
DIARRHOEA	38 (26.2)	2 (1.4)	0	65 (24.8)	4 (1.5)	0
ABDOMINAL PAIN	33 (22.8)	5 (3.4)	0	49 (18.7)	6 (2.3)	0
NAUSEA	23 (15.9)	0	0	45 (17.2)	2 (0.8)	0
CONSTIPATION	22 (15.2)	0	0	44 (16.8)	0	0
VOMITING	20 (13.8)	0	0	35 (13.4)	2 (0.8)	0
ABDOMINAL DISTENSION	16 (11.0)	0	0	29 (11.1)	0	0
ABDOMINAL PAIN UPPER	18 (12.4)	1 (0.7)	0	26 (9.9)	1 (0.4)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	91 (62.8)	12 (8.3)	0	158 (60.3)	16 (6.1)	0
FATIGUE	50 (34.5)	4 (2.8)	0	91 (34.7)	5 (1.9)	0
PYREXIA	23 (15.9)	1 (0.7)	0	40 (15.3)	1 (0.4)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	73 (50.3)	2 (1.4)	0	138 (52.7)	6 (2.3)	0
PRURITUS	39 (26.9)	1 (0.7)	0	78 (29.8)	1 (0.4)	0
RASH	25 (17.2)	1 (0.7)	0	52 (19.8)	2 (0.8)	0
INVESTIGATIONS	60 (41.4)	33 (22.8)	0	124 (47.3)	69 (26.3)	0
ASPARTATE AMINOTRANSFERASE INCREASED	19 (13.1)	14 (9.7)	0	49 (18.7)	33 (12.6)	0
ALANINE AMINOTRANSFERASE INCREASED	20 (13.8)	9 (6.2)	0	43 (16.4)	19 (7.3)	0
AMYLASE INCREASED	9 (6.2)	4 (2.8)	0	28 (10.7)	11 (4.2)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	54 (37.2)	4 (2.8)	0	103 (39.3)	8 (3.1)	0
BACK PAIN	19 (13.1)	2 (1.4)	0	42 (16.0)	4 (1.5)	0
ARTHRALGIA	9 (6.2)	1 (0.7)	0	28 (10.7)	3 (1.1)	0
METABOLISM AND NUTRITION DISORDERS	51 (35.2)	14 (9.7)	0	100 (38.2)	25 (9.5)	0
DECREASED APPETITE	29 (20.0)	2 (1.4)	0	54 (20.6)	2 (0.8)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	53 (36.6)	4 (2.8)	0	98 (37.4)	7 (2.7)	0
COUGH	31 (21.4)	0	0	55 (21.0)	0	0
DYSPNOEA	16 (11.0)	2 (1.4)	0	20 (7.6)	2 (0.8)	0

NERVOUS SYSTEM DISORDERS	36 (24.8)	2 (1.4)	0	70 (26.7)	6 (2.3)	0
HEADACHE	15 (10.3)	1 (0.7)	0	25 (9.5)	2 (0.8)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	29 (20.0)	5 (3.4)	0	57 (21.8)	12 (4.6)	0
ANAEMIA	22 (15.2)	3 (2.1)	0	43 (16.4)	5 (1.9)	0
PSYCHIATRIC DISORDERS	29 (20.0)	2 (1.4)	1 (0.7)	50 (19.1)	2 (0.8)	1 (0.4)
INSOMNIA	15 (10.3)	0	0	27 (10.3)	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	27 (18.6)	10 (6.9)	4 (2.8)	35 (13.4)	16 (6.1)	5 (1.9)
MALIGNANT NEOPLASM PROGRESSION	15 (10.3)	6 (4.1)	4 (2.8)	17 (6.5)	7 (2.7)	5 (1.9)
VASCULAR DISORDERS	14 (9.7)	3 (2.1)	0	35 (13.4)	4 (1.5)	0
HYPERTENSION	8 (5.5)	3 (2.1)	0	24 (9.2)	4 (1.5)	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.5-1 of CA209040 Interim CSR

Table 42: Drug-related Adverse Events by Worst CTC Grade Reported in ≥ 5% of Subjects - All Treated Subjects in the 2L EXP Cohort and ESC + EXP Cohort

System Organ Class (%) Preferred Term (%)	2L EXP Cohort N = 145			ESC + EXP Cohort N = 262		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	109 (75.2)	23 (15.9)	0	199 (76.0)	52 (19.8)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	54 (37.2)	2 (1.4)	0	103 (39.3)	6 (2.3)	0
PRURITUS	27 (18.6)	1 (0.7)	0	54 (20.6)	1 (0.4)	0
RASH	23 (15.9)	1 (0.7)	0	44 (16.8)	2 (0.8)	0
FATIGUE	34 (23.4)	3 (2.1)	0	53 (20.2)	4 (1.5)	0
GASTROINTESTINAL DISORDERS	46 (31.7)	3 (2.1)	0	83 (31.7)	7 (2.7)	0
DIARRHOEA	18 (12.4)	2 (1.4)	0	32 (12.2)	3 (1.1)	0
NAUSEA	11 (7.6)	0	0	20 (7.6)	0	0
DRY MOUTH	8 (5.5)	0	0	16 (6.1)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	49 (33.8)	3 (2.1)	0	75 (28.6)	4 (1.5)	0
FATIGUE	34 (23.4)	3 (2.1)	0	53 (20.2)	4 (1.5)	0
INVESTIGATIONS	31 (21.4)	13 (9.0)	0	67 (25.6)	34 (13.0)	0
ASPARTATE AMINOTRANSFERASE INCREASED	9 (6.2)	5 (3.4)	0	26 (9.9)	14 (5.3)	0
ALANINE AMINOTRANSFERASE INCREASED	10 (6.9)	3 (2.1)	0	24 (9.2)	8 (3.1)	0
AMYLASE INCREASED	4 (2.8)	2 (1.4)	0	19 (7.3)	7 (2.7)	0
LIPASE INCREASED	5 (3.4)	5 (3.4)	0	18 (6.9)	14 (5.3)	0
PLATELET COUNT DECREASED	8 (5.5)	3 (2.1)	0	8 (3.1)	3 (1.1)	0
METABOLISM AND NUTRITION DISORDERS	16 (11.0)	3 (2.1)	0	31 (11.8)	3 (1.1)	0
DECREASED APPETITE	8 (5.5)	1 (0.7)	0	16 (6.1)	1 (0.4)	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.

The overall frequency of AEs (regardless of causality) leading to a dose delay or reduction was 42.4% and 42.1% in the ESC + EXP and 2L EXP Cohorts, respectively.

Late-Emergent Adverse Events

Late emergent drug-related events were defined as drug-related events with an onset > 100 days after last dose of study therapy. In the ESC + EXP Cohort, 1 subject had Grade 1 late-emergent drug-related AEs of increased ALT and increased AST, and 1 subject had a Grade 2 late-emergent drug-related AE of hypothyroidism. In the 2L EXP Cohort, 1 subject had a Grade 2 late-emergent drug-related AE of hypothyroidism.

Serious adverse event / deaths / other significant events

Deaths

As of the 08-Aug-2016 clinical DBL, 38.5% of subjects had died in the ESC + EXP Cohort and 36.6% of subjects had died in the 2L EXP Cohort. Disease progression was the most common cause of death in both cohorts, including deaths occurring within 30 days of last dose and deaths occurring within 100 days of

last dose. No deaths were attributed to study drug toxicity.

Table 43 Death Summary - All Treated Subjects in ESC + EXP Cohort and 2L EXP Cohort

	2L EXP Cohort N = 145	ESC + EXP Cohort N = 262
NUMBER OF SUBJECTS WHO DIED (%)	53 (36.6)	101 (38.5)
PRIMARY REASON FOR DEATH (%)		
DISEASE PROGRESSION	48 (33.1)	91 (34.7)
STUDY DRUG TOXICITY	0	0
UNKNOWN	0	0
OTHER	5 (3.4)	10 (3.8)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	8 (5.5)	9 (3.4)
PRIMARY REASON FOR DEATH (%)		
DISEASE PROGRESSION	6 (4.1)	6 (2.3)
STUDY DRUG TOXICITY	0	0
UNKNOWN	0	0
OTHER	2 (1.4)	3 (1.1)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	29 (20.0)	54 (20.6)
PRIMARY REASON FOR DEATH (%)		
DISEASE PROGRESSION	27 (18.6)	49 (18.7)
STUDY DRUG TOXICITY	0	0
UNKNOWN	0	0
OTHER	2 (1.4)	5 (1.9)

Source: Refer to Table S.6.15 of CA209040 Interim CSR.

The reasons for the deaths classified as 'other' were: gastrointestinal bleeding, cerebral hemorrhage, hepatic failure due to upper GI bleeding probably disease progression, gastrointestinal bleeding, brain hemorrhage, suicide, septic shock, oesophageal variceal bleeding, intracranial hemorrhage and suspect infectious.

Other serious adverse events

The majority of SAEs reported in the ESC + EXP Cohort were considered not related to study drug and most were Grade 3-4.

SAEs were reported in 45.8% of subjects in the ESC + EXP Cohort and 46.9% of subjects in the 2L EXP Cohort (Table 2.3-1). Grade 3-4 SAEs were reported in 30.2% and 27.6% of subjects, respectively.

- In the 2L EXP Cohort, the most frequently reported SAEs were malignant neoplasm progression (10.3%), and pyrexia (3.4%)

Drug-related SAEs were reported in 7.3% of subjects in the ESC + EXP Cohort and 9.0% of subjects in the 2L EXP Cohort (Table 2.3-2). Grade 3-4 SAEs were reported in 4.2% and 4.1% of subjects, respectively.

- In the 2L EXP Cohort, the only drug-related SAEs reported in at least 2 subjects was pneumonitis (1.4%) and infusion related reactions (1.4%)

Table 44: SAEs by Worst CTC Grade Reported in (≥ 1 % of Subjects - All Treated Subjects in the 2L EXP Cohort and ESC + EXP Cohort

System Organ Class (%) Preferred Term (%)	2L EXP Cohort N = 145			ESC + EXP Cohort N = 262		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	68 (46.9)	40 (27.6)	5 (3.4)	120 (45.8)	79 (30.2)	7 (2.7)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	22 (15.2)	10 (6.9)	4 (2.8)	30 (11.5)	15 (5.7)	5 (1.9)
MALIGNANT NEOPLASM PROGRESSION	15 (10.3)	6 (4.1)	4 (2.8)	17 (6.5)	7 (2.7)	5 (1.9)
METASTASES TO CENTRAL NERVOUS SYSTEM	2 (1.4)	1 (0.7)	0	2 (0.8)	1 (0.4)	0
SQUAMOUS CELL CARCINOMA	2 (1.4)	0	0	2 (0.8)	0	0
GASTROINTESTINAL DISORDERS	12 (8.3)	8 (5.5)	0	23 (8.8)	17 (6.5)	1 (0.4)
ASCITES	2 (1.4)	1 (0.7)	0	5 (1.9)	4 (1.5)	0
OESOPHAGEAL VARICES HAEMORRHAGE	2 (1.4)	2 (1.4)	0	4 (1.5)	2 (0.8)	1 (0.4)
ABDOMINAL PAIN	3 (2.1)	2 (1.4)	0	3 (1.1)	2 (0.8)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	14 (9.7)	8 (5.5)	0	19 (7.3)	11 (4.2)	0
PYREXIA	5 (3.4)	1 (0.7)	0	7 (2.7)	1 (0.4)	0
GENERAL PHYSICAL HEALTH DETERIORATION	3 (2.1)	3 (2.1)	0	4 (1.5)	4 (1.5)	0
DISEASE PROGRESSION	2 (1.4)	2 (1.4)	0	2 (0.8)	2 (0.8)	0
INFECTIONS AND INFESTATIONS	11 (7.6)	6 (4.1)	0	17 (6.5)	12 (4.6)	0
PNEUMONIA	3 (2.1)	0	0	3 (1.1)	0	0
BILIARY SEPSIS	2 (1.4)	1 (0.7)	0	2 (0.8)	1 (0.4)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	7 (4.8)	3 (2.1)	0	11 (4.2)	4 (1.5)	0
INFUSION RELATED REACTION	2 (1.4)	0	0	2 (0.8)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (4.1)	3 (2.1)	0	11 (4.2)	6 (2.3)	0
PLEURAL EFFUSION	0	0	0	3 (1.1)	1 (0.4)	0
DYSPNOEA	2 (1.4)	1 (0.7)	0	2 (0.8)	1 (0.4)	0
PNEUMONITIS	2 (1.4)	1 (0.7)	0	2 (0.8)	1 (0.4)	0
METABOLISM AND NUTRITION DISORDERS	8 (5.5)	4 (2.8)	0	10 (3.8)	6 (2.3)	0
DECREASED APPETITE	2 (1.4)	0	0	2 (0.8)	0	0
HYPERGLYCAEMIA	2 (1.4)	2 (1.4)	0	2 (0.8)	2 (0.8)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	4 (2.8)	3 (2.1)	0	6 (2.3)	5 (1.9)	0
BACK PAIN	3 (2.1)	2 (1.4)	0	4 (1.5)	3 (1.1)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (1.4)	2 (1.4)	0	3 (1.1)	2 (0.8)	0
ANAEMIA	2 (1.4)	2 (1.4)	0	3 (1.1)	2 (0.8)	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.3-1 of CA209040 Interim CSR.

Table 45: Drug-related SAEs by Worst CTC Grade Reported in at Least 2 Subjects - All Treated Subjects in the 2L EXP Cohort and ESC + EXP Cohort

System Organ Class (%) Preferred Term (%)	2L EXP Cohort N = 145			ESC + EXP Cohort N = 262		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	13 (9.0)	6 (4.1)	0	19 (7.3)	11 (4.2)	0
INVESTIGATIONS	1 (0.7)	1 (0.7)	0	3 (1.1)	3 (1.1)	0
ALANINE AMINOTRANSFERASE INCREASED	1 (0.7)	1 (0.7)	0	1 (0.4)	1 (0.4)	0
ASPARTATE AMINOTRANSFERASE INCREASED	0	0	0	1 (0.4)	1 (0.4)	0
LIVER FUNCTION TEST INCREASED	0	0	0	1 (0.4)	1 (0.4)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (2.1)	1 (0.7)	0	3 (1.1)	1 (0.4)	0
PNEUMONITIS	2 (1.4)	1 (0.7)	0	2 (0.8)	1 (0.4)	0
DYSPNOEA	1 (0.7)	0	0	1 (0.4)	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.7)	0	0	3 (1.1)	2 (0.8)	0
PEMPHIGOID	0	0	0	1 (0.4)	1 (0.4)	0
PSORIASIS	0	0	0	1 (0.4)	1 (0.4)	0
SKIN DISORDER	1 (0.7)	0	0	1 (0.4)	0	0
GASTROINTESTINAL DISORDERS	2 (1.4)	2 (1.4)	0	2 (0.8)	2 (0.8)	0
COLITIS	1 (0.7)	1 (0.7)	0	1 (0.4)	1 (0.4)	0
DIARRHOEA	1 (0.7)	1 (0.7)	0	1 (0.4)	1 (0.4)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (1.4)	0	0	2 (0.8)	0	0
INFUSION RELATED REACTION	2 (1.4)	0	0	2 (0.8)	0	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.3-3 of CA209040 Interim CSR

Select Adverse Events

Across select AE categories, the majority of events were manageable, with resolution occurring when immune-modulating medications (mostly systemic corticosteroids) were administered.

Some endocrine select AEs, were not considered resolved due to the continuing need for hormone replacement therapy.

The majority of endocrine, gastrointestinal, pulmonary, renal, skin, and hypersensitivity/infusion reactions select AEs reported were Grade 1-2, while most hepatic select AEs reported were Grade 3. Most select AEs reported were considered drug related by the investigator.

The most frequently reported any-grade drug-related select AE categories in the ESC + EXP Cohort were pruritus (20.6%), rash (16.8%), diarrhea (12.2%), increased AST (9.9%), and increased ALT (9.2%). The frequency and type of select AEs reported in the 2L EXP Cohort were similar to those reported in the ESC + EXP Cohort. The most frequently reported any grade drug-related select AE categories in the 2L EXP Cohort were pruritus (18.6%), rash (15.9%), and diarrhea (12.4%).

- **Endocrine Events**

The endocrine select AE category included the following subcategories: adrenal disorders, diabetes, pituitary disorders, and thyroid disorders. For a list of all PTs included in the endocrine select AE category and subcategories.

Endocrine select AEs (all-causality, any grade) were reported in 25 subjects (9.5%) in the ESC + EXP Cohort and 13 subjects (9.0%) in the 2L EXP Cohort .

ESC + EXP Cohort

21 subjects (8.0%) had endocrine select AEs that were considered to be drug-related by the investigator. The most commonly reported drug-related event was hypothyroidism (3.4% of subjects). The majority of the drug-related endocrine events were Grade 1-2, and 1 Grade 3-4 SAE (adrenal insufficiency) was reported. No events led to permanent discontinuation of nivolumab.

The median time to onset of drug-related endocrine AEs was 16.00 weeks.2 subjects were treated with immune-modulating medication for a median duration of 29.43weeks, these events did not resolve at the time of DBL. Overall, 5 of the 21 subjects with drug-related endocrine select AEs resolved; the median time to resolution was not available at the time of DBL.

2L EXP Cohort

10 subjects (6.9%) had endocrine select AEs that were considered to be drug-related by the investigator. The most commonly reported drug-related event was hypothyroidism (3.4% of subjects). All the drug-related endocrine events were Grade 1-2.

The median time to onset of drug-related endocrine AEs was 15.00 weeks. 1 subject was treated with immune-modulating medication for a duration of 22.57 weeks, and the event did not resolve at the time of DBL. Overall, 1 of the 10 subjects with drug-related endocrine select AEs resolved; the time to resolution was not available at the time of DBL.

Table 46: Summary of Drug-related Endocrine Select Adverse Events Reported Up to 30 days After Last Dose – All Treated Subjects in the ESC + EXP Cohort and 2L EXP Cohort

Sub Category (%) Preferred Term (%)	2L EXP Cohort N = 145			ESC + EXP Cohort N = 262		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	10 (6.9)	0	0	21 (8.0)	1 (0.4)	0
THYROID DISORDER	9 (6.2)	0	0	18 (6.9)	0	0
HYPOTHYROIDISM	5 (3.4)	0	0	9 (3.4)	0	0
BLOOD THYROID STIMULATING HORMONE INCREASED	3 (2.1)	0	0	4 (1.5)	0	0
BLOOD THYROID STIMULATING HORMONE DECREASED	1 (0.7)	0	0	2 (0.8)	0	0
HYPERTHYROIDISM	1 (0.7)	0	0	2 (0.8)	0	0
AUTOIMMUNE HYPOTHYROIDISM	0	0	0	1 (0.4)	0	0
AUTOIMMUNE THYROIDITIS	0	0	0	1 (0.4)	0	0
ADRENAL DISORDER	1 (0.7)	0	0	2 (0.8)	1 (0.4)	0
ADRENAL INSUFFICIENCY	0	0	0	1 (0.4)	1 (0.4)	0
SECONDARY ADRENOCORTICAL INSUFFICIENCY	1 (0.7)	0	0	1 (0.4)	0	0
DIABETES	0	0	0	1 (0.4)	0	0
DIABETES MELLITUS	0	0	0	1 (0.4)	0	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.7.1-1 of the CA209040 Interim CSR

- **Gastrointestinal Events**

Gastrointestinal select AEs (all-causality, any grade) were reported in 65 subjects (24.8%) in the ESC + EXP Cohort and 38 subjects (26.2%) in the 2L EXP.

ESC + EXP Cohort

34 subjects (13.0%) had GI select AEs that were considered to be drug-related by the investigator. Most drug-related events were Grade 1-2; 3 subjects (1.1%) had Grade 3-4 drug-related events. No drug-related events led to permanent discontinuation of nivolumab.

The median time to onset of drug-related GI select AEs was 9.14 weeks. 6 subjects were treated with immune-modulating medication for a median duration of 4.00 weeks and 3 subjects had resolution of their events. Overall, 24 of the 34 subjects with drug-related GI select AEs had resolution of their events, with a median time to resolution of 3.71 weeks. 2L EXP Cohort 20 subjects (13.8%) had GI select AEs that were considered to be drug-related by the investigator. Most drug-related events were Grade 1-2; 2 subjects (1.4%) had Grade 3-4 drug-related events. No drug-related events led to permanent discontinuation of nivolumab.

The median time to onset of drug-related GI select AEs was 10.21 weeks. 5 subjects were treated with immune-modulating medication for a median duration of 3.14 weeks and 2 subjects had resolution of their events. Overall, 12 of the 20 subjects with drug-related GI select AEs had resolution of their events, with a median time to resolution of 6.71 weeks.

Table 47: Summary of Drug-related Gastrointestinal Select Adverse Events Reported Up to 30 days After Last Dose - All Treated Subjects in the ESC + EXP Cohort and 2L EXP Cohort

	2L EXP COHORT N = 145			ESC + EXP Cohort N = 262		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	20 (13.8)	2 (1.4)	0	34 (13.0)	3 (1.1)	0
DIARRHOEA	18 (12.4)	2 (1.4)	0	32 (12.2)	3 (1.1)	0
COLITIS	2 (1.4)	1 (0.7)	0	2 (0.8)	1 (0.4)	0
ENTERITIS	1 (0.7)	0	0	1 (0.4)	0	0
FREQUENT BOWEL MOVEMENTS	1 (0.7)	0	0	1 (0.4)	0	0

MedDRA Version: 19.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.7.2-1 of the CA209040 Interim CSR.

- **Hepatic Events**

Hepatic select AEs (all-causality, any grade) were reported in 74 subjects (28.2%) in the ESC + EXP Cohort and 31 subjects (21.4%) in the 2L EXP Cohort. For a list of all PTs included in the hepatic select AE category.

ESC + EXP Cohort

37 subjects (14.1%) subjects had hepatic select AEs considered to be drug-related by the investigator. Most drug-related events were Grade 1-2; 17 subjects (6.5%) had Grade 3-4 drug-related events. 2 (0.8%) subjects discontinued within 30 days of last dose due to drug-related events of increased ALT, increased blood bilirubin, and increased liver function test. One additional subject in the EXP Cohort discontinued due to Grade 3 AST increased more than 30 days after last dose.

The median time to onset of drug-related hepatic events was 5.14 weeks (Table 2.5.3-2). 5 subjects were treated with immune-modulating medication for a median duration of 9.43 weeks and had resolution of the event at the time of DBL. Overall, 24 of the 37 subjects with drug-related hepatic select AEs had resolution of their events, with a median time to resolution of 12 weeks.

2L EXP Cohort

13 subjects (9.0%) had hepatic select AEs considered to be drug related by the investigator. Most drug-related events were Grade 1-2; 6 subjects (4.1%) had Grade 3-4 drug-related events. No drug-related events led to permanent discontinuation of nivolumab within 30 days of last dose.

The median time to onset of drug-related hepatic events was 6.14 weeks. 2 subjects were treated with immune-modulating medication for a median duration of 6.93 weeks and both subjects had resolution of the event at the time of DBL. Overall, 9 of the 13 subjects with drug related hepatic select AEs had resolution of their events, with a median time to resolution of 8.71 weeks.

Table 48: Summary of Drug-related Hepatic Select Adverse Events Reported Up to 30 days After Last Dose – All Treated Subjects in the ESC + EXP Cohort and 2L EXP Cohort

	2L EXP COHORT			ESC + EXP COHORT		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	13 (9.0)	6 (4.1)	0	37 (14.1)	17 (6.5)	0
ASPARTATE AMINOTRANSFERASE INCREASED	9 (6.2)	5 (3.4)	0	26 (9.9)	14 (5.3)	0
ALANINE AMINOTRANSFERASE INCREASED	10 (6.9)	3 (2.1)	0	24 (9.2)	8 (3.1)	0
BLOOD ALKALINE PHOSPHATASE INCREASED	3 (2.1)	0	0	6 (2.3)	0	0
BLOOD BILIRUBIN INCREASED	3 (2.1)	0	0	6 (2.3)	1 (0.4)	0
HYPERBILIRUBINAEMIA	2 (1.4)	0	0	3 (1.1)	0	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED	0	0	0	1 (0.4)	1 (0.4)	0
HEPATITIS	0	0	0	1 (0.4)	1 (0.4)	0
LIVER DISORDER	0	0	0	1 (0.4)	0	0
LIVER FUNCTION TEST INCREASED	0	0	0	1 (0.4)	1 (0.4)	0

MedDRA Version: 19.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.7.3-1 of the CA209040 Interim CSR.

– **Pulmonary Events**

Pulmonary select AEs (all-causality, any grade) were reported in 3 subjects (1.1%) in the ESC + EXP Cohort and 2 subjects (1.4%) in the 2L EXP Cohort.

ESC + EXP Cohort

3 subjects (1.1%) had pulmonary select AEs considered to be drug-related by the investigator. All drug-related events were pneumonitis. For 1 subject the event was considered a Grade 3-4 event and led to permanent discontinuation of nivolumab.

The median time to onset of drug-related pulmonary events was 11.43 weeks. 2 subjects were treated with immune-modulating medication for a median duration of 17.93 weeks, and one of the subjects had resolution of the event. Overall, 2 of the 3 subjects with drug-related pulmonary select AEs had resolution of their events, with a median time to resolution of 7.14 weeks.

2L EXP Cohort

2 subjects (1.4%) had pulmonary select AEs considered to be drug related by the investigator. All drug-related events were pneumonitis. For 1 subject the event was considered a Grade 3-4 event and led to permanent discontinuation of nivolumab.

The median time to onset of drug-related pulmonary events was 6.36 weeks. 2 subjects were treated with immune-modulating medication for a median duration of 17.93 weeks, and 1 subject had resolution of the event. Overall, 1 of the 2 subjects with drug-related pulmonary select AEs had resolution of their events; the median time to resolution was not available at the time of DBL.

Table 49: Summary of Drug-related Pulmonary Select Adverse Events Reported Up to 30 days After Last Dose - All Treated Subjects in the2L EXP Cohort and ESC + EXP Cohort

	2L EXP COHORT N=145			ESC + EXP COHORT N=262		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	2 (1.4)	1 (0.7)	0	3 (1.1)	1 (0.4)	0
PNEUMONITIS	2 (1.4)	1 (0.7)	0	3 (1.1)	1 (0.4)	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.7.4-1 in the CA209040 Interim CSR.

– **Renal Events**

Renal select AEs (all-causality, any grade) were reported in 9 subjects (3.4%) in the ESC + EXP Cohort

and 3 subjects (2.1%) in the 2L EXP Cohort.

ESC + EXP Cohort

1 subject (0.4%) had a Grade 1-2 renal select AE of increased blood creatinine, considered to be drug related by the investigator. The subject did not discontinue from the study due to the AE.

The median time to onset of drug-related renal events was 47.14 weeks. The 1 subject with the drug-related renal select AE was not treated with immune-modulating medication or high-dose corticosteroids, and had resolution of their event, with a time to resolution of 2.71 weeks.

Table 50: Summary of Drug-related Renal Select Adverse Events Reported Up to 30 days After Last Dose - All Treated Subjects in the 2L EXP Cohort and ESC + EXP Cohort

	2L EXP COHORT N=145			ESC + EXP COHORT N=262		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	0	0	0	1 (0.4)	0	0
BLOOD CREATININE INCREASED	0	0	0	1 (0.4)	0	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.7.5-1 of the CA209040 Interim CSR.

- **Skin Events**

Skin select AEs (all-causality, any grade) were reported in 120 subjects (45.8%) in the ESC+ EXP Cohort and 59 subjects (40.7%) in the 2L EXP Cohort.

ESC + EXP Cohort

91 subjects (34.7%) had skin select AEs considered to be drug related by the investigator. The most frequently reported drug-related events were pruritus and rash. There was no event of toxic epidermal necrolysis reported. The majority of the drug-related events were Grade 1-2, 1 Grade 3 AE and 1 Grade 1-2 AE of psoriasis led to permanent discontinuation of nivolumab.

The median time to onset of drug-related skin select AEs was 3.57 weeks. 40 subjects were treated with immune-modulating medication (2 received a corticosteroid at a dose ≥ 40 mg) for a median duration of 18.64 weeks, and 24 of these subjects had resolution of the event. Overall, 57 of 91 subjects with skin select AEs had resolution of their events with a median time to resolution of 15.14 weeks.

2L EXP Cohort

45 subjects (31.0%) had skin select AEs considered to be drug related by the investigator. The most frequently reported drug-related events were pruritus and rash. There was no event of toxic epidermal necrolysis reported. The majority of the drug-related events were Grade 1-2 and none led to permanent discontinuation of nivolumab.

The median time to onset of drug-related skin select AEs was 2.57 weeks. 17 subjects were treated with immune-modulating medication (1 received a corticosteroid at a dose ≥ 40 mg) for a median duration of 17.86 weeks, and 9 of these subjects had resolution of the event. Overall, 24 of 45 subjects with skin select AEs had resolution of their events with a median time to resolution of 17.86 weeks.

Table 51: Summary of Drug-related skin adverse events - All Treated Subjects in the 2L EXP Cohort and ESC + EXP Cohort

	2L EXP COHORT N = 145			ESC + EXP COHORT N = 262		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	45 (31.0)	2 (1.4)	0	91 (34.7)	5 (1.9)	0
PRURITUS	27 (18.6)	1 (0.7)	0	54 (20.6)	1 (0.4)	0
RASH	23 (15.9)	1 (0.7)	0	44 (16.8)	2 (0.8)	0
RASH MACULO-PAPULAR	4 (2.8)	0	0	8 (3.1)	0	0
PSORIASIS	0	0	0	3 (1.1)	1 (0.4)	0
RASH PRURITIC	0	0	0	3 (1.1)	0	0
ECZEMA	1 (0.7)	0	0	2 (0.8)	0	0
ERYTHEMA	1 (0.7)	0	0	2 (0.8)	1 (0.4)	0
RASH PAPULAR	1 (0.7)	0	0	2 (0.8)	0	0
SKIN EXFOLIATION	2 (1.4)	0	0	2 (0.8)	0	0
DERMATITIS	0	0	0	1 (0.4)	0	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	0	0	0	1 (0.4)	0	0
RASH ERYTHEMATOUS	0	0	0	1 (0.4)	0	0
SKIN HYPOPIGMENTATION	0	0	0	1 (0.4)	0	0

MedDRA Version: 19.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.7.6-1 of the CA209040 Interim CSR.

- **Hypersensitivity / Infusion Reactions**

Hypersensitivity/infusion reactions (all-causality, any grade) were reported in 11 subjects (4.2%) in the ESC + EXP Cohort and 5 subjects (3.4%) in the 2L EXP Cohort.

ESC + EXP Cohort

11 subjects (4.2%) had hypersensitivity/infusion reactions select AEs considered to be drug-related by the investigator. All were Grade 1-2, and none led to permanent discontinuation of nivolumab.

The median time to onset of drug-related hypersensitivity/infusion reactions select AEs was 0.29 weeks. 4 subjects were treated with immune-modulating medication for a median duration of 0.21 weeks, and 3 of these subjects had resolution of the event. All subjects with hypersensitivity/infusion reactions select AEs had resolution of their events with a median time to resolution of 0.14 weeks.

2L EXP Cohort

5 subjects (3.4%) had hypersensitivity/infusion reactions select AEs considered to be drug-related by the investigator. All were Grade 1-2, and none led to permanent discontinuation of nivolumab.

The median time to onset of drug-related hypersensitivity/infusion reactions select AEs was 0.29 weeks. 2 subjects were treated with immune-modulating medication for a median duration of 0.14 weeks, and both subjects had resolution of the event. Overall, all subjects with hypersensitivity/infusion reactions select AEs had resolution of their events with a median time to resolution of 0.29 weeks.

Table 52: Summary of Drug-related Hypersensitivity / Infusion Reactions Reported Up to 30 days After Last Dose - All Treated Subjects in the 2L EXP Cohort and ESC + EXP Cohort

	2L EXP COHORT N=145			ESC + EXP COHORT N=262		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	5 (3.4)	0	0	11 (4.2)	0	0
INFUSION RELATED REACTION	4 (2.8)	0	0	9 (3.4)	0	0
HYPERSENSITIVITY	1 (0.7)	0	0	3 (1.1)	0	0

MedDRA Version: 19.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.7.7-1 of the CA209040 Interim CSR.

Other Events of Special Interest

OESI included the following categories: demyelination, encephalitis, Guillain-Barré syndrome, myasthenic syndrome, pancreatitis, and uveitis.

2 subjects had an OESI reported between first dose and 100 days after last dose of study therapy (extended follow-up) (both events were pancreatitis).The median time to onset was 35.43 weeks. Neither subject was treated with immune-modulating medication.

- CA209040-28-199: EXP uninfected naive/intolerant subject with Grade 3 pancreatitis event was considered drug related by the investigator, and drug was interrupted but did not lead to permanent discontinuation of nivolumab. The subject was not treated with high dose corticosteroids. At the time of DBL, the event was not resolved.
- CA209040-49-192: 2L EXP HBV-infected subject with Grade 3 pancreatitis event during the follow-up period, was considered unrelated to drug by the investigator, and the event resolved in 1.6 weeks.

Laboratory findings Abnormalities in laboratory results, on haematology parameters, kidney function tests, and electrolytes as observed in nivolumab patients were primarily CTC grade 1 or 2. Abnormalities in hepatic parameters (all abnormal parameters were elevations) were reported in the ESC + EXP cohort as well as in the 2L EXP cohort, and these were considered not extra-ordinary in view of the disease HCC in the patients studied in CA209040 (see Table 52). The elevations in AST amylase and lipase have been mentioned before. The elevations do not constitute a special alarm, this also in view of the malignancy HCC.

Table 53: Overall laboratory aberrations in response to nivolumab as found in CA209040 and in relation to use of nivolumab for other tumour-indications.

	CA209040 2L EXP Cohort n = 145 treated subjects			CA209040 ESC + EXP Cohort n = 262 treated subjects				Pooled Nivolumab Monotherapy Population in Other Tumor Types (excluding HCC) n = 2227 treated subjects[a]		
ADR[b, c, d]	No. of Subjects	% of subjects	Designation of frequency	No. of Subjects	% of subjects	Designation of frequency	Appendix Source Information for CA209040	No. of Subjects	% of subjects	Design-ation of frequency
Increased AST	84/141	59.6	Very common	156/258	60.5	Very common	2LHCC.1.9a.SCS	570/2151	26.5	Very common
Increased ALT	66/141	46.8	Very common	121/257	47.1	Very common	2LHCC.1.9a.SCS	456/2160	21.1	Very common
Increased alkaline phosphatase	60/142	42.3	Very common	113/258	43.8	Very common	2LHCC.1.9a.SCS	520/2148	24.2	Very common
Increased lipase	50/139	36.0	Very common	107/254	42.1	Very common	2LHCC.1.9a.SCS	169/871	19.4	Very common
Increased amylase	40/130	30.8	Very common	78/243	32.1	Very common	2LHCC.1.9a.SCS	100/752	13.3	Very common
Increased creatinine	24/141	17.0	Very common	46/258	17.8	Very common	2LHCC.1.9a.SCS	430/2167	19.8	Very common
lymphocyte absolute (lymphopaenia)	73/141	51.8	Very common	129/256	50.4	Very common	2LHCC.1.9a.SCS	881/2155	40.9	Very common
leukocyte absolute (leucopenia)	36/142	25.4	Very common	70/257	27.2	Very common	2LHCC.1.9a.SCS	316/2175	14.5	Very common
Platelet count (thrombocytopenia	51/141	36.2	Very common	79/256	30.9	Very common	2LHCC.1.9a.SCS	274/2169	12.6	Very common
Haemoglobin (anemia)	67/141	47.5	Very common	113/256	44.1	Very common	2LHCC.1.9a.SCS	772/2169	35.6	Very common
Hypercalcaemia	9/141	6.4	Common	16/257	6.2	Common	2LHCC.1.9a.SCS	227/2076	10.9	Very common
Hyperkalaemia	25/141	17.7	Very common	40/258	15.5	Very common	2LHCC.1.9a.SCS	396/2112	18.8	Very common
Hypokalaemia	16/141	11.3	Very common	32/258	12.4	Very common	2LHCC.1.9a.SCS	223/2112	10.6	Very common
Hypo-magnesaemia	17/140	12.1	Very common	36/255	14.1	Very common	2LHCC.1.9a.SCS	271/1878	14.4	Very common
Hyponatraemia	56/141	39.7	Very common	99/258	38.4	Very common	2LHCC.1.9a.SCS	575/2113	27.2	Very common
Increased total bilirubin	48/142	33.8	Very common	88/258	34.1	Very common	2LHCC.1.9a.SCS	177/2157	8.2	Common
Absolute neutrophil count (neutropenia)	26/141	18.4	Very common	57/256	22.3	Very common	2LHCC.1.9a.SCS	241/2158	11.2	Very common
Hypermagnesaemia	7/140	5.0	Common	12/255	4.7	Common	2LHCC.1.9a.SCS	82/1878	4.4	Common
Hypernatraemia	4/141	2.8	Common	8/258	3.1	Common	2LHCC.1.9a.SCS	107/2113	5.1	Common
Hypocalcaemia	40/141	28.4	Very common	74/257	28.8	Very common	2LHCC.1.9a.SCS	358/2076	17.2	Very common
Weight decreased	2	1.4	Common	7	2.7	Common	2LHCC.1.4-SCS	49	2.2	Common

The laboratory abnormalities as reported from study CA209040 show particularly elevation of hepatic parameters, as well as haematology parameters. Differences with aberrant laboratory markers in other indications for nivolumab are noted. Although the abnormalities in hepatic enzyme levels/functions can largely be explained by disease (and disease progression) itself, the vulnerability of hepatic tissue (including the hepatic haematopoietic tissues) may contribute to an explanation for the aberrations observed in CA209040. Also the nivolumab induced anti-cancer immunology by which anti-HCC reaction can be induced/strengthened may be responsible for the differences in laboratory parameters between the HCC indication and the other tumour types for which nivolumab is registered. Also in HCC a RCT

would best demonstrate the contribution of nivolumab-treatment in the aberrant laboratory parameters with hepatic/hepatobiliary involvement.

Safety in special populations

The frequencies of all-causality and drug-related AEs in subgroups of gender, race, age, and region were similar between the ESC + EXP Cohort and the 2L EXP Cohort. Small numerical differences in frequencies of AEs are of limited interpretability due to low sample sizes and event rates, and do not alter the overall safety profile of nivolumab in these subgroups.

Safety by age in Study CA209040

In CA209040, the frequency of total AEs, AEs leading to discontinuation, and AEs by MedDRA High-level Group Term (HLGT)/SMQs/SOC by age group are presented in Tables below. Interpretation is limited by the small number of subjects in the 75 to 84 years of age subgroup (n = 16 and n = 31 in the EXP + ESC and 2L EXP Cohorts, respectively), and that there were no subjects ≥ 85 years of age.

Table 54: Summary of safety by age group - Study CA209040

Treatment Group: Exp Post Sorafenib All N = 145	Age Group (Years)				
MedDRA Terms (%)	< 65 N = 81	65-74 N = 48	75-84 N = 16	>=85 N = 0	Total N = 145
TOTAL SUBJECTS WITH AN EVENT	81 (100.0)	47 (97.9)	16 (100.0)	0	144 (99.3)
SERIOUS AE - TOTAL	41 (50.6)	20 (41.7)	7 (43.8)	0	68 (46.9)
FATAL	11 (13.6)	3 (6.3)	0	0	14 (9.7)
HOSPITALIZATION/PROLONGATION	39 (48.1)	17 (35.4)	6 (37.5)	0	62 (42.8)
LIFE-THREATENING	0	1 (2.1)	1 (6.3)	0	2 (1.4)
CANCER	1 (1.2)	0	1 (6.3)	0	2 (1.4)
DISABILITY/INCAPACITY	0	0	0	0	0
IMPORTANT MEDICAL EVENT	1 (1.2)	2 (4.2)	1 (6.3)	0	4 (2.8)
AE LEADING TO DISCONTINUATION	10 (12.3)	4 (8.3)	1 (6.3)	0	15 (10.3)
PSYCHIATRIC DISORDERS	19 (23.5)	8 (16.7)	2 (12.5)	0	29 (20.0)
NERVOUS SYSTEM DISORDERS	15 (18.5)	17 (35.4)	4 (25.0)	0	36 (24.8)
ACCIDENT AND INJURIES	3 (3.7)	8 (16.7)	3 (18.8)	0	14 (9.7)
CARDIAC DISORDERS	4 (4.9)	5 (10.4)	2 (12.5)	0	11 (7.6)
VASCULAR DISORDERS	6 (7.4)	6 (12.5)	2 (12.5)	0	14 (9.7)
CEREBROVASCULAR DISORDERS	0	0	0	0	0
INFECTIONS AND INFESTATIONS	33 (40.7)	14 (29.2)	8 (50.0)	0	55 (37.9)
ANTICHOLINERGIC SYNDROME	27 (33.3)	18 (37.5)	6 (37.5)	0	51 (35.2)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	6 (7.4)	9 (18.8)	3 (18.8)	0	18 (12.4)

Treatment Group: Esc + Exp All N = 262	Age Group (Years)				
MedDRA Terms (%)	< 65 N = 142	65-74 N = 89	75-84 N = 31	>=85 N = 0	Total N = 262
TOTAL SUBJECTS WITH AN EVENT	142 (100.0)	88 (98.9)	31 (100.0)	0	261 (99.6)
SERIOUS AE - TOTAL	65 (45.8)	39 (43.8)	16 (51.6)	0	120 (45.8)
FATAL	12 (8.5)	4 (4.5)	1 (3.2)	0	17 (6.5)
HOSPITALIZATION/PROLONGATION	62 (43.7)	35 (39.3)	12 (38.7)	0	109 (41.6)
LIFE-THREATENING	2 (1.4)	1 (1.1)	2 (6.5)	0	5 (1.9)
CANCER	1 (0.7)	1 (1.1)	2 (6.5)	0	4 (1.5)
DISABILITY/INCAPACITY	0	0	0	0	0
IMPORTANT MEDICAL EVENT	2 (1.4)	2 (2.2)	1 (3.2)	0	5 (1.9)
AE LEADING TO DISCONTINUATION	16 (11.3)	9 (10.1)	2 (6.5)	0	27 (10.3)
PSYCHIATRIC DISORDERS	32 (22.5)	15 (16.9)	3 (9.7)	0	50 (19.1)
NERVOUS SYSTEM DISORDERS	36 (25.4)	28 (31.5)	6 (19.4)	0	70 (26.7)
ACCIDENT AND INJURIES	9 (6.3)	15 (16.9)	5 (16.1)	0	29 (11.1)
CARDIAC DISORDERS	8 (5.6)	8 (9.0)	4 (12.9)	0	20 (7.6)
VASCULAR DISORDERS	14 (9.9)	17 (19.1)	4 (12.9)	0	35 (13.4)
CEREBROVASCULAR DISORDERS	0	0	0	0	0
INFECTIONS AND INFESTATIONS	51 (35.9)	30 (33.7)	13 (41.9)	0	94 (35.9)
ANTICHOLINERGIC SYNDROME	47 (33.1)	34 (38.2)	9 (29.0)	0	90 (34.4)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	12 (8.5)	17 (19.1)	5 (16.1)	0	34 (13.0)

IMMUNOGENICITY

The incidence of nivolumab ADA in subjects treated with 3 mg/kg Q2W was 26.7%. ADA did not appear to have an effect on the safety of nivolumab in the ESC or EXP Cohorts. Narratives for the 2 neutralizing ADA positive subjects summarizing safety data are provided in Appendix 7.4A of the CA209040 Interim CSR.

Effect of ADA on nivolumab safety:

- 3 of 67 (4.5%) ADA positive and 8 of 180 (4.4%) ADA negative subjects experienced AEs in the hypersensitivity/infusion reaction category (refer to Table S.7.11 of the CA209040SCR). These findings suggest that ADA occurrence did not impact safety.

Discontinuation due to adverse events

The majority of AEs leading to discontinuation reported in the ESC + EXP Cohort were Grade 3-4 and considered not related to study drug. The frequency of AEs leading to discontinuation (regardless of causality and drug-related) reported in the 2L EXP Cohort was comparable to that reported in the ESC + EXP Cohort.

AEs leading to discontinuation were reported in 27 subjects (10.3%) in the ESC + EXP Cohort and 15 subjects (10.3%) in the 2L EXP Cohort. Grade 3-4 AEs leading to discontinuation were reported in 6.5% and 5.5% of subjects in the ESC + EXP and 2L EXP Cohorts, respectively.

- In the 2L EXP Cohort, AEs leading to discontinuation reported in at least 2 subjects included malignant neoplasm progression (4, 2.8%), metastases to central nervous system (2, 1.4%), and ascites (2, 1.4%).

Drug-related AEs leading to discontinuation were reported in 2.7% of subjects in the ESC + EXP Cohort and 2.1% of subjects in the 2L EXP Cohort (Table 2.4-2). Grade 3-4 drug-related AEs leading to discontinuation were reported in 1.5% and 1.4% of subjects in the ESC + EXP and 2L EXP Cohorts, respectively.

– In the 2L EXP Cohort, no drug-related AEs leading to discontinuation were reported in 2 or more subjects.

Table 55: Adverse Events Leading to Discontinuation by Worst CTC Grade Reported in at Least 2 Subjects – All Treated Subjects in the 2L EXP Cohort and ESC + EXP Cohort

System Organ Class (%) Preferred Term (%)	2L EXP Cohort N = 145			ESC + EXP Cohort N = 262		
	Any Grade	Grade 3–4	Grade 5	Any Grade	Grade 3–4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	15 (10.3)	8 (5.5)	1 (0.7)	27 (10.3)	17 (6.5)	1 (0.4)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	6 (4.1)	3 (2.1)	1 (0.7)	8 (3.1)	5 (1.9)	1 (0.4)
MALIGNANT NEOPLASM PROGRESSION	4 (2.8)	2 (1.4)	1 (0.7)	5 (1.9)	3 (1.1)	1 (0.4)
METASTASES TO CENTRAL NERVOUS SYSTEM	2 (1.4)	1 (0.7)	0	2 (0.8)	1 (0.4)	0
GASTROINTESTINAL DISORDERS	4 (2.8)	1 (0.7)	0	7 (2.7)	3 (1.1)	0
ASCITES	2 (1.4)	0	0	2 (0.8)	0	0
STOMATITIS	1 (0.7)	0	0	2 (0.8)	0	0
INVESTIGATIONS	2 (1.4)	1 (0.7)	0	7 (2.7)	6 (2.3)	0
ALANINE AMINOTRANSFERASE INCREASED	0	0	0	4 (1.5)	4 (1.5)	0
ASPARTATE AMINOTRANSFERASE INCREASED	1 (0.7)	1 (0.7)	0	3 (1.1)	3 (1.1)	0
BLOOD BILIRUBIN INCREASED	0	0	0	3 (1.1)	1 (0.4)	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.4-1 of CA209040 Interim CSR

Table 56: Drug-related Adverse Events Leading to Discontinuation by Worst CTC Grade - All Treated Subjects in the 2L EXP Cohort and ESC + EXP Cohort

System Organ Class (%) Preferred Term (%)	2L EXP Cohort N = 145			ESC + EXP Cohort N = 262		
	Any Grade	Grade 3–4	Grade 5	Any Grade	Grade 3–4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	3 (2.1)	2 (1.4)	0	7 (2.7)	4 (1.5)	0
GASTROINTESTINAL DISORDERS	1 (0.7)	0	0	2 (0.8)	0	0
STOMATITIS	1 (0.7)	0	0	2 (0.8)	0	0
INVESTIGATIONS	0	0	0	2 (0.8)	2 (0.8)	0
ALANINE AMINOTRANSFERASE INCREASED	0	0	0	2 (0.8)	2 (0.8)	0
BLOOD BILIRUBIN INCREASED	0	0	0	1 (0.4)	0	0
LIVER FUNCTION TEST INCREASED	0	0	0	1 (0.4)	1 (0.4)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.7)	1 (0.7)	0	1 (0.4)	1 (0.4)	0
POLYARTHRITIS	1 (0.7)	1 (0.7)	0	1 (0.4)	1 (0.4)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.7)	1 (0.7)	0	1 (0.4)	1 (0.4)	0
PNEUMONITIS	1 (0.7)	1 (0.7)	0	1 (0.4)	1 (0.4)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0	0	1 (0.4)	0	0
PSORIASIS	0	0	0	1 (0.4)	0	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table 8.4-2 of CA209040 Interim CSR

Updated safety information, using the 29-Nov-2016 clinical DBL, is reported for all treated subjects (N = 262) and 2L EXP subjects based on a 30-day window after last dose of study treatment for Study CA209040.

At the time of the updated clinical DBL, the majority of patients had either progressed or died and a minority continued on nivolumab treatment (2L EXP Cohort on treatment patients: N = 29, 20.0% and ESC+EXP Cohort on treatment patients: N = 49, 18.7%).

Table 57: Summary of Updated Safety Results (Based on 29-Nov-2016 Clinical DBL and 12-Dec-2016 BICR DBL)

	Number (%) Subjects			
	2L EXP Cohort N = 145		ESC + EXP All N = 262	
DEATHS	65 (44.8)		116 (44.3)	
WITHIN 30 DAYS OF LAST DOSE	8 (5.5)		9 (3.4)	
WITHIN 100 DAYS OF LAST DOSE	29 (20.0)		54 (20.6)	
DUE TO STUDY DRUG TOXICITY	1 (0.7)		1 (0.4)	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
ALL CAUSALITY SAEs	71 (49.0)	43 (29.7)	125 (47.7)	84 (32.1)
DRUG-RELATED SAEs	13 (9.0)	6 (4.1)	20 (7.6)	12 (4.6)
ALL CAUSALITY AEs LEADING TO DC	16 (11.0)	9 (6.2)	29 (11.1)	18 (6.9)
DRUG-RELATED AEs LEADING TO DC	3 (2.1)	2 (1.4)	8 (3.1)	4 (1.5)
ALL-CAUSALITY AEs	144 (99.3)	71 (49.0)	261 (99.6)	142 (54.2)
Most Frequent AEs (≥ 20% of Any Grade in either treatment group)				
DIARRHOEA	39 (26.9)	2 (1.4)	66 (25.2)	4 (1.5)
ABDOMINAL PAIN	35 (24.1)	5 (3.4)	51 (19.5)	6 (2.3)
FATIGUE	52 (35.9)	4 (2.8)	93 (35.5)	5 (1.9)
PRURITUS	41 (28.3)	1 (0.7)	81 (30.9)	1 (0.4)
DECREASED APPETITE	31 (21.4)	2 (1.4)	56 (21.4)	2 (0.8)
COUGH	32 (22.1)	0	56 (21.4)	0
DRUG-RELATED AEs	108 (74.5)	24 (16.6)	200 (76.3)	55 (21.0)
Most Frequent Drug-related AEs (≥15% of Any Grade in either treatment group)				
FATIGUE	35 (24.1)	3 (2.1)	55 (21.0)	4 (1.5)
PRURITUS	27 (18.6)	1 (0.7)	55 (21.0)	1 (0.4)
RASH	23 (15.9)	1 (0.7)	46 (17.6)	2 (0.8)
ALL CAUSALITY SELECT AES, BY CATEGORY				
ENDOCRINE	14 (9.7)	0	27 (10.3)	2 (0.8)
GASTROINTESTINAL	39 (26.9)	2 (1.4)	66 (25.2)	4 (1.5)
HEPATIC	31 (21.4)	21 (14.5)	76 (29.0)	45 (17.2)
PULMONARY	2 (1.4)	1 (0.7)	3 (1.1)	1 (0.4)
RENAL	4 (2.8)	1 (0.7)	10 (3.8)	1 (0.4)
SKIN	60 (41.4)	2 (1.4)	122 (46.6)	5 (1.9)
HYPERSENSITIVITY/INFUSION REACTIONS	5 (3.4)	0	11 (4.2)	0
DRUG-RELATED SELECT AES, BY CATEGORY				
ENDOCRINE	12 (8.3)	0	24 (9.2)	2 (0.8)
GASTROINTESTINAL	22 (15.2)	2 (1.4)	36 (13.7)	3 (1.1)
HEPATIC	12 (8.3)	5 (3.4)	37 (14.1)	17 (6.5)
PULMONARY	2 (1.4)	1 (0.7)	3 (1.1)	1 (0.4)
RENAL	1 (0.7)	0	2 (0.8)	0
SKIN	44 (30.3)	2 (1.4)	92 (35.1)	5 (1.9)
HYPERSENSITIVITY/INFUSION REACTIONS	5 (3.4)	0	11 (4.2)	0

MedDRA version 19.1; CTC version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Table 58: Summary of Safety (Regardless of Causality) Across Etiologic Subtypes in the ESC and EXP Cohorts

	No. of Subjects (%)				
	N	Deaths	SAEs	All AEs	AEs leading to discontinuation
ESC Cohort	**48**	**31 (64.6)**	**22 (45.8)**	**48 (100.0)**	**3 (6.3)**
Uninfected	23	17 (73.9)	8 (34.8)	23 (100.0)	2 (8.7)
HCV	10	3 (30.0)	4 (40.0)	10 (100.0)	0
HBV	15	10 (66.7)	10 (66.7)	15 (100.0)	1 (6.7)
EXP Cohort	**214**	**85 (39.7)**	**103 (48.1)**	**213 (99.5)**	**26 (12.1)**
Uninfected Naive/Intolerant	56	14 (25.0)	28 (50.0)	56 (100.0)	6 (10.7)
Uninfected progressor	57	31 (54.4)	27 (47.4)	56 (98.2)	7 (12.3)
HCV	50	17 (34.0)	27 (54.0)	50 (100.0)	9 (18.0)
HBV	51	23 (45.1)	21 (41.2)	51 (100.0)	4 (7.8)
ESC+EXP	**262**	**116 (44.3)**	**125 (47.7)**	**261 (99.6)**	**29 (11.1)**
Uninfected	136	62 (45.6)	63 (46.3)	135 (99.3)	15 (11.0)
HCV	60	20 (33.3)	31 (51.7)	60 (100.0)	9 (15.0)
HBV	66	33 (51.5)	31 (47.0)	66 (100.0)	5 (7.6)

Overall, the updated safety profile remains in line with that previously seen. The updated analysis captures up to 4 months of additional follow-up, analyses of adverse events (AEs) and related AEs by drug exposure time period show a safety profile consistent with the previously reported. No differences in drug-related AEs leading to discontinuation were observed within each aetiologic subtype.

Post marketing experience

Nivolumab was first approved on 04-Jul-2014 in Japan for unresectable melanoma and has since been approved in multiple countries, including the US and in the EU, and for other indications. Based on pharmacovigilance activities conducted by BMS Global Pharmacovigilance and Epidemiology, review of postmarketing safety data is consistent with, and confirms the clinical trial safety data for nivolumab. The safety profile of nivolumab in the postmarketing setting remains favourable and similar to the profile established during clinical trials. To date, no new significant safety concerns have been identified based on global postmarketing reports.

Postmarketing data for nivolumab are subject to continued active pharmacovigilance monitoring and are reported as per applicable post-marketing safety reporting requirements, as well as periodically to global health authorities.

2.5.1. Discussion on clinical safety

For the purpose this variation, the full safety dataset consist of 262 patients (ESC+EXP Cohort) who received at least one dose of nivolumab in the dose escalation or extension cohorts of trial CA209040. Target population of the proposed indication is however the subset of 2L EXP cohort of 145 patients that received nivolumab at a dose of 3 mg/Kg Q2W and were either intolerant or progressors to sorafenib.

At the date of the clinical database lock (8-Aug-2016), the majority of patients had either progressed or died and a minority continued on nivolumab treatment (2L EXP cohort on treatment patients: n=36, 24.8%) (ESC+EXP cohort on treatment patients: n=36, 24.8%). The Applicant should present an update on relevant safety data (e.g. deaths, SAEs, and selected AEs) at the time of efficacy data update (OC).

The main reason for not continuing in the treatment period was disease progression (66.2%2L EXP; 66.4% ESC+EXP), followed by study drug toxicity and AEs unrelated to study drug (same percentage for each 2.8%2L EXP; 3.4% ESC+EXP).

The median duration of study therapy was 4.4 months in the ESC+EXP cohort and 5.26 months in the 2L EXP cohort.
The majority of patients received over 90% of the planned dose intensity and did not require an infusion interruption or infusion rate decreased.
Dose delays were reported by 43.4% of patients in the ESC+EXP cohort and 43.5% in the 2L EXP cohort. The most common reason for the delay was "AE" (26.7% 2L EXP; 36.8% ESC+EXP), followed by "other reasons" (33.7% 2L EXP; 30.3% ESC+EXP), and "not reported" (39.6% 2L EXP; 33.0% ESC+EXP).

99.3% and 99.6% of patients in the 2L EXP and ESC+EXP respectively reported AEs of which 75.2% and 76.0% respectively were considered as TEAEs. The frequency of all-causality any-grade AEs, as observed in 99.3% of patients treated with nivolumab in CA209040, could, as a consequence of the design of this uncontrolled study, not be compared with the safety profile of other 2L therapy (for instance doctor's choice). This constitutes a problem by design.

The most common treatment-related AEs for the nivolumab-treated patients were the same and with similar rate in both cohorts: fatigue (23.4%2L EXP; 20.2% ESC+EXP), pruritus (18.6%2L EXP; 20.6% ESC+EXP), rash (15.9% 2L EXP; 16.8% ESC+EXP), and diarrhoea (12.4% 2L EXP; 12.2% ESC+EXP). Most of them were mild-moderate in severity.

The most common Grade 3≥ TEAEs were AST increased (3.4% 2L EXP; 5.3% ESC+EXP) and lipase increased (3.4% 2L EXP; 5.3% ESC+EXP). In general, the overall safety profile in the HCC does not differ from that observed in other indications.

Regarding laboratory parameters as AE in the context of CA209040, the hepatic laboratory parameter elevations were noted. In particular ATP lipase as well as amylase activity appeared risen. This phenomenon remains largely unexplained albeit that (anti-)HCC effects can be responsible for more profound release of hepatic enzymes (**OC**). (It is noted that also the patients with HCC that are treated with sorafenib also show elevated hepatic laboratory parameters).

Selected AEs
As with other authorized indications, selected AEs were more frequently reported in the skin and GI SOCs together with Hepatic SOC within this indication. Most of them were of mild-moderate intensity. In general, the observed profile of selected AEs is pretty similar to that observed in other indications.
The majority of endocrine, GI, pulmonary, renal, skin and hypersensitivity/infusion reactions were of mil-moderate severity whereas most hepatic select AEs were grade 3 (mostly ALT and AST increased). ALT and AST elevations are criteria for dose interruptions and discontinuations.

SAEs and deaths

SAEs (all causalities) were reported in approximately 46.9% of patients in the 2L-EXP cohort and 45.8% in the ESC+EXP cohort, with 27.6% and 30.4% of patients reporting grade 3-4 SAEs respectively. There were five grade 5 SAEs, in the 2l-EXP cohort4 of them due to malignant neoplasm progression.
Apparently 30-40% of the patients included in CA209040 encountered serious adverse events that were considered by the applicant as not drug-related. The applicant is asked to explain this high number of SAE as these are claimed to be non-related to nivolumab. This particularly in view of the fact that CA209040 is a non-controlled study (**OC**).

No deaths were attributed to study drug toxicity. At the time of the data cut- off, 53 subjects (36.6%) had died in the 2l-Ext cohort, most of them due to disease progression and 5 patients due to "other" reasons includinggastrointestinal bleeding, cerebral haemorrhage, hepatic failure due to upper GI bleeding

probably disease progression, gastrointestinal bleeding, brain haemorrhage, suicide, septic shock, oesophageal variceal bleeding, intracranial haemorrhage and suspect infectious.

AEs leading to discontinuation (all causality) were low (n=15, 10.3% in the 2L-EXP) (n=27, 10.3% in the ESC+EXP) most of them due to grade 3-4 AEs. The most frequent AE leading to discontinuation were malignant neoplasm progression (4, 2.8% in the 2L-EXP; 5, 1.9% in the ESC+EXP).

Special populations

Elderly

Few elderly and very elderly patients were included in the study. This should be adequately reflected in the SmPC and RMP.

Renal and hepatic impairment

Most patients included in trial CA209040 had adequate hepatic function. No patients with severe renal impairment were enrolled.

Safety according to aetiology

Higher frequencies of increased AST/ALT and bilirubin (approximately 2-fold) were observed in HCV-infected subjects vs. uninfected or HBV-infected subjects in ESC + EXP Cohort. Of note, HCV-infected subjects had higher AST, ALT, and bilirubin levels at baseline, and there was a similar frequency of high grade shifts in hepatic laboratory parameters in non-viral and virally-infected subjects.

Immunogenicity

The rate of ADA positive patients (56 out of 210 subjects (26.7%) HCC tested positive for treatment-emergent anti-nivolumab antibody).Of those who were anti-nivolumab antibody positive, 6 subjects (2.9% of the total) were persistent positive, and neutralizing antibodies were only detected in 1 subject (0.5% of the total).

This 26.7% of ADA positive patients is one of the highest observed throughout the nivolumab clinical development across different indications. Although the median exposure to drug (5.26 months) is not too long so as to explain this data the safety profiles of persistent positive or neutralizing positive subjects were no different than those in other subjects and there was no evidence of loss of efficacy in subjects with neutralizing antibodies. Thus, this issue is not further pursued.

Updated safety analysis capturing up to 4 months of additional follow-up, analyses of adverse events (AEs) and related AEs by drug exposure time period show a safety profile consistent with the previously reported. No differences in drug-related AEs leading to discontinuation were observed within each aetiologic subtype.

Assessment of paediatric data on clinical safety

NA

2.5.2. Conclusions on clinical safety

In the setting of a single, non-comparative phase 1/2 study for nivolumab in the treatment of adult patients with HCC after sorafenib, the safety profile of nivolumab appears overall acceptable. This is provisionally that the patient characteristics represent patients with PS $\leqslant$1 and Child-Pugh A and knowing that the patient population tested did not encounter therapy-compromising AE substantially. Considering the fact that AEs as high hepatic laboratory parameters can be explained by the nature of the underlying

disease, no new risks in addition to those identified in previous studies in other indications were identified. Further interpretation of the toxicity profile of nivolumab in the treatment of patients with HCC is considered hampered by the uncontrolled nature of the single pivotal registration study submitted (CA209040).

2.5.3. PSUR cycle

2.5.4. Direct Healthcare Professional Communication

2.6. Risk management plan

The RMP issue raised in the previous round has been addressed with the submission of an updated RMP version 8.1. The PRAC considered the RMP version 8.1 acceptable.

Please refer to the PRAC Rapporteur's RMP assessment report for further details.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated in order to add the new indication and update the safety information. The Package Leaflet is updated in accordance.

2.7.1. User consultation

We considered that the submitted variation type II submitted to extend the current approved therapeutic indication for OPDIVO to include "treatment of hepatocellular carcinoma (HCC) after prior sorafenib therapy in adults" does not involve a relevant impact on the PL. Therefore, the company´s justification to not undertake further consultation with target patient groups, is considered acceptable.

3. Benefit-Risk Balance

The claimed indication is: OPDIVO is indicated for the treatment of hepatocellular carcinoma after prior sorafenib therapy in adults. The recommended dose and schedule of nivolumab monotherapy for the HCC indication is 3 mg/kg administered as IV infusion over 60 minutes Q2W, which is consistent with existing approved dose and schedule of nivolumab monotherapy in adults.

3.1. Therapeutic Context

3.1.1. Disease or condition

Liver cancer is the sixth most common neoplasm and the third most frequent cause of cancer death globally. In most countries, HCC accounts for 70%–85% of primary liver cancer cases. Virtually any cause of liver damage that leads to cirrhosis can predispose a subject to HCC.

Most cases of HCC arise in eastern Asia and sub-Saharan Africa, where the dominant risk factor is chronic HBV, together with exposure to aflatoxin. In contrast, in North America, Europe, and Japan, infection with the HCV is the main risk factor, together with alcohol use. The 5-year HCC survival rate is approximately 5-6%. Untreated patients with advanced disease usually survive less than 6 months. Tumour staging plays an important role in guiding treatment decisions, but overall prognosis is affected by the severity of underlying liver dysfunction at the time of diagnosis.

3.1.2. Available therapies and unmet medical need

The current standard of care for subjects with advanced HCC is sorafenib. For HCC subjects who are intolerant to sorafenib or have progressed after sorafenib, there are no approved therapies.

3.1.3. Main clinical studies

Efficacy data in support of this application focus on data from a second-line dose escalation cohort of 37 patients that was subsequently expanded to a second-line expansion cohort of 145 patients (sorafenib progressors or intolerant). The application is based on data from CA209040, a multicohort Phase 1/2, Dose-escalation, Open-label, Non-comparative Study of Nivolumab or Nivolumab in Combination with Ipilimumab and a Randomized, Open label Study of Nivolumab vs Sorafenib in Advanced Hepatocellular Carcinoma Subjects who are Naive to Systemic Therapy. Data in the combination or comparative cohorts are not presented.

However, as only in the Expansion Phase, subjects were administered with a dose of 3 mg/kg nivolumab Q2W (besides a few patients in the escalation cohort) after second-line (sorafenib progressors or intolerant), these 145 patients from the expansion phase encompass the efficacy target population.

3.2. Favourable effects

Interim results from CA209040 study in the efficacy target population showed an ORR per BICR-assessed (RECIST 1.1) of 14.5%. This data is supported by mature results (75.9% of events) in terms of PFS (median 2.76 months (95%CI: 2.63, 4.04). Only one patient (0.7%) reported a complete response, 20 (13.8%) showed partial responses. SD was shown in 40.7% of the population. Median DoR by BIRC has not been reached at the time of this interim CSR, 19 out of 21 responses were ongoing at the time of clinical cut-off.

ORR using mRECIST criteria (BICR assessed) was higher than ORR according to RECIST 1.1 criteria with overlapping 95 % CI: 18.6% (95% CI 12.6, 25.9).

For PFS, 110 events in 145 patients (75.9%) have been reported by BICR assessment, which show a median PFS of 2.76 months (95%CI: 2.63, 4.04). TTP median was the same, 2.79 months (95%CI: 2.66, 4.11).

Updated efficacy data submitted by the applicant with a minimum of 15-months follow-up, confirmed previous findings for the 2L-EXP cohort in terms of ORR (14.5% by RECIST 1.1) and in the rather modest result in terms of PFS (median 2.79 months). A median DoR (not previously reached) of 16.6 months was reached observed and importantly, a median OS of 15.6 months (event rate 55.9%; 81/145) is observed for the 2L EXP cohort (OS rates at 6 months: 81.8%; 12 months: 59.9% and 18 months: 43.8%).

A landmark analysis of OS by responders vs. non-responders at 4.5 months showed that whereas the median OS was yet reached for the responders, a remarkably high median OS of 16.3 months (95% CI 13.83, 19.44) was reached for the non-responder population.

For patients with PD-L1 expression $\geqslant$5%, $\geqslant$1%, <1%, and PD-L1 expression non-quantifiable, the (updated) BICR-assessed ORR using RECIST 1.1 was 44.4%, 28.0%, 12.9%, and 5.3%, respectively.

For quality of life as measured by EQ-5D-3L, no major improvements (or decreases) from baseline were observed during the study.

Sensitivity analysis by investigator assessment using RECIST 1.1 showed an ORR of 18.6% (95% CI: 12.6-25.9) and a median PFS of 4.04 months (95% CI: 2.76-5.45).

3.3. Uncertainties and limitations about favourable effects

The main uncertainties in the knowledge about the beneficial effects can hardly be solved given the exploratory design of the study (open label, non-comparative), the relatively small sample size and the limited representativeness of the studied population.

The representativeness of the target population is questioned given that only patients with preserved hepatic function and ECOG 0-1 were included in the trial which may differ from clinical practice. However, this issue can be adequately addressed on SmPC.

More importantly, the 5-year survival for HCC is generally only approximately 5-6%, but for 20% of the 2L EXP cohort the time from initial diagnosis to first dose of study therapy was ⩾5 years. This fact combined with the fact that the data in this application are from a single pivotal study, complicates evaluation of the clinical relevance and external validity of the patient population.

Available results (OS supported by durable responses), if true, could be considered outstanding for the overall population. These should be seen within the context of a target population that lacks therapeutic alternatives and where a high unmet medical need exists after sorafenib progression.

Type I error control, sample size and power calculation was done for ORR in the (2L) EXP cohort only. This is in line with the exploratory nature of the trial but inevitably adds uncertainties on assessment of secondary endpoints (OS and PFS). Acknowledging that ORR cannot be considered a valid surrogate for true clinically relevant patient benefit, it could be reasonable to expect that patients experiencing prolonged responses could likely live longer, as previously observed with nivolumab in other tumour types.

However, an ORR of 14.5% entails that only 1 in seven 2L HCC patients treated with nivolumab responded to treatment. The arguments provided by the applicant do not address the issue whether the findings for OS are a chance finding. No replication of the data has been provided.

The fact that there could be selection bias for relatively indolent tumours in the study population is of concern and precludes from assessing efficacy data in trial population as a whole. The remarkably high median OS observed for patients not responding to nivolumab reinforces this idea.

This apparent selection bias for relatively indolent tumours in the study population creates a source of uncertainty regarding the study population with respect to a wide range of known and unknown factors that could affect the outcome, thus making it currently difficult to infer that any favourable outcome, i.e. long OS, is from the treatment alone. This uncertainty also hampers interpretation of results from any comparison with an external control, and thereby prevents assessment of the actual effect size and clinical relevance of the current study results. Only a randomized (comparative) study will reduce selection bias and systematic differences between groups with respect to known and unknown baseline variables/factors that could affect outcome.

Nevertheless, given that the majority of trial population (80%) have time from diagnosis < 5 years, and thus can be deemed representative of the target population it is considered worth it to try to discuss on the B/R on this subgroup of population that is considered comparable to target population and also to populations recruited in similar clinical trials.

Although the cut-off for time from diagnosis is arbitrary, in the absence of any other important prognostic factor/baseline characteristic identified that could impact results, the 80% of population with time from diagnosis < 5 years could be comparable to that enrolled in recent clinical trials (RESORCE). In this regard complete information on baseline characteristics of these subgroups should be also presented. Therefore, the company is asked to submit complete efficacy results dichotomized according to time from diagnosis ⩾ or < 5 years. A detailed discussion of the clinical relevance of results (OS data, ORR, DoR, SD and also influence of post-progression therapies) and B/R in the 80% of population more comparable to that of other clinical trials should be submitted. Discussion of results is also awaited for the population with most indolent disease (20%).

In addition, efficacy outcomes (time to tumour progression) from prior sorafenib therapy in the efficacy target population (n=145) of trial CA209040 could be of help when it comes to shedding light on this issue. Efficacy across different subgroups of study population (PD-L1 expression, on tumour cells and on tumour-associated immune cells, and aetiology) remains uncertain and therefore it is unknown which patients in clinical practice could benefit most from nivolumab treatment. Although better results could be intuitively anticipated for the subgroups of patients with higher PD-L1 expression, no sound conclusion can be drawn given the limited sample size of subgroups and the absence of further analyses based on immune cells PD-L1 expression.

In the same manner, no conclusions can be drawn regarding the three different etiologic subgroups enrolled in the trial (uninfected vs. HBV vs. HCV).

3.4. Unfavourable effects

The investigation of the toxicity profile of nivolumab in adult patients with HCC that have progressed after sorafenib has revealed that almost all patients (99.3% of patients in the 2L cohort of CA209040) experienced any grade of adverse events. At the date of the clinical database lock (8-Aug-2016), the majority of patients had either progressed or died and 24.8% of patients from the 2L EXP cohort continued on nivolumab treatment.

The most common treatment-related AEs for the nivolumab-treated patients were: fatigue, pruritus, rash and diarrhoea. Most of them were mild-moderate in severity.

SAEs (all causalities) were reported in 46.9% of patients, with 27.6% of them reporting G3-4 events.

No deaths due to the deployment of nivolumab were observed, but laboratory parameter elevations were frequently observed, as well as comparably high frequencies of high serum amylase and lipase.

In 10.3% AE led to treatment discontinuation. A relation with nivolumab here was plausible in 2.1%.

An unusual high percentage of patients with HCC treated with nivolumab have nivolumab anti-drug antibodies: 26.7%.

In view of the toxicity profile of nivolumab already known from earlier registration procedures and medical literature, in general, no new safety issues have been identified that preclude the deployment of nivolumab as 2L palliative therapy in adult patients with HCC after sorafenib.

3.5. Uncertainties and limitations about unfavourable effects

The safety in HCC patients with ECOG PS >1 and/or CP score other than A is not known, as these were excluded from study CA209040. This fact constitutes an important uncertainty as most patients in need for 2L therapy have PS >1 as well as Child-Pugh B.

The rate of ADA positive patients (56 out of 210 subjects (26.7%) HCC tested positive for treatment-emergent anti-nivolumab antibody) is one of the highest observed throughout the nivolumab clinical development across different indications. Updated data should be submitted.

In general, many safety issues related to the natural course of HCC that is treated with nivolumab cannot be addressed solidly and satisfactorily in the absence of a properly controlled trial. In CA209040 all patients included were treated with nivolumab and this situation precludes a clear observation of unfavourable effects.

3.6. Effects Table

Table 59 Effects Table for OPDIVO 2L HCC - CA209040 EXP Cohort (data cut-off: 17 March 2017)

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
ORR	ORR per BICR-assessed RECIST 1.1 in all treated	%	(14.5%) (9.2, 21.3)	N/A	Results from a single cohort of 145 patients	
DoR	Time between first radiographic documented objective response and the date of radiographic disease progression.	mo	16.6 (9.7, NA)	N/A		
mTTP	TTP by BICR	mo	2.83 (2.66, 4.11)	N/A	74.5% events (108/145)	
mPFS	PFS by BICR	mo	2.79 (2.63, 4.04)	N/A	82.1% events (119/145)	
mOS		mo	15.64 (13.24, 18.89)	N/A	56% events (81/145)	
Unfavourable Effects						
Fatigue	All-causality AEs	Proportion	AE 34.5% G3/4 2.8% SAE <1%			
Pruritus	All-causality AEs	Proportion	AE 26.9% G3/4 0.7% SAE <1%			
Rash	All-causality AEs	Proportion	AE 17.2% G3/4 0.7% SAE <1%			
Diarrhoea	All-causality AEs	Proportion	AE 26.2% G3/4 1.4% SAE <1%			
Malignant Neoplasms			AE 10.3% G3/4 4.1% SAE 15.2%			
ALT increased			AE 13.8% G3/4 6.2% SAE <1%			
AST increased			AE 13.1% G3/4 9.7% SAE <1%			

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Amylase			AE 6.2% G3/4 2.8% SAE <1%			
Tolerability			AE 99.3% SAE 46.2% ≥ 1 dose delay: 43.4% ≥ 1 infusion interruption: 6.9% ≥ 1 infusion rate reduction 2.8% AE leading to discontinuations 10.3%			

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In CA209040 nivolumab showed prolonged antitumour activity, supported by OS data (median 15.6 months (95%CI: 13.2, 18.9). These results could be considered outstanding as should be seen within the context of a target population with very poor prognosis that lacks therapeutic alternatives, thus with a high unmet medical need. However, the apparent selection bias creates a source of uncertainty regarding the study population, thus making it currently difficult to infer that any favourable outcome is from the treatment alone.

Controlled data are lacking as the application is based on the data of a single, non-comparative phase 1/2 study. In the 2L treatment of advanced HCC a comparative phase 3 study is feasible and undeniably there is a history in literature of phase 3 trials with negative results following phase 2 trials with seemingly convincing results. The phase I/II CA209040 trial has methodological limitations such as ORR being the primary endpoint and the absence of comparator. The former, cast doubts with regard to the correlation with OS, even though it could be reasonable to expect that patients experiencing prolonged responses could likely live longer, as previously observed with nivolumab in other tumour types. Though the arguments provided by the applicant do not address the issue whether the findings for OS are a chance finding.

The possibility that a selection bias is present, is most markedly reflected by the median OS of 16.3 months for the non-responders (at 4.5 months), which is much longer than can be expected for patients with HCC that have failed 1L systemic treatment and are (considered to be) non-responders to 2L treatment. This thus precludes assessing efficacy data in the study population, requiring further analyses in an attempt to assess the actual effect size and clinical relevance of the study results.

The safety profile of nivolumab in the intended indication has been characterised in study CA209040. The overall safety profile of nivolumab remains consistent with prior data in other indications. No new safety concerns were identified.

3.7.2. Balance of benefits and risks

To date, and in spite of the fact that no worrisome safety concerns have been identified, the evidence provided in support of this application is considered too limited. Despite the promising OS results and the poor prognosis of the intended target population, to what extent the population studied is representative of target population is questioned by an apparent selection bias. This is most markedly reflected by the median OS of 16.3 months for the non-responders (at 4.5 months), which is much longer than can be expected for patients with HCC that have failed 1L systemic treatment and are (considered to be) non-responders to 2L treatment. This selection bias creates a source of uncertainty regarding the study population with respect to a wide range of known and unknown factors that could affect the outcome. This makes it as such difficult to infer that any favourable outcome, i.e. long OS, is from the treatment alone, it is however remarkable that the majority of trial population (80%) have a time from diagnosis < 5 years. This uncertainty also hampers interpretation of results from any comparison with an external control, and thereby prevents assessment of the actual effect size and clinical relevance of the study results.

The pitfalls associated to design of trial are of major concern (mainly the lack of comparator and the potential overestimation of results) and, a confirmatory comparative study in 2L HCC patients should have been/be conducted in order to support a positive B/R of nivolumab in this setting.

Furthermore, the drawbacks related to some specific subgroups (PD-L1 expression and aetiology) raises further doubts on the robustness of the evidence provided that cannot be solved with available data.

3.8. Conclusions

The benefit risk balance for nivolumab in the treatment of advanced HCC **is considered negative** at present.

4. Recommendations

The application for: extension of Indication to include the treatment of hepatocellular carcinoma after prior sorafenib therapy in adults for OPDIVO. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.
Moreover, the updated RMP version 8.0 has been submitted.

☒**is not approvable** since major objection and other concerns have been identified, which preclude a recommendation at the present time.

☐ could be approvable since other concerns <has><have> been identified, which preclude a recommendation at the present time.

The details of these <major objections>< other concerns> are provided in Annex <> (RSI 1) and should be addressed in writing <and in an oral Explanation>.

☐ is approvable <since other concerns <major objections><has><have> all been resolved>.

Annex 1: Rapporteurs proposed Request for Supplementary Information

Clinical efficacy aspects

Major Objections

1. Despite the promising results in terms of antitumor responses, the exploratory, non-comparative design of the trial CA209040 and the immaturity of the results provide weak and limited evidence preventing assessment of the actual effect size and clinical relevance of the study results. The applicant is requested to respond to the main drawbacks identified, which pertain to the following:

    a) The evidence provided in support of the claimed indication is too limited. An ORR of 14.5% is not considered exceptionally compelling compared as to what is reported for other treatment options in literature. More importantly, it is not a valid surrogate for true, clinically relevant patient benefit, as in the literature on trials for 2L treatment of advanced HCC there are several reports on phase 3 studies in which differences in surrogate endpoints did not translate into improved OS. Moreover, the lack of mature OS data from the pivotal study is particularly alarming in this late line setting of advanced HCC. At minimum, the applicant should provide updated and (more) mature study results, i.e. ORR, duration of response, and OS data.

    b) Almost 40% of the study population had a time from initial diagnosis to first dose of study therapy ≥5 years, thus there appears to have been a selection bias for relatively indolent tumours

    c) Efficacy across different subgroups of study population (PD-L1 expression and HCC aetiology) remains uncertain. Although better results could be intuitively anticipated for the subgroups of patients with higher PD-L1 expression no sound conclusion can be drawn, as the number of patients per subgroup is small and OS data per subgroup are also immature. Also, further biomarker analyses such as immune cell PD-L1 expression, could be of help to facilitate interpretation of the results.

Moreover, the applicant is asked to justify how the data from the presented single, non-comparative exploratory study, should be considered as sufficient evidence to support a positive B/R in the target population, in particular as in 2L advanced HCC a comparative phase 3 study is feasible, considering the unclear relationship between surrogate endpoints and OS in the 2L HCC setting and taking into account the recently reported study results with regorafenib in 2L HCC. In this discussion, also the rationale to justify the study design should be provided and the applicant should further discuss on ways to generate confirmation of the available exploratory study results, including estimated timelines.

Other concerns

2. No type I error control, nor sample size and power calculation was pre-planned for the clinically more relevant endpoints PFS and OS. The applicant is requested to discuss the robustness of these results, including to replication of these findings for comparable groups and/or drugs**.**

3. As the 5-year survival for HCC is only approximately 5-6%, it seems remarkable that for almost 40% of the study population the time from initial diagnosis to first dose of study therapy was ≥5 years. The applicant is requested to provide the mean (including standard deviation) and median (including full range and interquartile range) for time from initial diagnosis to first dose of study therapy and comment.

4. Regarding prior sorafenib therapy, according to table 5.3.1-2 from CSR most patients had previously experienced prior progression to sorafenib (n=132; 91.0%) with a minority of patients being intolerants to sorafenib (n=12; 8.3%). These data differs from that in table 5.3.2.2-1 from CSR (74.5% patients reported disease progression, 0.7% maximum clinical benefit and 23.4% toxicity). The applicant is asked to clarify.

5. The applicant is requested to discuss the discrepancy between the sentence "The other 11 subjects who were reported with on treatment deviations were not considered true relevant protocol deviations because they either started radiotherapy after last dose of study therapy (3 subjects), had documented radiographic progression (6 subjects), or received palliative radiotherapy (2 subjects) as allowed per protocol (see Appendix 3.6 and Section 6.5.2)." in section 4.3 "Protocol Deviations" on page 68-9 of the study report and the sentence "All 11 cases had documented radiographic progression" in section 6.5.2 "Concurrent Anti-Cancer Therapy" on page 91.

6. Median TTP and PFS might be different, as in case a new anticancer treatment was started without a prior reported radiographic progression per RECIST 1.1, then a patient had not been censored, but counted as having progressed. Therefore, the applicant is requested to provide sensitivity analyses for both TTP and PFS and discuss the results.

7. As it was mentioned as a secondary endpoint in the study protocol, the applicant is requested to provide endpoint analysis for TTP rate and comment.

8. Although from a clinical point of view it seems reasonable to base discontinuations on both radiologic and clinical criteria, from a methodological point of view the most objective measure of progression would be radiographic. The applicant should provide subgroup analysis according to type of progression to prior sorafenib therapy.

9. Although the population enrolled in the 2L-Exp cohort of the trial can be considered representative of the target population, it is expected that in clinical practice not all patients have preserved liver function. There are no data on patients with Child-Plug status B and C or ECOG-PS>1. The applicant should discuss.

10. The applicant is requested to provide efficacy endpoints per baseline PD-L1 expression by BICR using RECIST 1.1 and discuss

11. The information in the study report concerning OS data per baseline PD-L1 expression is somewhat unclear. The applicant is requested to confirm that the passage on page 116 of the report "OS rate was not calculated beyond 9 months in subjects with ⩾1% PD-L1 expression (95% CI: 10.84, NA) and was 13.24 months (95% CI: 11.70, NA) in subjects with <1% PD-L1 expression." can be interpreted as "median OS was not reached in subjects with ⩾1% PD-L1 expression (95% CI: 10.84, NA) and was 13.24 months (95% CI: 11.70, NA) in subjects with <1% PD-L1 expression."

Clinical safety aspects

Other concerns

12. The Applicant should present an update on relevant safety data (e.g. deaths, SAEs, and selected AEs) at the time of efficacy data update.

13. Considering the capability of nivolumab to induce nivolumab-ADAs –also bearing in mind the possibility that patients may have pre-existent nivolumab-ADAs- the mere detection is not surprising. Nonetheless, taking into account the median time of treatment in CA209040 being 4.88 months (all treated population), the incidence of nivolumab ADAs here of 26.7% is

considered high. This in particular when comparing the incidence figure of, for instance, nivolumab-ADAs in the registration study for the indication renal cell cancer. Here nivolumab-ADAs appeared 7.3%, this with a median treatment duration of 3.71 months only. The applicant is asked to provide an explanation for this high incidence in HCC patients, and to discuss the overall importance of neutralizing antibodies.

14. A large quantity of non-drug related SAEs has been claimed in CA209040 (38.5% of patients in ESC+EXP and in 37.9% of patients in the 2L EXP cohort), this in relation to the relative small number of drug-related SAEs (in 7.3% of patients in the ESC+EXP and in 9.0% of the 2L EXP cohort). Apparently 35-40% of the patients included in CA209040 encountered SAEs that are not drug-related. In view of these high numbers, the applicant is asked to explain this high number of SAEs as these are claimed to be non-related to nivolumab.

15. In the 2L EXP cohort the most frequently reported grade 3-4 drug-related AEs were increased AST (3.4%), and increased lipase (3.4%). As the increase of lipase in peripheral blood is a common phenomenon in those treated with nivolumab, a relation with autoimmune effects leading to pancreatitiform phenomena cannot be excluded. Albeit that elevated laboratory parameters did not lead to treatment abrogation or dose adjustment in CA209040 the applicant is asked to mention to quantify the number of patients that needed countermeasures as immune modulation medications in this study.

RMP

Major Objections

Other concerns

16. Based on the submitted study and the lack of (sufficient) data of the following subgroups the applicant is requested to amend the RMP to include the following topics for missing information:

- 'Use of nivolumab in elderly (≥75 years) with HCC'
- 'Patients with moderate hepatic failure who start nivolumab as treatment for HCC'
- 'Use of nivolumab for HCC in patients with ECOG PS >1, Child-Pugh B and C, significant hepatic and/or renal impairment, a history of clinically meaningful variceal bleeding, and/or uncontrolled or clinically significant cardiac disease'

Summary of Product Characteristics

Other concerns

17. Not all proposed changes to the SmPC are acceptable, see separate document for comments and revisions. In addition, in Annex II to the SmPC the post-approval commitment should be extended to include HCC.

Annex 2: Rapporteurs preliminary assessment report of the MAH responses to the Request for Supplementary Information

Clinical efficacy aspects

Major objections

Question 1

Despite the promising results in terms of antitumor responses, the exploratory, non-comparative design of the trial CA209040 and the immaturity of the results provide weak and limited evidence preventing assessment of the actual effect size and clinical relevance of the study results. The applicant is requested to respond to the main drawbacks identified, which pertain to the following:

a) The evidence provided in support of the claimed indication is too limited. An ORR of 14.5% is not considered exceptionally compelling compared as to what is reported for other treatment options in literature. More importantly, it is not a valid surrogate for true, clinically relevant patient benefit, as in the literature on trials for 2L treatment of advanced HCC there are several reports on phase 3 studies in which differences in surrogate endpoints did not translate into improved OS. Moreover, the lack of mature OS data from the pivotal study is particularly alarming in this late line setting of advanced HCC. At minimum, the applicant should provide updated and (more) mature study results, i.e. ORR, duration of response, and OS data.

b) Almost 40% of the study population had a time from initial diagnosis to first dose of study therapy ≥5 years, thus there appears to have been a selection bias for relatively indolent tumours

c) Efficacy across different subgroups of study population (PD-L1 expression and HCC aetiology) remains uncertain. Although better results could be intuitively anticipated for the subgroups of patients with higher PD-L1 expression no sound conclusion can be drawn, as the number of patients per subgroup is small and OS data per subgroup are also immature. Also, further biomarker analyses such as immune cell PD-L1 expression, could be of help to facilitate interpretation of the results.

Moreover, the applicant is asked to justify how the data from the presented single, non-comparative exploratory study, should be considered as sufficient evidence to support a positive B/R in the target population, in particular as in 2L advanced HCC a comparative phase 3 study is feasible, considering the unclear relationship between surrogate endpoints and OS in the 2L HCC setting and taking into account the recently reported study results with regorafenib in 2L HCC. In this discussion, also the rationale to justify the study design should be provided and the applicant should further discuss on ways to generate confirmation of the available exploratory study results, including estimated timelines.

MAH answer

a) The evidence provided in support of the claimed indication is too limited. An ORR of 14.5% is not considered exceptionally compelling compared as to what is reported for other treatment options in literature. More importantly, it is not a valid surrogate for true, clinically relevant patient benefit, as in the literature on trials for 2L treatment of

advanced HCC there are several reports on phase 3 studies in which differences in surrogate endpoints did not translate into improved OS. Moreover, the lack of mature OS data from the pivotal study is particularly alarming in this late line setting of advanced HCC. At minimum, the applicant should provide updated and (more) mature study results, i.e. ORR, duration of response, and OS data.

ORR with Durability of Response is an Acceptable Surrogate Endpoint for Overall Survival in Nivolumab Clinical Trials

The Sponsor recognizes that there is a long history of Phase 3 advanced HCC trials with negative results, and there are no validated surrogate endpoints for overall survival in advanced HCC. Based on review of the data from targeted molecular therapies, there has not been compelling evidence for surrogate endpoints in advanced HCC since the only two TKIs to show a survival benefit in randomized Phase 3 studies have marginal response rates: sorafenib (ORR of 2.7% by RECIST and median OS of 10.7 months [95% CI: 9.4, 13.3] in the pivotal SHARP trial) and regorafenib (ORR of 6.6% by RECIST 1.1 and 10.6% by mRECIST, and OS of 10.6 months [95% CI: 9.1, 12.1] in the RESORCE trial). Moreover, these agents do not result in durability of response with median DOR only ranging from 3.5 to 4.5 months. Furthermore, historical data indicate a marginal response rate of < 10% for targeted compounds and chemotherapy agents, and this has not shown to correlate consistently with OS. As a result, expert panels in the past have discouraged the use of response rate as an endpoint for capturing the benefits of targeted drugs in Phase 2 studies in HCC.

Although response rates associated with TKIs are marginal, including those in failed Phase 3 trials, subjects with advanced HCC who manifest a response appear to have longer OS than subjects who are non-responders. Emerging data suggest that anti-tumour responses can be a predictor of OS in advanced HCC. First, in a randomized Phase 3 study in subjects who received a systemic multikinase inhibitor, brivanib (BRISK-PS), ORR by mRECIST was shown to be an independent predictor of OS by multivariate analysis with median OS of 14.3 months in brivanib responders vs 9.4 months for brivanib non-responders (HR 0.48; 95% CI: 0.26 - 0.91, p = 0.025). In addition, in 2 randomized Phase 2 trials comparing nintedanib vs. sorafenib, both RECIST and mRECIST response assessments predicted OS: median OS of 23.6 months and 16.7 months for responders vs 11.2 months and 10.9 months for non-responders by RECIST and mRECIST (HRs 0.32 [95% CI: 0.13, 0.82; p = 0.0122] and 0.54 [95% CI: 0.34, 0.88; p = 0.0122]), respectively. These observations are in agreement with previously reported retrospective studies in patients treated with sorafenib in the 1L setting that have also shown antitumour response to correlate with a survival advantage compared to those without a response.

ORR and DOR with Nivolumab Monotherapy has Been Shown to be a Reliable Surrogate Endpoint for Overall Survival across Multiple Studies with Nivolumab

As the unique mechanism of action allows the activation of memory T-cell clones that recognize tumour antigens expressed irrespective of histology or organ of origin, DOR is significantly longer than for therapies directed at the tumour itself, such as TKIs and cytotoxic chemotherapies. This has been clearly established for the indications with the longest follow up (melanoma [CA209037 and CA209066] and NSQ NSCLC [CA209057]). In addition, it is worth noting that improvement in ORR and DOR with nivolumab in other tumour types has translated into improvement in OS (eg, SCCHN [CA209141]10, and RCC [CA209025]). Therefore, based on these observations in other tumour types, BMS anticipates that the observed ORR with durable response are reasonably likely to predict improvement in OS in the 2L HCC population treated with nivolumab.

ORR with Durable Responses in CA209040 can be Considered an Acceptable Surrogate Endpoint for Overall Survival in Advanced HCC Patients Treated with Nivolumab Monotherapy

Subsequent to the initial Type II variation for the OPDIVO 2L HCC extension of indication submission on 30-Nov-2016, BMS performed additional database locks (DBLs) to evaluate the efficacy of nivolumab in 2L HCC cohorts of Study CA209040 (clinical DBL on 29-Nov-2016/BICR DBL on 12-Dec-2016, and a combined clinical and BICR DBL on 17-Mar-2017). The results from these additional DBLs further confirmed the benefit of nivolumab in 2L HCC. Additional details are summarized below in the next Section and in Table -1.

Based on the most recent DBL performed on 17-Mar-2017 with a minimum of 15 months follow up, the BICR-confirmed ORR is 14.5%, median DOR is 16.6 months, and median OS is 15.6 months (95% CI: 13.24, 18.89) for 2L EXP subjects. These data from CA209040, combined with the unique mechanism of action for nivolumab, are compelling when compared to historical data in the Phase 1 and Phase 2 studies that led to failed Phase 3 studies (Table -7), chemotherapy, and TKIs including regorafenib.

Table 60: Summary of Updated Efficacy Results Since Initial Submission with Indirect Comparison to Regorafenib or Placebo+BSC RESORCE Data

median (95% CI) unless otherwise noted	2L EXP N = 145		2L ESC N = 37		Regorafenib[3] N = 379		Placebo+BSC[3] N = 194	
	RECIST 1.1	mRECIST	RECIST 1.1	mRECIST	RECIST 1.1	mRECIST	RECIST 1.1	mRECIST
ORR, %[a,c]								
By BICR	14.5% (9.2, 21.3)	18.6% (12.6, 25.9)	18.9% (8.0, 35.2)	21.6% (9.8, 38.2)	-	-	-	-
By Investigator	19.3% (13.2, 26.7)	-	16.2% (6.2, 32.0)	-	6.6%	10.6%	2.6%	4.0%
BOR, n (%)								
By BICR								
CR	2 (1.4%)	4 (2.8%)	1 (2.7%)	2 (5.4%)	-	-	-	-
PR	19 (13.1%)	23 (15.9%)	6 (16.2%)	6 (16.2%)	-	-	-	-
By Investigator								
CR	3 (2.1%)	-	3 (8.1%)	-	0	2 (0.5%)	0	0
PR	25 (17.2%)	-	3 (8.1%)	-	25 (6.6%)	38 (10.1%)	5 (2.6%)	8 (4.1%)
DoR, months[b,c]								
By BICR	N.A. (11.30, N.A.)	N.A. (8.31, N.A.)	19.35 (2.83, N.A.)	8.64 (2.83, N.A.)	-	-	-	-
min, max[d]	3.2, 13.8+	-	2.8, 35.4+	-	-	-	-	-
By Investigator	12.35 (7.71, N.A.)	-	17.07 (7.16, N.A.)	-	-	3.5 (1.9, 4.5)	-	2.7 (1.9, NE)
min, max[d]	2.8, 13.8+	-	7.2, 35.4+	-	-	-	-	-
DoR, months[b,e]								
By BICR	16.59 (9.69, N.A.)	-	19.35 (2.83, N.A.)	-	-	-	-	-
min, max[d]	3.2, 16.8+	-	2.8, 38.2+	-	-	-	-	-
By Investigator	N.A. (9.53, N.A.)	-	17.07 (7.16, N.A.)	-	-	3.5 (1.9, 4.5)	-	2.7 (1.9, NE)
min, max[d]	2.8, 16.8+	-	7.2, 38.2+	-	-	-	-	-
PFS, months[b,c]								
By BICR	2.79 (2.63, 4.04)	-	3.45 (1.61, 4.14)	-	-	-	-	-
By Investigator	4.07 (2.76, 5.52)	-	3.40 (1.41, 5.72)	-	3.4 (2.9, 4.2)	3.1 (2.8, 4.2)	1.5 (1.4, 1.5)	1.5 (1.4, 1.6)
OS, months (based on 29-Nov-2016 clinical DBL)	16.66 (13.24, NA)[c]		14.95 (4.99, 28.06)[c]		10.6 (9.1, 12.1)		7.8 (6.3, 8.8)	
OS, months (based on 17-Mar-2017 clinical DBL)	15.64 (13.24, 18.89)[e]		14.95 (4.99, 28.06)[e]					

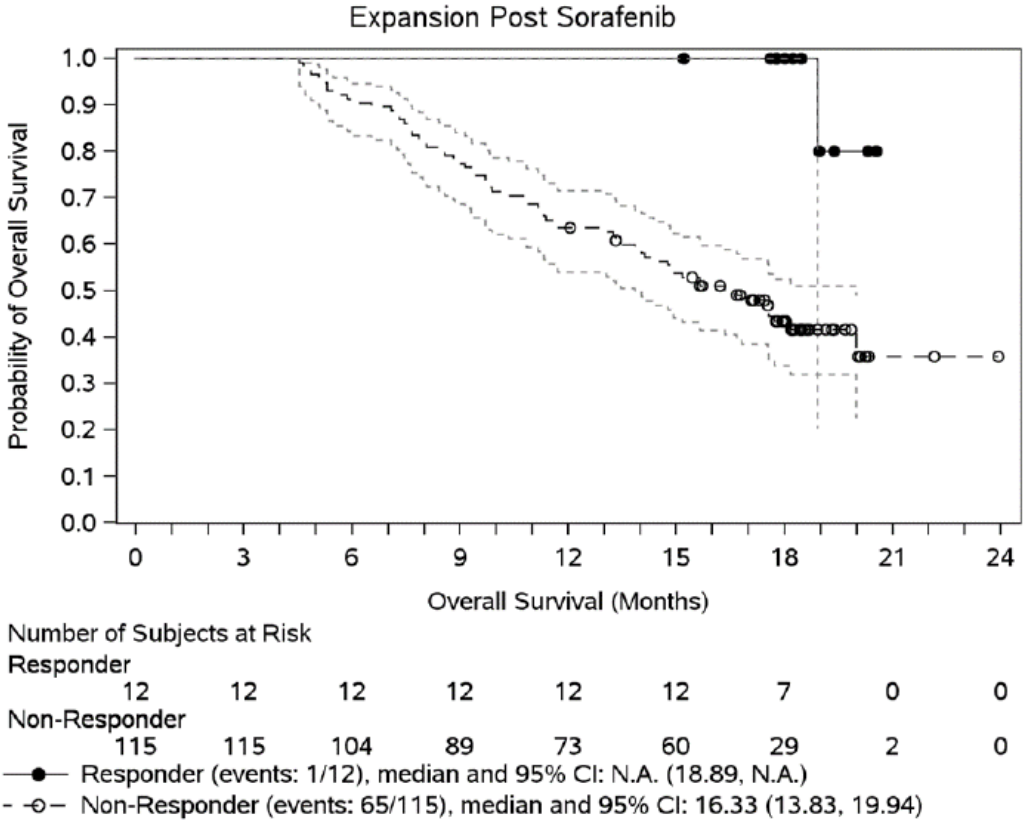
[a] Complete response + Partial response
[b] Median computed using Kaplan-Meier method
[c] Based on 29-Nov-2016 clinical DBL and 12-Dec-2016 BICR DBL
[d] Symbol + indicates a censored value
[e] Based on 17-Mar-2017 DBL

To further highlight the potential for ORR with durability to correlate with OS, a landmark analysis of OS by responders vs. non-responders at 4.5 months was conducted. Given that most responses to nivolumab occur within the first 3 months, the 4.5 months landmark was selected to allow up to 3 months (2 scans at Q6 week intervals) for subjects to respond and an additional 1.5 months to allow a follow-up scan to confirm the response. As shown in Figure 24, subjects who were confirmed responders per BICR RECIST

1.1 by 4.5 months had demonstrated an improved survival versus those who were not. The median OS was not reached even after a minimum of 15 months of follow-up in responders. The median OS was 16.3 months (95% CI 13.83, 19.44) for non-responders. Of note, among all responders by month 4.5 in the 2L EXP cohort, only one death occurred, with OS close to 19 months. In addition, a survival analysis was performed on all BICR confirmed responders, which revealed clinically meaningful results with all responders in 2L ESC having a minimum OS of ⩾ 18 months, and all responders in 2L EXP having a minimum OS of ⩾ 12 months.

Taken together, these data support the use of ORR with durability of response as an acceptable surrogate endpoint for OS.

Figure 24: Landmark Analysis of OS by Response Status per BICR RECIST 1.1 - For Subjects Having Survived Beyond and Including 4.5 Months in the 2L EXP Cohort



Symbols represent censored observations.

A period of 1.5 months is added to ensure an initial objective response as far as 3 months after study therapy to be confirmed by a subsequent tumour assessment

Responder: Initial response and its subsequent confirming response within 4.5 months after study therapy

Non-Responder: BOR other than PR and CR, or initial response not confirmed within 4.5 months after study therapy

Updated Median DOR and OS Data with Minimum 15 Months Follow-up based on Updated DBL of 17-Mar-2017 Further Support the Benefit of Nivolumab in 2L HCC

In order to further assess the benefit with nivolumab in the 2L HCC cohorts of Study CA209040, BMS has prioritized specific efficacy outputs, including BOR by OS category, median DOR, and OS efficacy data from a recent clinical and BICR DBL on 17-Mar-2017, with a minimum follow-up of 15 months for all subjects. No additional efficacy outputs are available currently from the 17-Mar-2017 DBL.

Median DOR by BICR for 2L ESC subjects is 19.4 months (95% CI: 2.83, NA) and for 2L EXP subjects is 16.6 months (95% CI: 9.69, NA). In addition, 1 of 7 2L ESC responders and 10 of 21 2L EXP responders has an ongoing response.

Survival analysis: The event rate in 2L ESC and 2L EXP subjects was 67.6% (25 of 37) and 55.9% (81 of 145). As shown in Figure -2, median OS for 2L ESC subjects was 15.0 months (95% CI: 4.99, 28.06) and for 2L EXP subjects was 15.6 months (95% CI: 13.24, 18.89), the lower bound of which exceeds the upper bound of regorafenib (10.6 months; 95% CI: 9.1, 12.1)3. The OS rate at 18 months was 46.4% and 43.8% for 2L ESC and 2L EXP subjects, respectively. A total of 32.4% and 44.1% of 2L ESC and 2L EXP subjects were censored. Of note, the K-M curves, as shown in Figure -2, highlight the similar OS findings between the 2L ESC and 2L EXP subjects, and reinforce the consistent observations observed between these 2 cohorts in all the efficacy parameters. Overall, with the additional DBL in Mar-2017, and a minimum of 15 months follow-up on all subjects, treatment with nivolumab demonstrated a compelling clinical outcome with a median DOR of 16.6 months and mature survival with a mOS of 15.6 months in the 2L EXP cohort.

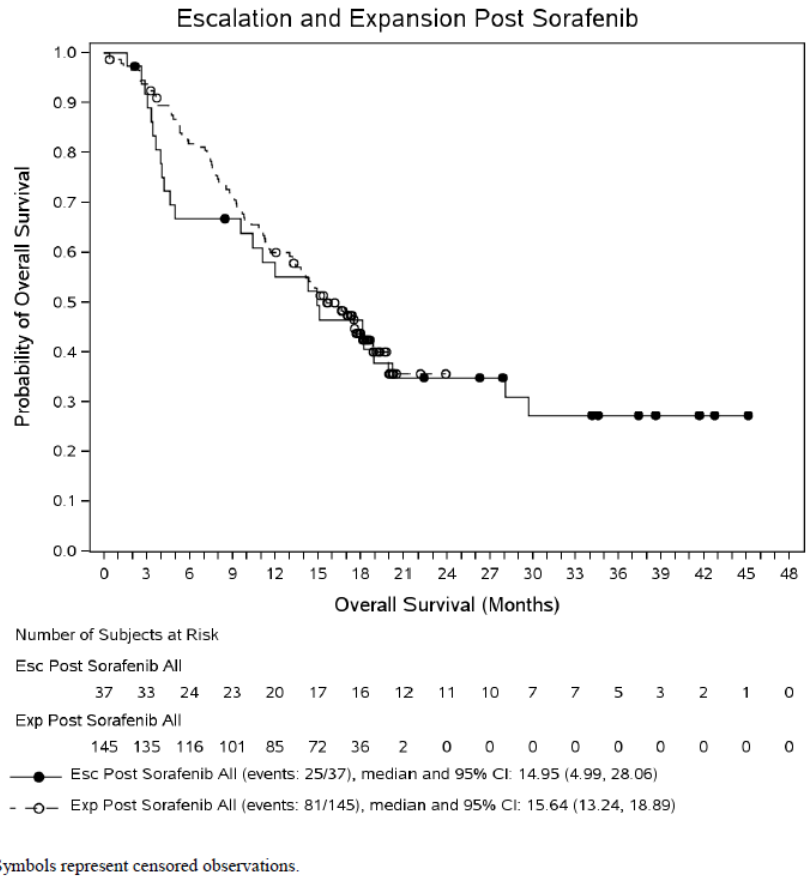


Figure 25 Kaplan-Meier Plot of Overall Survival in the 2L ESC and 2L EXP Cohorts

Table 61 Summary of Efficacy Results by Etiologic Subtype, per RECIST 1.1 (Based on 29-Nov-2016 Clinical DBL and 12-Dec-2016 BICR DBL) - All Treated, Post-sorafenib Subjects in the 2L EXP Cohort

	BICR ASSESSMENT		
	Uninfected N = 72	HCV-infected N = 30	HBV-infected N = 43
OBJECTIVE RESPONSE RATE (95% CI) (A)	9/72 (12.5%) (5.9, 22.4)	6/30 (20.0%) (7.7, 38.6)	6/43 (14.0%) (5.3, 27.9)
DISEASE CONTROL RATE (95% CI)	6/72 (63.9%) (B) (51.7, 74.9)	15/30 (50.0%) (B) (31.3, 68.7)	20/43 (46.5%) (B) (31.2, 62.3)
DCR WITH SD AT LEAST 6 MONTHS LONG (95% CI)	19/72 (26.4%) (16.7, 38.1)	10/30 (33.3%) (17.3, 52.8)	10/43 (23.3%) (11.8, 38.6)
BEST OVERALL RESPONSE:			
COMPLETE RESPONSE (CR) (95% CI)	0 (0.0, 5.0)	1 (3.3) (0.1, 17.2)	1 (2.3) (0.1, 12.3)
PARTIAL RESPONSE (PR) (95% CI)	9 (12.5) (5.9, 22.4)	5 (16.7) (5.6, 34.7)	5 (11.6) (3.9, 25.1)
STABLE DISEASE (SD)	37 (51.4)	9 (30.0)	14 (32.6)
NON-CR/NON-PD	0	0	0
PROGRESSIVE DISEASE (PD)	23 (31.9)	11 (36.7)	22 (51.2)
UNABLE TO DETERMINE (UTD)	3 (4.2)	4 (13.3)	1 (2.3)
NO FOLLOW-UP RADIOLOGICAL IMAGING AVAILABLE FOR ASSESSMENT	2 (2.8)	2 (6.7)	0
DEATH PRIOR TO DISEASE ASSESSMENT	0	0	0
OTHER	0	0	0
NOT REPORTED	1 (1.4)	2 (6.7)	1 (2.3)
NUMBER OF RESPONDERS	9	6	6
TIME TO RESPONSE (MONTHS)			
MEDIAN	4.04	2.10	2.00
MIN, MAX	2.6, 6.8	1.2, 7.0	1.2, 6.8
DURATION OF RESPONSE (MONTHS)			
MIN, MAX (C)	5.6, 13.8+	3.2+, 13.8+	6.9+, 13.7+
MEDIAN (95% CI) (D)	N.A.(5.55, N.A.)	N.A.(3.15, N.A.)	N.A.(8.31, N.A.)
NUMBER OF SUBJECTS WITH DURATION OF RESPONSE OF AT LEAST (%)			
3 MONTHS	9 (100.0)	6 (100.0)	6 (100.0)
6 MONTHS	8 (88.9)	5 (83.3)	6 (100.0)
10 MONTHS	4 (44.4)	3 (50.0)	3 (50.0)
12 MONTHS	2 (22.2)	3 (50.0)	3 (50.0)
SUBJECTS WITH ONGOING RESPONSE (E)	5 (55.6)	5 (83.3)	5 (83.3)
MEDIAN PFS (MONTHS) (F) (95% CI) # EVENTS / # SUBJECTS (%)	3.29 (2.69, 4.60) 58/72 (80.6)	2.83 (1.38, 6.90) 21/30 (70.0)	2.63 (1.35, 4.04) 36/43 (83.7)
TIME TO PROGRESSION (MONTHS)			
NUMBER OF EVENTS (%)	51/72 (70.8)	18/30 (60.0)	35/43 (81.4)
MEDIAN (95% CI) (F)	4.04 (2.73, 5.52)	4.01 (1.38, 7.23)	2.63 (1.35, 4.07)

MEDIAN OS (MONTHS)	16.66	N.A.	N.A.
(95% CI) (F)	(11.33, N.A.)	(11.17, N.A.)	(9.30, N.A.)
# EVENTS / # SUBJECTS (%)	34/72 (47.2)	11/30 (26.7)	20/43 (46.5)
OS RATE (95% CI)			
6-MONTH	80.6 (69.4, 88.0)	85.8 (66.3, 94.4)	81.4 (66.2, 90.2)
NO. AT RISK	58	23	35
12-MONTH	59.7 (47.4, 70.0)	67.1 (46.2, 81.4)	55.6 (39.6, 69.0)
NO. AT RISK	42	18	22

All confidence intervals are based on the Clopper and Pearson method except as otherwise specified.
(A) CR+PR
(B) CR+PR+SD+Non-CR/Non-PD
(C) Symbol + indicates a censored value.
(D) Median computed using Kaplan-Meier method.
(E) Subjects with Ongoing Response include responders who had neither progressed nor initiated subsequent therapy.
(F) Median and rates computed using Kaplan-Meier method.
N.A.: Not Available due to insufficient follow up.

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Indirect Comparison of OS in Nivolumab 2L EXP subjects Versus Historical Data Provides Additional Support of Clinically Meaningful Benefit Given that BSC or clinical trial participation are the recommended options for advanced HCC subjects after sorafenib treatment, BMS sought to perform an indirect treatment comparison of OS to describe the efficacy of nivolumab vs. BSC. Access to patient level data allowed for OS comparisons between 2L EXP subjects (n=145) from the 29-Nov-2016 DBL and the BSC+placebo (BSC+PBO) arm of the Phase 3 BRISK-PS trial (n=132). In this analysis, BMS observed that patients treated with nivolumab were more likely to survive compared to BSC+PBO (adjusted HR: 0.461 [95% CI: 0.334-0.637; p<.0001]) (Figure -3).

With the recently published data from the regorafenib RESOURCE trial3, an analysis using a Matching Adjusted Indirect Treatment Comparison (MAIC) method was used to compare 2L EXP subjects with BSC+PBO and regorafenib. Next, comparing OS from the 2L EXP subjects to the BSC+PBO arm (n=194) of the Phase 3 randomized regorafenib RESORCE trial; the adjusted HR observed was 0.403 (95% CI: 0.298-0.546) for nivolumab compared to the BSC arm, respectively. Furthermore, since regorafenib+BSC has shown OS benefit in the RESORCE trial relative to PBO+BSC, BMS subsequently performed an indirect OS comparison of the 2L EXP subjects to regorafenib-treated subjects (n=379) which demonstrated that patients treated with nivolumab were more likely to survive (HR: 0.600 [95% CI: 0.452-0.796]; p=.0004) (Figure -4).
Limitations associated with all analyses are the inability to adjust for unmeasured confounders and the lack of adjustment for trial effects, which may result in an under- or over-estimation of treatment effect. No adjustments for multiple comparisons were made. P-values and confidence intervals should be treated as descriptive, as all analyses were performed post-hoc and power calculations have not been performed. A summary of the methods associated with indirect treatment comparisons is provided in Appendix 2.

Nevertheless, these indirect OS comparisons highlight the potential for clinically meaningful survival of nivolumab in advanced HCC.

CHMP Assessment

Updated efficacy data submitted by the applicant with 3 months of additional minimum follow-up confirmed previous findings for the 2L-EXP cohort (145 patients intolerant or showing progression after sorafenib therapy) in terms of ORR (14.5% by RECIST 1.1.) and in the rather modest result in terms of PFS (median 2.79 months). A median DoR (not previously reached) of 16.6 months is now observed and although no OS data was initially available, a median OS of 15.6 months (event rate

55.9%; 81/145) is observed for the 2L-EXP cohort (OS rates at 6 months: 81.8%; 12months: 59.9% and 18 months: 43.8%).

Although at the time of initial assessment these data were not considered compelling "per se", this was seen within the context of a disease with dismal prognosis where no treatments are available after progression to sorafenib (7-8 months of survival if left untreated).

Putting findings into context of one on the most recent randomized, phase III trials performed in the same target population, CA209040 favourably compares with data from the RESORCE trial, where regorab¡fenib (TKI) showed superiority in terms of OS compared to placebo after first line treatment with sorafenib (OS median 10.6 months for regorafenib vs. 7.8 months placebo; ORR RECIST 1.1.: 6.6% vs. 2.1%). Safety data point out that nivolumab may be better tolerated than regorafenib based on the lower rates of deaths due to study drug toxicity, drug-related AEs, Grade 3-4 drug-related AEs, and drug related AEs leading to discontinuation when data from trials are compared. It should be highlighted that nivolumab results come from a phase I/II trial and only uncontrolled data from 145 patients is available. ORR, the primary endpoint of the CA209040 trial, cannot be assumed as a valid surrogate of OS, nevertheless is would be reasonable to expect that patients experiencing prolonged responses could likely live longer, as previously observed with nivolumab in other tumours.

In this regard, the company has submitted a landmark analysis of OS by responders which showed that after a minimum follow-up of 15 months no median was reached for the responders whereas a median of 16.3 months was observed for the non-responders. A dramatic split is observed in the K-M curves between both subgroups of patients.
On the one hand the results for the 14.5% of patients who are considered responders is considered outstanding and are well above what could be awaited for this setting. On the other hand, taking into account historical comparisons and the limited prognosis of the patient population, the median OS for the non-responder population is considered remarkably high (16.3 months (95% CI 13.83, 19.44)). Among the possible causes of this unexpected high OS median for the non-responders, could be partly due to the disease stabilization rate observed (40.7%) in the overall population or may be possible due to the influence of post-progression therapies. Regarding the former, despite SD and DCR (by BICR using RECIST 1.1) for nivolumab in study CA209040 (i.e. 41% and 56%, respectively) were lower than that for regorafenib in the RESORCE trial (i.e. 59% and 66%, respectively), the behaviour of immunotherapy within tumour micro environment has not been totally elucidated to date, so there could be some unknown pharmacodynamic effects that could be impacting in long-term benefit of nivolumab
In any case, none of these options seem to be solid arguments, though plausible, when it comes to explaining this finding.

Importantly, according to baseline characteristics, trial population was considered representative of the target population and was in line with populations recruited in phase III trials in the same setting but for the fact that 20% of the patients had a time from diagnosis ≥ 5 years, which could be pointing out a bias in the recruitment of patients towards a rather indolent disease (please refer to assessment of Q 1b). Although no other baseline characteristic or prognostic factor can be identified as possible cause of the high OS observed for the non-responder population, the enrolment of a population with less aggressive disease could have impacted in the study results.

On considering that there is 20% of the population that could have a better prognosis, it is however remarkable that the majority of trial population (80%) have a time from diagnosis < 5 years.

Unfortunately, methodological limitations such as the lack of a concurrent comparator precludes from easily clarifying to what extent the population is biased and is impacting results.

Although OS results supported by durable response rates are considered outstanding for the overall population, the pitfalls associated to the biases identified (mainly the lack of comparator and the potential overestimation of results) do not allow the achievement of a clear conclusion.

Taking all together, the company is asked to submit complete efficacy results dichotomized according to time from diagnosis ⩾ or < 5 years. A detailed discussion of the clinical relevance of results (OS data, ORR, DoR, SD and also influence of post-progression therapies) and B/R in the 80% of population more comparable to that of other clinical trials should be submitted. Discussion of results is also awaited for the population with most indolent disease (20%).

Issue not solved. Please refer to MO below.

b) Almost 40% of the study population had a time from initial diagnosis to first dose of study therapy ≥5 years, thus there appears to have been a selection bias for relatively indolent tumours

Study CA209040 was initially designed to explore the safety and preliminary antitumour activity of nivolumab in subjects with advanced HCC. The baseline demographic and disease characteristics and tumour assessments were generally well balanced across the 2L ESC and 2L EXP cohorts and consistent with those of an advanced HCC population. In addition, the patient population was comparable to the regorafenib Phase 3 study in terms of age, gender, race, ECOG, BCLC stage, Child Pugh score, presence of vascular invasion/extrahepatic spread, AFP values ≥ 400, and baseline risk factors. In addition, an exploratory objective was to characterize the potential antiviral properties of subjects with advanced HCC due to either chronic HCV or HBV infection. For subjects with HCV- or HBV-related HCC, a majority of investigators completed the time from initial diagnosis for subjects with the date of initial viral diagnosis (not HCC diagnosis), and this has resulted in a large number of subjects having a time from initial diagnosis to first dose of study therapy ≥ 5 years (37.2% of the 2L EXP subjects), including 12.5% of the uninfected, 57% of the HCV-infected, and 65% of the HBV-infected. To more accurately characterize the time from initial HCC diagnosis, BMS has re-queried all subjects, with or without viral hepatitis, to confirm the date of initial HCC diagnosis and included the updated CRF records in the 17-Mar-2017 DBL. From the 17-Mar-2017 DBL, the percentage of 2L EXP subjects with time from initial diagnosis ≥ 5 years is 20%, including 17% of the uninfected, 27% of the HCV-infected, and 21% of the HBV-infected subjects (also see response to Question 3).

In addition, the median time from HCC diagnosis to start of study treatment in CA209040 is 26.5 months (interquartile range [IQR] 12-51) for the 2L EXP subjects, which is comparable to other 2L HCC trials and the regorafenib-treated population in the RESORCE Phase 3 trial with a median of 21 months (IQR 11-38).

These findings in CA209040 are consistent with the natural history of HCC in which a minority of subjects survive more than 5 years from initial diagnosis, with a 5-year survival from large cancer registries in Europe and US ranging from 11.7% (EUROCARE-522) to 17.5% (SEER23) and even higher rates in Asia (up to 43% in Japan) due to implementation of liver cancer screening programs. In addition, unadjusted data from the BRIDGE study of 18,031 patients across the globe showed significant variability in 5 year survival rates from time of first HCC treatment ranging from approximately 20% in the EU to 70% in Taiwan (Figure -5). Taken together, these data indicate the patient population in CA209040 has similar

survival statistics to patients from EU and US population-based cancer registries and other historical 2L HCC trials including the recent Phase 3 regorafenib RESORCE trial, and there is no evidence for selecting subjects in CA209040 with indolent tumours.

In addition, to further support the lack of any selection bias for indolent tumours, BMS would like to highlight the similarity for the key inclusion criteria between CA209040 and other Phase 3 advanced 2L HCC trials, e.g. RESORCE, in terms of age, Child Pugh Class A, ECOG 0-1, and baseline laboratory values in the patient populations. Furthermore, the demographic characteristics for the 2L EXP subjects in CA209040 are consistent with 2L subjects in the Phase 3 regorafenib trial for age, gender, race, ECOG, BCLC, Child Pugh Score, vascular invasion, extrahepatic spread, elevated AFP, and risk factors (Table 1a of Appendix 1), which indicate a patient population with similar baseline and prognostic features between the two studies. In contrast to RESORCE, which enrolled a narrower population of only sorafenib radiographic progressors and no additional lines of systemic therapy, CA209040 enrolled subjects with sorafenib intolerance (8.3%) and also included those with >1 line of prior systemic therapy (18.6%) resulting in a population that is more consistent with patients encountered in real world clinical practice.

CHMP Assessment

The company argues that the initial high percentage of population with time from initial diagnosis to first dose of study therapy ⩾5 years was due to a mistake in data collection, as the data of HCC diagnosis was confounded with the time of viral diagnosis by some investigators. This has been amended resulting in a 20% of population with time from initial diagnosis ⩾5 years. This data would be closer to the 5-year survival data from large cancer registries in Europe and US ranging from 11.7% (EUROCARE-522) to 17.5% (SEER23) but still higher. The median time to HCC diagnosis (26 months) is also similar, though higher than in the RESORCE trial (21 months).

Efficacy results point out a remarkably high OS median for the population that did not show responses to nivolumab therapy, it is considered that the stabilization disease rate reached by nivolumab as well as the administration of post-progression therapies could have impacted OS data. Both factors though plausible, do not seem to be solid arguments to explain such findings. Nevertheless the fact that the population recruited could be slightly selected (of note this represents 20% of trial population) could likely have greater impact on OS results. The applicant is asked to further elaborate on this issue and to discuss on the B/R of this subgroup as well as of the remaining subgroup of patients (80%). Please refer to MO 1a.

Issue partly solved. Please refer to MO 1a.

c) Efficacy across different subgroups of study population (PD-L1 expression and HCC aetiology) remains uncertain. Although better results could be intuitively anticipated for the subgroups of patients with higher PD-L1 expression no sound conclusion can be drawn, as the number of patients per subgroup is small and OS data per subgroup are also immature. Also, further biomarker analyses such as immune cell PD-L1 expression, could be of help to facilitate interpretation of the results.

BMS acknowledges the importance for identification of potential subgroups that may benefit most from nivolumab therapy.

Efficacy by Patient Demographics

ORR analyses have been performed looking at a variety of different subsets including age, region, gender, presence of vascular invasion or extrahepatic spread, AFP, and BCLC stage, without identification of any particular subgroup with a greater propensity for response. ORRs were similar across these subgroups. BMS did not identify any particular subgroup with a meaningful better response rate recognizing the limitation that the subgroups typically have small sample size. These updated Nov-2016 DBL results were similar to those data in the initial submission package.

Efficacy by Viral Etiology

The 2L EXP cohort is comprised of uninfected (n=72), HCV-infected (n=30), and HBV-infected (n=43) subjects, and reflects the diversity in the global epidemiology of HCC. Analyses by etiology are limited due to the small sample sizes and were not designed for formal statistical comparisons. However, updated efficacy data from the 29-Nov-2016 clinical and 12-Dec-2016 BICR DBL suggest very similar results of nivolumab within each etiologic subtype in terms of ORR, DCR, TTR, DOR, subjects with an ongoing response, median PFS, median TTP, and OS rates up to 12 months (Table -1). Based on these findings, all patients with HCC, regardless of etiologic subtype, have clinically meaningful improvements in efficacy outcomes with nivolumab treatment.

Efficacy by Baseline Tumour Cell PD-L1 Expression and Viral Etiology Status

Table -3 summarizes BICR ORR for each viral etiological subgroup by tumour cell PD-L1 status (data based on updated 29-Nov-2016 clinical DBL and 12-Dec-2016 BICR DBL).

Since the prevalence of PD-L1 on tumour cells is low in 2L HCC, most of the subjects have PDL1 <1%. There are responders in each of the six subgroups presented in the table, which reinforces the potential for all 2L HCC subjects to derive clinically meaningful benefit with nivolumab regardless of baseline tumour cell PD-L1 expression. There is a trend for higher ORR for tumour cell PD-L1 ≥1% for each viral etiology, however no definitive conclusion can be drawn from these data since the number of patients per subgroup is too small, and the 95% CIs are broad and overlapping. Please refer to Figure 10.3b in Addendum 01 to the CA209040 Interim CSR21 for OS by baseline tumour cell PD-L1 expression. Similar 6- and 12-month survival rates were observed regardless of etiologic subtype.

Table 62 BOR and ORR by BICR RECIST 1.1 for ≥ 1% and < 1% PD-L1 Expression Status at Baseline by Viral Etiology in the 2L EXP Cohort

BASELINE PD-L1 STATUS	Exp Post Sorafenib Uninf N = 72	Exp Post Sorafenib HCV N = 30	Exp Post Sorafenib HBV N = 43
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1%	9 (12.5)	8 (26.7)	8 (18.6)
BEST OVERALL RESPONSE:			
COMPLETE RESPONSE (CR)	0	0	0
PARTIAL RESPONSE (PR)	2 (22.2)	3 (37.5)	2 (25.0)
STABLE DISEASE (SD) OR NON-CR/NON-PD	4 (44.4)	1 (12.5)	2 (25.0)
PROGRESSIVE DISEASE (PD)	3 (33.3)	3 (37.5)	3 (37.5)
UNABLE TO DETERMINE (UTD)	0	1 (12.5)	1 (12.5)
OBJECTIVE RESPONSE RATE (1)	2/9 (22.2%)	3/8 (37.5%)	2/8 (25.0%)
(95% CI)	(2.8, 60.0)	(8.5, 75.5)	(3.2, 65.1)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%	48 (66.7)	20 (66.7)	33 (76.7)
BEST OVERALL RESPONSE:			
COMPLETE RESPONSE (CR)	0	1 (5.0)	1 (3.0)
PARTIAL RESPONSE (PR)	6 (12.5)	2 (10.0)	3 (9.1)
STABLE DISEASE (SD) OR NON-CR/NON-PD	25 (52.1)	8 (40.0)	11 (33.3)
PROGRESSIVE DISEASE (PD)	15 (31.3)	7 (35.0)	18 (54.5)
UNABLE TO DETERMINE (UTD)	2 (4.2)	2 (10.0)	0
OBJECTIVE RESPONSE RATE (1)	6/48 (12.5%)	3/20 (15.0%)	4/33 (12.1%)
(95% CI)	(4.7, 25.2)	(3.2, 37.9)	(3.4, 28.2)

(1) CR+PR, 95% CI based on Clopper and Pearson method
(2) Includes PD-L1 tumour sample not available, PD-L1 not evaluable and indeterminate.

Efficacy by Tumour-Associated Immune Cell PD-L1 Expression

To investigate further whether there are potential subgroups of patients who may respond better to nivolumab, BMS has performed a preliminary, exploratory analysis of tumour-associated immune cell (TAIC) PD-L1 expression in baseline tumour samples from CA209040. At the time of tumour cell (TC) PD-L1 tumour assessment, an additional qualitative assessment of PD-L1-expressing tumour TAICs was also reported for each tumour sample; importantly, however this assay was not analytically validated for measurement of TAIC PD-L1 expression. TAIC PD-L1 expression in the tumour microenvironment was qualitatively assessed by pathologist assessments and both TAIC PD-L1 positive and negative groups consisted of combining multiple qualitatively-defined subgroups together.

The efficacy responses per baseline TC and TAIC PD-L1 expression by BICR using RECIST 1.1 from the updated clinical DBL of 29-Nov-2016 and BICR DBL of 12-Dec-2016, are provided in Table -6 and Table S.10.9b.4 (BOR and ORR by PD-L1 immune cell status) in Appendix 1. Unlike TC PD-L1 expression which has a low prevalence in 2L HCC (17.2% in 2L EXP), TAIC PD-L1 expression was frequently observed (in >75% or 121 out of the 161 cases with TAIC PD-L1 data available). Also, samples that were TC PD-L1 ≥ 1% (N = 34) were generally TAIC PD-L1 positive (N = 30; >88%). The 7 responders with TC PD-L1 ≥ 1% were the same 7 responders who were TC PD-L1 ≥ 1% and TAIC PD-L1 positive. TAIC PD-L1 positive is highly correlated with TC PD-L1 ≥ 1% and therefore does not provide additional clinical utility in identifying HCC patient subgroups who benefit from nivolumab treatment.

Additional data is available for PD-L1 expression on TC and TAIC by viral etiology (refer to Table S.10.9b.4 [BOR and ORR by PD-L1 immune cell status], Table S.10.9b.5 [BOR and ORR for joint PD-L1 tumour expression and immune cell staining status], and Table S.10.10b [BOR and ORR for each PD-L1 expression status] in Appendix 1). Due to the small numbers of patients in the subgroups, and the exploratory and qualitative nature of the analysis, no definitive conclusions can be drawn from these data.

Table 63 Efficacy (ORR) by Tumour Cell and Tumour Associated Immune Cell PD-L1 Expression (CA209040)

Baseline PD-L1 Status (TC = Tumour Cell, TAIC[a] = Tumour Associated Immune Cells)	ORR 2L EXP per BICR (N=145)	ORR 2L ESC per BICR (n=37)
TC PD-L1 ≥1%	7/25 (28.0%) (95% CI: 12.1, 49.4)	2/9 (22.2%) (95% CI: 2.8, 60.0)
TC PD-L1 <1%	13/101 (12.9%) (95% CI: 7.0, 21.0)	5/26 (19.2%) (95% CI: 6.6, 39.4)
TAIC PD-L1 positive	18/94 (19.1%) (95% CI: 11.8, 28.6)	7/27 (25.9%) (95% CI: 11.1, 46.3)
TAIC PD-L1 negative	2/32 (6.3%) (95% CI: 0.8, 20.8)	0/8 (0%) (95% CI: 0.0, 36.9)
TC PD-L1 ≥1% and TAIC PD-L1 positive	7/23 (30.4%) (95% CI: 13.2, 52.9)	2/7 (28.6%) (95% CI: 3.7, 71.0)
TC PD-L1 ≥1% or TAIC PD-L1 positive	18/96 (18.8%) (95% CI: 11.5, 28.0)	7/29 (24.1%) (95% CI: 10.3, 43.5)
TC PD-L1 <1% and TAIC PD-L1 negative	2/30 (6.7%) (95% CI: 0.8, 22.1)	0/6 (0%) (95% CI: 0.0, 45.9)

[a] PD-L1+ TAIC in the tumour microenvironment were qualitatively assessed, and characterised as "Lymphocytes and Macrophages", "Lymphocytes Only", "Macrophages Only", "Neither Lymphocytes or Macrophages" based on PD-L1 Immune Cell Membrane Staining by pathologist assessments. "Lymphocytes and Macrophages", "Lymphocytes Only", and "Macrophages Only" were combined to define the TAIC PD-L1 positive group. "Neither Lymphocytes or macrophages" and tumours without the presence of any tumour associated immune cells were combined to define the TAIC PD-L1 negative group.

To continue to build upon the extensive translational biomarker program across tumour indications, BMS is committed to the evaluation of clinical samples collected in CA209040, and proposes to update ANNEX II accordingly. To support exploratory biomarker endpoints in the CA209040 study, tumour samples were collected at screening from treated patients to identify biomarkers potentially predictive of nivolumab efficacy. Growing evidence in the literature suggests that biomarkers beyond (or in addition to) PD-L1 may also be associated with clinical benefit to checkpoint inhibition; these include tumour mutation burden (TMB) and immune cell infiltration within the tumour as measured by IHC and gene expression.28,29,30 These assessments have been prioritized using available tumour samples collected from CA209040.

CHMP Assessment ad c)

The MAH holds the opinion that no factor could be identified to differentiate responders and non-responders, not using demographics, (viral) aetiology, nor (PD-L1 expression-based) biomarkers.

The search for biomarker analysis to define the useful tumour- and TAIC characteristics required to define

those patients that will experience the most benefit of nivolumab as 2L treatment for HCC remains difficult, but of obvious importance. On the basis of results provided by the MAH in response to the question by the CHMP on the importance of PD-L1, the predefined postulated cut off values of positivity for PD-L1 (1%) on tumour tissue and/or TAIC cannot be considered to provide solid proof. Nevertheless, there is (still) a clear trend for higher ORR with a higher percentage of tumour cell (TC) PD-L1 expression (Table N), as well as with TAIC PD-L1 positivity, and with the combination of both (Table 4). Also, being 'TAIC PD-L1 negative' resulted in an ORR of only 6.3% in the EXP population of study CA209040. Taken together, these observations suggest, the importance of PD-L1 expression, in particular on the TAICs.

Table N. BICR-assessed overall response rate (ORR) using RECIST 1.1

Baseline PD-L1 expression		2L EXP cohort N=145
≥5%	N	9 (6.2%)
	ORR	**4/9 (44.4%)**
<5%	N	117 (80.7%)
	ORR	**16/117 (13.7%)**
≥1%	N	25 (17.2%)
	ORR	**7/25 (28.0%)**
<1%	N	101 (69.7%)
	ORR	**13/101 (12.9%)**
Non-quantifiable*	N	19 (13.1%)
	ORR	**1/19 (5.3%)**

(ORR=CR+PR; * includes PD-L1 tumour sample not available, PD-L1 not evaluable and indeterminate)

In conclusion, in line with the MAH's intentions to define biomarkers for clinical benefit in this indication, these observations urge for further exploration of the value of PD-L1 expression on TCs as well on TAICs in HCC patients in a prospective manner. This in an attempt to identify the patients that will and the patients that will not benefit from nivolumab treatment. In addition, the relationship between TC and/or TAIC PD-L1 expression and OS should be further investigated. Furthermore, (as stated by the MAH) biomarkers beyond (or in addition to) PD-L1 (including TMB and immune cell infiltration within the tumour) may also be associated with clinical benefit to checkpoint inhibition. Therefore, the MAH's commitment to further evaluate the relevance of (new) biomarkers in HCC is appreciated. However, the non-comparative nature of study CA209040 and the small numbers will probably prevent firm conclusions to be drawn.

Issue (MO-c) considered resolved, further biomarker analysis studies to be included in Annex II of MA.

Moreover, the applicant is asked to justify how the data from the presented single, non-comparative exploratory study, should be considered as sufficient evidence to support a positive B/R in the target population, in particular as in 2L advanced HCC a comparative phase 3 study is feasible, considering the unclear relationship between surrogate endpoints and OS in the 2L HCC setting and taking into account the recently reported study results with regorafenib in 2L HCC. In this discussion, also the rationale to justify the study design should be provided and the applicant should further discuss on ways to generate confirmation of the available exploratory study results, including estimated timelines.

Nivolumab Efficacy Data in 2L HCC from CA209040 are Compelling When Compared to Other Treatment Options from the Literature.

As described above in the response to Question 1a, although there are no currently approved treatment options for advanced HCC patients previously treated with sorafenib, durable responses are observed from the 29-Nov-2016 clinical and 12-Dec-2016 BICR DBLs in Study CA209040 with a lower bound of the response rate from the pooled 2L ESC and 2L EXP analysis (10.5% by RECIST 1.1) that is higher than tyrosine kinase inhibitors, including regorafenib, as well as chemotherapy agents. Furthermore, the median DOR of nivolumab of 19.4 months in pooled 2L ESC and 2L EXP subjects highlights the potential for clinical benefit compared to regorafenib (median DOR 3.5 months). In addition, the median OS and OS rates compare favourably to what has been described with other agents used in the 2L setting.

Whereas ORR as a surrogate endpoint for survival may not be appropriate for systemic chemotherapy and targeted agents in HCC, BMS believes a moderate ORR with evidence of significant durability is likely to predict clinical benefit from nivolumab. This is evidenced by analysis of ORR and DOR vs chemotherapy across nivolumab studies in NSCLC, melanoma, and SCCHN.

Previous 2L HCC Trial Failures in Other Investigational Study Drugs and Why CA209040 is Unique BMS acknowledges that there are multiple Phase 1-2 studies that have subsequently failed in Phase 3. Reasons for failure are multifactorial including potential flaws in trial design due to heterogeneity or selection bias, toxicity, and marginal antitumoural activity.31 BMS contends that the preliminary signals observed in Phase 1-2 studies from these failed and ongoing Phase 3 studies in 2L HCC subjects as shown in Table -7 (ORR ranging from 3-11% and median OS ranging from ~7 to 12 months 32, 34, 35, 36, 37, 38) were not as compelling as the results from CA209040. Moreover, there are several features in CA209040 that are unique when compared to these prior studies:

- Objective response rates by BICR in CA209040 by either RECIST or mRECIST whose lower bound is higher than the response rates observed for other agents

- Complete responses confirmed by BICR using RECIST 1.1 and mRECIST in CA209040 of 2.7% and 5.4% for 2L ESC and 1.4% and 2.8% for 2L EXP subjects, respectively. These findings are notable as CRs were not observed in any of these prior Phase 1-2 studies.
- Durability of response for pooled 2L ESC and 2L EXP subjects = 19.4 months which is significantly greater than that observed with tyrosine kinase inhibitors (typically range from 3.5-4.5 months)

- A novel mechanism of action as an immuno-oncology therapy with evidence from other tumour types suggest that durable ORR correlates with survival benefit

- Efficacy population with sample size of 182 2L subjects (37 in 2L ESC and 145 in 2L EXP cohorts), with consistent findings observed between the 2 cohorts, which is far greater than the sample size in most Phase 1-2 advanced HCC studies (most range from ~ 40-70 subjects) and allows for a more precise estimate of ORR and median OS. In addition, a minimum follow-up of 12 months in the Nov-2016 DBL and 15 months in the Mar-2017 DBL allows a stable estimate of DOR and OS rates at 12 months and 18 months.

- Median OS of 15 months for 2L ESC and 15.6 months for 2L EXP subjects as of the 17-Mar-2017 clinical DBL which is favourable compared to studies of other treatment options.
  The OS rates in the 2L ESC and 2L EXP cohorts at 12 months were 58.0% and 59.9% and at 18 months were 46.4% and 43.8%, respectively.
- Safety population with sample size of 262 subjects to allow a robust assessment of the overall safety of nivolumab in advanced HCC, including a profile that is similar to that across multiple

tumour types and > 40,000 subjects with no new signals.

- Inclusion of patients in the 2L EXP cohort from 11 countries including US, Canada, Spain, United Kingdom, Italy, Germany, Japan, Korea, Taiwan, Hong Kong, and Singapore, thereby making the results more applicable to real world settings and the global burden of disease.

Table 64 Efficacy Outcomes of Prior Phase 1/2 2L HCC Trials Compared to CA209040

Study Drug	2L HCC Sample Size	ORR	Median OS
Nivolumab	145 2L EXP	14.5% by RECIST 1.1 18.6% by mRECIST	15.64 months (95% CI: 13.24-18.89)
	37 2L ESC	18.9% by RECIST 1.1 21.6% by mRECIST	14.95 months (95% CI: 4.99-28.06)
Everolimus[34]	39	2.6% by RECIST	33.4 weeks (95% CI: 9.2-57.6)
Everolimus[35]	38	4% by RECIST	8.4 months (95% CI: 3.9-22.1)
Brivanib[32]	46	4.3% by WHO 10.9% by mRECIST	9.8 months
Ramucirumab[36]	42	9.5% by RECIST	12.0 months (95% CI: 6.1-19.7)
Tivantinib[37]	71[a]	1.4% by RECIST 1.1	6.6 months (95% CI: 4.6-9.0); MET-high subgroup (n=37) 7.2 months (95% CI: 3.9-14.6)
Cabozantinib[38]	41[b]	Overall population 5% by RECIST	Overall population 11.5 months (95% CI: 7.3-15.6)
Regorafenib[39]	36	2.8% by mRECIST	13.8 months (95% CI: 9.3-18.3)

[a] 71 subjects received tivantinib and 36 received placebo

[b] 22 subjects had prior sorafenib and 24 had prior TKIs

Clinical Relevance and Justification of the CA209040 Study Design

CA209040 was originally designed in 2012 and started as a Phase 1, 3+3 dose escalation design to explore safety and antitumour activity of nivolumab across uninfected, HCV-infected, and HBV-infected subjects. In late 2014, after observing investigator-assessed responses across all etiologic subtypes and establishing safety up to 10 mg/kg (including CRs, durable responses, and favourable OS) and promising OS in the escalation cohort, the study was expanded to a Phase 2 part with a primary endpoint of ORR in 4 additional cohorts of 50 subjects each (uninfected sorafenib naive/intolerant, uninfected sorafenib progressors, HCV-infected, and HBV-infected).

Combined with the observation that antitumour responses in HCC can correlate with OS (as discussed in Question 1a), BMS concluded that in the absence of an approved standard of care (SOC) in the 2L HCC setting, a single arm design had the potential to demonstrate clinical benefit.
Additionally, BMS subsequently initiated plans to establish the safety and efficacy of nivolumab in sorafenib-naive patients in a large, randomized Phase 3 study - Study CA209459 (nivolumabvs. sorafenib in 1L advanced HCC) as outlined below.

Nivolumab and other PD1/PD-L1 inhibitors have been extensively studied in many tumour types which have significantly changed the treatment paradigm for cancer patients. These agents, including nivolumab, have demonstrated an established safety profile and long-term efficacy benefit in patients with advanced cancers. With the preliminary support of the promising efficacy and safety findings in the ESC cohort and the considerations provided above, a single arm study design was deemed justifiable in patients with 2L advanced HCC whose disease course is predictable and invariably fatal in a matter of months. In addition, the large sample size and sufficient follow-up enabled robust and stable estimates of ORR, DOR, and median OS and OS rates at 12 and 18 months. The EXP cohort demonstrated consistent efficacy and safety results observed in the original, smaller ESC cohort. Furthermore, similar baseline demographic characteristics between CA209040 and the RESORCE trial (Table 1a of Appendix 1) allow for further cross trial comparison on safety and efficacy between nivolumab and regorafenib in the 2L HCC setting. Without identification of a significant selection bias in the CA209040 study, nivolumab has demonstrated favourable OS benefit when indirectly compared to regorafenib, and the ORR, DOR and OS data (Table -1) are compelling when compared to published data of regorafenib.

In summary, the intent to pursue registration on the basis of CA209040 was only established following demonstration of compelling data, which suggested the potential for clinically relevant improvement in outcomes for advanced HCC patients previously treated with sorafenib. Although a single-arm study, CA209040 was well-conducted and with a robust statistical analysis plan.

Consistent results were observed across endpoints in the ESC and EXP cohorts in a patient population that reflected clinical practice (sorafenib progressors and intolerant). While the lack of a comparator in this study does limit the assessment of time-based endpoints such as OS, indirect comparisons with historical data suggest that long term survival in 2L EXP treated subjects with a median of 15.6 months (95% CI: 13.2, 18.9) compares favorably to historical data, including comparisons to regorafenib and placebo (median OS of 10.6 months, 95% CI: 9.1, 12.1 and 7.8 months, 95% CI: 6.3, 8.8, respectively).

Confirmatory Trial in the 1L Setting of HCC

Given the promising efficacy data observed in CA209040 in 2L HCC subjects, as outlined in response to Question 1a, and manageable safety profile, BMS is conducting a Phase 3 randomized trial in the 1L setting comparing nivolumab vs. sorafenib (CA209459) with ORR and OS as co-primary endpoints. Study design details and study milestones are provided in Table -8. The study is currently fully enrolled and data are expected to be available in 3Q2017 (ORR endpoint) and 1Q2018 (OS endpoint); therefore, BMS does not plan to conduct a confirmatory randomized Phase 3 trial in 2L HCC subjects and believes the data from a randomized Phase 3 trial in the 1L advanced HCC setting is sufficient to further confirm the efficacy and safety profile of nivolumab in 2L advanced HCC.

	CA209459
Study name	A Randomized, Multi-center Phase III Study of Nivolumab versus Sorafenib as First-Line Treatment in Patients with Advanced Hepatocellular Carcinoma
Number of subjects	726 to be randomized 1:1
Key inclusion criteria	• Subject's disease not amenable for surgical or loco-regional therapy or who have progressed after surgery or loco-regional therapy • Subjects must not have received prior systemic therapy for advanced HCC • Histologically confirmed HCC with at least one RECIST v1.1 measureable untreated lesion • Additional criteria include: Child-Pugh A status, ECOG performance status 0-1, adequate hepatic function (albumin $\geq$ 2.8 g/dl, total bilirubin $\leq$ 3 mg/dl, AST/ALT $\leq$ 5x ULN), and adequate renal and hematologic function
Key exclusion criteria	• History of hepatic encephalopathy • Ascites by physical examination at screening or prior or current treatment for ascites • Co-infection with HBV/HCV or HBV/HDV
Treatments	nivolumab: 240 mg IV or sorafenib: 400 mg BID
Stratification factors	1) etiology (HCV- vs non-infected HCC), 2) presence or absence of vascular invasion and/or extrahepatic spread, and 3) geography (Asia vs non-Asia)
Primary endpoint(s)	OS and ORR by BICR
Secondary endpoint(s)	PFS by BICR and efficacy by PD-L1 tumour expression
Enrolment completion	07-Mar-2017
Last patient, last visit	07-Jul-2017 for primary ORR analysis
Database lock for primary ORR analysis (1st 368 randomized patients)	21-Aug-2017
Database lock for primary OS interim analysis (416 deaths, 80% of target events)	1Q 2018
Database lock for primary OS final analysis (520 deaths)	4Q 2018

CHMP Assessment

The contemporary approach of patients with advanced HCC that have shown intolerance for sorafenib or who have progressed on this TKI is hampered by limited options. It is readily agreed with the MAH that currently there are no registered therapies that can provide clinically relevant benefit for these patients. Therefore, the investigation of the potential benefits of checkpoint inhibitor nivolumab in this population is welcomed. However, this is by no means a valid excuse for not conducting (nor planning) a comparative study. The MAH's arguments for not pursuing a controlled trial are not convincing.

In conclusion, the MAH has not satisfactorily justified how the data from a single, non-comparative exploratory study should be considered as sufficient evidence to support a positive B/R in the target population. Importantly, a comparative study, which is deemed feasible, would also have a primary endpoint encompassing true, clinically relevant patient benefit (e.g. OS), which would improve the

external validity of the study results (due to the comparative nature), and provide more biomarker data to try and identify the patient population that could benefit most from nivolumab treatment. Unfortunately, the MAH has no plans to conduct a confirmatory comparative study in 2L HCC patients. Importantly (and as stated earlier), the patients in the EXP cohort of study CA209040 seem to be characterized by a particular and relatively favourable profile. Due to the non-controlled study design of study CA209040, this profile hampers comparison data from study CA209040, e.g. DoR, PFS, and OS, with external data. Moreover, this apparent selection bias cannot be corrected posthoc in this single arm setting, as both known and unknown factors will have contributed. Therefore, the B/R-balance in the broad 2L (post-sorafenib) indication applied for remains negative.

Issue (MO-'justification') not resolved.

Overall Conclusion of the Benefit-Risk of Nivolumab in Advanced HCC

Nivolumab monotherapy presents a favourable benefit risk profile in patients with HCC after prior sorafenib therapy as shown in CA209040.

The current SOC for subjects with advanced HCC is sorafenib. Most patients will progress with sorafenib treatment or be intolerant to long-term sorafenib therapy. There are no approved therapies for subjects with HCC who are intolerant to sorafenib or have progressed after sorafenib.
Currently, ESMO and other guidelines recommend BSC measures or clinical trial participation to patient with progression or intolerance to sorafenib with unresectable disease, metastatic disease, or extensive tumour burden. New effective therapies with novel mechanisms of action would be particularly impactful given the dismal outcomes and limited options for those affected with advanced HCC. No SOC has demonstrated durable benefit in this advanced patient population, therefore, the single-arm design of CA209040, which shows favourable ORR and DOR compared to historical data, is appropriate for supporting the benefit risk assessment.

Recently, the multi-tyrosine kinase inhibitor regorafenib, (in a similar class as sorafenib), demonstrated an improvement in OS compared to placebo in patients (mOS: 10.6 months for regorafenib+BSC and 7.8 months with placebo+BSC) who have progressed on sorafenib. Although that difference was statistically significant, the incidence of drug-related AEs was relatively high. Drug-related AEs were reported in 93% of regorafenib-treated subjects with the most clinically relevant grade 3-4 events including hypertension (13%), hand-foot skin reaction (13%), increased blood bilirubin (7%), fatigue (6%), and increased AST (5%). In addition, deaths due to study drug toxicity were reported in 2% of subjects and drug-related AEs leading to discontinuation were reported in 10% of subjects. These data suggest the safety profile of nivolumab may be better tolerated which has overall fewer drug-related AEs, drug-related grade 3-4 AEs, and drug-related AEs leading to discontinuation. Furthermore, the HRQoL assessed by FACT-Hep and EQ-5D questionnaires showed that regorafenib was not better than placebo. Regorafenib is not currently approved for the treatment of HCC.

Data from CA209040 demonstrates that nivolumab monotherapy has antitumour activity and an acceptable safety profile across all 3 etiologic subtypes of advanced HCC (see updated safety from 29-Nov-2016 DBL in response to Question 12). The nivolumab efficacy data from the 2L setting for HCC indicates the potential for nivolumab to fulfill a significant unmet medical need, and are favourable relative to the results reported for BSC, sorafenib in the 1L setting, and to the multi-tyrosine kinase inhibitor, regorafenib, in the 2L setting.
Efficacy in CA209040 was assessed using both RECIST 1.1 and mRECIST criteria. Although mRECIST was developed for the assessment of locoregional therapy and subsequently extrapolated for use in

anti-angiogenic therapy, its utility for assessing tumour response to immuno-oncology therapies has not been tested. In addition, mRECIST for HCC is relevant only for the assessment of liver tumours. In CA209040 and in similar studies, the majority of patients with advanced HCC (approximately 70%) have target lesions outside the liver. Such lesions are not amenable for assessment by mRECIST for HCC. Therefore, RECIST 1.1 was chosen for analysis of the primary objective in CA209040 to allow for comparison to historical data and mRECIST assessment was included as an exploratory objective.

In CA209040, with the updated efficacy/safety from the Nov-2016 DBL, BICR confirmed ORRs of 18.9% and 21.6% in 2L ESC and 14.5% and 18.6% in 2L EXP subjects using RECIST 1.1 and mRECIST criteria, respectively, were favourable to those historically noted with sorafenib (2% to 6.9%, RECIST or RECIST 1.1 and 8.8%, mRECIST5), regorafenib (6.6%, RECIST 1.1 and 10.6%, mRECIST) or chemotherapy regimens (<10% by RECIST). Consistent with this, a pooled analysis of the 2L ESC and 2L EXP subjects from the 29-Nov-2016 DBL demonstrated a BICR confirmed ORR of 15.4% (95% CI: 10.5, 21.5) per RECIST 1.1. Of these subjects in CA209040 with confirmed ORR by RECIST 1.1, 2.7% and 1.4% had a CR in the 2L ESC and 2L EXP cohorts, respectively. Most recently, from the 17-Mar-2017 DBL, with a minimum follow-up of 15 months on all subjects, the median DOR for 2L ESC and 2L EXP subjects is 19.4 months and 16.6 months, respectively.

These durable responses are further supported by comparable median OS and OS rates at 12 months (58.0% and 59.9%) and 18 months (46.4% and 43.8%), in the 2L ESC and 2L EXP cohorts, respectively. In addition, median OS from the 17-Mar-2017 DBL in CA209040 was clinically meaningful relative to BSC (7 to 8 months) and to regorafenib (10.6 months) for subjects in the 2L ESC and 2L EXP cohorts (15.0 months [95% CI: 4.99, 28.06] and 15.6 months [95% CI: 13.24, 18.99] with minimum follow-up of 15 months for all subjects). It is important to highlight that the lower bound of the 95% CI for OS in CA209040 (13.24 months) exceeds the upper bound for regorafenib (12.1 months). This indicates a potential long-term benefit with nivolumab treatment. Although there are no currently approved treatment options for advanced HCC patients previously treated with sorafenib, durable responses are observed in Study CA209040 with a lower bound of the response rate from the pooled 2L ESC and 2L EXP analysis that is higher than tyrosine kinase inhibitors, including regorafenib, as well as chemotherapy agents. Furthermore, the median DOR of nivolumab of 19.4 months and 16.6 months in 2L ESC and 2L EXP subjects highlights the potential for clinical benefit compared to regorafenib (median DOR 3.5 months). In addition, the median OS and OS rates compare favourably to what has been described with other agents used in the 2L setting. Improvement in ORR and DOR with nivolumab in other tumour types has translated into improvement in OS. Consistent with the experience of nivolumab in multiple tumour types including 2L NSCLC, RCC, melanoma, SCCHN, and cHL, a subset of subjects in CA209040 had clinically meaningful objective and durable responses, which is likely to predict demonstration of improvements in OS in the 2L HCC population treated with nivolumab.

Immuno-oncology agents like nivolumab have improved cancer treatment in recent years. The benefit-risk assessment for nivolumab, as shown in CA209040, with its different mechanism of action from the multi-tyrosine kinase inhibitors is favourable with compelling results for BICR-assessed ORR and mDOR which correlate with substantially longer OS (mOS 15.6 months in 2L EXP) relative to BSC (7-8 months) or regorafenib (10.6 months). These results are unprecedented in advanced HCC subjects with prior sorafenib treatment who have no other approved therapies and a high unmet need.

Overall CHMP conclusion on MO 1

Updated efficacy data from a minimum of 15-months follow-up is now available and confirms previous findings in terms of ORR, and PFS for the overall population and importantly provides an estimate of median DoR and median OS data.
OS findings seem to be well-above what it can be expected to date for a 2L HCC population that lacks effective therapies. The phase I/II CA209040 trial has methodological limitations such as ORR (the primary endpoint) or the absence of comparator. The former, cast doubts with regard to the correlation with OS, even though it would be reasonable to expect that patients experiencing prolonged responses could likely live longer, as previously observed with nivolumab in other tumour types.

OS results according to responder status show a marked difference between responders and no responders. Whereas OS for the population showing response to nivolumab (ORR: 14.5% 2L-EXP) is considered outstanding (OS median not reached, minimum OS≥12 months), the median OS for the non-responder population is considered remarkably high (16.3 months (95% CI 13.83, 19.44)) and is well-above what could be expected for this setting. Among the possible causes of this unexpected high OS median for the non-responders, partly could be due to the disease stabilization rate observed (40.7%) for the overall population or due to the possible influence of post-progression therapies, however none of them seem to be solid arguments, though plausible, when it comes to explaining this finding.

In conclusion, it is considered that MO-a) and -b) are only partially resolved and that MO-'justification' is not resolved. The following new Major Objection is proposed: The evidence provided by the exploratory, non-comparative trial CA209040 is considered insufficient to support a positive B/R in the target population applied for. The key issues identified pertain to the non-comparative design of the study and an apparent selection bias for relatively indolent tumours in the study population. This selection bias creates a source of uncertainty regarding the study population with respect to a wide range of known and unknown factors that could affect the outcome, thus making it difficult to infer that any favourable outcome, i.e. long OS, is from the treatment alone. This uncertainty cannot be solved post hoc and also hampers interpretation of the results when compared to an external control. Together, the actual effect size and clinical relevance of the study results cannot be assessed and this renders the benefit/risk negative.

Other concerns

Question 2

No type I error control, nor sample size and power calculation was pre-planned for the clinically more relevant endpoints PFS and OS. The applicant is requested to discuss the robustness of these results, including to replication of these findings for comparable groups and/or drugs.

Summary of MAH answer

BMS acknowledges that the type I error control was not planned for PFS and OS in Study CA209040. This was due to the nature of the single-arm design where an indirect comparison to historical data for time to event analysis is a challenge.
Considering the large sample size of the 2L EXP and 2L ESC cohorts (N=182) and a minimum 48 week follow-up as per the 29-Nov-2016 clinical DBL and 12-Dec-2016 BICR DBL, the study provided a robust estimate of ORR, DOR, mPFS, PFS at 6 and 12 months, mOS, and OS rates at 6, 12, and 18 months which can be indirectly compared with historical data.
The absence of a control arm in Study CA209040 is acknowledged as a limitation which makes it challenging to filter out the natural history of disease from treatment effect as measured by time to event endpoint (e.g., PFS or OS). However, ORR, the primary endpoint in Study CA209040, is generally regarded as an effect attributable to drug, not natural history. Data from a single-arm study, as evaluated by an independent radiological review committee, is able to produce objective and clinically meaningful

evidence of durable clinical activity, and of clinical benefit in the refractory setting where there are few options for patients. Data from CA209040 suggest that patients receiving treatment with nivolumab have the opportunity to derive clinically meaningful benefit, and addresses a significant unmet medical need for advanced HCC patients. The available data are considered supportive of registration given that ORR and durability of responses compare favourably to that of sorafenib (ORR 2% to 6.9%, mRECIST or RECIST 1.1) and regorafenib (6.6% by RECIST 1.1 and 10.6% by mRECIST). In addition, the median OS and OS rates compare favourably to what has been described in the literature with sorafenib and regorafenib.

CHMP Assessment

The arguments provided by the Applicant do not address the issue whether the findings for PFS and OS are a chance finding. For instance, type I error control could have been planned for testing PFS/OS survival rates at 12 months. Also, if one lets aside the ESC cohort that contains other doses than the one applied for, the size of the EXP cohort means that a certain precision in estimates is attained, but this does not show an independent replication. As a matter of fact, the 6 and 9 months OS data in the ESC cohort (66.7% (48.9, 79.5% and 66.7 (48.9, 79.5%), Appendix 1, p.50 of the response document) are different from that in the EXP cohort (81.8% (74.4, 87.2%) and 71.2 (63.0, 77.9)%), which may be explained by different doses used in the ESC, but in any case stipulates that the ESC and EXP are no replication of each other. Finally, a comparison with historical data from other product does neither address the chance finding issue and neither does the Applicant's point that effects on ORR/DOR are no chance finding (being not in line with expected natural course), as the proposed surrogacy of ORR with sustained response with OS is based on the findings of this trial, and has to be replicated as well.

The importance of a controlled arm in a single pivotal trial is underpinned by several EMA guidelines, e.g. the guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4). Albeit that the pursuit of phase 2 exploratory studies with the objective to estimate single agent anti-tumour activity in patients with a defined tumour type is allowed, any encouraging results must lead to identification of auspicious compounds by bringing forward results from (a) confirmatory trial(s). Therefore, also in this case a phase 3 RCT is needed, as no replication has been provided.

Issue not resolved. Please refer to Overall Conclusion on the Major Objection for the new Major Objection.

Question 3

As the 5-year survival for HCC is only approximately 5-6%, it seems remarkable that for almost 40% of the study population the time from initial diagnosis to first dose of study therapy was ≥5 years. The applicant is requested to provide the mean (including standard deviation) and median (including full range and interquartile range) for time from initial diagnosis to first dose of study therapy and comment.

Summary of MAH answer

As indicated in the response to Question 1b under Major Objection (red. ad b)), the investigators reported the time from initial viral diagnosis and not HCC diagnosis, which resulted in a majority of the virally-infected subjects having a time from initial diagnosis of ≥5 years. To clarify the time from HCC diagnosis, these data have been updated in the most recent 17-Mar-2017 DBL with 20%, 11%, and 6.2% of 2L EXP subjects having a time from initial diagnosis to start of study drug ≥5, ≥6, and ≥7 years, respectively (Table M).

Table M. Time from Initial Diagnosis to First Dose of Study Therapy

	Exp Post Sorafenib All N = 145
MEAN	3.038
MEDIAN	2.212
MIN , MAX	0.05 , 24.57
Q1 , Q3	1.018 , 4.233
STANDARD DEVIATION	3.2101
< 1 YEAR	35 (24.1)
1- < 2 YEARS	35 (24.1)
2- < 3 YEARS	24 (16.6)
3- < 4 YEARS	11 (7.6)
4- < 5 YEARS	11 (7.6)
>= 5 YEARS	29 (20.0)
>= 6 YEARS	16 (11.0)
>= 7 YEARS	9 (6.2)

(Time is in years, percentages are in brackets)

Although there are reports in the literature of 5-year survival rates as low as 5-6%, large databases of thousands of patients in the EU (EUROCARE-5) and US (SEER) report 5-year survival rates ranging from 11.7% to 17.5%. In summary, given that CA209040 is a global trial, a 5-year time from initial diagnosis to starting study drug is aligned with the natural history and global epidemiologic HCC data; therefore, a selection bias for indolent tumours is not likely. See also Table N.

Table N. Time from Initial HCC Diagnosis to First Dose of Study Therapy (CA209040)

	2L EXP Cohort N = 145	2L ESC Cohort N = 37	Regorafenib[4] N = 379	Brivanib (BRISK-PS)[5] N = 263
Mean (SD), months	36 (38)	32 (35)	29 (28)	32 (32)
Median, months	26	21	21	21
Full Range	0.6-295	5-142	NR	2-221
Interquartile Range	12-51	9-32	11-38	NR

CHMP Assessment

The MAH has argued that the 5 year survival rate of patients with advanced HCC from the initial diagnosis is usually higher than 5%. A higher survival rate has indeed also been observed and this statement is therefore readily acknowledged. Notwithstanding this higher 5 year survival rate, the patients that were included in the EXP cohort of CA209040 had experienced the disease for a median time of 26 months whereas patients that were studied in the other 2L HCC studies (RESORCE and BRISK-PS) took a median time of 21 months in order to start with the next line treatment. Also the mean time between the diagnosis HCC and the moment of starting with nivolumab appeared to be ⩾4 months longer than with those that started regorafenib or brivanib as 2L for HCC (36 vs. 29 and 32 months, respectively). These figures are shown in Table N.

From this information the conclusion can be drawn that patients that were enrolled in the 2L EXP cohort of CA209040 may indeed be characterized by a particular and relatively favourable profile until onset of nivolumab therapy. This profile cannot be corrected when comparing data on DoR, PFS, and/or OS from CA209040 with historical data. Therefore, in order to entwine the unknown influences that may affect

essential outcome parameters of studied patients the pursuit of a confirmatory phase 3 RCT is stressed.

Issue only partially resolved. Please refer to the new Major Objection.

Question 4

Regarding prior sorafenib therapy, according to table 5.3.1-2 from CSR most patients had previously experienced prior progression to sorafenib (n=132; 91.0%) with a minority of patients being intolerants to sorafenib (n=12; 8.3%). These data differs from that in table 5.3.2.2-1 from CSR (74.5% patients reported disease progression, 0.7% maximum clinical benefit and 23.4% toxicity). The applicant is asked to clarify.

Summary of MAH answer

The discrepancies in Tables 5.3.1-2 and 5.3.2.2-1 are due to the usage of data from different domains as collected in the case report forms (CRFs) and programmatic derivations. Table 5.3.2.2-1 shows off-treatment reasons as assessed by the investigator, e.g. disease progression and toxicity, using a simple summary of the CRF data. Table 5.3.1-2 used more information collected in CRFs and was programmatically derived. Details are provided below:

- Sorafenib progressor and intolerance to sorafenib, which are shown in Table 5.3.1-2, are derived from CRF data including sorafenib treatment BOR, sorafenib regimen progression date, sorafenib progression type, sorafenib off-treatment reason, and intolerability to sorafenib.
- In Table 5.3.1-2, a subject is a sorafenib progressor when any of the following is satisfied: radiographic progression, clinical progression, BOR of PD, and non-missing progression date. Therefore, any progression during or after sorafenib treatment results in the classification of progressor and explains the higher frequency of progression in Table 5.3.1-2 vs. Table 5.3.2.2-1.

A subject is deemed to be intolerant to sorafenib in Table 5.3.1-2 if the subject is not a progressor and the off-treatment reason of sorafenib is toxicity, or the CRF question of prior sorafenib treatment, “Has the subject ever had intolerance to Sorafenib”, is checked “Yes”. By utilizing all relevant information on affects from prior sorafenib usage, the 2L population is believed to be better characterized by mutually exclusive “progressor” and “intolerant” categories. Table 5.3.2.2-1, however, reports data from the investigator’s assessment on the CRF without any derivation. Therefore, the derived frequency of intolerance in Table 5.3.1-2 is lower than the toxicity reported in Table 5.3.2.2-1 since subjects with both progression and intolerance were categorized as progressors.

CHMP Assessment

The discrepancies observed in CSR regarding the type of progression are due to differences in data collection from the CRF regarding the definition of a patient as progressor. Table 5.3.1-2 (please rerfer to assessment report) where 91.0% of patients were classified as progressors to sorafenib and 8.3% as intolerants is considered to more accurately define trial population.

Issue solved

Question 5

The applicant is requested to discuss the discrepancy between the sentence “The other 11 subjects who were reported with on treatment deviations were not considered true relevant protocol deviations because they either started radiotherapy after last dose of study therapy (3 subjects), had documented radiographic progression (6 subjects), or received palliative radiotherapy (2 subjects) as allowed per protocol (see Appendix 3.6 and Section 6.5.2).” in section 4.3 “Protocol Deviations” on page 68-9 of the study report and the sentence “All 11 cases

had documented radiographic progression" in section 6.5.2 "Concurrent Anti-Cancer Therapy" on page 91.

Summary of MAH answer

BMS acknowledges the discrepancy in the text reporting the number of subjects with radiographic progression on page 68-69 vs page 91 and has corrected it with the updated analysis using the 29-Nov-2016 DBL. Potential relevant protocol deviations related to use of anti-cancer therapy are programmatically identified and directly reported as any anti-cancer therapy having happened prior to the discontinuation decision date and after the first dosing date. Because the CA209040 protocol allowed for palliative treatment to be given for clinically symptomatic tumour sites including palliative radiation and surgical resection after clinical or radiographic progression, a case-by-case review would determine if the identified relevant protocol deviation was indeed of palliative usage and thus not an actual protocol deviation. In addition, anti-cancer therapy given after last dose is not considered as protocol deviation even prior to the discontinuation decision date.

Potential relevant protocol deviations were reported in 14 (5.3%) subjects in the total population. Of the 14 potential protocol deviations, the only actual relevant protocol deviation at study entry was in a subject in the 2L EXP cohort who did not have evaluable disease at baseline. In addition, the other 13 subjects who were listed as a relevant protocol deviation due to receiving "concurrent" anti-cancer therapy were not considered true relevant protocol deviations as palliative therapy after progression was allowed per protocol.

CHMP Assessment

The MAH has provided an explanation for the discrepancy as requested. The reason for regarding these patients not having had a true protocol deviation can be understood. However, it also means that the actual number of patients that encountered radiographic progression and/or required additional palliative treatment during study CA209040 can be regarded not in favour of the nivolumab approach.

Issue resolved.

Question 6

Median TTP and PFS might be different, as in case a new anticancer treatment was started without a prior reported radiographic progression per RECIST 1.1, then a patient had not been censored, but counted as having progressed. Therefore, the applicant is requested to provide sensitivity analyses for both TTP and PFS and discuss the results.

Summary of MAH answer

Sensitivity analyses for both TTP and PFS using subsequent anti-cancer therapy as an event with the other censoring algorithms unchanged from the original TTP and PFS definitions are provided in Table N.

Table N. Summary of TTP and PFS Primary Analysis and Sensitivity Analysis Using Subsequent Anti-cancer Therapy as an Event (CA209040)

	2L EXP (RECIST 1.1)		2L ESC (RECIST 1.1)	
Median, months (95% CI)	BICR	Inv.	BICR	Inv.
Progression-free Survival				
Primary Analysis[a]	2.79 (2.63, 4.04)	4.01 (2.76, 5.42)	3.45 (1.61, 4.14)	3.12 (1.61, 5.49)
Sensitivity Analysis[a]	2.79 (2.63, 4.01)	4.01 (2.73, 5.42)	3.45 (1.41, 4.14)	2.79 (1.61, 5.49)
Time to Progression				
Primary Analysis[a]	2.83 (2.66, 4.11)	4.07 (2.76, 5.52)	4.01 (1.41, 6.97)	3.40 (1.41, 5.72)
Sensitivity Analysis[a]	2.79 (2.63, 4.07)	4.07 (2.76, 5.52)	4.01 (1.41, 6.97)	3.40 (1.41, 5.72)

[a] Based on the 29-Nov-2016 clinical DBL and 12-Dec-2016 BICR DBL

Overall, results from the sensitivity analyses of median TTP and median PFS using RECIST 1.1 were consistent with the primary analyses. Further, PFS rates from the sensitivity analysis were similar in the 2L EXP and in the 2L ESC cohorts at 3, 6, and 9 months (46.7% vs 50.2%, 28.3% vs 30.4%, 20.5% vs 27.4%, respectively) and were comparable to the primary analysis (48.5% vs 51.6%, 29.6% vs 31.3%, and 21.8% vs 28.2%, respectively).

CHMP Assessment

Sensitivity analyses on PFS and TTP were performed, now counting for a new anticancer treatment, that started without considering a prior reported radiographic progression per RECIST 1.1 as an event. The results did not substantially change results for both TTP and PFS.

Issue resolved.

Question 7

As it was mentioned as a secondary endpoint in the study protocol, the applicant is requested to provide endpoint analysis for TTP rate and comment.

Summary of MAH answer

In Study CA209040, the time to progression (TTP) rate by RECIST 1.1 was defined as the proportion of subjects with disease progression at a time point using the Kaplan-Meier method. The TTP rate in the 2L EXP and 2L ESC cohorts was comparable between the cohorts and was 50.7% and 48.6% at 3 months, 68.0% and 64.9% at 6 months, 76% and 68.8% at 9 months, and 80.3% and 76.6% at 12 months, respectively. These rates are of clinical relevance as the data demonstrate the time to progression is delayed when compared to the placebo arm of the Phase 3 2L advanced HCC BRISK-PS trial with TTP rate estimated from the KM curve of approximately 55% at 3 months, 80% at 6 months, 90% at 9 months, and 95% at 12 months (Llovet et al. J Clin Oncol. 2013 Oct 1;31(28):3509-16.).

CHMP Assessment

The MAH has provided endpoint analysis for TTP rate, as requested. The comparison of these results obtained in a single, non-comparative study with results from the literature should however be interpreted with the usual caution, as differences between the patient populations cannot be excluded.

Issue resolved.

Question 8

Although from a clinical point of view it seems reasonable to base discontinuations on both radiologic and clinical criteria, from a methodological point of view the most objective measure of progression would be radiographic. The applicant should provide subgroup analysis according to type of progression to prior sorafenib therapy.

Summary of MAH answer

BMS has performed additional subgroup analyses based on the type of progression to prior sorafenib therapy (radiographic, clinical, neither radiographic nor clinical, and unable to determine) as shown below in Table XX. As a subject could be reported by the investigator to have both radiographic and clinical progression, the following algorithm was used to determine the type of progression:

- Radiographic: radiographic progression status is "Yes" regardless of clinical progression status;
- Clinical: clinical progression status is 'Yes' and radiographic progression is either "No" or missing;
- Neither Radiographic nor Clinical: radiographic and clinical status are both 'No';
- Unable to Determine: radiographic progression and clinical progression status are both missing.

The vast majority of subjects had radiographic progression in the 2L EXP (83%) and 2L ESC (86%) cohorts based on BMS derivation as defined in response to Question 4. ORR in the subset of radiographic progressors was clinically meaningful and ranged from 14.2% to 21.9% in the 2L EXP and 2L ESC subjects. These data are similar to the ORR of 14.5% and 18.9% observed in the overall 2L EXP and 2L ESC subjects. In addition, although the number of 2L EXP subjects with either clinical progression (n=11) or neither radiographic nor clinical progression (n=10) was relatively small, responses were observed in each subgroup. Subgroup comparisons within the 2L ESC cohort were not possible given only 1 or 4 subjects has clinical progression or neither radiographic nor clinical progression, respectively. Therefore, these data suggest that the ORR in subgroups without radiographic progression is similar to the subjects with radiographic progression (n=120) as well as the overall 2L EXP cohort (n=145). Taken together, these data indicate that advanced HCC subjects can have clinically meaningful responses to nivolumab regardless of the type of progression to prior sorafenib therapy. ORR per investigator by prior sorafenib progression is provided in Table S.5.5b-2-INV of Appendix 8.

Table 65 : Objective Response Rate per BICR RECIST 1.1 by Prior Sorafenib Progression

Objective Response Rate (%) 95% CI	2L EXP Cohort N = 145	2L ESC Cohort N = 37
PRIOR SORAFENIB PROGRESSION		
RADIOGRAPHIC PROGRESSION	17/120 (14.2%) (8.5, 21.7)	7/32 (21.9%) (9.3, 40.0)
CLINICAL PROGRESSION	1/11 (9.1%) (0.2, 41.3)	0/1 (0.0, 97.5)
NEITHER RADIOGRAPHIC NOR CLINICAL PROGRESSION	1/10 (10.0%) (0.3, 44.5)	0/4 (0.0, 60.2)
UNABLE TO DETERMINE	2/4 (50.0%) (6.8, 93.2)	0/0 (N.A., N.A.)

Confidence interval based on the Clopper and Pearson method
Subject with both radiographic progression and clinical progression is considered to be radiographic progression

CHMP Assessment

Most patients in 2L EXP cohort of trial CA209040 reported radiographic progression irrespective of clinical progression and only 11 patients reported clinical progression only. This is not unexpected. ORR according to the type of progression show similar results for the subgroup of patients showing radiographic progression to the overall population (14.2% vs 14.5%) and the ORR for the subgroup of patients with only clinical progression is lower (9.1% vs. 14.5%). However, this result is hampered by the very limited sample size of the subgroup.

Taking into account that it seems reasonable in clinical practice both types of progression trigger sorafenib discontinuation, though radiologic progression is the most objective, and considering that the limited sample sized of the subgroup of patients with only clinical progression precludes from drawing any firm conclusion. No concerns arise from the criteria to recruit patients that progressed to sorafenib.

Issue resolved.

Question 9

Although the population enrolled in the 2L-Exp cohort of the trial can be considered representative of the target population, it is expected that in clinical practice not all patients have preserved liver function. There are no data on patients with Child-Plug status B and C or ECOG-PS>1. The applicant should discuss.

Summary of MAH answer

BMS acknowledges the current lack of data on patients with Child Pugh (CP) status B and C and ECOG PS >1.

Patients with more compromised liver function (CP B and C) have competing risks of death from liver failure and have largely been excluded from most advanced HCC clinical trials as their inclusion may confound evaluation of efficacy and safety in the overall population. The selection of patients with well-preserved liver function (CP A) is reflected in the patient populations of the sorafenib and regorafenib registration trials (Table XX).

Table 66 Percentage of Patients with Child-Pugh A and ECOG 0-1 Status in the Pivotal Sorafenib and Regorafenib HCC Trials

	Child-Pugh A	ECOG 0-1
Sorafenib 1st line SHARP trial (N=602)[1]	96%	92%
Sorafenib 1st line Asia-Pacific trial (N=226)[2]	97%	95%
Regorafenib 2nd line trial (N=573)[3]	98%	100%

In a subanalysis of SHARP, those with an ECOG performance status of 0 had an OS of 13.3 months compared with 8.9 months for those with performance status 1-2, illustrating the relevance of performance status to OS in a Western population.4 A similar trend was observed in the subset analysis of the sorafenib Asia-Pacific trial, (7.1 months OS for ECOG PS 0 and 6.1 months for ECOG PS 1-2).

More recent studies on sorafenib treatment outcomes are consistent with the trends observed in the pivotal trials. A retrospective study using time-dependent receiver operating characteristic analysis identified CP status as one of the significant predictors of OS. ECOG performance status was identified as a significant predictor of progression free survival (PFS). In a UK audit of patients treated with sorafenib in clinical practice or on trial, significant differences in OS comparing CP A versus CP B were observed (9.5 versus 4.6 months). A significantly decreased risk of death was seen in patients with ECOG performance status 0. CP status also has safety implications. Patients with CP B status have a higher incidence of AEs than patients with CP A status. In a prospective evaluation of safety and efficacy of patients with CP A and B, liver dysfunction (defined as any grade encephalopathy, > Grade 3 ascites, or > Grade 3 bilirubin increase) was significantly higher in patients with a CP score > 8 (CP B) even though no significant differences were seen in AEs, dose modification, and treatment discontinuation across CP scores of 5-8. In an analysis of the GIDEON data across CP subgroups the type and incidence of AEs were generally consistent across CP subgroups. However, serious AEs were more common in CP B patients (36% for CP A, 54-69% for CP B scores from 7-9). In total, AEs leading to permanent discontinuation were more common in CP B (40%) and C (43%) patients than in CP A patients (29%), although the incidences of drug related AEs leading to discontinuation were similar (21%, 15%, and 17%, respectively). In a similar analysis of the Japanese subset of the GIDEON study, AEs resulting in permanent discontinuation of sorafenib and deaths were observed more frequently in patients with CP B compared with CP A. Duration of treatment tended to be shorter as the CP score worsened.10

These efficacy and safety data on sorafenib treatment outcomes validate the need to have a more homogeneous trial population in terms of CP and ECOG status. Nonetheless, BMS acknowledges the need to generate data in patients with worse liver function as the non-Child Pugh A population comprises a substantial proportion of the advanced HCC patient population ranging from 30 - 50%. This will allow an assessment of nivolumab safety in a broader clinical population. Furthermore, the CA209040 study was amended in 2016 to include a CP-B cohort to explore the potential clinical utility of nivolumab in this patient population.

In conclusion, the CA209040 clinical study design of the ESC and EXP cohorts is consistent with other HCC trials with its inclusion of CP status and ECOG.

CHMP Assessment

HCC patients are expected to be an heterogeneous population in the clinical practice, with patients with different CP scores (including B and C), ECOG >1, requiring antiviral therapies and with other significant

co-morbidities that could likely affect patient´s prognosis. Having said that, it is not unusual that clinical trials, especially in HCC, try to recruit a population as homogeneous as possible.

Although ideally, trial population should be completely representative of the target population, the limitations derived from the exclusion of certain patients can be adequately address by a clear description of the population enrolled under section 5.1 of SmPC.

Issue resolved.

Question 10

The applicant is requested to provide efficacy endpoints per baseline PD-L1 expression by BICR using RECIST 1.1 and discuss.

Summary of MAH answer

Prevalence of tumour cell PD-L1 expression ≥1% is 17.2% for HCC patients in the 2L EXP cohort in the CA209040 study. For this same population, the prevalence of tumour cell PD-L1 expression ≥5% is approximately 6.2% (Table N). Unlike other tumour types such as NSCLC and melanoma, the prevalence and expression levels of tumour cell PD-L1 in 2L HCC are remarkably low.

Efficacy responses per baseline tumour cell PD-L1 expression by BICR using RECIST 1.1 were comparable to those by investigator assessment. The updated 29-Nov-2016 clinical DBL and 12-Dec-2016 BICR DBL was used for the efficacy analysis per baseline PD-L1 expression by BICR assessment.

Objective responses by BICR assessment were observed in both the 2L EXP and 2L ESC cohorts regardless of tumour cell PD-L1 expression. Only a minority of subjects are PD-L1 positive (17.2% for 2L EXP and 4.3% for 2L ESC subjects). Although there was a trend of higher ORR in the PD-L1 positive vs. PD-L1 negative subjects in the 2L EXP subjects (28% vs. 12.9%), the confidence intervals are broad and overlapping. In addition, this trend was not consistently observed as the ORR in 2L ESC subjects was similar regardless of PD-L1 expression. Importantly, CRs by BICR were observed only in the PD-L1 negative group (2 in 2L EXP and 1 in 2L ESC subjects). There was no enrichment for response in the PD-L1 positive subjects in either the 2L EXP or 2L ESC cohorts. Moreover, there were several PD-L1 negative subjects with evidence of greater antitumour activity (based on change from baseline and deeper responses) than PD-L1 positive subjects. PFS by BICR assessment by baseline tumour cell PD-L1 expression for all treated subjects in the 2L EXP cohort was comparable between subjects with ≥1% (2.79 months), <1% (2.83 months), and non-quantifiable PD-L1 expression (2.79 months). Likewise, median OS for 2L EXP subjects at the different PD-L1 expression levels were NA (95% CI: 10.84, NA), 14.36 months (95% CI: 11.70, 16.66), and 10.84 (95% CI: 5.88, NA) at ⩾1%, <1%, and not quantifiable expression levels, respectively.

In summary, the efficacy endpoints (ORR, best change from baseline, PFS, and OS) for PD-L1 expression by BICR suggest clinical benefit with nivolumab regardless of tumour cell PD-L1 expression.

CHMP Assessment

The MAH's analysis in response to OC 10 is in line with the response to MO-c). From the presented data it seems likely that PD-L1 expression on tumour cells (TCs) alone has not convincingly shown to be clinically relevant and neither to clearly distinguish benefits related to the use of nivolumab in 2L HCC. Nevertheless, there is (still) a clear trend for higher ORR with a higher percentage of TC PD-L1 expression. Regrettably, analysis of the efficacy endpoints per baseline PD-L1 expression by BICR using RECIST 1.1 was not extended to include tumour-associated immune cells (TAICs), as in our opinion, the analysis of PD-L1 expression on TAICs does seem of value. Please refer to the Summary of MAH answer to MO-c) and Assessment thereof.

Issue resolved.

Question 11

The information in the study report concerning OS data per baseline PD-L1 expression is somewhat unclear. The applicant is requested to confirm that the passage on page 116 of the report "OS rate was not calculated beyond 9 months in subjects with ⩾1% PD-L1 expression (95% CI: 10.84, NA) and was 13.24 months (95% CI: 11.70, NA) in subjects with <1% PD-L1 expression." can be interpreted as "median OS was not reached in subjects with ⩾1% PD-L1 expression (95% CI: 10.84, NA) and was 13.24 months (95% CI: 11.70, NA) in subjects with <1% PD-L1 expression."

Summary of MAH answer

The clinical evaluator's interpretation of the text on page 116 is correct. The median OS was not reached in subjects with ≥1% PD-L1 expression (95% CI: 10.84, NA) and was 13.24 months (95% CI: 11.70, NA) in subjects with < 1% PD-L1 expression. In addition, the median OS (using the 29-Nov-2016 clinical and 12-Dec-2016 BICR DBL) was similar and was not reached in subjects with ≥1% PD-L1 expression and was 14.4 months (95% CI: 11.70, 16.66) in subjects with < 1% PD-L1 expression.

CHMP Assessment

The MAH confirmation is appreciated.

Issue resolved.

4. Clinical safety aspects

4.1. Other concerns

Question 12

The Applicant should present an update on relevant safety data (e.g. deaths, SAEs, and selected AEs) at the time of efficacy data update.

Summary of MAH answer

Updated safety information, using the 29-Nov-2016 clinical DBL, is reported for all treated subjects (N = 262) and 2L EXP subjects based on a 30-day window after last dose of study treatment for Study CA209040 (Table XX).

At the time of the updated clinical DBL, the majority of patients had either progressed or died and a minority continued on nivolumab treatment (2L EXP Cohort on treatment patients: N = 29, 20.0% and ESC+EXP Cohort on treatment patients: N = 49, 18.7%).

Deaths

As of the 29-Nov-2016 clinical DBL, 116 (44.3%) subjects had died in the ESC + EXP Cohort and 44.8% of subjects had died in the 2L EXP Cohort. In both the ESC + EXP and 2L EXP Cohorts, disease progression was the most common cause of death, including deaths occurring within 30 days of last dose and within 100 days of last dose.

After the 08-Aug-2016 clinical DBL for the Interim CSR, 1 death due to study drug toxicity (pneumonitis) was reported in the 2L EXP cohort in Subject# CA209040-36-261. After a BOR of PR and 8 months of nivolumab therapy, the subject was discontinued due to disease progression and started sorafenib therapy. Thirty-five days after the 18th (last) dose of nivolumab and 6 days after initiation of sorafenib, the subject was hospitalized with Grade 3 pneumonitis after presenting with complaints of 3 day history of respiratory discomfort, fever, and cough. Fever and cough resolved after 3 days of pulse steroids.

Infectious workup was unrevealing. The subject was managed with steroids and a prolonged taper, then suddenly worsened 155 days after last dose of nivolumab. High dose steroids were given; however, the subject did not respond and died due to pneumonitis 159 days after administration of the last dose of nivolumab.

SAEs

As of the 29-Nov-2016 clinical DBL, SAEs were reported in 47.7% of subjects in the ESC + EXP Cohort and 49.0% of subjects in the 2L EXP Cohort. Grade 3-4 SAEs were reported in 32.1% and 29.7% of subjects, respectively. In the ESC + EXP Cohort, the most frequently reported SAEs were malignant neoplasm progression (7.3%), and pyrexia (2.7%). In the 2L EXP Cohort, the most frequently reported SAEs were malignant neoplasm progression (11.7%), and pyrexia (3.4%).

Drug-related SAEs were reported in 7.6% of subjects in the ESC + EXP Cohort and 9.0% of subjects in the 2L EXP Cohort. Grade 3-4 SAEs were reported in 4.6% and 4.1% of subjects, respectively. In the ESC + EXP Cohort, drug-related SAEs consisted mainly of events in the SOCs of investigations, respiratory, thoracic and mediastinal disorders, and skin and subcutaneous tissue disorders. Drug-related SAEs reported in at least 2 subjects were pneumonitis, AST increased, and infusion-related reactions; each reported in 0.8% of subjects. Drug-related SAEs of ALT increased and liver function test increased were reported in 1 subject each. No drug-related SAE of blood bilirubin increased was reported. In the 2L EXP Cohort, drug-related SAEs consisted mainly of events in the SOC of respiratory, thoracic and mediastinal disorders, gastrointestinal disorders, and injury, poisoning, and procedural complications. Drug-related SAEs reported in at least 2 subjects were pneumonitis (1.4%) and infusion-related reactions (1.4%).

SAEs were similar in frequency across uninfected, HCV-infected, and HBV-infected subjects in the ESC + EXP Cohort (Table XX-2 and Table XX-3).

AEs Leading to Discontinuation

As of the 29-Nov-2016 clinical DBL, AEs leading to discontinuation were reported in 11.1% of subjects in the ESC + EXP Cohort. Grade 3-4 AEs leading to discontinuation were reported in 6.9% of subjects in the ESC + EXP Cohort. AEs leading to discontinuation reported in at least 2 subjects included malignant neoplasm progression (5, 1.9%), increased ALT (4, 1.5%), increased AST (3, 1.1%), increased blood bilirubin (3, 1.1%), metastases to central nervous system (2, 0.8%), ascites (2, 0.8%), and stomatitis (2, 0.8%).

AEs leading to discontinuation were reported in 11.0% of subjects in the 2L EXP Cohort. Grade 3-4 AEs leading to discontinuation were reported in 6.2% of subjects. AEs leading to discontinuation reported in at least 2 subjects included malignant neoplasm progression (4, 2.8%), metastases to central nervous system (2, 1.4%), and ascites (2, 1.4%). AEs leading to discontinuation were reported in 3 (6.3%) subjects in the ESC cohort.

Drug-related AEs leading to discontinuation were reported in 3.1% of subjects in the ESC + EXP Cohort. Grade 3-4 drug-related AEs leading to discontinuation were reported in 1.5% of subjects. Drug-related AEs leading to discontinuation reported in at least 2 subjects were stomatitis and increased ALT; 2 (0.8%) subjects each.

No differences in drug-related AEs leading to discontinuation were observed within each etiologic subtype (Table XX-2 and Table XX-3).

Select Adverse Events

As of the 29-Nov-2016 DBL, across select AE categories, the majority of events were manageable, with resolution occurring when immune-modulating medications (mostly systemic corticosteroids) were

administered. Some endocrine select AEs, were not considered resolved due to the continuing need for hormone replacement therapy.

The majority of endocrine, gastrointestinal, pulmonary, renal, skin, and hypersensitivity/infusion reactions select AEs reported in the ESC + EXP Cohort were Grade 1-2, while most hepatic select AEs reported were Grade 3 (Table 12-1). Most select AEs reported were considered drug-related by the investigator. The most frequently reported any-grade drug-related select AE categories were pruritus (21.0%), rash (17.6%), diarrhea (13.0%), increased AST (9.9%), and increased ALT (9.5%).

The majority of endocrine, gastrointestinal, pulmonary, renal, skin, and hypersensitivity/infusion reactions select AEs reported in the 2L EXP Cohort were Grade 1-2, while most hepatic select AEs reported were Grade 3. Most select AEs reported were considered drug-related by the investigator. The most frequently reported any-grade drug-related select AE categories were pruritus (18.6%), rash (15.9%), and diarrhea (13.8%).

Other Events of Special Interest

Other events of special interest (OESI) included the following categories: demyelination, encephalitis, Guillain-Barré syndrome, myasthenic syndrome, myocarditis, myositis, pancreatitis, rhabdomyolysis, and uveitis.

As of the 29-Nov-2016 DBL, no additional OESIs were reported beyond the 2 subjects with pancreatitis described in the interim report included in the initial submission.

The safety profile of nivolumab remains overall acceptable in patients with advanced HCC after prior sorafenib therapy. No new risks, beyond those identified in previous studies in other indications, were identified.

Comparison of Safety Data to Regorafenib

As shown in Table XX-4, nivolumab in CA209040 may be better tolerated than regorafenib with fewer deaths due to study drug toxicity, drug-related AEs, Grade 3-4 drug-related AEs, and drug related AEs leading to discontinuation. The minimum and median follow-up for subjects in the regorafenib RESORCE trial were < 2 months and 7.0 months, which is shorter than the follow-up times for 2L EXP subjects in CA209040 based on the 29-Nov-2016 DBL of 48 weeks and 12.9 months, respectively.

Table 67 Summary of Updated Safety Results (Based on 29-Nov-2016 Clinical DBL and 12-Dec-2016 BICR DBL)

	Number (%) Subjects			
	2L EXP Cohort N = 145		ESC + EXP All N = 262	
DEATHS	65 (44.8)		116 (44.3)	
WITHIN 30 DAYS OF LAST DOSE	8 (5.5)		9 (3.4)	
WITHIN 100 DAYS OF LAST DOSE	29 (20.0)		54 (20.6)	
DUE TO STUDY DRUG TOXICITY	1 (0.7)		1 (0.4)	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
ALL CAUSALITY SAEs	71 (49.0)	43 (29.7)	125 (47.7)	84 (32.1)
DRUG-RELATED SAEs	13 (9.0)	6 (4.1)	20 (7.6)	12 (4.6)
ALL CAUSALITY AEs LEADING TO DC	16 (11.0)	9 (6.2)	29 (11.1)	18 (6.9)
DRUG-RELATED AEs LEADING TO DC	3 (2.1)	2 (1.4)	8 (3.1)	4 (1.5)
ALL-CAUSALITY AEs	144 (99.3)	71 (49.0)	261 (99.6)	142 (54.2)
Most Frequent AEs (≥ 20% of Any Grade in either treatment group)				
DIARRHOEA	39 (26.9)	2 (1.4)	66 (25.2)	4 (1.5)
ABDOMINAL PAIN	35 (24.1)	5 (3.4)	51 (19.5)	6 (2.3)
FATIGUE	52 (35.9)	4 (2.8)	93 (35.5)	5 (1.9)
PRURITUS	41 (28.3)	1 (0.7)	81 (30.9)	1 (0.4)
DECREASED APPETITE	31 (21.4)	2 (1.4)	56 (21.4)	2 (0.8)
COUGH	32 (22.1)	0	56 (21.4)	0
DRUG-RELATED AEs	108 (74.5)	24 (16.6)	200 (76.3)	55 (21.0)
Most Frequent Drug-related AEs (≥15% of Any Grade in either treatment group)				
FATIGUE	35 (24.1)	3 (2.1)	55 (21.0)	4 (1.5)
PRURITUS	27 (18.6)	1 (0.7)	55 (21.0)	1 (0.4)
RASH	23 (15.9)	1 (0.7)	46 (17.6)	2 (0.8)
ALL CAUSALITY SELECT AES, BY CATEGORY				
ENDOCRINE	14 (9.7)	0	27 (10.3)	2 (0.8)
GASTROINTESTINAL	39 (26.9)	2 (1.4)	66 (25.2)	4 (1.5)
HEPATIC	31 (21.4)	21 (14.5)	76 (29.0)	45 (17.2)
PULMONARY	2 (1.4)	1 (0.7)	3 (1.1)	1 (0.4)
RENAL	4 (2.8)	1 (0.7)	10 (3.8)	1 (0.4)
SKIN	60 (41.4)	2 (1.4)	122 (46.6)	5 (1.9)
HYPERSENSITIVITY/INFUSION REACTIONS	5 (3.4)	0	11 (4.2)	0
DRUG-RELATED SELECT AES, BY CATEGORY				
ENDOCRINE	12 (8.3)	0	24 (9.2)	2 (0.8)
GASTROINTESTINAL	22 (15.2)	2 (1.4)	36 (13.7)	3 (1.1)
HEPATIC	12 (8.3)	5 (3.4)	37 (14.1)	17 (6.5)
PULMONARY	2 (1.4)	1 (0.7)	3 (1.1)	1 (0.4)
RENAL	1 (0.7)	0	2 (0.8)	0
SKIN	44 (30.3)	2 (1.4)	92 (35.1)	5 (1.9)
HYPERSENSITIVITY/INFUSION REACTIONS	5 (3.4)	0	11 (4.2)	0

MedDRA version 19.1; CTC version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Table 68 Summary of Safety (Regardless of Causality) Across Etiologic Subtypes in the ESC and EXP Cohorts

	No. of Subjects (%)				
	N	Deaths	SAEs	All AEs	AEs leading to discontinuation
ESC Cohort	**48**	**31 (64.6)**	**22 (45.8)**	**48 (100.0)**	**3 (6.3)**
Uninfected	23	17 (73.9)	8 (34.8)	23 (100.0)	2 (8.7)
HCV	10	3 (30.0)	4 (40.0)	10 (100.0)	0
HBV	15	10 (66.7)	10 (66.7)	15 (100.0)	1 (6.7)
EXP Cohort	**214**	**85 (39.7)**	**103 (48.1)**	**213 (99.5)**	**26 (12.1)**
Uninfected Naive/Intolerant	56	14 (25.0)	28 (50.0)	56 (100.0)	6 (10.7)
Uninfected progressor	57	31 (54.4)	27 (47.4)	56 (98.2)	7 (12.3)
HCV	50	17 (34.0)	27 (54.0)	50 (100.0)	9 (18.0)
HBV	51	23 (45.1)	21 (41.2)	51 (100.0)	4 (7.8)
ESC+EXP	**262**	**116 (44.3)**	**125 (47.7)**	**261 (99.6)**	**29 (11.1)**
Uninfected	136	62 (45.6)	63 (46.3)	135 (99.3)	15 (11.0)
HCV	60	20 (33.3)	31 (51.7)	60 (100.0)	9 (15.0)
HBV	66	33 (51.5)	31 (47.0)	66 (100.0)	5 (7.6)

Table 69 Summary of Safety (Drug-related) Across Etiologic Subtypes in the 2L EXP and ESC+EXP Cohorts

	No. of Subjects (%)							
	N	Deaths	SAEs		All AEs		AEs leading to discontinuation	
			Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
2L EXP Cohort	**145**	**1 (0.7)**	**13 (9.0)**	**6 (4.1)**	**109 (75.2)**	**29 (20.0)**	**3 (2.1)**	**2 (1.4)**
Uninfected	72	1 (1.4)	9 (12.5)	4 (5.6)	53 (73.6)	11 (15.3)	1 (1.4)	1 (1.4)
HCV	30	0	2 (6.7)	1 (3.3)	25 (83.3)	9 (30.0)	2 (6.7)	1 (3.3)
HBV	43	0	2 (4.7)	1 (2.3)	30 (69.8)	4 (9.3)	0	0
ESC+EXP	**262**	**1 (0.4)**	**20 (7.6)**	**12 (4.6)**	**202 (77.1)**	**61 (23.3)**	**8 (3.1)**	**4 (1.5)**
Uninfected	136	1 (0.7)	10 (7.4)	4 (2.9)	105 (77.2)	26 (19.1)	5 (3.7)	2 (1.5
HCV	60	0	6 (10.0)	5 (8.3)	48 (80.0)	22 (36.7)	3 (5.0)	2 (3.3)
HBV	66	0	4 (6.1)	3 (4.5)	47 (71.2)	7 (10.6)	0	0

Table 70 Safety with Nivolumab (CA209040) Relative to Regorafenib+BSC (RESORCE)

	% of Subjects		
	CA209040		RESORCE 2L HCC[2]
	2L EXP n = 145	ESC+EXP N = 262	Regorafenib+BSC N = 379
Death due to study drug toxicity	0.7	0.4	2
Drug-related AEs	75	76	93
Grade 3-4	14	21	50
Drug-related AEs leading to DC	2.1	3.1	10
Drug-related SAEs	9	7.6	10

Abbreviations: AE: adverse event, DC: discontinuation, ESC: escalation cohort, EXP: expansion cohort, HCC: hepatocellular carcinoma, SAE: serious adverse event

CHMP Assessment

Updated safety information, using the 29-Nov-2016 clinical DBL, has been submitted (previous DBL 8-Aug-2016). The majority of patients had either progressed or died and a minority continued on nivolumab treatment (2L EXP Cohort on treatment patients: N = 29, 20.0% and ESC+EXP Cohort on treatment patients: N = 49, 18.7%).

99.3% and 99.6% of patients in the 2L EXP and ESC+EXP respectively reported AEs of which 74.5% and 76.3% respectively were considered as TEAEs.

A slight increase in the frequency of SAEs is observed, SAESs were reported in 49.0% of subjects in the 2L EXP Cohort. Grade 3-4 SAEs were reported in 29.7% of subjects.

44.8% of subjects had died in the 2L EXP Cohort, the most frequently reported cause of death was disease progression and 1 death was registered due to study drug toxicity caused by pneumonitis.

AEs leading to discontinuation (all causality) were low (n=16, 11% in the 2L-EXP). Grade 3-4 AEs leading to discontinuation were reported in 6.2% of subjects.

Overall, the updates safety profile remains in line with that previously seen. The updated analysis captures up to 4 months of additional follow-up, analyses of adverse events (AEs) and related AEs by drug exposure time period show a safety profile consistent with the previously reported.

A comparison has been submitted between the overall safety profile of nivolumab vs. data from the RESORCE trial of regorafenib. This analysis points out that nivolumab may be better tolerated than regorafenib with fewer percentage of deaths due to study drug toxicity, drug-related AEs, Grade 3-4 drug-related AEs, and drug related AEs leading to discontinuation. The minimum and median follow-up for subjects in the regorafenib RESORCE trial were < 2 months and 7.0 months, which is shorter than the follow-up times for 2L EXP subjects in CA209040 based on the 29-Nov-2016 DBL of 48 weeks and 12.9 months, respectively.

Issue resolved.

Question 13

Considering the capability of nivolumab to induce nivolumab-ADAs –also bearing in mind the possibility that patients may have pre-existent nivolumab-ADAs- the mere detection is not surprising. Nonetheless, taking into account the median time of treatment in CA209040 being 4.88 months (all treated population), the incidence of nivolumab ADAs here of 26.7% is considered high. This in particular when comparing the incidence figure of, for instance, nivolumab-ADAs in the registration study for the indication renal cell cancer. Here nivolumab-ADAs appeared 7.3%, this with a median treatment duration of 3.71 months only. The applicant is asked to provide an explanation for this high incidence in HCC patients, and to discuss the overall importance of neutralizing antibodies.

Summary of MAH answer

The incidence of ADAs after treatment with nivolumab varies from tumour to tumour, ranging from 0.6% in subjects with cHL (study CA209205) to 26.7% in subjects with HCC (study CA209040). Among the solid tumors, subjects with UC (study CA209275) had a numerically similar incidence rate (23.7%) to that of subjects with HCC (study CA209040). Table XXX-1 shows the summary of nivolumab ADA assessment for all the studies that had been used to support various indications. The assay used across all these studies was the current sensitive and drug tolerant assay (ICDIM 140) for immunogenicity analysis.

Immunogenicity of therapeutic proteins could be affected by many factors, including patient-related factors, such as genetic background and type of disease, and treatment-related factors, such as type of protein, route of administration, dose frequency, duration of treatment, manufacturing process, handling, and storage. As there were few changes in treatment-related factors for nivolumab across various tumors, the numerically higher incidence of ADAs in HCC subjects in study CA209040 could be due to the nature of the disease. Unlike other tumor types, HCC generally occurs in the setting of an underlying chronic hepatic disease and impaired liver function. It has been suggested that patients with infectious diseases, chronic liver diseases, or proinflammatory predisposition may have a higher risk of immunogenicity. In Study CA209040, among patients who received nivolumab 3 mg/kg Q2W and had an evaluable ADA assessment, 30.9% (34/110) of subjects with uninfected etiology, 30.4% (14/46) of subjects with HCV etiology, and 14.8% (8/54) of subjects with HBV etiology developed ADAs. The relatively low incidence in HBV-infected subjects could be due to the impaired immune system in these subjects. Since chronicity would impair the immune system and HBV-infected patients are, in general, in a worse condition with weak T cell responses and exhaustion of virus specific adaptive immunity due to ongoing HBV replication and production of viral antigens, dendritic cell impairment, the influence of regulatory T cells, or the immunological features of the liver environment, the immune system of patients with HBV etiology might be further impaired, and make them potentially less likely to develop ADAs.

Table 71 Summary of Nivolumab Antibody Assessments Using Method ICDIM 140 Following Nivolumab 3 mg/kg every 2 weeks

	Number of Subjects (%)													
Indication	Melanoma			NSCLC			RCC	cHL		SCCHN	UC		HCC	
Study Number (CA209)	066[a] (N=107)	067[a] (N=288)	037[a] (N=181)	063[a] (N=101)	017[a] (N=109)	057[a] (N=251)	025[b] (N=371)	039[c] (N=19)	205[c] (N=159)	141[d] (N=148)	032[e] (N=69)	275[e] (N=219)	040 3 mg/kg ESC + EXP[f] (N=210)	Pooled Summary (N=2232)
Baseline ADA Positive	3 (2.8)	10 (3.5)	9 (5.0)	11 (10.9)	8 (7.3)	18 (7.2)	10 (2.7)	3 (15.8)	7 (4.4)	13 (8.8)	4 (5.8)	11 (5.0)	20 (9.5)	127 (5.7)
ADA Positive	6 (5.6)	33 (11.5)	13 (7.2)	12 (11.9)	21 (19.3)	43 (17.1)	27 (7.3)	1 (5.3)	1 (0.6)	13 (8.8)	9 (13.0)	52 (23.7)	56 (26.7)	287 (12.9)
Persistent Positive	0	0	0	0	1 (0.9)	0	1 (0.3)	0	0	0	0	0	6 (2.9)	8 (0.4)
Only Last Sample Positive	2 (1.9)	10 (3.5)	9 (5.0)	8 (7.9)	4 (3.7)	12 (4.8)	7 (1.9)	1(5.3)	1(0.6)	9 (6.1)	1 (1.4)	24 (11)	14 (6.7)	102 (4.6)
Other Positive	4 (3.7)	23 (8.0)	4 (2.2)	4 (4.0)	16 (14.7)	31 (12.4)	19 (5.1)	0	0	4 (2.7)	8 (11.6)	28 (12.8)	36 (17.1)	177 (7.9)
Neutralizing ADA Positive	0	1 (0.3)	2 (1.1)	0	3 (2.8)	3 (1.2)	0	0	0	1 (0.7)	1 (1.4)	4 (1.8)	1 (0.5)	16 (0.7)
ADA Negative	101 (94.4)	255 (88.5)	168 (92.8)	89 (88.1)	88 (80.7)	208 (82.9)	344 (92.7)	18 (94.7)	158 (99.4)	135 (91.2)	60 (87.0)	167 (76.3)	154 (73.3)	1945 (87.1)

Note: Persistent positive subject defined as a subject with ADA-positive samples at 2 or more consecutive time points, where the first and last ADA positive samples were at least 16 weeks apart.

CHMP Assessment

The ADA rate registered in trial CA209040 is to date the highest registered in any nivolumab trial. With a median time on treatment of 4.88 months for all treated population the 26.7% of ADA positivity is only comparable to that registered in one trial in UC in which median time on treatment was 3.25 months (ADA positive: 23.7%).

Among the 26.7% of patients with ADA positivity, the percentage of patients that were persistently positive 2.9% (n=6) is also the highest to date although only 1 patient (0.5%) tested positively for neutralizing antibodies. Moreover ADA titters in ADA positive subjects were higher than those previously seen in nivolumab clinical development. The highest titer value observed in ADA positive subjects was 256, which occurred in 1 subject in the 3 mg/kg Q2W dose regimen who was persistent positive for ADA and NAb negative. All other ADA positive subjects had titer values of 128 or less.

Reasonably this high ADA positive rate could be attributable to the nature of the disease and also the different aetiologies enrolled in CA209040 trial could have impact. Although apparently there was no evidence of loss of efficacy in subjects with neutralizing antibodies and there were no associated adverse events, the applicant is asked to submit updated immunogenicity data (according to the most recent DBL).

Issue not resolved.

Question 14

A large quantity of non-drug related SAEs has been claimed in CA209040 (38.5% of patients in ESC+EXP and in 37.9% of patients in the 2L EXP cohort), this in relation to the relative small number of drug-related SAEs (in 7.3% of patients in the ESC+EXP and in 9.0% of the 2L EXP cohort). Apparently 35-40% of the patients included in CA209040 encountered SAEs that are not drug-related. In view of these high numbers, the applicant is asked to explain this high number of SAEs as these are claimed to be non-related to nivolumab.

Summary of MAH answer

On the High frequency of non-drug-related SAEs. Similar to the prior DBL in Aug. 2016, non-drug related SAEs from the 29-Nov-2016 DBL, as defined by the investigator, constituted a large proportion of SAEs observed in CA209040 in the ESC+EXP (44.3%) and 2L EXP (44.8%) cohorts. A review of these non-drug related SAEs indicates that the patients in these cohorts experienced SAEs that were mainly due to conditions related to the underlying HCC and the underlying cirrhosis. This is an expected observation in

HCC as there are 3 potential underlying risks for AEs in HCC clinical trials: (1) drug exposure, (2) the malignancy [HCC], and (3) compromised liver function due to the underlying cirrhosis.

In CA209040, non-drug related SAEs were mainly due to progression of the HCC and other cancer-related AEs (any grade reported in 16.6% in 2L EXP subjects and 12.2% in ESC+EXP subjects). Complications of HCC were also common with any grade ascites, esophageal variceal hemorrhage, abdominal pain, and gastrointestinal hemorrhage reported in 6.2% (9/146) in the 2L EXP Cohort and 4.1% (11/262) in the ESC+EXP Cohort. Other less frequent non-drug related SAEs that could be related to worsening of the HCC or the underlying liver dysfunction included hepatobiliary disorders (bile duct abnormalities) and blood & lymphatic disorders (anemia). Finally, infections & infestations were reported with a frequency ranging from 6.9-8.3% for any grade. The pattern of non-drug-related SAEs on extended follow-up (up to 100 days) was similar.

The frequency with which non-drug related AEs and SAEs occur in HCC trials is reflected in the placebo arms of pivotal HCC trials (related AE range: 38.7-52% and related SAE range: 1.3-3%, see Table N). As these patients were treated with placebo and were not exposed to drug, the reported 'drug-related AEs' were likely due to non-drug factors related to the underlying HCC and underlying cirrhosis.

Table 72 Drug-related Adverse Events in the Placebo Arms in the Pivotal Sorafenib & Regorafenib HCC Trials

Clinical Trial	Incidence of drug-related adverse events of any grade	Incidence of SAEs	Incidence of drug-related SAEs
Sorafenib 1st line SHARP trial, N=303 (placebo)[1]	52%	54%	NR
Sorafenib 1st line Asia-Pacific trial, N=76 (placebo)[2]	38.7%	45.3%	1.3%
Regorafenib 2nd line trial, N=194 (placebo)[3]	52%	47%	3%

NR, not reported

On the Low frequency of drug-related SAEs. Drug-related SAEs were reported in 7.3% of patients in the ESC+EXP cohort and in 9.0% of patients in the 2L EXP cohort of CA209040. This is consistent with observations from other nivolumab trials in other indications (Table N). Grade 3-4 drug-related AEs occurred in 3.4-9.0% of melanoma, non-squamous NSCLC, head and neck squamous cell carcinoma, and classical Hodgkin lymphoma subjects treated with nivolumab monotherapy.

Table 73 Drug-related Serious Adverse Events with Nivolumab Monotherapy

	Drug-related SAEs	
Clinical Trial	Any Grade	Grade 3-4
CA209040 (Advanced HCC)		
ESC+EXP	45.8%	7.3%
2L EXP	46.9%	9.0%
CA209037 (Advanced Melanoma)	34.3%	9.0%
CA209057 (Advanced Non-squamous NSCLC)	46.7%	5.2%
CA209066 (Unresectable or Metastatic Melanoma)	31.1%	5.8%
CA209141 (Squamous Cell Carcinoma Head & Neck)	53.8%	4.7%
CA209205 (Classical Hodgkin Lymphoma Cohort B)	20.9%	3.4%

The low incidence of nivolumab drug-related SAEs possibly reflects the overall favourable tolerability profile of immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway. A recent meta-analysis of 7 randomized clinical trials compared the tolerability of immune checkpoint inhibitors targeting PD-1/PD-L1 pathway (4 nivolumab, 2 pembrolizumab, 1 atezolizumab) and standard-of-care chemotherapy in patients with advanced cancer. Analysis of summary toxicity endpoints revealed a lower risk of any all- and high-grade AEs and treatment discontinuation in the PD-1/PD-L1 inhibitor group. Their data highlighted the favourable risk/benefit ratio for PD-1/PD-L1 inhibitors.

CHMP Assessment:

The high rate of non-drug related SAE can indeed also be explained by the crucial role of hepatic functions as well as the condition of the liver itself within the patient's QoL and performance. The low frequency of nivolumab-related SAEs in CA209040 appears consistent with observations of nivolumab's safety profile in other tumour types.

Issue resolved.

Question 15

In the 2L EXP cohort the most frequently reported grade 3-4 drug-related AEs were increased AST (3.4%), and increased lipase (3.4%). As the increase of lipase in peripheral blood is a common phenomenon in those treated with nivolumab, a relation with autoimmune effects leading to pancreatitiform phenomena cannot be excluded. Albeit that elevated laboratory parameters did not lead to treatment abrogation or dose adjustment in CA209040 the applicant is asked to mention to quantify the number of patients that needed countermeasures as immune modulation medications in this study.

Summary of MAH answer

The overall experience with asymptomatic elevations of lipase and amylase in the nivolumab clinical development program is that they are often transient. Laboratory values tend to fluctuate on a day-to-day basis and eventually return to baseline or low grade over the course of weeks, whether or not subjects receive corticosteroids. In monotherapy studies, lipase and amylase levels were not systematically monitored, so an estimate of the frequency of asymptomatic elevations is unknown.

In Study CA209040, Grade 3-4 drug-related increases in lipase were reported in 3.4% of subjects in the 2L EXP Cohort. Lipase increases have mostly been asymptomatic. Two subjects had pancreatitis reported between the first dose and 100 days after the last dose of study therapy (extended follow-up) (1 case in the EXP Cohort and 1 case in the 2L EXP Cohort). The median time to onset was 35.43 weeks. Neither subject was treated with immune-modulating medication. In addition, no treatment with immune modulators was administered in the subjects who had an AE report of pancreatitis, increased lipase, or increased amylase.

In a review of toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies, elevated lipase levels were reported in the evaluated studies of both anti-CTLA-4 and anti-PD-1/PD-L1 mAb. The studies indicated that these elevations are usually asymptomatic laboratory abnormalities that can be monitored without immunosuppressive therapy. Pancreatitis was reported infrequently in studies of anti-CTLA-4 and anti-PD1 agents.

In summary, the elevations in pancreatic enzymes in CA209040 were consistent with what has been reported previously with the nivolumab program, had no clinical consequence, and did not require treatment with immune-modulating medications.

CHMP Assessment:

Although the frequencies of elevated lipase and or amylase as laboratory parameters - when analysed- were low, the actual causes remain enigmatic. Nevertheless, clinical implications are limited. In particular, the proposed 2L HCC indication seems not to affect the frequency of pancreatitiform AEs when induced by nivolumab.

Issue resolved.

5. RMP

Major objections

none

Other concerns
Question 16

Based on the submitted study and the lack of (sufficient) data of the following subgroups the applicant is requested to amend the RMP to include the following topics for missing information:

- 'Use of nivolumab in elderly (≥75 years) with HCC'
- 'Patients with moderate hepatic failure who start nivolumab as treatment for HCC'
- 'Use of nivolumab for HCC in patients with ECOG PS >1, Child-Pugh B and C, significant hepatic and/or renal impairment, a history of clinically meaningful variceal bleeding, and/or uncontrolled or clinically significant cardiac disease'

RMP Assessment

Please see PRAC assessment report

6. PI

Question 17

Not all proposed changes to the SmPC are acceptable, see separate document for comments and revisions. In addition, in Annex II to the SmPC the post-approval commitment should be extended to include HCC.

Summary of MAH answer

See separate document.

CHMP Assessment

All currently proposed changes to the SmPC are considered acceptable, see separate document for revisions and comments. However, the wording of the HCC indication may still have to be revised within this procedure. Please refer to new MO. The proposed post-approval commitment in Annex II is not considered acceptable yet, see separate document for revisions and comments.

Issue partially resolved.

Annex 3: 2nd CHMP request for Supplementary Information

Clinical efficacy aspects

Major Objections

1. The evidence provided by the exploratory, non-comparative trial CA209040 is presently considered insufficient to support a positive B/R in the target population applied for. The key issues identified pertain to the non-comparative design of the study and an apparent selection bias for relatively indolent tumours in the study population. This creates a source of uncertainty regarding the study population with respect to a wide range of known and unknown factors that could affect the outcome, thus making it difficult to infer that a favourable outcome in terms of OS, is from the treatment alone. This uncertainty also hampers interpretation of the results when compared to an external control. In an attempt to assess the actual effect size and clinical relevance of the study results the company is asked to submit the following exploratory analyses. The applicant is asked to further address available data in the light of these concerns, to justify the positive B/R in the applied indication.

Other concerns

2. Complete data regarding baseline characteristics (including median time from diagnosis) and efficacy results dichotomized according to time from diagnosis ≥ or < 5 years should be submitted. A detailed discussion of the clinical relevance of results (OS data, landmark analysis of OS by response status, ORR, DoR, SD and also discuss influence of post-progression therapies on OS results). Separate discussion on the B/R should be submitted for the 80% of the population that could be more comparable to that of other clinical trials and also for the remaining 20% that could be considered to clearly have a rather indolent disease.

3. Efficacy outcomes (time to tumour progression) from prior sorafenib therapy in the efficacy target population (n=145) of trial CA209040 should be provided, and a comparison of TTP on sorafenib to PFS on Opdivo should be made, e.g. calculated using the starting date of and the date for PD on the patients' prior regimen (for the patients for whom this information is available).

4. The applicant is asked to submit updated immunogenicity data (according to the most recent DBL).