30 January 2025
EMA/CHMP/59173/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Yervoy	Ipilimumab
OPDIVO	Nivolumab

Procedure No. EMEA/H/C/xxxx/WS/2717

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Term	Definition
1L	first-line
2L	second-line
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AFP	alpha fetoprotein
BCLC	Barcelona Clinic Liver Cancer Staging System
BICR	blinded independent central review
BID	twice daily
BMS	Bristol-Myers Squibb
BW	body weight
Cavg	average concentration
chemo	chemotherapy
CI	confidence interval
CL	clearance
CMH	Cochran-Mantel-Haenszel
CoC	contribution of components
CR	complete response
CRC	colorectal cancer
CSR	clinical study report
CV	coefficient of variation
DBL	database lock
DC	discontinuation
DCR	disease control rate
DDC	duration of disease control
DLT	dose-limiting toxicity
DMC	data monitoring committee
dMMR	deficient mismatch repair
DOR	duration of response
DURVA	durvalumab
EBE	empirical Bayes estimate
ECOG PS	Eastern Cooperative Oncology Group performance status
EGD	esophagogastroduodenoscopy
EHS	extrahepatic spread
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-3L	EuroQoL 5-dimension quality–of-life 3-level version
E-R	exposure-response
ESC	escalation
ESCC	esophageal squamous-cell carcinoma
EU	European Union

Term	Definition
EXP	expansion
FACT-Hep	Functional Assessment of Cancer Therapy-Hepatobiliary
FU	follow-up
Gr2+	Grade 2 and above
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HCP	health care practitioner
HCS	Hepatobiliary Cancer Subscale
HLGT	high level group term
HR	hazard ratio
HRQoL	health-related quality of life
ICH	International Conference on Harmonisation
ICI	immune checkpoint inhibitor
IMAE	immune-mediated adverse event
IND	Investigational New Drug
ipi	Ipilimumab
IRT	Interactive Response Technology
ITT	intention-to-treat
IV	Intravenous
IVRS	Interactive Voice Response System
K-M	Kaplan Meier
LENVA	lenvatinib
LLOQ	lower limit of quantification
LPLV	last patient last visit
LRT	locoregional therapy(ies)
MedDRA	Medical Dictionary for Regulatory Activities
Mono	monotherapy
mOS	median overall survival
mos	months
mPFS	median progression-free survival
MPM	malignant pleural mesothelioma
MSI-H	microsatellite instability high
MTD	maximum tolerated dose
MVI	macrovascular invasion
N1I3	nivolumab 1 mg/kg IV plus ipilimumab 3 mg/kg IV
N3I1	nivolumab 3 mg/kg IV plus ipilimumab 1 mg/kg IV
NA	not applicable
NCCN	National Comprehensive Cancer Network
NCT	National Clinical Trial
nivo	nivolumab
NSCLC	non-small cell lung cancer

Term	Definition
OESI	other events of special interest
ORR	objective response rate
OS	overall survival
PC	Positive control
PD	progressive disease
PD-1	Programmed cell death-1
PD-L1	programmed cell death ligand-1
PFS	progression-free survival
PFS2	progression-free survival on next line of treatment (time to second progression)
PK	pharmacokinetic(s)
PL	package leaflet
PO	by mouth route of administration
popPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcomes
PT	preferred term
QD	once daily
QoL	quality of life
QXW	once every X weeks
RCC	renal cell carcinoma
RAAA	African American race
RAAS	Asian race
RSE	Relative standard error
RECIST	response evaluation criteria in solid tumors
SAE	serious adverse event
SAP	statistical analysis plan
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	stable disease
SmPC	Summary of Product Characteristics
SMQ	standard medical query
SOC	standard of care
SOR	sorafenib
sora	sorafenib
TKI	tyrosine kinase inhibitor
TREME	tremelimumab
TTP	time to progression
TTSD	time to symptom deterioration
TTR	time to response
USA	United States of America
VEGF	vascular endothelial growth factor

Term	Definition
VEGFR	vascular endothelial growth factor receptor
WOCBP	Women of Childbearing Potential
W&P	warnings & precautions

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 2 July 2024 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

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

A Worksharing application for OPDIVO and YERVOY, as follows:

Extension of indication to include a new indication for OPDIVO in combination with ipilimumab as first line treatment of adult patients with unresectable or advanced hepatocellular carcinoma (HCC) based on study CA2099DW. This is a phase 3 randomised, multi-centre, open label study of Nivolumab in combination with Ipilimumab compared to Sorafenib or Lenvatinib as first-line treatment in participants with advanced HCC. 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. Version 41.0 of the RMP has also been submitted.

Extension of indication to include a new indication for YERVOY in combination with nivolumab as first line treatment of adult patients with unresectable or advanced hepatocellular carcinoma (HCC) based on study CA2099DW. This is a phase 3 randomised, multi-centre, open label study of Nivolumab in combination with Ipilimumab compared to Sorafenib or Lenvatinib as first-line treatment in participants with advanced HCC. 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. Version 44.0 of the RMP has also been submitted.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0432/2020 for OPDIVO and P/00085/2015 for Yervoy on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0432/2020 for OPDIVO was completed and the PIP P/00085/2015 for Yervoy was completed.

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 WSA did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The WSA did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Appointed Rapporteurs for the WS procedure:

CHMP Rapporteur: Antonio Gomez-Outes

Timetable	Actual dates
Submission date	2 July 2024
Start of procedure:	20 July 2024
CHMP Rapporteur Assessment Report	16 September 2024
PRAC Rapporteur Assessment Report	19 September 2024
PRAC Outcome	3 October 2024
CHMP members comments	7 October 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 October 2024
Request for supplementary information (RSI)	17 October 2024
CHMP Rapporteur Assessment Report	2 January 2025
PRAC Rapporteur Assessment Report	6 January 2025
PRAC members comments	8 January 2025
Updated PRAC Rapporteur Assessment Report	9 January 2025
PRAC Outcome	16 January 2025
CHMP members comments	20 January 2025
Updated CHMP Rapporteur Assessment Report	23 January 2025
Opinion	30 January 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

OPDIVO

"*OPDIVO in combination with ipilimumab is indicated for the first line treatment of adult patients with unresectable or advanced hepatocellular carcinoma*."

YERVOY

"*YERVOY, in combination with nivolumab, is indicated for the first-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma* ".

Epidemiology and risk factors, screening tools/prevention

Primary liver cancer is the sixth most common cancer worldwide and the third leading cause of cancer-related death, with approximately 906,000 new cases and 830,000 deaths in 2020. HCC is the most frequently reported primary liver cancer, accounting for approximately 75% to 85% of cases.[1] The incidence of HCC increases progressively with advancing age in all populations, reaching a peak at 70 years; and incidence and mortality are 2-3 times higher among men than women in most regions.

Europe contributes 9.7% of the global HCC incidence, but incidence rates/risk factors vary across the region[2], with age-standardized rates of 6.7 cases per 100,000 individuals (viral-related HCC) in the Southern region and age-standardized rates of 4.3 cases per 100,000 individuals (non-viral related HCC) in the Central/Eastern region.

The main risk factors for HCC are chronic infection with HBV or HCV, aflatoxin-contaminated foods, heavy alcohol intake, excess body weight, type 2 diabetes, and smoking. The major risk factors vary from region to region, which is reflected in the incidence of HCC across geographic regions. The highest incidence rates are seen in East Asia and Sub-Saharan Africa, while lower rates are seen in Europe and North America.

HCC usually occurs in the setting of liver cirrhosis because of chronic HBV or HCV infections, alcohol consumption, metabolic dysfunction-associated steatohepatitis, or metabolic disorders such as obesity or diabetes.[3] Cirrhosis is the leading risk factor for HCC; once cirrhosis is established, the annual incidence ranges from 1%-18%, and one-third of these individuals will develop HCC over their lifetime.[4] In western countries, non-viral aetiologies, together with HCV, are the main risk factors for HCC.[5]

The prevalence of obesity and type 2 diabetes has greatly increased in the past decades, leading to a rising incidence of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), which can lead to fibrosis and cirrhosis and, eventually, HCC. HCC related to NAFLD/NASH is probably underestimated and it is expected to rise in the future, possibly overtaking the other aetiologies in some areas of the world. A significant proportion of patients with NAFLD/NASH-associated HCC do not have histological evidence of cirrhosis.[6]

Biologic feature

Normal liver tolerogenic mechanisms are likely responsible for chronic liver inflammation or carcinogenesis. Chronic presentation of pathological antigens in the liver can actively suppress immune responses, thus inducing a state of immune tolerance to the pathogen or tumour. Hepatocellular carcinoma takes advantage of peripheral tolerance to evade cell-mediated immune responses, which allows the tumour to grow. Chronic hepatic inflammatory responses are the number one risk factor for liver tumour development (Makarova-Rusher et al 2015).

Moreover, increased expression of immunosuppressive cell populations, such as regulatory T cells and myeloid derived suppressor cells, and inhibitory signalling molecules, such as CTLA 4 and PD 1, have been observed in HCC (Gao et al 2009, Hato et al 2014, Pardee and Butterfield 2012) and is

[1] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209-49.
[2] Singal AG, Kanwal F, Llovet JM. Global trends in hepatocellular carcinoma epidemiology: implications for screening, prevention and therapy. Nat Rev Clin Oncol. 2023;20(12):864-84.
[3] Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018; 391(10127):1301-14.
[4] Purcell Y, Copin P, Paulatto L, et al. Hepatocellular carcinoma surveillance: Eastern and Western perspectives. Ultrasonography. 2019;38(3):191-99.
[5] Forner A, Llovet J, Bruix J. Hepatocellular carcinoma. Lancet. 2012;379:1245-55.
[6] Vogel, A. et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology, Volume 29, iv238 - iv255

additionally associated with HBV and HCV infection. This upregulation contributes to the immunosuppressive environment for HCC and highlights the importance of the PD-(L)1 and CTLA-4 pathways in HCC (Golden-Mason et al 2007, Pardee and Butterfield 2012, Peng et al 2008).

Clinical presentation, diagnosis and stage/prognosis

HCC is an aggressive tumour associated with poor prognosis, particularly in advanced stages. The overall estimated 5-year survival rate for patients with HCC is 18%, ranging from 33% in those diagnosed with localized disease to < 5% in those with advanced or metastatic disease at diagnosis. In approximately 50% of cases, HCC is diagnosed at advanced stages when curative therapies are no longer an option. Moreover, the risk of recurrence and progression to advanced stages remain significantly high (> 70% at 5 years) after curative therapy.[7]

Management

The treatment landscape in unresectable HCC has significantly evolved over the past few years. Five systemic therapies are currently approved by the EMA for first-line treatment: two VEGFR TKIs (sorafenib and lenvatinib) and two immunotherapy-based combinations (atezolizumab + bevacizumab and durvalumab + tremelimumab), as well as an immunotherapy as monotherapy (durvalumab).

Sorafenib, an oral TKI targeting multiple kinases, including VEGFR-1, -2, and -3 and BRAF, has been the standard of care (SOC) for advanced HCC in the first-line setting since its approval in 2007 (EMEA/H/C/000690/II/0005, 29 October 2007), which was based on improvement compared to placebo, establishing a median OS of 10.7 months (vs 7.9 months for placebo [Llovet et al 2008]) in the Phase III SHARP study. Subsequent studies have demonstrated a median OS ranging from 10.7 to 13.4 months (Finn et al 2021, Llovet et al 2008, Yamashita et al 2020).

Lenvatinib, another multiple kinase inhibitor against VEGFR-1, -2, and -3 and fibroblast growth factor receptor-1, -2, -3, and -4, was approved in 2018 (EMEA/H/C/003727/II/0011/G, 20 August 2018) as first-line treatment for advanced HCC based on non-inferior survival as compared to sorafenib in a Phase III study (study REFLECT), with a median OS of 13.6 months vs 12.3 months with sorafenib (Kudo et al 2018).

Atezolizumab (a PD-L1 inhibitor) in combination with bevacizumab (an angiogenesis inhibitor targeting vascular endothelial growth factor A) was also approved in the first-line setting in 2020 (EMEA/H/C/004143/II/0039, 27 October 2020), after the Phase III IMbrave150 study showed improvements in OS (19.2 months vs. 13.4 months) and PFS (6.9 months vs. 4.3 months) compared to sorafenib (Finn et al 2020b, Finn et al 2021). The ESMO guidelines[8] were updated in 2020 to recommend atezolizumab in combination with bevacizumab as the preferred option to treat first-line HCC. This recommendation is currently in force.

Durvalumab in combination with tremelimumab was approved in 2022 (EMEA/H/C/004771/II/0045, 30 January 2023) for the first-line treatment based on the demonstration of superiority of the combination of durvalumab+tremelimumab vs. sorafenib in the study HIMALAYA (primary objective of the study). Durvalumab+tremelimumab resulted in a median overall survival of 16.6 months, compared with a median of 13.8 months with sorafenib.

[7] Falette Puisieux M, Pellat A, Assaf A, et al. Therapeutic Management of Advanced Hepatocellular Carcinoma: An Updated Review. Cancers (Basel). 2022;14(10):2357.
[8] ESMO Guidelines Committee. Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO Clinical Practice Guidelines. March 2021.

In 2023 durvalumab as monotherapy was also approved as first-line treatment (EMEA/H/C/004771/II/0057, 15 November 2023), based on the demonstration of non-inferiority vs. sorafenib in the study HIMALAYA (key secondary objective of the study).

Regorafenib, cabozantinib and ramucirumab are the available treatment options for patients who have been previously treated with sorafenib.

Unmet medical need

HCC is an aggressive tumour associated with poor prognosis, particularly in advanced stages. Despite significant advancements in the treatment of unresectable HCC, prognosis remains suboptimal, highlighting the need for additional therapies that provide better clinical outcomes, longer-term survival benefits, and maintain safety and quality of life.

Additionally, it is noteworthy to mention that the safety profile of the available therapies makes some patients ineligible for treatment with them, or forces them to discontinue treatment. Notably, atezo+beva, which is currently considered as the preferred first-line treatment, is associated with a relevant risk of bleeding / proteinuria / thromboembolic events, and patients should be screened for the presence of oesophageal varices or other risk factors for serious bleeding prior to treatment.

Therefore, there is a need for new therapies that prolong overall survival, with different (ideally better) safety profile which enable all patients (and not only the current subset of eligible patients) to receive an optimal treatment.

2.1.2. About the products

OPDIVO (nivolumab) is a programmed death receptor-1 blocking antibody which binds to the programmed death 1 (PD 1) receptor and blocks its interaction with PD L1 and PD L2. The PD 1 receptor is a negative regulator of T cell activity that has been shown to be involved in the control of T cell immune responses. Engagement of PD 1 with the ligands PD L1 and PD L2, which are expressed in 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 potentiates T cell responses, including anti-tumour responses, through blockade of PD 1 binding to PD L1 and PD L2 ligands.

Nivolumab as a single agent has been approved in the EU for the treatment of patients with melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), classical Hodgkin lymphoma (cHL), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma (UC), and oesophageal cancers.

Ipilimumab is a human monoclonal antibody that targets CTLA-4. CTLA-4 inhibition can induce de novo T-cell responses and recruit novel/additional T cells to the tumour. Ipilimumab as a single agent has been approved in the EU for the treatment of patients with advanced (unresectable or metastatic) melanoma.

Nivolumab and ipilimumab combination therapy has been approved in the EU for the treatment of advanced (unresectable or metastatic) melanoma, first-line intermediate/poor risk advanced RCC, first-line unresectable malignant pleural mesothelioma, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) as first-line treatment and after prior fluoropyrimidine-based combination chemotherapy, and first-line unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (tumour cell ≥1%).

Nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy has been approved for first-line treatment of metastatic NSCLC.

Nivolumab in combination with cabozantinib has been approved for the treatment of advanced RCC.

Nivolumab in combination with chemotherapy has been approved for NSCLC, gastric cancer, gastroesophageal junction cancer, oesophageal adenocarcinoma and urothelial carcinoma.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Both nivolumab and ipilimumab are proteins composed of natural amino acids. Proteins are expected to biodegrade in the environment and not be a significant risk. As a protein, nivolumab and ipilimumab are exempt from preparation of an Environmental Risk Assessment under the 1 June 2006 "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/S/4447/00). Nivolumab, ipilimumab and the product excipients do not pose a significant risk to the environment.

2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP. Nivolumab and ipilimumab are monoclonal antibodies and are not expected to pose a significant risk to the environment, thus the lack of ERA studies is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the WSA. The WSA 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 Tabular Listing of Nivolumab Clinical Studies in Subjects with Unresectable/Advanced Hepatocellular Carcinoma (HCC)

Study Type	Study Identifier; Report Location in CTD	Primary Study Objectives	Study Design	Test Product(s); Dosage Regimen; Route of Administration*	No. Subjects	Study Population	Study Status; Type of Report
Efficacy/ Safety	Study Identifier: CA2099DW (NCT04039607) Report location: Module 5.3.5.1	OS	Phase 3, randomized, multi-center study of nivo+ipi vs sorafenib or lenvatinib	• **Nivo+Ipi (Arm A)**: nivo 1 mg/kg + ipi 3 mg/kg Q3W for up to 4 cycles followed by nivo 480 mg (flat dose) Q4W • **SOC (Arm B)**: sorafenib 400 mg PO BID or lenvatinib 8 mg PO QD or 12 mg PO QD	**Nivo+Ipi:** N=335 randomized N=332 treated **SOC:** N=333 randomized N=325 treated (275 treated with lenvatinib; 50 treated with sorafenib)	Adults (≥ 18 years) with advanced HCC (histologically confirmed) not eligible for curative surgical and/or LRT or progressive disease after surgical and/or LRT. Subjects must not have received prior systemic therapy for advanced HCC.	Study Status: The study is ongoing. Clinical database lock for the CSR: 28-Feb-2024. Type of Report: Primary CSR
Efficacy/ Safety	Study Identifier: CA209459 (NCT02576509) Report location: Module 5.3.5.1	OS	Phase 3, randomized, multi-center study of nivo vs sorafenib	• **Nivo:** 240 mg IV Q2W • **Sorafenib**: 400 mg (2 tablets of 200 mg) BID	**Nivo**: N=371 randomized N=367 treated **Sorafenib**: N=372 randomized N=363 treated	Adults (≥ 18 years) with advanced HCC (histologically confirmed) not eligible for curative surgical and/or LRT or progressive disease after surgical and/or LRT. Subjects must not have received prior systemic therapy for advanced HCC.	Study Status: The study is ongoing. Clinical database lock: 05-Jun-2019. Type of Report: Final CSR
Efficacy/ Safety	Study Identifier: CA209040 (NCT01658878) Report location: Module 5.3.5.1	ORR and DOR per BICR using RECIST 1.1	Phase 1/2, multi-cohort, dose escalation, open-label, non-comparative study	**Cohort 1&2 (ESC + EXP Cohort):** • **ESC Cohort:** administered 0.1-10 mg/kg nivo monotherapy Q2W • **EXP Cohort:** administered 3 mg/kg nivo monotherapy Q2W	**Cohort 1&2 (ESC + EXP Cohort):** N=262 total treated subjects (ESC: 48, EXP: 214), including N = 182 sorafenib-treated 2L subjects (ESC: 37 and EXP: 145), and N = 154 2L subjects treated with 3 mg/kg nivo (ESC: 9, EXP: 145).	Adults (≥ 18 years) with HCC (histologically confirmed) and ECOG PS of 0 to 1 **Cohort 1&2 (ESC + EXP Cohort):** composed of both sorafenib-naive and post sorafenib treatment:	Study Status: The study is ongoing. Clinical database lock: 20-Mar-2018. Type of Report: Addendum 03 CSR
		ORR and DOR per investigator using RECIST 1.1		**Cohort 4** • **Arm A** nivo 1 mg/kg IV + ipi 3 mg/kg IV Q3W for 4 cycles, followed by nivo 240 mg IV Q2W (N1I3 Q3 arm) • **Arm B** nivo 3 mg/kg IV + ipi 1 mg/kg IV Q3W for 4 cycles, followed by nivo 240 mg IV Q2W (N3I1 Q3 arm) • **Arm C** nivo 3 mg/kg IV Q2W+ ipi 1 mg/kg IV Q6W (N3I1 Q6 arm)	**Cohort 4:** **Arm A:** N=49 randomized N=49 treated **Arm B:** N=49 randomized N=49 treated **Arm C:** N=50 randomized N=48 treated	**Cohort 4:** uninfected, HCV infected, or HBV infected subjects with advanced HCC who have been previously treated with sorafenib	Clinical database lock: 22-Mar-2019 Type of Report: Final CSR

Abbreviations: BICR - blinded independent central review, CSR - clinical study report, DOR - duration of response, ECOG - Eastern Cooperative Oncology Group, ESC - escalation, EXP- expansion, HBV - hepatitis B virus, HCC - hepatocellular, HCV - hepatitis C virus, ipi - ipilimumab, IV - intravenous, LRT - locoregional therapies, nivo - nivolumab, ORR - objective response rate, OS - overall survival, PS - performance status, RECIST - response evaluation criteria in solid tumors, QXW - every X weeks

2.3.2. Clinical Pharmacology

2.3.2.1. Bioanalytical methods

Sample analysis from study CA2099DW (India and USA)

Quantification of nivolumab

Samples were received from study CA2099DW between 20th March 2020 and 21st November 2023. Of those, a majority were analysed and reported between 29th October 2020 and 24th January 2024. The maximum storage time was 1455 days at -70ºC.

Overall, a few samples were not reported or not eligible for analysis per method/SOP.

One calibration curve and 6 quality controls (QCs) (2 of each level) were included in every run. Three diluted QCs were also included. For the accepted runs, at least 2/3 of the QCs and 50% at each concentration level were within ±20% of the nominal value at each concentration level.

Several samples were reassayed per method procedure.

Incurred sample reanalysis was performed and the percent difference in more than 67% of the samples were within ±30%.

Determination of anti-nivolumab antibodies

Multiple samples were received from study CA2099DW between 20th March 2020 and 5th October 2023. Of those, a majority were analysed and reported between 19th February 2021 and 21st December 2023.

Of the runs performed, 89.74% were accepted. Each run contained two sets of LPC, HPC and LLPC and four sets of negative control (NC). Coefficient of variation (CV) between control duplicates was ≤20% in at least one at each level.

Overall, a few samples were not eligible for reporting as per protocol/SOP and some were pending analysis or reporting of result before the study conclusion.

During ADA determination, a number of samples were reanalysed as per method procedure.

Determination of anti-nivolumab neutralizing antibodies

Samples were received from study CA2099DW between 25th January 2023 and 1st February 2024. Of those, a majority were analysed and reported between 2nd February 2023 and 7th February 2024. A few samples were not analysed as they were PK backup.

Of the runs performed all of them were accepted (100%). Each run contained two sets of LPC, HPC and LPC-EXC and four sets of NC. CV between control duplicates was ≤30% in at least one at each level.

One sample was repeated due to CV>30%.

Quantification of ipilimumab

Samples were received from study CA2099DW between 20th March 2020 and 21st November 2023. Of those, a majority were analysed and reported between 27th April 2020 and 10th January 2024. The maximum storage time was 986 days at -80ºC.

Overall, a few samples were not analysed as per protocol/SOP.

One calibration curve and 6 QCs (2 of each level) were included in every run. Three diluted QCs were also included (when needed). For the accepted runs, at least 2/3 of the QCs and 50% at each concentration level were within ±20% of the nominal value at each concentration level.

A few samples were reassayed as per method procedure.

Incurred sample reanalysis was performed and the percent difference in more than 67% of the samples were within ±30%.

Determination of anti-ipilimumab antibodies

Samples were received from study CA2099DW between 19th March 2020 and 31st May 2023. Of those, a majority were analysed and reported between 16th September 2020 and 25th January 2024.

Overall, a few samples were not analysed as per protocol/SOP.

Of the runs performed, 94.4% were accepted. Each run contained two sets of PC (PC1, PC2 and PC3) and four sets of NC. CV between control duplicates was ≤20% in at least one at each level.

Determination of anti-ipilimumab neutralizing antibodies

Samples were received from study CA2099DW between 13th December 2022 and 30th January 2024. Of those, a majority were analysed and reported between 22nd December 2022 and 1st February 2024. A couple of the samples were not analysed as they were PK backup.

Of the runs performed, all of them were accepted (100%). Each run contained two sets of LPC, HPC and LPC-EXC and three sets of NC. CV between control duplicates was ≤25% in at least one at each level.

Overall, a few samples were reanalysed as per method procedure.

Sample analysis from study CA2099DW (China)

Quantification of nivolumab

Samples were received from study CA2099DW between 12th March 2021 and 15th November 2023. Of those, a majority were analysed and reported between 26th April 2022 and 9th January 2024. The maximum storage period was 822 days at -70ºC.

Overall, 1 sample was analysed but not reported as per protocol.

One calibration curve and 6 QCs (2 of each level) were included in every run. Three diluted QCs were also included. For the accepted runs, at least 2/3 of the QCs and 50% at each concentration level were within ±20% of the nominal value at each concentration level.

A few samples were reanalysed as per method procedure.

Incurred sample reanalysis was performed and the percent difference in more than 67% of the samples were within ±30%.

Determination of anti-nivolumab antibodies

Samples were received from study CA2099DW between 12th March 2021 and 20th November 2023. Of those, most samples were analysed and reported between 30th June 2022 and 11st December 2023.

Of the runs performed, 81.3% were accepted. Each run contained two sets of LPC, HPC and LLPC and four sets of NC. CV between control duplicates was ≤20% in at least one at each level.

Overall, 1 sample was not analysed as per protocol while a few samples were reanalysed as per method procedure.

Determination of anti-nivolumab neutralizing antibodies

Samples were received from study CA2099DW between 12th March 2021 and 14th March 2024. Of those, a subset of samples were analysed (those reported as ADA positive) between 12th December 2023 and 13th December 2023.

All of the samples were analysed. The run contained two sets of LPC, HPC and LPC-EXC and 4 sets of NC. CV between control duplicates was ≤25% in at least one at each level.

No reanalysis was carried out.

Quantification of ipilimumab

Samples were received from study CA2099DW between 12th March 2021 and 15th November 2023. Of those, a majority were analysed and reported between 28th July 2022 and 9th January 2024. The maximum storage time was 992 days at -70ºC.

Overall, 1 sample was not analysed as per protocol.

Samples were analysed with a 100% pass rate. One calibration curve and 6 QCs (2 of each level) were included in every run. Two diluted QCs were also included (when needed). For the accepted runs, at least 2/3 of the QCs and 50% at each concentration level were within ±20% of the nominal value at each concentration level.

There was no reanalysis.

Incurred sample reanalysis was performed and the percent difference in more than 67% of the samples were within ±30%.

Determination of anti-ipilimumab antibodies

Samples were received from study CA2099DW between 12th March 2021 and 14th September 2023. Of those, a majority were analysed and reported between 27th September 2022 and 4th December 2023 and 1 sample was not analysed per protocol.

Of the runs were performed, 88.9% were accepted. Each run contained two sets of PC and two sets of NC. In every accepted run, CV between control duplicates was ≤20% and NC< LPC< MPC< HPC.

There was no reanalysis.

Determination of anti-ipilimumab neutralizing antibodies

Samples were analysed from study CA2099DW between 11th January 2024 and 12th January 2024.

The analytical run contained two sets of LPC, HPC and LPC-EXC and four sets of NC and CV between control duplicates was ≤30% in at least one at each level.

There was no reanalysis.

2.3.2.2. Pharmacokinetics

Pharmacokinetics in the target population

Population Pharmacokinetic Analysis

The purpose of the popPK analyses is to characterize the PK of nivolumab and ipilimumab when administered in combination as 1L therapy in unresectable or advanced HCC subjects as evaluated in Phase 3 study CA2099DW. CA2099DW is a randomized, multi-centre, Phase 3, open-label, 2-arm clinical trial of nivolumab plus ipilimumab combination therapy compared to investigator's choice (sorafenib or lenvatinib) in unresectable or advanced HCC as 1L therapy.

The PK of nivolumab and ipilimumab, following co-administration, have been well characterized by separate 2-compartment models using data from subjects across multiple tumour types and lines of therapy.

Nivolumab and ipilimumab PK data from study CA2099DW were pooled with the popPK dataset from historical studies with nivolumab monotherapy, ipilimumab monotherapy, or in combination in multiple tumour types. As a popPK analysis of nivolumab and ipilimumab when administered in combination,

which included 2L HCC population, has been previously conducted and evaluated, this updated analysis was primarily to re-estimate the parameters and variability using a revised popPK model and to evaluate nivolumab and ipilimumab PK in subjects with 1L HCC following nivolumab and ipilimumab combination therapy. In addition, impacts of line of therapy, combination therapy, ethnicity, and immunogenicity on nivolumab and impacts of line of therapy and ethnicity on ipilimumab PK were evaluated. Additionally, the nivolumab and ipilimumab exposures were simulated for E-R analyses.

Population Pharmacokinetic Analysis: Nivolumab

Final Model

Parameter estimates of the final model following backward elimination are presented in Table 2.

Table 2 Parameter Estimates of the Nivolumab Final Population Pharmacokinetic Model

Parameter [Units][a]	Symbol	Estimate[b]	Standard Error (%RSE)[c]	95% Confidence Interval[d]
		Fixed Effects[e]		
$CL0_{REF}$ [mL/h][e]	θ_1	10.2	0.268 (2.63)	9.69 - 10.7
VC_{REF} [L][e]	θ_2	4.27	0.0536 (1.26)	4.17 - 4.38
Q_{REF} [mL/h][e]	θ_3	31.9	2.63 (8.22)	26.8 - 37.1
VP_{REF} [L][e]	θ_4	3.14	0.124 (3.93)	2.9 - 3.39
CL_{WTBL}	θ_7	0.42	0.0427 (10.2)	0.336 - 0.504
CL_{EGFRBL}	θ_8	0.171	0.0309 (18)	0.111 - 0.232
CL_{ALBBL}	θ_9	-0.935	0.0625 (6.68)	(-1.06) - (-0.813)
CL_{FEMALE}	θ_{10}	-0.2	0.0183 (9.17)	(-0.236) - (-0.164)
CL_{PS}	θ_{11}	0.107	0.0168 (15.7)	0.0741 - 0.14
CL_{RAAA}	θ_{12}	0.076	0.0399 (52.4)	(-0.00213) - 0.154
CL_{RAAS}	θ_{13}	-0.124	0.0187 (15.1)	(-0.16) - (-0.087)
VC_{WTBL}	θ_{14}	0.66	0.0369 (5.59)	0.587 - 0.732
VC_{FEMALE}	θ_{15}	-0.154	0.0211 (13.6)	(-0.196) - (-0.113)
$EMAX_{REF}$[e]	θ_{16}	-0.133	0.0365 (27.4)	(-0.205) - (-0.0618)
$T50_{REF}$ [h][e]	θ_{17}	2070	108 (5.22)	1860 - 2280
HILL	θ_{18}	5.44	2.88 (52.9)	(-0.203) - 11.1
$CL_{IPI\ 1\ mg\ Q6W}$	θ_{19}	0.183	0.0193 (10.5)	0.145 - 0.221
$CL_{IPI\ 3\ mg\ Q3W}$	θ_{20}	0.273	0.034 (12.4)	0.207 - 0.34
$EMAX_{PS}$	θ_{21}	-0.0528	0.0241 (45.6)	(-0.1) - (-0.00561)
$EMAX_{IPICO}$	θ_{22}	-0.222	0.0234 (10.6)	(-0.268) - (-0.176)
CL_{LDHBL}	θ_{23}	0.399	0.0933 (23.4)	0.216 - 0.581
$CL_{2L+\ HCC}$	θ_{25}	0.0598	0.0229 (38.3)	0.0149 - 0.105
CL_{OTH}	θ_{27}	0.179	0.0322 (18)	0.115 - 0.242
$T50_{1L\ HCC}$	θ_{28}	0.48	0.0945 (19.7)	0.295 - 0.665
$T50_{2L+\ HCC}$	θ_{29}	0.353	0.125 (35.4)	0.109 - 0.598
		Random Effects		
ZCL	$\omega_{1,1}$	0.113 (0.337)	0.00656 (5.79)	0.101 - 0.126
ZVC:ZCL	$\omega_{2,1}$	0.0304 (0.174)	0.00619 (20.4)	0.0182 - 0.0425
ZVC	$\omega_{2,2}$	0.111 (0.333)	0.0113 (10.2)	0.0887 - 0.133
ZQ	$\omega_{3,3}$	0.113	SAME	SAME
ZVP:ZQ	$\omega_{4,3}$	0.0304	SAME	SAME

Parameter [Units][a]	Symbol	Estimate[b]	Standard Error (%RSE)[c]	95% Confidence Interval[d]
ZVP	$\omega_{4,4}$	0.111	SAME	SAME
ZEMAX	$\omega_{5,5}$	0.0694 (0.263)	0.0105 (15.2)	0.0487 - 0.09
		Residual Error		
Proportional RV [-]	θ_6	0.224	0.00397 (1.77)	0.217 - 0.232

[a] Random effects and residual error parameter names containing a colon (:) denote correlated parameters.

[b] Random effects and residual error parameter estimates are shown as Variance (Standard Deviation) for diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$) and covariance (correlation) for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$).

[c] %RSE is the relative standard error (standard error as a percentage of estimate).

[d] Confidence intervals of random effects and residual error parameters are for variance or covariance.

[e] CL_{REF}, VC_{REF}, Q_{REF}, VP_{REF}, $T50_{REF}$, and $EMAX_{REF}$ are typical values of CL, VC, Q, VP, T50, and EMAX at the reference covariate values. Covariate effects were estimated relative to a reference subject who is male, with 2L+ NSCLC receiving nivolumab monotherapy, ALBBL of 4.0 g/dL, LDHBL of 200 IU/L, WTBL of 80.0 kg, EGFRBL of 90.0 mL/min/1.73 m^2, PS of 0, and race = white.

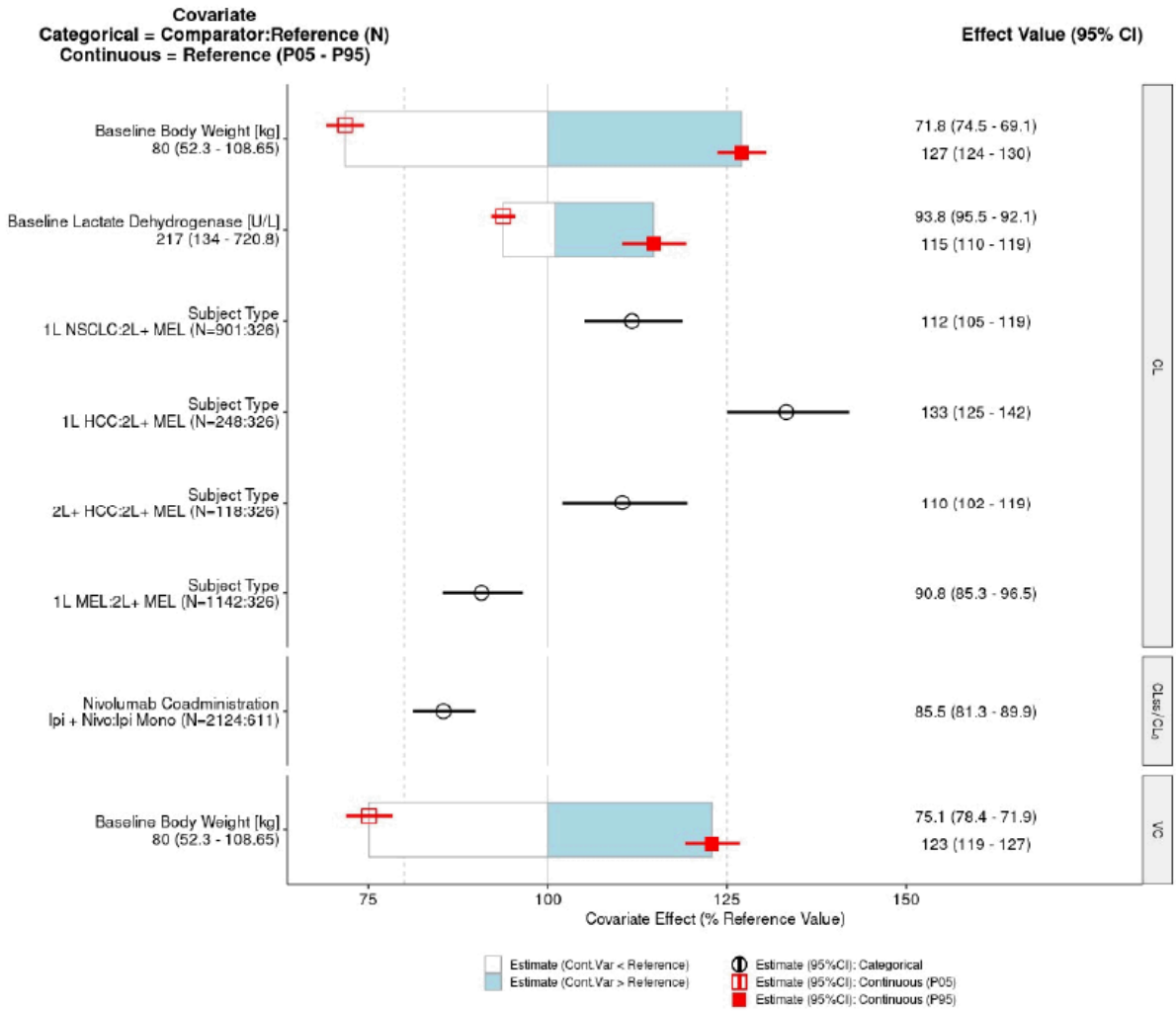
Population Pharmacokinetic Analysis: Ipilimumab

Final Model

The final base model represents the final model for this ipilimumab analysis.

Graphical representations of the effect of categorical and continuous covariates on the typical value of the structural model parameters of CL, VC, and Emax are presented in Figure 1.

Figure 1 Covariate Effects on Ipilimumab Pharmacokinetic Model Parameters (Ipilimumab Final Population Pharmacokinetic Model)



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 of 2L+ MEL subject type, WTBL = 80 kg, LDHBL = 217 IU/L and received ipilimumab monotherapy. Parameter estimate in a reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 125% of this value.

Note 4: The effect of WTBL was also added on Q and VP and their estimates were fixed to be similar to that of CL and VC, respectively (data not shown).

Immunogenicity

In CA2099DW, the treatment-emergent ADA positive incidences were 44.6% (100/224) for nivolumab (4.9% (11/224) persistent positive) and 5.3% (13/244) for ipilimumab (0.4% (1/244) persistent positive) following nivo+ipi treatment in subjects with 1L HCC. The nivolumab NAb incidence was 7.1% (16/224) and no subject was ipilimumab NAb positive.

Table 3 Incidence of ADA - All Nivo+Ipi Treated Subjects with Baseline and at Least One Post-baseline Evaluable ADA Assessment

	Nivo+Ipi	
Subject ADA Status (%)	Nivo ADA N = 224	Ipi ADA N = 244
BASELINE ADA POSITIVE	19 (8.5)	18 (7.4)
ADA POSITIVE	100 (44.6)	13 (5.3)
PERSISTENT POSITIVE (PP)	11 (4.9)	1 (0.4)
NOT PP - LAST SAMPLE POSITIVE	38 (17.0)	2 (0.8)
OTHER POSITIVE	51 (22.8)	10 (4.1)
NEUTRALIZING POSITIVE	16 (7.1)	0
ADA NEGATIVE	124 (55.4)	231 (94.7)

Baseline ADA Positive: A subject with baseline ADA-positive sample;

ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater than baseline positive titer) at any time after initiation of treatment;

Persistent Positive (PP): ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA-positive samples are at least 16 weeks apart;

Not PP-Last Sample Positive: Not persistent but with ADA-positive sample at the last sampling timepoint;

Other Positive: Not persistent but some ADA-positive samples with the last sample being negative;

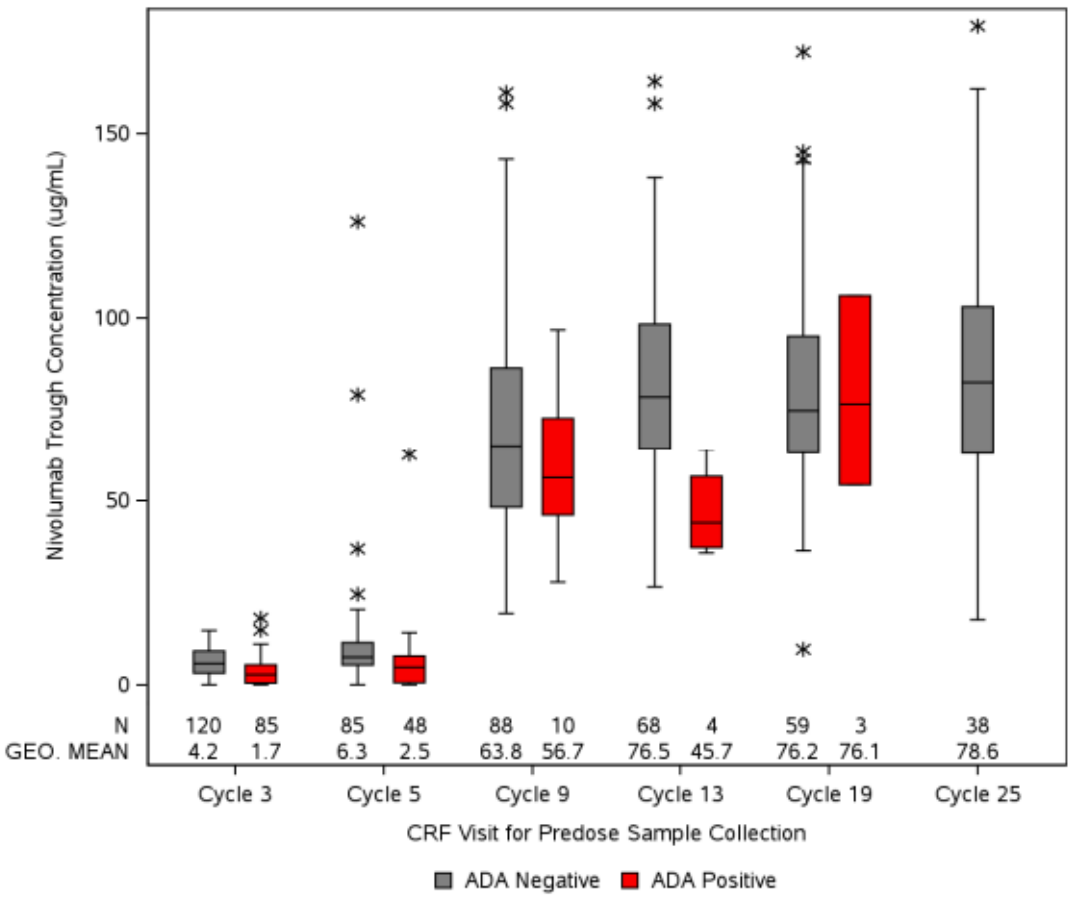
Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline;

ADA Negative: A subject with no ADA-positive sample after initiation of treatment.

Post-baseline assessments are assessments reported after initiation of treatment.

The majority of ADA positive samples were observed within 5 cycles after receiving nivo+ipi treatment (Figure 2 and Figure 3).

Figure 2 Distribution of Nivolumab Trough Concentrations at Each Assessment Timepoint Over Time by ADA Status - All Nivolumab + Ipilimumab Treated Subjects with ADA Positive or ADA Negative



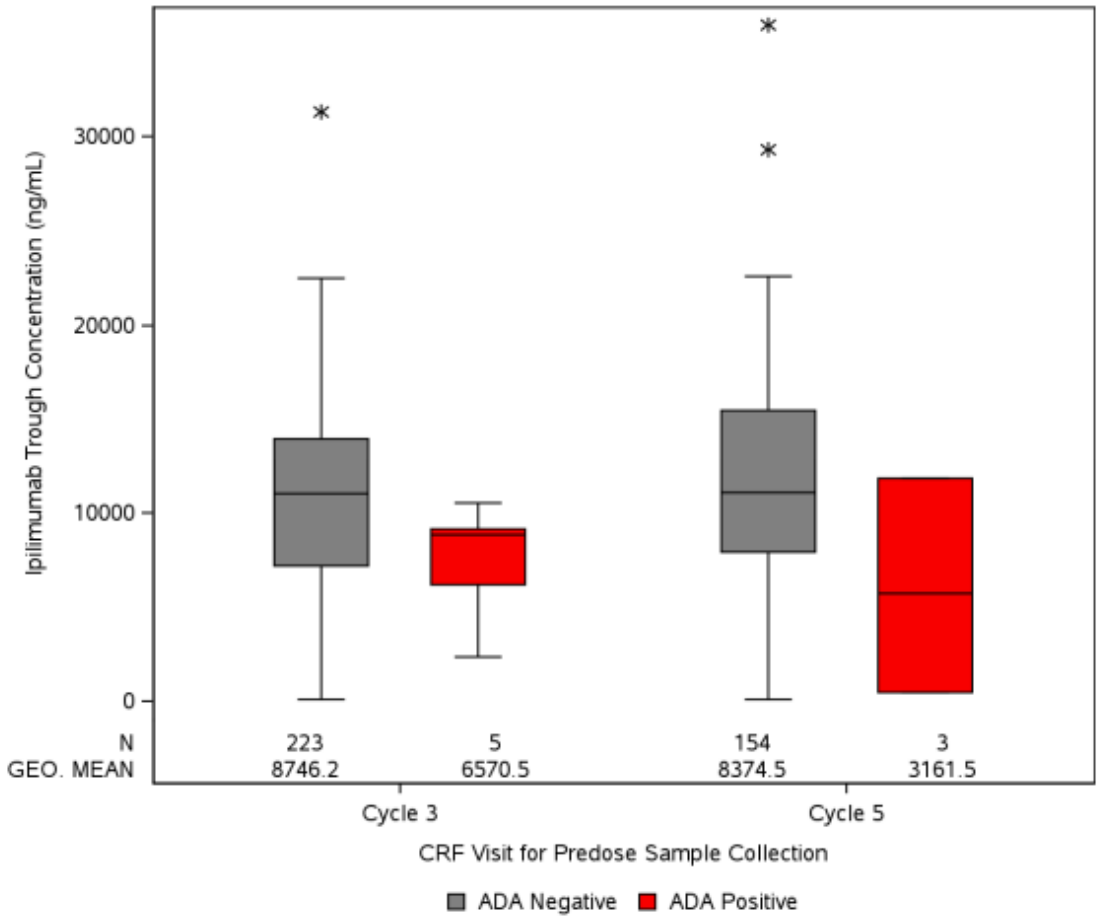
Source: Figure 14.5.1.4

Each box represents the median, 25th, and 75th percentile of trough concentration distribution.

The whiskers represent 5th and 95th percentile of the distribution

The stars indicate outliers.

Figure 3 Distribution of Ipilimumab Trough Concentrations at Each Assessment Timepoint Over Time by ADA Status - All Nivolumab + Ipilimumab Treated Subjects with ADA Positive or ADA Negative



Source: Figure 14.5.1.4
Each box represents the median, 25th, and 75th percentile of trough concentration distribution.
The whiskers represent 5th and 95th percentile of the distribution
The stars indicate outliers.

Analysis of the effect of immunogenicity on PK in CA2099DW showed the observed trough concentrations in subjects with positive ADA (for either nivolumab or ipilimumab) were generally within the concentration range observed in subjects with negative ADA (for either nivolumab or ipilimumab), although the distribution of observed trough concentrations in subjects with positive ADA appeared to be slightly lower compared to that in subjects with negative ADA at some assessment time points. It should be noted that the sample sizes for nivolumab ADA positive subjects were relatively small at later assessment time points, and the sample sizes for ipilimumab ADA positive subjects were relatively small in all assessment time points. A similar conclusion was drawn based on popPK analysis. Overall, there was no clinically relevant impact of immunogenicity on the observed PK and model-predicted PK of nivolumab.

Hepatic impairment

The Applicant proposes to update the hepatic impairment section of the SmPC based on previous population PK analysis. The proposed language is as follows: The effect of hepatic impairment on the CL of nivolumab was evaluated in patients with different tumour types (NSCLC, SCLC, melanoma, RCC, SCCHN, UC, GC, and cHL) with mild hepatic impairment (total bilirubin 1.0 × to 1.5 × ULN or AST > ULN as defined using the National Cancer Institute criteria of hepatic dysfunction; n = 351) and in

patients with moderate hepatic impairment (total bilirubin > 1.5 × to 3 × ULN and any AST; n = 10) compared to patients with normal hepatic function (total bilirubin and AST ≤ ULN; n = 3,096) in a population PK analysis. No clinically important differences in the CL of nivolumab were found between patients with mild or moderate hepatic impairment and normal hepatic function. Similar results were observed in patients with HCC (mild hepatic impairment: n = 152; moderate hepatic impairment: n = 13). Nivolumab has not been studied in patients with severe hepatic impairment (total bilirubin > 3 × ULN and any AST).

2.3.2.3. PK/PD modelling

The purpose of the E-R analyses described in this report was to support the benefit-risk assessment of nivolumab (BMS-936558, MDX-1106, ONO-4538) and ipilimumab (BMS-734016, MDX-010), administered in combination as 1L therapy in unresectable or advanced HCC as evaluated in Phase 3 study CA2099DW.

Given the extensive characterization of E-R relationships, the E-R analyses of efficacy (OS) and safety (Gr2+ IMAEs) focused on graphical characterization of the relationship between these endpoints and nivolumab/ipilimumab exposures predicted from the popPK analysis of study CA2099DW. OS was chosen as the measure of efficacy because it was the primary efficacy endpoint in study CA2099DW supporting the benefit-risk assessment. Gr2+ IMAEs were selected to reflect AEs specific to cancer immunotherapy due to the increased activity of the immune system from the treatment.

Objectives

- To characterize the relationship between nivolumab and ipilimumab exposures (Cavg1) and efficacy as measured by OS in all treated 1L unresectable or advanced HCC subjects.
- To characterize the relationship between nivolumab and ipilimumab exposures (Cavg1) and safety as measured by time to the first occurrence of Gr2+ IMAEs in all treated 1L unresectable or advanced HCC subjects.

Data

The E-R analyses of efficacy and safety were performed with data from subjects who received nivolumab + ipilimumab versus investigator's choice (sorafenib or lenvatinib) in subjects with 1L unresectable or advanced HCC from study CA2099DW (Table 4).

Table 4 Description of Clinical Studies Included in the Nivolumab Exposure-Response Analyses

Protocol #: Title *Study Population*	Treatment	Planned Sample Size[a]	PK Assessments	Analyses
CA2099DW: A phase 3, randomized, open-label, multi-center 2-arm clinical trial of nivolumab plus ipilimumab combination therapy compared to sorafenib or lenvatinib as 1L treatment in *unresectable or advanced HCC*	**Arm A**: Nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W for up to 4 cycles, followed by nivolumab 480 mg Q4W **Arm B**: Sorafenib 400 mg PO BID or lenvatinib 8 mg or 12 mg PO QD	~650	**Arm A**: predose on C1D1, C3D1, C5D1, C9D1, C13D1, C19D1, C25D1	E-R efficacy E-R safety

[a] As per protocol.

Nivolumab Exposure-Response

Exposure-Response Efficacy Analysis

Analysis population

Table 5 Subjects Included in the Nivolumab Exposure-Response of OS Analysis Dataset

Study CA2099DW Treatment Regimen	Treated Subjects (n = 657)	Excluded Due to No Nivo Exposures (%) (n = 91)	Included (%) (n = 566)
Nivolumab + Ipilimumab (Arm A)	332 (100.0)	91 (27.4)	241 (72.6)
Sorafenib or Lenvatinib (Arm B)	325 (100.0)	0 (0.0)	325 (100.0)

Summary of Events

Table 6 Summary of Events in the Nivolumab Exposure-Response of OS Analysis Dataset

Study CA2099DW Treatment Regimen	Included in Analysis (n = 566)	Number of Events (%) (n = 346)	Censored (%) (n = 220)
Nivolumab + Ipilimumab (Arm A)	241 (100.0)	122 (50.6)	119 (49.4)
Sorafenib or Lenvatinib (Arm B)	325 (100.0)	224 (68.9)	101 (31.1)

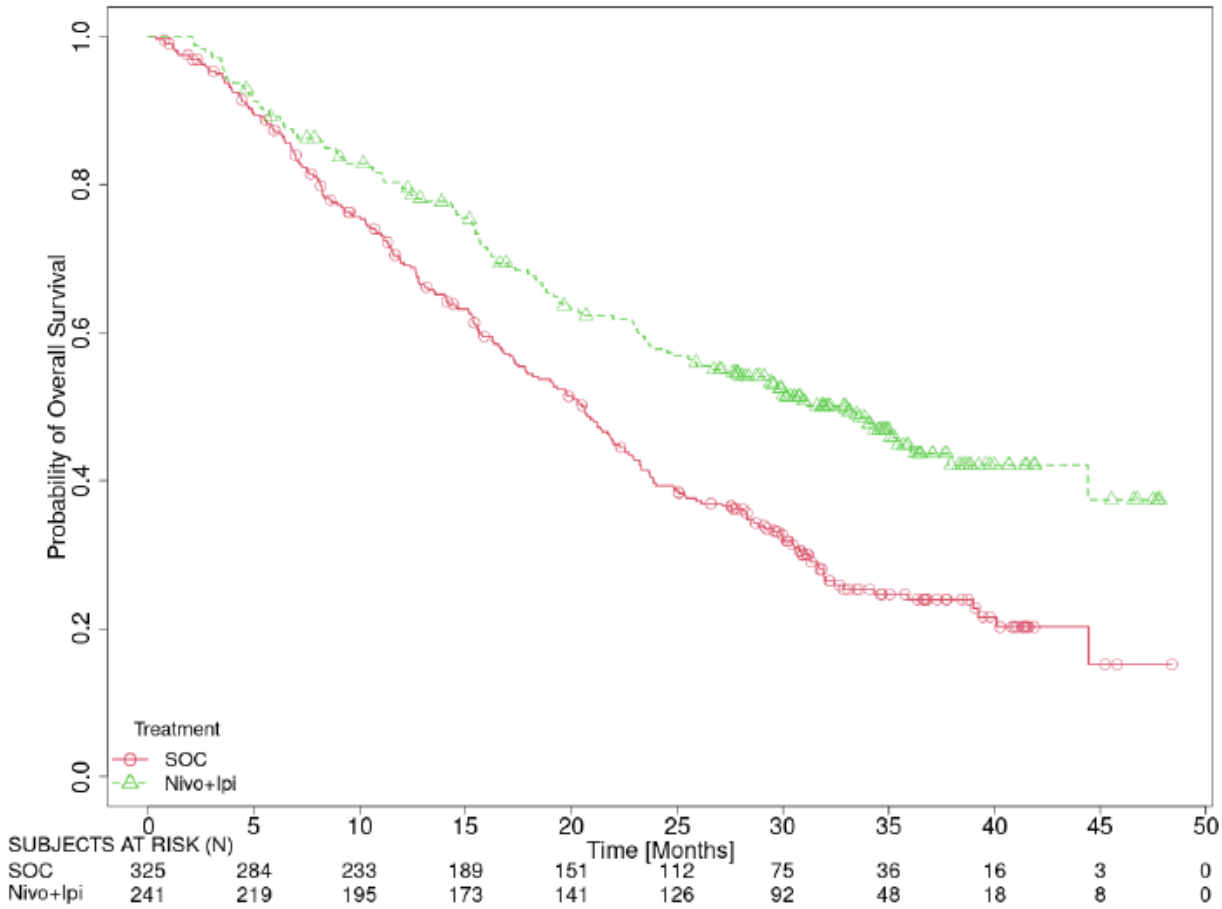
Summary of Exposure Measures and Baseline Demographics

Table 7 Summary of Exposures Measures and Baseline Demographics in the Nivolumab Exposure-Response of OS Analysis Dataset

Covariate	Nivolumab + Ipilimumab (n = 241)	Sorafenib or Lenvatinib (n = 325)	Total (n = 566)
Nivolumab Cavg1 (µg/mL)			
Mean (SD)	7.26 (1.84)	NA	3.09 (3.79)
Median	7.07	NA	NA
Min, Max	2.7, 18.4	NA	0.0, 18.4
Missing, N (%)	0 (0.0)	NA	NA
Age (yr)			
Mean (SD)	64.07 (9.49)	65.45 (10.26)	64.86 (9.95)
Median	64.00	66.00	65.00
Min, Max	37.0, 86.0	20.0, 89.0	20.0, 89.0
Missing, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
Baseline Body Weight (kg)			
Mean (SD)	73.63 (15.52)	72.43 (16.29)	72.94 (15.96)
Median	71.50	70.00	70.70
Min, Max	39.0, 128.1	36.5, 160.0	36.5, 160.0
Missing, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
Sex, N (%)			
Female	44 (18.3)	56 (17.2)	100 (17.7)
Male	197 (81.7)	269 (82.8)	466 (82.3)

Visual inspection of K-M curves by treatment arm suggested that subjects treated with nivolumab + ipilimumab have better (i.e. longer) OS as compared to subjects treated with sorafenib or lenvatinib in nivolumab PK evaluable population (Figure 4).

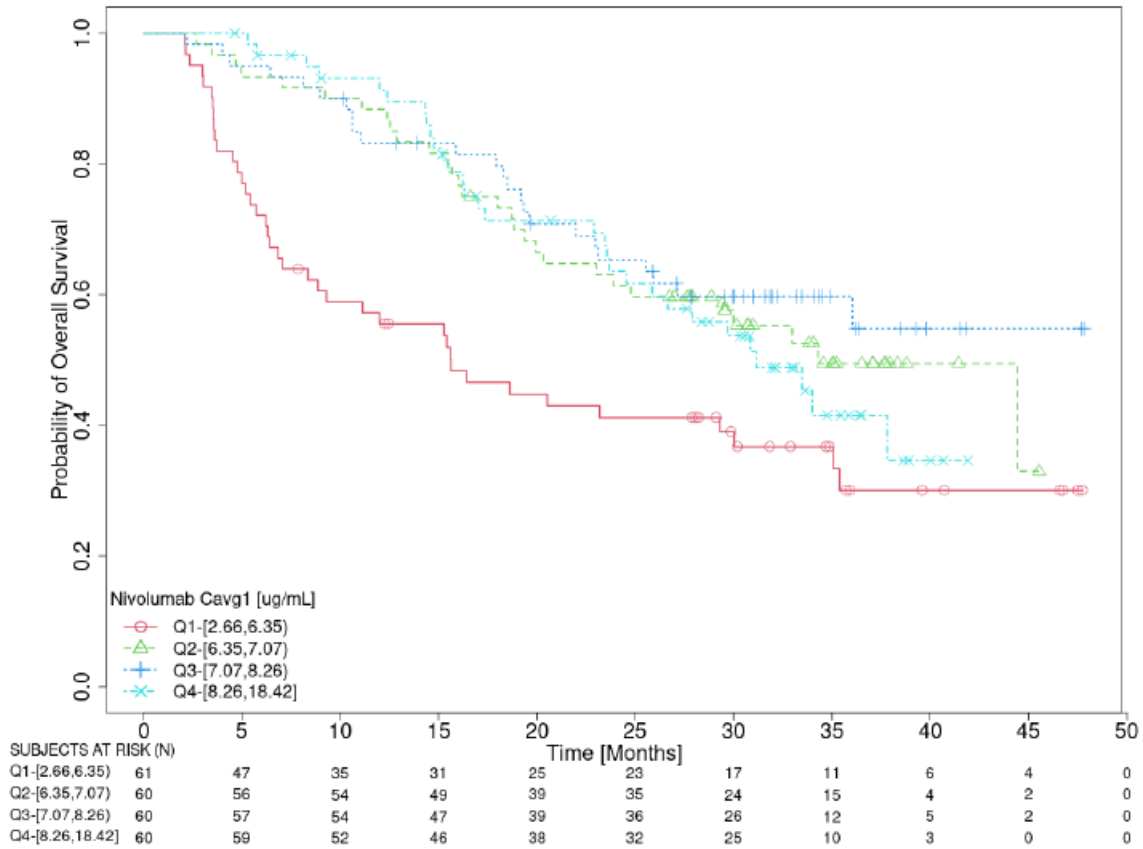
Figure 4 K-M Curves of OS Stratified by Treatment Arm in Nivolumab PK Evaluable Population



Note: For Nivo+Ipi arm, only subjects with available nivolumab exposures were included.

Further K-M analysis of the E-R relationship for OS stratified by nivolumab exposure (Cavg1) quartiles in nivolumab + ipilimumab –treated subjects showed that subjects with nivolumab Cavg1 in the lowest quartile had a lower probability of OS compared to higher Cavg1 as observed in Quartiles 2, 3, and 4 (Figure 5).

Figure 5 K-M Curves of OS Stratified by Nivolumab Exposure Quartiles (Nivolumab + Ipilimumab –Treated Subjects)



Note: Quartile range numbers are provided. Numbers flanked by a square bracket indicate inclusion in respective quartile. Numbers flanked by parenthesis indicate non-inclusion in respective interval.

Exposure-Response Safety Analysis

Analysis population

Table 8 Subjects Included in the Nivolumab Exposure-Response of Gr2+IMAE Analysis Dataset

Study CA2099DW Treatment Regimen	Treated Subjects (n = 657)	Excluded Due to No Nivo Exposures (%) (n = 91)	Included (%) (n = 566)
Nivolumab + Ipilimumab (Arm A)	332 (100.0)	91 (27.4)	241 (72.6)
Sorafenib or Lenvatinib (Arm B)	325 (100.0)	0 (0.0)	325 (100.0)

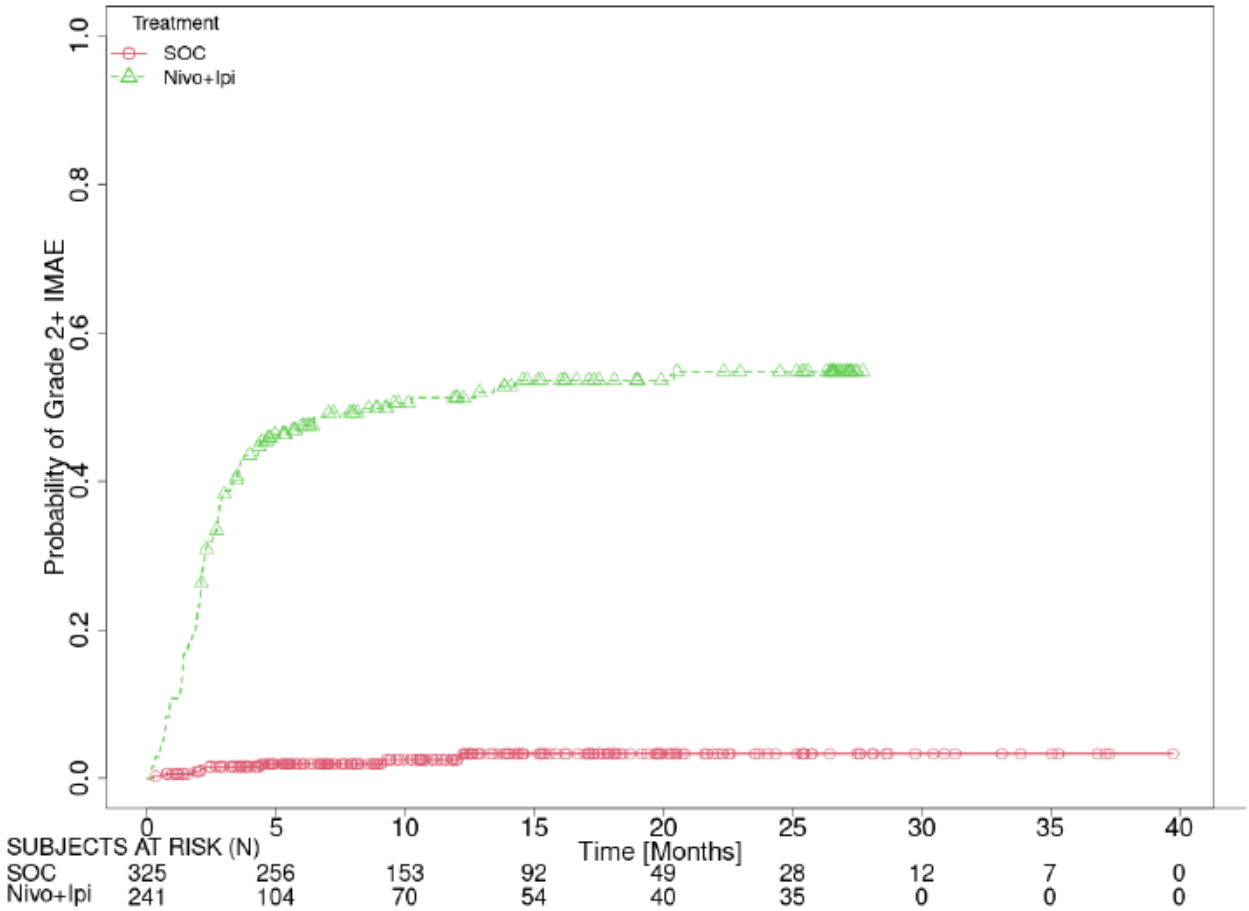
Summary of Events

Table 9 Summary of Events in the Nivolumab Exposure-Response of Gr2+IMAE Analysis Dataset

Study CA2099DW Treatment Regimen	Included in Analysis (n = 566)	Number of Events (%) (n = 130)	Censored (%) (n = 436)
Nivolumab + Ipilimumab (Arm A)	241 (100.0)	122 (50.6)	119 (49.4)
Sorafenib or Lenvatinib (Arm B)	325 (100.0)	8 (2.5)	317 (97.5)

Visual inspection of K-M curves by treatment arm suggested that treatment with nivolumab +ipilimumab was associated with a higher risk of Gr2+ IMAEs as compared to the risk in subjects treated with sorafenib or lenvatinib in nivolumab PK evaluable population (Figure 6).

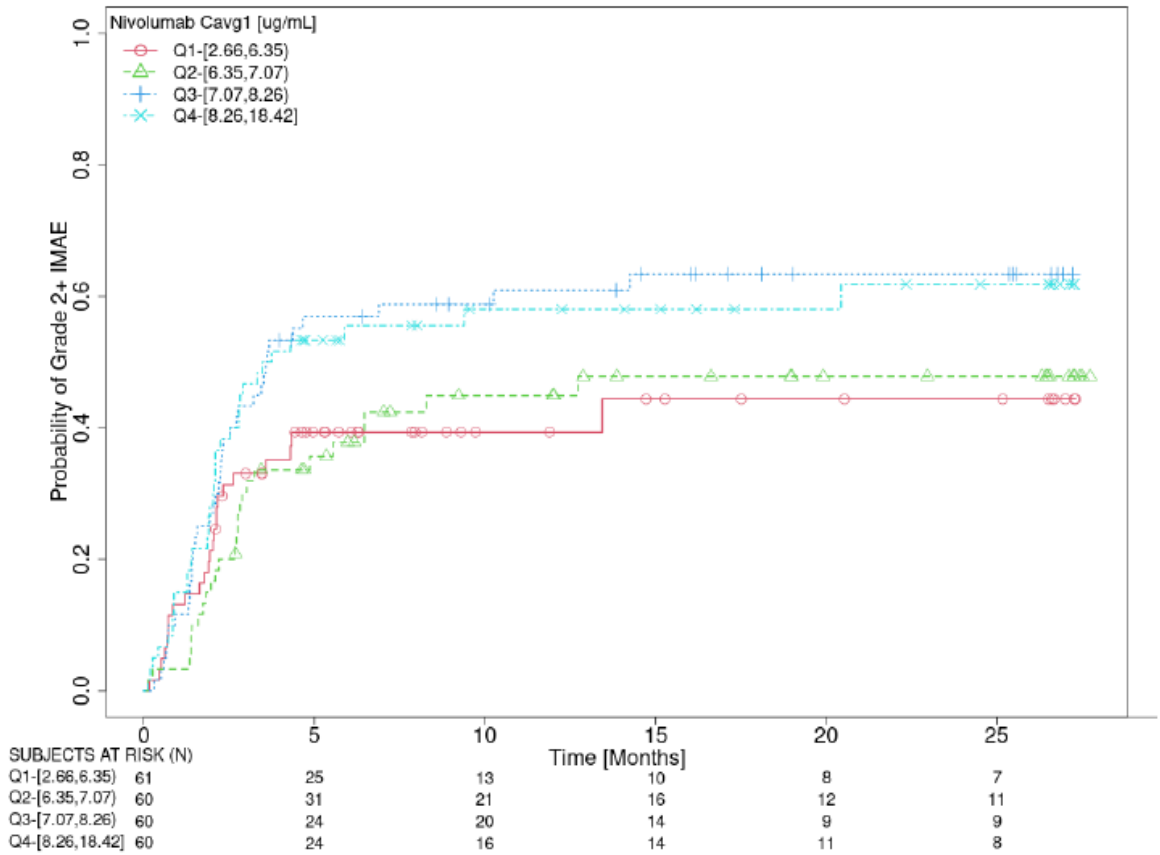
Figure 6 K-M Curves of Gr2+ IMAEs Stratified by Treatment Arm in Nivolumab PK Evaluable Population



Note: For Nivo+Ipi arm, only subjects with available nivolumab exposures were included.

Further K-M analysis of the E-R relationship for Gr2+ IMAEs stratified by nivolumab exposure (Cavg1) quartiles in nivolumab + ipilimumab –treated subjects showed the probability of Gr2+ IMAEs was higher in the 2 higher exposure quartiles of nivolumab (Quartiles 3 and 4) compared to the 2 lower exposure quartiles of nivolumab (Quartiles 1 and 2) (Figure 7).

Figure 7 K-M Curve of Gr2+ IMAEs Stratified by Nivolumab Exposure Quartiles (Nivolumab + Ipilimumab –Treated Subjects)



Note: Quartile range numbers are provided. Numbers flanked by a square bracket indicate inclusion in respective quartile. Numbers flanked by parenthesis indicate non-inclusion in respective interval.

Ipilimumab Exposure-Response

Exposure-Response Efficacy Analysis

Analysis population

Table 10 Subjects Included in the Ipilimumab Exposure-Response of OS Analysis Dataset

Study CA2099DW Treatment Regimen	Treated Subjects (n = 657)	Excluded Due to No Ipi Exposures (%) (n = 85)	Included (%) (n = 572)
Nivolumab + Ipilimumab (Arm A)	332 (100.0)	85 (25.6)	247 (74.4)
Sorafenib or Lenvatinib (Arm B)	325 (100.0)	0 (0.0)	325 (100.0)

Visual inspection of K-M curves suggested that subjects treated with nivolumab + ipilimumab have better (i.e. longer) OS as compared to those treated with sorafenib or lenvatinib in ipilimumab PK evaluable population (Figure 8).

Summary of Events

Table 11 Summary of Events in the Ipilimumab Exposure-Response of OS Analysis Dataset

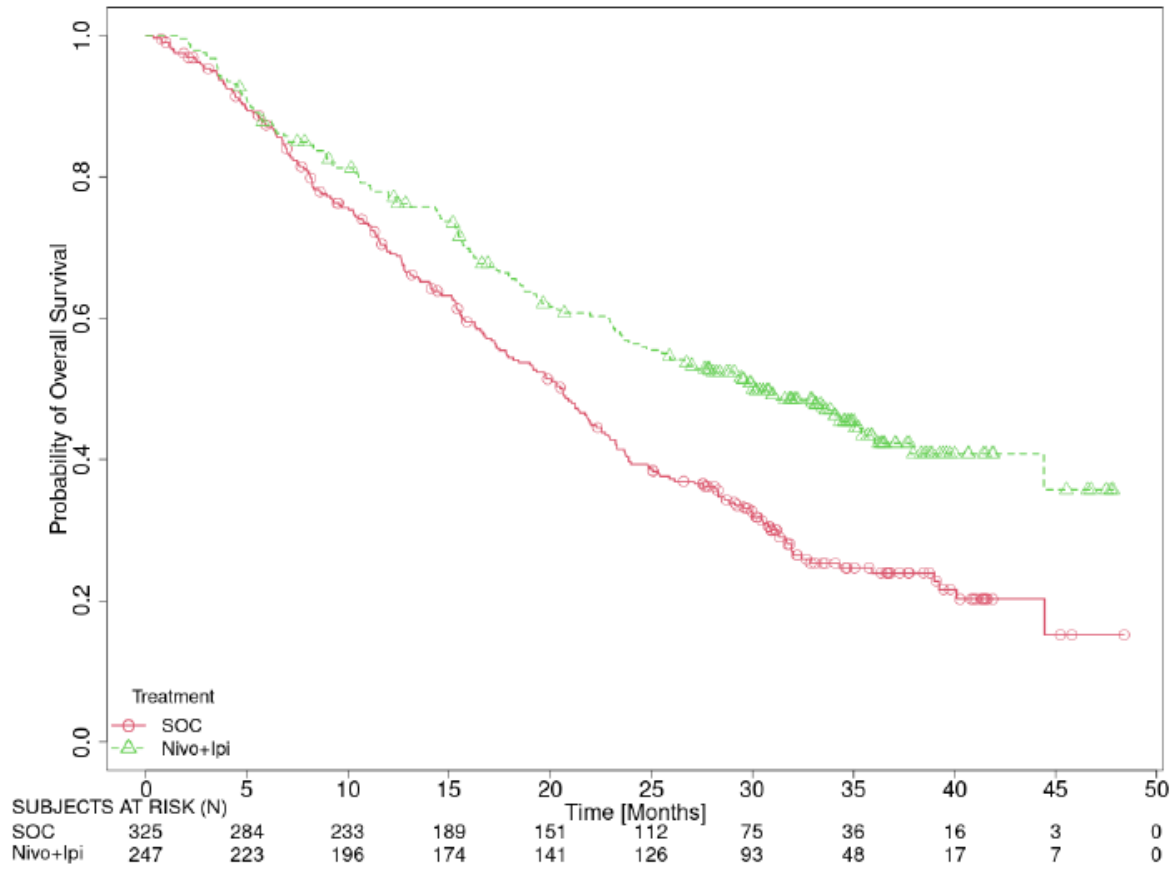
Study CA2099DW Treatment Regimen	Included in Analysis (n = 572)	Number of Events (%) (n = 353)	Censored (%) (n = 219)
Nivolumab + Ipilimumab (Arm A)	247 (100.0)	129 (52.2)	118 (47.8)
Sorafenib or Lenvatinib (Arm B)	325 (100.0)	224 (68.9)	101 (31.1)

Summary of Exposure Measures and Demographics

Table 12 Summary of Exposures and Baseline Demographics in the Ipilimumab Exposure-Response of OS Analysis Dataset

Covariate	Nivolumab + Ipilimumab (n = 247)	Sorafenib or Lenvatinib (n = 325)	Total (n = 572)
Ipilimumab Cavg1 (µg/mL)			
Mean (SD)	19.49 (3.41)	NA	8.42 (9.92)
Median	19.58	NA	NA
Min, Max	9.2, 32.8	NA	0.0, 32.8
Missing, N (%)	0 (0.0)	NA	NA
Age (yr)			
Mean (SD)	63.71 (10.08)	65.45 (10.26)	64.70 (10.21)
Median	64.00	66.00	65.00
Min, Max	20.0, 86.0	20.0, 89.0	20.0, 89.0
Missing, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
Baseline Body Weight (kg)			
Mean (SD)	73.31 (15.38)	72.43 (16.29)	72.81 (15.89)
Median	71.20	70.00	70.65
Min, Max	39.0, 128.1	36.5, 160.0	36.5, 160.0
Missing, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
Sex, N (%)			
Female	47 (19.0)	56 (17.2)	103 (18.0)
Male	200 (81.0)	269 (82.8)	469 (82.0)

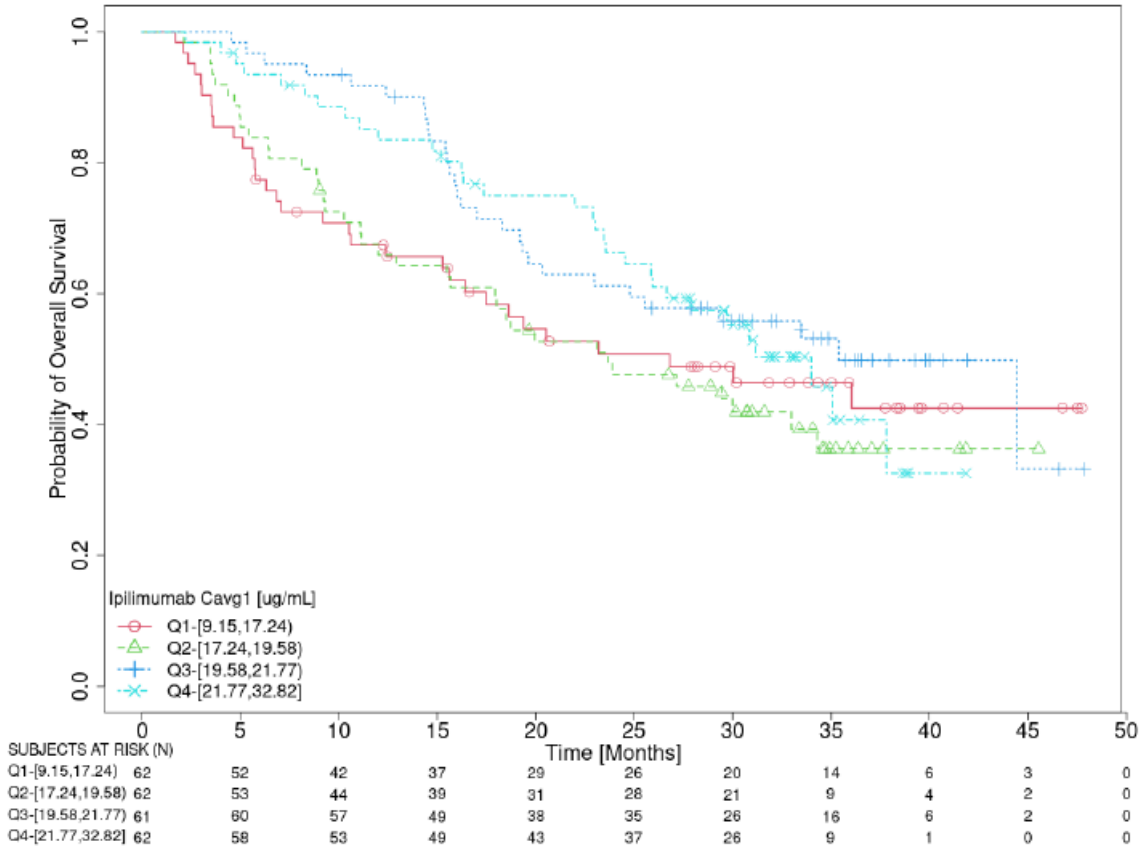
Figure 8 K-M Curves of OS Stratified by Treatment Arm in Ipilimumab PK Evaluable Population



Note: For Nivo+Ipi arm, only subjects with available ipilimumab exposures were included.

Further K-M analysis of the E-R relationship for OS stratified by ipilimumab exposure (Cavg1) quartiles in nivolumab + ipilimumab –treated subjects showed higher probability of survival was observed in the 2 higher exposure quartiles (Quartiles 3 and 4) compared to the 2 lower exposure quartiles (Quartiles 1 and 2), and the trend was not clear after ~30 months (Figure 9).

Figure 9 K-M Curves of OS Stratified by Ipilimumab Exposure Quartiles (Nivolumab + Ipilimumab –Treated Subjects)



Note: Quartile range numbers are provided. Numbers flanked by a square bracket indicate inclusion in respective quartile. Numbers flanked by parenthesis indicate non-inclusion in respective interval.

Exposure-Response Safety Analysis

Analysis population

Table 13 Subjects Included in the Ipilimumab Exposure-Response of Gr2+IMAE Analysis Dataset

Study CA2099DW Treatment Regimen	Treated Subjects (n = 657)	Excluded Due to No Ipi Exposures (%) (n = 85)	Included (%) (n = 572)
Nivolumab + Ipilimumab (Arm A)	332 (100.0)	85 (25.6)	247 (74.4)
Sorafenib or Lenvatinib (Arm B)	325 (100.0)	0 (0.0)	325 (100.0)

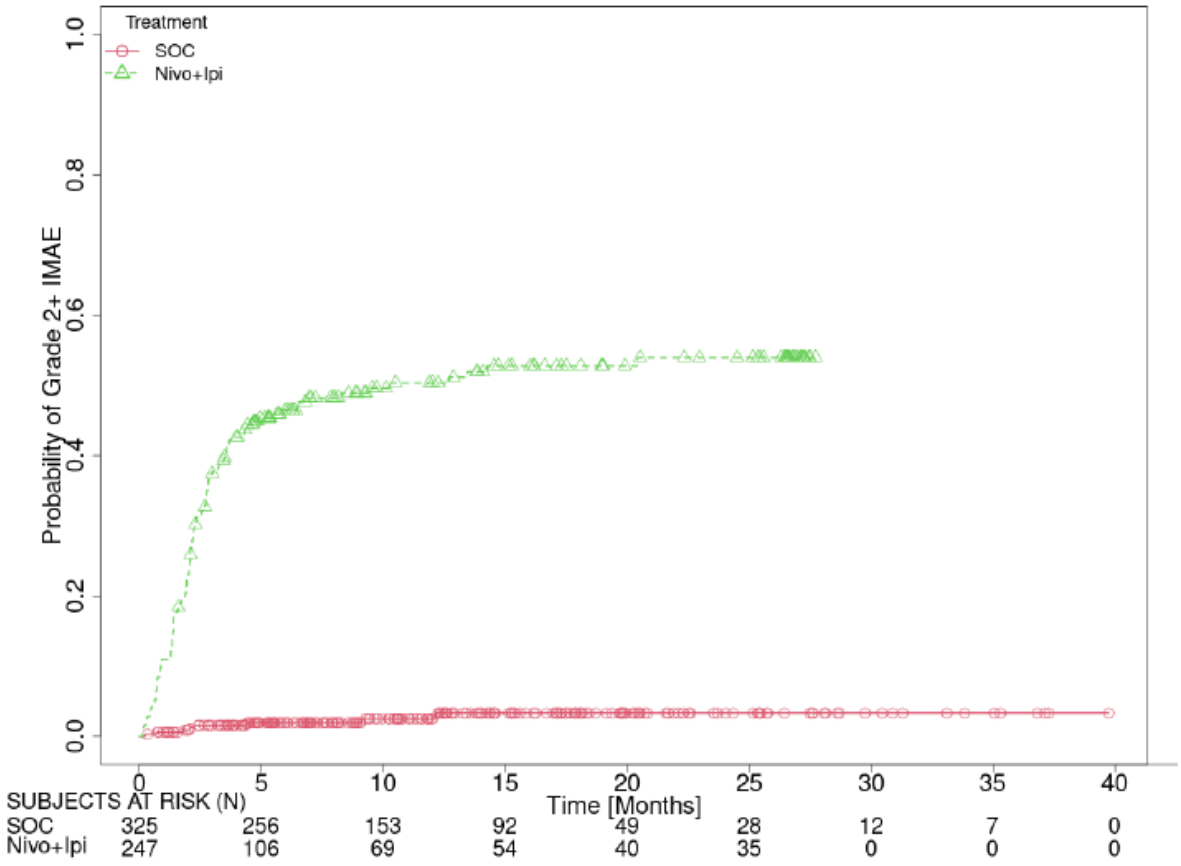
Summary of Events

Table 14 Summary of Events in the Ipilimumab Exposure-Response of Gr2+IMAE Analysis Dataset

Study CA2099DW Treatment Regimen	Included in Analysis (n = 572)	Number of Events (%) (n = 130)	Censored (%) (n = 442)
Nivolumab + Ipilimumab (Arm A)	247	122 (49.4)	125 (50.6)
Sorafenib or Lenvatinib (Arm B)	325	8 (2.5)	317 (97.5)

Visual inspection of K-M curves suggested that treatment with nivolumab + ipilimumab was associated with a higher risk of Gr2+ IMAEs as compared to the risk in subjects treated with sorafenib or lenvatinib in ipilimumab PK evaluable population (Figure 10).

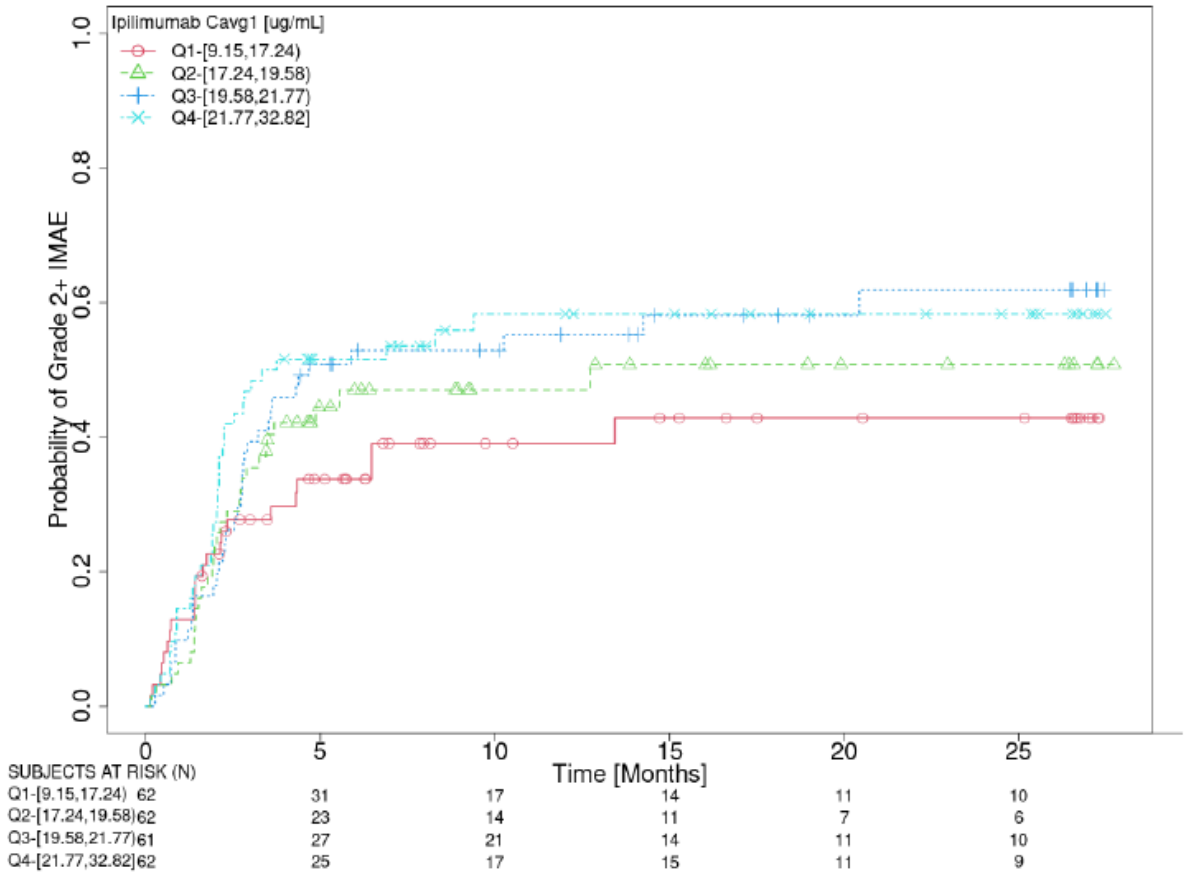
Figure 10 K-M Curves of Gr2+ IMAEs Stratified by Treatment Arm for Ipilimumab E-R in Ipilimumab PK Evaluable Population



Note: For Nivo+Ipi arm, only subjects with available ipilimumab exposures were included.

Further K-M analysis of the E-R relationship for Gr2+ IMAEs stratified by ipilimumab exposure (Cavg1) quartiles in nivolumab + ipilimumab –treated subjects showed a higher probability of Gr2+ IMAEs with higher ipilimumab Cavg1 (Figure 11).

Figure 11 K-M Curve of Gr2+ IMAEs Stratified by Ipilimumab Exposure Quartiles (Nivolumab + Ipilimumab –Treated Subjects)



Note: Quartile range numbers are provided. Numbers flanked by a square bracket indicate inclusion in respective quartile. Numbers flanked by parenthesis indicate non-inclusion in respective interval.

Dose selection

The dosing regimen in CA2099DW for the 1L treatment of adults with unresectable or advanced HCC is nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W for up to 4 doses followed by nivolumab 480 mg Q4W.

This dosing regimen is selected based on the following rationale:

- In CA209040, the anti-tumour activity of the combination of nivolumab and ipilimumab were evaluated in 2L treatment subjects with HCC treated with 3 dosing regimens (nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W for 4 doses, followed by nivolumab 240 mg Q2W; nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses, followed by nivolumab 240 mg Q2W; nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W). Overall, response rates were similar between the different dosing regimens; however, the dosing regimen of nivolumab 1 mg/kg + ipilimumab 3 mg/kg for 4 doses, followed by nivolumab 240 mg Q2W was associated with longer OS, a higher rate of CR, and a more consistent benefit across aetiologies, without significantly compromised safety.
- The exposure of nivolumab was expected to be similar between subjects receiving nivolumab 240 mg Q2W and 480 mg Q4W as maintenance dose (after 4 doses of nivo+ipi combination) based on prior popPK analysis.

- The E-R relationships of nivolumab were flat for efficacy and safety within the range of exposures studied; the E-R relationship of ipilimumab was flat for efficacy and shallow for safety within the range of exposure studies.
- The safety of nivolumab was well-established up to the 10 mg/kg Q2W dose level.
- The dose of 3 mg/kg ipilimumab in the nivo+ipi combination has been evaluated in clinical studies across multiple tumour types, with favourable efficacy and safety profiles.

No PK interaction was expected between nivolumab 1 mg/kg Q3W and ipilimumab 3 mg/kg Q3W.

2.3.2.1. Discussion on clinical pharmacology

PK data from the pivotal Phase 3 study CA2099DW have been pooled with data from previous studies to conduct population PK and exposure-response analyses.

The two proposed dose regimens for this indication are first nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W for up to 4 doses followed by nivolumab monotherapy 480 mg Q4W as maintenance dose that is the same regimen studied in the pivotal study CA2099DW and second the same combination regimen used in the pivotal study followed by nivolumab monotherapy 240 mg Q2W as maintenance dose based solely on simulation analysis.

Analytical methods

Different methods were used to analyse samples from study CA2099DW. All of them were assessed and found acceptable in previous procedures. Moreover, cross-validation reports between bioanalytical methods used to analyse samples from study CA2099DW sites in all countries except China with methods used to analyse samples from sites in China has been provided and are acceptable.

Sample analysis

For study CA2099DW, different determinations were carried out: nivolumab and ipilimumab concentrations, anti-nivolumab and anti-ipilimumab antibodies and anti-nivolumab and anti-ipilimumab neutralizing antibodies. Sample analysis was carried out in different laboratories located in China, USA or India. Sample analysis has been carried out in accordance with method validation, ICHM10 Guideline and taking into account also the state of the art for ADA and NAb analysis.

For future procedures, the MAH should take into account for ADA and NAbs analytical methods that, according to the state of the art (Myler, Heather et al.), the acceptance criteria between duplicates of NC and PC controls should be CV≤20% for ADA analysis and CV≤25% for NAb analysis.

PopPK analysis of Nivolumab

The pharmacokinetic properties of nivolumab have been characterised using a previous population PK model. The modelling strategy is endorsed, since it allows to re-use and apply the previous knowledge of the structural and covariate effects to describe its concentration time-course in patients treated with the proposed dose regimen.

The current population PK analysis was based on a pooled dataset from nine clinical studies (CA209001/MDX-1106-01, CA209003/MDX-1106-03, CA209017, CA209057, CA209459, CA209012, CA209227, CA209040, CA2099DW), which includes data from patients with nivolumab monotherapy or nivolumab+ipilimumab combination treatment.

The analysis contained 2893 subjects (241 from study CA2099DW) and a total of 14165 observations. PK samples below limit of quantification (BLQ) of total observations were 2.21% and were excluded in the population PK analysis. M1 method for handling BLQ-data is considered acceptable.

The base model was established by re-estimating the model parameters from a previous PK model using the pooled dataset including data from study CA2099DW. All significant covariates previously identified except for the effect of chemo regimen on CL were retained in the analysis. Subsequently, a full model was developed by incorporating additional covariates representing the effect of subject type (1L HCC, 2L+ HCC, 1L NSCLC, Others versus 2L+NSCLC), ALBBL, and LDHBL on nivolumab CL and subject type (1L HCC, 2L+ HCC versus Others) on T50 for time-varying CL. And finally, a stepwise backward elimination was performed to select the final model.

PopPK analysis of Ipilimumab

The pharmacokinetic properties of ipilimumab have been characterised using a previous population PK model. The modelling strategy is endorsed, since it allows to re-use and apply the previous knowledge of the structural and covariate effects to describe its concentration time-course in patients treated with the proposed dose regimen.

The current population PK analysis was based on a pooled dataset from 11 clinical studies (CA184004, CA184022, CA209004, CA209067, CA209069, CA209511, CA209568, CA209012, CA209227, CA209040, and CA2099DW), which includes data from patients with ipilimumab monotherapy or nivolumab+ipilimumab combination treatment.

The analysis contained 2735 subjects (247 from study CA2099DW) and a total of 10032 observations. PK samples below limit of quantification (BLQ) of total observations were 11.75% and were excluded in the population PK analysis. However, many of them (814) were collected after >2000 hours, which is more than 5-fold the ipilimumab half-life (T1/2=15.4 days). In the study CA2099DW, 306 out of 314 BLQ observations were collected in cycle 9 or later, which is more that >2000 hours after the last dose of ipilimumab. Therefore, no measurable concentration could be expected, and those values could be deleted from the dataset. The final dataset contains 522 BLQ (4.59%) of a total number of observations (11368). For this reason, M1 method for handling BLQ-data is considered acceptable.

The base model was established by re-estimating the model parameters from a previous PK model using the pooled dataset including data from study CA2099DW. The effects of SCLC tumour type, nivolumab regimen, and line of therapy on CL from the previous model were removed, and subject type effects for CL was added in this analysis. The final model was selected by removing of PK records with |CWRES| > 6. No backward elimination was performed.

Immunogenicity

The immunogenicity was assessed in study CA2099DW. 100 out of 224 (44.6 %) patients tested for treatment-emergent nivolumab ADA positive and 11 out of 224 (4.9%) were persistent positive and 16 (7.1%) neutralizing positive. On the other hand, 13 out of 224 (5.3%) patients tested for treatment-emergent ipilimumab ADA positive and 1 out of 224 (0.4%) was persistent positive and none of them were neutralizing.

The impact on ADA status on nivolumab trough concentrations was evaluated. Observed Ctrough concentrations for ADA positive patients are slightly lower compared to negative ADA patients. Similar results were obtained based on simulation analysis. However, comparable results have been observed previously in other indications and were concluded to not be clinically relevant.

Hepatic impairment

Section 5.2 of the OPDIVO SmPC has been updated based on a previous population PK analysis of hepatic impairment.

Exposure-Response analysis

The Exposure –Response of efficacy (OS) and safety (Gr2+ IMAEs) is based on the graphical characterization of the relationship between the efficacy and safety endpoints and predicted exposures (Cavg1) for 1 L HCC subjects in study CA2099DW. No clear trend between OS and exposure quartiles was detected. On the other hand, the relationship between Gr2+ IMAEs and nivolumab/ipilimumab exposure (Cavg1) quartiles suggested a higher probability of Gr2+ IMAEs with higher exposures. This is consistent with previous studies in other tumour types using the combination treatment. Overall, a 40% probability of GR2+ IMAEs was observed in patients before 5 months of treatment. The dose selection for the pivotal study was based on the results from the supportive study CA209040 that demonstrated longer OS and higher rate of CR in 2L advance HCC for the dosing regimen of nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W for 4 doses followed by 240 mg Q2W compared to the standard dosing regimen of nivolumab 3 mg/kg +ipilimumab 1 mg/kg Q3W. An additional exposure-safety analysis has been performed with retrospective data from study CA209040 in subjects with 2L+HCC treated with high (3m/kg) and low (1mg/kg) doses of ipilimumab in combination with nivolumab (1mg/kg and 3mg/kg respectively) and from study CA209214 in subjects with RCC treated with low dose (1mg/kg) of ipilimumab in combination with nivolumab (3mg/kg).

In order to compare the exposure-safety profile between the high and low doses of ipilimumab, data from study CA209040 (2L+HCC) were pooled with data from study CA2099DW. The high dose of ipilimumab was associated with a higher risk of Gr2+ IMAEs. Study CA2099DW had lower risk of Gr2+IMAEs compared to study CA209040 possibly due to differences in study population and sample size.

The Exposure-Response for Gr2+ IMAE was stratified by ipilimumab exposure (Cavg1) quartiles and study and treatment arm. In the KM analysis of study CA2099DW, a trend was observed with higher probability of Gr2+IMAEs with higher ipilimumab exposure. In study CA209040 no trend was observed probably because of the small sample size per quantile.

The KM analysis from study CA209214 in RCC subjects showed that the low ipilimumab dose (1mg/kg) was similar to that observed with the high ipilimumab dose (3mg/kg) in study CA2099DW.

Therefore, the results suggest that the risk of Gr2+ IMAE following the high dose of ipilimumab (3mg/kg) in HCC patients is similar to other indications and doses.

2.3.2.2. Conclusions on clinical pharmacology

The clinical pharmacology properties of the combination of nivolumab + ipilimumab in adult patients with unresectable or advance hepatocellular carcinoma have been defined based on the data from the pivotal phase 3 study CA2099DW. PK data from the pivotal study have been pooled with data from previous studies to conduct population PK and exposure-response analysis.

2.4. Clinical efficacy

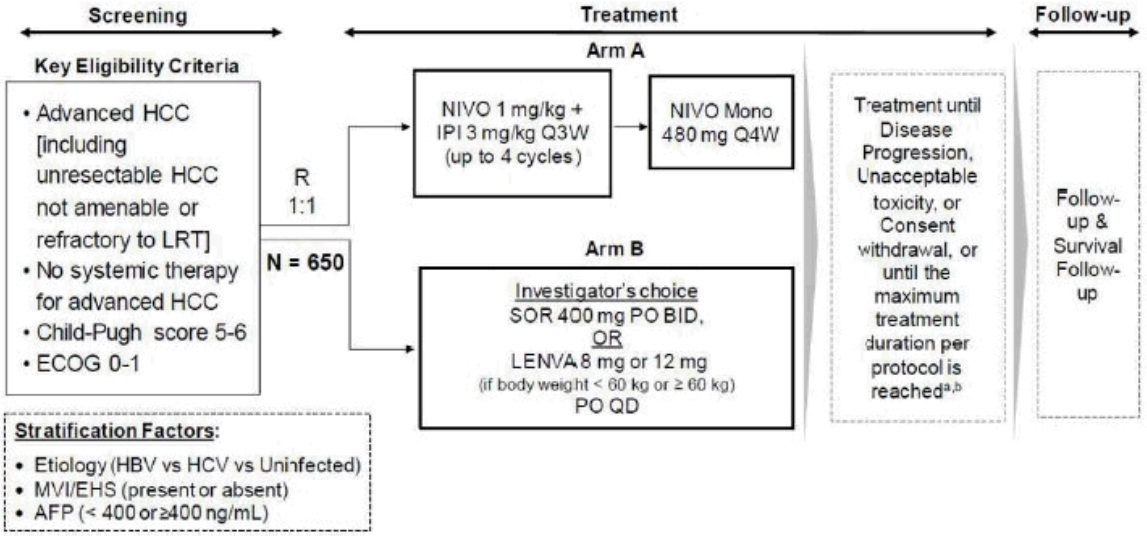
2.4.1. Dose response study

No dose response study has been presented within this submission.

2.4.2. Main study

Study CA2099DW: a Phase 3 study of nivolumab+ipilimumab vs. Investigator's choice (sorafenib/lenvatinib) in unresectable/advanced hepatocellular carcinoma (uHCC)

Figure 12 CA2099DW study design schematic



[a]→On nivo+ipi arm (Arm A), treatment continued until disease progression (unless treatment beyond PD is permitted), unacceptable toxicity, or consent withdrawal for a maximum duration of treatment of 2 years. A minimum of 1 dose of nivo+ipi was required before proceeding to nivo monotherapy dosing.

[b]→On both arms, subjects may have been treated beyond disease progression under protocol-defined conditions.

Methods

Study participants

Inclusion criteria

1) Signed Written Informed Consent (details in the protocol)

2) Type of Participant and Target Disease Characteristics

a) Participants must have a diagnosis of HCC based on histological confirmation

b) Participants must have an advanced HCC, defined as:

   i. Disease not eligible for curative surgical and/or locoregional therapies, OR

   ii. Progressive disease after surgical and/or locoregional therapies

c) Participants must have at least one RECIST 1.1 measurable previously untreated lesion

d) Participants must not have received any systemic therapy for unresectable/advanced HCC. Note: Prior neo-adjuvant or adjuvant systemic therapy is permitted if recurrence occurs ≥12 months after treatment completion.

e) Participants are eligible to enrol if they have non-viral related-HCC, or if they have HBV-HCC, or HCV-HCC defined as follows:

   i. HBV-HCC: resolved HBV infection, or chronic HBV infection

ii. HCV-HCC: resolved HCV infection, or chronic HCV infection.

f) Child-Pugh score 5 or 6.

g) ECOG PS 0 or 1.

3) Age and Reproductive Status

a) Males and Females, ages ≥18 years

Exclusion criteria

1) Target Disease Exceptions

a) Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC.

b) Prior liver transplant.

c) Participants with any of the following findings in imaging tests:

i. HCC with ≥50% liver occupation

ii. Clear invasion into the bile duct

iii. Portal vein invasion at the main portal branch (Vp4)

d) Episodes of hepatic encephalopathy (≥Grade 2) within 12 months prior to randomization.

e) Clinically significant ascites

f) Presence of portal hypertension with history of bleeding due to oesophageal or gastric varices within 6 months prior to randomization.

g) Active brain metastases or leptomeningeal metastases

2) Medical Conditions

a) Infections

i. Active co-infection with:

1) Both hepatitis B and C as evidenced by detectable HBV surface antigen or HBV DNA and HCV RNA, OR

2) Hepatitis D infection in participants with hepatitis B

ii. Known history of positive test for HIV or known AIDS.

iii. Active bacterial or fungal infections requiring systemic treatment within 1 week prior to randomization.

b) Significant cardiovascular impairment.

c) History of thrombotic or embolic events (except HCC tumour thrombus) within 6 months prior to randomization.

d) History of any haemorrhage/bleeding event ≥CTCAE Grade 3 within 8 weeks prior to randomization.

e) History of non-healing wounds or skin ulcers, within 3 months prior randomization.

f) History of bone fractures at risk of bleeding, within 3 months prior randomization.

g) History of major surgical procedure, open biopsy, or significant traumatic injury within 4 weeks prior to randomization, or history of minor surgical procedures (e.g. core biopsy) within 1 week prior to randomization.

h) History of gastrointestinal or non-gastrointestinal fistula or gastrointestinal perforation

i) Prior organ allograft or allogeneic bone marrow transplantation.

j) Interstitial lung disease that is symptomatic or may interfere with the detection and management of suspected drug-related pulmonary toxicity.

k) Pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range with medication.

l) Participants with an active, known or suspected autoimmune disease. Participants with type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement, and skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enrol.

m) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg/day prednisone equivalent) or other immunosuppressive medications within 14 days of study administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg/day prednisone equivalents are permitted in the absence of active autoimmune disease, with the exception of those allowed as per exclusion criteria 2.m.

n) Concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within the previous 2 years prior to randomization.

3) Prior/Concomitant Therapy

a) Participants with history of life-threatening toxicity related to prior systemic anticancer therapy except those that are unlikely to re-occur with standard countermeasures.

b) Treatment with strong CYP3A4 inducers within 1 week prior to randomization, including rifampin (and its analogues) or St. John's wort.

c) Use of anticoagulants such as, warfarin or similar agents requiring therapeutic INR monitoring. Note: Treatment with low molecular weight heparin is allowed.

d) Treatment with anti-platelet therapy (aspirin at dose ≥ 300 mg/day, clopidogrel at dose ≥75 mg/day)

e) Radiotherapy within 4 weeks prior to randomization. Note: Palliative radiotherapy for symptomatic control is acceptable if completed at least 2 weeks prior to randomization and no additional radiotherapy for the same lesion is planned.

f) Participants who have received a live/attenuated vaccine within 30 days of randomization (e.g., varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]).

g) Treatment with complementary medications (e.g. herbal supplements or traditional Chinese medicines) intended to treat the disease under study within 2 weeks prior to randomization. Such medications are permitted if they are used as supportive care.

4) Physical and Laboratory Test Findings

a) Baseline serum sodium < 130 mmol/L.

b) Baseline serum potassium < 3.5 mmol/L (potassium supplementation may be given to restore the serum potassium above this level prior to study entry).

c) Urine protein ≥1g/24h. Note: Participants having > 1+ proteinuria on urine dipstick testing require quantitative assessment of proteinuria (24-hours urine collection) at screening.

5) Sex and Reproductive Status

a) WOCBP who are pregnant or breastfeeding

Treatments

Subjects were randomized to receive open-label treatment with one of the following:

- Arm A: **nivo 1 mg/kg + ipi 3 mg/kg** Q3W for up to 4 cycles **followed by nivo 480 mg (flat dose)** Q4W until disease progression (unless treatment beyond PD is permitted), unacceptable toxicity, or consent withdrawal, or for a maximum duration of treatment of 2 years.
- Arm B: **sorafenib** 400 mg PO BID **or lenvatinib** 8 mg PO QD (if body weight <60 kg) or 12 mg PO QD (if body weight ≥60 kg) until disease progression (unless treatment beyond PD is permitted), unacceptable toxicity, or consent withdrawal.

Dose escalation or reductions for nivo and/or ipi were not permitted. Doses of nivo and/or ipi were allowed to be delayed or discontinued. Separate assessments for discontinuation of nivo and ipi were made. During the combination phase, if discontinuation criteria were met for ipi but not for nivo, subjects were allowed to continue treatment with nivo (480 mg flat dose) while ipi was discontinued.

Doses of sorafenib or lenvatinib were allowed to be reduced, interrupted or discontinued. First dose reductions of sorafenib were allowed to 400 mg once daily and dose reductions of lenvatinib were allowed to 8 mg (if body weight ≥ 60 kg) or 4 mg (if body weight < 60 kg). Additional reductions in sorafenib or lenvatinib dose were allowed per respective local SmPCs or locally approved product labels.

Subjects in Arm A were permitted to continue nivo+ipi or nivo monotherapy beyond initial RECIST 1.1-defined PD, as assessed by the investigator up to a maximum of 2 years from date of first dose. Subjects in Arm B were permitted to continue sorafenib or lenvatinib beyond initial RECIST 1.1-defined PD, as assessed by the investigator.

Objectives and endpoints

Table 15 Study CA2099DW Objectives and endpoints

Objective	Endpoints
Primary:	
To compare the OS of nivo+ipi versus SOC (sorafenib or lenvatinib) in all randomized participants with advanced HCC who have not received prior systemic therapy.	OS, defined as the time between the date of randomization and the date of death (by any cause).
Secondary:	
To compare the ORR [as assessed by BICR based on RECIST 1.1] of nivo+ipi to SOC (sorafenib or lenvatinib) in all randomized participants with advanced HCC who have not received prior systemic therapy.	ORR, defined as the percentage of participants whose BOR is either a confirmed CR or PR.
To evaluate DOR [as assessed by BICR based on RECIST 1.1] of nivo+ipi and SOC (sorafenib or lenvatinib) in all randomized participants with advanced HCC who have not received prior systemic therapy.	DOR, defined as the time from the first documented evidence of a response of CR or PR until the first documented disease progression or death due to any cause, whichever occurs first
To compare the cancer-related symptom burden for participants randomized to nivo+ipi or SOC (sorafenib or lenvatinib).	TTSD, defined as the time from randomization until a clinically meaningful decline in the HCS subscale score of the FACT-Hep.
Exploratory	
To evaluate PFS (per BICR-RECIST 1.1) of nivo+ipi and SOC in all randomized subjects	PFS, defined as the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.
To evaluate TTP (per BICR-RECIST 1.1) of nivo+ipi and SOC in all randomized subjects	TTP, defined as the time from randomization to the first documented disease progression
To evaluate DCR, DDC, and TTR (per BICR-RECIST 1.1) of nivo+ipi and SOC in all randomized subjects	DCR, defined as the percentage of subjects who have a BOR of CR, PR, SD, or NON-CR/NON-PD DDC, defined as the time from the date of randomization to the date of the first documented tumor progression or death due to any cause in participants whose BOR is CR or PR or SD or NON-CR/NON-PD TTR, defined as the time from randomization to the date of the first confirmed CR or PR
To assess antitumor activity of nivo+ipi vs SOC based on results of BICR using mRECIST in all randomized subjects	ORR, DCR, DOR, PFS, TTP, TTR, and DDC as defined above
To assess antitumor activity of nivo+ipi vs SOC based on investigator assessment using RECIST 1.1 in all randomized subjects	ORR, DCR, DOR, PFS, TTP, TTR, and DDC as defined above
To evaluate OS in subjects treated with nivo+ipi and SOC with baseline AFP < 400 ng/ml vs ≥ 400 ng/ml	OS as defined above
To analyze biomarkers in tumor (ie, PD-L1) and peripheral blood to evaluate association with clinical efficacy and/or incidence of AEs	PD-L1 CPS: The number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by100 by validated Dako PD-L1 IHC 28-8 pharmDx assay (Agilent)
To assess subjects' cancer-related QoL (using the FACT-Hep) of nivo+ipi and SOC	FACT-Hep scores: Change from baseline and the proportion of patients without meaningful symptomatic deterioration based on the FACT-Hep total and subscale scores
To assess subjects' health utilities and overall health status using the EQ-5D-3L index and VAS	EQ-5D-3L scores: Change from baseline and time to deterioration as measured by the EQ-5D-3L VAS and utility index

Sample size

The sample size determination of this study is based on OS comparison between participants randomized to Arm A (nivolumab plus ipilimumab followed by nivolumab monotherapy) or Arm B (Investigator's choice SOC). With a total of 650 participants randomized in a 1:1 ratio to each treatment arm, approximately 87% power will be achieved for an average HR of 0.74 (Arm A over Arm B) with an overall two-sided type I error 0.05. The sample size determination is based on simulation using EAST v6.4.1:

General assumptions:

- Piecewise-exponential distribution is assumed for OS in each treatment arm.
- The OS data of lenvatinib from the LEAP-002 study were considered the most relevant to the SOC arm (following the original protocol assumption that all participants receive lenvatinib). A piecewise-exponential model is assumed based on observation of LEAP-002 data. The median OS of the SOC arm is approximately 19 months.
- The target average hazard ratio (HR) of 0.74 for nivolumab plus ipilimumab over SOC is modelled as a 2-piece hazard ratio with a delayed effect of a HR of 1 in the first 15 months followed by a constant HR of 0.6 afterwards. The median OS of the nivolumab plus ipilimumab arm is approximately 23 months.
- The following assumptions are made for anticipated drop-out rate using internal data on file.

The hazard rate of participant drop-out per month is assumed to be 0.006 in each arm during the first 6 months, 0.002 during the second 6 months, and 0.0001 afterwards.

Table 16 OS Hazard Rates and Hazard Ratios (Nivolumab plus Ipilimumab vs SOC)

Starting at Time (month)	Hazard Rates for SOC	Hazard Rates for Nivolumab plus Ipilimumab	Hazard Ratio
0	0.013	0.013	1.0
4	0.032	0.032	1.0
8	0.041	0.041	1.0
12	0.041	0.041	1.0
15	0.057	0.034	0.6
19	0.045	0.027	0.6

Sample size determination for OS

Based on simulations under the assumptions stated above, approximately 650 participants will be randomized and followed until at least 520 OS events are observed in order to provide 87% power for an average HR of 0.74 with a two-sided type I error of 0.05. This accounts for a group sequential testing procedure with one interim analysis and one final analysis.

The interim analysis (IA) will be conducted when 80% OS events are observed. The alpha allocation for the interim and final analyses is based on the Lan-DeMets alpha spending function approach using an O'Brien-Fleming stopping boundary controlling for a two-sided overall type I error of 5%. The stopping boundary will depend on the actual number of deaths at the time of the IA and the final analysis (FA).

Randomisation

The specific treatment arm was assigned using an IRT. Once enrolled using the IRT system, subjects who had met all eligibility criteria were randomized through IRT in a 1:1 ratio to receive either nivo+ipi or SOC, with stratification by ethology (per central lab) (HBV vs HCV vs Uninfected), vascular invasion and/or extrahepatic spread (present or absent), and baseline AFP level (<400 ng/mL or ≥400 ng/mL).

Blinding (masking)

The treatments in this study were open label. The study centre staff members and the enrolled subjects were not blinded to treatment assignment.

A BICR was utilized for determination of BICR assessed endpoints including the secondary and exploratory endpoints (i.e. ORR per BICR, PFS per BICR); the BICR remained blinded to subject treatment assignment. To prevent bias and objectively assess efficacy and safety, an external independent statistician prepared summaries of the unblinded aggregate efficacy and safety data for the DMC review. The MAH remained blinded to any aggregate analyses by treatment arm (until this IA was performed) and comparisons between treatment arms performed for the DMC.

Statistical methods

All analyses will be tabulated by treatment group as randomized for all randomized subjects, unless otherwise specified.

The stratification factors for stratified analysis will be the following ones as entered into the IRT, unless otherwise specified:

- Aetiology (HBV vs HCV vs Uninfected)
- Vascular invasion and/or extrahepatic spread (present or absent)
- Alpha-fetoprotein (AFP) (< 400 ng/mL or ≥400 ng/mL).

Analysis of Overall Survival

The primary objective of the study was to compare the overall survival (OS) between treatment groups in all randomized subjects. The distribution of OS will be compared in the two randomized arms at the interim and final analyses via a two-sided α, log-rank test stratified by the stratification factors. The stratification factors are those recorded at randomization per IRT.

Supportive analyses of overall survival

The following OS sensitivity analyses were planned to be conducted:

- OS using stratification factors as obtained from the baseline CRF pages for MVI/EHS or from central lab for aetiology and AFP (instead of IRT). The HR associated with treatment was to be presented along with the associated two-sided 95% CIs. This analysis was to be performed only if at least one stratification factor at randomization as per IRT and baseline as per CRF or per central lab are not concordant for at least 10% of the randomized participants.
- OS using an unstratified log rank test.
- OS using an unstratified Cox proportional hazard model. The hazard ratio associated with treatment was to be presented along with the associated two-sided 95% CIs.
- To examine the assumption of proportional hazards in the Cox regression model, in addition to treatment, a time-dependent variable defined by treatment by time interaction was added into the

model. This treatment by time interaction was defined as the product of the treatment allocation and the non-missing binary time-dependent variable indicating if OS time is greater than or equal to X months. A two-sided Wald Chi-square p-value of less than 0.1 may indicate a potential non constant treatment effect. If the p-value of the treatment by time interaction was less than 0.1 or a visual examination of the KM curves indicates a delayed separation of the curves, the following analyses were to be performed to show the treatment effect when taking delayed effect into consideration:

- The estimate of the OS HR were to be estimated in two periods using a stratified Cox with a time-dependent covariate approach. A two-sided 95% CI for HRs were also be presented. The two periods were defined by a cut-off point. The optimal cut-off point were determined using a stratified time-dependent Cox model with effects for treatment and period-by-treatment interaction. The optimal cut-off point were estimated using a grid of possible cut-off point and obtained by maximizing the partial log likelihood. Ties were handled using the exact method.
- The unstratified Max-Combo test were to be applied to estimate the OS between treatment groups. The following parameter settings (rho, gamma) of Fleming-Harrington class of weight were used: (rho = 0, gamma = 0) attributes equal weights to all; (rho = 1, gamma = 0) emphasizes early difference in survival curves; (rho = 0, gamma = 1) weight more for late difference; (rho = 1, gamma = 1) emphasizes middle difference. The estimated HR along with the two-sided 95% CI and the p-value were reported. Since the stratification is not involved, the results of this sensitivity analysis should only be compared with the unstratified analysis of OS.
- Delayed effect of immunotherapy interventions may cause a late separation in the OS KM curves and/or non-proportional hazards. OS were compared between treatment groups using the difference in Restricted Mean Survival Time (RMST). A two-sided 95% confidence interval of the difference in RMST were performed. The RMST represents the area under the survival curve up to a time point (i.e., restricted period). The pre-specified time point for this analysis were the clinical cutoff date.

- OS in all randomized subjects excluding subjects from Russian sites.

Analysis Timing Projections

One IA for OS was planned.

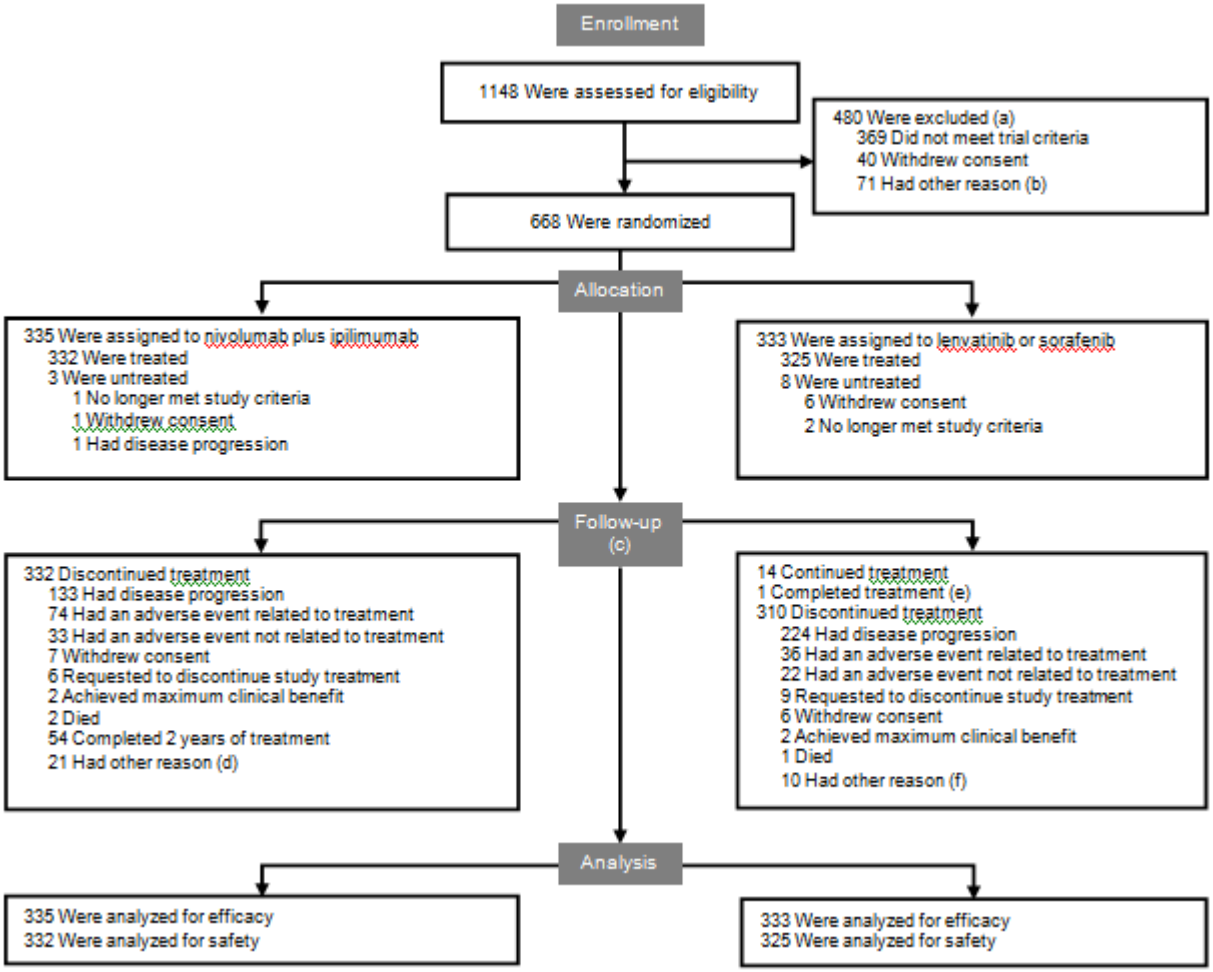
- It will take approximately 24 months to complete the enrolment.
- IA for OS was projected to occur when there are at least 416 deaths (80% of target events) among approximately 650 randomized participants, approximately 47 months after the first participant's randomization date (24 months for enrolment and 23 months for survival follow-up).

FA for OS was projected to occur when there are at least 520 deaths among approximately 650 randomized participants, approximately 68 months after the first participant's randomization date (24 months for enrolment and 44 months for survival follow-up). If the planned number of 520 OS events is unlikely to be reached for any unforeseen reasons, the OS FA may occur when at least 44 months minimum follow-up (defined as the time from the last participant's randomization date to the clinical cut-off date) is reached.

Results

Participant flow

Figure 13 Participant flowchart – all randomized subjects – CA2099DW



Subject disposition

Table 17 Subject disposition – All enrolled, Randomized and Treated subjects

	No. of Subjects (%)		
	Nivo+Ipi	SOC	Total
Enrolled	N.A.	N.A.	1148 (100)
Randomized	335	333	668 (58.2)
Treated	332 (99.1)	325 (97.6)	657 (98.4)
Not Treated	3 (0.9)	8 (2.4)	11 (1.6)
Reason for Not Treated			
Disease Progression	1 (0.3)	0	1 (0.1)
Subject Withdrew Consent	1 (0.3)	6 (1.8)	7 (1.0)
Subject no Longer Meets Study Criteria	1 (0.3)	2 (0.6)	3 (0.4)
Continuing in the Treatment Period	0	15 (4.6)[a]	15 (2.3)[a]
Not Continuing in the Treatment Period	332 (100)	310 (95.4)	642 (97.7)
Reason for Not Continuing in the Treatment Period			
Disease Progression	133 (40.1)	224 (68.9)	357 (54.3)
Study Drug Toxicity	74 (22.3)	36 (11.1)	110 (16.7)
Subject Request to Discontinue Study Treatment	6 (1.8)	9 (2.8)	15 (2.3)
Death	2 (0.6)	1 (0.3)	3 (0.5)
Adverse Event Unrelated to Study Drug	33 (9.9)	22 (6.8)	55 (8.4)
Subject Withdrew Consent	7 (2.1)	6 (1.8)	13 (2.0)
Lost to Follow-Up	1 (0.3)	0	1 (0.2)
Maximum Clinical Benefit	2 (0.6)	2 (0.6)	4 (0.6)
Poor/Non-Compliance	0	1 (0.3)	1 (0.2)
Administrative Reasons by Sponsor[b]	9 (2.7)	2 (0.6)	11 (1.7)
Other	65 (19.6)[c]	7 (2.2)[d]	72 (11.0)
Continuing in the Study	261 (78.6)	273 (84.0)	534 (81.3)
Not Continuing in the Study[e]	71 (21.4)	52 (16.0)	123 (18.7)
Reason for Not Continuing in the Study			
Death	50 (15.1)	26 (8.0)	76 (11.6)
Lost to Follow-Up	1 (0.3)	0	1 (0.2)
Subject Withdrew Consent	12 (3.6)	20 (6.2)	32 (4.9)
Other	8 (2.4)[f]	6 (1.8)[g]	14 (2.1)

[a] Includes 2 subjects from Russia that are no longer on treatment but reported as "on treatment" and 1 subject reported as "treatment completed" due to Russian exit.

[b] Closure of Russian Sites due to increased logistical challenges due to the Russian /Ukrainian political crisis.

[c] Includes subjects who completed 2 years of treatment (n=54), PI's decision free text reasons (n=5), Dose delay lasting > 8 weeks (per protocol) (n=2), Subject's decision (n=2), and Russian subjects that discontinued treatment (n = 2).

[d] Includes PI's decision (n=5); Subject's decision (n=2).

[e] Status at the end of treatment period.

[f] Includes subjects involved in Russian exit=7; and General Condition deterioration n=1.

[g] Includes subjects involved in Russian exit=4, Subject's decision=2.

Percentages based on subjects entering period.

Recruitment

First Subject Randomized: 06 January 2020

Last Subject Randomized: 08 November 2021

Clinical Cut-off Date: 31 January 2024

Database Lock: 28 February 2024

Minimum Follow-up: 26.8 months

Median Follow-up (min, max): 35.20 (26.8, 48.9)

A total of 1148 subjects were enrolled at 163 sites in 25 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Czech Republic, France, Germany, Hong Kong, Italy, Japan, Korea, New Zealand, Poland, Romania, Russia, Singapore, Spain, Taiwan, United Kingdom of Great Britain and Northern Ireland, United States [including Puerto Rico]).

Due to the Russian/Ukrainian political crisis, the 8 sites in Russia (with 32 randomized subjects) were closed by 17 June 2022. At that time, all 17 Russian subjects, who were on treatment, in safety follow-up, or in survival follow-up, were discontinued from the study.

Conduct of the study

Protocol amendments

The original protocol for this study was dated 01 April 2019. As of the 31 January 2024 data cut-off, there were a total of 2 global amendments, 8 country-specific amendments, and 7 administrative letters.

Table 18 Summary of global changes to protocol CA2099DW

Document (Amendment)/ Date	Summary of Key Changes	Planned Sample Size	Total Subjects Randomizedat Time of Protocol Amendment
Original Protocol/ 01-Apr-2019	Not applicable.	650	NA

Protocol Amendment 01/ 02-Aug-2021	• The primary reasons for the changes were:
	  • Modify the statistical assumptions on power calculation and modify the number of expected events and follow-up time to trigger interim and final analyses based on survival results from study CA209459
	  • Align dose modification criteria and IO agent management algorithms with the current CTCAE version 5
	  • Add serologic testing for SARS-CoV-2 status
	  • Incorporate additional changes to or clarify eligibility, assessments, sample collections, treatment administration, and country-specific requirements
		650	543

Protocol Amendment 02/ 01-Feb-2023	The main purpose of this protocol amendment was to modify the statistical assumptions on power calculation, based on survival results from external data (LEAP-002 study). To maintain the study power, modification to the number of expected events and follow-up time to trigger interim and final analyses was required. Additionally, the study population in which the PRO data was analyzed was harmonized as PRO analyses occurred in all randomized participants.	650	668

Table 19 Summary of Changes in Statistical Assumptions versus Original Protocol, in Protocol Amendment 01 (PA 01) and Protocol Amendment 02 (PA 02)

Version	Original Design	PA 01	PA 02
Amendment Date	01-Apr-2019	02-Aug-2021	01-Feb-2023
Piecewise HR Assumption	HR=1 for 0-6 months HR=0.6 for 6-24 months HR=0.8 for the remaining period	HR=1 for 0-9 months HR=0.6 for the remaining period	HR=1 for 0-15 months HR=0.6 for the remaining period
Target Average HR	0.72	0.74	0.74
Median OS (months), SOC	14	14	19
Median OS (months), Nivo+Ipi	20	17	23
Alpha	0.05	0.05	0.05
Power	90%	87%	87%
Number of events to trigger IA (Information Fraction)	298 (75%)	392 (80%)	416 (80%)
Number of events to trigger FA	397	490	520
Sample size	650	650	650

Protocol deviations

Relevant protocol deviations (RPDs) are Important protocol deviations (IPDs) that could affect the interpretability of key study results, are programmable deviations from clinical database and are protocol specific.

Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

Table 20 Relevant Protocol Deviations - All Randomized Subjects

	Number of Subjects (%)		
	Nivo + Ipi N = 335	Sora / Lenva N = 333	Total N = 668
SUBJECTS WITH AT LEAST ONE DEVIATION	15 (4.5)	11 (3.3)	26 (3.9)
AT ENTRANCE			
SUBJECTS WITH ECOG PS > 1	0	0	0
SUBJECTS WITH CHILD-PUGH B OR HIGHER (SCORE ≥ 7) (a)	7 (2.1)	7 (2.1)	14 (2.1)
SUBJECTS WITHOUT EVALUABLE DISEASE AT BASELINE	0	1 (0.3)	1 (0.1) (b)
SUBJECTS WHO RECEIVED PRIOR SYSTEMIC THERAPY	0	0	0
SUBJECTS WITH SERUM ALBUMIN < 2.8 G/DL (c)	2 (0.6)	3 (0.9)	5 (0.7)
SUBJECTS WITH TOTAL BILIRUBIN > 3 MG/DL	1 (0.3)	0	1 (0.1)
SUBJECTS WITH AST > 5 TIMES THE INSTITUTIONAL UPPER LIMITS OF NORMAL	6 (1.8)	2 (0.6)	8 (1.2) (d)
SUBJECTS WITH ALT > 5 TIMES THE INSTITUTIONAL UPPER LIMITS OF NORMAL	0	0	0
SUBJECTS WITH ACTIVE CO-INFECTION OF HBV AND HCV	0	0	0
SUBJECTS WITH ACTIVE CO-INFECTION OF HBV AND HDV	0	0	0
ON-STUDY DEVIATIONS			
SUBJECT WHO RECEIVED ANTI-CANCER THERAPY	2 (0.6)	3 (0.9)	5 (0.7)
SUBJECT TREATED DIFFERENTLY AS RANDOMIZED	0	0	0

(a) Includes 1 subject with Child-Pugh score 7 at screening but Child-Pugh score 6 (per lab results) prior to first dose

(b) Subject randomized by mistake, never treated

(c) Includes 1 subject with serum albumin <2.8 g/dL at screening but albumin > 2.8 g/dL (meeting eligibility criteria) in a subsequent sample taken prior to randomization.

(d) Includes 1 subject never treated (death prior to first dose); 1 subject with AST=5xULN as permitted per protocol

Table 21 Important Protocol Deviations Summary - All Randomized Subjects

	Number of Subjects (%)		
Important Protocol Deviations Category	Nivo + Ipi N = 335	Sora / Lenva N = 333	Total N = 668
TOTAL NUMBER OF SUBJECTS WITH AT LEAST ONE DEVIATION	225 (67.2)	232 (69.7)	457 (68.4)
INCLUSION/EXCLUSION CRITERIA	42 (12.5)	35 (10.5)	77 (11.5)
INFORMED CONSENT/ETHICS (IEC/IRB)	50 (14.9)	61 (18.3)	111 (16.6)
PROHIBITED CONCOMITANT MEDICATIONS	6 (1.8)	5 (1.5)	11 (1.6)
SAFETY REPORTING	31 (9.3)	27 (8.1)	58 (8.7)
STUDY INTERVENTION (STUDY TREATMENT)	18 (5.4)	26 (7.8)	44 (6.6)
TRIAL PROCEDURES	175 (52.2)	182 (54.7)	357 (53.4)
DISCONTINUATION	8 (2.4)	1 (0.3)	9 (1.3)

The sum of all deviations is reported per category as a subject may have more than one deviation.

- Impact of COVID-19

This study was conducted during the COVID-19 pandemic. FPFV was 30 September 2019 and the clinical cut-off for this CSR occurred on 31 January 2024. Some measures were implemented to minimize the impact of COVID-19 on the conduct of the clinical study and analysis of data.

Prior to the database lock, a comprehensive situational analysis was performed by the BMS Data Review Committee to assess the potential impact on the database lock and data quality. It was determined that the database lock should proceed as planned given that no outstanding critical issues were identified that could have any impact on the integrity of the study or the interpretability of its results.

The study was successfully conducted despite disruptions due to the COVID-19 pandemic. The COVID-19 pandemic did not compromise the ability to collect both safety and efficacy data and did not significantly impact the results of the study.

- Impact of Russian site closures

Of the 668 subjects who were randomized as of the clinical cut-off, 32 subjects were randomized at 8 sites in Russia. By the end of May 2022, the dispensing of drug was stopped at all 8 sites in Russia and all Russian subjects (N= 17: 11 on treatment, 2 in safety follow up, 4 in survival follow up) were discontinued from the study by 17 June 2022. It was recommended that all active subjects at these sites complete the end of study activities and transition to local SOC treatment.

Due to the closure of Russian sites, not all queries for Russian subjects were resolved and SDV was not completed for all subjects. Of the 6494 total queries sent to the 8 Russian sites with randomized subjects, a total of 195 queries were not addressed (3%): 44 were cancelled (not answered by the sites), and 151 were closed with insufficient responses. A total of 245 (9.8%) pages requiring SDV could not be verified before site closure.

All SAEs for subjects at sites in Russia were reconciled prior to DBL.

There were no IPDs related to the Russian site closures.

A sensitivity analysis evaluating the effect of closing sites in Russia on OS, by removing all 32 randomized Russian subjects, was performed. The OS analysis results are consistent in all randomized subjects including and excluding Russian subjects.

Baseline data

Table 22. Baseline Demographic and Disease Characteristics Summary - All Randomized Subjects

	Nivo + Ipi N = 335	Sora / Lenva N = 333	Total N = 668
AGE (YEARS)			
N	335	333	668
MEAN	64.5	65.3	64.9
MEDIAN	65.0	66.0	66.0
MIN , MAX	20 , 86	20 , 89	20 , 89
Q1 , Q3	59.0 , 71.0	59.0 , 73.0	59.0 , 72.0
SD	9.95	10.51	10.24
AGE CATEGORIZATION (%)			
< 65	162 (48.4)	149 (44.7)	311 (46.6)
≥ 65 AND < 75	126 (37.6)	123 (36.9)	249 (37.3)
≥ 75	47 (14.0)	61 (18.3)	108 (16.2)
SEX (%)			
MALE	271 (80.9)	277 (83.2)	548 (82.0)
FEMALE	64 (19.1)	56 (16.8)	120 (18.0)
RACE (%)			
WHITE	179 (53.4)	174 (52.3)	353 (52.8)
BLACK OR AFRICAN AMERICAN	11 (3.3)	4 (1.2)	15 (2.2)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (0.3)	0	1 (0.1)
ASIAN	140 (41.8)	152 (45.6)	292 (43.7)
ASIAN INDIAN	3 (0.9)	0	3 (0.4)
CHINESE	76 (22.7)	88 (26.4)	164 (24.6)
JAPANESE	25 (7.5)	31 (9.3)	56 (8.4)
ASIAN OTHER	36 (10.7)	33 (9.9)	69 (10.3)
OTHER	4 (1.2)	3 (0.9)	7 (1.0)
ETHNICITY (%)			
HISPANIC OR LATINO	47 (14.0)	30 (9.0)	77 (11.5)
NOT HISPANIC OR LATINO	166 (49.6)	157 (47.1)	323 (48.4)
NOT REPORTED	122 (36.4)	146 (43.8)	268 (40.1)
REGION (%)			
NORTH AMERICA	15 (4.5)	5 (1.5)	20 (3.0)
EUROPE	129 (38.5)	140 (42.0)	269 (40.3)
ASIA	133 (39.7)	147 (44.1)	280 (41.9)
REST OF THE WORLD [ROW]	58 (17.3)	41 (12.3)	99 (14.8)
BASELINE ECOG PERFORMANCE STATUS (%)			
0	233 (69.6)	243 (73.0)	476 (71.3)
1	102 (30.4)	89 (26.7)	191 (28.6)
NOT REPORTED	0	1 (0.3)	1 (0.1)

	Nivo + Ipi N = 335	Sora / Lenva N = 333	Total N = 668
WEIGHT (KG)			
N	335	332	667
MEAN	73.42	72.45	72.93
MEDIAN	71.20	70.00	70.70
MIN - MAX	39.0 - 134.9	36.5 - 160.0	36.5 - 160.0
Q1 - Q3	62.50 - 84.00	62.00 - 82.00	62.30 - 82.70
SD	15.565	16.251	15.906
TIME FROM INITIAL DIAGNOSIS OF HCC TO RANDOMIZATION (%)			
< 1 YEAR	195 (58.2)	174 (52.3)	369 (55.2)
1 - <2 YEARS	48 (14.3)	51 (15.3)	99 (14.8)
2 - <3 YEARS	26 (7.8)	30 (9.0)	56 (8.4)
3 - <4 YEARS	13 (3.9)	14 (4.2)	27 (4.0)
4 - <5 YEARS	16 (4.8)	17 (5.1)	33 (4.9)
≥5 YEARS	37 (11.0)	47 (14.1)	84 (12.6)
ETIOLOGY PER CRF (%) (1)			
HBV	114 (34.0)	115 (34.5)	229 (34.3)
HCV	90 (26.9)	96 (28.8)	186 (27.8)
UNINFECTED	124 (37.0)	119 (35.7)	243 (36.4)
HBV/HCV (2)	7 (2.1)	3 (0.9)	10 (1.5)
ETIOLOGY PER CENTRAL LAB (%) (3)			
HBV	99 (29.6)	98 (29.4)	197 (29.5)
HCV	27 (8.1)	27 (8.1)	54 (8.1)
UNINFECTED	209 (62.4)	208 (62.5)	417 (62.4)
VASCULAR INVASION (MVI) (CRF) (%)			
YES	77 (23.0)	92 (27.6)	169 (25.3)
NO	258 (77.0)	241 (72.4)	499 (74.7)
EXTRAHEPATIC SPREAD (EHS) (CRF) (%)			
YES	188 (56.1)	172 (51.7)	360 (53.9)
NO	147 (43.9)	161 (48.3)	308 (46.1)
MVI/EHS (CRF) (%)			
YES	221 (66.0)	217 (65.2)	438 (65.6)
NO	114 (34.0)	116 (34.8)	230 (34.4)

AFP (NG/ML)			
N	335	333	668
MEAN	12107.73	5876.71	9001.55
MEDIAN	52.20	47.70	49.90
MIN - MAX	0.9 - 529738.0	0.6 - 152378.0	0.6 - 529738.0
Q1 - Q3	7.00 - 858.00	5.20 - 1069.00	5.93 - 953.45
SD	55633.850	17935.461	41469.515
AFP CATEGORY I (%)			
< 200 NG/ML	209 (62.4)	201 (60.4)	410 (61.4)
≥ 200 NG/ML	126 (37.6)	132 (39.6)	258 (38.6)
AFP CATEGORY II (%)			
< 400 NG/ML	227 (67.8)	220 (66.1)	447 (66.9)
≥ 400 NG/ML	108 (32.2)	113 (33.9)	221 (33.1)
CHILD-PUGH SCORE (%)			
5	254 (75.8)	263 (79.0)	517 (77.4)
6	72 (21.5)	58 (17.4)	130 (19.5)
7	8 (2.4)	11 (3.3)	19 (2.8)
8	1 (0.3)	0	1 (0.1)
NOT REPORTED	0	1 (0.3)	1 (0.1)
BCLC STAGING (%)			
0	3 (0.9)	3 (0.9)	6 (0.9)
A	25 (7.5)	18 (5.4)	43 (6.4)
B	61 (18.2)	67 (20.1)	128 (19.2)
C	246 (73.4)	242 (72.7)	488 (73.1)
D	0	0	0
UNKNOWN	0	3 (0.9)	3 (0.4)

(1) HBV and HCV categories included subjects with past/resolved infection.
(2) No subjects had active HBV and HCV co-infection
(3) HBV includes subjects with HBsAg positive and/or detectable HBV-DNA at randomization; HCV includes subjects with detectable HCV RNA at randomization; Subjects with past/resolved HBV or HCV infection categorized as "Uninfected" for stratification purpose.

Previous treatments

In all randomized subjects, no subjects received prior systemic anticancer therapy for advanced HCC, in accordance with the inclusion criteria. Note: two subjects received adjuvant systemic therapy as permitted by protocol (if recurrence occurred ≥12 months after treatment completion).

Table 23 Prior Systemic Cancer Therapy Summary - All Randomized Subjects

	Number of Subjects (%)		
	Nivo + Ipi N = 335	Sora / Lenva N = 333	Total N = 668
VEGFR TARGETED THERAPY	0	1 (0.3)	1 (0.1)
SORAFENIB	0	1 (0.3)	1 (0.1)
OTHER SYSTEMIC ANTICANCER THERAPY	1 (0.3)	0	1 (0.1)
LENTINAN	1 (0.3)	0	1 (0.1)
TRAMETES ROBINIOPHILA	1 (0.3)	0	1 (0.1)

Table 24 Prior Cancer Therapy Summary: All Randomized Subjects

	Number of Subjects (%)		
	Nivo + Ipi N = 335	Sora / Lenva N = 333	Total N = 668
SUBJECTS WITH PRIOR SYSTEMIC THERAPY			
YES	1 (0.3)	1 (0.3)	2 (0.3)
NO	334 (99.7)	332 (99.7)	666 (99.7)
PRIOR SYSTEMIC THERAPY REGIMEN SETTING (A)			
ADJUVANT	1 (0.3)	1 (0.3)	2 (0.3)
NEO-ADJUVANT	0	0	0
METASTATIC	0	0	0
PRIOR SURGERY RELATED TO CANCER			
YES	133 (39.7)	133 (39.9)	266 (39.8)
NO	202 (60.3)	200 (60.1)	402 (60.2)
PRIOR RADIOTHERAPY			
YES	32 (9.6)	24 (7.2)	56 (8.4)
NO	303 (90.4)	309 (92.8)	612 (91.6)
PRIOR NON-SYSTEMIC CANCER THERAPY RELATED TO HCC LOCAL ONLY			
YES	142 (42.4)	158 (47.4)	300 (44.9)
NO	193 (57.6)	175 (52.6)	368 (55.1)
PRIOR NON-SYSTEMIC TREATMENT FOR HCC CATEGORY			
TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION (TACE)	118 (35.2)	129 (38.7)	247 (37.0)
RADIO-FREQUENCY ABLATION (RFA)	51 (15.2)	60 (18.0)	111 (16.6)
TRANSCATHETER ARTERIAL EMBOLIZATION(TAE)	12 (3.6)	14 (4.2)	26 (3.9)
MICROWAVE ABLATION (MWA)	9 (2.7)	16 (4.8)	25 (3.7)
YTTRIUM-90 MICROSPHERES	8 (2.4)	8 (2.4)	16 (2.4)
OTHER	5 (1.5)	6 (1.8)	11 (1.6)
HEPATIC ARTERIAL INFUSION CHEMOTHERAPY	5 (1.5)	2 (0.6)	7 (1.0)
PERCUTANEOUS ETHANOL INJECTION (PEI)	4 (1.2)	2 (0.6)	6 (0.9)

(A) Some subjects may have been treated with more than 1 type of therapy.

Subsequent cancer therapies

Table 25 Subsequent Cancer Therapy Summary - All Randomized Subjects

	Number of Subjects (%)	
	Nivo + Ipi N = 335	Sora / Lenva N = 333
SUBJECTS WITH ANY SUBSEQUENT THERAPY (%) (1)	151 (45.1)	185 (55.6)
SUBJECTS WHO RECEIVED SUBSEQUENT RADIOTHERAPY (%)	21 (6.3)	25 (7.5)
SUBJECTS WHO RECEIVED SUBSEQUENT SURGERY (%)	12 (3.6)	6 (1.8)
SUBJECTS WHO RECEIVED SUBSEQUENT NON-SYSTEMIC FOR HCC (LOCAL ONLY) (%)	29 (8.7)	27 (8.1)
SUBJECTS WHO RECEIVED SUBSEQUENT SYSTEMIC THERAPY (%)	128 (38.2)	172 (51.7)
ANY IO-CONTAINING REGIMEN	44 (13.1)	115 (34.5)
IO MONO REGIMEN	10 (3.0)	47 (14.1)
IO-CONTAINING COMBO REGIMEN	36 (10.7)	78 (23.4)
IO MONO REGIMEN	10 (3.0)	47 (14.1)
ANTI-PD1 OR ANTI-PDL1	10 (3.0)	47 (14.1)
ATEZOLIZUMAB	1 (0.3)	1 (0.3)
DURVALUMAB	0	3 (0.9)
INCB 086550	0	1 (0.3)
NIVOLUMAB	9 (2.7)	35 (10.5)
PEMBROLIZUMAB	0	5 (1.5)
SINTILIMAB	0	1 (0.3)
TISLELIZUMAB	0	1 (0.3)
IO-CONTAINING COMBO REGIMEN	36 (10.7)	78 (23.4)
COMBO ANTI-CTLA4 + ANTI-PD1 + VEGF OR COMBO ANTI-CTLA4 + ANTI-PDL1 + VEGF	2 (0.6)	3 (0.9)
BEVACIZUMAB;IPILIMUMAB;NIVOLUMAB	0	1 (0.3)
CABOZANTINIB;IPILIMUMAB;PEMBROLIZUMAB	0	1 (0.3)
IPILIMUMAB;LENVATINIB;NIVOLUMAB	0	1 (0.3)
IPILIMUMAB;NIVOLUMAB;SORAFENIB TOSILATE	1 (0.3)	0
IPILIMUMAB;PEMBROLIZUMAB;RAMUCIRUMAB	1 (0.3)	0
COMBO ANTI-CTLA4 + ANTI-PD1 OR COMBO ANTI-CTLA4 + ANTI-PDL1	2 (0.6)	10 (3.0)
DURVALUMAB;TREMELIMUMAB	2 (0.6)	4 (1.2)
IPILIMUMAB;NIVOLUMAB	0	6 (1.8)

IO-CONTAINING COMBO REGIMEN (CONTINUED)		
COMBO ANTI-PD1 + OTHER SYSTEMIC ANTICANCER THERAPY OR COMBO ANTI-PDL1 + OTHER SYSTEMIC ANTICANCER THERAPY	3 (0.9)	0
ANTINEOPLASTIC MONOCLONAL ANTIBODIES;TISLELIZUMAB	1 (0.3)	0
CEMIPLIMAB;SAR 439459	1 (0.3)	0
DOCETAXEL;FLUOROURACIL;NIVOLUMAB;OXALIPLATIN	1 (0.3)	0
OTHER MONOCLONAL ANTIBODIES AND ANTIBODY DRUG CONJUGATES;PEMBROLIZUMAB	1 (0.3)	0
COMBO ANTI-PD1 + VEGF OR COMBO ANTI-PDL1 + VEGF	29 (8.7)	67 (20.1)
ATEZOLIZUMAB;BEVACIZUMAB	20 (6.0)	64 (19.2)
ATEZOLIZUMAB;LENVATINIB MESILATE	1 (0.3)	0
BEVACIZUMAB;SINTILIMAB	1 (0.3)	0
CABOZANTINIB;PEMBROLIZUMAB	1 (0.3)	0
CAMRELIZUMAB;LENVATINIB	1 (0.3)	0
CAMRELIZUMAB;SORAFENIB TOSILATE	0	1 (0.3)
LENVATINIB MESILATE;SINTILIMAB	1 (0.3)	0
LENVATINIB MESILATE;TISLELIZUMAB	1 (0.3)	0
LENVATINIB;NIVOLUMAB	0	1 (0.3)
LENVATINIB;PEMBROLIZUMAB	2 (0.6)	0
NIVOLUMAB;REGORAFENIB	0	1 (0.3)
PEMBROLIZUMAB;REGORAFENIB	6 (1.8)	1 (0.3)
PEMBROLIZUMAB;SORAFENIB	0	1 (0.3)
REGORAFENIB;TISLELIZUMAB	1 (0.3)	0
SINTILIMAB;SORAFENIB TOSILATE	1 (0.3)	0
SORAFENIB;TISLELIZUMAB	1 (0.3)	0
COMBO PD1/PDL1 AND LAG3	0	12 (3.6)
NIVOLUMAB;RELATLIMAB	0	8 (2.4)
TEBOTELIMAB	0	4 (1.2)
NON-IO REGIMEN	97 (29.0)	104 (31.2)
INVESTIGATIONAL ANTINEOPLASTIC AGENTS	1 (0.3)	3 (0.9)
INVESTIGATIONAL ANTINEOPLASTIC DRUGS	1 (0.3)	1 (0.3)
INVESTIGATIONAL DRUG	0	2 (0.6)
PLATINUM COMPOUNDS	4 (1.2)	3 (0.9)
CISPLATIN;DOXORUBICIN HYDROCHLORIDE	1 (0.3)	0
CISPLATIN;GEMCITABINE	0	1 (0.3)
FLUOROURACIL;FLUOROURACIL;FOLINIC ACID;OXALIPLATIN	1 (0.3)	0
FLUOROURACIL;OXALIPLATIN	1 (0.3)	0
GEMCITABINE HYDROCHLORIDE;OXALIPLATIN	1 (0.3)	0
GEMCITABINE;OXALIPLATIN	0	2 (0.6)

NON-IO REGIMEN (CONTINUED)		
VEGFR TARGETED THERAPY	95 (28.4)	99 (29.7)
BEVACIZUMAB	0	1 (0.3)
CABOZANTINIB	8 (2.4)	27 (8.1)
CABOZANTINIB S-MALATE	1 (0.3)	6 (1.8)
CATEQUENTINIB HYDROCHLORIDE	1 (0.3)	0
LENVATINIB	37 (11.0)	13 (3.9)
LENVATINIB MESILATE	10 (3.0)	9 (2.7)
RAMUCIRUMAB	3 (0.9)	3 (0.9)
REGORAFENIB	9 (2.7)	26 (7.8)
SORAFENIB	40 (11.9)	43 (12.9)
SORAFENIB TOSILATE	8 (2.4)	9 (2.7)
OTHER SYSTEMIC ANTICANCER THERAPY	1 (0.3)	5 (1.5)
CAPECITABINE	0	1 (0.3)
CAPECITABINE;OXALIPLATIN;RAMUCIRUMAB	0	1 (0.3)
CAPECITABINE;THALIDOMIDE	0	1 (0.3)
EPIRUBICIN HYDROCHLORIDE;ETOPOSIDE	1 (0.3)	0
LAROTRECTINIB	0	1 (0.3)
TRAMETES ROBINIOPHILA	0	1 (0.3)

(1) Subject may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (randomization date if subject never treated).

Numbers analysed

Table 26 Analysis populations – All enrolled subjects

Population	Nivo+Ipi	SOC	Total
Enrolled: Subjects who signed the informed consent form and were registered into the IRT.			1148
Randomized: All subjects who were randomized to any treatment arm in the study. Unless otherwise specified, this is the dataset for analyses of study conduct, study population and efficacy.	335	333	668
Treated: All subjects who received at least one dose of study drug. Unless otherwise specified, this is the dataset for analyses of exposure and safety.	332	325	657
Treated Beyond Progression: Subjects whose last dose date is after the date of progression based on investigator assessment of RECIST 1.1.	62	157	219
Responders: All randomized subjects with BOR of confirmed CR or confirmed PR (per BICR RECIST 1.1)	121	44	165

Outcomes and estimation

Primary endpoint: Overall survival (OS)

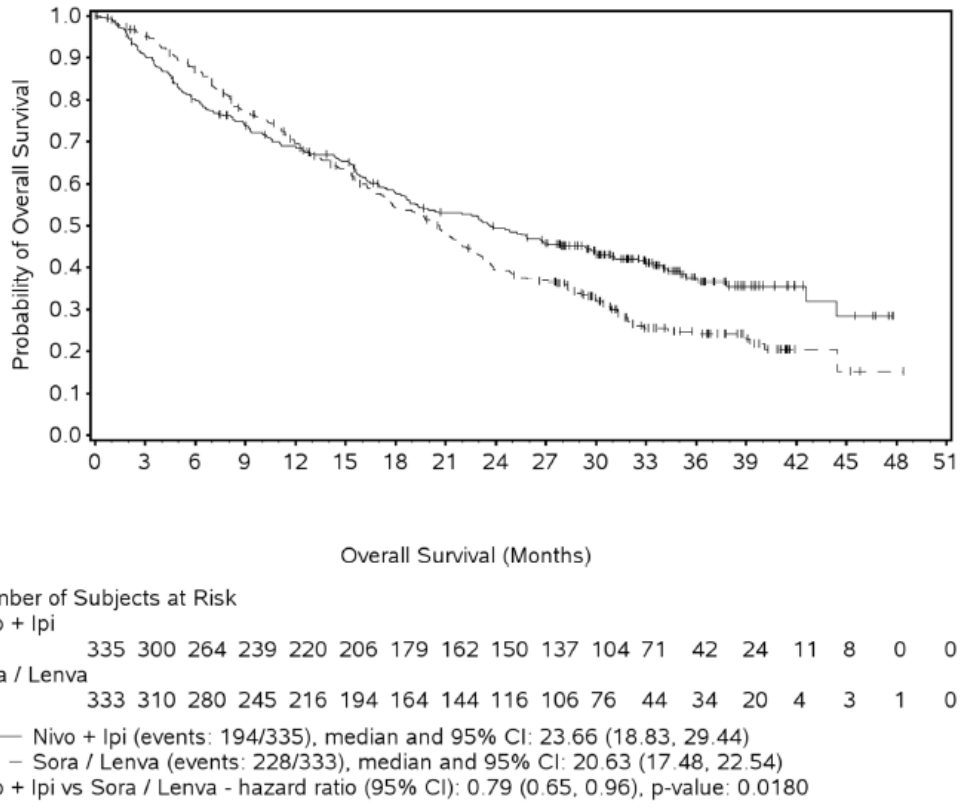
In CA2099DW, the median follow-up for OS was 35.20 months and the minimum follow-up for OS was 26.8 months.

Table 27 Overall Survival – All Randomized Subjects

	Nivo + Ipi N = 335	Sora / Lenva N = 333
# EVENTS / # SUBJECTS (%)	194/335 (57.9)	228/333 (68.5)
MEDIAN OS (MONTHS) (1) (95% CI)	23.66 (18.83, 29.44)	20.63 (17.48, 22.54)
HR	0.79 (A)	
(95% CI)	(0.65, 0.96)	
(97.43% CI)	(0.64, 0.99)	
P-VALUE (2)	0.0180	
Overall Survival Rate (95% CI)		
3-MONTH	90.4 (86.7, 93.1)	95.1 (92.2, 97.0)
6-MONTH	80.1 (75.4, 84.0)	87.1 (83.0, 90.3)
9-MONTH	73.7 (68.6, 78.1)	77.4 (72.4, 81.6)
12-MONTH	68.4 (63.1, 73.2)	69.7 (64.4, 74.5)
18-MONTH	57.9 (52.3, 63.1)	54.3 (48.6, 59.7)
24-MONTH	49.4 (43.8, 54.8)	39.2 (33.7, 44.7)
36-MONTH	37.5 (31.6, 43.4)	24.1 (19.0, 29.6)

(1) Based on Kaplan-Meier Estimates
(A) Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab + Ipilimumab over Sorafenib / Lenvatinib.
(2) Two-sided p-value from stratified log-rank test.
Stratification factors for stratified analysis are Etiology (viral related-HCC vs non-viral related-HCC), Vascular invasion and/or extrahepatic spread (present or absent), Alpha-fetoprotein (AFP) (< 400 ng/mL or ≥ 400 ng/mL) as entered into the IRT.
Boundary for statistical significance p-value <= 0.0257.

Figure 14 Kaplan-Meier Plot of Overall Survival - All Randomized Subjects



Hazard ratio from stratified Cox proportional hazard model. Hazard Ratio is Nivolumab + Ipilimumab over Sorafenib / Lenvatinib.
Two-sided p-value from stratified log-rank test.
Stratification factors for stratified analysis are Etiology (viral related-HCC vs non-viral related-HCC, Vascular invasion and/or extrahepatic spread (present or absent), Alpha-fetoprotein (AFP) (< 400 ng/mL or ≥ 400 ng/mL) as entered into IRT.
Symbols represent censored observations.

Secondary endpoints

ORR per BICR (RECIST 1.1) - Key secondary endpoint

ORR per BICR was included in the hierarchical testing procedure; and, therefore, it was multiplicity-controlled.

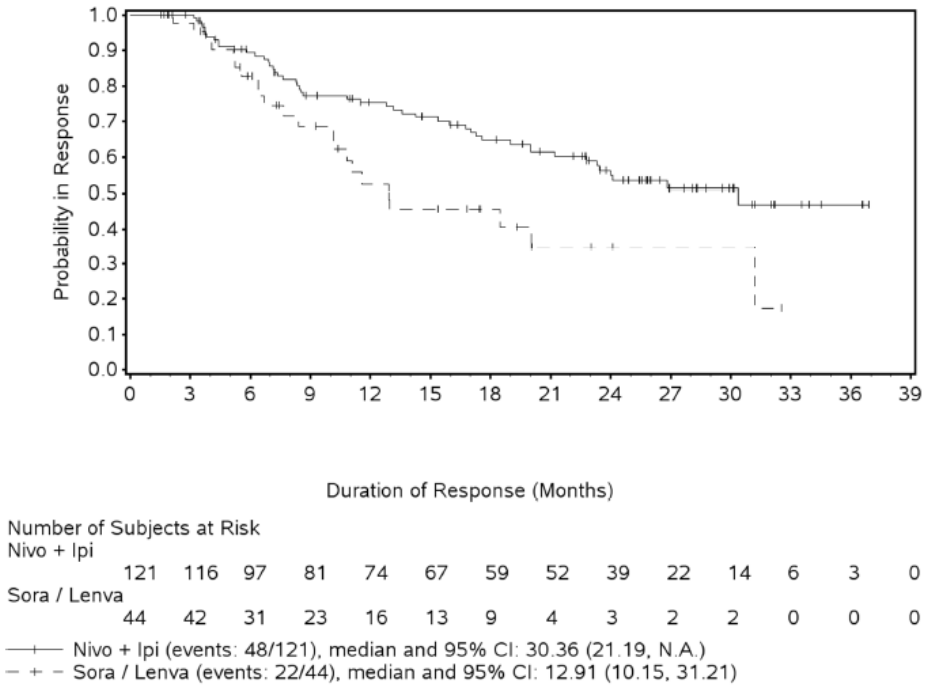
Table 28 Best Overall Response per BICR (RECIST 1.1) – All randomized subjects

	Number of Subjects (%)	
	Nivo + Ipi N = 335	Sora / Lenva N = 333
CONFIRMED BEST OVERALL RESPONSE		
COMPLETE RESPONSE (CR)	23 (6.9)	6 (1.8)
PARTIAL RESPONSE (PR)	98 (29.3)	38 (11.4)
STABLE DISEASE (SD)	102 (30.4)	198 (59.5)
NON-CR/NON-PD	6 (1.8)	7 (2.1)
PROGRESSIVE DISEASE (PD)	67 (20.0)	47 (14.1)
UNABLE TO DETERMINE (UTD) *	39 (11.6)	37 (11.1)
OBJECTIVE RESPONSE RATE (1)	121/335 (36.1%)	44/333 (13.2%)
(95% CI)	(31.0, 41.5)	(9.8, 17.3)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2, 3)	22.9%	
(95% CI)	(16.6, 29.2)	
(97.5% CI)	(15.7, 30.1)	
ESTIMATE OF ODDS RATIO (3, 4)	3.61	
(95% CI)	(2.46, 5.29)	
(97.5% CI)	(2.33, 5.59)	
P-VALUE (5)	<0.0001	
DISEASE CONTROL RATE (6)	229/335 (68.4%)	249/333 (74.8%)
(95% CI)	(63.1, 73.3)	(69.8, 79.4)

(1) CR+PR, confidence interval based on the Clopper and Pearson method.
(2) Strata adjusted difference in objective response rate (Nivolumab + Ipilimumab - Sorafenib / Lenvatinib) based on Cochran-Mantel-Haenszel (CMH) method of weighting.
(3) Stratified by Etiology (viral related-HCC vs non-viral related-HCC), Vascular invasion and/or extrahepatic spread (present or absent), Alpha-fetoprotein (AFP) (< 400 ng/mL or ≥ 400 ng/mL) as entered into the IRT.
(4) Strata adjusted odds ratio (Nivolumab + Ipilimumab over Sorafenib / Lenvatinib) using Mantel-Haenszel method.
(5) Two-sided p-value from stratified CMH Test.
(6) CR+PR+SD+NON-CR/NON-PD, confidence interval based on the Clopper and Pearson method.
* Include one subject from SOC arm that did not have any baseline lesion per review of a BICR radiologist and thus did not have response evaluated.

TTR (Exploratory Endpoint) and DOR per BICR (RECIST 1.1)

Figure 15 Kaplan-Meier Plot of Duration of Response per BICR (RECIST 1.1) – All Confirmed Responders



Symbols represent censored observations.

Table 29 Time to Objective Response and Duration of Response per BICR (RECIST 1.1) - All Confirmed Responders

	Nivo + Ipi N = 121	Sora / Lenva N = 44
TIME TO OBJECTIVE RESPONSE (MONTHS)		
MEAN	3.17	4.19
MEDIAN	2.17	3.65
MIN, MAX	1.1, 11.6	0.6, 11.2
Q1, Q3	2.07, 3.78	2.10, 5.59
STANDARD DEVIATION	1.876	2.307
DURATION OF RESPONSE (MONTHS)		
MIN, MAX (A)	1.5+, 36.9+	2.1+, 32.5+
MEDIAN (95% CI) (B)	30.36 (21.19, N.A.)	12.91 (10.15, 31.21)
N EVENT/N RESP (%)	48/121 (39.7)	22/44 (50.0)
PROPORTION OF SUBJECTS WITH DURATION OF RESPONSE OF AT LEAST (95% CI) (C)		
3 MONTHS	1.00 (1.00, 1.00)	0.98 (0.85, 1.00)
6 MONTHS	0.89 (0.82, 0.94)	0.83 (0.67, 0.91)
9 MONTHS	0.77 (0.68, 0.84)	0.68 (0.51, 0.81)
12 MONTHS	0.75 (0.66, 0.82)	0.52 (0.35, 0.68)
18 MONTHS	0.65 (0.55, 0.73)	0.46 (0.28, 0.61)
24 MONTHS	0.55 (0.44, 0.64)	0.35 (0.17, 0.53)
30 MONTHS	0.51 (0.40, 0.61)	0.35 (0.17, 0.53)
36 MONTHS	0.47 (0.34, 0.59)	N.A.

(A) Symbol + indicates a censored value.
(B) Median computed using Kaplan-Meier method.
(C) Based on Kaplan-Meier estimates of duration of response.

Time to Symptom Deterioration in HCS Score (TTSD)

TTSD was included in the hierarchical statistical analysis and, therefore, it was multiplicity-controlled.

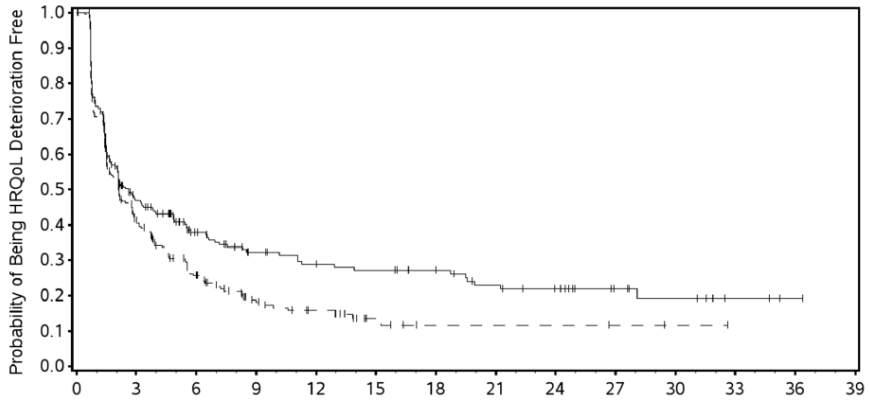
Table 30 Time to Symptom Deterioration of HCS Score - All Randomized Subjects

	Nivo + Ipi N = 335	Sora / Lenva N = 333
# EVENTS / # SUBJECTS (%)	185/335 (55.2)	226/333 (67.9)
MEDIAN TTSD (MONTHS) (1) (95% CI)	2.60 (2.00, 3.94)	2.14 (1.64, 2.79)
HR	0.76 (A)	
(95% CI)	(0.62, 0.93)	
(98.03% CI)	(0.60, 0.96)	
P-VALUE (2)	0.0059	

Source: Table 14.2.4.1.1

(1) Based on Kaplan-Meier Estimates
(A) Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab + Ipilimumab over Sorafenib / Lenvatinib.
(2) Two-sided P-values from stratified log-rank test.
Stratification factors for stratified analysis are Etiology (viral related-HCC vs non-viral related-HCC), Vascular invasion and/or extrahepatic spread (present or absent), Alpha-fetoprotein (AFP) (< 400 ng/mL or ≥ 400 ng/mL) as entered into the IRT.
Symptom Deterioration is defined as a clinically meaningful decline (at least a 6 point decrease from baseline) in the Hepatobiliary Cancer Subscale (HCS) score of the functional assessment of cancer therapy hepatobiliary cancer (FACT-Hep).

Figure 16 Kaplan-Meier Plot of Time to Symptom Deterioration of HCS Score - All Randomized Subjects



Time to HRQoL Deterioration (Months)

Number of Subjects at Risk

Nivo + Ipi	335	98	58	40	34	31	28	21	17	10	7	3	1	0
Sora / Lenva	333	102	52	26	17	7	3	3	3	2	1	0	0	0

—+— Nivo + Ipi (events: 185/335), median and 95% CI: 2.60 (2.00, 3.94)
– + – Sora / Lenva (events: 226/333), median and 95% CI: 2.14 (1.64, 2.79)
Nivo + Ipi vs. Sora / Lenva - hazard ratio (95% CI): 0.76 (0.62, 0.93), p-value: 0.0059

Hazard ratio from stratified Cox proportional hazard model. Hazard Ratio is Nivolumab + Ipilimumab over Sorafenib / Lenvatinib.
Two-sided p-value from stratified log-rank test.
Stratification factors for stratified analysis are Etiology (viral related-HCC vs non-viral related-HCC), Vascular invasion and/or extrahepatic spread (present or absent), Alpha-fetoprotein (AFP) (< 400 ng/mL or ≥ 400 ng/mL) as entered into IRT.
Symbols represent censored observations.
HCS=Hepatobiliary Cancer Subscale of the functional assessment of cancer therapy hepatobiliary cancer (FACT-Hep)
HROoL=Health-Related Quality of Life

In a sensitivity analysis, the K-M plot of TTSD while accounting for death or disease progression per BICR RECIST 1.1 as symptom deterioration event showed consistent trend favoring nivo+ipi over SOC.

Exploratory endpoints

ORR per investigator (RECIST 1.1)

Table 31 Confirmed Best Overall Response per Investigator RECIST 1.1 – All Randomized Subjects

	Number of Subjects (%)	
	Nivo + Ipi N = 335	Sora / Lenva N = 333
CONFIRMED BEST OVERALL RESPONSE		
COMPLETE RESPONSE (CR)	15 (4.5)	4 (1.2)
PARTIAL RESPONSE (PR)	105 (31.3)	42 (12.6)
STABLE DISEASE (SD)	118 (35.2)	193 (58.0)
PROGRESSIVE DISEASE (PD)	67 (20.0)	62 (18.6)
UNABLE TO DETERMINE (UTD)	30 (9.0)	32 (9.6)
NEVER TREATED	3 (0.9)	7 (2.1)
DEATH PRIOR TO DISEASE ASSESSMENT	14 (4.2)	9 (2.7)
EARLY DISCONTINUATION DUE TO TOXICITY	0	3 (0.9)
OTHER	12 (3.6)	13 (3.9)
NOT REPORTED	1 (0.3)	0
OBJECTIVE RESPONSE RATE (1)	120/335 (35.8%)	46/333 (13.8%)
(95% CI)	(30.7, 41.2)	(10.3, 18.0)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2, 3)	22.0%	
(95% CI)	(15.7, 28.3)	
ESTIMATE OF ODDS RATIO (3, 4)	3.44	
(95% CI)	(2.35, 5.03)	
DISEASE CONTROL RATE (5)	238/335 (71.0%)	239/333 (71.8%)
(95% CI)	(65.9, 75.8)	(66.6, 76.5)

(1) CR+PR, confidence interval based on the Clopper and Pearson method.
(2) Strata adjusted difference in objective response rate (Nivolumab + Ipilimumab - Sorafenib / Lenvatinib) based on Cochran-Mantel-Haenszel (CMH) method of weighting.
(3) Stratified by Etiology (viral related-HCC vs non-viral related-HCC), Vascular invasion and/or extrahepatic spread (present or absent), Alpha-fetoprotein (AFP) (< 400 ng/mL or ≥ 400 ng/mL) as entered into the IRT.
(4) Strata adjusted odds ratio (Nivolumab + Ipilimumab over Sorafenib / Lenvatinib) using Mantel-Haenszel method.
(5) CR+PR+SD, confidence interval based on the Clopper and Pearson method.

Table 32 Concordance between BICR and Investigator Assessments per RECIST 1.1 - All Randomized Subjects

Treatment Arm: Nivolumab + Ipilimumab N = 335

	Number of Subjects (%)		
	BICR ASSESSMENT		
	RESPONDERS	NON-RESPONDERS	UTD*
INVESTIGATOR ASSESSMENT			
RESPONDERS	105 (31.3)	14 (4.2)	1 (0.3)
NON-RESPONDERS	16 (4.8)	159 (47.5)	10 (3.0)
UTD	0	2 (0.6)	28 (8.4)
CONCORDANCE RATE OF RESPONDERS (1):		90.7%	

Treatment Arm: Sorafenib / Lenvatinib N = 333

	Number of Subjects (%)		
	BICR ASSESSMENT		
	RESPONDERS	NON-RESPONDERS	UTD*
INVESTIGATOR ASSESSMENT			
RESPONDERS	24 (7.2)	21 (6.3)	1 (0.3)
NON-RESPONDERS	20 (6.0)	231 (69.4)	4 (1.2)
UTD	0	0	32 (9.6)
CONCORDANCE RATE OF RESPONDERS (1):		87.4%	

Treatment Arm: Total N = 668

	Number of Subjects (%)		
	BICR ASSESSMENT		
	RESPONDERS	NON-RESPONDERS	UTD*
INVESTIGATOR ASSESSMENT			
RESPONDERS	129 (19.3)	35 (5.2)	2 (0.3)
NON-RESPONDERS	36 (5.4)	390 (58.4)	14 (2.1)
UTD	0	2 (0.3)	60 (9.0)
CONCORDANCE RATE OF RESPONDERS (1):		89.1%	

Responders: Subjects with confirmed PR/CR. UTD: Unable to Determine
(1) Quantifies the frequency with which INV and BICR agreed on classification of a subject as responder vs. non-responder/UTD as a proportion of the total number of subjects assessed by both the investigator and BICR.
* Include one subject from SOC arm that did not have any baseline lesion per review of a BICR radiologist and thus did not have response evaluated.

ORR per BICR (mRECIST for HCC)

Nivo+ipi demonstrated higher ORR (95% CI) per BICR (mRECIST for HCC) (41.5% [95% CI: 36.2, 47.0]) than SOC (37.2% [95% CI: 32.0, 42.7]).

The DCR was 65.7% in the nivo+ipi arm and 74.2% in the SOC arm.

The median (95% CI) duration of disease control was 15.67 (10.61, 19.42) months for the nivo+ipi arm and 9.20 (7.98, 10.97) in the SOC arm (Table 14.2.7.1.3). DDC of at least 24 months was observed in 38% of subjects in the nivo+ipi arm and 7% in the SOC arm.

TTR and DOR

TTR and DOR per Investigator

The median time to objective response per investigator RECIST 1.1 was 2.18 months for the nivo+ipi arm and 3.56 months for the SOC arm. Median DOR was 25.76 (95% CI: 20.01, NA) months for the nivo+ipi arm and 10.15 (95% CI: 7.33, 14.03) months for the SOC arm.

Table 33 Time to Objective Response and Duration of Response per Investigator RECIST 1.1 - All Confirmed Responders

	Nivo + Ipi N = 120	Sora / Lenva N = 46
TIME TO OBJECTIVE RESPONSE (MONTHS)		
MEAN	3.56	4.13
MEDIAN	2.18	3.56
MIN, MAX	1.2, 21.7	1.9, 18.2
Q1, Q3	2.07, 3.78	2.10, 5.36
STANDARD DEVIATION	2.787	3.124
DURATION OF RESPONSE (MONTHS)		
MIN, MAX (A)	1.1, 43.8+	3.5, 26.7+
MEDIAN (95% CI) (B)	25.76 (20.01, N.A.)	10.15 (7.33, 14.03)
N EVENT/N RESP (%)	54/120 (45.0)	41/46 (89.1)
PROPORTION OF SUBJECTS WITH DURATION OF RESPONSE OF AT LEAST (95% CI) (C)		
3 MONTHS	0.97 (0.92, 0.99)	1.00 (1.00, 1.00)
6 MONTHS	0.88 (0.80, 0.93)	0.74 (0.58, 0.84)
9 MONTHS	0.82 (0.73, 0.88)	0.56 (0.40, 0.69)
12 MONTHS	0.78 (0.69, 0.84)	0.39 (0.25, 0.53)
18 MONTHS	0.65 (0.55, 0.73)	0.26 (0.14, 0.39)
24 MONTHS	0.52 (0.42, 0.61)	0.06 (0.01, 0.17)
30 MONTHS	0.44 (0.33, 0.55)	N.A.
36 MONTHS	0.44 (0.33, 0.55)	N.A.
42 MONTHS	0.44 (0.33, 0.55)	N.A.

(A) Symbol + indicates a censored value.
(B) Median computed using Kaplan-Meier method.
(C) Based on Kaplan-Meier estimates of duration of response.

TTR and DOR per BICR mRECIST for HCC

The median time to objective response per BICR mRECIST for HCC was 2.14 months for the nivo+ipi arm and 2.10 months for the SOC arm. Median DOR was 28.09 (95% CI: 17.28, NA) months for the nivo+ipi arm and 8.31 (95% CI: 7.16, 10.02) months for the SOC arm.

Table 34 Time to Objective Response and Duration of Response per BICR mRECIST for HCC - All Confirmed Responders

	Nivo + Ipi N = 139	Sora / Lenva N = 124
TIME TO OBJECTIVE RESPONSE (MONTHS)		
MEAN	2.86	2.94
MEDIAN	2.14	2.10
MIN, MAX	1.0, 25.5	0.6, 14.5
Q1, Q3	2.04, 3.48	2.00, 3.55
STANDARD DEVIATION	2.359	2.110
DURATION OF RESPONSE (MONTHS)		
MIN, MAX (A)	1.4+, 43.8+	1.6+, 34.1+
MEDIAN (95% CI) (B)	28.09 (17.28, N.A.)	8.31 (7.16, 10.02)
N EVENT/N RESP (%)	58/139 (41.7)	88/124 (71.0)
PROPORTION OF SUBJECTS WITH DURATION OF RESPONSE OF AT LEAST (95% CI) (C)		
3 MONTHS	0.97 (0.92, 0.99)	0.97 (0.91, 0.99)
6 MONTHS	0.85 (0.78, 0.90)	0.67 (0.57, 0.75)
9 MONTHS	0.76 (0.68, 0.83)	0.46 (0.36, 0.55)
12 MONTHS	0.71 (0.62, 0.78)	0.32 (0.23, 0.41)
18 MONTHS	0.58 (0.48, 0.66)	0.24 (0.16, 0.33)
24 MONTHS	0.54 (0.44, 0.62)	0.15 (0.08, 0.23)
30 MONTHS	0.46 (0.35, 0.56)	0.08 (0.03, 0.17)
36 MONTHS	0.46 (0.35, 0.56)	N.A.
42 MONTHS	0.46 (0.35, 0.56)	N.A.

(A) Symbol + indicates a censored value.
(B) Median computed using Kaplan-Meier method.
(C) Based on Kaplan-Meier estimates of duration of response.

Progression-free Survival per BICR

PFS per BICR- RECIST 1.1 (Primary Definition)

Table 35 Progression Free Survival Primary Definition, Progression Free Survival Rates Primary Definition, and Time to Progression per BICR RECIST 1.1- All Randomized Subjects

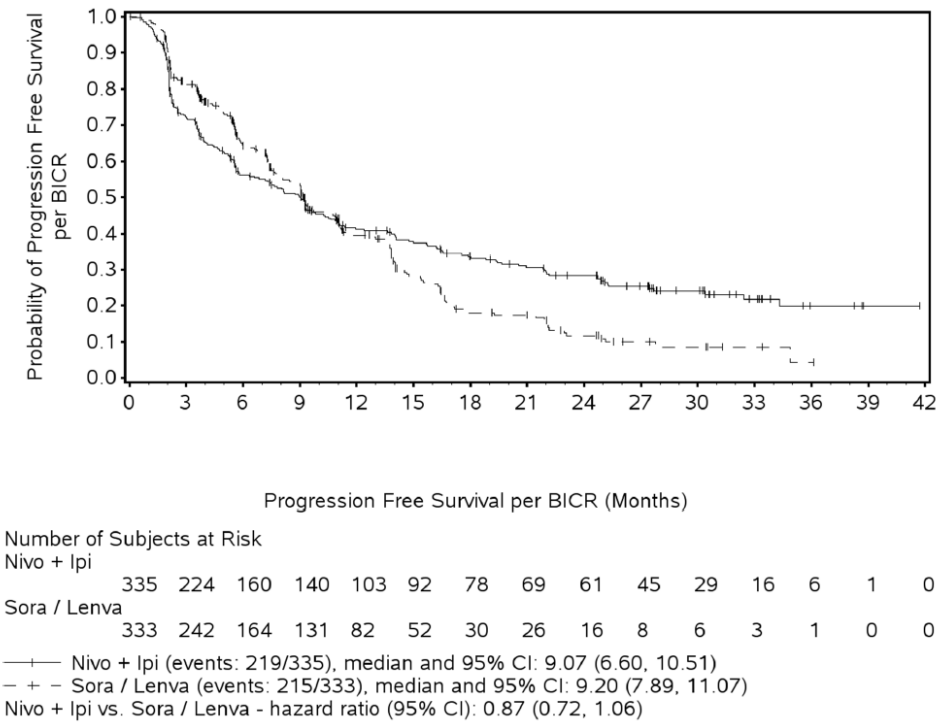
Progression Free Survival	Nivo + Ipi N = 335	Sora / Lenva N = 333
# EVENTS / # SUBJECTS (%)	219/335 (65.4)	215/333 (64.6)
MEDIAN PFS (MONTHS) (1) (95% CI)	9.07 (6.60, 10.51)	9.20 (7.89, 11.07)
HR (95% CI)	0.87 (A) (0.72, 1.06)	

Progression Free Survival Rate (95% CI)	Nivo + Ipi N = 335	Sora / Lenva N = 333
3-MONTH	72.1 (66.8, 76.7)	81.1 (76.3, 85.1)
6-MONTH	56.2 (50.4, 61.5)	64.2 (58.3, 69.5)
9-MONTH	50.1 (44.3, 55.6)	54.1 (47.9, 59.8)
12-MONTH	41.1 (35.4, 46.7)	39.5 (33.4, 45.5)
18-MONTH	33.7 (28.2, 39.3)	18.0 (13.0, 23.6)
24-MONTH	28.4 (23.1, 33.9)	11.7 (7.5, 17.0)

Time to Progression	Nivo + Ipi N = 335	Sora / Lenva N = 333
# EVENTS / # SUBJECTS (%)	149/335 (44.5)	165/333 (49.5)
MEDIAN TTP (MONTHS) (1) (95% CI)	16.46 (11.07, 22.14)	11.07 (9.26, 13.83)

(1) Based on Kaplan-Meier Estimates
(A) Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab + Ipilimumab over Sorafenib / Lenvatinib. Stratification factors for stratified analysis are Etiology (viral related-HCC vs non-viral related-HCC), Vascular invasion and/or extrahepatic spread (present or absent), Alpha-fetoprotein (AFP) (< 400 ng/mL or ≥ 400 ng/mL) as entered into the IRT.

Figure 17 Kaplan-Meier Plot of Progression Free Survival per BICR RECIST 1.1, Primary Definition – All Randomized Subjects



PFS per BICR RECIST 1.1 -(Secondary Definition)

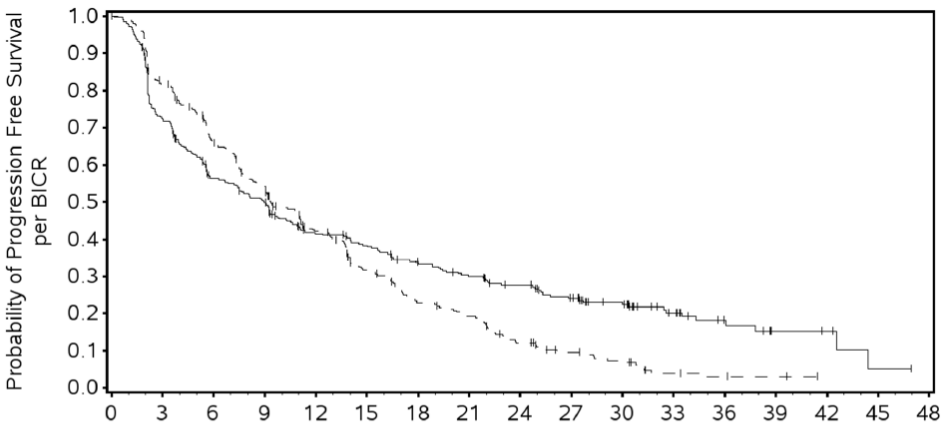
Table 36 Progression Free Survival and Progression Free Survival Rates per BICR RECIST 1.1, Secondary Definition - All Randomized Subjects

Progression Free Survival	Nivo + Ipi N = 335	Sora / Lenva N = 333
# EVENTS / # SUBJECTS (%)	247/335 (73.7)	272/333 (81.7)
MEDIAN PFS (MONTHS) (1) (95% CI)	8.97 (6.67, 10.51)	9.33 (8.31, 11.14)
HR (95% CI)	0.82 (A) (0.69, 0.98)	

Progression Free Survival Rate (95% CI)	Nivo + Ipi N = 335	Sora / Lenva N = 333
3-MONTH	72.4 (67.2, 76.9)	81.7 (77.0, 85.5)
6-MONTH	56.3 (50.7, 61.5)	65.8 (60.2, 70.8)
9-MONTH	49.8 (44.3, 55.2)	54.9 (49.2, 60.2)
12-MONTH	41.5 (36.0, 46.9)	42.3 (36.6, 47.8)
18-MONTH	33.7 (28.5, 39.0)	22.8 (18.0, 27.8)
24-MONTH	27.8 (22.8, 33.0)	12.0 (8.4, 16.3)

Source: Table 14.2.5.3.1, Table 14.2.5.4.1
(1) Based on Kaplan-Meier Estimates

Figure 18 Kaplan-Meier Plot of Progression Free Survival per BICR RECIST 1.1, Secondary Definition – All Randomized Subjects



Progression Free Survival per BICR (Months)

Number of Subjects at Risk

Nivo + Ipi	335	238	175	154	120	109	92	81	71	56	38	24	13	5	4	1	0
Sora / Lenva	333	257	201	165	120	86	60	49	29	18	12	5	3	2	0	0	0

—+— Nivo + Ipi (events: 247/335), median and 95% CI: 8.97 (6.67, 10.51)
– + – Sora / Lenva (events: 272/333), median and 95% CI: 9.33 (8.31, 11.14)
Nivo + Ipi vs. Sora / Lenva - hazard ratio (95% CI): 0.82 (0.69, 0.98)

PFS on Next Line of Therapy per Investigator (PFS2) and TSST

Table 37 PFS on Next-line Therapy per Investigator Assessment (PFS2) - All Randomized Subjects

	Nivo + Ipi N = 335	Sora / Lenva N = 333
# EVENTS / # SUBJECTS (%)	206/335 (61.5)	257/333 (77.2)
MEDIAN PFS2 (MONTHS) (1) (95% CI)	19.32 (16.23, 24.54)	15.44 (13.83, 17.02)
HR	0.70 (A)	
(95% CI)	(0.58, 0.84)	

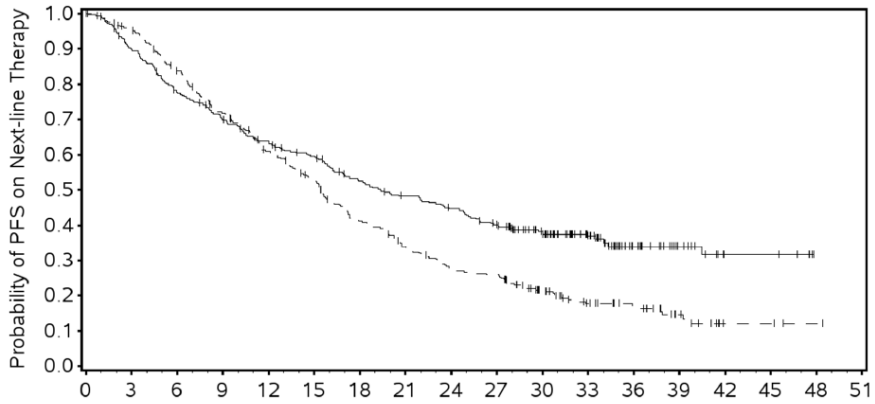
(1) Based on Kaplan-Meier Estimates
(A) Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab + Ipilimumab over Sorafenib / Lenvatinib.
Stratification factors for stratified analysis are Etiology (viral related-HCC vs non-viral related-HCC), Vascular invasion and/or extrahepatic spread (present or absent), Alpha-fetoprotein (AFP) (< 400 ng/mL or ≥ 400 ng/mL) as entered into the IRT.

Table 38 Time to Second Subsequent Therapy - All Randomized Subjects

	Nivo + Ipi N = 335	Sora / Lenva N = 333
# EVENTS / # SUBJECTS (%)	200/335 (59.7)	251/333 (75.4)
MEDIAN TSST (MONTHS) (1) (95% CI)	21.98 (17.94, 25.76)	16.59 (15.34, 18.10)
HR	0.70 (A)	
(95% CI)	(0.58, 0.84)	

(1) Based on Kaplan-Meier Estimates
(A) Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab + Ipilimumab over Sorafenib / Lenvatinib.
Stratification factors for stratified analysis are Etiology (viral related-HCC vs non-viral related-HCC), Vascular invasion and/or extrahepatic spread (present or absent), Alpha-fetoprotein (AFP) (< 400 ng/mL or ≥ 400 ng/mL) as entered into the IRT.

Figure 19 Kaplan-Meier Plot of PFS on Next-line Therapy per Investigator Assessment (PFS2) - All Randomized Subjects



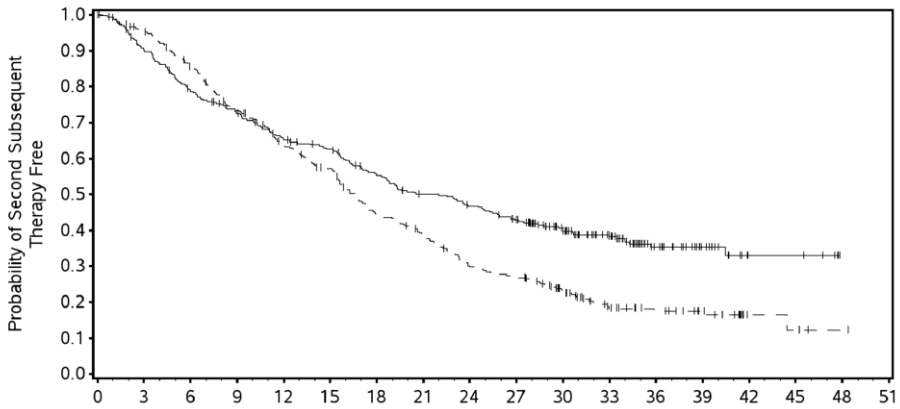
PFS on Next-line Therapy (Months)

Number of Subjects at Risk

Nivo + Ipi	335	298	256	228	205	189	163	148	136	120	90	61	33	18	6	6	0	0
Sora / Lenva	333	310	269	229	190	162	124	101	80	76	50	32	25	13	3	3	1	0

—+— Nivo + Ipi (events: 206/335), median and 95% CI: 19.32 (16.23, 24.54)
– + – Sora / Lenva (events: 257/333), median and 95% CI: 15.44 (13.83, 17.02)
Nivo + Ipi vs. Sora / Lenva - hazard ratio (95% CI): 0.70 (0.58, 0.84)

Figure 20 Kaplan-Meier Plot of Time to Second Subsequent Therapy - All Randomized Subjects



Second Subsequent Therapy Free Time (Months)

Number of Subjects at Risk

Nivo + Ipi	335	299	261	236	210	198	172	153	142	128	95	64	36	20	6	6	0	0
Sora / Lenva	333	310	275	234	198	175	135	115	88	81	55	34	26	16	4	3	1	0

—+— Nivo + Ipi (events: 200/335), median and 95% CI: 21.98 (17.94, 25.76)
– + – Sora / Lenva (events: 251/333), median and 95% CI: 16.59 (15.34, 18.10)
Nivo + Ipi vs. Sora / Lenva - hazard ratio (95% CI): 0.70 (0.58, 0.84)

Efficacy by PD-L1 Status at Baseline

Tumour Tissue Disposition and Frequency of PD-L1 Expression

- PD-L1 TPS

Table 39 Frequency of Tumour Cell PD-L1 Expression Status - All Randomized Subjects

	Nivo + Ipi N = 335	Sora / Lenva N = 333	Total N = 668
SUBJECTS WITH PD-L1 EXPRESSION MISSING AT BASELINE (N(%))	170 (50.7)	178 (53.5)	348 (52.1)
SUBJECTS WITH PD-L1 QUANTIFIABLE AT BASELINE (N(%))	148 (44.2)	143 (42.9)	291 (43.6)
PD-L1 EXPRESSION (%)			
MEAN	1.4	0.0	0.7
MEDIAN	0.0	0.0	0.0
MIN , MAX	0 , 100	0 , 2	0 , 100
Q1 , Q3	0.0 , 0.0	0.0 , 0.0	0.0 , 0.0
STANDARD DEVIATION	11.05	0.19	7.90
SUBJECTS WITH BASELINE PD-L1 EXPRESSION ≥ 1%	8/148 (5.4)	2/143 (1.4)	10/291 (3.4)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%	140/148 (94.6)	141/143 (98.6)	281/291 (96.6)
SUBJECTS WITH INDETERMINATE PD-L1 EXPRESSION AT BASELINE (N(%))	0	0	0
SUBJECTS WITH PD-L1 EXPRESSION AT BASELINE NOT EVALUABLE (N(%))	17 (5.1)	12 (3.6)	29 (4.3)

- PD-L1 CPS

Table 40 Frequency of PD-L1 CPS Status - All Randomized Subjects

	Nivo + Ipi N = 335	Sora / Lenva N = 333	Total N = 668
SUBJECTS WITH PD-L1 CPS MISSING AT BASELINE (N(%))	170 (50.7)	178 (53.5)	348 (52.1)
SUBJECTS WITH PD-L1 QUANTIFIABLE AT BASELINE (N(%))	148 (44.2)	143 (42.9)	291 (43.6)
PD-L1 CPS			
MEAN	3.7	0.9	2.3
MEDIAN	0.0	0.0	0.0
MIN , MAX	0 , 100	0 , 20	0 , 100
Q1 , Q3	0.0 , 0.0	0.0 , 0.0	0.0 , 0.0
STANDARD DEVIATION	14.46	3.30	10.65
SUBJECTS WITH BASELINE PD-L1 CPS ≥ 1	31/148 (20.9)	24/143 (16.8)	55/291 (18.9)
SUBJECTS WITH BASELINE PD-L1 CPS < 1	117/148 (79.1)	119/143 (83.2)	236/291 (81.1)
SUBJECTS WITH BASELINE PD-L1 CPS ≥ 5	21/148 (14.2)	8/143 (5.6)	29/291 (10.0)
SUBJECTS WITH BASELINE PD-L1 CPS < 5	127/148 (85.8)	135/143 (94.4)	262/291 (90.0)
SUBJECTS WITH BASELINE PD-L1 CPS ≥ 10	12/148 (8.1)	7/143 (4.9)	19/291 (6.5)
SUBJECTS WITH BASELINE PD-L1 CPS < 10	136/148 (91.9)	136/143 (95.1)	272/291 (93.5)
SUBJECTS WITH INDETERMINATE PD-L1 CPS AT BASELINE (N(%))	0	0	0
SUBJECTS WITH PD-L1 CPS AT BASELINE NOT EVALUABLE (N(%))	17 (5.1)	12 (3.6)	29 (4.3)

CPS = Combined Positive Score

Tumour Cell PD-L1 Expression and Efficacy

Table 41 Efficacy by Tumour Cell PD-L1 Expression at Baseline – All Randomized Subjects

	PD-L1 < 1%		PD-L1 ≥ 1%		PD-L1 not quantifiable at baseline	
	Nivo+Ipi	SOC	Nivo+Ipi	SOC	Nivo+Ipi	SOC
OS	**N=140**	**N=141**	**N=8**	**N=2**	**N=187**	**N=190**
Median (95% CI), months	19.94 (12.39, 24.84)	18.99 (15.64, 21.22)	14.67 (2.10, 27.89)	6.39 (1.38, NA)	29.70 (20.53, 36.04)	21.95 (17.81, 25.43)
Hazard ratio (95%CI)[a]	0.84 (0.63, 1.12)		NA		0.74 (0.56, 0.96)	
ORR per BICR RECIST 1.1	**N=140**	**N=141**	**N=8**	**N=2**	**N=187**	**N=190**
Rate, % (95% CI)[b]	34.3 (26.5, 42.8)	14.9 (9.5, 21.9)	37.5 (8.5, 75.5)	0 (0.0, 84.2)	37.4 (30.5, 44.8)	12.1 (7.8, 17.6)
Odds Ratio (95% CI)[c]	2.98 (1.67, 5.33)		NA		4.34 (2.56, 7.36)	

[a] HR is not computed for subset category with 10 or less subjects per treatment arm. Unstratified Cox proportional hazard model.

[b] CR+PR, confidence interval based on the Clopper-Pearson method

[c] Odds ratio (nivolumab + iplimumab over sorafenib/lenvatinib) and associated unstratified 95% exact CI.

PD-L1 CPS and Efficacy

Table 42 Efficacy by PD-L1 CPS at Baseline - All Randomized Subjects

	Nivo+Ipi	SOC	Nivo+Ipi	SOC
	PD-L1 < 1		PD-L1 ≥ 1	
	N=117	N=119	N=31	N=24
Median OS (95% CI), months	16.33 (8.97, 24.54)	18.43 (15.80, 21.06)	19.94 (15.28, NA)	13.21 (8.08, 27.60)
Hazard ratio (95%CI)	0.92 (0.68, 1.24)		0.63 (0.32, 1.22)	
ORR per BICR, n (%)	33 (28.2)	18 (15.1)	18 (58.1)	3 (12.5)
(95% CI)	(20.3, 37.3)	(9.2, 22.8)	(39.1, 75.5)	(2.7, 32.4)
Odds Ratio (95% CI)	2.20 (1.16, 4.19)		9.69 (2.38, 39.48)	
	PD-L1 < 5		PD-L1 ≥ 5	
	N=127	N=135	N=21	N=8
Median OS (95% CI), months	17.87 (9.33, 24.77)	19.15 (16.26, 21.22)	19.94 (10.51, NA)	9.81 (4.90, 23.29)
Hazard ratio (95%CI)	0.90 (0.68, 1.21)		NA	
ORR per BICR, n (%)	38 (29.9)	20 (14.8)	13 (61.9)	1 (12.5)
(95% CI)	(22.1, 38.7)	(9.3, 21.9)	(38.4, 81.9)	(0.3, 52.7)
Odds Ratio (95% CI)	2.46 (1.34, 4.51)		NA	
	PD-L1 < 10		PD-L1 ≥ 10	
	N=136	N=136	N=12	N=7
Median OS (95% CI), months	18.83 (11.99, 24.54)	19.15 (15.80, 21.22)	16.20 (3.58, NA)	11.40 (6.44, 23.29)
Hazard ratio (95%CI)	0.88 (0.66, 1.16)		NA	
ORR per BICR, n (%)	44 (32.4)	20 (14.7)	7 (58.3)	1 (14.3)
(95% CI)	(24.6, 40.9)	(9.2, 21.8)	(27.7, 84.8)	(0.4, 57.9)
Odds Ratio (95% CI)	2.77 (1.53, 5.03)		NA	
PD-L1 Not Quantifiable at Baseline				
	N = 187	N = 190		
Median OS (95% CI), months	29.70 (20.53, 36.04)	21.95 (17.81, 25.43)		
Hazard ratio (95%CI)	0.74 (0.56, 0.96)			
ORR per BICR, n (%)	70 (37.4)	23 (12.1)		
(95% CI)	(30.5, 44.8)	(7.8, 17.6)		
Odds Ratio (95% CI)	4.34 (2.56, 7.36)			

ORR = CR+PR, confidence interval based on the Clopper and Pearson method. Odds ratio (Nivolumab + Ipilimumab over Sorafenib / Lenvatinib) and associated unstratified 95% exact CI.

OS: Statistical model for HR = unstratified Cox proportional hazard model.

Difference and odds ratio are not computed for subgroups with 10 or less subjects per treatment arm.

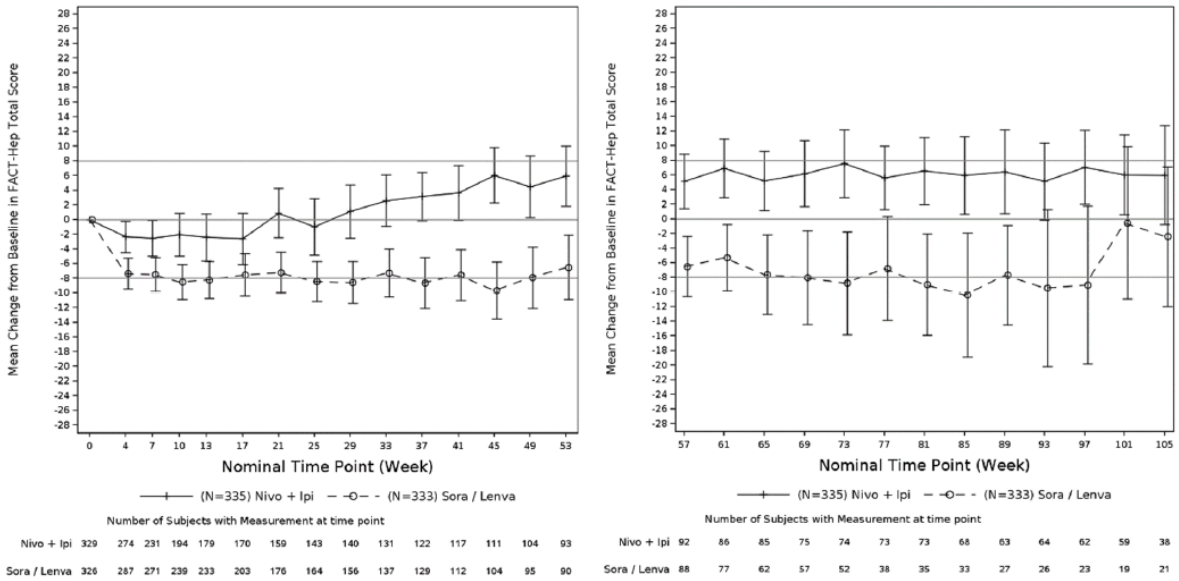
Patient-reported Outcomes (PROs)

Patient-reported outcomes were assessed using the FACT-Hep and the EQ-5D-3L (VAS and Utility Index). TTSD based on the HCS subscale of the FACT-Hep was a key secondary endpoint.

FACT-Hep

FACT-Hep questionnaire completion rates were >99% in both the nivo+ipi and SOC arms, at baseline, and >85% for most weeks during the treatment period. Completion rates ranged from 56.2% to 77.5% during Follow-Up Visits 1 & 2, and were <60% during Survival Follow-Up Visits.

Figure 21 Mean changes in FACT-Hep total score from baseline – All randomized subjects.



Error bars represent standard error for the mean.

Horizontal reference line indicates a minimally important difference (MID), considered a change ≥ 8 points from baseline.

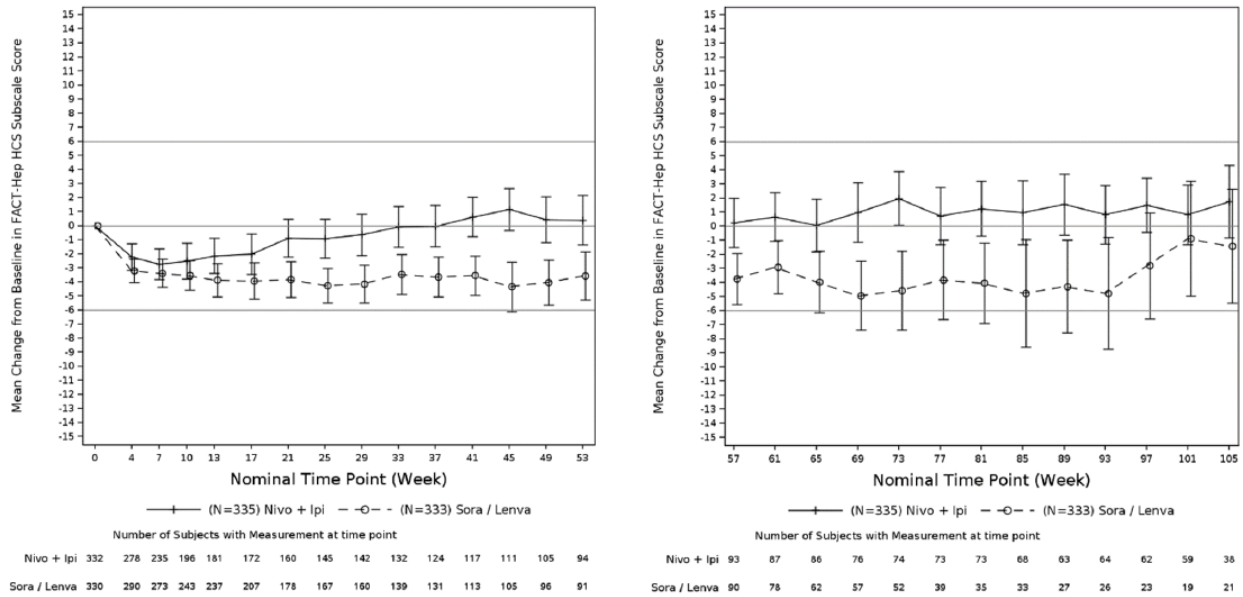
Only time points where data available for ≥5 subjects in each treatment arm are plotted.

A greater proportion of subjects in the SOC arm experienced at least an 8 point decrease from baseline in FACT-Hep total score as compared to subjects in the nivo+ipi arm. Through Week 105, which was the timepoint where there were still at least 5 subjects in each arm, the proportion of subjects in the nivo+ipi arm who had at least a 8 point decrease from baseline ranged from 19.4% to 38.1%, while the range for the SOC arm was 31.6% to 56.7%.

Mean (SD) baseline HCS subscale scores were 59.44 (8.727) in the nivo+ipi arm and 59.43 (8.875) in the SOC arm. Subjects in both treatment arms experienced an initial decline in mean HCS change from baseline. Subjects in the nivo+ipi arm returned to their baseline score at Week 33, with a trend for improvement thereafter, however the changes were less than the MID (6 points).

Subjects in the SOC arm had a sustained decrease in the range of -3 to -5 points through Week 93, which was less than the MID.

Figure 22 Mean changes in HCS score from baseline – All randomized subjects



Error bars represent standard error for the mean.

Horizontal reference line indicates a minimally important difference (MID), considered a change ≥ 6 points from baseline.

HCS=Hepatobiliary Cancer Subscale

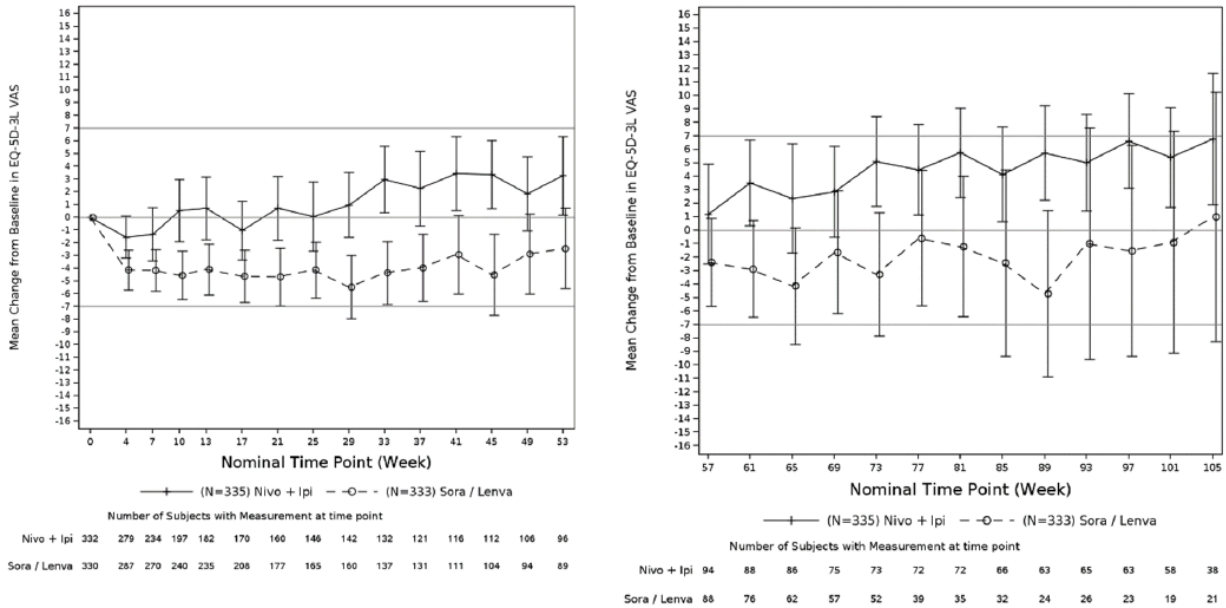
Only time points where data available for ≥5 subjects in each treatment arm are plotted.

A greater proportion of subjects in the SOC arm experienced at least a 6-point decrease from baseline in HCS subscale score as compared to subjects in the nivo+ipi arm. Through Week 105, which was the time point where there were still at least 5 subjects in each arm, the proportion of subjects in the nivo+ipi arm who had at least a 6-point decrease from baseline ranged from 7.9% to 31.5%, while the range for the SOC arm was 31.4% to 48.6%.

EQ-5D-3L Utility Index and Visual Analog Scale

The EQ-5D-3L questionnaire completion rates were >99% in both the nivo+ipi and SOC arms, at baseline, and >85% for most weeks during the treatment period. Completion rates ranged from 56.7% to 76.7% during Follow-Up Visits 1 & 2, and were in general <60% during Survival Follow-Up Visits.

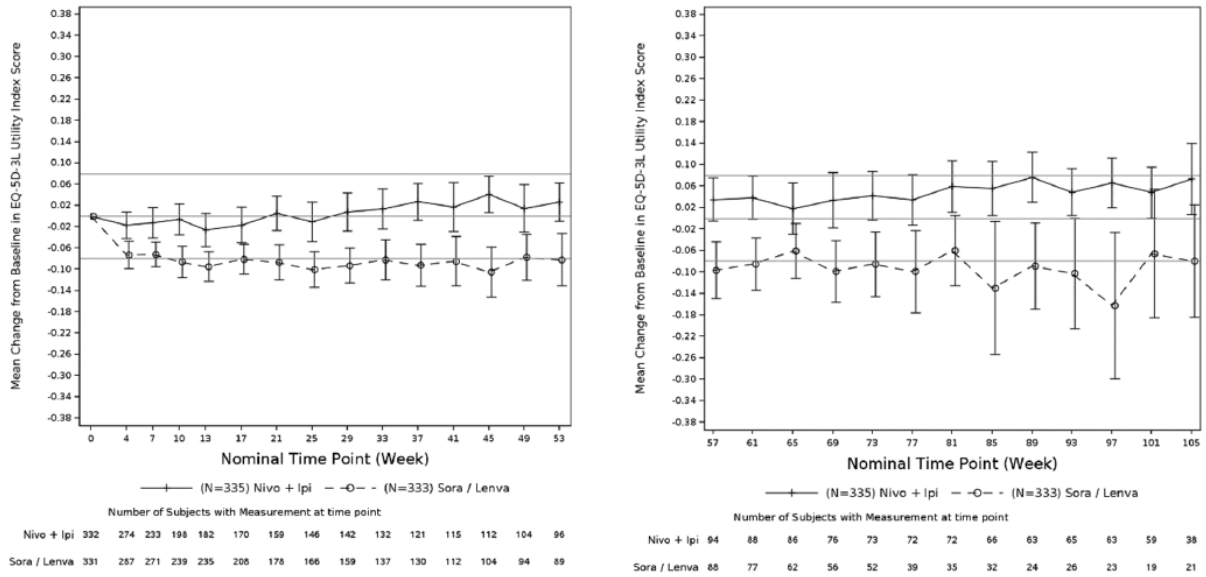
Figure 23 Mean changes in overall self-rated health status EQ-VAS from baseline – All randomized subjects



Error bars represent standard error for the mean.
Horizontal reference line indicates a minimally important difference (MID), considered a change of ≥ 7 from baseline.
Only time points where data available for ≥5 subjects in each treatment arm are plotted.

Mean (SD) baseline EQ-5D-3L health utility index scores were 0.8268 (0.19841) and 0.8345 (0.21862) in the nivo+ipi and SOC arms, respectively. Subjects in the nivo+ipi had relatively stable EQ-5D utility index scores during the treatment period, with mean changes less than the MID of 0.08 points. Subjects in the SOC had a trend for worsening, with decreases from baseline exceeding the MID starting at Week 10.

Figure 24 Mean changes in EQ-5D-3L Utility Index Score from Baseline – All randomized subjects



Error bars represent standard error for the mean.

Horizontal reference line indicates a minimally important difference (MID), considered a change of ≥ 0.08 from baseline.

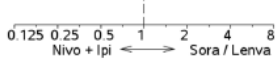
Only time points where data available for ≥5 subjects in each treatment arm are plotted.

Ancillary analyses

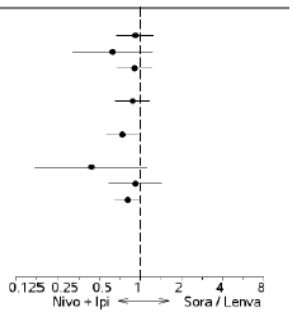
Subgroup analysis of Overall Survival

Figure 25 Forest Plot of Treatment Effect on Overall Survival in Subsets - All Randomized Subjects

	N	Nivolumab + Ipilimumab N of Events (N of Subjects)	Nivolumab + Ipilimumab mOS (95% CI)	Sorafenib / Lenvatinib N of Events (N of Subjects)	Sorafenib / Lenvatinib mOS (95% CI)	Hazard Ratio (1) (95% CI) [a] Nivo + Ipi vs. Sora / Lenva
Overall	668	194 (335)	23.66 (18.83, 29.44)	228 (333)	20.63 (17.48, 22.54)	0.79 (0.65, 0.96)
Age categorization						
< 65	311	88 (162)	26.81 (22.97, 32.99)	98 (149)	22.74 (19.12, 26.15)	0.78 (0.58, 1.04)
65 - < 75	249	78 (126)	18.73 (15.67, 24.54)	85 (123)	19.15 (15.34, 21.95)	0.86 (0.63, 1.17)
75 - < 85	100	25 (43)	27.14 (9.33, N.A.)	44 (57)	16.72 (10.28, 22.28)	0.63 (0.38, 1.03)
>= 65	357	106 (173)	18.83 (15.67, 27.14)	130 (184)	18.17 (15.64, 21.45)	0.81 (0.63, 1.05)
>= 75	108	28 (47)	25.92 (9.30, N.A.)	45 (61)	17.35 (11.83, 22.54)	0.72 (0.45, 1.15)
>= 85	8	3 (4)	8.71 (2.53, N.A.)	1 (4)	N.A. (17.08, N.A.)	N.A.
Sex						
Male	548	162 (271)	22.97 (17.87, 29.31)	190 (277)	21.06 (17.84, 22.97)	0.83 (0.68, 1.03)
Female	120	32 (64)	26.87 (19.61, N.A.)	38 (56)	17.25 (11.60, 23.29)	0.63 (0.39, 1.00)
Race						
White	353	118 (179)	18.30 (14.39, 24.77)	132 (174)	17.74 (15.34, 21.06)	0.84 (0.65, 1.07)
Black or African American	15	7 (11)	19.94 (4.67, N.A.)	4 (4)	22.98 (20.50, N.A.)	N.A.
Native Hawaiian or Other Pacific Islander	1	0 (1)	N.A.	0 (0)	N.A.	N.A.
Asian	292	68 (140)	34.00 (23.13, N.A.)	90 (152)	21.95 (18.17, 30.00)	0.73 (0.53, 1.00)
Asian Indian	3	1 (3)	N.A. (24.84, N.A.)	0 (0)	N.A.	N.A.
Chinese	164	43 (76)	25.30 (18.73, 44.42)	63 (88)	15.80 (12.78, 21.22)	0.64 (0.43, 0.94)
Japanese	56	8 (25)	N.A. (16.89, N.A.)	15 (31)	32.00 (20.90, N.A.)	0.64 (0.27, 1.50)
Asian Other	69	16 (36)	N.A. (14.75, N.A.)	12 (33)	39.00 (21.82, N.A.)	1.27 (0.60, 2.68)
Other	7	1 (4)	N.A. (20.34, N.A.)	2 (3)	31.70 (4.90, N.A.)	N.A.
Region						
North America	20	11 (15)	17.87 (5.42, 33.48)	4 (5)	8.08 (1.38, N.A.)	N.A.
Europe	269	80 (129)	23.56 (14.39, 29.70)	102 (140)	20.63 (16.26, 22.74)	0.83 (0.62, 1.11)
Asia	280	65 (133)	34.00 (20.53, N.A.)	86 (147)	22.54 (19.12, 30.00)	0.75 (0.54, 1.03)
Rest of the Word [ROW]	99	38 (58)	18.83 (15.28, 26.87)	36 (41)	12.39 (6.44, 20.50)	0.67 (0.43, 1.06)
Baseline ECOG PS						
0	476	128 (233)	27.89 (23.13, 34.00)	157 (243)	22.54 (20.07, 25.07)	0.78 (0.62, 0.98)
1	191	66 (102)	16.43 (10.02, 22.97)	71 (89)	15.31 (10.28, 17.35)	0.78 (0.55, 1.09)
Not Reported	1	0 (0)	N.A.	0 (1)	N.A.	N.A.
Child-Pugh Score						
5	517	135 (254)	27.89 (22.97, 35.38)	167 (263)	23.23 (21.22, 25.43)	0.80 (0.64, 1.01)
6	130	50 (72)	18.30 (8.84, 25.76)	50 (58)	10.28 (5.88, 15.41)	0.61 (0.41, 0.91)
>= 7	20	9 (9)	7.06 (2.00, 17.94)	11 (11)	9.13 (1.71, 17.08)	N.A.
Not Reported	1	0 (0)	N.A.	0 (1)	N.A.	N.A.
Etiology per CRF [d]						
HBV	229	63 (114)	23.46 (18.00, 37.82)	74 (115)	22.28 (19.78, 23.98)	0.84 (0.60, 1.17)
HCV	186	43 (90)	32.99 (18.83, N.A.)	64 (96)	17.84 (14.03, 23.75)	0.68 (0.46, 1.00)
Uninfected	243	84 (124)	19.32 (15.54, 26.87)	87 (119)	18.43 (15.80, 23.29)	0.84 (0.63, 1.14)
HBV/HCV	10	4 (7)	29.44 (4.60, N.A.)	3 (3)	13.21 (5.59, N.A.)	N.A.
Etiology per central lab [b]						
HBV	197	57 (99)	23.20 (16.00, 34.00)	61 (98)	22.74 (19.78, 27.60)	0.95 (0.66, 1.36)
HCV	54	17 (27)	16.20 (4.60, 32.56)	17 (27)	17.84 (11.83, 28.85)	1.16 (0.59, 2.27)
Uninfected	417	120 (209)	25.76 (18.83, 32.99)	150 (208)	17.91 (15.54, 22.01)	0.70 (0.55, 0.89)
Vascular invasion (CRF)						
Yes	169	42 (77)	22.90 (15.18, N.A.)	68 (92)	15.41 (10.28, 20.07)	0.59 (0.40, 0.87)
No	499	152 (258)	23.89 (18.83, 29.44)	160 (241)	21.88 (19.32, 23.89)	0.89 (0.71, 1.11)
Extrahepatic spread (CRF)						
Yes	360	121 (188)	18.73 (15.64, 24.84)	127 (172)	16.56 (14.03, 20.27)	0.82 (0.64, 1.05)
No	308	73 (147)	33.48 (23.00, N.A.)	101 (161)	22.54 (20.50, 28.32)	0.72 (0.53, 0.97)
MVI/EHS (CRF)						
Yes	438	137 (221)	19.38 (16.20, 25.86)	155 (217)	17.74 (15.18, 20.90)	0.80 (0.64, 1.01)
No	230	57 (114)	33.48 (23.13, N.A.)	73 (116)	22.97 (20.27, 30.00)	0.74 (0.52, 1.04)
Baseline AFP category						
< 200 ng/ml	410	114 (209)	25.92 (19.94, 32.99)	126 (201)	23.98 (21.36, 29.93)	0.90 (0.69, 1.15)
>= 200 ng/ml	258	80 (126)	18.00 (12.55, 26.81)	102 (132)	12.78 (9.69, 16.33)	0.68 (0.50, 0.91)
< 400 ng/ml	447	122 (227)	25.92 (21.98, 33.48)	138 (220)	23.75 (21.22, 29.14)	0.86 (0.68, 1.10)
>= 400 ng/ml	221	72 (108)	16.43 (10.32, 25.53)	90 (113)	12.09 (8.67, 16.26)	0.69 (0.50, 0.95)
PD-L1 TPS status						
< 1%	281	87 (140)	19.94 (12.39, 24.84)	108 (141)	18.99 (15.64, 21.22)	0.84 (0.63, 1.12)
>= 1%	10	7 (8)	14.67 (2.10, 27.89)	2 (2)	6.39 (1.38, N.A.)	N.A.
Unknown	377	100 (187)	29.70 (20.53, 36.04)	118 (190)	21.95 (17.81, 25.43)	0.74 (0.56, 0.96)



PD-L1 CPS status						
< 1	236	77 (117)	16.33 (8.97, 24.54)	92 (119)	18.43 (15.80, 21.06)	0.92 (0.68, 1.24)
>= 1	55	17 (31)	19.94 (15.28, N.A.)	18 (24)	13.21 (8.08, 27.60)	0.63 (0.32, 1.22)
< 5	262	82 (127)	17.87 (9.33, 24.77)	103 (135)	19.15 (16.26, 21.22)	0.90 (0.68, 1.21)
>= 5	29	12 (21)	19.94 (10.51, N.A.)	7 (8)	9.81 (4.90, 23.29)	N.A.
< 10	272	87 (136)	18.83 (11.99, 24.54)	104 (136)	19.15 (15.80, 21.22)	0.88 (0.66, 1.16)
>= 10	19	7 (12)	16.20 (3.58, N.A.)	6 (7)	11.40 (6.44, 23.29)	N.A.
Unknown	377	100 (187)	29.70 (20.53, 36.04)	118 (190)	21.95 (17.81, 25.43)	0.74 (0.56, 0.96)
BCLC category at baseline						
0/A	49	9 (28)	42.58 (31.15, N.A.)	10 (21)	31.64 (11.56, N.A.)	0.44 (0.17, 1.12)
B	128	34 (61)	26.81 (15.67, 37.82)	45 (67)	22.97 (20.50, 30.55)	0.92 (0.59, 1.44)
C	488	151 (246)	20.34 (16.89, 25.76)	171 (242)	17.84 (15.54, 21.06)	0.81 (0.65, 1.01)
Unknown	3	0 (0)	N.A.	2 (3)	8.23 (4.57, N.A.)	N.A.



(a) Etiology per CRF: HBV and HCV categories included subjects with past/resolved infection.
(b) Etiology per central lab: HBV includes subjects with HBsAg positive and/or detectable HBV-DNA at randomization; HCV includes subjects with detectable HCV RNA at randomization; Subjects with past/resolved HBV and/or HCV infection categorized as "Uninfected" for stratification purpose.
mOS = median overall survival
(1) Unstratified Cox proportional hazard model. Hazard Ratio is Nivolumab + Ipilimumab over Sorafenib / Lenvatinib.

Sensitivity analyses of overall survival

Results of nivo+ipi vs SOC OS sensitivity analyses were consistent with the primary OS analysis.

- The unstratified Cox model reported an OS HR of 0.79 (95% CI: 0.65, 0.96).
- The stratified Cox model excluding subjects from Russian sites reported an OS HR of 0.78 (95% CI: 0.64, 0.95).

Table 43 Overall survival sensitivity analysis – All randomized subjects

SENSITIVITY ANALYSIS	Nivo + Ipi N = 335		Sora / Lenva N = 333		Nivo + Ipi vs Sora / Lenva	
	#EVENTS /#SUBJECTS (%)	Median OS (MONTHS) (95% CI) (1)	#EVENTS /#SUBJECTS (%)	Median OS (MONTHS) (95% CI) (1)	HR (95% CI)	p-value
UNSTRATIFIED ANALYSIS (A)	194/335 (57.9)	23.66 (18.83, 29.44)	228/333 (68.5)	20.63 (17.48, 22.54)	0.79 (0.65, 0.96)	0.0159
STRATIFIED ANALYSIS ANALYSIS USING POPULATION EXCLUDING SUBJECTS FROM RUSSIAN SITES (IRT SOURCE) (B)	186/316 (58.9)	23.89 (19.19, 29.70)	223/320 (69.7)	20.63 (17.74, 22.54)	0.78 (0.64, 0.95)	

(1) Based on Kaplan-Meier Estimates.
(A) Unstratified Cox proportional hazards model. P-value from unstratified log-rank test.
(B) Stratified Cox proportional hazards model. Stratified by Etiology (viral related-HCC vs non-viral related-HCC), Vascular invasion and/or extrahepatic spread (present or absent), Alpha-fetoprotein (AFP) (< 400 ng/mL or >= 400 ng/mL).

Supportive analyses of overall survival

The proportional hazard assumption was examined. The interaction p-value is <0.0001, which suggests a violation of the proportional hazard assumption. The following analyses were performed:

- Piecewise HR Analysis

The piecewise HR were calculated for the first 6 months (HR = 1.65 [95% CI: 1.12, 2.43]) and after 6 months (HR = 0.61 [95% CI: 0.48, 0.77]).

Table 44 Overall survival, supportive analysis – Piecewise Hazard Ratio – All randomized subjects

	Nivo + Ipi N = 335	Sora / Lenva N = 333
HR <= 6 MONTHS (1) (95% CI)	1.65 (1.12, 2.43)	
# EVENTS / # SUBJECTS AT RISK	66 / 335	42 / 333
HR > 6 MONTHS (1) (95% CI)	0.61 (0.48, 0.77)	
# EVENTS / # SUBJECTS AT RISK	128 / 264	186 / 280

- Max-Combo Test Analysis

Max-combo test result of OS for nivo+ipi vs. SOC was consistent with the primary OS analysis, HR = 0.62 (95% CI: 0.5, 0.78), descriptive p-value <0.0001.

- Restricted Mean Survival Time Analysis

The restricted mean survival time (RMST) of OS at 26 months was numerically higher in nivo+ipi arm compared with SOC arm: 17.89 (95% CI: 16.88, 18.91) vs 17.77 (95% CI: 16.84, 18.70) months. The RMST of OS at 36 months was numerically higher in nivo+ipi arm compared with SOC arm: 22.16 (95% CI: 20.70, 23.62) vs 20.80 (95% CI: 19.49, 22.11). At 47 months, when the maximum OS was approximately reached in both treatment arms and all observed OS events were captured, the RMST for OS was 25.83 months (95% CI: 23.85, 27.80) in the nivo+ipi arm compared to 23.04 months (95% CI: 21.32, 24.77) in the SOC arm, resulting in a difference of 2.78 months (95% CI: 0.16, 5.41).

Table 45 Restricted Mean Survival Time Analysis – All Randomized Subjects

	Nivo + Ipi N = 335	Sora / Lenva N = 333	
	RMST (95% CI)	RMST (95% CI)	Difference (95% CI)
26 MONTHS	17.89 (16.88, 18.91)	17.77 (16.84, 18.70)	0.12 (-1.25, 1.50)

Table 46 Restricted Mean Survival Time of Overall Survival – Extended – All Randomized Subjects

	Nivo + Ipi N = 335	Sora / Lenva N = 333	
	RMST (95% CI)	RMST (95% CI)	Difference (95% CI)
6 MONTHS	5.45 (5.31, 5.59)	5.68 (5.56, 5.79)	-0.22 (-0.40, -0.05)
12 MONTHS	9.88 (9.49, 10.27)	10.37 (10.03, 10.70)	-0.49 (-1.00, 0.02)
18 MONTHS	13.72 (13.06, 14.37)	14.12 (13.53, 14.71)	-0.40 (-1.28, 0.48)
24 MONTHS	16.92 (16.00, 17.85)	17.00 (16.15, 17.85)	-0.08 (-1.33, 1.18)
30 MONTHS	19.71 (18.51, 20.90)	19.19 (18.09, 20.28)	0.52 (-1.10, 2.14)
36 MONTHS	22.16 (20.70, 23.62)	20.80 (19.49, 22.11)	1.36 (-0.61, 3.32)

Early deaths analyses

Statistical Methodology: Method to Define Early Death

- Piecewise Cox Model

A stratified piecewise Cox regression model with treatment group as the only covariate (nivo+ipi vs SOC) was adopted to calculate HRs in different time periods for all randomized subjects. Three settings of piecewise time intervals are considered: 1) ≤13 months and > 13 months; 2) 0-3, > 3-6, > 6-9, > 9-13 and > 13 months; 3) every 1 month to 13 months, and > 13 months. According to the SAP, the stratification factors considered in the stratified analyses included etiology per central lab (viral related-HCC vs. non-viral related-HCC), vascular invasion and/or extrahepatic spread (present or absent), AFP (< 400 ng/ml or ≥ 400 ng/ml) based on data recorded in IRT. OS HR within each interval was presented along with two-sided 95% CI, ties were handled using the exact method.

This model allowed: 1) to quantify the possible early deaths, and 2) to get a preliminary estimate of the hazard crossing time points. The point estimate of the piecewise HR of death between arms was evaluated for each time interval. The HR together with the visual interpretation of the crossing of the KM curves helped to assess the presence of early death in OS and characterize the corresponding timing.

- Smoothed Hazard Curve Plots

Plots of smoothed instantaneous hazard of death for nivo+ipi vs SOC were produced for all randomized subjects.

The kernel-smoothing method was used, using Epanechnikov kernel with a bandwidth of 3 months and estimated on a grid of 100 points per month. In case of early crossing of the hazards, i.e. higher risk of death in the nivo+ipi arm vs the SOC arm followed by lower risk of death in the nivo+ipi arm vs the SOC arm, the first time point (after the first month during which estimates could be very unstable due to small number of deaths) when the hazard curves were equal was retained with a precision of 2 decimal places and defined as the timing cut-off of early death. An early death was defined as a death of a subject with a death date prior to or on the timing cut-off when hazard for the treatment arms were equal, with crossing of the hazard curves.

The timing cut-off found in all randomized subjects in the nivo+ipi arm vs SOC arm was used for all early-death analyses related to the study. The population for early-death analyses was all randomized subjects unless otherwise specified.

Results of early-death analyses

a) Definition of early deaths

- Piecewise HRs by Different Time Periods

Table 47 Piecewise Hazard Ratio of Overall Survival - All Randomized Subjects

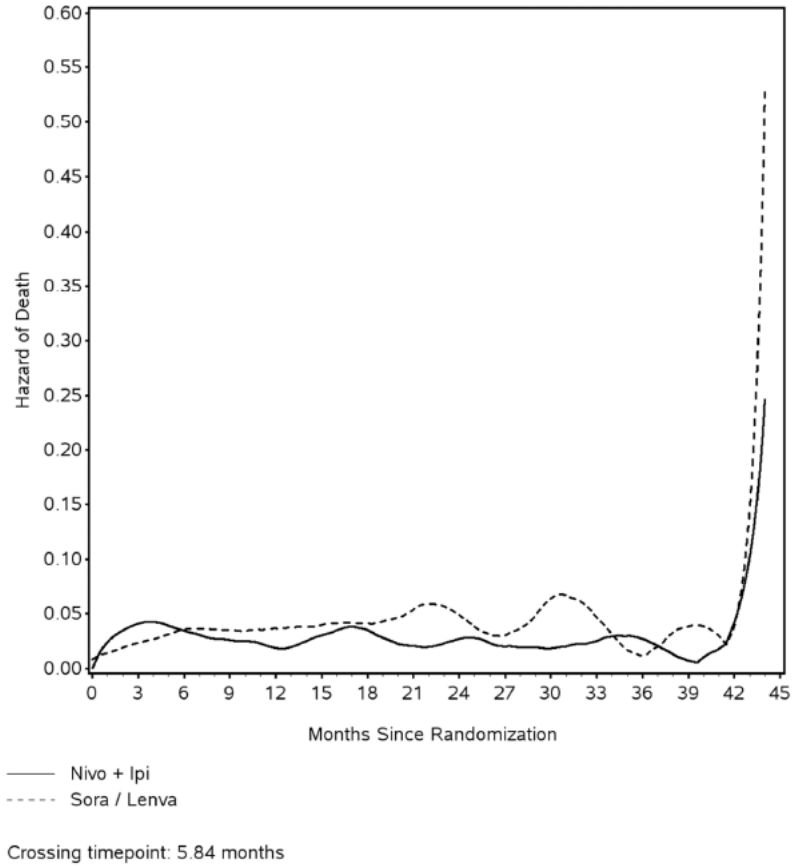
Overall Survival Interval in Months	Nivo + Ipi N = 335 # EVENTS / # SUBJECTS (%)	Sora / Lenva N = 333 # EVENTS / # SUBJECTS (%)	HR (1) (95% CI)
Split at 13 Months			
0 to <= 13	108/335 (32.2)	106/333 (31.8)	1.05 (0.80, 1.38)
> 13	86/213 (40.4)	122/207 (58.9)	0.58 (0.44, 0.77)
Split By 3 Months for the first 13 Months			
0 to <= 3	32/335 (9.6)	16/333 (4.8)	2.04 (1.12, 3.72)
> 3 to <= 6	34/300 (11.3)	26/310 (8.4)	1.40 (0.84, 2.34)
> 6 to <= 9	21/264 (8.0)	31/280 (11.1)	0.70 (0.40, 1.21)
> 9 to <= 13	21/239 (8.8)	33/245 (13.5)	0.64 (0.37, 1.10)
> 13	86/213 (40.4)	122/207 (58.9)	0.58 (0.44, 0.77)
Split Monthly for the first 13 Months			
0 to <= 1	2/335 (0.6)	3/333 (0.9)	0.65 (0.11, 3.90)
> 1 to <= 2	15/332 (4.5)	7/326 (2.1)	2.15 (0.88, 5.28)
> 2 to <= 3	15/316 (4.7)	6/318 (1.9)	2.62 (1.01, 6.75)
> 3 to <= 4	11/300 (3.7)	9/310 (2.9)	1.32 (0.54, 3.18)
> 4 to <= 5	14/289 (4.8)	10/300 (3.3)	1.50 (0.66, 3.37)
> 5 to <= 6	9/274 (3.3)	7/289 (2.4)	1.38 (0.51, 3.70)
> 6 to <= 7	9/264 (3.4)	12/280 (4.3)	0.78 (0.33, 1.84)
> 7 to <= 8	4/255 (1.6)	8/267 (3.0)	0.52 (0.16, 1.73)
> 8 to <= 9	8/247 (3.2)	11/258 (4.3)	0.74 (0.30, 1.84)
> 9 to <= 10	5/239 (2.1)	5/245 (2.0)	1.00 (0.29, 3.47)
> 10 to <= 11	7/233 (3.0)	7/238 (2.9)	1.01 (0.35, 2.89)
> 11 to <= 12	5/225 (2.2)	12/230 (5.2)	0.44 (0.15, 1.24)
> 12 to <= 13	4/220 (1.8)	9/216 (4.2)	0.41 (0.13, 1.34)
> 13	86/213 (40.4)	122/207 (58.9)	0.58 (0.44, 0.77)

(1) Stratified Cox model with a time-dependent covariate. Stratified by Etiology (viral related-HCC vs non-viral related-HCC), Vascular invasion and/or extrahepatic spread (present or absent), Alpha-fetoprotein (AFP) (< 400 ng/mL or ≥ 400 ng/mL) based on data recorded in the IRT. Hazard Ratios are Nivolumab + Ipilimumab over Sorafenib / Lenvatinib.

- Smoothed Instantaneous Hazard Curves

A plot of smoothed instantaneous hazard of death for each treatment arm was produced in all randomized subjects to define early deaths for further exploration. The first time point (after the first month) when the smoothed curves of instantaneous hazard of death for two treatment arms crossed (i.e. hazards of death were equal) was at 5.84 months, which was also consistent with results from the piecewise HRs analysis. Therefore, to investigate potential risk factors associated with the events in this period, an early death was defined as a death with date prior to or on 5.84 months after randomization (subjects censored or subjects died after 5.84 months were considered as having non-early deaths).

Figure 26 Plot of smoothed instantaneous hazard of death overtime – All randomized subjects



Kernel-smoothed estimates using Epanechnikov kernel with a bandwidth of 3 months.

b) Potential role of early discontinuations

Table 48 Overall Survival - All early discontinued subjects

	Nivo + Ipi N = 185	Sora / Lenva N = 160
TOTAL SUBJECTS WITH EARLY DISCONTINUATION	185	160
MEDIAN OS (MONTHS) (95% CI) (1)	11.04 (7.39, 15.54)	10.74 (8.25, 13.57)
SUBJECTS WITH EARLY DEATH (<=5.84 MONTHS) (%)	66 (35.7)	39 (24.4)
MEDIAN OS (MONTHS) (95% CI) (1)	3.24 (2.53, 3.71)	3.58 (2.50, 4.24)
SUBJECTS WITHOUT EARLY DEATH (%)	119 (64.3)	121 (75.6)
MEDIAN OS (MONTHS) (95% CI) (1)	23.20 (17.48, 32.56)	16.56 (12.71, 19.78)

(1) Based on Kaplan-Meier Estimates
Early discontinuation is defined as treated subjects who have discontinued the treatment and with last dose date <= 5.84 months from randomization or subject who are randomized but not treated.

Table 49 Reasons for early discontinuation of treatment - All treated subjects discontinued treatment ≤5.84 months

Status (%)	Nivo + Ipi N = 64	Sora / Lenva N = 38	Total N = 102
DISCONTINUED TREATMENT WITH EARLY DEATH	64 (100.0)	38 (100.0)	102 (100.0)
REASON FOR DISCONTINUATION OF TREATMENT			
DISEASE PROGRESSION	28 (43.8)	23 (60.5)	51 (50.0)
STUDY DRUG TOXICITY	14 (21.9)	4 (10.5)	18 (17.6)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	0	2 (5.3)	2 (2.0)
DEATH	1 (1.6)	0	1 (1.0)
ADVERSE EVENT UNRELATED TO STUDY DRUG	19 (29.7)	9 (23.7)	28 (27.5)
SUBJECT WITHDREW CONSENT	2 (3.1)	0	2 (2.0)

Status (%)	Nivo + Ipi N = 118	Sora / Lenva N = 114	Total N = 232
DISCONTINUED TREATMENT WITHOUT EARLY DEATH	118 (100.0)	114 (100.0)	232 (100.0)
REASON FOR DISCONTINUATION OF TREATMENT			
DISEASE PROGRESSION	51 (43.2)	76 (66.7)	127 (54.7)
STUDY DRUG TOXICITY	52 (44.1)	19 (16.7)	71 (30.6)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	4 (3.4)	3 (2.6)	7 (3.0)
ADVERSE EVENT UNRELATED TO STUDY DRUG	4 (3.4)	7 (6.1)	11 (4.7)
SUBJECT WITHDREW CONSENT	2 (1.7)	6 (5.3)	8 (3.4)
LOST TO FOLLOW-UP	1 (0.8)	0	1 (0.4)
MAXIMUM CLINICAL BENEFIT	0	1 (0.9)	1 (0.4)
POOR/NON-COMPLIANCE	0	1 (0.9)	1 (0.4)
OTHER	4 (3.4)	1 (0.9)	5 (2.2)

Percentages based on subjects entering period.
Subjects discontinued treatment <= 5.84 months is defined as subjects who have discontinued the treatment and with last dose date <= 5.84 months from randomization.

c) Cause of early deaths

Table 50 Early deaths - All randomized subjects

	Nivo + Ipi N = 66	Sora / Lenva N = 39
NUMBER OF SUBJECTS WITH EARLY DEATH (%)	66 (100.0)	39 (100.0)
PRIMARY REASON FOR DEATH (%)		
DISEASE	36 (54.5) (1)	31 (79.5)
STUDY DRUG TOXICITY	11 (16.7)	1 (2.6) (2)
PRIOR PD	0	0
RADIOGRAPHIC PD	0	0
NO PRIOR PD	11 (16.7)	1 (2.6)
OTHER	18 (27.3)	6 (15.4) (2)
PRIOR PD	0	2 (5.1)
RADIOGRAPHIC PD	0	1 (2.6)
NO PRIOR PD	18 (27.3)	4 (10.3)
UNKNOWN	1 (1.5)	1 (2.6) (3)
PRIOR PD	0	0
RADIOGRAPHIC PD	0	0
NO PRIOR PD	1 (1.5)	1 (2.6)

(1) Includes 2 subjects randomized but never treated
(2) All subjects received treatment with lenvatinib
(3) Includes 1 subject randomized but never treated
Early Death is defined as a subject who died prior to or on 5.84 months after randomization.
Cutoff defined based on smoothed hazard curves figure.
PRIOR PD (Progressive Disease) means progressive disease (the earliest occurrence of progression (clinical or radiographic) as assessed per investigator) had occurred before or on the death date. Otherwise NO PRIOR PD.

Table 51 Early deaths with reasons of "Study Drug Toxicity"/"Other"/ "Unknown" in the nivo+ipi and SOC arms

Early Death	Age/ Sex/ Race	Cause of Death	SAE with Fatal Outcome	Death Days Since Last Dose	Causality of SAE if Applicable	Disease Progression	Additional Comments
Nivo+Ipi Arm							
1	69/M/ C	Study drug toxicity	Immune mediated hepatitis	34	Related	Death prior to disease assessment	Viral HCC (Past HCV) Liver nodules (>3) / Distant Metastasis Grade 4 sepsis during hospitalization
2	70/M/ C	Study drug toxicity	Autoimmune hepatitis	132	Related	No	Non-viral HCC Liver nodule (<3) / PVT/ Lymph node metastasis Diagnosed with advanced cirrhosis refractory to clinical measures prior to death (Child-Pugh C) (127 days after last dose)
3	61/F/C	Study drug toxicity	Immune-mediated hepatitis	22	Related	Death prior to disease assessment	Non-viral HCC Liver nodules (<3) Distant Metastasis CT-scan performed at another hospital showed progression with necrotic lesions
4	73/M/ C	Study drug toxicity	Hepatic cirrhosis	19	Related	Death prior to disease assessment	Viral HCC (Active HCV) / Child-Pugh 7B Liver nodule (1; 180 mm) / Left portal branch vascular invasion Abdominal US: large pattern of ascitic effusion, voluminous expansive formation in the left hepatic lobe, additional focal lesions.
5	60/M/ C	Study drug toxicity	Colitis, hypovolemic shock	13	Related	Death prior to disease assessment	
6	59/M/ C	Study drug toxicity	Hepatic failure	53	Related	No	Viral HCC (Active HBV) Liver nodules (>3) / Lymph node metastasis
7	77/M/ C	Study drug toxicity	Hepatic failure/autoimmune hemolytic anemia	37	Related	Death prior to disease assessment	Non-viral HCC Liver nodules (>3) / Lymph node metastasis
8	73/M/ C	Study drug toxicity	Dysautonomia	40	Related	No	
9	72/M/ C	Study drug toxicity	Liver failure	90	Related	No	Viral HCC (Past HCV) Liver nodules (>3) Hospitalized due to decompensated liver cirrhosis prior to death event
10	54/M/ CH	Study drug toxicity	Autoimmune hepatitis	28	Related	No	Viral HCC (Active HBV) Liver nodules (>3) / PVT CT scan (one more prior to death): right lobe liver

							lesion increased in size (139 mm to 160 mm)
11	67/M/CH	Study drug toxicity	Hepatic failure	26	Related	Yes[a]	Viral HCC (Past HCV) Liver nodules (< 2) / PVT
12	53/M/C	Other	Pneumonia associated with COVID-19	28	Not related	Death prior to disease assessment	
13	69/F/C	Other	COVID-19	18	Not related	No	
14	70/M/C	Other	Pneumococcus lower lobar pneumonia	44	Not related	Death prior to disease assessment	History of cardiovascular disease, DM, Stroke CT scan: Apex-frosted glass appearance consistent with COVID-19 infection associated with right and left lower lobal lung disease SARS-COV-2 swab test negative / Pneumococcus antigen positive
15	75/M/C	Other	Septic encephalopathy	43	Not related	No	History of HTA, resection colon adenomas During hospitalization renal insufficiency, nosocomial pneumonia, Clostridium difficile colitis
16	73/M/CH	Other	Hospital acquired pneumonia	44	Not related	No	Viral HBV / History of esophageal varices Multiple hospitalizations due to hepatic decompensation (ascites) PS 1
17	68/M/C	Other	Haemoptysis	41	Not related	No	History of cirrhosis related with HBV
18	71/M/C	Other	Dyspnoea	28	Not related	Death prior to disease assessment	History of DM COVID PCR test negative
19	61/F/C	Other	COVID-19	50	Not related	No	
20	82/M/C	Other	General physical health deterioration	38	Not related	Yes[a]	
21	81/M/C	Other	Septic shock due to pulmonary infection	15	Not related	Death prior to disease assessment	History of HTA, DM
22	58/F/C	Other	Pulmonary embolism	51	Not related	No	History of cirrhosis (Active HCV)
23	82/F/CH	Other	Aspiration pneumonia	96	Not related	Death prior to disease assessment[b]	History of HTA, DM, Asthma, Chronic HCV
24	67/M/C	Other	Liver failure secondary to sepsis of respiratory focus	38	Not related	No	History of DM, Chronic liver disease
25	85/M/C	Other	Sepsis	50	Not related	Death prior to disease assessment[c]	History of HTA, Cirrhosis, Stroke On palliative care (nursing home)

26	80/M/JA	Other	Acute circulatory insufficiency	39	Not related	No	History of HTA, Hypercholesterolemia, Hypertriglyceridemia, Chronic liver disease Sepsis diagnosis during hospitalization
27	71/M/CH	Other	COVID-19 pneumonia	20	Not related	Death prior to disease assessment	
28	70/M/C	Other	Pertrochanteric fracture of the right femur	26	Not related	No	
29	65/M/C	Other	Severe hyponatremia	79	Not related	No	History of Hemochromatosis, Diabetic Neuropathy
30	72/M/C	Unknown	Death due to unknown cause	16	Not related	Death prior to disease assessment	Death at home (cause unknown)
SOC Arm							
1	72/M/CH	Study Drug Toxicity	Hepatorenal syndrome	9	Related	No	
2	66/M/CH	Other	Pneumonia	10	Not related	Yes (Clinical)	
3	71/M/C	Other	Hepatorenal syndrome	24	Not related	No	
4	53/F/C	Other	Septic shock + cholangitis	18	Not related	Yes	
5	59/M/C	Other	Aspiration pneumonia	2	Not related	Yes[a]	
6	82/M/C	Other	Pneumonia	75	Not related	Death prior to disease assessment[c]	
7	58/M/C	Other	Septic shock	4	Not related	No	
8	61/M/C	Unknown	Unknown	Never treated	Not related	Death prior to disease assessment[d]	

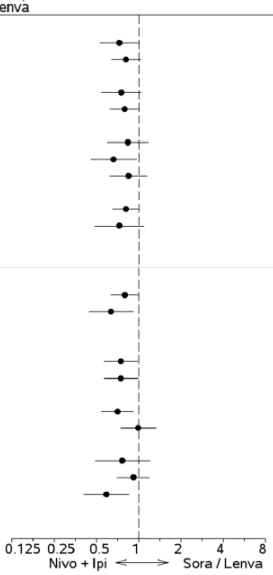
a Progressive disease per BICR. This case was categorized as a case without prior progression per investigator in Table 3.3 2.
b Unable to determine as subject withdrew before 1st CT assessment
c Unable to determine without specific reason other than no on-study tumor assessment
d Unable to determine as subject was never treated

Deaths may be captured on death, adverse event, ECOG performance status, subject status, clinical complaints and follow-up case report form pages.
The primary source of Death date is the death case report form.
Early Death is defined as a subject who died prior to or on 5.84 months after randomization.
Cutoff defined based on smoothed hazard curves figure.
Sex: F=Female; M=Male
Race: C=White; CH=Chinese; JA=Japanese

d) Subgroup analyses for overall survival

Figure 27 Forest Plot of Treatment Effect on Overall Survival in Subgroups (not included in the CA2099DW Primary CSR) - All Randomized Subjects

	N	Nivolumab + Ipilimumab N of Events (N of Subjects)	Nivolumab + Ipilimumab mOS (95% CI)	Sorafenib / Lenvatinib N of Events (N of Subjects)	Sorafenib / Lenvatinib mOS (95% CI)	Hazard Ratio (1) (95% CI) Nivo + Ipi vs. Sora / Lenva
Race						
Asian	292	68 (140)	34.00 (23.13, N.A.)	90 (152)	21.95 (18.17, 30.00)	0.73 (0.53, 1.00)
non-Asian	376	126 (195)	19.38 (16.00, 26.64)	138 (181)	18.99 (15.61, 21.36)	0.81 (0.64, 1.03)
Region						
Asia	280	65 (133)	34.00 (20.53, N.A.)	86 (147)	22.54 (19.12, 30.00)	0.75 (0.54, 1.03)
non-Asia	388	129 (202)	20.34 (16.23, 26.81)	142 (186)	18.43 (15.61, 21.22)	0.79 (0.62, 1.00)
Etiology per CRF (A)						
HBV	229	63 (114)	23.46 (18.00, 37.82)	74 (115)	22.28 (19.78, 23.98)	0.84 (0.60, 1.17)
HCV	196	47 (97)	32.99 (19.94, N.A.)	67 (99)	17.84 (13.21, 22.01)	0.66 (0.45, 0.96)
Uninfected	243	84 (124)	19.32 (15.54, 26.87)	87 (119)	18.43 (15.80, 23.29)	0.84 (0.63, 1.14)
BCLC Category at Baseline						
C	488	151 (246)	20.34 (16.89, 25.76)	171 (242)	17.84 (15.54, 21.06)	0.81 (0.65, 1.01)
non-C	177	43 (89)	33.48 (23.13, N.A.)	55 (88)	27.14 (20.67, 31.28)	0.72 (0.49, 1.08)
Unknown	3	0 (0)	N.A.	2 (3)	8.23 (4.57, N.A.)	N.A.
Child-Pugh Score						
5	517	135 (254)	27.89 (22.97, 35.38)	167 (263)	23.23 (21.22, 25.43)	0.80 (0.64, 1.01)
> 5	150	59 (81)	16.20 (7.06, 21.98)	61 (69)	10.28 (6.74, 14.16)	0.64 (0.44, 0.92)
Not Reported	1	0 (0)	N.A.	0 (1)	N.A.	N.A.
ALBI Grade [a]						
1	396	90 (186)	35.38 (23.89, N.A.)	128 (210)	23.23 (21.36, 28.29)	0.75 (0.57, 0.98)
> 1	272	104 (149)	16.89 (12.55, 22.97)	100 (123)	14.03 (11.14, 16.56)	0.75 (0.57, 0.99)
Number of Liver Nodules						
<= 3	395	109 (208)	30.03 (23.66, 36.04)	119 (187)	21.45 (17.35, 23.66)	0.71 (0.54, 0.92)
> 3	273	85 (127)	16.99 (14.52, 22.90)	109 (146)	19.71 (16.26, 21.82)	1.00 (0.75, 1.32)
Baseline Tumor Burden per INV						
Small: < 40	161	34 (78)	42.58 (25.53, N.A.)	44 (83)	28.29 (20.50, 39.00)	0.77 (0.49, 1.20)
Medium: >= 40 and < 125	348	112 (185)	23.00 (16.43, 27.89)	109 (163)	22.54 (19.71, 23.98)	0.92 (0.70, 1.19)
Large: >= 125	158	48 (72)	16.99 (12.55, 26.81)	74 (86)	13.08 (8.94, 15.80)	0.59 (0.41, 0.85)
Not Reported	1	0 (0)	N.A.	1 (1)	1.71 (N.A., N.A.)	N.A.



a Based on ALBI Score, defined as -0.085 x (albumin g/L) + 0.66 x [log]_10(TBil µmol/L). ALBI Grade 1 if ALBI Score ≤ -2.60, ALBI Grade >1 otherwise.
mOS = median overall survival
HR is not computed for subset category with 10 or less subjects per treatment group.
(1) Unstratified Cox proportional hazard model. Hazard Ratio is Nivolumab + Ipilimumab over Sorafenib / Lenvatinib.
(A) Etiology per CRF: HBV and HCV categories included subjects with past/resolved infection. 10 HBV-HCV co-infection subjects based on CRF are categorized to into HCV.

e) Baseline variables with imbalance in early deaths

There were five baseline demographic and disease variables with imbalance ≥10% in at least one of their subgroups among early-death subjects between the nivo+ipi and SOC arms.

Table 52 Variables with Imbalance in Early-Death Subjects Between Nivolumab + Ipilimumab and SOC Arms

Age (< 65, ≥ 65)
Vascular invasion per CRF (Yes, No)
Child-Pugh Score (5 & not reported, >5)
Baseline AFP category (<400 ng/ml, ≥400 ng/ml)
Baseline tumor burden per Investigator (sum of target lesion diameter per Investigator, Small & Unknown: < 40mm or unknown, Medium: ≥ 40 mm and < 125mm, Large: ≥ 125 mm)

Table 53 Summary of Prevalence of Subgroups Defined by Identified Baseline Variables - All Randomized Subjects

		Nivo + Ipi Arm N=335		SOC Arm N=333	
Parameter	**Subgroup Category**	**Early Death n=66**	**Non-Early Death n=269**	**Early Death n=39**	**Non-Early Death n=294**
Overall		66/335 (19.7)	269/335 (80.3)	39/333 (11.7)	294/333 (88.3)
Age	< 65	25/ 66 (37.9)	137/269 (50.9)	19/ 39 (48.7)	130/294 (44.2)
	≥ 65	41/ 66 (62.1)	132/269 (49.1)	20/ 39 (51.3)	164/294 (55.8)
Vascular Invasion (CRF)	Yes	20/ 66 (30.3)	57/269 (21.2)	20/ 39 (51.3)	72/294 (24.5)
	No	46/ 66 (69.7)	212/269 (78.8)	19/ 39 (48.7)	222/294 (75.5)
Child-Pugh Score	5 & Not Reported	40/ 66 (60.6)	214/269 (79.6)	16/ 39 (41.0)	248/294 (84.4)
	> 5	26/ 66 (39.4)	55/269 (20.4)	23/ 39 (59.0)	46/294 (15.6)
Baseline AFP Category	< 400 ng/mL	34/ 66 (51.5)	193/269 (71.7)	15/ 39 (38.5)	205/294 (69.7)
	≥ 400 ng/mL	32/ 66 (48.5)	76/269 (28.3)	24/ 39 (61.5)	89/294 (30.3)
Baseline tumor burden per Investigator (sum of target lesion diameter per Investigator)	Small & Unknown: < 40 or Unknown	8/ 66 (12.1)	70/269 (26.0)	4/ 39 (10.3)	80/294 (27.2)
	Medium: ≥40 and < 125	37/ 66 (56.1)	148/269 (55.0)	16/ 39 (41.0)	147/294 (50.0)
	Large: ≥ 125	21/ 66 (31.8)	51/269 (19.0)	19/ 39 (48.7)	67/294 (22.8)

Percentages for OVERALL are based on N. Percentages for subsets are based on n.
Early Death is defined as a subject who died prior to or on 5.84 months after randomization.
Cutoff defined based on smoothed hazard curves figure.

Table 54 Baseline disease characteristics summary – All early death subjects vs. all randomized subjects

		Early Death N=105			All Randomized N=668		
Parameter	**Subgroup Category**	**NIVO+IPI n=66**	**SOC n=39**	**Total n=105**	**NIVO+IPI n=335**	**SOC n=333**	**Total N=668**
Age	< 65	25 (37.9)	19 (48.7)	44 (41.9)	162 (48.4)	149 (44.7)	311 (46.6)
	≥ 65	41 (62.1)	20 (51.3)	61 (58.1)	173 (51.6)	184 (55.3)	357 (53.4)
Sex	Male	58 (87.9)	31 (79.5)	89 (84.8)	271 (80.9)	277 (83.2)	548 (82.0)
	Female	8 (12.1)	8 (20.5)	16 (15.2)	64 (19.1)	56 (16.8)	120 (18.0)
Race	Asian	19 (28.8)	14 (35.9)	33 (31.4)	140 (41.8)	152 (45.6)	292 (43.7)
	Non-Asian	47 (71.2)	25 (64.1)	72 (68.6)	195 (58.2)	181 (54.4)	376 (56.3)
Region	Asia	18 (27.3)	14 (35.9)	32 (30.5)	133 (39.7)	147 (44.1)	280 (41.9)
	Non-Asia	48 (72.7)	25 (64.1)	73 (69.5)	202 (60.3)	186 (55.9)	388 (58.1)
Etiology per CRF (A)	HBV	19 (28.8)	11 (28.2)	30 (28.6)	114 (34.0)	115 (34.5)	229 (34.3)
	HCV	20 (30.3)	13 (33.3)	33 (31.4)	97 (29.0)	99 (29.7)	196 (29.3)
	Uninfected	27 (40.9)	15 (38.5)	42 (40.0)	124 (37.0)	119 (35.7)	243 (36.4)
Etiology per Central Lab	HBV	16 (24.2)	10 (25.6)	26 (24.8)	99 (29.6)	98 (29.4)	197 (29.5)
	HCV	8 (12.1)	3 (7.7)	11 (10.5)	27 (8.1)	27 (8.1)	54 (8.1)
	Uninfected	42 (63.6)	26 (66.7)	68 (64.8)	209 (62.4)	208 (62.5)	417 (62.4)
MVI (CRF)	Yes	20 (30.3)	20 (51.3)	40 (38.1)	77 (23.0)	92 (27.6)	169 (25.3)
	No	46 (69.7)	19 (48.7)	65 (61.9)	258 (77.0)	241 (72.4)	499 (74.7)
EHS	Yes	44 (66.7)	29 (74.4)	73 (69.5)	188 (56.1)	172 (51.7)	360 (53.9)
	No	22 (33.3)	10 (25.6)	32 (30.5)	147 (43.9)	161 (48.3)	308 (46.1)
ECOG PS	0 & NR	38 (57.6)	21 (53.8)	59 (56.2)	233 (69.6)	244 (73.3)	477 (71.4)
	1	28 (42.4)	18 (46.2)	46 (43.8)	102 (30.4)	89 (26.7)	191 (28.6)
Baseline BCLC category	C	52 (78.8)	34 (87.2)	86 (81.9)	246 (73.4)	242 (72.7)	488 (73.1)
	Non-C & Unknown	14 (21.2)	5 (12.8)	19 (18.1)	89 (26.6)	91 (27.3)	180 (26.9)
Child-Pugh Score	5 & Not Reported	40 (60.6)	16 (41.0)	56 (53.3)	254 (75.8)	264 (79.3)	518 (77.5)
	> 5	26 (39.4)	23 (59.0)	49 (46.7)	81 (24.2)	69 (20.7)	150 (22.5)
Baseline AFP Category	< 400 ng/mL	34 (51.5)	15 (38.5)	49 (46.7)	227 (67.8)	220 (66.1)	447 (66.9)
	≥ 400 ng/mL	32 (48.5)	24 (61.5)	56 (53.3)	108 (32.2)	113 (33.9)	221 (33.1)
ALBI Grade	1	26 (39.4)	13 (33.3)	39 (37.1)	186 (55.5)	210 (63.1)	396 (59.3)
	> 1	40 (60.6)	26 (66.7)	66 (62.9)	149 (44.5)	123 (36.9)	272 (40.7)
Number of Liver Nodules	≤ 3	35 (53.0)	22 (56.4)	57 (54.3)	208 (62.1)	187 (56.2)	395 (59.1)
	> 3	31 (47.0)	17 (43.6)	48 (45.7)	127 (37.9)	146 (43.8)	273 (40.9)
Baseline Tumor Burden per INV	Small & Unknown: < 40 mm or Unknown	8 (12.1)	4 (10.3)	12 (11.4)	78 (23.3)	84 (25.2)	162 (24.3)
	Medium: ≥ 40 mm and < 125 mm	37 (56.1)	16 (41.0)	53 (50.5)	185 (55.2)	163 (48.9)	348 (52.1)
	Large: ≥ 125 mm	21 (31.8)	19 (48.7)	40 (38.1)	72 (21.5)	86 (25.8)	158 (23.7)

(A) 10 HBV-HCV co-infection subjects are categorized into HCV.
NR: Not Reported
Early death is defined as subject who died prior to or on 5.84 months after randomization.

f) Risk factors associated with early death

In the univariate models, the identified potential risk factors (with p-value <0.15 for treatment-by-covariate interaction) for early death included age (<65 vs. ≥65), gender (male vs. female), vascular invasion per CRF (Yes vs. No), and Child-Pugh score (5 and not reported vs. >5).

Table 55 Univariate Logistic Regression - Death Occurring ≤ 5.84 Months from Randomization Including Treatment, One Risk Factor and its Interaction with Treatment - All Randomized Subjects

		Nivolumab + Ipilimumab	Sorafenib / Lenvatinib	Nivolumab + Ipilimumab vs Sorafenib / Lenvatinib		
Subgroup	N	Total Subjects With an Event (N Subjects)	Total Subjects With an Event (N Subjects)	Odds Ratio (95% Wald CI)	P-value	Test for Interaction P-value
AGE CATEGORIZATION					0.428	0.107
< 65	311	25 (162)	19 (149)	1.25 (0.66, 2.37)		
≥ 65	357	41 (173)	20 (184)	2.55 (1.42, 4.56)		
GENDER					0.535	0.116
MALE	548	58 (271)	31 (277)	2.16 (1.35, 3.47)		
FEMALE	120	8 (64)	8 (56)	0.86 (0.30, 2.46)		
VASCULAR INVASION (CRF)					<0.001	0.133
YES	169	20 (77)	20 (92)	1.26 (0.62, 2.57)		
NO	499	46 (258)	19 (241)	2.54 (1.44, 4.47)		
CHILD-PUGH SCORE CATEGORIZATION					<0.001	0.016
5 & NR	518	40 (254)	16 (264)	2.90 (1.58, 5.32)		
> 5	150	26 (81)	23 (69)	0.95 (0.48, 1.87)		

Odds Ratios and p-values based on univariate logistic model
Reference level for baseline covariates are Age < 65; Gender Female; Vascular invasion No from CRF; Child-Pugh Score =5 & NR
NR: Not Reported;

However, in each of the subgroups of the four factors, there were some imbalances between nivo+ipi and SOC in other baseline characteristics. Multivariate analyses were performed to adjust other covariates for reducing confounding effects.

Table 56 Multivariate Logistic Regression - Death Occurring in ⩽ 5.84 Months from Randomization - Risk Factors in All Randomized Subjects in the Nivolumab + Ipilimumab Arm

	Odds Ratio (95% Wald CI)	P-value
AGE CATEGORIZATION (≥ 65, REFERENCE= < 65)	1.76 (0.96, 3.25)	0.068
RACE CATEGORIZATION (ASIAN, REFERENCE = NON-ASIAN)	0.54 (0.29, 1.01)	0.055
VASCULAR INVASION (CRF) (YES, REFERENCE = NO)	2.01 (0.95, 4.23)	0.067
EXTRAHEPATIC SPREAD PRESENT (CRF) (YES, REFERENCE = NO)	2.81 (1.14, 6.93)	0.025
BASELINE ECOG PS CATEGORIZATION (≥ 1, REFERENCE = 0 & NR)	2.03 (1.03, 4.03)	0.042
BCLC CATEGORY AT BASELINE (C, REFERENCE = NON-C & UNKNOWN)	0.34 (0.11, 1.08)	0.068
CHILD-PUGH SCORE CATEGORIZATION (> 5, REFERENCE = 5 & NR)	1.52 (0.75, 3.09)	0.246
BASELINE AFP CATEGORY (≥ 400 NG/ML, REFERENCE = < 400 NG/ML)	2.31 (1.27, 4.21)	0.006
ALBI GRADE AT BASELINE CATEGORIZATION (> 1, REFERENCE = 1)	1.75 (0.90, 3.40)	0.097
NUMBER OF LIVER NODULES CATEGORIZATION (> 3, REFERENCE = <= 3)	1.84 (1.01, 3.34)	0.047

P-values and odds ratios from multivariate logistic regression model.
Prognostic covariates identified using backward selection method (SLSTAY=0.25).
Covariates considered include Age (ref= <65); Gender (ref = Female); Race (ref= Non-Asian); Etiology per CRF (ref = Uninfected);
Etiology per central lab (ref= Uninfected); Vascular invasion from CRF (ref= No); Extrahepatic spread present from CRF (ref= No);
Baseline ECOG PS (ref= 0 & NR); BCLC category at baseline (ref= Non-C & Unknown); Child-Pugh Score (ref= 5 & NR);
Baseline AFP category (ref= <400 ng/ml); ALBI Grade at baseline (ref= 1); Number of liver nodules (ref= <=3);
Baseline tumor burden per INV (ref= Small/Medium & Unknown).
NR: Not Reported.

Table 57 Multivariate Logistic Regression - Death Occurring in ⩽ 5.84 Months from Randomization - Risk Factors in All Randomized Subjects in the SOC Arm

	Odds Ratio (95% Wald CI)	P-value
VASCULAR INVASION (CRF) (YES, REFERENCE = NO)	1.95 (0.88, 4.30)	0.099
EXTRAHEPATIC SPREAD PRESENT (CRF) (YES, REFERENCE = NO)	2.18 (0.95, 5.04)	0.067
BASELINE ECOG PS CATEGORIZATION (≥ 1, REFERENCE = 0 & NR)	1.64 (0.75, 3.59)	0.218
CHILD-PUGH SCORE CATEGORIZATION (> 5, REFERENCE = 5 & NR)	3.50 (1.40, 8.75)	0.007
BASELINE AFP CATEGORY (≥ 400 NG/ML, REFERENCE = < 400 NG/ML)	2.63 (1.22, 5.70)	0.014
ALBI GRADE AT BASELINE CATEGORIZATION (> 1, REFERENCE = 1)	1.82 (0.73, 4.56)	0.200
BASELINE TUMOR BURDEN PER INV (LARGE: ≥ 125, REFERENCE = SMALL/MEDIUM & UNKNOWN: < 125 OR UNKNOWN)	1.77 (0.81, 3.86)	0.150

P-values and odds ratios from multivariate logistic regression model.
Prognostic covariates identified using backward selection method (SLSTAY=0.25).
Covariates considered include Age (ref= <65); Gender (ref = Female); Race (ref= Non-Asian); Etiology per CRF (ref = Uninfected); Etiology per central lab (ref= Uninfected); Vascular invasion from CRF (ref= No); Extrahepatic spread present from CRF (ref= No); Baseline ECOG PS (ref= 0 & NR); BCLC category at baseline (ref= Non-C & Unknown); Child-Pugh Score (ref= 5 & NR); Baseline AFP category (ref= <400 ng/ml); ALBI Grade at baseline (ref= 1); Number of liver nodules (ref= <=3); Baseline tumor burden per INV (ref= Small/Medium & Unknown).
NR: Not Reported.

The multivariate results identified no potential risk factors based on the prespecified threshold 0.15 (all p-values of the treatment interaction terms > 0.15). For age and Child-Pugh score covariates, the p-values of their treatment interaction terms were close to 0.15: p =0.169 for age by treatment interaction, p = 0.179 for Child-Pugh score by treatment interaction. All the other interaction terms had p-value >0.5. To further characterize age and Child-Pugh score, a multivariate logistic regression model was produced to include only their interaction terms with treatment while adjusting other baseline covariates.

Table 58 Multivariate Logistic Regression - Death Occurring in ⩽ 5.84 Months from Randomization - Risk Factors in All Randomized Subjects - Focusing on Age and Child-Pugh by Treatment Interactions

			No. of Early Death/ No. Randomized Subjects	
	Odds Ratio (95% Wald CI)	P-value	Nivolumab + Ipilimumab	Sorafenib / Lenvatinib
TREATMENT (NIVOLUMAB + IPILIMUMAB, REFERENCE = SORAFENIB / LENVATINIB)		0.020		
TREATMENT * AGE CATEGORIZATION		0.121		
TREATMENT * CHILD-PUGH SCORE CATEGORIZATION		0.071		
TREATMENT (NIVOLUMAB + IPILIMUMAB, REFERENCE = SORAFENIB / LENVATINIB) AT AGE CATEGORIZATION VALUE < 65, AT CHILD-PUGH SCORE CATEGORIZATION VALUE 5 & NR	1.95 (0.87, 4.34)		16/127	8/123
AT AGE CATEGORIZATION VALUE < 65, AT CHILD-PUGH SCORE CATEGORIZATION VALUE > 5	0.78 (0.30, 2.05)		9/ 35	11/ 26
AT AGE CATEGORIZATION VALUE ≥ 65, AT CHILD-PUGH SCORE CATEGORIZATION VALUE 5 & NR	4.20 (1.89, 9.31)		24/127	8/141
AT AGE CATEGORIZATION VALUE ≥ 65, AT CHILD-PUGH SCORE CATEGORIZATION VALUE > 5	1.69 (0.72, 3.93)		17/ 46	12/ 43
AGE CATEGORIZATION (≥ 65, REFERENCE= < 65)		0.334		
RACE CATEGORIZATION (ASIAN, REFERENCE = NON-ASIAN)		0.057		
VASCULAR INVASION (CRF) (YES, REFERENCE = NO)		0.010		
EXTRAHEPATIC SPREAD PRESENT (CRF) (YES, REFERENCE = NO)		0.005		
BASELINE ECOG PS CATEGORIZATION (≥ 1, REFERENCE = 0 & NR)		0.028		
BCLC CATEGORY AT BASELINE (C, REFERENCE = NON-C & UNKNOWN)		0.048		
CHILD-PUGH SCORE CATEGORIZATION (> 5, REFERENCE = 5 & NR)		0.004		
BASELINE AFP CATEGORY (≥ 400 NG/ML, REFERENCE = < 400 NG/ML)		<0.001		
ALBI GRADE AT BASELINE CATEGORIZATION (> 1, REFERENCE = 1)		0.040		
NUMBER OF LIVER NODULES CATEGORIZATION (> 3, REFERENCE = <= 3)		0.023		
BASELINE TUMOR BURDEN PER INV (LARGE: ≥ 125, REFERENCE = SMALL/MEDIUM & UNKNOWN: < 125 OR UNKNOWN)		0.090		

Prognostic covariates identified within each arm using backward selection method (SLSTAY=0.25).
Covariates with p-value < 0.15 and selected treatment arm by covariate interaction effects included.
P-values and odds ratios from multivariate logistic regression model.
Covariates considered include Age (ref= <65); Race (ref= Non-Asian); Vascular invasion from CRF (ref= No); Extrahepatic spread present from CRF (ref= No); Baseline ECOG PS (ref= 0 & NR); BCLC category at baseline (ref= Non-C & Unknown); Child-Pugh Score (ref= 5 & NR); Baseline AFP category (ref= <400 ng/ml); ALBI Grade at baseline (ref= 1); Number of liver nodules (ref= <=3); Baseline tumor burden per INV (ref= Small/Medium & Unknown).
NR: Not Reported.

The results of the multivariate logistic model suggested that subjects with age ≥ 65 and Child-Pugh score = 5 may have increased risk of early death in the nivo+ipi arm compared with the SOC arm. However, the small number of events may limit the interpretability of the results. In addition, there is a lack of biological plausibility and/or clinical rationale to interpret the observed association, suggesting that such result might be due to chance or other unobserved covariates. Thus, additional analyses to further investigate the potential role of liver function were performed.

Child-Pugh score is a measure reflecting liver function status, with Child-Pugh score = 5 indicating a better status than Child-Pugh score >5; however, according to the MAH some evidence suggests that the Child-Pugh classification may not fully capture more subtle heterogeneity in liver functional reserve, particularly within the same Child-Pugh class, and it is not considered a reliable measurement of liver function in non-cirrhotic patients. Thus, to check the robustness of the findings, the MAH examined whether another liver function measure, ALBI grade (that has shown prognostic superiority over Child-Pugh classification and better discrimination within Child-Pugh class: A5 vs A6), can lead to similar results. ALBI grade = 1 suggests a better liver function status than ALBI grade >1.

With the same approach except from removing Child-Pugh-by-treatment interaction, the full model identified age-by-treatment and ALBI-by-treatment as the top two interaction terms, although none of their p-value was <0.15. A model was examined by including only these two interaction terms and other baseline covariates.

Table 59 Multivariate Logistic Regression - Death Occurring in ⩽ 5.84 Months from Randomization - Risk Factors in All Randomized Subjects - Focusing on Age and ALBI by Treatment Interactions

	Odds Ratio (95% Wald CI)	P-value	No. of Early Death/ No. Randomized Subjects	
			Nivolumab + Ipilimumab	Sorafenib / Lenvatinib
TREATMENT (NIVOLUMAB + IPILIMUMAB, REFERENCE = SORAFENIB / LENVATINIB)		0.004		
TREATMENT * AGE CATEGORIZATION		0.131		
TREATMENT * ALBI GRADE AT BASELINE CATEGORIZATION		0.347		
TREATMENT (NIVOLUMAB + IPILIMUMAB, REFERENCE = SORAFENIB / LENVATINIB) AT AGE CATEGORIZATION VALUE < 65, AT ALBI GRADE AT BASELINE CATEGORIZATION VALUE 1	1.79 (0.75, 4.25)		10/ 99	6/105
AT AGE CATEGORIZATION VALUE < 65, AT ALBI GRADE AT BASELINE CATEGORIZATION VALUE > 1	1.12 (0.47, 2.66)		15/ 63	13/ 44
AT AGE CATEGORIZATION VALUE >= 65, AT ALBI GRADE AT BASELINE CATEGORIZATION VALUE 1	3.78 (1.54, 9.26)		16/ 87	7/105
AT AGE CATEGORIZATION VALUE >= 65, AT ALBI GRADE AT BASELINE CATEGORIZATION VALUE > 1	2.37 (1.13, 4.94)		25/ 86	13/ 79
AGE CATEGORIZATION (>= 65, REFERENCE= < 65)		0.305		
RACE CATEGORIZATION (ASIAN, REFERENCE = NON-ASIAN)		0.055		
VASCULAR INVASION (CRF) (YES, REFERENCE = NO)		0.007		
EXTRAHEPATIC SPREAD PRESENT (CRF) (YES, REFERENCE = NO)		0.005		
BASELINE ECOG PS CATEGORIZATION (>= 1, REFERENCE = 0 & NR)		0.022		
BCLC CATEGORY AT BASELINE (C, REFERENCE = NON-C & UNKNOWN)		0.038		
CHILD-PUGH SCORE CATEGORIZATION (> 5, REFERENCE = 5 & NR)		0.010		
BASELINE AFP CATEGORY (>= 400 NG/ML, REFERENCE = < 400 NG/ML)		<0.001		
ALBI GRADE AT BASELINE CATEGORIZATION (> 1, REFERENCE = 1)		0.025		
NUMBER OF LIVER NODULES CATEGORIZATION (> 3, REFERENCE = <= 3)		0.023		
BASELINE TUMOR BURDEN PER INV (LARGE: >= 125, REFERENCE = SMALL/MEDIUM & UNKNOWN: < 125 OR UNKNOWN)		0.070		

Prognostic covariates identified within each arm using backward selection method (SLSTAY=0.25).
Covariates with p-value < 0.15 and selected treatment arm by covariate interaction effects from full model (v2) included.
P-values and odds ratios from multivariate logistic regression model.
Covariates considered include Age (ref= <65); Race (ref= Non-Asian); Vascular invasion from CRF (ref= No); Extrahepatic spread present from CRF (ref= No); Baseline ECOG PS (ref= 0 & NR); BCLC category at baseline (ref= Non-C & Unknown); Child-Pugh Score (ref= 5 & NR); Baseline AFP category (ref= <400 ng/ml); ALBI Grade at baseline (ref= 1); Number of liver nodules (ref= <=3); Baseline tumor burden per INV (ref= Small/Medium & Unknown).
NR: Not Reported.

According to the MAH, the results were inconsistent with the result of requiring a better liver function status (Child- Pugh score = 5) in conjunction with age ≥65 as an early death risk indicator for the nivo+ipi arm. Therefore, liver function was not considered further as a potential risk factor.

However, it appeared that age ≥ 65 was consistently identified as a potential risk factor. Therefore, following the same approach, a multivariate model only including the age-by-treatment interaction term while adjusting the prognostic effect of other baseline covariates.

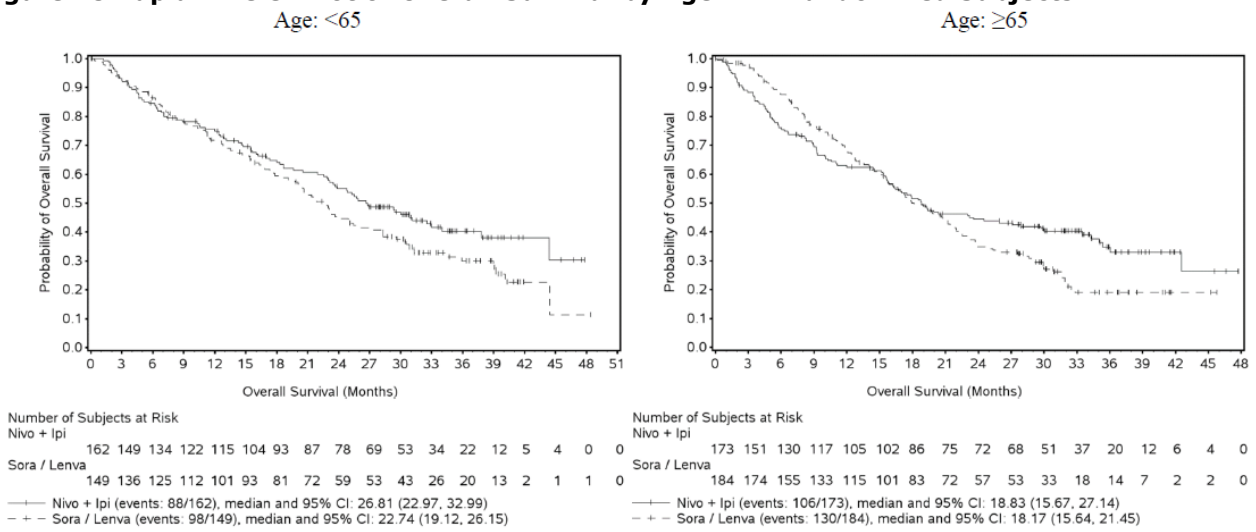
KM OS curves and KM OS curves after using the propensity score matching approach to adjust for baseline imbalance between the treatment arms were presented.

Table 60 Multivariate Logistic Regression Death Occurring in ⩽ 5.84 Months from Randomization - Risk Factors in All Randomized Subjects - Focusing on Age by Treatment Interaction Only

			No. of Early Death/ No. Randomized Subjects	
	Odds Ratio (95% Wald CI)	P-value	Nivolumab + Ipilimumab	Sorafenib / Lenvatinib
TREATMENT (NIVOLUMAB + IPILIMUMAB, REFERENCE = SORAFENIB / LENVATINIB)		0.005		
TREATMENT * AGE CATEGORIZATION		0.161		
TREATMENT (NIVOLUMAB + IPILIMUMAB, REFERENCE = SORAFENIB / LENVATINIB)				
AT AGE CATEGORIZATION VALUE < 65	1.42 (0.70, 2.90)		25/162	19/149
AT AGE CATEGORIZATION VALUE >= 65	2.82 (1.48, 5.36)		41/173	20/184
AGE CATEGORIZATION (>= 65, REFERENCE= < 65)		0.266		
RACE CATEGORIZATION (ASIAN, REFERENCE = NON-ASIAN)		0.051		
VASCULAR INVASION (CRF) (YES, REFERENCE = NO)		0.006		
EXTRAHEPATIC SPREAD PRESENT (CRF) (YES, REFERENCE = NO)		0.004		
BASELINE ECOG PS CATEGORIZATION (>= 1, REFERENCE = 0 & NR)		0.019		
BCLC CATEGORY AT BASELINE (C, REFERENCE = NON-C & UNKNOWN)		0.036		
CHILD-PUGH SCORE CATEGORIZATION (> 5, REFERENCE = 5 & NR)		0.009		
BASELINE AFP CATEGORY (>= 400 NG/ML, REFERENCE = < 400 NG/ML)		<0.001		
ALBI GRADE AT BASELINE CATEGORIZATION (> 1, REFERENCE = 1)		0.036		
NUMBER OF LIVER NODULES CATEGORIZATION (> 3, REFERENCE = <= 3)		0.021		
BASELINE TUMOR BURDEN PER INV (LARGE: >= 125, REFERENCE = SMALL/MEDIUM & UNKNOWN: < 125 OR UNKNOWN)		0.070		

Prognostic covariates identified within each arm using backward selection method (SLSTAY=0.25).
Covariates with p-value < 0.15 and selected treatment arm by covariate interaction effects from full model (v2) included.
P-values and odds ratios from multivariate logistic regression model.
Covariates considered include Age (ref= <65); Race (ref= Non-Asian); Vascular invasion from CRF (ref= No); Extrahepatic spread present from CRF (ref= No); Baseline ECOG PS (ref= 0 & NR); BCLC category at baseline (ref= Non-C & Unknown); Child-Pugh Score (ref= 5 & NR); Baseline AFP category (ref= <400 ng/ml); ALBI Grade at baseline (ref= 1); Number of liver nodules (ref= <=3); Baseline tumor burden per INV (ref= Small/Medium & Unknown).
NR: Not Reported.

Figure 28 Kaplan-Meier Plot of Overall Survival by Age - All Randomized Subjects



Symbols represent censored observations.
NR: Not Reported.

Figure 29 Kaplan-Meier Plot of Overall Survival by Age- After Propensity Score Matching - All Randomized Subjects with Age < 65 and ⩾ 65

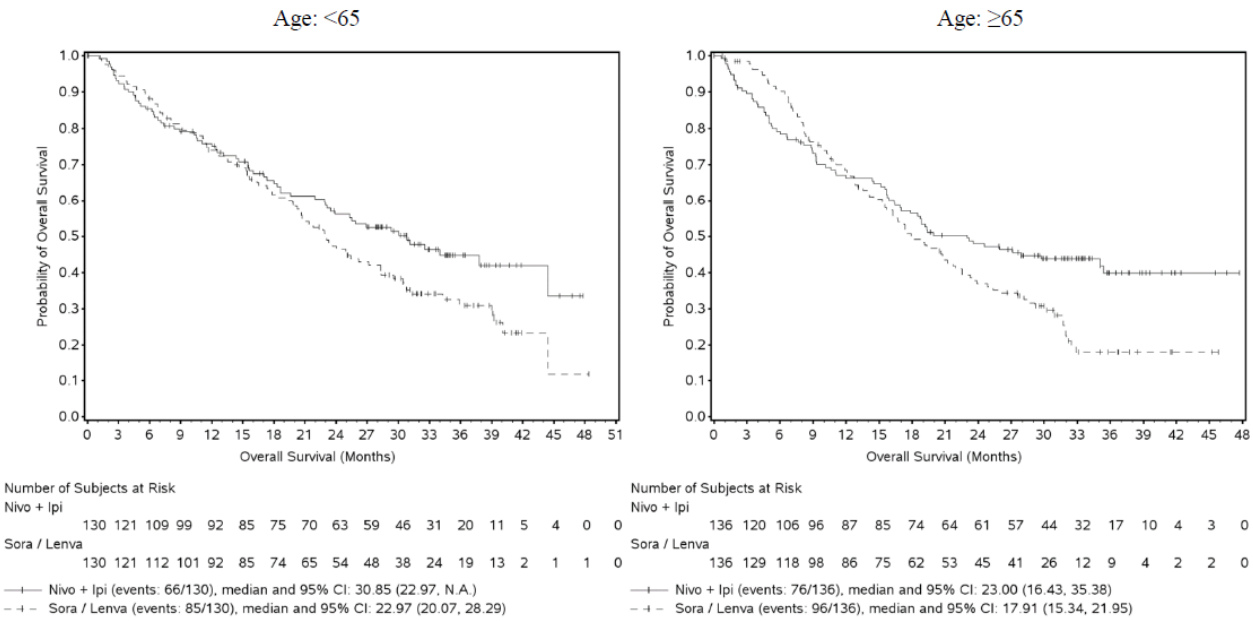


Table 61 Baseline disease characteristics summary – All age ≥ 65 years subjects vs. all randomized subjects

		Age ≥ 65 years N=357		All Randomized N=668	
Parameter	**Subgroup Category**	**NIVO+IPI n=173**	**SOC n=184**	**NIVO+IPI n=335**	**SOC n=333**
Sex	Male	144 (83.2)	150 (81.5)	271 (80.9)	277 (83.2)
	Female	29 (16.8)	34 (18.5)	64 (19.1)	56 (16.8)
Race	Asian	65 (37.6)	83 (45.1)	140 (41.8)	152 (45.6)
	Non-Asian	108 (62.4)	101 (54.9)	195 (58.2)	181 (54.4)

		Age ≥ 65 years N=357		All Randomized N=668	
Parameter	**Subgroup Category**	**NIVO+IPI n=173**	**SOC n=184**	**NIVO+IPI n=335**	**SOC n=333**
Region	Asia	63 (36.4)	81 (44.0)	133 (39.7)	147 (44.1)
	Non-Asia	110 (63.6)	103 (56.0)	202 (60.3)	186 (55.9)
Etiology per CRF	HBV	43 (24.9)	52 (28.3)	114 (34.0)	115 (34.5)
	HCV	46 (26.6)	54 (29.3)	97 (29.0)	99 (29.7)
	Uninfected	84 (48.6)	78 (42.4)	124 (37.0)	119 (35.7)
Etiology per Central Lab	HBV	32 (18.5)	42 (22.8)	99 (29.6)	98 (29.4)
	HCV	6 (3.5)	14 (7.6)	27 (8.1)	27 (8.1)
	Uninfected	135 (78.0)	128 (69.6)	209 (62.4)	208 (62.5)
Vascular Invasion (CRF)	Yes	33 (19.1)	42 (22.8)	77 (23.0)	92 (27.6)
	No	140 (80.9)	142 (77.2)	258 (77.0)	241 (72.4)
Extrahepatic Spread Present	Yes	89 (51.4)	80 (43.5)	188 (56.1)	172 (51.7)
	No	84 (48.6)	104 (56.5)	147 (43.9)	161 (48.3)
ECOG PS	0 & NR	114 (65.9)	134 (72.8)	233 (69.6)	244 (73.3)
	≥1	59 (34.1)	50 (27.2)	102 (30.4)	89 (26.7)
Baseline BCLC category	C	122 (70.5)	127 (69.0)	246 (73.4)	242 (72.7)
	Non-C & Unknown	51 (29.5)	57 (31.0)	89 (26.6)	91 (27.3)
Child-Pugh Score	5 & NR	127 (73.4)	141 (76.6)	254 (75.8)	264 (79.3)
	> 5	46 (26.6)	43 (23.4)	81 (24.2)	69 (20.7)
Baseline AFP Category	< 400 ng/mL	119 (68.8)	128 (69.6)	227 (67.8)	220 (66.1)
	≥ 400 ng/mL	54 (31.2)	56 (30.4)	108 (32.2)	113 (33.9)
ALBI Grade	1	87 (50.3)	105 (57.1)	186 (55.5)	210 (63.1)
	> 1	86 (49.7)	79 (42.9)	149 (44.5)	123 (36.9)
Number of Liver Nodules	≤ 3	113 (65.3)	96 (52.2)	208 (62.1)	187 (56.2)
	> 3	60 (34.7)	88 (47.8)	127 (37.9)	146 (43.8)
Baseline Tumor Burden per INV	Small & Unknown: < 40mm or Unknown	41 (23.7)	47 (25.5)	78 (23.3)	84 (25.2)
	Medium: ≥ 40mm and < 125mm	97 (56.1)	93 (50.5)	185 (55.2)	163 (48.9)
	Large: ≥ 125mm	35 (20.2)	44 (23.9)	72 (21.5)	86 (25.8)

NR: not reported

Table 62 Demographic characteristics summary – Age distribution by 5-year categories – All randomized subjects

	Nivo + Ipi N = 335	Sora / Lenva N = 333	Total N = 668
AGE			
< 50	25 (7.5)	28 (8.4)	53 (7.9)
>= 50 AND < 55	23 (6.9)	15 (4.5)	38 (5.7)
>= 55 AND < 60	43 (12.8)	42 (12.6)	85 (12.7)
>= 60 AND < 65	71 (21.2)	64 (19.2)	135 (20.2)
< 65	162 (48.4)	149 (44.7)	311 (46.6)
>= 65	173 (51.6)	184 (55.3)	357 (53.4)
>= 65 AND < 70	65 (19.4)	56 (16.8)	121 (18.1)
>= 70 AND < 75	61 (18.2)	67 (20.1)	128 (19.2)
>= 75 AND < 80	30 (9.0)	38 (11.4)	68 (10.2)
>= 80	17 (5.1)	23 (6.9)	40 (6.0)

g) Results by different SOC treatments

To evaluate the potential role of the comparator agent (Lenvatinib or Sorafenib), additional analyses were performed by SOC treatment. Of note, this analysis was based on treated subjects rather than randomized subjects because SOC selection was not required prior to randomization per protocol.

Table 63 Demographics Characteristics Summary - All Treated Subjects - Sorafenib and Lenvatinib Displayed Separately

	Nivo + Ipi N = 332	Lenva N = 275	Sora N = 50	Total N = 657
AGE (YEARS)				
N	332	275	50	657
MEAN	64.4	65.1	67.4	64.9
MEDIAN	65.0	66.0	70.0	66.0
MIN , MAX	20 , 86	20 , 89	46 , 83	20 , 89
Q1 , Q3	59.0 , 71.0	60.0 , 73.0	60.0 , 75.0	59.0 , 72.0
SD	9.97	10.37	9.45	10.12
AGE CATEGORIZATION (%)				
< 65	162 (48.8)	125 (45.5)	18 (36.0)	305 (46.4)
>= 65 AND < 75	124 (37.3)	105 (38.2)	18 (36.0)	247 (37.6)
>= 75	46 (13.9)	45 (16.4)	14 (28.0)	105 (16.0)
SEX (%)				
MALE	269 (81.0)	228 (82.9)	41 (82.0)	538 (81.9)
FEMALE	63 (19.0)	47 (17.1)	9 (18.0)	119 (18.1)
RACE (%)				
WHITE	177 (53.3)	128 (46.5)	41 (82.0)	346 (52.7)
BLACK OR AFRICAN AMERICAN	11 (3.3)	2 (0.7)	1 (2.0)	14 (2.1)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (0.3)	0	0	1 (0.2)
ASIAN	139 (41.9)	142 (51.6)	8 (16.0)	289 (44.0)
ASIAN INDIAN	3 (0.9)	0	0	3 (0.5)
CHINESE	76 (22.9)	81 (29.5)	6 (12.0)	163 (24.8)
JAPANESE	24 (7.2)	29 (10.5)	2 (4.0)	55 (8.4)
ASIAN OTHER	36 (10.8)	32 (11.6)	0	68 (10.4)
OTHER	4 (1.2)	3 (1.1)	0	7 (1.1)
ETHNICITY (%)				
HISPANIC OR LATINO	46 (13.9)	23 (8.4)	6 (12.0)	75 (11.4)
NOT HISPANIC OR LATINO	166 (50.0)	128 (46.5)	24 (48.0)	318 (48.4)
NOT REPORTED	120 (36.1)	124 (45.1)	20 (40.0)	264 (40.2)
REGION (%)				
NORTH AMERICA	15 (4.5)	3 (1.1)	2 (4.0)	20 (3.0)
EUROPE	128 (38.6)	97 (35.3)	37 (74.0)	262 (39.9)
ASIA	132 (39.8)	137 (49.8)	8 (16.0)	277 (42.2)
REST OF THE WORLD [ROW]	57 (17.2)	38 (13.8)	3 (6.0)	98 (14.9)

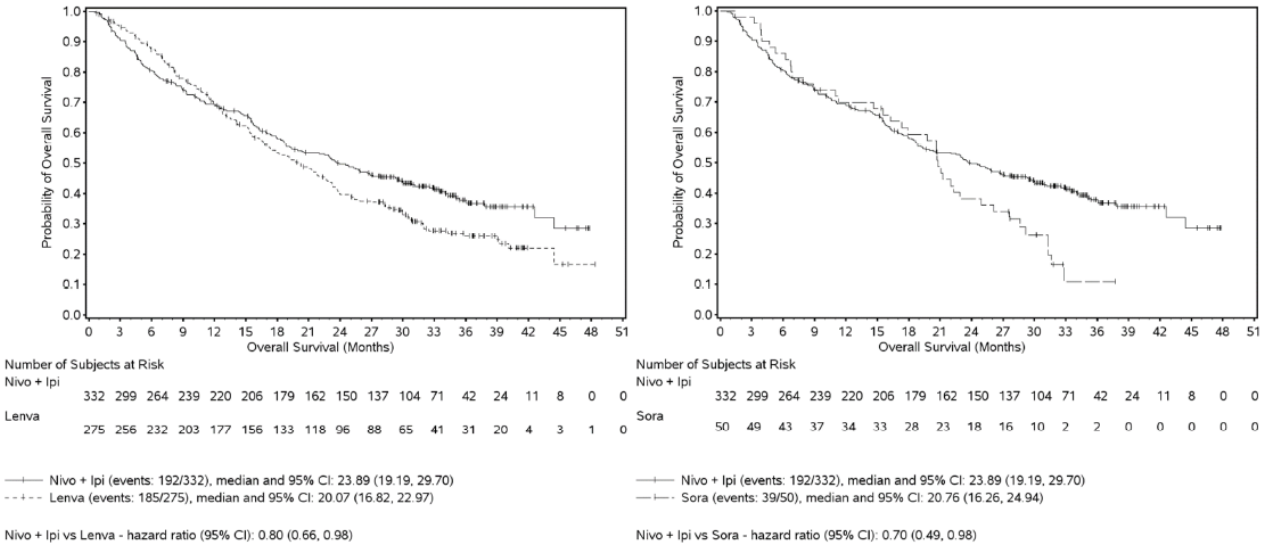
Source: Table 14.1.3.5

Table 64 Baseline Disease Characteristics Summary - All Treated Subjects - Sorafenib and Lenvatinib Displayed Separately

	Number of Subjects (%)			
	Nivo + Ipi N = 332	Lenva N = 275	Sora N = 50	Total N = 657
BASELINE ECOG PERFORMANCE STATUS (%)				
0	232 (69.9)	201 (73.1)	35 (70.0)	468 (71.2)
1	100 (30.1)	74 (26.9)	15 (30.0)	189 (28.8)
WEIGHT (KG)				
N	332	275	50	657
MEAN	73.32	71.24	78.97	72.88
MEDIAN	71.15	69.00	77.45	70.70
MIN - MAX	39.0 - 134.9	36.5 - 160.0	49.3 - 109.0	36.5 - 160.0
Q1 - Q3	62.50 - 83.70	60.00 - 79.80	66.70 - 90.00	62.30 - 82.50
SD	15.565	16.442	13.825	15.921
HCC RISK FACTORS PER CRF (%) (1)				
ALCOHOLIC LIVER DISEASE	66 (19.9)	46 (16.7)	9 (18.0)	121 (18.4)
HEPATITIS B	120 (36.1)	102 (37.1)	13 (26.0)	235 (35.8)
HEPATITIS C	97 (29.2)	81 (29.5)	16 (32.0)	194 (29.5)
NON-ALCOHOLIC FATTY LIVER DIS/STEATOHEPATITIS	39 (11.7)	28 (10.2)	7 (14.0)	74 (11.3)
AFLATOXIN EXPOSURE	0	0	0	0
HEMOCHROMATOSIS	6 (1.8)	4 (1.5)	0	10 (1.5)
NO HCC RISK FACTORS REPORTED	46 (13.9)	42 (15.3)	12 (24.0)	100 (15.2)
TIME FROM INITIAL DIAGNOSIS OF HCC TO RANDOMIZATION (%)				
< 1 YEAR	192 (57.8)	140 (50.9)	29 (58.0)	361 (54.9)
1 - <2 YEARS	48 (14.5)	42 (15.3)	7 (14.0)	97 (14.8)
2 - <3 YEARS	26 (7.8)	23 (8.4)	7 (14.0)	56 (8.5)
3 - <4 YEARS	13 (3.9)	10 (3.6)	3 (6.0)	26 (4.0)
4 - <5 YEARS	16 (4.8)	17 (6.2)	0	33 (5.0)
>=5 YEARS	37 (11.1)	43 (15.6)	4 (8.0)	84 (12.8)
ETIOLOGY PER CENTRAL LAB (%)				
HBV	98 (29.5)	85 (30.9)	10 (20.0)	193 (29.4)
HCV	27 (8.1)	18 (6.5)	7 (14.0)	52 (7.9)
UNINFECTED	207 (62.3)	172 (62.5)	33 (66.0)	412 (62.7)
ETIOLOGY PER CRF (%)				
HBV	113 (34.0)	99 (36.0)	13 (26.0)	225 (34.2)
HCV	90 (27.1)	78 (28.4)	16 (32.0)	184 (28.0)
UNINFECTED	122 (36.7)	95 (34.5)	21 (42.0)	238 (36.2)
HBV/HCV	7 (2.1)	3 (1.1)	0	10 (1.5)
VASCULAR INVASION (MVI) (CRF) (%)				
YES	76 (22.9)	71 (25.8)	17 (34.0)	164 (25.0)
NO	256 (77.1)	204 (74.2)	33 (66.0)	493 (75.0)
EXTRAHEPATIC SPREAD (EHS) (CRF) (%)				
YES	186 (56.0)	153 (55.6)	14 (28.0)	353 (53.7)
NO	146 (44.0)	122 (44.4)	36 (72.0)	304 (46.3)
MVI/EHS (CRF) (%)				
YES	219 (66.0)	183 (66.5)	27 (54.0)	429 (65.3)
NO	113 (34.0)	92 (33.5)	23 (46.0)	228 (34.7)
AFP (NG/ML)				
N	332	275	50	657
MEAN	12186.61	6187.83	3918.44	9046.47
MEDIAN	51.80	46.00	99.50	50.00
MIN - MAX	0.9 - 529738.0	0.6 - 152378.0	1.6 - 39162.2	0.6 - 529738.0
Q1 - Q3	6.95 - 849.75	5.20 - 905.10	6.10 - 4054.00	5.96 - 871.00
SD	55878.026	19146.767	8790.773	41770.451
AFP CATEGORY I (%)				
< 200 NG/ML	208 (62.7)	166 (60.4)	30 (60.0)	404 (61.5)
>= 200 NG/ML	124 (37.3)	109 (39.6)	20 (40.0)	253 (38.5)
AFP CATEGORY II (%)				
< 400 NG/ML	226 (68.1)	184 (66.9)	31 (62.0)	441 (67.1)
>= 400 NG/ML	106 (31.9)	91 (33.1)	19 (38.0)	216 (32.9)
CHILD-PUGH SCORE (%)				
5	253 (76.2)	216 (78.5)	42 (84.0)	511 (77.8)
6	70 (21.1)	51 (18.5)	6 (12.0)	127 (19.3)
7	8 (2.4)	8 (2.9)	2 (4.0)	18 (2.7)
8	1 (0.3)	0	0	1 (0.2)
BCLC STAGING (%)				
0	3 (0.9)	2 (0.7)	1 (2.0)	6 (0.9)
A	25 (7.5)	14 (5.1)	4 (8.0)	43 (6.5)
B	60 (18.1)	53 (19.3)	13 (26.0)	126 (19.2)
C	244 (73.5)	204 (74.2)	32 (64.0)	480 (73.1)
D	0	0	0	0
UNKNOWN	0	2 (0.7)	0	2 (0.3)

(1) Subjects may have more than one HCC factor.
Source: Table 14.1.4.8

Figure 30 Kaplan-Meier Plot of Overall Survival - All Treated Subjects - Nivo+Ipi vs Lenvantinib and vs Sorafenib



Hazard ratios are from unstratified Cox proportional hazard model.
Hazard ratios are Nivolumab + Ipilimumab over Lenvatinib and Nivolumab + Ipilimumab over Sorafenib.
Symbols represent censored observations.

h) Tolerability of the combination

Table 65 Summary of safety – all nivolumab + ipilimumab treated subjects from CA2099DW, Pooled excluding CA2099DW, and Pooled including CA2099DW

Safety Parameters	CA2099DW Nivo + Ipi (N = 332)		Pooled Nivo + Ipi Excluding CA2099DW (N = 2094)		Pooled Nivo + Ipi Including CA2099DW (N = 2426)	
	Adverse Event Grade		Adverse Event Grade		Adverse Event Grade	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-causality SAEs	176 (53.0)	154 (46.4)	1263 (60.3)	931 (44.5)	1439 (59.3)	1085 (44.7)
Drug-related SAEs	94 (28.3)	83 (25.0)	676 (32.3)	517 (24.7)	770 (31.7)	600 (24.7)
All-causality AEs leading to DC	88 (26.5)	69 (20.8)	661 (31.6)	476 (22.7)	749 (30.9)	545 (22.5)
Drug-Related AEs leading to DC	59 (17.8)	44 (13.3)	497 (23.7)	368 (17.6)	556 (22.9)	412 (17.0)
All-causality AEs	331 (99.7)	230 (69.3)	2080 (99.3)	1342 (64.1)	2411 (99.4)	1572 (64.8)
Drug-related AEs	278 (83.7)	137 (41.3)	1854 (88.5)	900 (43.0)	2132 (87.9)	1037 (42.7)
All-Causality Select AEs	**302 (91.0)**	**119 (35.8)**	**1742 (83.2)**	**602 (28.7)**	**2044 (84.3)**	**721 (29.7)**
Endocrine	105 (31.6)	12 (3.6)	645 (30.8)	112 (5.3)	750 (30.9)	124 (5.1)
Gastrointestinal	83 (25.0)	20 (6.0)	816 (39.0)	168 (8.0)	899 (37.1)	188 (7.7)
Hepatic	172 (51.8)	72 (21.7)	516 (24.6)	216 (10.3)	688 (28.4)	288 (11.9)
Pulmonary	9 (2.7)	2 (0.6)	166 (7.9)	42 (2.0)	175 (7.2)	44 (1.8)
Renal	25 (7.5)	7 (2.1)	248 (11.8)	49 (2.3)	273 (11.3)	56 (2.3)
Skin	206 (62.0)	20 (6.0)	1117 (53.3)	106 (5.1)	1323 (54.5)	126 (5.2)
Hypersensitivity/ Infusion Reactions	8 (2.4)	1 (0.3)	125 (6.0)	7 (0.3)	133 (5.5)	8 (0.3)

Safety Parameters	CA2099DW Nivo + Ipi (N = 332)		Pooled Nivo + Ipi Excluding CA2099DW (N = 2094)		Pooled Nivo + Ipi Including CA2099DW (N = 2426)	
	Adverse Event Grade		Adverse Event Grade		Adverse Event Grade	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Drug-Related Select AEs	**265 (79.8)**	**101 (30.4)**	**1576 (75.3)**	**537 (25.6)**	**1841 (75.9)**	**638 (26.3)**
Endocrine	94 (28.3)	12 (3.6)	582 (27.8)	104 (5.0)	676 (27.9)	116 (4.8)
Gastrointestinal	56 (16.9)	17 (5.1)	580 (27.7)	145 (6.9)	636 (26.2)	162 (6.7)
Hepatic	114 (34.3)	56 (16.9)	403 (19.2)	187 (8.9)	517 (21.3)	243 (10.0)
Pulmonary	7 (2.1)	1 (0.3)	145 (6.9)	32 (1.5)	152 (6.3)	33 (1.4)
Renal	6 (1.8)	1 (0.3)	128 (6.1)	30 (1.4)	134 (5.5)	31 (1.3)
Skin	172 (51.8)	19 (5.7)	969 (46.3)	99 (4.7)	1141 (47.0)	118 (4.9)
Hypersensitivity/ Infusion Reactions	8 (2.4)	1 (0.3)	102 (4.9)	6 (0.3)	110 (4.5)	7 (0.3)
All-causality Non-Endocrine IMAEs within 100 days of Last Dose Treated With Immune Modulating Medication, by Category						
Any	**136 (41.0)**	**80 (24.1)**	**802 (38.3)**	**382 (18.2)**	**938 (38.7)**	**462 (19.0)**
Diarrhoea/Colitis	28 (8.4)	15 (4.5)	241 (11.5)	126 (6.0)	269 (11.1)	141 (5.8)
Hepatitis	63 (19.0)	51 (15.4)	167 (8.0)	135 (6.4)	230 (9.5)	186 (7.7)
Pneumonitis	7 (2.1)	3 (0.9)	111 (5.3)	41 (2.0)	118 (4.9)	44 (1.8)
Nephritis/Renal Dysfunction	5 (1.5)	3 (0.9)	54 (2.6)	27 (1.3)	59 (2.4)	30 (1.2)
Rash	51 (15.4)	14 (4.2)	378 (18.1)	77 (3.7)	429 (17.7)	91 (3.8)
Hypersensitivity/ Infusion Reactions	4 (1.2)	0	23 (1.1)	1 (<0.1)	27 (1.1)	1 (<0.1)
All-causality Endocrine IMAEs within 100 days of Last Dose With or Without Immune Modulating Medication, by Category						
Any	**95 (28.6)**	**14 (4.2)**	**600 (28.7)**	**117 (5.6)**	**695 (28.6)**	**131 (5.4)**
Adrenal Insufficiency	18 (5.4)	6 (1.8)	114 (5.4)	45 (2.1)	132 (5.4)	51 (2.1)
Hypothyroidism/ Thyroiditis	62 (18.7)	1 (0.3)	382 (18.2)	15 (0.7)	444 (18.3)	16 (0.7)
Diabetes Mellitus	2 (0.6)	2 (0.6)	27 (1.3)	14 (0.7)	29 (1.2)	16 (0.7)
Hyperthyroidism	36 (10.8)	2 (0.6)	179 (8.5)	10 (0.5)	215 (8.9)	12 (0.5)
Hypophysitis	9 (2.7)	4 (1.2)	116 (5.5)	48 (2.3)	125 (5.2)	52 (2.1)
All-causality OESIs within 100 days of Last Dose With or Without Immune Modulating Medication						
Any	**16 (4.8)**	**9 (2.7)**	**83 (4.0)**	**43 (2.1)**	**99 (4.1)**	**52 (2.1)**
Pancreatitis	9 (2.7)	4 (1.2)	34 (1.6)	19 (0.9)	43 (1.8)	23 (0.9)
Myositis/Rhabdomyolysis	4 (1.2)	3 (0.9)	13 (0.6)	5 (0.2)	17 (0.7)	8 (0.3)
Uveitis	0	0	15 (0.7)	4 (0.2)	15 (0.6)	4 (0.2)
Myocarditis	3 (0.9)	2 (0.6)	4 (0.2)	2 (<0.1)	7 (0.3)	4 (0.2)
Encephalitis	0	0	11 (0.5)	8 (0.4)	11 (0.5)	8 (0.3)
Autoimmune Cytopenia	2 (0.6)	1 (0.3)	2 (<0.1)	1 (<0.1)	4 (0.2)	2 (<0.1)
Myasthenic Syndrome	1 (0.3)	1 (0.3)	3 (0.1)	3 (0.1)	4 (0.2)	4 (0.2)
Demyelination	1 (0.3)	0	0	0	1 (<0.1)	0
Guillain-Barre Syndrome	0	0	2 (<0.1)	2 (<0.1)	2 (<0.1)	2 (<0.1)
Immune Mediated Arthritis	0	0	1 (<0.1)	0	1 (<0.1)	0

Summary of main study

The following table summarises 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 section 3.).

Table 66 Summary of Efficacy for trial CA2099DW

Title: A Randomized, Multi-center, Phase 3 Study of Nivolumab in Combination with Ipilimumab Compared to Sorafenib or Lenvatinib as First-Line Treatment in Participants with Advanced Hepatocellular Carcinoma			
Study identifier	Study CA2099DW EudraCT: 2019-000252-34		
Design	CA2099DW is a randomized, multi-center, open-label, controlled study of nivolumab+ipilimumab compared with the Investigator's choice (sorafenib or lenvatinib) as first-line therapy for unresectable hepatocellular carcinoma. Patients were randomized to receive nivolumab in combination with ipilimumab for 4 cycles, followed by nivolumab monotherapy; or sorafenib/lenvatinib.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		From 06 Jan 2020. Ongoing. Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Nivolumab in combination with ipilimumab		Nivolumab 1 mg/kg + ipi 3 mg/kg Q3W for up to 4 cycles followed by nivo 480 mg (flat dose) Q4W until disease progression or for a maximum duration of treatment of 2 years. N=335
	Sorafenib or lenvatinib		Sorafenib 400 mg PO BID or lenvatinib 8 mg PO QD (if body weight < 60 kg) or 12 mg PO QD (if body weight ⩾ 60 kg) until disease progression. N=333
Endpoints and definitions	Primary endpoint	OS	Time between the date of randomization and the date of death (by any cause).
	Key secondary endpoint	ORR by BICR	Percentage of participants whose BOR is either a confirmed CR or PR.
	Key secondary endpoint	TTSD	Time from randomization until a clinically meaningful decline in the HCS subscale score of the FACT-Hep.
Database lock	28 Feb 2024 (DCO: 31 Jan 2024)		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat, interim analysis (converted to final analysis)		
Descriptive statistics and estimate variability	Treatment group	Nivolumab in combination with ipilimumab	Sorafenib or lenvatinib
	Number of subject	335	333
	OS (median, months)	23.66	20.63
	95 % CI	(18.83, 29.44)	(17.48, 22.54)
	ORR by BICR (%)	36.1	13.2
	95 % CI	(31.0, 41.5)	(9.8, 17.3)
	TTSD (median, months) 95 % CI	2.60 (2.00, 3.94)	2.14 (1.64, 2.79)
Effect estimate per comparison	Primary endpoint OS	Comparison groups	Nivo+ipi vs. sora/lenva
		HR	0.79
		95 % CI	(0.65, 0.96)
		P-value	0.0180
	Key secondary endpoint ORR by BICR	Comparison groups	Nivo+ipi vs. sora/lenva
		Odds ratio	3.61
		95 % CI	2.46, 5.29
		P-value	<0.0001
	Key secondary endpoint TTSD	Comparison groups	Nivo+ipi vs. sora/lenva
		HR	0.76
		95 % CI	(0.62, 0.93)
		P-value	0.0059

Clinical studies in special populations

Table 67 Subjects by age range and in patients with renal and hepatic impairment

Study CA2099DW - All Randomised Subjects			
	Nivo + Ipi N=335	**Sora / Lenva N=333**	**Total N=668**
Age <65 years subjects number /total number (%)	162/335 (48.4)	149/333 (44.7)	311/668 (46.6)
Age 65 to <75 years subjects number /total number (%)	126/335 (37.6)	123/333 (36.9)	249/668 (37.3)
Age 75 to <85 years subjects number /total number (%)	43/335 (12.8)	57/333 (17.1)	100/668 (15.0)
Age ≥85 years subjects number /total number (%)	4/335 (1.2)	4/333 (1.2)	8/668 (1.2)
Renal impairment* patients subjects number /total number (%)	1/335 (0.3)	1/333 (0.3)	2/668 (0.3)
Hepatic impairment patients** subjects number /total number (%)	8/335 (2.4)	4/333 (1.2)	12/668 (1.8)

* Renal impairment is defined as having serum creatinine ≥1.5 x ULN
** Hepatic impairment is defined as having total bilirubin > 1.5 x ULN with ALT/AST > 3 x ULN

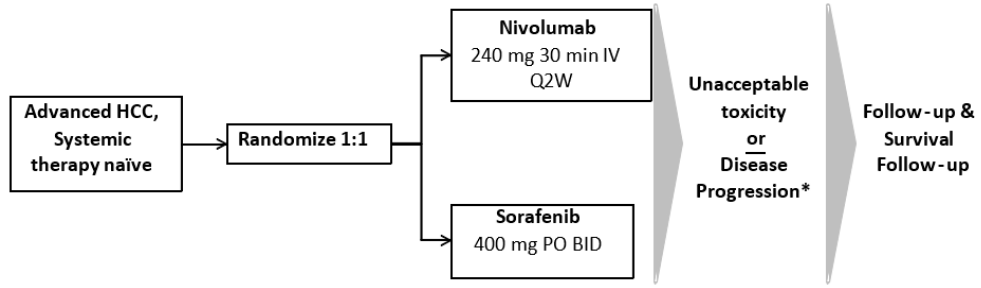
Supportive study(ies)

Supportive study CA209459

CA209459 is an open-label, two-arm, randomized, Phase 3 study of nivolumab vs sorafenib as 1L treatment in unresectable HCC. The study enrolled adult (≥ 18 years) male and female subjects with unresectable HCC not eligible for, or with progressive disease after, curative surgical and/or locoregional therapies who had not received prior systemic therapy for unresectable HCC. The primary objective of the study was to compare the OS of nivolumab to sorafenib in patients with HCC who have not received prior systemic therapy.

Study CA209459 (DBL 05 June 2019; 22.8 months minimum follow-up) provides efficacy data for 1L nivolumab monotherapy vs sorafenib to support the contribution of components (CoC) with similar patient population, study endpoints, and follow-up schedule as study CA2099DW.

Figure 31 CA209459 Study Design Schematic



* Subjects may be treated beyond disease progression under protocol-defined conditions.

Stratification factors:

- Etiology (HCV vs. non-HCV [ie, HBV- and HCC with no history of hepatitis virus infection]),
- Vascular invasion &/or extra hepatic spread (present or absent),
- Geography (Asia vs Non-Asia).

OS was the primary endpoint of study CA209459. ORR and PFS per BICR using RECIST 1.1 were the secondary endpoints. Endpoint definitions were the same as in study CA2099DW. Efficacy analyses were performed for all treated subjects and were descriptive in nature.

Table 68 Summary of Efficacy Results - All Randomized Subjects - CA2099DW and CA209459

	CA2099DW		CA209459[a]	
	Nivo+Ipi N = 335	SOC N = 333	Nivo (N = 371)	Sorafenib (N = 372)
OS				
Events, n (%)	194/335 (57.9)	228/333 (68.5)	244/371 (65.8)	275/372 (73.9)
Median OS (95% CI), mo[b]	23.66 (18.83, 29.44)	20.63 (17.48, 22.54)	16.39 (13.93, 18.37)	14.69 (11.89, 17.22)
HR (95% CI)[c]	0.79 (0.65, 0.96)		0.85 (0.72, 1.02)	
p-value[d]	0.0180		0.0752	
OS Rates, % (95% CI)				
Rate at 12 mo	68.4 (63.1, 73.2)	69.7 (64.4, 74.5)	59.7 (54.4, 64.6)	55.1 (49.8, 60.1)
Rate at 18 mo	57.9 (52.3, 63.1)	54.3 (48.6, 59.7)	46.7 (41.4, 51.8)	43.6 (38.4, 48.6)
Rate at 24 mo	49.4 (43.8, 54.8)	39.2 (33.7, 44.7)	36.8 (31.8, 41.8)	33.1 (28.3, 38.0)
ORR per BICR (RECIST 1.1)				
N Responders (ORR, %) (95% CI)[e]	121/335 (36.1) (31.0, 41.5)	44/333 (13.2) (9.8, 17.3)	57/371 (15.4) (11.8, 19.4)	26/372 (7.0) (4.6, 10.1)
Difference (95% CI)[f]	22.9 (16.6, 29.2)		8.3 (3.9, 12.7)	
Odds Ratio (95% CI)[g]	3.61 (2.46, 5.29)		2.41 (1.48, 3.92)	
p-value[h]	<0.0001[i]		NA	
Complete Response (CR), n (%)	23 (6.9)	6 (1.8)	14 (3.8)	5 (1.3)
Partial Response (PR), n (%)	98 (29.3)	38 (11.4)	43 (11.6)	21 (5.6)
TTR per BICR (RECIST 1.1), mo				
Median	2.17	3.65	3.25	3.71
Min, Max	1.1, 11.6	0.6, 11.2	1.6, 19.4	1.5, 11.1
DOR per BICR (RECIST 1.1)				
# Events / # Responders (%)	48/121 (39.7)	22/44 (50.0)	30/57 (52.6)	10/26 (38.5)
Median DOR (95% CI), mo[b]	30.36 (21.19, N.A.)	12.91 (10.15, 31.21)	23.26 (16.95, 31.54)	23.39 (8.51, NA)
Min, Max, mo	1.5+, 36.9+	2.1+, 32.5+	3.1, 34.5+	1.9+, 28.7+
PFS per BICR (RECIST 1.1)				
# Events/# Subjects (%)	219/335 (65.4)	215/333 (64.6)	305/371 (82.2)	288/372 (77.4)

	CA2099DW		CA209459[a]	
	Nivo+Ipi N = 335	SOC N = 333	Nivo (N = 371)	Sorafenib (N = 372)
Median PFS[b] (95% CI), mo	9.07 (6.60, 10.51)	9.20 (7.89, 11.07)	3.68 (3.06, 3.88)	3.75 (3.71, 4.47)
Hazard Ratio[b] (95% CI)	0.87 (0.72, 1.06)		0.93 (0.79, 1.10)	
TTP per BICR (RECIST 1.1)				
Median TTP[b] (95% CI), mo	16.46 (11.07, 22.14)	11.07 (9.26, 13.83)	3.75 (3.61, 5.45)	3.94 (3.75, 5.55)

[a] DBL: 05-Jun-2019; Minimum follow-up: 22.8 months

[b] Based on Kaplan-Meier Estimates.

[c] Stratified Cox proportional hazard model. HR is nivo+ipi over SOC for CA2099DW/ HR is Nivolumab 240 mg over Sorafenib 400 mg for CA209459.

[d] Log-rank Test stratified by the stratification factors as entered into the IRT (CA2099DW)/ IVRS (CA209459).

[e] Number of (CR+PR) / number of all randomized subjects, CI based on the Clopper-Pearson method.

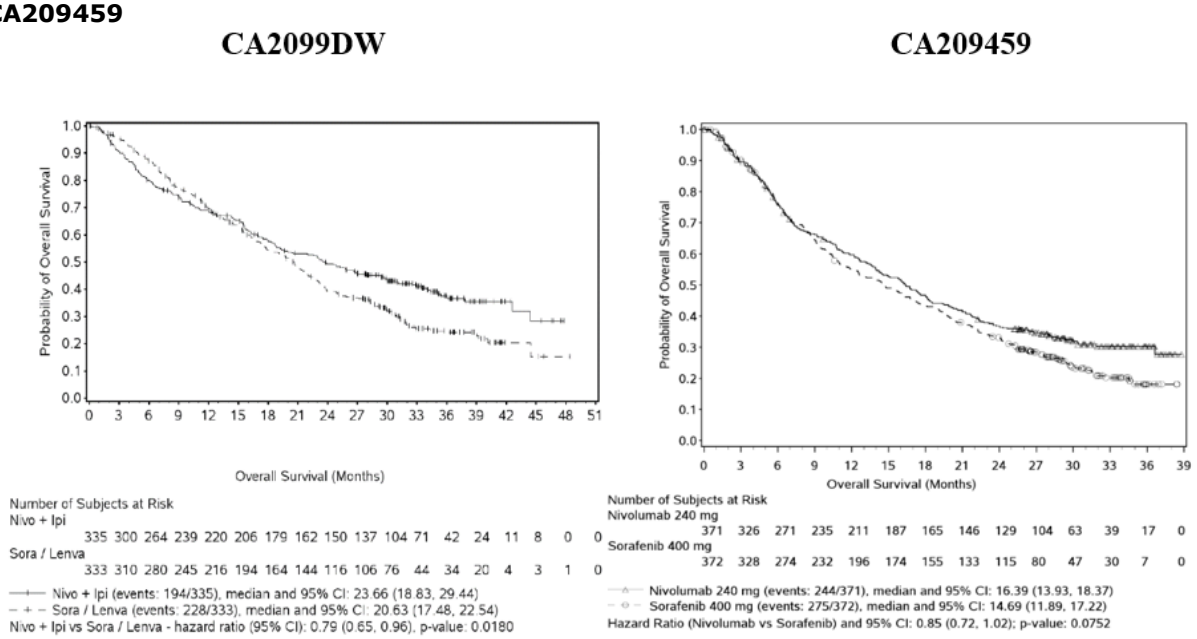
[f] Based on CMH method of weighting, adjusting for stratification factors.

[g] Mantel-Haenszel estimator

[h] Two-sided p-value from stratified CMH test

[i] Boundary for statistical significance for ORR: two-sided p-value ≤ 0.025.

Figure 32 Kaplan-Meier Plot of Overall Survival - All Randomized Subjects - CA2099DW and CA209459



Symbols represent censored observations.
Hazard ratio from stratified Cox proportional hazard model using randomized group as a single covariate.

Supportive study CA209040

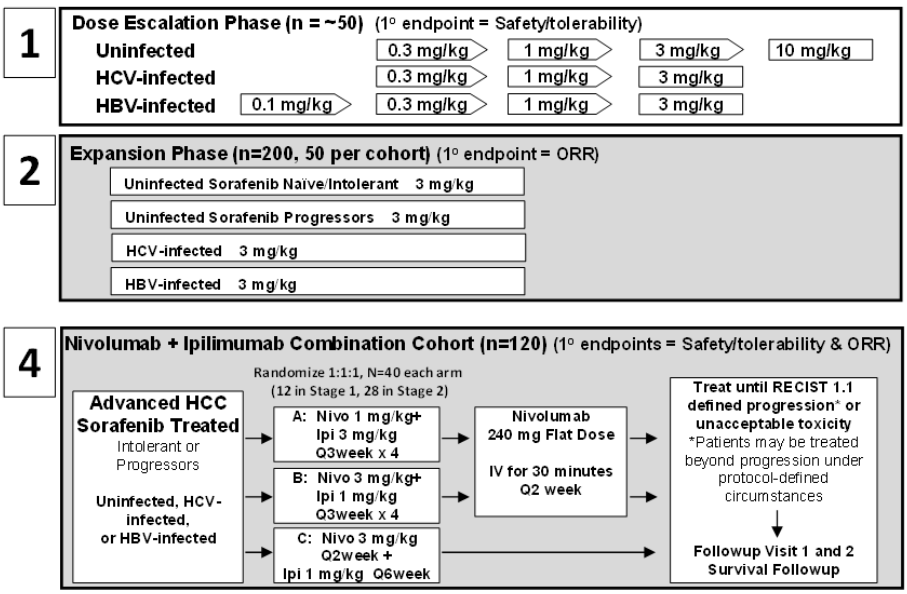
CA209040 is a Phase 1/2 non-comparative, multi-cohort, dose-escalation, open-label study of nivolumab (alone or in combination with ipilimumab or cabozantinib) as 2L treatment in subjects with unresectable HCC with or without chronic viral hepatitis. The primary objectives of the study were:

- ESC Cohort: To establish the safety, tolerability, DLT and MTD for nivolumab administered every 14 days to subjects with unresectable HCC.

- EXP Cohort: To estimate the ORR and duration of response of nivolumab monotherapy in subjects with unresectable HCC who are naive to sorafenib or have been previously treated with sorafenib. ORR will be determined with a BICR-assessed tumour response based on RECIST 1.1.
- Nivo+Ipi Combination Cohort (Cohort 4):
  - To establish the safety and tolerability of nivo+ipi in subjects with advanced HCC.
  - To estimate the ORR and DOR for nivo+ipi combination therapy in subjects with advanced HCC who have been previously treated with sorafenib. ORR will be determined with Investigator-assessed tumour response based on RECIST 1.1

Study CA209040 (Cohort 1&2 and Cohort 4) provides indirect comparison of efficacy data of 2L nivolumab vs nivo+ipi with similar patient population, study endpoints, and follow-up schedule to support CoC and dose selection in study CA2099DW.

Figure 33 CA209040 Study Design Schematic



ORR per investigator using RECIST 1.1 was the primary endpoint of study CA209040 Cohort 4, and ORR per BICR using RECIST 1.1 was the primary endpoint of Cohort 2. OS and PFS were the secondary endpoints. Endpoint definitions were the same as in study CA2099DW Efficacy analyses were performed for all treated subjects and were descriptive in nature.

Table 69 Summary of efficacy results - All treated post-sorafenib subjects - Cohort 1&2 and Cohort 4 - CA209040

	CA209040 Cohort 4 (2L)[a]				CA209040 Cohort 1&2 (2L)[b]
Endpoint	N1I3 Q3W (N = 50)	N3I1 Q3W (N = 49)	N3I1 Q6W (N = 49)	All (N = 148)	Nivo (3 mg/kg Q2W) (n=154)
Median OS, months, (95% CI)[c]	22.80 (9.43, N.A.)	12.48 (7.62, 16.39)	12.75 (7.43, 32.95)	14.16 (10.51, 20.83)	15.15 (13.04, 18.23)
ORR (CR+PR), RECIST 1.1, n(%) (95% CI)[d]	16/50 (32.0) (19.5, 46.7)	15/49 (30.6) (18.3, 45.4)	15/49 (30.6) (18.3, 45.4)	46/148 (31.1) (23.7, 39.2)	22/154 (14.3) (9.2, 20.8)
Median DOR, months (95% CI)[c]	17.48 (8.31, N.A.)	22.21 (4.44, N.A.)	16.59 (4.34, N.A.)	17.48 (11.07, N.A.)	N.A. (3.2 - 51.1+)

a Database lock: 22-Mar-2019; Minimum follow-up: 28.2 months.

b Database lock: 20-Mar-2018; Minimum follow-up: 27 months.

c Kaplan-Meier estimate

d Proportion with CR or PR; confidence interval based on the Clopper and Pearson method

2.4.1. Discussion on clinical efficacy

The efficacy of nivolumab+ipilimumab (hereinafter referred as nivo+ipi) combination therapy as first-line treatment for unresectable hepatocellular carcinoma (HCC) is primarily based on the results of the Phase 3 study CA2099DW, which compared nivo+ipi followed by nivo as monotherapy vs. Investigator's choice (lenvatinib/sorafenib).

This pivotal Phase 3 study CA2099DW is further supported by the Phase 3 study CA209459, which compared nivolumab as monotherapy vs. sorafenib; and by the Phase 1/2 study CA209040, in which the efficacy after treatment with sorafenib (i.e. in second-line) of nivolumab as monotherapy (Cohort 1&2) and in combination with ipilimumab (Cohort 4) were assessed. These studies are considered as supportive, namely to help establishing the contribution of the individual components of the nivo+ipi combination.

Design and conduct of clinical studies

Study CA2099DW is a randomized, multi-centre, open-label Phase 3 study of nivolumab in combination with ipilimumab compared with the Investigator's choice between sorafenib or lenvatinib, as first-line treatment in patients with advanced hepatocellular carcinoma. The MAH did not seek scientific advice from the CHMP for this study.

Patients included were not eligible for curative surgical and/or locoregional therapies or with progressive disease after surgical and/or locoregional therapies; had not received any prior systemic therapy for advanced disease; and with a rather good hepatic performance (Child Pugh A), which might not necessarily be reflective of the general patient population with uHCC. The inclusion and exclusion criteria are adequately reflected in sections 4.4 and 5.1 of the SmPC.

Patients were randomized 1:1 to nivo 1 mg/kg + ipi 3 mg/kg Q3W for up to 4 cycles followed by nivo 480 mg (flat dose) Q4W until disease progression, unacceptable toxicity or for a maximum duration of treatment of 2 years, or to sorafenib 400 mg orally twice daily or lenvatinib 8 mg orally daily (if body

weight <60 kg) or 12 mg orally daily (if body weight ≥60 kg) until disease progression or unacceptable toxicity. Stratification factors were aetiology (HCV vs. HBV vs. uninfected), vascular invasion and/or extrahepatic spread (present/absent) and baseline AFP level (<400 ng/mL or ≥400 ng/mL). Although ECOG status could have also been chosen as stratification factor, the selected stratification factors are considered acceptable.

Maximum duration of treatment with nivo+ipi in the study CA2099DW was 2 years, as stated in section 4.2 of the SmPC. The rationale provided by the MAH is that, according to prior studies in other settings, patients on treatment with immunotherapy no longer benefit from the treatment after two years, while the risk of suffering from adverse events remains. The justification provided by the MAH is considered acceptable and it is in line with prior IO studies. Treatment beyond progression was allowed in both arms if there was evidence of clinical benefit. This is a frequent approach in clinical trials with immunotherapy agents or TKIs, and it is considered acceptable. In the nivo+ipi arm 185 patients had investigator-assessed radiographic progression, of which 62 (62/185; 33.5%) continued treatment beyond progression. The median number of doses received beyond progression was 3.0 (min – max: 1 – 24), and the median duration of treatment beyond progression was 2.14 months (min – max: 0.1 – 21.7). The information about the number of patients whose last treatment dose was after the date of confirmed PD may be relevant. For this reason, it is detailed in this report but not described in the SmPC.

The proposed recommended dose is 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab administered intravenously every 3 weeks for up to 4 doses. This is then followed by a second phase in which nivolumab monotherapy can be administered intravenously at either 240 mg every 2 weeks or at 480 mg every 4 weeks. Of note, study CA2099DW was only conducted with the 480 mg dose of nivolumab (refer to Clinical Pharmacology section 2.3.).

Demographic and baseline disease characteristics were overall balanced between both arms. Most patients in both arms were males (82%) with a median age of 66 years old and 51.5% of patients ≥ 65 years old. 52.8% of patients were White and 43.7% Asian; with a total of 40.3% patients from Europe. In terms of the disease, most patients had an ECOG of 0 (71.3%), had non-viral related HCC (62.4%), had vascular invasion or extrahepatic spread (65.6%), a Child-Pugh score of 5 (77.4%) and a BCLC staging of C (73.1%).

In this trial, the comparator was the Investigator's choice between sorafenib or lenvatinib, which were the first-line treatments recommended by the ESMO guidelines until 2021, when the guidelines were updated to recommend as preferred option the combination of atezolizumab+bevacizumab. This updated recommendation was based on the results of the IMbrave150 study, in which atezo+beva demonstrated statistically significance over sorafenib, with a mOS of 19.2 months vs. 13.4 months. It is noted that the mOS that sorafenib or lenvatinib have demonstrated in prior clinical trials is shorter (around 10-13 months) than the mOS with the atezo+beva combination; meaning that study CA2099DW was not conducted using as a comparator the current standard of care treatment, as it would be the ideal scenario. It is also noted that, although the ESMO guidelines have not yet included durvalumab or the combination of durvalumab and tremelimumab, durvalumab both as monotherapy and in combination also resulted in longer mOS than sorafenib or lenvatinib (around 16 months) in prior clinical trials, and it is currently another treatment option.

However, it should be noted that study CA2099DW started before atezo+beva was approved (CHMP opinion: September 2020); and, therefore, this study used as comparator the approved standard of care treatment at that moment. Similarly, CHMP's opinion for durva+treme was adopted in December 2022, and for durva as monotherapy in October 2023. Acknowledging the already-mentioned limitation, the comparators used in study CA2099DW are considered acceptable since at the moment of the start of the study the only available treatments were these two TKIs. It is worth mentioning

that, although lenvatinib was approved based on a non-inferiority study vs sorafenib, a SOC comparator arm which contemplates the use of lenvatinib in a representative number of patients is expected to show a better response than only sorafenib.

This study was open-label, which is justified by the major differences in dosing schedules and unique and characteristic drug-related AEs of each drug with different dose management requirements. Additionally, the objective nature of the primary endpoint (overall survival), together with the fact that the key secondary endpoints included in the hierarchical analysis were assessed by BICR instead of by Investigator, provide reassurance in this regard. It should be noted that other studies in this same setting (e.g. HIMALAYA, IMbrave 150) were also open-label.

The primary endpoint was overall survival (OS), which is considered the most reliable endpoint and adequate in this specific clinical setting. Key secondary endpoints were overall response rate (ORR) by BICR and time to symptom deterioration (TTSD), which were included in that order following a statistical testing hierarchy. TTSD was defined as the time from randomization until a clinically meaningful decline (at least a 6-point decrease from baseline) in the HCS score of the FACT-Hep in all randomized subjects. Other exploratory endpoints assessed were PFS by BICR and other antitumor activity endpoints such as time to progression (TTP), disease control rate (DCR), duration of disease control (DDC), time to response (TTR) and duration of response (DOR); assessed by BICR following RECIST 1.1 and mRECIST 1.1 criteria, as well as by Investigator.

Of note, the design of this study does not allow to directly establish the contribution of each of the components of the combination (i.e. nivolumab and ipilimumab), since it only included one arm with the experimental combination and one arm with the comparator, with no arms with the mono-components. The MAH has submitted supportive studies (Phase 3 CA209459 and Phase 1/2 CA209040) to help establishing the contribution of each component. The results of these studies are further commented below.

Statistical considerations

Regarding the primary endpoint, the MAH considered OS function between two treatment arms, regardless of the start of subsequent anticancer therapy, following the "treatment policy" approach for this intercurrent event. In the case of the secondary endpoints (ORR, DOR and TTSD), the MAH applied a "while-on treatment strategy" when patients received another subsequent anticancer therapy prior to progression. These approaches are acceptable. The MAH also conducted sensitivity analyses using the "treatment policy" to handle intercurrent events, which resulted in similar results as obtained in the primary analysis.

In terms of interim analyses, an interim analysis of OS was planned in which the alpha level applied at the interim and final analyses depended on a spending function using an O'Brien Fleming approach. This approach controls an overall 2-sided 5% type I error across the planned analysis of OS.

Regarding the sample size calculation, the original sample size proposal was increased to fulfil China's regulatory authority requirements. Therefore, the Applicant randomized approximately 60 participants after global recruitment. The Chinese patients were added as a planned China sub-study, which is considered acceptable. Additionally, the initial sample size was modified in the second protocol amendment, which was considered acceptable since it was based on external results (see further discussion in the "protocol amendments and protocol deviations" section).

Protocol amendments and protocol deviations

As of the data cut-off (31 January 2024) there were two protocol amendments implemented on the original protocol.

In the first amendment (02 August 2021), the most relevant changes were the modification of the number of expected events and follow-up time triggering the interim and final analyses, based on survival results from study CA209459. In the second amendment (01 February 2023), the results of the LEAP-002 study led to modify the statistical assumptions again. Although the comparator arm in study CA2099DW is the Investigator's choice of sorafenib or lenvatinib, the original protocol assumed that all participants would receive lenvatinib for power calculation. To maintain the study power, a modification of the follow-up time to trigger interim and final analyses was required and the information fraction to trigger OS IA was then increased from 75% to 80%.

Given the possibility of increased bias in an ongoing open- label study, the MAH was requested to clarify how the study integrity was maintained and to submit the statistical analyses as originally planned. After carefully analysing the changes on the statistical assumptions implemented to the protocol, the claimed sources of evidence for those changes, and their timing, it is considered unlikely that the protocol amendments were data driven. The changes implemented on the statistical assumptions were fully aligned with external data (results of the studies CA209459 and LEAP-002) and implemented in a timely manner after the release of these external data. Additionally – and importantly-, the results of retrospective analyses conducted by the MAH at the time of each protocol amendment were relevantly different from the statistical assumptions updated with each of the protocol amendments, suggesting that it is highly unlikely that the protocol amendments were based on CA2099DW data since, if the statistical assumptions were based on the CA2099DW data, the assumptions would have been much different from the statistical assumptions actually implemented.

The MAH also submitted the results of the analyses as planned in the original protocol (number of OS events at IA: 298) and in the protocol amendment 1 (number of OS events at IA: 392). As expected, OS would not have been statistically significant in the interim analysis conducted as planned in the original protocol [HR: 0.94 (95% CI: 0.75, 1.18)]. These results are not surprising, since the MAH changed the statistical assumptions foreseeing a lack of maturity in the primary endpoint (OS) after the results of the studies CA209459 and LEAP-002. It should be noted that if the "as planned" interim analysis had not been statistically significant, it would have proceeded to the final analysis, which was planned at 397 OS events. Reassuringly, the MAH submitted the results of the final analysis following the original protocol, which would have reached statistically significance [HR: 0.81 (95% CI: 0.66, 0.98; p-value: 0.0328; boundary: 0.0442)], which is reassuring and alleviates the concerns raised. In terms of the secondary endpoint ORR, it is noted that all responders achieved their initial response before the occurrence of 298 OS events (per original protocol); therefore, the results were the same as in the primary analysis. In terms of the secondary endpoint TTSD, the majority of TTSD events had already been observed at the time of occurrence of 298 OS events (per original protocol), and all TTSD were observed before the occurrence of 392 OS events (per protocol amendment 1).

The MAH has also submitted the results of three additional analyses conducted to handle the lack of proportional hazards assumptions (max-combo test analysis, restricted mean survival time analysis and piecewise HR analysis). The results of these analyses were consistent with the primary analysis.

Relevant protocol deviations were reported with a low frequency in both arms (4.5% in nivo+ipi vs. 3.3% in sora/lenva). However, important protocol deviations, those which may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being, were reported in a relevant percentage of patients in both arms (67.2% in nivo+ipi vs. 69.7% in sora/lenva). The percentage of deviations, although high, is balanced between both arms; and it is considered unlikely that additional sensitivity analyses will impact the final study conclusions.

Efficacy data and additional analyses

The study CA2099DW met its primary endpoint OS at the pre-planned IA (DCO: 31 January 2024), with an information fraction of 81.2% (422 events), a median follow-up of 35.20 months, and a minimum follow-up of 26.8 months. Nivo+ipi demonstrated statistically significant and clinically relevant improvement in OS over sora/lenva: HR= 0.79 (95% CI: 0.65, 0.96), stratified two-sided log-rank test p-value = 0.0180, boundary for statistical significance ≤0.0257. There were 194 events (57.9%) in the nivo+ipi arm compared with 228 events (68.5%) in the sora/lenva arm, and mOS in the nivo+ipi arm was 23.66 months (95% CI: 18.83, 29.44) compared with a mOS of 20.63 months (95% CI: 17.48, 22.54) in the sora/lenva arm. It should be highlighted that the efficacy of the comparator arm in this study has shown to be better than the one reported in prior trials (for instance, their respective pivotal) but this was already considered for the second protocol amendment, in view of the results from the LEAP-002 study. In the nivo+ipi arm, the number of censored patients was higher compared with the sora/lenva arm: 141 (42.1%) vs. 105 (31.5%), with most of censored subjects (34.9% in nivo+ipi vs. 16.5% in sora/lenva) in follow-up and only 7.2% and 11.1% off-study. Although the KM curve shows a crossing and separation after month 13, it is noted that before that moment the KM curve for nivo+ipi lays below the curve for sora/lenva; suggesting that nivo+ipi is associated with a higher risk of death than sora/lenva for the patients with a poorer prognosis. Additionally, it is noted that the KM OS curves of the supportive study CA209459, which investigated nivolumab as monotherapy in this same setting, do not show this trend; suggesting that this increased number of early deaths could be somehow associated with ipilimumab or the combination of ipilimumab and nivolumab. Of note, the comparator treatment in study CA209459 was sorafenib.

The MAH has conducted and provided several analyses to investigate the reasons for these early deaths, which is defined as a death of a subject with a death date prior to or on the timing cut-off when hazard for the treatment arms were equal, with crossing of the hazard curves.

Apart from the early deaths, the MAH has also investigated the early discontinuations, since the tolerability of this combination could also play a role in the observed results. This investigation revealed that a higher percentage of patients in the nivo+ipi arm discontinued treatment during the first 5.84 months (considered as "early discontinuation"): 55.2% of randomized subjects in nivo+ipi vs. 48% in sora/lenva. A higher percentage of patients who had an early discontinuation in nivo+ipi also died: 35.7% (66/185) in nivo+ipi vs. 24.4% (39/160) in sora/lenva. This translates into a relevant difference of 10% more deaths in the nivo+ipi arm than in the sora/lenva arm in the early discontinued patients. In terms of tolerability, a comparative table displaying the safety profile of nivo+ipi in the study CA2099DW vs. a pool of nivo+ipi in other approved indications showed a similar safety profile of nivo+ipi in HCC and nivo+ipi in other approved indications.

The supportive analyses of the reasons for early discontinuations and early deaths showed that both in patients who had an early death and in patients who did not have an early death, there was a relevantly lower percentage of patients with disease progressions in the nivo+ipi arm compared with the sora/lenva arm and a higher percentage of patients with study drug toxicity in the nivo+ipi arm than in the sora/lenva arm. These results did not support the main hypothesis for the observed difference in terms of the higher number of deaths in the nivo+ipi arm over the sora/lenva arm during the first months; which was that the immunotherapy effects usually take longer to be observed than the TKI effects, and therefore more deaths due to progression disease could be expected in the first months, potentially explaining this observation. The reasons for early deaths provided by the MAH further discarded this hypothesis. It is noted that in the nivo+ipi arm there were 11 of 66 deaths (16.7%) due to study drug toxicity, compared with one death of 39 (2.6%) in the sora/lenva arm. Additionally, there were 18 of 66 deaths (27.3%) in the nivo+ipi attributed to "other reasons" (AEs unrelated to study drug), while in the sora/lenva arm there were only 6 of 39 deaths (15.4%). These

"other reasons" were carefully analysed and overall, they do not show clear evidence of immune-mediated aetiology. The MAH conducted competing risk analyses to illustrate deaths occurring over time due to various causes, as deaths due to different reasons compete for the risk of death. The cumulative incidence curves for different death reasons suggest that, in the absence of the "other deaths", the early crossing of the curves would not have been as pronounced.

The MAH also investigated the baseline variables with imbalances in early deaths, with the aim of identifying any associated risk factors. From all the baseline variables, the one for which more evidence seemed to exist suggesting a role in the early deaths' observation was age (<65; ≥65). There were 25/66 (37.9%) patients < 65 years old suffering an early death in the nivo+ipi arm, compared with 41/66 (62.1%) patients ≥ 65 years old. This trend was not observed in the sora/lenva arm, in which 19/39 (48.7%) < 65 years old suffered an early death, compared with 20/39 (51.3%) patients ≥65 years old. A multivariate model including the age-by-treatment interaction term while adjusting the prognostic effect of other baseline covariates was conducted. For subjects with age ≥65, the odds ratio 2.82 (95% CI: 1.48, 5.36) indicated that these subjects had a higher chance of early death in the nivo+ipi arm vs. the sora/lenva arm, while this trend was much less obvious or inconclusive in subjects with age <65. The KM OS curves in patients ≥65 showed a similar trend as for the overall population, while in patients <65 there was no early crossing of the KM curves; only an initial overlapping of both curves. It is important to note the inherent limitations associated with the post-hoc nature of these analyses as well as the uncertainties of the multivariate logistic analyses conducted, which only identify factors with a strong association to an outcome from a reduced set of possible causal factors.

Bearing in mind all these limitations and after carefully assessing all the additional data regarding the potential role of age in the early deaths, no firm conclusions could be drawn regarding its potential role. The evidence available was not deemed robust enough to conclude on a potential higher risk of early death in patients ≥ 65 years old. Although the underlying reasons for the increased risk observed could not be fully elucidated, concluding that patients ≥ 65 years old are at higher risk was considered misleading. Additionally, no relevant differences were observed in the baseline characteristics of patients ≥65 years old vs. the overall population. Therefore, the role of age in the increased risk of early death was considered uncertain and it was not possible to conclude on a potential higher risk in patients ≥ 65 years old.

Upon request, the MAH also submitted a comparative table displaying the baseline characteristics of patients who suffered an early death vs. the baseline characteristics of the overall population. When analysing the data, it was noted that a higher percentage of patients in the nivo+ipi arm who suffered an early death had factors associated with a worse prognosis compared to the nivo+ipi arm of the overall population ("all randomized patients"). Patients in the nivo+ipi arm who suffered an early death had higher rates of EHS (66.7% vs. 56.1%), MVI (30.3% vs. 23%) and AFP ≥ 400 ng/ml (48.5% vs. 32.2%), larger tumours (tumours ≥ 125 mm: 31.8% vs. 21.5%), poorer liver function (Child-Pugh score > 5: 39.4% vs. 24.2%; ALBI grade > 1: 60.6% vs. 44.5%), worse performance status (ECOG PS 1: 42.4% vs. 30.4%) and higher number of liver nodules (>3: 47% vs. 37.9%) when compared to patients in the nivo+ipi arm in the overall population. A similar trend was observed in the comparator arm. All those factors are associated with worse prognosis, suggesting that the patients who suffered an early death were indeed patients with worse prognosis than the overall population included in the clinical trial. Therefore, based on these findings, the adequacy of starting treatment with nivo+ipi in patients with identified poor prognosis factors could be questioned. A warning in section 4.4 of the SmPC was added in order to make prescribers aware of this risk and advising physicians to consider this risk before initiating treatment with nivolumab in combination with ipilimumab in patients with poor prognostic features.

The MAH will submit the extended follow-up analysis of OS when available (**REC**).

ORR by BICR was included in the hierarchical testing procedure after OS, and formally tested since OS was statistically significant. Nivo+ipi demonstrated a statistically significant ORR improvement over sora/lenva; with an odds ratio of 3.61 (95% CI: 2.46, 5.29): ORR in nivo+ipi was 36.1% (95% CI: 31, 41.5) and 13.2% (95% CI: 9.8, 17.3) in sora/lenva, with no overlapping confidence intervals. Although most responses were PRs (29.3% in nivo+ipi vs. 11.4% in sora/lenva), it is noted that there were more CRs in nivo+ipi (6.9%) than in sora/lenva (1.8%). However, it is also noted that there were more SDs in sora/lenva (59.5%) than in nivo+ipi (30.4%); and, unexpectedly, more PDs in nivo+ipi (20%) than in sora/lenva (14.1%). Although the reasons for the fact that more PDs were observed in nivo+ipi than in sora/lenva are not fully elucidated and seem to be multifactorial, it is noted that this finding was already observed in other clinical trial investigating two ICIs in the same setting (i.e. HIMALAYA). **DoR** was significantly longer with nivo+ipi [30.36 (95% CI: 21.19 - NE)] than with sora/lenva [12.91 (95% CI: 10.15 - 31.21)]. Results of ORR by investigator and ORR by BICR but following the mRECIST for HCC were consistent with results of ORR by BICR; although in ORR by BICR following the mRECIST for HCC the difference between arms is subtler than when following the classical RECIST criteria [41.5% (95% CI: 36.2, 47) vs. 37.2% (95% CI: 32, 42.7)]. Of note, concordance between ORR by BICR and by investigator was 89.1%.

Time to symptom deterioration (TTSD) was included in the last place of the hierarchical testing procedure, and formally tested since ORR by BICR was statistically significant. Nivo+ipi also resulted in a significant reduction in the risk of symptom deterioration (TTSD) compared with sora/lenva, with a HR point estimate of 0.76 (95% CI: 0.62, 0.93). In nivo+ipi there was a 55.2% of patients with symptom deterioration, while in sora/lenva there was a 67.9%. Median TTSD was 2.60 months (95% CI: 2, 3.94) in nivo+ipi compared with 2.14 months (95% CI: 1.64, 2.79) in sora/lenva; with a separation in the KM curves at around month 2.

PFS by BICR, considered as an exploratory endpoint, was not clinically relevant following either of the primary or secondary definition: PFS following the primary definition (i.e. adjusting for subsequent anticancer therapy) resulted in a HR point estimate of 0.87 (95% CI: 0.72, 1.06) with a mPFS of 9.07 months in the nivo+ipi arm compared with 9.20 months in the sora/lenva; and PFS following the secondary definition (i.e. not applying censoring at subsequent anticancer therapy initiation) resulted in a HR point estimate of 0.82 (95% CI: 0.69, 0.98) with a mPFS of 8.97 months in nivo+ipi compared with 9.33 months in sora/lenva. KM curves for PFS following both definitions showed a separation at around month 13, although it is noted that curves crossed at around that month, with the curve of nivo+ipi laying below the sora/lenva curve before that moment. These KM curves are in line with the KM curves observed for OS. Although no PFS benefit was observed with nivo+ipi over sora/lenva, this is in line with the results observed in prior studies assessing immunotherapy in this setting (i.e. HIMALAYA study), highlighting the limited role of PFS as a surrogate endpoint of OS in the unresectable HCC setting.

PFS2 by investigator resulted in longer mPFS2 in nivo+ipi than in sora/lenva; although it is noted that since it was assessed by investigator in the context of an open-label study, it should be interpreted with caution.

Subgroups analyses were overall consistent with the analysis in the overall population. Treatment effect seems to be slightly lower in the "Asian other" (N=69) and "HCV aetiology per central lab" (N=54) subgroups, but the interpretation of the results is highly hampered by the low number of events and patients of these subgroups. Other subgroups such as "B BCLC category at baseline" (N=128), "HBV aetiology per central lab" (N=197) and "< 200 ng/ml baseline AFP category" also resulted in HR point estimates close to 1, but considering that the reported HR point estimate for the overall population is 0.79 (95% CI: 0.65, 0.96), these results could be considered as consistent with the overall population.

Subgroup analysis in PD-L1 CPS<1% patients showed a slightly higher HR point estimate [HR= 0.92 (95% CI: 0.68, 1.24)] than PD-L1 ≥1% patients [HR= 0.63 (95% CI: 0.32, 1.22)] and that patients with unknown PD-L1 status [HR= 0.74 (95% CI: 0.56, 0.96)]. However, it is noted that quantifiable PD-L1 test results at baseline were only available for 43.6% of subjects (291/668); meaning than the PD-L1 status of more than half of subjects is unknown (N=377). Reassuringly, the percentage of missing values was similar in both arms. The majority of the available values were PD-L1 negative (TPS≥ 1%: 3.4% of subjects; CPS≥ 1%: 18.9% of subjects); which translate into very low PD-L1 positive values, hampering the interpretation of the scarce data available. Therefore, considering the low number of PD-L1 test results and the low number of PD-L1 positive test results, no conclusion can be drawn regarding potential subgroup differences by PD-L1 status.

Contribution of each component

The MAH has provided additional data to establish the contribution of each component in the nivo+ipi combination: the results of the Phase 3 study CA209459 and the results of the Phase 1/2 study CA209040.

Study CA209459 was a Phase 3 study evaluating nivolumab as monotherapy vs. sorafenib as first-line treatment in systemic therapy-naive patients with advanced HCC. Study CA209459 was a randomized, open-label, multicentre study, with a similar design as the pivotal study for this submission, CA2099DW. CA209459 did not achieve statistical significance [HR: 0.85 (95% CI: 0.72, 1.02); p=0.752], although KM curves showed a delayed benefit of nivo over sora, reflected by a slight increase in mOS (16.39 months vs. 14.69 months) and an improvement in ORR (15.4% vs. 7.0%). Of note, baseline characteristics of the patients included in this study were similar to the baseline characteristics of study CA2099DW. Additionally, the comparator was sorafenib, one of the comparators allowed in study CA2099DW, which, although administered to only 15% of patients (in comparison with lenvatinib, administered to 85% of patients), is associated with similar OS benefits as lenvatinib, to some extent. This study could therefore be considered as supportive – acknowledging all the inherent limitations of indirect comparisons - for establishing the contribution of the components of the nivo+ipi combination, namely the contribution of ipilimumab. In this regard, it is noted that nivolumab as monotherapy in 1L uHCC seems to be associated with an anti-tumour activity which is not sufficient as to be considered as clinically relevant nor statistically significant. The addition of 4 cycles of ipilimumab seems to enhance the anti-tumour activity of nivolumab, reflected both in clinically relevant OS improvements and in an improved anti-tumour activity (i.e. ORR and DOR). Therefore, although the data provided only serve as supportive evidence since it only allows indirect comparisons, the contribution of ipilimumab could be considered established.

The MAH also considered the Phase 1/2 study CA209040 as supportive evidence to justify the contribution of both components. However, it is noted that this study included a considerably lower number of patients and that the investigated setting was not exactly the same investigated in CA2099DW since in this study patients had to have received sorafenib before (i.e. second-line treatment). Additionally, this study was not comparative, further hampering its interpretation. Baseline characteristics also differed from the baseline characteristics of study CA2099DW, since – as expected – patients seemed to be in a more advanced stage of the disease, with an overall poorer health status. Therefore, this study is not considered supportive to establish the contribution of each component.

Wording of the indication

The indications sought by the MAH are the following:

"*OPDIVO in combination with ipilimumab is indicated for the first line treatment of adult patients with unresectable or advanced hepatocellular carcinoma*."

"YERVOY in combination with nivolumab is indicated for the first-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma."

The proposed indications are considered acceptable and in line with other indications in the same setting.

2.4.2. Conclusions on the clinical efficacy

Nivolumab in combination with ipilimumab followed by nivolumab as monotherapy has demonstrated a statistically significant improvement in OS, with a clinically relevant increase in mOS of around 3 months. This OS benefit was further supported by benefit in terms of ORR, with durable responses. Although most of the responses were partial responses, a higher percentage of complete responses was observed with nivo+ipi. Results of TTSD also favoured nivo+ipi over sora/lenva.

A higher number of deaths was observed during the first 6 months with nivolumab in combination with ipilimumab compared to lenvatinib or sorafenib. Early death was associated with the presence of poor prognostic features in patients (presence of EHS or MVI, AFP levels ≥ 400 ng/ml, larger tumours and higher number of liver nodules (>3), poorer liver function (Child-Pugh score > 5; ALBI grade > 1), and worse performance status (ECOG PS 1)). A warning in section 4.4 of the SmPC has been included advising physicians to consider this risk before initiating treatment with nivo+ipi in patients with poor prognosis features.

2.5. Clinical safety

Introduction

The safety assessment for this application is based on the use of nivo+ipi for 1L treatment of patients with unresectable or advanced hepatocellular carcinoma (HCC) based on All Treated Population in the nivo+ipi (N=332) and SOC (N=325) in the pivotal study CA2099DW. This is a phase 3, open label, randomized controlled study evaluating the safety and efficacy of nivolumab combined with ipilimumab ('nivo+ipi') vs investigator's choice of sorafenib or lenvatinib (SOC) as 1L therapy for adult subjects with unresectable or advanced HCC.

The clinical cut-off occurred on 31 January 2024 and DBL occurred on 28 February 2024 for the CA2099DW Primary CSR, providing a minimum follow-up (calculating from the date of last patient randomized to the date of LPLV) of 26.8 months and a median follow-up of 35.20 months.

Patient exposure

With the DBL of 28 February 2024, 332 subjects were treated with nivo (1 mg/kg) + ipi (3 mg/kg), with 200 subjects receiving nivo monotherapy (480 mg). Of the 325 treated subjects in the SOC arm, 50 received sorafenib (400 mg), 62 received lenvatinib 8 mg and 213 subjects received lenvatinib 12 mg. A total of 62 subjects in the nivo+ipi arm and 157 subjects in the SOC arm were treated beyond progression (defined as subjects whose last available dose date is after the date of radiographic progression per investigator RECIST 1.1).

Subjects treated with nivolumab and ipilimumab could discontinue ipilimumab and continue to receive nivolumab monotherapy (480 mg flat dose Q4W) before completing 4 doses of ipi.

As of the clinical cut-off date (31 January 2024), 332 (100%) and 310 (95.4%) subjects in the nivo+ipi and SOC arms, respectively, had discontinued study treatment. The most common reason for not continuing on study treatment was disease progression: 40.1% in the nivo+ipi arm, 68.9% in the

SOC arm. Study drug toxicity was reported as the reason for not continuing in the treatment period for the 22.3% of subjects in the nivo+ipi arm, 11.1% in the SOC arm.

Table 70 Subject Disposition – All Enrolled, Randomized, and Treated Subjects

	No. of Subjects (%)		
	Nivo+Ipi	SOC	Total
Enrolled	N.A.	N.A.	1148 (100)
Randomized	335	333	668 (58.2)
Treated	332 (99.1)	325 (97.6)	657 (98.4)
Not Treated	3 (0.9)	8 (2.4)	11 (1.6)
Reason for Not Treated			
Disease Progression	1 (0.3)	0	1 (0.1)
Subject Withdrew Consent	1 (0.3)	6 (1.8)	7 (1.0)
Subject no Longer Meets Study Criteria	1 (0.3)	2 (0.6)	3 (0.4)
Continuing in the Treatment Period	0	15 (4.6)[a]	15 (2.3)[a]
Not Continuing in the Treatment Period	332 (100)	310 (95.4)	642 (97.7)
Reason for Not Continuing in the Treatment Period			
Disease Progression	133 (40.1)	224 (68.9)	357 (54.3)
Study Drug Toxicity	74 (22.3)	36 (11.1)	110 (16.7)
Subject Request to Discontinue Study Treatment	6 (1.8)	9 (2.8)	15 (2.3)
Death	2 (0.6)	1 (0.3)	3 (0.5)
Adverse Event Unrelated to Study Drug	33 (9.9)	22 (6.8)	55 (8.4)
Subject Withdrew Consent	7 (2.1)	6 (1.8)	13 (2.0)
Lost to Follow-Up	1 (0.3)	0	1 (0.2)
Maximum Clinical Benefit	2 (0.6)	2 (0.6)	4 (0.6)
Poor/Non-Compliance	0	1 (0.3)	1 (0.2)
Administrative Reasons by Sponsor[b]	9 (2.7)	2 (0.6)	11 (1.7)
Other	65 (19.6)[c]	7 (2.2)[d]	72 (11.0)
Continuing in the Study	261 (78.6)	273 (84.0)	534 (81.3)
Not Continuing in the Study[e]	71 (21.4)	52 (16.0)	123 (18.7)
Reason for Not Continuing in the Study			
Death	50 (15.1)	26 (8.0)	76 (11.6)
Lost to Follow-Up	1 (0.3)	0	1 (0.2)
Subject Withdrew Consent	12 (3.6)	20 (6.2)	32 (4.9)
Other	8 (2.4)[f]	6 (1.8)[g]	14 (2.1)

[a] Includes 2 subjects from Russia that are no longer on treatment but reported as "on treatment" and 1 subject reported as "treatment completed" due to Russian exit.

[b] Closure of Russian Sites due to increased logistical challenges due to the Russian /Ukrainian political crisis.

[c] Includes subjects who completed 2 years of treatment (n=54), PI's decision free text reasons (n=5), Dose delay lasting > 8 weeks (per protocol) (n=2), Subject's decision (n=2), and Russian subjects that discontinued treatment (n = 2).

[d] Includes PI's decision (n=5); Subject's decision (n=2).

[e] Status at the end of treatment period.

[f] Includes subjects involved in Russian exit=7; and General Condition deterioration n=1.

[g] Includes subjects involved in Russian exit=4, Subject's decision=2.

Percentages based on subjects entering period.

Among all treated subjects, the median duration of therapy was 4.68 months for the nivo+ipi arm and 6.93 months for the SOC arm. The proportion of subjects with treatment durations >12 months was 30.1% in the nivo+ipi arm and 28.9% in the SOC arm. While for >18 months, the percentage of subjects on treatment for was numerically higher in the nivo+ipi (22.9%) compared with SOC arm (12.6%).

The maximum duration of treatment per protocol was 24 months for nivo+ipi.

The median (min - max) number of doses of each therapy per arm were:

- Nivo + ipi arm (N=332): 4.0 (1-4) doses of nivo, 4.0 (1-4) doses of ipi
- SOC arm (N=325): 127.5 (8-792) dose of sorafenib (N=50), 196.0 (3-1097) for the 8 mg dose of lenvatinib (N=62), 211.0 (1-1135) for the 12 mg dose of lenvatinib (N=213).

The proportions of subjects who received ≥90% of the planned relative dose intensity of each therapy were as follows by arm (Table 71, Table 72):

- Nivo + ipi arm (N=332): 80.1% for nivo, 79.5% for ipi, and 93.5% for nivo monotherapy
- SOC arm (N=325): 24.0% for sorafenib (N=50), 53.2% for the 8 mg dose of lenvatinib (N=62), 26.3% for the 12 mg dose of lenvatinib (N=213).

Table 71 Cumulative Dose and Relative Dose Intensity Summary – All Nivo+Ipi Treated Subjects

	Nivo + Ipi N = 332		
	Nivo* (mg/kg) N = 332	Ipi (mg/kg) N = 332	Nivo* (mg) N = 200
NUMBER OF DOSES RECEIVED			
MEAN (SD)	3.3 (1.01)	3.3 (1.02)	12.0 (8.56)
MEDIAN (MIN - MAX)	4.0 (1 - 4)	4.0 (1 - 4)	10.0 (1 - 24)
CUMULATIVE DOSE			
MEAN (SD)	3.3 (1.08)	9.8 (3.10)	5750.5 (4109.83)
MEDIAN (MIN - MAX)	4.0 (1 - 10)	11.9 (3 - 13)	4800.0 (65 - 11520)
RELATIVE DOSE INTENSITY (%)			
≥ 110%	3 (0.9)	2 (0.6)	0
90% TO < 110%	266 (80.1)	264 (79.5)	187 (93.5)
70% TO < 90%	45 (13.6)	48 (14.5)	11 (5.5)
50% TO < 70%	16 (4.8)	16 (4.8)	1 (0.5)
< 50%	2 (0.6)	2 (0.6)	1 (0.5)

* The unit for Nivolumab is mg/kg in combination phase and mg in monotherapy phase.

Table 72 Cumulative Dose and Relative Dose Intensity Summary – All Sorafenib or Lenvatinib Treated Subjects

	Sora / Lenva N = 325		
		Lenvatinib (mg) N = 275	
	Sorafenib (mg) N = 50	Lenvatinib 8 mg N = 62	Lenvatinib 12 mg N = 213
NUMBER OF DOSES RECEIVED			
MEAN (SD)	203.9 (202.68)	259.9 (236.53)	281.6 (248.25)
MEDIAN (MIN - MAX)	127.5 (8 - 792)	196.0 (3 - 1097)	211.0 (1 - 1135)
CUMULATIVE DOSE			
MEAN (SD)	120868.0 (118864.23)	1795.5 (1698.39)	2589.1 (2272.69)
MEDIAN (MIN - MAX)	85700.0 (4600 - 472400)	1214.0 (24 - 8720)	1976.0 (12 - 11988)
RELATIVE DOSE INTENSITY (%)			
≥ 110%	0	1 (1.6)	0
90% TO < 110%	12 (24.0)	33 (53.2)	56 (26.3)
70% TO < 90%	11 (22.0)	9 (14.5)	57 (26.8)
50% TO < 70%	14 (28.0)	12 (19.4)	60 (28.2)
< 50%	13 (26.0)	7 (11.3)	40 (18.8)
AVERAGE DAILY DOSE (MG/DAY)			
MEAN (SD)	571.36 (200.819)	6.94 (1.538)	9.25 (2.510)
MEDIAN (MIN - MAX)	573.68 (79.3 - 800.0)	7.83 (3.3 - 9.5)	9.60 (2.8 - 12.0)

Table 73 Duration of Study Therapy Summary – All Treated Subjects

	Nivo + Ipi N = 332	Sora / Lenva N = 325
DURATION OF THERAPY (MONTHS)		
MEAN (MIN, MAX)	8.73 (<0.1, 24.4)	9.30 (<0.1, 45.8)
MEDIAN	4.68	6.93
> 3 MONTHS (%)	196 (59.0)	245 (75.4)
> 6 MONTHS (%)	150 (45.2)	170 (52.3)
> 9 MONTHS (%)	121 (36.4)	134 (41.2)
> 12 MONTHS (%)	100 (30.1)	94 (28.9)
> 15 MONTHS (%)	87 (26.2)	68 (20.9)
> 18 MONTHS (%)	76 (22.9)	41 (12.6)
> 21 MONTHS (%)	66 (19.9)	30 (9.2)
> 24 MONTHS (%)	6 (1.8)	22 (6.8)
> 27 MONTHS (%)	0	18 (5.5)
> 30 MONTHS (%)	0	13 (4.0)
> 33 MONTHS (%)	0	8 (2.5)
> 36 MONTHS (%)	0	3 (0.9)
> 39 MONTHS (%)	0	1 (0.3)
> 42 MONTHS (%)	0	1 (0.3)
> 45 MONTHS (%)	0	1 (0.3)

Dose modifications

Dose reductions of nivo and/or ipi were not permitted. Dose reductions for SOC (sorafenib or lenvatinib) were permitted. First dose reductions of sorafenib were allowed to 400 mg once daily and dose reductions of lenvatinib were allowed to 8 mg (if body weight ≥60 kg) or 4 mg (if body weight <60 kg). Additional reductions in sorafenib or lenvatinib dose were allowed as per respective local SmPCs or locally approved product labels.

Dose delays of nivo and/or ipi were allowed. Most treated subjects in the nivo+ipi arm received their study medication without an infusion interruption or rate reduction; however, dose delays (mostly due to AEs) were frequently reported. In all SOC treated subjects, dose interruption was the most common type of dose modification; most dose interruptions were due to AEs.

- Nivo+Ipi Arm

Dose delays (proportion of subjects with at least 1 dose delay) were reported in 27.1% subjects for nivo and 26.5% subjects for ipi during combination phase, and in 60.5% subjects for nivo during monotherapy phase. Nearly one third of the dose delays for both lasted 4-7 days. The most common cause of dose delay in the nivo+ipi arm was 'adverse event'.

Table 74 Dose Delay Summary for Nivolumab and Ipilimumab - All Nivolumab + Ipilimumab Treated Subjects

	Nivo + Ipi N = 332		
	Nivo* (mg/kg) N = 332	Ipi (mg/kg) N = 332	Nivo* (mg) N = 200
SUBJECTS WITH AT LEAST ONE DOSE DELAYED (%)	90 (27.1)	88 (26.5)	121 (60.5)
NUMBER OF DOSES DELAYED PER SUBJECT (%)			
0	242 (72.9)	244 (73.5)	79 (39.5)
1	71 (21.4)	69 (20.8)	68 (34.0)
2	15 (4.5)	15 (4.5)	31 (15.5)
3	4 (1.2)	4 (1.2)	12 (6.0)
≥ 4	0	0	10 (5.0)
TOTAL NUMBER OF DOSES DELAYED/ TOTAL NUMBER OF DOSES RECEIVED (%) (A)	113/752 (15.0)	111/749 (14.8)	213/2197 (9.7)
REASON FOR DOSE DELAY (%) (B)			
ADVERSE EVENT	99 (87.6)	97 (87.4)	134 (62.9)
OTHER	7 (6.2)	6 (5.4)	32 (15.0)
NOT REPORTED	7 (6.2)	8 (7.2)	47 (22.1)
LENGTH OF DOSE DELAY (%) (B)			
4 - 7 DAYS	36 (31.9)	36 (32.4)	70 (32.9)
8 - 14 DAYS	26 (23.0)	25 (22.5)	57 (26.8)
15 - 42 DAYS	41 (36.3)	41 (36.9)	67 (31.5)
43 - 84 DAYS	10 (8.8)	9 (8.1)	12 (5.6)
≥ 85 DAYS	0	0	7 (3.3)

* The unit for Nivolumab is mg/kg in combination phase and mg in monotherapy phase.
A dose was considered as actually delayed if the delay is exceeding 3 days for Nivolumab or Ipilimumab.
(A) TOTAL NUMBER OF DOSES RECEIVED is excluding first dose.
(B) Percentages are computed out of the total number of doses delayed.

Infusion interruptions: During the combination phase, 2 (0.6%) subjects were reported with a nivo infusion interruption, and 7 (2.1%) subjects were reported with an ipi infusion interruption. During the monotherapy phase, 5 (2.5%) subjects were reported with a nivo infusion interruption. Of the subjects, who were reported with infusion interruption, the majority were reported with 1 interrupted infusion.

Table 75 Dose Infusion Interruption Summary for Nivolumab and Ipilimumab – All Nivolumab + Ipilimumab Treated Subjects

	Nivo + Ipi N = 332		
	Nivo* (mg/kg) N = 332	Ipi (mg/kg) N = 332	Nivo* (mg) N = 200
SUBJECTS WITH AT LEAST ONE INFUSION INTERRUPTED (%)	2 (0.6)	7 (2.1)	5 (2.5)
NUMBER OF INFUSIONS INTERRUPTED PER SUBJECT (%)			
0	330 (99.4)	325 (97.9)	195 (97.5)
1	2 (0.6)	5 (1.5)	5 (2.5)
2	0	2 (0.6)	0
3	0	0	0
≥ 4	0	0	0
TOTAL NUMBER OF INFUSIONS INTERRUPTED/ TOTAL NUMBER OF DOSES RECEIVED (%)	2/1084 (0.2)	9/1081 (0.8)	5/2397 (0.2)
REASON FOR INFUSION INTERRUPTION (%) (A)			
HYPERSENSITIVITY REACTION	1 (50.0)	7 (77.8)	0
ADMINISTRATION ISSUES	1 (50.0)	0	1 (20.0)
OTHER	0	2 (22.2)	4 (80.0)

* The unit for Nivolumab is mg/kg in combination phase and mg in monotherapy phase.
(A) Percentages are computed out of the total number of doses interrupted by treatment arm.

Infusion rate reductions: During the combination phase, infusion rate reductions were reported in 4 (1.2%) subjects for nivo and 7 (2.1%) subjects for ipi. During the monotherapy phase, infusion rate reduction was reported in 1 (0.5%) subject for nivo.

Table 76 Infusion Rate Reduction Summary for Nivolumab and Ipilimumab – All Nivolumab + Ipilimumab Treated Subjects

	Nivo + Ipi N = 332		
	Nivo* (mg/kg) N = 332	Ipi (mg/kg) N = 332	Nivo* (mg) N = 200
SUBJECTS WITH AT LEAST ONE INFUSION WITH IV RATE REDUCED (%)	4 (1.2)	7 (2.1)	1 (0.5)
NUMBER OF INFUSIONS WITH IV RATE REDUCTIONS PER SUBJECT (%)			
0	328 (98.8)	325 (97.9)	199 (99.5)
1	3 (0.9)	4 (1.2)	0
2	1 (0.3)	3 (0.9)	0
3	0	0	0
≥ 4	0	0	1 (0.5)
TOTAL NUMBER OF IV RATES REDUCED/ TOTAL NUMBER OF DOSES RECEIVED (%)	5/1084 (0.5)	10/1081 (0.9)	5/2397 (0.2)
REASON FOR IV RATE REDUCTION (%) (A)			
HYPERSENSITIVITY REACTION	2 (40.0)	6 (60.0)	4 (80.0)
ADMINISTRATION ISSUES	0	1 (10.0)	0
OTHER	3 (60.0)	3 (30.0)	1 (20.0)

* The unit for Nivolumab is mg/kg in combination phase and mg in monotherapy phase.
(A) Percentages are computed out of the total number of infusions with IV rate reduction by treatment arm.

The most frequently reported drug-related AEs leading to a dose delay or infusion interruption were: AST increased (10.2%), ALT increased (9.9%), and diarrhoea (4.5%).

- SOC Arm

Dose interruptions were reported in 80.0% subjects for sorafenib, 56.5% subjects for lenvatinib 8 mg and 74.6% subjects for lenvatinib 12 mg. Adverse event was the most commonly reported cause for dose interruption.

Dose reductions were reported in 12.0% subjects for sorafenib, 35.5% subjects for lenvatinib 8 mg and 67.6% subjects for lenvatinib 12 mg. Adverse event was the most commonly reported cause for dose reduction.

The most frequently reported drug-related AEs leading to a dose interruption for SOC arm were: proteinuria (7.4%), hypertension and palmar-plantar erythrodysaesthesia syndrome (6.2% each), and diarrhoea (5.5%).

Adverse events

AEs (all causality) were reported for 99.7% in the nivo+ipi arm and 98.5% in the SOC arm. Grade 3-4 AEs were reported in 69.3% of patients in the nivo+ipi arm and 62.5% in the SOC arm.

Table 77 Overall Safety Summary - All Treated Subjects in the Nivo+Ipi and SOC Arms - CA2099DW

	Number (%) of Subjects			
Safety Parameters, n (%)	**Nivo+Ipi (N = 332)**		**SOC (N = 325)**	
Deaths (overall)	192 (57.8)		224 (68.9)	
Primary Reason for Death				
Disease	139 (41.9)		202 (62.2)	
Study Drug Toxicity[a]	12 (3.6)		3 (0.9)	
Unknown	6 (1.8)		5 (1.5)	
Other [b,c]	35 (10.5)		14 (4.3)	
	Adverse Event Grades			
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	176 (53.0)	154 (46.4)	143 (44.0)	115 (35.4)
Drug-related SAEs	94 (28.3)	83 (25.0)	47 (14.5)	42 (12.9)
All-causality AEs leading to DC[d]	88 (26.5)	69 (20.8)	75 (23.1)	51 (15.7)
Drug-related AEs leading to DC[d]	59 (17.8)	44 (13.3)	34 (10.5)	21 (6.5)
All-causality AEs	331 (99.7)	230 (69.3)	320 (98.5)	203 (62.5)
Drug-related AEs	278 (83.7)	137 (41.3)	297 (91.4)	138 (42.5)
≥ 15% of Subjects in Either Arm, by PT				
Pruritus	93 (28.0)	5 (1.5)	10 (3.1)	0
AST increased	65 (19.6)	20 (6.0)	27 (8.3)	2 (0.6)
Rash	64 (19.3)	6 (1.8)	29 (8.9)	3 (0.9)
ALT increased	63 (19.0)	16 (4.8)	19 (5.8)	3 (0.9)
Diarrhea	47 (14.2)	4 (1.2)	114 (35.1)	10 (3.1)
Hypothyroidism	40 (12.0)	0	79 (24.3)	0
Asthenia	34 (10.2)	1 (0.3)	51 (15.7)	5 (1.5)
Fatigue	27 (8.1)	0	50 (15.4)	6 (1.8)
Decreased appetite	23 (6.9)	1 (0.3)	70 (21.5)	5 (1.5)
Palmar-plantar erythrodysaesthesia syndrome	6 (1.8)	0	99 (30.5)	11 (3.4)
Hypertension	5 (1.5)	0	134 (41.2)	38 (11.7)
Proteinuria	0	0	65 (20.0)	17 (5.2)
Endocrine	105 (31.6)	12 (3.6)	116 (35.7)	0
Gastrointestinal	83 (25.0)	20 (6.0)	127 (39.1)	11 (3.4)
Hepatic	172 (51.8)	72 (21.7)	96 (29.5)	28 (8.6)
Pulmonary	9 (2.7)	2 (0.6)	2 (0.6)	1 (0.3)
All-causality Select AEs, by Category (continued)				
Renal	25 (7.5)	7 (2.1)	23 (7.1)	6 (1.8)
Skin	206 (62.0)	20 (6.0)	155 (47.7)	19 (5.8)
Hypersensitivity/Infusion Reactions	8 (2.4)	1 (0.3)	1 (0.3)	0
Drug-related Select AEs, by Category				

Safety Parameters, n (%)	Number (%) of Subjects			
	Nivo+Ipi (N = 332)		SOC (N = 325)	
Endocrine	94 (28.3)	12 (3.6)	102 (31.4)	0
Gastrointestinal	56 (16.9)	17 (5.1)	114 (35.1)	10 (3.1)
Hepatic	114 (34.3)	56 (16.9)	61 (18.8)	16 (4.9)
Pulmonary	7 (2.1)	1 (0.3)	0	0
Renal	6 (1.8)	1 (0.3)	11 (3.4)	2 (0.6)
Skin	172 (51.8)	19 (5.7)	139 (42.8)	16 (4.9)
Hypersensitivity/Infusion Reactions	8 (2.4)	1 (0.3)	0	0
All-causality Non-Endocrine IMAEs within 100 days of Last Dose Treated with Immune Modulating Medication, by Category				
Diarrhea/Colitis	28 (8.4)	15 (4.5)	1 (0.3)	1 (0.3)
Hepatitis	63 (19.0)	51 (15.4)	0	0
Pneumonitis	7 (2.1)	3 (0.9)	0	0
Nephritis/Renal Dysfunction	5 (1.5)	3 (0.9)	0	0
Rash	51 (15.4)	14 (4.2)	2 (0.6)	1 (0.3)
Hypersensitivity/ Infusion Reactions	4 (1.2)	0	0	0
All-causality Endocrine IMAEs within 100 days of Last Dose With or Without Immune Modulating Medication, by Category				
Adrenal Insufficiency	18 (5.4)	6 (1.8)	0	0
Hypothyroidism/ Thyroiditis	62 (18.7)	1 (0.3)	11 (3.4)	0
Diabetes Mellitus	2 (0.6)	2 (0.6)	0	0
Hyperthyroidism	36 (10.8)	2 (0.6)	0	0
Hypophysitis	9 (2.7)	4 (1.2)	0	0
All-causality OESIs within 100 days of last dose[e] With or Without Immune Modulating Medication, by Category				
Myasthenic Syndrome	1 (0.3)	1 (0.3)	0	0
Demyelination	1 (0.3)	0	0	0
Pancreatitis	9 (2.7)	4 (1.2)	2 (0.6)	2 (0.6)
Myocarditis	3 (0.9)	2 (0.6)	0	0
Myositis/Rhabdomyolysis	4 (1.2)	3 (0.9)	1 (0.3)	1 (0.3)
Autoimmune Cytopenia	2 (0.6)	1 (0.3)	0	0

[a] Deaths considered related to study drug per investigator in the nivo+ipi arm (4 due to immune-mediated hepatitis, 3 due to hepatic failure, 1 due to hepatic insufficiency, 1 due to decompensated cirrhosis, 1 due to diarrhoea-colitis, 1 due to autoimmune haemolytic anaemia/hepatic failure, and 1 due to dysautonomia) and in the SOC arm (1 due to hepatorenal syndrome, 1 due to ischemic stroke, 1 due to acute kidney injury).
[b] The verbatim terms reported for the 'other' reasons for death were consistent with events anticipated in the study population and in the context of the COVID-19 pandemic. None were considered related to study drug (per the investigator).
[c]Included 7 subjects who died due to COVID-19 infection.
[d]Discontinuation of any drug in the regimen.
[e]No OESIs were reported in the following categories: Guillain-Barre syndrome, uveitis, encephalitis, graft vs host disease, autoimmune eye disorder, and immune mediated arthritis.
MedDRA version 26.1; CTC version 5.0.
Includes events reported between first dose and 30 days after last dose of study therapy, unless otherwise indicated.

For nivo+ipi, the most frequently reported AEs (all grades, PTs) were pruritus (34.3%), AST increased (29.5%), and rash (24.4%). The most frequently reported Grade 3-4 AEs (PTs) were AST increased (7.5%), lipase increased (7.2%), and ALT increased and malignant neoplasm progression (5.7% each).

For SOC the most frequently reported AEs (all grades, PTs) were hypertension (44.6%), diarrhoea (39.1%), and palmar-plantar erythrodysaesthesia syndrome (32.0%). The most frequently reported Grade 3-4 AEs (PTs) were hypertension (13.2%), malignant neoplasm progression (7.1%), and proteinuria (5.2%).

When the AE frequencies were exposure-adjusted, AE incidence rates (per 100 person-years) were lower with nivo+ipi (1211.1) than with SOC (1305.9) in treated patients.

COVID-19 AEs between first treatment and 30 days after last dose of study therapy were reported in 9.3% of patients in the nivo+ipi arm and 4.9% of patients in the SOC arm.

Table 78 Adverse Events by Worst CTC Grade Reported ≥10% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivo + Ipi N = 332			Sora / Lenva N = 325		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	331 (99.7)	230 (69.3)	7 (2.1)	320 (98.5)	203 (62.5)	15 (4.6)
Skin and subcutaneous tissue disorders	211 (63.6)	21 (6.3)	0	177 (54.5)	21 (6.5)	0
Pruritus	114 (34.3)	5 (1.5)	0	21 (6.5)	1 (0.3)	0
Rash	81 (24.4)	6 (1.8)	0	32 (9.8)	4 (1.2)	0
Palmar-plantar erythrodysaesthesia syndrome	7 (2.1)	0	0	104 (32.0)	13 (4.0)	0
Gastrointestinal disorders	192 (57.8)	49 (14.8)	0	233 (71.7)	38 (11.7)	0
Diarrhoea	73 (22.0)	7 (2.1)	0	127 (39.1)	11 (3.4)	0
Nausea	32 (9.6)	1 (0.3)	0	53 (16.3)	3 (0.9)	0
Constipation	27 (8.1)	0	0	50 (15.4)	1 (0.3)	0
Abdominal pain	25 (7.5)	3 (0.9)	0	55 (16.9)	6 (1.8)	0
Vomiting	23 (6.9)	2 (0.6)	0	36 (11.1)	1 (0.3)	0
Investigations	185 (55.7)	70 (21.1)	0	168 (51.7)	48 (14.8)	0
Aspartate aminotransferase increased	98 (29.5)	25 (7.5)	0	44 (13.5)	4 (1.2)	0
Alanine aminotransferase increased	79 (23.8)	19 (5.7)	0	35 (10.8)	6 (1.8)	0
Lipase increased	59 (17.8)	24 (7.2)	0	24 (7.4)	5 (1.5)	0
Amylase increased	50 (15.1)	6 (1.8)	0	13 (4.0)	2 (0.6)	0
Blood bilirubin increased	39 (11.7)	6 (1.8)	0	34 (10.5)	7 (2.2)	0
Weight decreased	28 (8.4)	1 (0.3)	0	67 (20.6)	9 (2.8)	0
General disorders and administration site conditions	174 (52.4)	19 (5.7)	1 (0.3)	184 (56.6)	29 (8.9)	1 (0.3)
Asthenia	63 (19.0)	4 (1.2)	0	67 (20.6)	7 (2.2)	0
Fatigue	48 (14.5)	4 (1.2)	0	64 (19.7)	6 (1.8)	0
Pyrexia	48 (14.5)	1 (0.3)	0	30 (9.2)	5 (1.5)	0
Oedema peripheral	37 (11.1)	4 (1.2)	0	39 (12.0)	5 (1.5)	0
Metabolism and nutrition disorders	139 (41.9)	35 (10.5)	0	148 (45.5)	29 (8.9)	0
Decreased appetite	53 (16.0)	4 (1.2)	0	91 (28.0)	6 (1.8)	0
Endocrine disorders	95 (28.6)	11 (3.3)	0	105 (32.3)	0	0
Hypothyroidism	45 (13.6)	0	0	88 (27.1)	0	0
Hyperthyroidism	37 (11.1)	2 (0.6)	0	5 (1.5)	0	0
Musculoskeletal and connective tissue disorders	95 (28.6)	9 (2.7)	0	120 (36.9)	5 (1.5)	0
Arthralgia	41 (12.3)	1 (0.3)	0	43 (13.2)	2 (0.6)	0
Respiratory, thoracic and mediastinal disorders	93 (28.0)	11 (3.3)	0	111 (34.2)	8 (2.5)	0
Cough	40 (12.0)	0	0	23 (7.1)	0	0

System Organ Class (%) Preferred Term (%)	Nivo + Ipi N = 332 Any Grade	Grade 3-4	Grade 5	Sora / Lenva N = 325 Any Grade	Grade 3-4	Grade 5
Dysphonia	6 (1.8)	0	0	59 (18.2)	0	0
Blood and lymphatic system disorders	77 (23.2)	20 (6.0)	0	68 (20.9)	19 (5.8)	0
Anaemia	42 (12.7)	9 (2.7)	0	26 (8.0)	9 (2.8)	0
Thrombocytopenia	22 (6.6)	5 (1.5)	0	38 (11.7)	4 (1.2)	0
Nervous system disorders	72 (21.7)	14 (4.2)	0	87 (26.8)	16 (4.9)	1 (0.3)
Headache	26 (7.8)	0	0	35 (10.8)	1 (0.3)	0
Vascular disorders	47 (14.2)	13 (3.9)	0	154 (47.4)	52 (16.0)	0
Hypertension	32 (9.6)	9 (2.7)	0	145 (44.6)	43 (13.2)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	39 (11.7)	24 (7.2)	5 (1.5)	53 (16.3)	29 (8.9)	13 (4.0)
Malignant neoplasm progression	30 (9.0)	19 (5.7)	5 (1.5)	43 (13.2)	23 (7.1)	13 (4.0)
Renal and urinary disorders	27 (8.1)	7 (2.1)	0	95 (29.2)	27 (8.3)	0
Proteinuria	2 (0.6)	0	0	71 (21.8)	17 (5.2)	0

MedDRA Version: 26.1, CTCAE Version 5.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Drug-related AEs were reported in 83.7 of patients in the nivo+ipi arm and in 91.4% in the SOC arm (all grades); Grade 3-4 drug-related AEs (41.3% vs 42.5%).

For nivo+ipi the most frequently reported drug-related AEs (all grades, PTs) were pruritus (28.0%), AST increased (19.6%) and rash (19.3%). The most frequently reported drug-related Grade 3-4 AEs (PTs) were AST increased (6.0%), lipase increased (5.1%), and ALT increased (4.8%).

For SOC the most frequently reported drug-related AEs (all grades, PTs) were hypertension (41.2%), diarrhoea (35.1%), and palmar-plantar erythrodysaesthesia syndrome (30.5%). The most frequently reported drug-related Grade 3-4 AEs (PTs) were hypertension (11.7%), proteinuria (5.2%), and palmar-plantar erythrodysaesthesia syndrome (3.4%).

Table 79 Drug-related Adverse Events by Worst CTC Grade Reported ≥10% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivo + Ipi N = 332 Any Grade	Grade 3-4	Grade 5	Sora / Lenva N = 325 Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	278 (83.7)	137 (41.3)	0	297 (91.4)	138 (42.5)	0
Skin and subcutaneous tissue disorders	174 (52.4)	20 (6.0)	0	154 (47.4)	18 (5.5)	0
Pruritus	93 (28.0)	5 (1.5)	0	10 (3.1)	0	0
Rash	64 (19.3)	6 (1.8)	0	29 (8.9)	3 (0.9)	0
Palmar-plantar erythrodysaesthesia syndrome	6 (1.8)	0	0	99 (30.5)	11 (3.4)	0
Investigations	116 (34.9)	45 (13.6)	0	120 (36.9)	32 (9.8)	0
Aspartate aminotransferase increased	65 (19.6)	20 (6.0)	0	27 (8.3)	2 (0.6)	0
Alanine aminotransferase increased	63 (19.0)	16 (4.8)	0	19 (5.8)	3 (0.9)	0
Lipase increased	37 (11.1)	17 (5.1)	0	18 (5.5)	4 (1.2)	0
Weight decreased	7 (2.1)	0	0	37 (11.4)	5 (1.5)	0
Endocrine disorders	88 (26.5)	11 (3.3)	0	96 (29.5)	0	0
Hypothyroidism	40 (12.0)	0	0	79 (24.3)	0	0
Hyperthyroidism	34 (10.2)	2 (0.6)	0	5 (1.5)	0	0
General disorders and administration site conditions	86 (25.9)	2 (0.6)	0	130 (40.0)	18 (5.5)	0
Asthenia	34 (10.2)	1 (0.3)	0	51 (15.7)	5 (1.5)	0
Fatigue	27 (8.1)	0	0	50 (15.4)	6 (1.8)	0
Gastrointestinal disorders	83 (25.0)	22 (6.6)	0	177 (54.5)	18 (5.5)	0
Diarrhoea	47 (14.2)	4 (1.2)	0	114 (35.1)	10 (3.1)	0
Metabolism and nutrition disorders	39 (11.7)	8 (2.4)	0	93 (28.6)	12 (3.7)	0
Decreased appetite	23 (6.9)	1 (0.3)	0	70 (21.5)	5 (1.5)	0
Vascular disorders	7 (2.1)	1 (0.3)	0	137 (42.2)	39 (12.0)	0
Hypertension	5 (1.5)	0	0	134 (41.2)	38 (11.7)	0
Renal and urinary disorders	6 (1.8)	2 (0.6)	0	74 (22.8)	21 (6.5)	0
Proteinuria	0	0	0	65 (20.0)	17 (5.2)	0
Respiratory, thoracic and mediastinal disorders	17 (5.1)	3 (0.9)	0	65 (20.0)	3 (0.9)	0
Dysphonia	1 (0.3)	0	0	48 (14.8)	0	0

MedDRA Version: 26.1 / CTCAE Version 5.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Serious adverse event/deaths/other significant events

Serious adverse events (SAEs)

The overall frequencies of all-causality and drug-related SAEs (any grade, Grade 3-4) were higher in the nivo+ ipi (53.0% any grade, 46.4% Grade 3-4) than in the SOC arm (44.0% any grade, 35.4% Grade 3-4).

For nivo+ipi, the most frequently reported SAEs (all causality, PTs) were malignant neoplasm progression (7.2%), colitis (2.7%), ascites (2.4%), and hepatic failure and immune-mediated hepatitis (1.8% each). The most frequently reported drug-related SAEs (PTs) were colitis (2.7%), immune-mediated hepatitis (1.8%), acute kidney injury (1.8%), and adrenal insufficiency, autoimmune hepatitis and hepatic failure (1.2% each).

For SOC, the most frequently reported SAEs (all causality, PTs) were malignant neoplasm progression (9.8%), pyrexia (3.7%), abdominal pain and hepatic encephalopathy (2.2% each). The most frequently reported drug-related SAEs (PTs) were hypertension (1.2%) and oedema peripheral (0.9%).

SAEs of COVID-19 infection (between the first treatment and 30 days after last dose of study therapy) were reported in 1.5% of patients in the nivo+ipi arm. No patients in the SOC arm had SAEs of COVID-19 infection.

Table 80 Serious Adverse Events Summary by Worst CTC Grade Reported in at Least 2 Subjects (Any Grade, Grade 3-4, Grade 5) - All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivo + Ipi N = 332			Sora / Lenva N = 325		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	176 (53.0)	154 (46.4)	7 (2.1)	143 (44.0)	115 (35.4)	15 (4.6)
Gastrointestinal disorders	42 (12.7)	41 (12.3)	0	33 (10.2)	25 (7.7)	0
Colitis	9 (2.7)	8 (2.4)	0	0	0	0
Ascites	8 (2.4)	8 (2.4)	0	6 (1.8)	4 (1.2)	0
Gastrointestinal haemorrhage	5 (1.5)	5 (1.5)	0	2 (0.6)	2 (0.6)	0
Haematemesis	3 (0.9)	3 (0.9)	0	2 (0.6)	2 (0.6)	0
Immune-mediated enterocolitis	3 (0.9)	3 (0.9)	0	0	0	0
Abdominal pain	2 (0.6)	2 (0.6)	0	7 (2.2)	5 (1.5)	0
Diarrhoea	2 (0.6)	2 (0.6)	0	2 (0.6)	1 (0.3)	0
Upper gastrointestinal haemorrhage	2 (0.6)	2 (0.6)	0	2 (0.6)	2 (0.6)	0
Vomiting	2 (0.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Pancreatitis acute	1 (0.3)	1 (0.3)	0	2 (0.6)	2 (0.6)	0
Constipation	0	0	0	2 (0.6)	1 (0.3)	0
Melaena	0	0	0	2 (0.6)	2 (0.6)	0
Nausea	0	0	0	2 (0.6)	2 (0.6)	0
Hepatobiliary disorders	36 (10.8)	34 (10.2)	0	17 (5.2)	17 (5.2)	0
Hepatic failure	6 (1.8)	6 (1.8)	0	2 (0.6)	2 (0.6)	0
Immune-mediated hepatitis	6 (1.8)	6 (1.8)	0	0	0	0
Autoimmune hepatitis	4 (1.2)	4 (1.2)	0	0	0	0
Hypertransaminasaemia	3 (0.9)	2 (0.6)	0	0	0	0
Acute hepatic failure	2 (0.6)	2 (0.6)	0	0	0	0
Drug-induced liver injury	2 (0.6)	2 (0.6)	0	0	0	0
Hepatic cirrhosis	2 (0.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Hepatic function abnormal	2 (0.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Cholangitis	1 (0.3)	0	0	3 (0.9)	3 (0.9)	0
Hepatorenal syndrome	1 (0.3)	1 (0.3)	0	3 (0.9)	3 (0.9)	0
Cholecystitis	0	0	0	2 (0.6)	2 (0.6)	0
Infections and infestations	32 (9.6)	27 (8.1)	1 (0.3)	27 (8.3)	23 (7.1)	0
COVID-19	5 (1.5)	4 (1.2)	0	0	0	0
Pneumonia	3 (0.9)	2 (0.6)	1 (0.3)	4 (1.2)	2 (0.6)	0
Urinary tract infection	3 (0.9)	2 (0.6)	0	4 (1.2)	4 (1.2)	0
COVID-19 pneumonia	2 (0.6)	2 (0.6)	0	0	0	0
Cellulitis	2 (0.6)	2 (0.6)	0	0	0	0
Septic shock	2 (0.6)	2 (0.6)	0	5 (1.5)	5 (1.5)	0
Spontaneous bacterial peritonitis	2 (0.6)	2 (0.6)	0	0	0	0
Sepsis	1 (0.3)	1 (0.3)	0	2 (0.6)	2 (0.6)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	29 (8.7)	20 (6.0)	5 (1.5)	39 (12.0)	25 (7.7)	13 (4.0)
Malignant neoplasm progression	24 (7.2)	16 (4.8)	5 (1.5)	32 (9.8)	19 (5.8)	13 (4.0)

System Organ Class (%) Preferred Term (%)	Nivo + Ipi N = 332			Sora / Lenva N = 325		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Tumour associated fever	2 (0.6)	1 (0.3)	0	0	0	0
General disorders and administration site conditions	15 (4.5)	10 (3.0)	1 (0.3)	24 (7.4)	12 (3.7)	1 (0.3)
Pyrexia	5 (1.5)	1 (0.3)	0	12 (3.7)	5 (1.5)	0
Oedema peripheral	4 (1.2)	4 (1.2)	0	5 (1.5)	3 (0.9)	0
Non-cardiac chest pain	1 (0.3)	1 (0.3)	0	2 (0.6)	1 (0.3)	0
Fatigue	0	0	0	2 (0.6)	1 (0.3)	0
Nervous system disorders	14 (4.2)	13 (3.9)	0	19 (5.8)	15 (4.6)	1 (0.3)
Cognitive disorder	2 (0.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Dizziness	2 (0.6)	1 (0.3)	0	0	0	0
Hepatic encephalopathy	2 (0.6)	2 (0.6)	0	7 (2.2)	5 (1.5)	0
Encephalopathy	1 (0.3)	1 (0.3)	0	2 (0.6)	2 (0.6)	0
Haemorrhagic stroke	0	0	0	2 (0.6)	1 (0.3)	1 (0.3)
Ischaemic stroke	0	0	0	2 (0.6)	1 (0.3)	0
Endocrine disorders	12 (3.6)	11 (3.3)	0	0	0	0
Adrenal insufficiency	4 (1.2)	3 (0.9)	0	0	0	0
Hyperthyroidism	2 (0.6)	2 (0.6)	0	0	0	0
Lymphocytic hypophysitis	2 (0.6)	2 (0.6)	0	0	0	0
Investigations	12 (3.6)	8 (2.4)	0	7 (2.2)	6 (1.8)	0
Aspartate aminotransferase increased	4 (1.2)	3 (0.9)	0	1 (0.3)	1 (0.3)	0
Blood bilirubin increased	3 (0.9)	1 (0.3)	0	2 (0.6)	1 (0.3)	0
Transaminases increased	3 (0.9)	2 (0.6)	0	0	0	0
Lipase increased	2 (0.6)	2 (0.6)	0	0	0	0
General physical condition abnormal	1 (0.3)	0	0	3 (0.9)	3 (0.9)	0
Skin and subcutaneous tissue disorders	10 (3.0)	10 (3.0)	0	2 (0.6)	2 (0.6)	0
Pruritus	2 (0.6)	2 (0.6)	0	0	0	0
Toxic skin eruption	2 (0.6)	2 (0.6)	0	0	0	0
Rash	1 (0.3)	1 (0.3)	0	2 (0.6)	2 (0.6)	0
Metabolism and nutrition disorders	9 (2.7)	8 (2.4)	0	11 (3.4)	11 (3.4)	0
Hyperglycaemia	3 (0.9)	3 (0.9)	0	0	0	0
Hyponatraemia	3 (0.9)	3 (0.9)	0	5 (1.5)	5 (1.5)	0
Hypoglycaemia	1 (0.3)	1 (0.3)	0	3 (0.9)	3 (0.9)	0
Dehydration	0	0	0	2 (0.6)	2 (0.6)	0
Respiratory, thoracic and mediastinal disorders	9 (2.7)	8 (2.4)	0	7 (2.2)	7 (2.2)	0
Pneumonitis	2 (0.6)	1 (0.3)	0	0	0	0
Dyspnoea	1 (0.3)	1 (0.3)	0	3 (0.9)	3 (0.9)	0
Musculoskeletal and connective tissue disorders	8 (2.4)	7 (2.1)	0	4 (1.2)	4 (1.2)	0
Myositis	3 (0.9)	2 (0.6)	0	0	0	0
Arthralgia	0	0	0	2 (0.6)	2 (0.6)	0
Renal and urinary disorders	8 (2.4)	6 (1.8)	0	11 (3.4)	11 (3.4)	0
Acute kidney injury	6 (1.8)	5 (1.5)	0	4 (1.2)	4 (1.2)	0
Renal failure	1 (0.3)	0	0	2 (0.6)	2 (0.6)	0
Nephrotic syndrome	0	0	0	2 (0.6)	2 (0.6)	0
Blood and lymphatic system disorders	7 (2.1)	5 (1.5)	0	3 (0.9)	3 (0.9)	0
Anaemia	5 (1.5)	4 (1.2)	0	3 (0.9)	3 (0.9)	0
Autoimmune haemolytic anaemia	2 (0.6)	1 (0.3)	0	0	0	0
Cardiac disorders	6 (1.8)	5 (1.5)	0	7 (2.2)	6 (1.8)	0
Myocarditis	2 (0.6)	1 (0.3)	0	0	0	0
Coronary artery stenosis	0	0	0	3 (0.9)	3 (0.9)	0
Vascular disorders	4 (1.2)	4 (1.2)	0	10 (3.1)	10 (3.1)	0
Peripheral arterial occlusive disease	2 (0.6)	1 (0.3)	0	0	0	0
Deep vein thrombosis	0	0	0	2 (0.6)	2 (0.6)	0
Hypertension	0	0	0	4 (1.2)	4 (1.2)	0

MedDRA Version: 26.1
CTCAE Version 5.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Table 81 Drug-related Serious Adverse Events Summary by Worst CTC Grade Reported in at Least 2 Subjects (Any Grade, Grade 3-4, Grade 5) - All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivo + Ipi N = 332			Sora / Lenva N = 325		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	94 (28.3)	83 (25.0)	0	47 (14.5)	42 (12.9)	0
Hepatobiliary disorders	28 (8.4)	27 (8.1)	0	7 (2.2)	7 (2.2)	0
Immune-mediated hepatitis	6 (1.8)	6 (1.8)	0	0	0	0
Autoimmune hepatitis	4 (1.2)	4 (1.2)	0	0	0	0
Hepatic failure	4 (1.2)	4 (1.2)	0	1 (0.3)	1 (0.3)	0
Hypertransaminasaemia	3 (0.9)	2 (0.6)	0	0	0	0
Acute hepatic failure	2 (0.6)	2 (0.6)	0	0	0	0
Drug-induced liver injury	2 (0.6)	2 (0.6)	0	0	0	0
Hepatic function abnormal	2 (0.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Gastrointestinal disorders	19 (5.7)	18 (5.4)	0	9 (2.8)	7 (2.2)	0
Colitis	9 (2.7)	8 (2.4)	0	0	0	0
Immune-mediated enterocolitis	3 (0.9)	3 (0.9)	0	0	0	0
Diarrhoea	2 (0.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Endocrine disorders	12 (3.6)	11 (3.3)	0	0	0	0
Adrenal insufficiency	4 (1.2)	3 (0.9)	0	0	0	0
Hyperthyroidism	2 (0.6)	2 (0.6)	0	0	0	0
Lymphocytic hypophysitis	2 (0.6)	2 (0.6)	0	0	0	0
Skin and subcutaneous tissue disorders	10 (3.0)	10 (3.0)	0	1 (0.3)	1 (0.3)	0
Pruritus	2 (0.6)	2 (0.6)	0	0	0	0
Toxic skin eruption	2 (0.6)	2 (0.6)	0	0	0	0
Investigations	7 (2.1)	4 (1.2)	0	4 (1.2)	4 (1.2)	0
Aspartate aminotransferase increased	2 (0.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Blood bilirubin increased	2 (0.6)	0	0	0	0	0
Lipase increased	2 (0.6)	2 (0.6)	0	0	0	0
Transaminases increased	2 (0.6)	1 (0.3)	0	0	0	0
General physical condition abnormal	1 (0.3)	0	0	2 (0.6)	2 (0.6)	0
Musculoskeletal and connective tissue disorders	6 (1.8)	5 (1.5)	0	1 (0.3)	1 (0.3)	0
Myositis	3 (0.9)	2 (0.6)	0	0	0	0
Metabolism and nutrition disorders	5 (1.5)	4 (1.2)	0	4 (1.2)	4 (1.2)	0
Hyperglycaemia	2 (0.6)	2 (0.6)	0	0	0	0
Nervous system disorders	4 (1.2)	4 (1.2)	0	8 (2.5)	6 (1.8)	0
Hepatic encephalopathy	1 (0.3)	1 (0.3)	0	2 (0.6)	1 (0.3)	0
Cardiac disorders	3 (0.9)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Myocarditis	2 (0.6)	1 (0.3)	0	0	0	0
General disorders and administration site conditions	3 (0.9)	0	0	6 (1.8)	5 (1.5)	0
Pyrexia	3 (0.9)	0	0	1 (0.3)	1 (0.3)	0
Oedema peripheral	0	0	0	3 (0.9)	2 (0.6)	0
Respiratory, thoracic and mediastinal disorders	3 (0.9)	2 (0.6)	0	3 (0.9)	3 (0.9)	0
Pneumonitis	2 (0.6)	1 (0.3)	0	0	0	0
Blood and lymphatic system disorders	2 (0.6)	1 (0.3)	0	1 (0.3)	1 (0.3)	0
Autoimmune haemolytic anaemia	2 (0.6)	1 (0.3)	0	0	0	0
Renal and urinary disorders	2 (0.6)	1 (0.3)	0	5 (1.5)	5 (1.5)	0
Acute kidney injury	1 (0.3)	0	0	2 (0.6)	2 (0.6)	0
Nephrotic syndrome	0	0	0	2 (0.6)	2 (0.6)	0
Vascular disorders	1 (0.3)	1 (0.3)	0	5 (1.5)	5 (1.5)	0
Hypertension	0	0	0	4 (1.2)	4 (1.2)	0

MedDRA Version: 26.1
CTCAE Version 5.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Deaths

As of the 31 January 2024 clinical data cut-off, a lower proportion of patients in the nivo+ipi arm died compared with the SOC arm: 57.8% vs 68.9%. Disease progression was the most frequently reported cause of death in both arms, including deaths occurring within 30 and 100 days of last dose of study drug.

Note that only events that led to death within 24 hours were documented as Grade 5. Events leading to death > 24 hours after onset are reported with the worst grade before death.

Table 82 Death Summary - All Treated Subjects in the Nivo+Ipi and SOC Arms – CA2099DW

	Nivo + Ipi N = 332	Sora / Lenva N = 325
NUMBER OF SUBJECTS WHO DIED (%)	192 (57.8)	224 (68.9)
PRIMARY REASON FOR DEATH (%)		
DISEASE	139 (41.9)	202 (62.2)
STUDY DRUG TOXICITY	12 (3.6)	3 (0.9)
UNKNOWN	6 (1.8)	5 (1.5)
OTHER	35 (10.5)	14 (4.3)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	24 (7.2)	31 (9.5)
PRIMARY REASON FOR DEATH (%)		
DISEASE	8 (2.4)	20 (6.2)
STUDY DRUG TOXICITY	6 (1.8)	3 (0.9)
UNKNOWN	1 (0.3)	1 (0.3)
OTHER	9 (2.7)	7 (2.2)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	75 (22.6)	76 (23.4)
PRIMARY REASON FOR DEATH (%)		
DISEASE	38 (11.4)	63 (19.4)
STUDY DRUG TOXICITY	11 (3.3)	3 (0.9)
UNKNOWN	1 (0.3)	1 (0.3)
OTHER	25 (7.5)	9 (2.8)

Seven patients in the nivo+ipi arm died due to a COVID-19 infection. No COVID-19 related deaths were reported in the SOC arm.

Twelve (3.6%) patients in the nivo+ipi arm died 4 due to immune-mediated hepatitis, 3 due to hepatic failure, 1 due to hepatic insufficiency, 1 due to decompensated cirrhosis, 1 due to diarrhea/colitis, 1 due to autoimmune hemolytic anemia/hepatic failure, and 1 due to dysautonomia. Three (0.9%) patients (1 due to hepatorenal syndrome, 1 due to ischemic stroke, 1 due to acute kidney injury) in the SOC arm died due to study drug toxicity (per the investigator).

Deaths attributed to other reasons (other than study drug toxicity, disease, or unknown reasons) per the investigator, at any time after randomization (e.g. including survival follow-up) were reported in 10.5% of patients in the nivo+ipi arm and 4.3% of patients in the SOC arm.

Other Significant Adverse Events

- Select Adverse Events

Across select AE categories, most select AEs reported in all treated patients were Grade 1-2. The majority were considered drug-related by the investigator.

For nivo+ipi the most frequently reported drug related selected AE categories (any grade) were: skin (51.8%), hepatic (34.3%), and endocrine (28.3%). For the SOC arm those were skin (42.8%), gastrointestinal (35.1%), and endocrine (31.4%).

The most frequently reported drug-related select AEs by PT (any grade) were for nivo+ipi; pruritus (28.0%), AST increased (19.6%), and rash (19.3%). For the SOC arm the most frequently reported drug-related AEs by PT were diarrhoea (35.1%), palmar-plantar erythrodysaesthesia syndrome (30.5%), and hypothyroidism (24.3%).

Drug-related serious select AEs were infrequent in the nivo+ipi (≤8.7%) and SOC (≤1.5%) arms.

Table 83 Onset, Management, and Resolution of Drug-Related Select AEs - All Nivo+Ipi Treated Subjects (N=332)

Category	N (%) Treated Subj. with Any Grade/ Grade 3-4 Drug-Related Select AE	Median Time to Onset of Drug-Related Select AE (range), wks	% Treated Subj. with Drug-Related Select AE Leading to DC	% Subj. with Drug-Related Select AE Treated with IMM / High-dose Corticosteroids[a]	Median Time [b] to Resolution of Drug-Related Select AE (range), wks [c,d,e]	% Subj. with Drug-Related Select AE that Resolved[d,e]
Endocrine	94 (28.3)/ 12 (3.6)	8.71 (0.1-102.3)	6 (1.8)	28.7 / 10.6	NA (0.6-191.1+)	43 (45.7)
Gastrointestinal	56 (16.9)/ 17 (5.1)	6.29 (0.3-93.6)	7 (2.1)	48.2 / 46.4	3.57 (0.3 - 170.0+)	51 (91.1)
Hepatic	114 (34.3)/ 56 (16.9)	4.71 (0.9-88.9)	20 (6.0)	54.4 / 47.4	6.00 (0.4+ - 129.3+)	94 (82.5)
Pulmonary	7 (2.1)/ 1 (0.3)	9.14 (4.7-33.6)	2 (0.6)	71.4 / 57.1	16.14 (3.9 - 100.1+)	5 (71.4)
Renal	6 (1.8)/ 1 (0.3)	12.50 (1.9-58.1)	1 (0.3)	50.0 / 33.3	3.64 (0.6 - 23.9)	6 (100.0)
Skin	172 (51.8)/ 19 (5.7)	3.00 (0.1-104.1)	4 (1.2)	48.3 / 8.1	15.71 (0.1 - 170.7+)	119 (69.6)
Hypersensitivity/ Infusion Reaction	8 (2.4)/ 1 (0.3)	3.21 (0.1-6.1)	1 (0.3)	50.0 / 37.5	0.14 (0.1 - 0.7)	8 (100.0)

a Denominator is based on the number of subjects who experienced the event

b From Kaplan-Meier estimation.

c Symbol + indicates a censored value.

d Subjects reported with a select adverse event without worsening from baseline grade were excluded from time to resolution analysis.

e Events without a stop date or with a stop date equal to the death as well as Grade 5 events are considered unresolved.

Symbol + indicates a censored value.

MedDRA Version: 26.1, CTC Version 5.0

Includes events reported between first treatment and 30 days after last treatment of study therapy.

- Immune-mediated Adverse Events (IMAEs)

  IMAE analyses included events, all causality, reported within 100 days of the last dose (i.e., with extended follow-up). These analyses include patients who received Immune-Modulating Medications (IMM) for treatment of the event, except for endocrine events, which were included in the analysis regardless of treatment since these events are often managed without immunosuppression. In addition, these analyses include events identified by the investigator as IMAEs with no clear alternate etiology and an immune-mediated component.

  The majority of IMAEs (non-endocrine/endocrine) were Grade 1-2 except for hepatitis. Grade 3-4 hepatitis was reported in 15.4% of subjects.

  The most frequently reported IMAEs (any grade, by category) were for nivo+ipi: hepatitis (19.0%), hypothyroidism/thyroiditis (18.7%), and rash (15.4%). For the SOC arm were hypothyroidism/thyroiditis (3.4%), rash (0.6%), and diarrhoea/colitis (0.3%).

Table 84 Onset, Management, and Resolution of All-causality IMAEs within 100 Days of Last Dose - All Nivo+Ipi Treated Subjects (N=332)

IMAE Category	N (%) Subj. with Any Grade/ Grade 3-4 IMAEs	Median Time to IMAE Onset (range), wks	% Subj. with IMAE leading to DC / Dose Delay	% Subj. with IMAEs Receiving IMM / High-dose Corticosteroids[a]	Median Duration IMM (range), wks	% Subj. with Resolution of IMAE[b,c]	Median[d] Time to Resolution (range), wks[b,c]
Pneumonitis	7 (2.1)/ 3 (0.9)	9.14 (4.7 - 15.7)	3 (0.9)/ 5 (1.5)	7 (100.0)/ 6 (85.7)	17.29 (6.1 - 132.0)	85.7	8.71 (1.4 - 99.1+)
Diarrhea/Colitis	28 (8.4)/ 15 (4.5)	8.64 (0.7 - 62.0)	9(2.7)/ 19 (5.7)	28 (100.0)/ 27 (96.4)	3.50 (0.7 - 133.9)	92.9	3.86 (0.7 - 137.3+)
Hepatitis	63 (19.0)/ 51 (15.4)	6.00 (0.9 - 88.9)	19 (5.7)/ 47 (14.2)	63 (100.0)/ 56 (88.9)	7.71 (0.6 - 128.0)	74.6	10.29 (0.9 - 129.3+)
Nephritis/ Renal Dysfunction	5 (1.5)/ 3 (0.9)	15.00 (1.9 - 58.1)	2 (0.6)/ 2 (0.6)	5 (100.0)/ 3 (60.0)	2.29 (1.4 - 102.0)	100.0	7.86 (1.0 - 106.0)
Rash	51 (15.4)/ 14 (4.2)	4.57 (0.1 - 55.3)	1 (0.3)/ 14 (4.2)	51 (100.0)/ 10 (19.6)	9.86 (0.3 - 182.6)	76.5	12.57 (0.6 - 161.4+)
Hypersensitivity	4 (1.2)/ 0	3.21 (3.0 - 3.7)	0 / 0	4 (100.0)/ 3 (75.0)	0.21 (0.1 - 0.4)	100.0	0.14 (0.1 - 0.7)
Adrenal Insufficiency	18 (5.4)/ 6 (1.8)	20.71 (9.6 - 106.9)	4 (1.2)/ 8 (2.4)	16 (88.9)/ 2 (11.1)	88.29 (0.6 - 133.9)	27.8	N.A (0.6 - 143.1+)
Hypothyroidism/ Thyroiditis	62 (18.7)/ 1 (0.3)	9.71 (2.9 - 52.3)	0/ 10 (3.0)	4 (6.5)/ 2 (3.2)	8.64 (2.0 - 80.7)	41.9	N.A (1.1 - 186.0+)
Diabetes Mellitus	2 (0.6)/ 2 (0.6)	41.86 (9.0 - 74.7)	0 / 0	0 / 0	-	50.0	N.A (8.9 - 53.3+)
Hyperthyroidism	36 (10.8)/ 2 (0.6)	6.07 (2.7 - 36.0)	0/ 8 (2.4)	5 (13.9)/ 3 (8.3)	3.29 (0.9 - 6.1)	77.8	6.86 (2.1 - 155.1+)
Hypophysitis	9 (2.7)/ 4 (1.2)	11.43 (0.1 - 28.1)	4 (1.2)/ 5(1.5)	9 (100.0)/ 3 (33.3)	38.57 (0.4 - 135.0)	33.3	N.A (8.4 - 142.4+)

a Denominator is based on the number of subjects who experienced the event.

b Reported IMAEs that did not worsen from baseline grade were excluded from time to resolution analysis.

c Events without a stop date or with a stop date equal to the death as well as Grade 5 events are considered unresolved.

d From Kaplan-Meier estimation. Note that the number of events was very low for most categories.

MedDRA version 26.1; CTC version 5.0.

- Other Events of Special Interest (OESIs)

  Twenty OESIs (all causality, with or without IMM treatment) were reported (between the first dose of study drug and 100 days after the last dose of study drug) in 16 patients in the nivo+ipi arm. Three OESIs were reported in 3 patients in the SOC arm.

  Frequency of all OESI categories (any grade; any causality) with nivo+ipi were < 1%, except for pancreatitis (2.1%). All OESIs in the nivo+ipi arm were considered drug-related by the investigator.

  In the SOC arm, drug-related OESI (pancreatitis acute) was reported in 1 (0.3%) subject.

  Most subjects with OESIs were treated with IMMs and the majority of OESIs resolved.

Table 85 Other Events of Special Interest Summary by Worst CTC Grade by Category (Any Grade, Grade 3-4, Grade 5) –All Treated Subjects

	Nivo + Ipi N = 332			Sora / Lenva N = 325		
Other Events of Special Interest Category: MYASTHENIC SYNDROME						
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	1 (0.3)	1 (0.3)	0	0	0	0
Myasthenia gravis	1 (0.3)	1 (0.3)	0	0	0	0
Other Events of Special Interest Category: DEMYELINATION EVENT						
TOTAL SUBJECTS WITH AN EVENT	1 (0.3)	0	0	0	0	0
Demyelinating polyneuropathy	1 (0.3)	0	0	0	0	0
Other Events of Special Interest Category: PANCREATITIS EVENT						
TOTAL SUBJECTS WITH AN EVENT	9 (2.7)	4 (1.2)	0	2 (0.6)	2 (0.6)	0
Pancreatitis	7 (2.1)	2 (0.6)	0	0	0	0
Autoimmune pancreatitis	1 (0.3)	1 (0.3)	0	0	0	0
Pancreatitis acute	1 (0.3)	1 (0.3)	0	2 (0.6)	2 (0.6)	0
Other Events of Special Interest Category: MYOCARDITIS EVENT						
TOTAL SUBJECTS WITH AN EVENT	3 (0.9)	2 (0.6)	0	0	0	0
Myocarditis	2 (0.6)	1 (0.3)	0	0	0	0
Autoimmune myocarditis	1 (0.3)	1 (0.3)	0	0	0	0
Other Events of Special Interest Category: MYOSITIS/RHABDOMYOLYSIS EVENT						
TOTAL SUBJECTS WITH AN EVENT	4 (1.2)	3 (0.9)	0	1 (0.3)	1 (0.3)	0
Myositis	3 (0.9)	2 (0.6)	0	0	0	0
Autoimmune myositis	1 (0.3)	1 (0.3)	0	0	0	0
Rhabdomyolysis	0	0	0	1 (0.3)	1 (0.3)	0
Other Events of Special Interest Category: AUTOIMMUNE CYTOPENIA						
TOTAL SUBJECTS WITH AN EVENT	2 (0.6)	1 (0.3)	0	0	0	0
Autoimmune haemolytic anaemia	2 (0.6)	1 (0.3)	0	0	0	0

MedDRA Version: 26.1/ CTCAE Version 5.0
Includes events reported between first dose and 100 days after last dose of study therapy.

Laboratory findings

Laboratory abnormalities (hematology, liver tests, kidney function tests, thyroid function tests, and electrolytes) including Grade 3-4 events, seen in treated patients in the nivo+ipi and SOC arm during the treatment period or within 30 days of last dose of study drug.

Hematology

In treated patients, Grade 3 or 4 hematologic abnormalities were reported in ≥5% of treated subjects. In nivo+ipi arm, hemoglobin decreased (5.2% Grade 3) and total absolute lymphocytes decreased (7.3% Grade 3). In the SOC arm, total absolute lymphocytes decreased (8.0% Grade 3). Per the anemia criteria in CTC version 5.0, there is no Grade 4 for hemoglobin.

Serum Chemistry

Liver Function Tests

In treated patients, Grade 3 or 4 abnormalities in hepatic parameters were reported in ≥5% of treated subjects.

The incidence of Grade 3 or 4 hepatic abnormalities (AST, ALT, total bilirubin increased) in patients treated with nivo+ipi were: increased ALT (10.0% Grade 3), increased AST (13.6% Grade 3), total increased bilirubin (6.6% Grade 3).

For patients treated with SOC, Grade 3 or 4 hepatic abnormalities were total increased bilirubin (5.1% Grade 3), increased AST (5.1% Grade 3).

44 (13.3%) patients in the nivo+ipi arm and 28 (8.9%) patients in the SOC arm were reported with concurrent ALT or AST >3 x ULN with total bilirubin >2 x ULN (within 30 days).

28 (8.9%) and 4 (1.3%) patients were reported with concurrent ALT or AST elevation >10 x ULN with total bilirubin > 2xULN (within 30 days) in the nivo+ipi and SOC arms, respectively.

Table 86 Laboratory Test Results Summary of Laboratory Abnormalities in Specific Liver Tests (SI Units) – All Treated Subjects

Abnormality (%)	Nivo + Ipi N = 332	Sora / Lenva N = 325	Total N = 657
	N = 331	N = 315	N = 646
ALT OR AST > 3XULN	161 (48.6)	95 (30.2)	256 (39.6)
ALT OR AST > 5XULN	105 (31.7)	53 (16.8)	158 (24.5)
ALT OR AST > 10XULN	43 (13.0)	16 (5.1)	59 (9.1)
ALT OR AST > 20XULN	9 (2.7)	6 (1.9)	15 (2.3)
	N = 331	N = 315	N = 646
TOTAL BILIRUBIN > 2XULN	59 (17.8)	59 (18.7)	118 (18.3)
	N = 330	N = 315	N = 645
ALP > 1.5XULN	163 (49.4)	164 (52.1)	327 (50.7)
	N = 331	N = 315	N = 646
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 1.5XULN WITHIN 1 DAY	54 (16.3)	43 (13.7)	97 (15.0)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 1.5XULN WITHIN 30 DAYS	58 (17.5)	43 (13.7)	101 (15.6)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 1 DAY	42 (12.7)	26 (8.3)	68 (10.5)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 30 DAYS	44 (13.3)	28 (8.9)	72 (11.1)
CONCURRENT ALT ELEVATION ≥ 10XULN WITH (TOTAL BILIRUBIN ≥ 2XULN OR ≥ 2X BASELINE, IF ELEVATED BILIRUBIN AT STUDY ENTRY) WITHIN 1 DAY	7 (2.1)	4 (1.3)	11 (1.7)
CONCURRENT ALT ELEVATION ≥ 10XULN WITH (TOTAL BILIRUBIN ≥ 2XULN OR ≥ 2X BASELINE, IF ELEVATED BILIRUBIN AT STUDY ENTRY) WITHIN 30 DAYS	8 (2.4)	4 (1.3)	12 (1.9)

Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
Denominator corresponds to subjects with at least one on-treatment measurement of the corresponding laboratory parameter.

Kidney Function Tests

Most patients (with at least 1 on-treatment measurement) were reported with normal (Grade 0) creatinine values (70.0% nivo+ipi; 74.3% SOC) during the treatment period. Grade 3 abnormalities in creatinine (increases) were reported (1.4% overall) in 7 (2.1%) patients in the nivo+ipi arm and in 2 (0.6%) patients in the SOC arm. While Grade 4 abnormalities in creatinine (increases) were reported (0.2% overall) in 1 (0.3%) patient in the nivo+ipi arm and in no patients in the SOC arm.

Thyroid Function Tests

TSH increases to > ULN from a baseline level ≤ ULN were reported in 31.4% of patients in the nivo+ipi arm and 64.6% of patients in the SOC arm. TSH decreases to < LLN from a baseline level ≥ LLN were reported in 33.2% and 12.4% of subjects in the nivo+ipi and SOC arms, respectively.

Table 87 Laboratory Test Results Summary of Laboratory Abnormalities in Specific Thyroid Tests (SI Units) - All Treated Subjects with at Least One On-Treatment TSH Measurement

Abnormality (%)	Nivo + Ipi N = 325	Sora / Lenva N = 314	Total N = 639
TSH > ULN	121 (37.2)	230 (73.2)	351 (54.9)
TSH > ULN WITH TSH <= ULN AT BASELINE	102 (31.4)	203 (64.6)	305 (47.7)
TSH > ULN WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	64 (19.7)	89 (28.3)	153 (23.9)
TSH > ULN WITH ALL OTHER FT3/FT4 TEST VALUES ≥ LLN (A)	80 (24.6)	173 (55.1)	253 (39.6)
TSH > ULN WITH FT3/FT4 TEST MISSING (A) (B)	34 (10.5)	81 (25.8)	115 (18.0)
TSH < LLN	114 (35.1)	41 (13.1)	155 (24.3)
TSH < LLN WITH TSH ≥ LLN AT BASELINE	108 (33.2)	39 (12.4)	147 (23.0)
TSH < LLN WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	60 (18.5)	22 (7.0)	82 (12.8)
TSH < LLN WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	70 (21.5)	21 (6.7)	91 (14.2)
TSH < LLN WITH FT3/FT4 TEST MISSING (A) (B)	23 (7.1)	11 (3.5)	34 (5.3)

Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
(A) Within a 2-week window after the abnormal TSH test date.
(B) Includes subjects with TSH abnormality and with no FT3/FT4 test values in the 2-week window or with non-abnormal value(s) from only one of the two tests and no value from the other test.

Electrolytes

Most patients showed normal electrolyte levels during the treatment period. Abnormalities in electrolyte levels (during treatment or within 30 days of last dose of study drug) were primarily Grade 1 or 2 in severity across treatment arms. No Grade 3 or 4 electrolyte level abnormalities were reported in ≥5% of treated subjects with on-treatment laboratory results in either treatment arm.

Hepatitis Virus Load Tests

VB was reported in 30 subjects in total. In the nivo+ipi arm, VB was reported in 11 subjects with HBV and 3 subjects with HCV. In the SOC arm, VB was reported in 10 subjects with HBV and 6 subjects with HCV.

HBV VB occurred shortly after disease progression in 3 subjects in the nivo+ipi arm and 1 subject in the SOC arm. HCV VB occurred shortly after disease progression in 2 subjects in the nivo+ipi arm and no subject in the SOC arm.

In 2 cases of VB in HCV infected subjects in the nivo+ipi arm, a dose of study drug was delayed; no dose delays were reported in cases of VB in HBV infected subjects. In 3 cases of VB in HCV infected subjects and 2 cases of VB in HBV infected subjects in the SOC arm, a dose of study drug was delayed. In 5 subjects (2 cases of VB in HBV infected subjects and 3 cases of VB in HCV infected subjects) treatment was interrupted. No discontinuations due to VB were reported.

Immunogenicity

Effect of Immunogenicity on Safety

Overall, the presence of nivo ADA or ipi ADA did not appear to have an impact on safety of the nivo+ipi regimen. Of the nivo+ipi treated subjects evaluable for ADA, hypersensitivity/infusion reaction select AEs were reported in a small number of subjects with a similar proportion of nivo ADA-negative subjects (0.8%, 1/124) and nivo ADA-positive subjects (2.0%, 2/100) and in a similar proportion of ipi ADA-negative subjects (1.7%, 4/231) and ipi ADA positive subjects (0%, 0/13).

Table 88 Selected Adverse Events of Hypersensitivity/Infusion Reaction by ADA Status (Positive, Negative) - All Nivo+Ipi Treated Subjects

	Nivolumab + Ipilimumab			
	Nivolumab ADA		Ipilimumab ADA	
Preferred Term (%)	POSITIVE N = 100	NEGATIVE N = 124	POSITIVE N = 13	NEGATIVE N = 231
TOTAL SUBJECTS WITH AN EVENT	2 (2.0)	1 (0.8)	0	4 (1.7)
Hypersensitivity	2 (2.0)	0	0	2 (0.9)
Infusion related reaction	1 (1.0)	1 (0.8)	0	3 (1.3)

MedDRA Version: 26.1; CTC Version: 5.0

Includes events between first dose and 100 days after last dose of study therapy.

Safety in special populations

Subgroup Analysis by Intrinsic and Extrinsic Factors

In the nivo+ipi and SOC arms, the frequencies of AEs all causality and drug-related for subgroups of age, sex, race, and region, were generally consistent with the corresponding frequencies reported for the overall study population by treatment arm. Some numerical differences between subgroups cannot be interpreted due to small numbers of patients.

Table 89 All-Causality Adverse Events by Worst CTC Grade and by Baseline- All Treated Subjects

	Number (%) of Subjects							
	Nivo+Ipi				SOC			
	N	Any Grade	Grade 3-4	Grade 5	N	Any Grade	Grade 3-4	Grade 5
Total	332	331 (99.7)	230 (69.3)	7 (2.1)	325	320 (98.5)	203 (62.5)	15 (4.6)
Sex								
Female	63	62 (98.4)	48 (76.2)	0	56	55 (98.2)	39 (69.6)	2 (3.6)
Male	269	269 (100.0)	182 (67.7)	7 (2.6)	269	265 (98.5)	164 (61.0)	13 (4.8)
Age Category								
<65	162	161 (99.4)	111 (68.5)	2 (1.2)	143	139 (97.2)	80 (55.9)	8 (5.6)
≥65 - <75	124	124 (100.0)	82 (66.1)	5 (4.0)	123	123 (100.0)	85 (69.1)	4 (3.3)
≥75	46	46 (100.0)	37 (80.4)	0	59	58 (98.3)	38 (64.4)	3 (5.1)
Race								
White	177	177 (100.0)	129 (72.9)	4 (2.3)	169	165 (97.6)	102 (60.4)	12 (7.1)
Black or African American	11	11 (100.0)	6 (54.5)	1 (9.1)	3	3 (100.0)	3 (100.0)	0
Asian	139	138 (99.3)	93 (66.9)	2 (1.4)	150	149 (99.3)	95 (63.3)	3 (2.0)
Native Hawaiian or Other Pacific Islander	1	1 (100.0)	0	0	0	0	0	0
Other	4	4 (100.0)	2 (50.0)	0	3	3 (100.0)	3 (100.0)	0
Region								
North America	15	15 (100.0)	11 (73.3)	0	5	5 (100.0)	3 (60.0)	0
Europe	128	128 (100.0)	90 (70.3)	4 (3.1)	134	131 (97.8)	81 (60.4)	6 (4.5)
Asia	132	131 (99.2)	86 (65.2)	2 (1.5)	145	144 (99.3)	93 (64.1)	3 (2.1)
Rest of World	57	57 (100.0)	43 (75.4)	1 (1.8)	41	40 (97.6)	26 (63.4)	6 (14.6)

MedDRA version 26.1; CTC version 5.0.
Includes events reported between first treatment and 30 days after last treatment of study therapy.

Table 90 Drug-Related Adverse Events by Worst CTC Grade and by Baseline Characteristics – All Treated Subjects

	Number (%) of Subjects							
	Nivo+Ipi				SOC			
	N	Any Grade	Grade 3-4	Grade 5	N	Any Grade	Grade 3-4	Grade 5
Total	332	278 (83.7)	137 (41.3)	0	325	297 (91.4)	138 (42.5)	0
Sex								
Female	63	57 (90.5)	29 (46.0)	0	56	51 (91.1)	28 (50.0)	0
Male	269	221 (82.2)	108 (40.1)	0	269	246 (91.4)	110 (40.9)	0
Age Category								
<65	162	136 (84.0)	65 (40.1)	0	143	126 (88.1)	50 (35.0)	0
≥65 - <75	124	104 (83.9)	54 (43.5)	0	123	115 (93.5)	59 (48.0)	0
≥75	46	38 (82.6)	18 (39.1)	0	59	56 (94.9)	29 (49.2)	0
Race								
White	177	148 (83.6)	73 (41.2)	0	169	149 (88.2)	67 (39.6)	0
Black or African American	11	9 (81.8)	3 (27.3)	0	3	3 (100.0)	2 (66.7)	0
Asian	139	118 (84.9)	60 (43.2)	0	150	142 (94.7)	66 (44.0)	0
Other	4	3 (75.0)	1 (25.0)	0	3	3 (100.0)	3 (100.0)	0
Region								
North America	15	13 (86.7)	8 (53.3)	0	5	5 (100.0)	1 (20.0)	0
Europe	128	109 (85.2)	53 (41.4)	0	134	117 (87.3)	51 (38.1)	0
Asia	132	111 (84.1)	57 (43.2)	0	145	137 (94.5)	65 (44.8)	0
Rest of World	57	45 (78.9)	19 (33.3)	0	41	38 (92.7)	21 (51.2)	0

MedDRA version 26.1; CTC version 5.0.
Includes events reported between first treatment and 30 days after last treatment of study therapy.

Safety related to drug-drug interactions and other interactions

No new information has been submitted.

Discontinuation due to adverse events

The overall frequencies of all causality and drug-related AEs leading to discontinuation of study drug were higher in the nivo+ ipi arm than in the SOC arm (all causality: 26.5% vs 23.1%; drug-related: 17.8% vs 10.5%). Grade 3-4 AEs leading to discontinuation of study drug (all causality and drug-related) were reported in a higher proportion of patients in the nivo+ipi arm (20.8% all causality; 13.3% drug-related) as compared to the SOC arm (15.7% all causality; 6.5% drug-related).

For nivo+ipi, the most frequently reported all causality AEs leading to discontinuation was malignant neoplasm progression (2.7%). The most frequently reported drug-related AEs leading to discontinuation were AST increased (1.2%) and proteinuria (1.5%).

For SOC, the most frequently reported all causality AEs leading to discontinuation were malignant neoplasm progression (6.2%), proteinuria (1.5%), and asthenia (1.2%). The most frequently reported drug-related AEs leading to discontinuation was proteinuria (1.5%).

AEs leading to discontinuation related to COVID-19 infection were reported in 4 patients in the nivo+ipi arm and no patients in the SOC arm.

Table 91 Adverse Events Leading to Discontinuation Summary by Worst CTC Grade in At Least 2 Subjects (Any Grade, Grade 3-4, Grade 5) - All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivo + Ipi N = 332			Sora / Lenva N = 325		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	88 (26.5)	69 (20.8)	0	75 (23.1)	51 (15.7)	1 (0.3)
Hepatobiliary disorders	18 (5.4)	17 (5.1)	0	8 (2.5)	7 (2.2)	0
Autoimmune hepatitis	3 (0.9)	3 (0.9)	0	0	0	0
Immune-mediated hepatitis	3 (0.9)	3 (0.9)	0	0	0	0
Acute hepatic failure	2 (0.6)	2 (0.6)	0	0	0	0
Drug-induced liver injury	2 (0.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Hepatic failure	2 (0.6)	2 (0.6)	0	2 (0.6)	2 (0.6)	0
Cholestasis	0	0	0	2 (0.6)	1 (0.3)	0
Gastrointestinal disorders	11 (3.3)	10 (3.0)	0	5 (1.5)	2 (0.6)	0
Colitis	3 (0.9)	2 (0.6)	0	0	0	0
Immune-mediated enterocolitis	2 (0.6)	2 (0.6)	0	0	0	0
Pancreatitis	2 (0.6)	2 (0.6)	0	0	0	0
Diarrhoea	1 (0.3)	0	0	2 (0.6)	1 (0.3)	0
Nausea	0	0	0	2 (0.6)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (2.7)	9 (2.7)	0	22 (6.8)	16 (4.9)	1 (0.3)
Malignant neoplasm progression	9 (2.7)	9 (2.7)	0	20 (6.2)	14 (4.3)	1 (0.3)
Infections and infestations	8 (2.4)	7 (2.1)	0	5 (1.5)	5 (1.5)	0
COVID-19	2 (0.6)	2 (0.6)	0	0	0	0
COVID-19 pneumonia	2 (0.6)	2 (0.6)	0	0	0	0
Septic shock	1 (0.3)	1 (0.3)	0	2 (0.6)	2 (0.6)	0
Investigations	7 (2.1)	3 (0.9)	0	8 (2.5)	7 (2.2)	0
Aspartate aminotransferase increased	5 (1.5)	2 (0.6)	0	1 (0.3)	0	0
Alanine aminotransferase increased	3 (0.9)	1 (0.3)	0	0	0	0
Blood bilirubin increased	1 (0.3)	0	0	2 (0.6)	2 (0.6)	0
Weight decreased	0	0	0	2 (0.6)	2 (0.6)	0
Musculoskeletal and connective tissue disorders	7 (2.1)	4 (1.2)	0	0	0	0
Myositis	3 (0.9)	2 (0.6)	0	0	0	0
Endocrine disorders	6 (1.8)	3 (0.9)	0	0	0	0
Adrenal insufficiency	3 (0.9)	1 (0.3)	0	0	0	0
Lymphocytic hypophysitis	2 (0.6)	2 (0.6)	0	0	0	0
Cardiac disorders	4 (1.2)	2 (0.6)	0	3 (0.9)	3 (0.9)	0
Myocarditis	2 (0.6)	1 (0.3)	0	0	0	0
Nervous system disorders	4 (1.2)	4 (1.2)	0	7 (2.2)	2 (0.6)	0
Hepatic encephalopathy	0	0	0	2 (0.6)	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	4 (1.2)	3 (0.9)	0	2 (0.6)	1 (0.3)	0
Pneumonitis	2 (0.6)	1 (0.3)	0	0	0	0
Skin and subcutaneous tissue disorders	4 (1.2)	3 (0.9)	0	4 (1.2)	2 (0.6)	0
Psoriasis	2 (0.6)	1 (0.3)	0	0	0	0
Rash	0	0	0	2 (0.6)	1 (0.3)	0
Blood and lymphatic system disorders	3 (0.9)	2 (0.6)	0	0	0	0
Autoimmune haemolytic anaemia	2 (0.6)	1 (0.3)	0	0	0	0
General disorders and administration site conditions	3 (0.9)	3 (0.9)	0	5 (1.5)	2 (0.6)	0
Asthenia	0	0	0	4 (1.2)	1 (0.3)	0
Renal and urinary disorders	2 (0.6)	0	0	7 (2.2)	4 (1.2)	0
Nephrotic syndrome	0	0	0	2 (0.6)	2 (0.6)	0
Proteinuria	0	0	0	5 (1.5)	2 (0.6)	0

MedDRA Version: 26.1
CTCAE Version 5.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Table 92 Drug-related Adverse Events Leading to Discontinuation Summary by Worst CTC Grade in At Least 2 Subjects (Any Grade, Grade 3-4, Grade 5) - All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivo + Ipi N = 332			Sora / Lenva N = 325		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	59 (17.8)	44 (13.3)	0	34 (10.5)	21 (6.5)	0
Hepatobiliary disorders	15 (4.5)	15 (4.5)	0	4 (1.2)	3 (0.9)	0
Autoimmune hepatitis	3 (0.9)	3 (0.9)	0	0	0	0
Immune-mediated hepatitis	3 (0.9)	3 (0.9)	0	0	0	0
Acute hepatic failure	2 (0.6)	2 (0.6)	0	0	0	0
Drug-induced liver injury	2 (0.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Hepatic failure	2 (0.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Gastrointestinal disorders	10 (3.0)	9 (2.7)	0	5 (1.5)	2 (0.6)	0
Colitis	3 (0.9)	2 (0.6)	0	0	0	0
Immune-mediated enterocolitis	2 (0.6)	2 (0.6)	0	0	0	0
Pancreatitis	2 (0.6)	2 (0.6)	0	0	0	0
Diarrhoea	1 (0.3)	0	0	2 (0.6)	1 (0.3)	0
Nausea	0	0	0	2 (0.6)	0	0
Endocrine disorders	6 (1.8)	3 (0.9)	0	0	0	0
Adrenal insufficiency	3 (0.9)	1 (0.3)	0	0	0	0
Lymphocytic hypophysitis	2 (0.6)	2 (0.6)	0	0	0	0
Investigations	6 (1.8)	3 (0.9)	0	7 (2.2)	6 (1.8)	0
Aspartate aminotransferase increased	4 (1.2)	2 (0.6)	0	1 (0.3)	0	0
Alanine aminotransferase increased	3 (0.9)	1 (0.3)	0	0	0	0
Weight decreased	0	0	0	2 (0.6)	2 (0.6)	0
Musculoskeletal and connective tissue disorders	6 (1.8)	4 (1.2)	0	0	0	0
Myositis	3 (0.9)	2 (0.6)	0	0	0	0
Skin and subcutaneous tissue disorders	4 (1.2)	3 (0.9)	0	3 (0.9)	2 (0.6)	0
Psoriasis	2 (0.6)	1 (0.3)	0	0	0	0
Rash	0	0	0	2 (0.6)	1 (0.3)	0
Blood and lymphatic system disorders	3 (0.9)	2 (0.6)	0	0	0	0
Autoimmune haemolytic anaemia	2 (0.6)	1 (0.3)	0	0	0	0
Cardiac disorders	3 (0.9)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Myocarditis	2 (0.6)	1 (0.3)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	2 (0.6)	1 (0.3)	0	2 (0.6)	1 (0.3)	0
Pneumonitis	2 (0.6)	1 (0.3)	0	0	0	0
Renal and urinary disorders	1 (0.3)	0	0	7 (2.2)	4 (1.2)	0
Nephrotic syndrome	0	0	0	2 (0.6)	2 (0.6)	0
Proteinuria	0	0	0	5 (1.5)	2 (0.6)	0
General disorders and administration site conditions	0	0	0	3 (0.9)	1 (0.3)	0
Asthenia	0	0	0	3 (0.9)	1 (0.3)	0

MedDRA Version: 26.1
CTCAE Version 5.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Adverse Events Leading to Dose Modifications

AEs (all causality) leading to a dose delay or interruption were reported in 206 (62.0%) patients in the nivo+ipi arm and 180 (55.4%) patients in the SOC arm. Grade 3-4 AEs leading to dose delay or interruption were reported in 119 (35.8%) subjects in the nivo+ipi arm, and 114 (35.1%) subjects in the SOC arm.

The most frequently reported AEs (all causality) leading to a dose delay or reduction were for nivo+ipi AST increased (13.3%), ALT increased (11.1%), and blood bilirubin and diarrhoea increased (5.1% each).

For SOC, the most frequently reported AEs leading to a dose delay or reduction were, diarrhoea and hypertension (7.1% each), palmar-plantar erythrodysaesthesia syndrome (6.5%), and asthenia (4.3%).

Drug-related AEs leading to a dose delay or reduction were reported in 142 (42.8%) patients in the nivo+ipi arm and 133 (40.9%) patients in the SOC arm. Drug-related Grade 3-4 AEs leading to dose delay or interruption were reported in 73 (22.0%) subjects in the nivo+ipi arm, and 78 (24.0%) subjects in the SOC arm.

For nivo+ipi, the most frequently reported drug-related AEs leading to a dose delay or reduction were AST increased (10.2% each), ALT increased (9.9%), and diarrhoea (4.5%).

For SOC, the most frequently reported drug-related AEs leading to a dose delay or reduction were proteinuria (7.4%), hypertension and palmar-plantar erythrodysaesthesia syndrome (6.2% each), and diarrhoea (5.5%).

AE leading to dose reduction were reported in 58.2% of subjects in the SOC arm; Grade 3-4 events were reported in 16.9% of subjects, and there were no Grade 5 events.

The most frequently reported events were palmar-plantar erythrodysaesthesia syndrome (9.2%), decreased appetite (6.8%), hypertension (6.8%), proteinuria (6.8%), diarrhoea (6.8%), asthenia (6.2%), and weight decreased (5.2%).

Safety data to support Product Information update in section 4.8

Sections 4.8 of OPDIVO and Yervoy SmPCs have been updated in order to include safety data from Study CA2099DW. The standard methodology used by the MAH in prior updates has been implemented to identify ADRs and calculate resulting incidences. The following studies have been included in the Integrated Safety Analysis and the pooled dataset *Nivolumab in combination with ipilimumab (with or without chemotherapy)* has been updated in section 4.8.

Table 93 List of studies for the integrated safety analysis with nivo+ipi

Study (Data Cutoff), Number of Subjects Included	**Tumour Indications**						
	HCC	**Mel**	**NSCLC**	**RCC**	**Meso**	**CRC**	**ESCC**
CA2099DW (Jan-2024), N=332	x						
CA209069 (Sep-2014), N=94		x					
CA209004 (cohort 8) (Jun-2014), N=41		x					
CA209067 (combo arm) (Sep-2016), N=313		x					
CA2099LA[a] (Oct-2019), N=358			x				
CA209214 (Aug-2017), N=547				x			
CA209743 (Apr-2020), N=300					x		
CA209142 (cohort 2, dMMR/MSI-H CRC) (Oct-2020), N=119						x	
CA209648 (Oct-2021), N=322							x
CA2098HW (first line) (Nov-2023), N = 200						x	

[a] Includes nivolumab + ipilimumab + chemotherapy

No new ADRs have been identified, however, some incidences have been updated as a result of the updated pool of nivo+ipi including study CA2099DW (see Table 94).

Table 94 Summary of Any Adverse Events using Re-mapped Terms Occurring in at Least 10% of Subjects - All Nivolumab + Ipilimumab Treated Subjects from CA2099DW and Pooled Including CA2099DW

System Organ Class (%) Preferred Term (%)	CA2099DW Nivo + Ipi (N = 332)		Pooled Nivo + Ipi Including CA2099DW (N = 2626)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
TOTAL SUBJECTS WITH AN EVENT	**331 (99.7)**	**230 (69.3)**	**2608 (99.3)**	**1668 (63.5)**
Gastrointestinal disorders	**193 (58.1)**	**49 (14.8)**	**1833 (69.8)**	**398 (15.2)**
Diarrhoea	73 (22.0)	7 (2.1)	917 (34.9)	126 (4.8)
Nausea	32 (9.6)	1 (0.3)	719 (27.4)	42 (1.6)
Abdominal pain	45 (13.6)	4 (1.2)	476 (18.1)	43 (1.6)
Vomiting	23 (6.9)	2 (0.6)	467 (17.8)	37 (1.4)
Constipation	27 (8.1)	0	463 (17.6)	9 (0.3)
General disorders and administration site conditions	**173 (52.1)**	**19 (5.7)**	**1760 (67.0)**	**216 (8.2)**
Fatigue	109 (32.8)	8 (2.4)	1229 (46.8)	133 (5.1)
Pyrexia	48 (14.5)	2 (0.6)	600 (22.8)	25 (1.0)
Oedema	42 (12.7)	4 (1.2)	332 (12.6)	11 (0.4)
Skin and subcutaneous tissue disorders	**213 (64.2)**	**22 (6.6)**	**1564 (59.6)**	**144 (5.5)**
Rash	119 (35.8)	12 (3.6)	959 (36.5)	105 (4.0)
Pruritus	114 (34.3)	5 (1.5)	767 (29.2)	26 (1.0)
Metabolism and nutrition disorders	**140 (42.2)**	**35 (10.5)**	**1239 (47.2)**	**336 (12.8)**
Decreased appetite	53 (16.0)	4 (1.2)	572 (21.8)	47 (1.8)
Respiratory, thoracic and mediastinal disorders	**93 (28.0)**	**11 (3.3)**	**1190 (45.3)**	**191 (7.3)**
Cough	43 (13.0)	0	556 (21.2)	8 (0.3)
Dyspnoea	29 (8.7)	3 (0.9)	447 (17.0)	59 (2.2)
Infections and infestations	**107 (32.2)**	**29 (8.7)**	**1170 (44.6)**	**287 (10.9)**
Upper respiratory tract infection	10 (3.0)	0	343 (13.1)	8 (0.3)
Investigations	**184 (55.4)**	**73 (22.0)**	**1210 (46.1)**	**480 (18.3)**
Transaminases increased	120 (36.1)	40 (12.0)	512 (19.5)	181 (6.9)
Lipase increased	59 (17.8)	24 (7.2)	331 (12.6)	198 (7.5)
Amylase increased	50 (15.1)	6 (1.8)	263 (10.0)	84 (3.2)
Blood bilirubin increased	39 (11.7)	6 (1.8)	99 (3.8)	14 (0.5)
Musculoskeletal and connective tissue disorders	**95 (28.6)**	**9 (2.7)**	**1078 (41.1)**	**109 (4.2)**
Musculoskeletal pain	57 (17.2)	2 (0.6)	682 (26.0)	52 (2.0)
Arthralgia	41 (12.3)	1 (0.3)	474 (18.1)	22 (0.8)

System Organ Class (%) Preferred Term (%)	CA2099DW Nivo + Ipi (N = 332)		Pooled Nivo + Ipi Including CA2099DW (N = 2626)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Nervous system disorders	**74 (22.3)**	**14 (4.2)**	**918 (35.0)**	**113 (4.3)**
Headache	26 (7.8)	0	380 (14.5)	16 (0.6)
Dizziness	16 (4.8)	1 (0.3)	254 (9.7)	8 (0.3)
Endocrine disorders	**95 (28.6)**	**11 (3.3)**	**747 (28.4)**	**127 (4.8)**
Hypothyroidism	46 (13.9)	0	415 (15.8)	8 (0.3)
Hyperthyroidism	37 (11.1)	2 (0.6)	237 (9.0)	12 (0.5)
Blood and lymphatic system disorders	**93 (28.0)**	**23 (6.9)**	**739 (28.1)**	**213 (8.1)**
Anaemia	42 (12.7)	9 (2.7)	485 (18.5)	106 (4.0)
Thrombocytopenia	42 (12.7)	6 (1.8)	146 (5.6)	32 (1.2)

MedDRA Version: 26.1
CTCAE Version: 5.0 for CA2099DW, 3.0 for CA209004, and 4.0 for other pooled studies
Includes events reported between first dose and 30 days after last dose of study therapy.
Pooled group includes the following studies: CA2099DW, CA209069, CA209004 (cohort 8), CA209067 (combo arm), CA2098HW (first line), CA2099LA (includes nivolumab + ipilimumab + chemotherapy), CA209214, CA209743, CA209142 (cohort 2, dMMR/MSI-H CRC), CA209648.
Some preferred terms are re-mapped based on BMS medical review.

Post marketing experience

Based on pharmacovigilance activities, post-marketing safety data is consistent with, and confirms the clinical trial safety data for nivolumab and ipilimumab.

2.5.1. Discussion on clinical safety

The current safety assessment focuses on the use of nivo+ipi for the 1L treatment of adult patients with unresectable or advanced HCC. Main safety results were obtained from the pivotal study CA2099DW, which is a phase 3, open-label, randomized controlled study evaluating the safety and efficacy of nivo+ipi vs investigator's choice of sorafenib or lenvatinib (SOC). The safety population from study CA2099DW comprises 657 patients: 332 patients treated with nivo+ipi and 325 patients treated with SOC.

Patients treated with nivo+ipi (N=332) received nivolumab at a dose of 1 mg/kg followed by ipilimumab at a dose of 3 mg/kg administered IV Q3W for up to 4 cycles, followed by nivo 480 mg (flat dose) Q4W until disease progression or unacceptable toxicity for a maximum duration of treatment of 2 years. Subjects treated with nivolumab and ipilimumab could discontinue ipilimumab and continue to receive nivolumab monotherapy (480 mg flat dose Q4W) before completing 4 doses of ipi. Although based on the exposure data, not many patients seem to have discontinued ipilimumab (before completing the 4 cycles) due to toxicity while continuing nivolumab monotherapy, having this exact number is of most importance in a scenario where the contribution of ipilimumab could be somehow questioned. There were 200 patients who discontinued ipilimumab and continued to receive treatment with nivolumab as monotherapy. A total of 180 patients entered the nivolumab monotherapy after receiving the 4 doses of ipilimumab, 12 after receiving 3 doses of ipilimumab, 4 after receiving 2 doses, and 4 patients after the first dose of ipilimumab.

Participants randomized to the SOC arm (N=325) could receive one of 2 SOC regimens (investigator´s

choice): sorafenib 400 mg PO BID (N=50), or lenvatinib 8 mg (N=62) PO QD (if body weight <60 kg), or 12 mg (N=213) PO QD (if body weight <60 kg or ≥60 kg) until disease progression or unacceptable toxicity.

At the time of the clinical cut-off date (31 January 2024), with a minimum follow-up of 26.8 months, a total of 642 subjects discontinued treatment, 332 (100%) from the nivo+ipi arm and 310 (95.4%) from the SOC arm. The main reasons for not continuing in the treatment period were firstly disease progression (40.1% in the nivo+ipi; 68.9% in the SOC arm) and secondly study drug toxicity (22.3% in nivo+ipi; 11.1% in the SOC arm).

Patient exposure

The median duration of therapy was shorter in the nivo+ipi arm (4.68 months) than in the SOC arm (6.93 months). Less than 50% of patients (45.2%) received more than 6 months of treatment in the nivo+ipi arm vs. 52.3% in the SOC arm. Hence, the exposure to the proposed regimen may be considered slightly lower than expected. However, this is partly due to the higher rate of disease progression (40.1% vs. 68.9%), first reason for not continuing in the treatment period. Nevertheless, 62 subjects (18.67%) in the nivo+ipi arm (N=332) and 157 patients (48.31%) in the SOC arm (N=325) were treated beyond progression (defined as subjects whose last available dose date is after the date of radiographic progression per investigator RECIST 1.1).In addition to the higher rate of disease progression, another relevant contribution to the shorter median duration of treatment in the nivo+ipi arm (4.68 months) is the higher incidence of early discontinuations (55.2% vs. 48.0%), which include randomized subjects never treated (N=11) and treated subjects who discontinued treatment with last dose date ≤ 5.84 months from randomization (N=334). Data about early discontinuations is included in the early death analysis report, section 2.4.2.

The median number of treatment doses received by subjects in the nivo+ipi arm was 4.0 (1-4) for each one of the components and 10.0 (1-24) for nivo monotherapy; while in the SOC arm the median number of doses was 127.5 (8-792) for sorafenib, 196.0 (3-1097) for lenvatinib 8 mg and 211.0 (1-1135) for lenvatinib 12 mg.

The proportion of patients who received ≥90% of the planned relative dose intensity was higher in the nivo+ipi arm (80.1% for nivo, 79.5% for ipi, and 93.5% for nivo monotherapy) compared to the SOC arm (24.0% for sorafenib, 53.2% for the 8 mg dose of lenvatinib, 26.3% for the 12 mg dose of lenvatinib). However, as dose reductions of nivo and/or ipi were not allowed and additional dose reductions of sorafenib or lenvatinib were allowed according to local SmPCs, these differences are to be expected.

Adverse events (AEs)

Almost all patients experienced at least one AE (99.7% in the nivo+ipi; 98.5% in the SOC arm). Grade 3-4 AEs were reported in a higher proportion of patients in the nivo+ipi arm compared with the SOC arm (69.3% vs 62.5%), although frequencies of drug-related Grade 3-4 AEs were similar between arms (41.3% vs 42.5% for nivo+ipi and SOC, respectively).

The most frequently reported (≥10%) all-causality AEs in the nivo+ipi arm were pruritus (34.3%), AST increased (29.5%) and rash (24.4%). While in the SOC arm were hypertension (44.6%), diarrhoea (39.1%), and palmar-plantar erythrodysaesthesia syndrome (32.0%). The most frequently reported Grade 3-4 all causality AEs in the nivo+ipi arm were AST increased (7.5%), lipase increased (7.2%), ALT increased and malignant neoplasm progression (5.7% each). While in the SOC arm were hypertension (13.2%), malignant neoplasm progression (7.1%), and proteinuria (5.2%).

Regarding drug-related AEs, the frequency was lower in the nivo+ipi arm compared to the SOC arm (83.7% vs 91.4%), although the Grade 3-4 drug-related AEs were comparable between the treatment

arms (41.3% vs 42.5%). The most frequently reported drug-related AEs were pruritus (28.0%), AST increased (19.6%) and rash (19.3%) in the nivo+ipi arm; while in the SOC arm were hypertension (41.2%), diarrhoea (35.1%), and palmar-plantar erythrodysaesthesia syndrome (30.5%). When considering only Grade 3-4 AEs, the most common were AST increased (6.0%), lipase increased (5.1%), and ALT increased (4.8%) in the nivo+ipi arm, and hypertension (11.7%), proteinuria (5.2%), and palmar-plantar erythrodysaesthesia syndrome (3.4%) in the SOC arm.

Serious adverse events (SAEs)

The overall frequencies of all-causality SAEs (any grade, Grade 3-4) were higher in the nivo+ ipi (53.0% any grade, 46.4% Grade 3-4) than in the SOC arm (44.0% any grade, 35.4% Grade 3-4). In the same way, the frequency of drug-related SAEs (any grade, Grade 3-4) was higher in the nivo+ ipi (28.3%, 25.0%) than in the SOC arm (14.5%, 12.9%).

The most frequently reported all-causality SAEs for the nivo+ipi arm were malignant neoplasm progression (7.2%), colitis (2.7%), ascites (2.4%), and hepatic failure and immune-mediated hepatitis (1.8% each). Whilst those in the SOC arm were malignant neoplasm progression (9.8%), pyrexia (3.7%), abdominal pain and hepatic encephalopathy (2.2% each). In respect of drug-related SAEs, the most frequently reported in the nivo+ipi were colitis (2.7%), immune-mediated hepatitis (1.8%), acute kidney injury (1.8%), and adrenal insufficiency, autoimmune hepatitis and hepatic failure (1.2% each). While for SOC arm these were hypertension (1.2%) and oedema peripheral (0.9%).

Deaths

Regardless of causality, as of the clinical data cut (31 January 2024), 192 (57.8%) patients in the nivo+ipi arm and 224 (68.9%) in the SOC arm died. Disease progression was the most frequently reported cause of death in both arms (41.9% vs 62.2%, for respectively the nivo+ipi and the SOC arm). Deaths attributable to study drug toxicity, the secondary reason for death, were higher in the nivo+ipi arm [12 (3.6%)], compared to the SOC arm [3 (0.9%)]. In the same way, patients who died due to other reasons (unrelated to study treatment - other than study drug toxicity, disease, or unknown reasons) were also higher in the nivo+ipi arm [35 (10.5%)], compared with the SOC arm [14 (4.3%)].

Early deaths (defined as a death prior to or on 5.84 months after randomization) were reported for 105 of the 345 patients with early discontinuation of study treatment, 66 of the 185 patients (35.7%) who early discontinued in the nivo+ipi arm and 39 of 160 patients (24.4%) who early discontinued in the SOC arm. The majority of early deaths were attributable to disease, [36/66 (54.5%)] in the nivo+ipi arm and [31/39 (79.5%)] in the SOC arm. However, early deaths due to study drug toxicity were [11/66 (16.7%)], most pertained to hepatic failure and immune-mediated hepatitis, vs [1/39 (2.6%)]. Additionally, the early deaths attributable to other reasons were [18/66 (27.3%)], mainly related to pulmonary events (especially pneumonia), vs [6/39 (15.4%)]. For a discussion on early deaths, refer to section 2.4.1.

Other Significant Adverse Events

Adverse events of special interest (AESI) for nivolumab and ipilimumab are classified into Select Adverse Events, immune-mediated AEs (IMAEs) and other events of special interest (OESIs).

The majority of select AEs were Grade 1-2 and most of them were considered drug-related by the investigator. The most frequently reported drug-related select AE categories in the nivo+ipi are were skin (51.8%), hepatic (34.3%) and endocrine (28.3%). While in the SOC arm were skin (42.8%), gastrointestinal (35.1%), and endocrine (31.4%). By PT, the most common select AEs were pruritus (28.0%), AST increased (19.6%), and rash (19.3%) in the nivo+ipi arm; whilst in the SOC arm were

diarrhoea (35.1%), palmar-plantar erythrodysaesthesia syndrome (30.5%), and hypothyroidism (24.3%).

As seen with other nivolumab therapeutic indications, endocrine AEs tend to have the lowest rate of resolved events (45.7% of 43 subjects), followed by skin (69.6% of 119 subjects), pulmonary (71.4% of 5 subjects), hepatic (82.5% of 94 subjects), gastrointestinal (91.1% of 51 subjects). Renal (6 subjects) and hypersensitivity infusion reaction (8 subjects) were completed resolved (100%) in the nivo+ipi treatment arm.

Regarding IMAEs, analyses included endocrine events (regardless of treatment) in addition to all events (reported within 100 days of the last dose) which required immunosuppressive therapy for their management. The majority of IMAEs (non-endocrine/endocrine) were Grade 1-2 except for hepatitis. Grade 3-4 hepatitis was reported in 15.4% of subjects. In the nivo+ipi arm, the most common IMAE were hepatitis (19.0%), hypothyroidism/thyroiditis (18.7%), and rash (15.4%). For the SOC arm were hypothyroidism/thyroiditis (3.4%), rash (0.6%), and diarrhoea/colitis (0.3%).

The proportion of patients with resolution of the above-mentioned IMAEs was 74.6%, 41.9%, and 76.5% for hepatitis, hypothyroidism/thyroiditis and rash, respectively.

Twenty OESIs were reported in 16 (4.82%) patients in the nivo+ipi arm, including myasthenic syndrome (1 patient), demyelination (1 patient), pancreatitis (9 patients), myocarditis (3 patients), myositis/rhabdomyolysis (4 patients), autoimmune cytopenia (2 patients). While three OESIs were reported in 3 (0.92%) patients in the SOC arm. In the nivo+ipi arm, all OESIs were considered drug-related by investigator and the frequencies were <1% except for pancreatitis (2.1%). Eleven OESIs were Grade 3-4 and including events of myasthenia gravis, pancreatitis, myocarditis, myositis, and autoimmune haemolytic anaemia, in the nivo+ipi arm.

Laboratory findings

With regards to laboratory findings, reported increases in hepatic parameters were higher in the nivo+ipi arm compared with the SOC arm.

Concurrent ALT or AST >3×ULN with total bilirubin >2×ULN after the first dose and within 30 days of last dose of study therapy was reported in 44 (13.3%) patients in the nivo+ipi arm and 28 (8.9%) patients in the SOC arm.

The most common thyroid function test abnormality was TSH increase (>ULN) which was reported by the 31.4% and the 64.6% of subjects from the nivo + ipi arm and the SOC arm, respectively.

There were Grade 3 and Grade 4 abnormalities in creatinine (increases), respectively: Grade 3 in 7 (2.1%) patients in the nivo+ipi arm and 2 (0.6%) patients in the SOC arm; and Grade 4 in 1 (0.4%) patient in nivo+ipi arm.

Immunogenicity

Concerning immunogenicity, 100 subjects and 13 subjects were nivolumab and ipilimumab ADA positive, respectively. Of the 224 nivolumab ADA-evaluable subjects in the nivo+ipi arm, 19 (8.5%) subjects were nivolumab ADA positive at baseline, and 100 (44.6%) subjects were treatment-emergent ADA-positive [11 (4.9%) were persistent positive, and 16 (7.1%) were positive for neutralizing ADA]. For ipilimumab, from the 244 ipilimumab ADA-evaluable subjects in the nivo+ipi arm, 18 (7.4%) were ADA positive at baseline and 13 (5.3%) were treatment-emergent ADA-positive [1 (0.4%) subject was persistent positive, and no subject was neutralizing ADA-positive].

Differences were found in the frequency of hypersensitivity/infusion reactions between ADA positive and ADA negative subjects for both, nivolumab and ipilimumab in treated subjects evaluable for ADA:

(0.8%, 1/124) in nivo ADA-negative subjects and (2.0%, 2/100) in nivo ADA-positive subjects. And in a similar proportion of ipi ADA-negative subjects (1.7%, 4/231) and ipi ADA positive subjects (0%, 0/13).

Special populations

Considering safety in special populations, some differences in safety were reported between elderly (≥65 years; 124 patients) and younger patients (<65 years; 162 patients). The safety data from patients 75 years of age or older are limited to a sample size of 46 patients.

Grade 3-4 AEs (all-causality) incidences were higher in the nivo+ipi arm compared to the SOC arm for the age category <65 (68.5% vs. 55.9%) and for ≥75 (80.4% vs. 64.4%). However, for ≥65 - <75 age range, Grade 5 AEs (all causality) incidences were slightly higher in the nivo+ipi (4.0%) arm compared to the SOC arm (3.3%). In the same way, Grade 3-4 drug-related AEs presented higher incidences in subjects < 65 (40.1% vs. 35.0%) and Grade 5 drug-related AEs were not reported for any age category in both arms.

In the group of patients aged ≥65 years treated with nivo+ipi, a higher deaths rate due to any reason [except for deaths due to disease which are higher in SOC arm (64.8%) was reported compared to nivo+ipi (39.4%)]. Similarly, higher incidences of SAEs (all-causality and drug-related), AEs leading to discontinuation (all-causality and drug-related), and all-causality AEs, were reported for the experimental arm, compared to those treated with SOC and also with respect to patients <65 years age group. Within the ≥65 years age group in the nivo+ipi arm, in the ≥75 years [N=46] subgroup, the number of deaths due to other reasons was higher (28.3%) compared to the ≥65-<75 years [N=124] (11.3%) age subgroup. Comparably, Grade 3-4 SAEs were also higher (all-causality and drug-related) [(60.9% and 28.3%) in ≥75 age subgroup vs (46.0% and 27.4%) in ≥65-<75 age subgroup, respectively]. The same trend was identified for All-causality AEs leading to discontinuation (26.1% vs 22.6%) and Grade 3-4 all-causality AEs (80.4% vs 66.1%). However, drug-related AEs and drug-related AEs leading to discontinuation incidences were higher in ≥65-<75 years compared to ≥75 age subgroup. Moreover, patients in the age group ≥ 65 years (N=352) compared to <65 age group (N=305) experienced higher incidences of deaths (with the exception of deaths attributed to "unknown" causes), Grade 3-4 AEs, SAEs and AEs leading to discontinuation (all-causality and drug-related each parameter), regardless of treatment arm.

Therefore, a worse safety profile in patients ≥65 years, even if expected, seems to be established based on this study results.

Information has been added in section 4.8 of the SmPC informing that in HCC patients there were higher rates of serious adverse reactions and discontinuation due to adverse reactions in patients aged 75 years or older (67% and 35%, respectively) relative to all patients who received ipilimumab with nivolumab (53% and 27%, respectively).

Focusing on data to support the safety information in section 4.8, the tables with the pooled safety data per age group show no notable differences between pooled nivo + ipi excluding study CA2099DW (N=1111) and pooled nivo + ipi including study CA2099DW (N=1273) for <65 age group as well as for ≥65 age group, in terms of SAEs, AEs, AEs leading to discontinuation (all-causality and drug-related each parameter), except for some minor imbalances with higher incidences of any Grade and Grade 3-4 SAEs and AEs leading to discontinuation (all causality and drug-related) in pooled data excluding CA2099DW compared to the pool including CA2099DW. However, in terms of deaths there are several differences to highlight. The frequencies of deaths (overall and any reason) in the pooled including study CA2099DW are slightly higher than in the pooled excluding study CA2099DW, except for the deaths due to disease for age group ≥65 years (39.7% in the pooled including CA2099DW vs 39.8% in the pooled excluding CA2099DW).

Discontinuation due to adverse events

The proportion of subjects with all causality and drug-related AEs leading to discontinuation of study drug were higher in the nivo+ ipi arm vs. the SOC arm (all causality: 26.5% vs 23.1%; drug-related: 17.8% vs 10.5%). Grade 3-4 AEs leading to discontinuation of study drug (all causality and drug-related) were reported in a higher proportion of patients in the nivo+ipi arm (20.8% all causality; 13.3% drug-related) as compared to the SOC arm (15.7% all causality; 6.5% drug-related). The most frequently reported AEs leading to discontinuation (all-causality) were malignant neoplasm progression (2.7%) in the nivo+ipi arm; while in the SOC arm were malignant neoplasm progression (6.2%), proteinuria (1.5%), and asthenia (1.2%). Focusing on drug-related AEs leading to discontinuation, the most frequently reported were AST increased (1.2%) and proteinuria (1.5%) in the nivo+ipi arm; whilst in the SOC arm was proteinuria (1.5%).

SmPC

Regarding data to support safety information included in section 4.8 of the PI, the pooled safety data from the current nivolumab + ipilimumab combination pool, including pooled AEs frequencies, have been provided by the MAH. The proposed changes are considered acceptable.

2.5.2. Conclusions on clinical safety

The safety profile of nivolumab in combination with ipilimumab for the 1L treatment of adult patients with unresectable or advanced HCC has been characterised based on the results from study CA2099DW, by comparison with subjects who received SOC (sorafenib or lenvatinib).

For the HCC indication, the proposed posology, the same one used in the study, is nivolumab 1 mg/kg + ipilimumab 3 mg/kg for 4 cycles, followed by nivolumab monotherapy. This higher dose of ipilimumab, currently only authorized for melanoma, is expected to significantly increase the toxicity in relation to other nivo + ipi approved indications, although this is not clearly reflected in study CA2099DW's results. The fact that the comparators also present a relevant toxicity profile might have also contributed.

Overall, based on the study results, the safety profile of the combination of nivolumab and ipilimumab in this HCC setting appears in principle consistent with the already known safety profile of the combination, in terms of the type of events reported. However, deaths attributable to study drug toxicity and other reasons (unrelated to study treatment - other than study drug toxicity, disease, or unknown reasons) were higher in the nivo+ipi arm. In addition, early deaths were reported higher in the nivo+ipi arm during the first 6 months of treatment, especially in the subgroup of patients with identified poor prognosis (presence of EHS or MVI, AFP levels ≥ 400 ng/ml, larger tumours and higher number of liver nodules (>3), poorer liver function (Child-Pugh score > 5; ALBI grade > 1), and worse performance status (ECOG PS 1) than the overall population included in the clinical trial. The high rate of treatment discontinuations gives rise to concern regarding the tolerability of this combination in the HCC setting. A warning has been added in section 4.4 of the SmPC to inform about the higher number of deaths within 6 months in nivolumab+ipilimumab compared to lenvatinib or sorafenib and advising physicians to consider this risk before initiating treatment with nivolumab in combination with ipilimumab in patients with poorer prognostic features.

Moreover, higher incidences of Grade 3-4 AEs as well as all-causality SAEs (any grade, Grade 3-4) and drug-related SAEs have been reported in the nivo+ipi arm compared to the SOC arm.

No new safety signals were identified.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The WSA submitted an updated RMP version 44.2 for Yervoy and RMP version 41.1. for OPDIVO with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the RMP version 44.2 for Yervoy and RMP version 41.1. for OPDIVO are acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

OPDIVO RMP v41.1

Summary of Safety Concerns

Important identified risks	Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs) Severe infusion reactions
Important potential risks	Embryofetal toxicity Immunogenicity Risk of GVHD with Nivolumab after allogeneic HSCT
Missing information	Patients with severe hepatic and/or renal impairment Patients with autoimmune disease Patients already receiving systemic immunosuppressants before starting nivolumab Long-term safety in adolescent patients ≥ 12 years of age

Yervoy RMP v44.2

Summary of Safety Concerns

Important identified risks	Immune-related adverse reactions (including GI, hepatic, skin, neurologic, endocrine and other irARs) Severe infusion reactions
Important potential risks	None
Missing information	Long-term safety in adolescent patients ≥ 12 years of age

Pharmacovigilance plan

OPDIVO:

Besides routine pharmacovigilance, additional pharmacovigilance activities are in place:

Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice Ongoing	To assess use pattern, effectiveness, and safety of nivolumab, and management of important identified risks of nivolumab in patients with lung cancer or melanoma in routine oncology practice	Post marketing use safety profile, management and outcome of immune-related ARs (including pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, rash, other irARs [uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, encephalitis, myositis, myocarditis, rhabdomyolysis, solid organ transplant rejection, and Vogt-Koyanagi-Harada disease]), and severe infusion reactions	1. Interim report 2. Final CSR submission	Interim results provided annually Q4 2024
Long-term follow-up of ipilimumab, nivolumab and nivolumab in combination with ipilimumab treated paediatric patients enrolled in the DMTR (CA184557) Voluntary PASS Planned	To assess safety and long-term outcomes in children and adolescents.	Long-term safety in adolescent patients ≥ 12 years of age	1. Submission of protocol 2. Interim Study Report 3. Final report of study results	Q4 2023 Q4 2026 Q4 2033

Yervoy:

Besides routine pharmacovigilance, additional pharmacovigilance activities are in place:

Post-Authorization Safety Studies Short Name Summary

Study short name and title	Rationale and study objectives	Study design	Study population	Milestone(s)	Due Date(s)
Long-term follow-up of Nivolumab and Ipilimumab (as monotherapy and as combination therapy)-treated paediatric patients enrolled in the Dutch Melanoma Treatment Registry (DMTR) (CA184557)[a] Category 3	Rationale: Limited clinical data due to the rarity of the paediatric melanoma population. Data on long-term outcomes are lacking. Objectives: To assess safety and long-term outcomes in children and adolescents.	Observational, national, retrospective study	Paediatric patients consisting of 2 cohorts (12 to < 18 and < 12 years of age) treated with ipilimumab, nivolumab or nivolumab in combination with ipilimumab for advanced (unresectable or metastatic) melanoma or with nivolumab as adjuvant treatment of melanoma	1. Synopsis of the DMTR	16-Apr-2018
				2. Submission of protocol	02-Nov-2019
				3. Start of data collection	End of 2Q 2019
				4. Recruitment period[b]	2Q 2019 until 1Q 2029
				5. Progress Report	End of 2Q 2022
				6. Interim Study Report	4Q 2026
				7. End of data collection	End of Q1 2029
				8. Final report of study results	End of 3Q 2029

Risk minimisation measures

Next to routine risk minimisation measures, additional risk minimisation measures are in place for both products:

OPDIVO

Additional Risk Minimisation Measures

Additional Risk Minimisation:	Objectives/Rationale
Patient Alert Card	**Objectives:** To further raise awareness of patients on signs and symptoms of important risks of immune-related ARs. **Rationale for the additional risk minimisation activity:** This tool will provide the opportunity for reinforcing key messages of early recognition and appropriate management of important identified risks of immune-related ARs to maintain favourable benefit-risk profile of nivolumab with post-marketing use. **Target audience and planned distribution path:** Patients via HCPs.

Additional Risk Minimisation Measures

Additional Risk Minimisation:	Objectives/Rationale
	Plans to evaluate the effectiveness of the interventions and criteria for success: Routine pharmacovigilance activities will provide information on any changes in the occurrence, severity, and outcome of important identified risks as it relates to the established safety profile and will be reported in future regulatory safety reports (eg, PSUR).

Yervoy

Additional Risk Minimisation Measures

Additional Risk Minimisation	Objectives:
Educational materials: Patient Card	To ensure that patients are aware of the severe inflammatory adverse reactions, understand the importance of early detection, and have access to appropriate treatment guidelines. **Rationale for the additional risk minimisation activity:** The educational materials will provide the opportunity for reinforcing key messages to early recognition and appropriate management of inflammatory adverse reactions to maintain favourable benefit/risk of ipilimumab in market use. **Target audience and planned distribution path:** Target audience: Patients Distribution via healthcare professionals agreed at national level. **Plans to evaluate the effectiveness of the interventions and criteria for success:** Routine pharmacovigilance activities will provide information on any changes in the occurrence, severity, and outcome of important risks as it relates to the established safety profile, and will be reported in future regulatory safety reports (eg, PSUR).

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 ,5.1 and 5.2 of the OPDIVO SmPC and sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the Yervoy SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the WSA and has been found acceptable for the following reasons: the submitted type II variation to extend the currently approved indications for OPDIVO (nivolumab) and YERVOY (ipilimumab) to include OPDIVO in combination with YERVOY (ipilimumab) for the first-line treatment of adult patients with unresectable or advanced hepatocellular carcinoma does not involve a

relevant impact on the PIL.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The recommended indication for **YERVOY (ipilimumab)** is: YERVOY in combination with nivolumab is indicated for the first line treatment of adult patients with unresectable or advanced hepatocellular carcinoma.

The recommended indication for **OPDIVO (nivolumab)** is: OPDIVO in combination with ipilimumab is indicated for the first line treatment of adult patients with unresectable or advanced hepatocellular carcinoma.

3.1.2. Available therapies and unmet medical need

Five systemic therapies are currently approved by the EMA for first-line treatment of advanced HCC: two VEGFR TKIs (sorafenib and lenvatinib) and two immunotherapy-based combinations (atezolizumab + bevacizumab and durvalumab + tremelimumab), as well as an immunotherapy as monotherapy (durvalumab).

Sorafenib, an oral TKI targeting multiple kinases, has been the standard of care (SOC) for advanced HCC in the first-line setting since its approval in 2007 (EMEA/H/C/000690/II/0005, 29 October 2007), which was based on an improved efficacy compared to placebo, establishing a median OS of 10.7 months (vs 7.9 months for placebo) in the Phase III SHARP study. Subsequent studies have demonstrated a median OS ranging from 10.7 to 13.4 months.

Lenvatinib, another multiple kinase inhibitor, was approved in 2018 (EMEA/H/C/003727/II/0011/G, 20 August 2018) as first-line treatment for advanced HCC based on non-inferior survival, as compared to sorafenib in the Phase III study REFLECT, with a median OS of 13.6 months vs 12.3 months with sorafenib.

Atezolizumab (a PD-L1 inhibitor) in combination with bevacizumab (an angiogenesis inhibitor) was also approved in the first-line setting in 2020 (EMEA/H/C/004143/II/0039, 27 October 2020), after the Phase III IMbrave150 study showed improvements in OS (19.2 months vs. 13.4 months) and PFS (6.9 months vs. 4.3 months) compared to sorafenib. The ESMO guidelines were updated in 2020 to recommend atezolizumab in combination with bevacizumab as the preferred option to treat first-line HCC, but further updates have not taken place yet.

Durvalumab in combination with tremelimumab was approved in 2022 (EMEA/H/C/004771/II/0045, 30 January 2023) for the first-line treatment based on the demonstration of superiority of the combination of durva+treme vs. sorafenib in the study HIMALAYA (primary objective of the study). Durva+treme resulted in a median overall survival of 16.6 months, compared with a median of 13.8 months with sorafenib. In 2023, durvalumab as monotherapy was also approved as first-line treatment (EMEA/H/C/004771/II/0057, 15 November 2023), based on the demonstration of non-inferiority vs. sorafenib in the study HIMALAYA (key secondary objective of the study).

Unmet medical need

HCC is an aggressive tumour associated with poor prognosis, particularly in advanced stages. Prognosis remains suboptimal despite significant advancements in the treatment of unresectable HCC.

Additionally, the safety profile of the available therapies makes some patients ineligible for treatment with them, or forces them to discontinue treatment. Notably, atezo+beva, which is currently considered as the preferred first-line treatment, is associated with a relevant risk of bleeding / proteinuria / thromboembolic events, and patients should be screened for the presence of esophageal varices or other risk factors for serious bleeding prior to treatment.

Therefore, there is a need for new therapies that prolong overall survival, with different (ideally better) safety profiles which enable all patients (and not only the current subset of eligible patients) to receive an optimal treatment.

3.1.3. Main clinical studies

The pivotal study CA2099DW is a randomized, multi-centre, open-label Phase 3 study of nivolumab in combination with ipilimumab compared with the Investigator's choice between sorafenib or lenvatinib, as first-line treatment in participants with advanced hepatocellular carcinoma.

Patients included were not eligible for curative surgical and/or locoregional therapies or with progressive disease after surgical and/or locoregional therapies; with no prior systemic therapy for advanced disease; and Child Pugh A score. Stratification factors were aetiology (HCV vs. HBV vs. uninfected), vascular invasion and/or extrahepatic spread (present/absent) and baseline AFP level (<400 ng/mL or ≥400 ng/mL).

Subjects were randomized to receive treatment with nivo 1 mg/kg + ipi 3 mg/kg Q3W for up to 4 cycles followed by nivo 480 mg (flat dose) Q4W until disease progression or for a maximum duration of treatment of 2 years; or sorafenib 400 mg PO BID or lenvatinib 8 mg PO QD (if body weight < 60 kg) or 12 mg PO QD (if body weight ≥60 kg) until disease progression.

The primary endpoint was OS. Key secondary endpoints were ORR by BICR and time to symptom deterioration (TTSD), which were included in that order following a statistical testing hierarchy; and, therefore, multiplicity-controlled. Other endpoints assessed were PFS by BICR and other antitumor activity endpoints such as time to progression (TTP), disease control rate (DCR), duration of disease control (DDC), time to response (TTR) and duration of response (DOR); assessed by BICR following RECIST 1.1 and mRECIST 1.1 criteria, as well as by Investigator.

3.2. Favourable effects

The primary endpoint for the CA2099CW study was met, showing a statistically significant improvement in **OS** [HR: 0.79 (95% CI: 0.65, 0.96); mOS 23.66 months in nivo+ipi vs. 20.63 months in sora/lenva; p-value: 0.0180] in a prespecified interim analysis, with a median follow-up of 35.20 months and a minimum follow-up of 26.8 months (IF: 81%). Sensitivity and subgroup analyses were overall consistent with the main analysis.

ORR by BICR, key secondary endpoint and multiplicity-protected, also showed favourable results for nivo+ipi, with an odds ratio of 3.61 (95% CI: 2.46, 5.29): 36.1% (95% CI: 31, 41.5) vs. 13.2% (95% CI: 9.8, 17.3). Although most responses were PRs (29.3% in nivo+ipi vs. 11.4% in sora/lenva), there were more CRs in nivo+ipi (6.9%) than in sora/lenva (1.8%). **DoR** was 30.4 (95% CI: 21.2, NA) in nivo+ipi and 12.9 (95% CI: 10.2, 31.2) in sora/lenva.

TTSD, also key secondary endpoint and multiplicity-protected, also resulted in a significant reduction in the risk of symptom deterioration of nivo+ipi compared with sora/lenva [HR: 0.76 (95% CI: 0.62, 0.93); mTTSD 2.60 months in nivo+ipi vs. 2.14 months in sora/lenva].

3.3. Uncertainties and limitations about favourable effects

- The comparators used in this study (sorafenib/lenvatinib) are not the current first-line treatment recommended by the ESMO guidelines in this setting. Therefore, no direct comparison between the applied combination (nivo+ipi) and the current recommended first-line treatment (atezo+beva) is available. Additionally, no direct comparison with durvalumab either as monotherapy or in combination with tremelimumab, is available.
- An early crossing of KM OS curves is observed suggesting an increased risk of death during the first 6 months of treatment with nivo+ipi arm. Early death was associated with the presence of poor prognostic features in patients. A warning in section 4.4 of the SmPC advising physicians to consider this risk before initiating treatment with nivo+ipi in patients with poor prognostic features.

3.4. Unfavourable effects

The safety assessment is based on a safety analysis set of 657 patients with unresectable or advanced HCC, 332 patients treated in the nivolumab+ipilimumab arm and 325 patients treated in the SOC arm (sorafenib or lenvatinib), included in study CA2099DW. Median treatment duration was 4.68 months for nivo+ipi and 6.93 months for SOC.

Almost all patients reported at least one AE of any grade (all-causality) with a higher incidence in the nivo+ipi arm (99.7%) compared to the SOC arm (98.5%). The most frequently reported (≥10%) all-causality AEs in the nivo+ipi arm were pruritus (34.3%), AST increased (29.5%) and rash (24.4%). AEs of Grade 3-4 were reported in a higher proportion of patients in the nivo+ipi arm compared with the SOC arm (69.3% vs 62.5%), the most frequently were AST increased (7.5%), lipase increased (7.2%), ALT increased and malignant neoplasm progression (5.7% each) for nivo+ipi. Most AEs were considered treatment-related and previously identified for nivo+ipi combination treatment.

SAEs have been observed in 53.0% of subjects in the nivo+ipi arm and 44.0% in the SOC arm, 28.3% patients reported a drug-related SAE in the nivo+ipi arm and 14.5% in the SOC arm.

Select immune-mediated AEs (IMAEs) in patients treated with nivo+ipi include endocrine and non-endocrine IMAEs: pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, hypersensitivity, adrenal insufficiency, hypothyroidism/thyroiditis, diabetes mellitus, hyperthyroidism, hypophysitis. The majority were Grade 1-2 except for hepatitis (Grade 3-4) which was reported in 15.4% of patients.

As of the DCO date of 31 January 2024, 192 (57.8%) patients had died in the nivo+ipi arm, most of them due to disease progression [139 (41.9%)]; although there were twelve (3.6%) patients who died due to study drug toxicity in the nivo+ipi arm while in the SOC arm were three (0.9%) patients. There were also more deaths attributed to other reasons in the nivo+ipi arm [35 (10.5%)] compared with the SOC arm [14 (4.3%)]. A causality relation cannot be excluded.

Treatment discontinuation rates showed also a worrisome trend, suggesting a difficult tolerability for this combination. Focusing on drug-related AEs leading to discontinuation, the most frequently reported were AST increased (1.2%) and proteinuria (1.5%) in the nivo+ipi arm; whilst in the SOC arm was proteinuria (1.5%).

Concerning special populations, the number of patients who were 65 years or older and experienced early death was higher [41/66 (62.1%)] than for those patients <65 years of age [25/66 (37.9%)] in the nivo+ipi arm.

3.5. Uncertainties and limitations about unfavourable effects

The recommended dose for this HCC indication is 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab every 3 weeks for up to 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered at a flat dose, as monotherapy. This higher dose of ipilimumab (only authorized for melanoma) is expected to carry a relevant toxicity that might not have been fully reflected on the reported results from study CA2099DW.

3.6. Effects Table

Table 95 Effects Table for nivolumab in combination with ipilimumab for the treatment of unresectable hepatocellular carcinoma (data cut-off: 31 January 2024)

Effect	Short description	Unit	Treatment (n=335)	Control (n=333)	Uncertainties / Strength of evidence	References
Favourable Effects						
OS	Overall survival: time between the date of randomization and the date of death (by any cause).	Median, months (95% CI)	23.66 (18.83, 29.44)	20.63 (17.48, 22.54)	HR: 0.79 (0.65, 0.96) P=0.0180	CSR (DCO:31 Jan 2024)
ORR by BICR	Objective Response Rate: percentage of participants whose BOR is either a confirmed CR or PR.	% (95% CI)	36.1 (31.0, 41.5)	13.2 (9.8, 17.3)	Difference: 22.9 (16.6, 29.2) Odds ratio: 3.61 (2.46, 5.29) P<0.0001	
DOR	Duration of Response: time between the date of first confirmed documented response of CR or PR to the date of the first documented tumor progression or death due to any cause, whichever occurred first.	Median, months (95% CI)	30.4 (21.2, N.A.)	12.9 (10.2, 31.2)		
TTSD	Time to Symptom Deterioration: time from randomization until a clinically meaningful decline in the HCS subscale score of the FACT-Hep.	Median, months (95% CI)	2.60 (2.00, 3.94)	2.14 (1.64, 2.79)	HR: 0.76 (0.62, 0.93) P=0.0059	
Unfavourable Effects						
Grade 3-4 AEs	All causality (drug-related)	%	69.3 (41.3)	62.5 (42.5)	Worse safety profile based on Grade ≥3 AEs, Deaths not attributable to disease[a], SAEs and AEs leading to discontinuation.	CSR (DCO:31 Jan 2024)
Deaths	Due to study drug toxicity	%	3.6	0.9		
	Due to other reasons (other than study drug toxicity, disease, or unknown reasons)	%	10.5	4.3		
SAEs	All causality (drug-related)	%	53 (28.3)	44 (14.5)		
AEs leading to discontinuations	All causality (drug-related)	%	26.5 (17.8)	23.1 (10.5)		
IMAEs	Hepatitis	%	19.0	0		
	Hypothyroidism/thyroiditis	%	18.7	3.4		
	Rash	%	15.4	0.6		
OESIs	Pancreatitis	%	2.1	0.3		

Abbreviations: OS: overall survival; ORR: objective response rate; BICR: blinded independent central review; TTSD: time to symptom deterioration; HR: hazard ratio; CSR: clinical study report; AE: adverse event; SAE: serious adverse event; IMAEs: Immune-mediated adverse events; OESIs: other events of special interest.

Notes: [a] Death summary. Early deaths (defined as a death prior to or on 5.84 months after randomization) were reported higher in nivo+ipi arm for any reason, including disease progression.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Nivo+ipi has demonstrated a statistically significant improvement in overall survival of around 3 months (HR: 0.79 (0.65, 0.96); p=0.0180), compared with sorafenib or lenvatinib; active comparators having both of them previously established an OS benefit. The OS benefit was supported by an improvement in ORR; mainly represented by partial responses although there also was a higher number of complete responses. In the current setting in which patients have a poor prognosis this increase is clinically relevant; particularly considering that the mOS reached with nivo+ipi was almost 2 years. The improvements in ORR further support the efficacy of nivo+ipi, although it is noted that PFS (exploratory endpoint) was not improved; this observation is in line with other studies in the same setting. TTSD, which was included in the hierarchical statistical testing, was also statistically significant; further supporting the efficacy of nivo+ipi.

The most relevant uncertainty was the observation of a higher number of deaths during the first 6 months of treatment with nivo+ipi, compared to sora/lenva. The analysis of the baseline characteristics of patients who suffered an early death vs. the baseline characteristics of the overall population revealed that patients in the nivo+ipi arm who suffered an early death had more factors associated with a worse prognosis compared to the patients in the nivo+ipi arm of the overall population. These factors were the presence of EHS or MVI, AFP levels ≥ 400 ng/ml, larger tumours and higher number of liver nodules (>3), poorer liver function (Child-Pugh score > 5; ALBI grade > 1), and worse performance status (ECOG PS 1). Therefore, it could be concluded that the patients at higher risk of early death were the patients with a poorer disease prognosis at baseline. A warning has been included in section 4.4 of the SmPC to inform prescribers on the risk of early death and to advise them to consider this risk before initiating treatment with nivolumab in combination with ipilimumab in patients with poor prognostic features.

No new safety signal has been identified and, overall, the safety profile appears in line with what is known for the nivo+ipi combination and consistent with what was previously observed in other indications.

3.7.2. Balance of benefits and risks

Nivo+ipi has demonstrated a statistically significant improvement in OS with a mOS of around 3 additional months compared with sora/lenva, which is considered as clinically relevant.

The OS benefit of nivo+ipi as shown in study CA2099DW, in a condition with poor prognosis, is considered to outweigh the risks identified, which although non-negligible, are considered overall manageable.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of nivolumab in combination with ipilimumab for the first-line treatment of adults with unresectable or advanced HCC is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**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, II and IIIB

A Worksharing application for OPDIVO and YERVOY, as follows:

Extension of indication to include a new indication for OPDIVO in combination with ipilimumab as first line treatment of adult patients with unresectable or advanced hepatocellular carcinoma (HCC) based on study CA2099DW. This is a phase 3 randomised, multi-centre, open label study of Nivolumab in combination with Ipilimumab compared to Sorafenib or Lenvatinib as first-line treatment in participants with advanced HCC. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 41.1 of the OPDIVO RMP has also been submitted.

Extension of indication to include a new indication for YERVOY in combination with nivolumab as first line treatment of adult patients with unresectable or advanced hepatocellular carcinoma (HCC) based on study CA2099DW. This is a phase 3 randomised, multi-centre, open label study of Nivolumab in combination with Ipilimumab compared to Sorafenib or Lenvatinib as first-line treatment in participants with advanced HCC. 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. Version 44.2 of the Yervoy RMP has also been submitted. In addition the MAH implemented some minor changes to annex II.D.

The worksharing procedure leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to Annexes I, II and IIIB for Yervoy and annexes I and IIIB for OPDIVO and to the Risk Management Plan are recommended.