17 September 2020
EMA/584169/2020
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Tecentriq

International non-proprietary name: atezolizumab

Procedure No. EMEA/H/C/004143/II/0039

Marketing authorisation holder (MAH) Roche Registration GmbH

Note

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

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Table of contents

List of abbreviations

Abbreviation	Definition
1L	first-line
2L	second-line
AASLD	American Association for the Study of Liver Diseases
ADA	anti-drug antibody (same as anti-therapeutic antibody [ATA])
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AFP	α-fetoprotein
Atezo + Bev	atezolizumab in combination with bevacizumab
BCLC	Barcelona Clinic Liver Cancer
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum serum or plasma concentration
C_{min}	minimum serum or plasma concentration
CR	complete response
CSR	clinical study report
DCR	disease control rate
DOR	duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EHS	extrahepatic spread
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for the Research and Treatment of Cancer Quality–of–Life Questionnaire Core 30
EORTC QLQ-HCC18	European Organisation for the Research and Treatment of Cancer HCC Disease-Specific Quality–of–Life Questionnaire
EU	European Union
FDA	Food and Drug Administration
GHS	global health status
HBV	Hepatitis B virus
HCC	hepatocellular carcinoma
HCV	Hepatitis C virus
HR	hazard ratio
IgG1	immunoglobulin G1
IRF	independent review facility
IRR	infusion-related reaction
ITT	intent-to-treat
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	modified RECIST
MVI	macrovascular invasion
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death–1
PD-L1	programmed death–ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PopPK	population pharmacokinetics
PRO	patient-reported outcome
PT	preferred term
Q3W	every three weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RTOR	Real-Time Oncology Review
SAE	serious adverse event
sBLA	supplemental Biologics License Application
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics

US	United States
USPI	United States Prescribing Information
VEGF	vascular endothelial growth factor

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 23 January 2020 an application for a variation.

The following variation was requested:

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

Extension of Indication to include, in combination with bevacizumab, the treatment of patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy, based on the results of the pivotal study YO40245 (IMbrave150) as well as data from Arms A and F of the supportive Phase Ib study GO30140.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the Tecentriq 1200 mg concentrate for solution for infusion SmPC are updated. The Package Leaflet is updated in accordance.

An updated RMP version 13.0 was provided as part of the application.

The variation requested 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(s) P/0207/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP 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 MAH 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 MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	23 January 2020
Start of procedure:	29 February 2020
CHMP Rapporteur Assessment Report	24 April 2020
CHMP Co-Rapporteur Assessment Report	23 April 2020
PRAC Rapporteur Assessment Report	28 April 2020
PRAC members comments	06 May 2020
Updated PRAC Rapporteur Assessment Report	07 May 2020
PRAC Outcome	14 May 2020
CHMP members comments	18 May 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 May 2020
Request for Supplementary Information	28 May 2020
Rapporteur's preliminary assessment report circulated on:	18 August 2020
PRAC Rapporteur's Assessment Report	26 August 2020
PRAC outcome	04 September 2020
Updated CHMP Rapporteur(s) Assessment Report	10 September 2020
CHMP opinion:	17 September 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. It occurs in patients with chronic liver inflammation due to HBV, HCV, excessive alcohol intake or other toxins such as aflatoxin. Furthermore, haemochromatosis, alpha 1-antitrypsin deficiency, metabolic syndrome and NASH increase the risk of HCC.

State the claimed therapeutic indication

Tecentriq in combination with bevacizumab for the treatment of patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

Epidemiology

Hepatocellular carcinoma (HCC) is the sixth most common cancer type in the world, and the fourth most deadly cancer (Globocan 2018). There are over 700,000 new cases diagnosed each year worldwide with large geographic variation in both risk factors and incidence (El-Serag 2011, Ferlay et al. 2010). HCC is the fifth most common cancer in Europe and has been predicted to be responsible for 77,400 deaths in Europe in 2018.

Hepatocellular carcinoma (HCC) is a highly lethal disease with a mortality to incidence rate ratio of 0.98 and 0.95 in males and females, respectively (Kamangar et al. 2006). Up to 80% of patients first presenting with HCC have advanced, unresectable or metastatic disease because of the late appearance of symptoms.

Biologic features

The majority (> 80%) of cases occur in Sub-Saharan Africa and Eastern Asia, and China alone accounts for 55% of cases worldwide. Hepatitis B virus (HBV) infection is the main risk factor for HCC in Asia (> 70%), while in Western countries and Japan, the main risk factor is Hepatitis C virus (HCV) infection (50% to 70%) and excessive alcohol intake (20%), along with other causes of cirrhosis (10%) (Llovet et al. 2003).

Clinical presentation, diagnosis and stage/prognosis

It is a medically complex and difficult to treat disease as the majority of HCC patients have underlying cirrhosis requiring management of both the malignancy and underlying liver disease. HCC patients with locally advanced or metastatic disease have a poor prognosis, with rapid progression and short OS.

Management

Sorafenib remains as the global standard of care for treatment of patients with unresectable HCC based on two multicenter, randomized, double–blind, placebo-controlled Phase III trials: the Sorafenib HCC Assessment Randomized Protocol (SHARP) trial in Western regions and a trial conducted in the Asia-Pacific region (Asia-Pacific Trial) (Llovet et al. 2008, Cheng et al. 2009). Both studies demonstrated a survival benefit of sorafenib vs. placebo. Sorafenib is often poorly tolerated, and dose reductions or drug discontinuations due to AEs are common (Llovet et al. 2008).

Recently, treatment with lenvatinib, a multi-targeted receptor tyrosine kinase inhibitor, was shown to be non-inferior to sorafenib in terms of the primary efficacy endpoint of OS (lenvatinib vs. sorafenib hazard ratio HR 95% confidence interval [CI]: 0.79, 1.06; non-inferiority margin = 1.08) (REFLECT, Kudo et al. 2018).

2.1.2. About the product

Tecentriq (atezolizumab) is an Fc-engineered humanised immunoglobulin G1 (IgG1) monoclonal antibody that binds to programmed death−ligand 1 (PD-L1) and inhibits its interactions with programmed death-1 (PD-1) and B7.1 receptors, both of which can provide inhibitory signals to T cells. Avastin (bevacizumab) is a recombinant humanised monoclonal IgG1 antibody that binds to and inhibits

the biologic activity of human vascular endothelial growth factor (VEGF) in both *in vitro* and *in vivo* assay systems.

Combining anti–PD-L1 and anti-VEGF therapies has shown synergy and positive outcomes in Phase I to III studies, particularly in settings where high VEGF levels are known to play an important role in tumor growth (Chen and Hurwitz 2018). HCC is a highly vascularised tumor in which several proangiogenic factors play a role in its pathogenesis. In HCC, increased VEGF correlates with vascular density, tumor invasiveness and metastasis, and poor prognosis (Frenette 2012; Boige et al. 2012). In addition, VEGF-A signaling is known to activate angiogenesis-independent, inductive angiocrine signals from sinusoidal endothelium that stimulate hepatocyte-mediated liver regeneration (LeCouter et al. 2003; Ding et al. 2010).

In addition to its role in angiogenesis and liver regeneration, the VEGF-A pathway also plays a crucial role in exerting and maintaining an immunosuppressive tumor microenvironment through several mechanisms. For instance, VEGF-A has been shown to induce Fas ligand (FasL) expression on endothelial cells, which have the ability to kill effector CD8+ T cells, but not T-reg cells (Motz et al. 2014). Administration of anti-VEGF-A attenuated tumor endothelial FasL expression and produced a significant increase in the influx of tumor-rejecting CD8+ over FoxP3+ T cells, which was FasL-dependent, and led to CD8-dependent tumor growth suppression (Motz et al. 2014). Furthermore, bevacizumab can restore and/or maintain the antigen presentation capacity of dendritic cells, leading to enhanced T-cell infiltration in tumors (Oelkrug et al 2014; Wallin et al. 2016). In addition to increased trafficking of T cells into tumors (Manning et al. 2007), several publications have illustrated that anti-VEGF therapies can also reduce frequency of myeloid-derived suppressor cells, decrease production of suppressive cytokines, and lower expression of inhibitory checkpoints on CD8+ T cells in tumors (Roland et al. 2009; Voron et al. 2015). Therefore, the immunomodulatory effect of bevacizumab is expected to increase CD8-positive T-cell recruitment and relieve intratumoral immunosuppression, thereby boosting the effects of atezolizumab.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical development of atezolizumab in unresectable HCC comprises one pivotal Phase III study (IMbrave150), and three supportive Phase I studies (GO30140, PCD4989g, and YO29233). In addition, a Phase III study (WO41535 [IMbrave050]) of Atezo + Bev versus active surveillance as adjuvant therapy in HCC patients at high risk of recurrence after surgical resection or ablation is currently ongoing.

The Sponsor sought Scientific Advice feedback on the proposed Phase III study design (IMbrave150) from the Committee for Medicinal Products for Human Use (CHMP) and received a written advice in November 2017.

Overall, the CHMP supported the proposed Phase III study design with Atezo + Bev in unresectable HCC; the CHMP agreed with the proposed study population, the study design including the comparator (sorafenib) and stratification factors, the statistical analysis plan and the planned safety database.

The CHMP did not fully support the open-label design of the study as they considered double-blind design feasible. However, the CHMP noted that with OS as the primary endpoint, this may not be a critical concern. The CHMP did not agree with having ORR by investigator as co-primary endpoint with the

concern being that it could lead to a potential premature end of the study not allowing to capture final OS. The Sponsor consequently changed the co-primary endpoint of ORR by investigator to PFS by IRF per RECIST v1.1. In addition, the CHMP did not encourage the inclusion of an interim analysis for OS. However, in case the Sponsor decided to include an interim analysis, it was noted that randomization should be retained to ensure final OS data could be captured and trial integrity maintained.

The applicant held separate meetings with the Rapporteur (Danish Medicines Agency) and Co-Rapporteur (Paul-Ehrlich-Institute) in December 2018 to discuss the acceptability of a proposed filing strategy and content based on the Phase Ib Study GO30140, to provide updated efficacy and safety data from Arm A of Study GO30140 and to provide an update on the ongoing HCC clinical development plan. In general, both Agencies did not recommend the filing based on single arm Phase Ib data due to the exploratory nature of such studies and the limitations associated with non-randomized comparisons.

2.1.4. General comments on compliance with GCP

The study was conducted in compliance with GCP.

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

Atezolizumab is an IgG1 monoclonal antibody produced by recombinant DNA technology, a protein with a molecular mass of ~150 kDa. As an unaltered protein, being extensively degraded in the patient's body by regular proteolytic mechanisms before excretion, atezolizumab is unlikely to result in a significant environmental exposure. Atezolizumab is expected to biodegrade in the environment and does not pose a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), atezolizumab is exempt from the submission of Environmental Risk Assessment studies as the product and excipients do not pose a significant risk to the environment.

2.2.2. Discussion and conclusion on non-clinical aspects

No new non-clinical data has been provided for this extension. No further data is required.

2.3. Clinical aspects

2.3.1. Introduction

The clinical pharmacology evaluations of atezolizumab and bevacizumab (herein referred to as Atezo + Bev) are based on pharmacokinetic and immunogenicity data obtained from four clinical studies where atezolizumab was administered as a single agent or in combination with bevacizumab to HCC patients. All atezolizumab and bevacizumab doses were administered as an IV infusion.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH 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: Summary of atezolizumab studies conducted in monotherapy and combination settings in patients with HCC

Atezolizumab Monotherapy Study	Phase	Indication	N Enrolled/ PK evaluable (Total 595/579)	Design/Dose/Primary Clinical Endpoint
PCD4989g (GO27831)	I	Multiple solid and hematologic tumors (data provided only for subset of patients with 1L and 2L+ HCC)	15/15	Monotherapy/ 1200 mg q3w/ PK and safety
YO29233	I	Multiple solid tumors (data provided only for subset of patients with 1L and 2L+ HCC)	21/21	Monotherapy in Chinese Pts/ 1200 mg q3w/ PK and safety
GO30140	Ib	Multiple solid tumors (data provided only for subset of patients with advanced or metastatic and/or unresectable HCC who have received no prior systemic therapy enrolled in Arms A and F)	223/219	Arm A: Single arm study/ Atezo 1200 mg q3w & Bev 15 mg/kg q3w/ORR Arm F: 2-arm/Atezo 1200 mg q3w & Bev 15 mg/kg q3w vs. Atezo 1200 mg q3w/PFS
IMbrave150 (YO40245)	III	Patients with locally advanced or metastatic and/or unresectable HCC who have received no prior systemic therapy	336/324	2-arm/Atezo (1200 mg q3w) + Bev (15 mg/kg q3w) vs. Sorafenib (400 mg PO BID)/OS and PFS

HCC=hepatocellular carcinoma; Bev=bevacizumab 15 mg/kg q3w; PK=pharmacokinetic; q3w=every 3 weeks; ORR=overall response rate; OS=overall survival PFS=progression free survival.

Source: CSR PCD4989g (Report No. 1064914), CSR YO29233 (Report No. 1092638), CSR GO30140 (Report No. 1091227), CSR IMbrave150 (Report No. 1092943).

Clinical cutoff dates: Study PCD4989g (2 December 2014); Study YO29233 (19 November 2018); Study GO30140 (14 June 2019); Study IMbrave150 (YO40245) (29 August 2019)

2.3.2. Pharmacokinetics

Population PK in Study IMbrave150

Pharmacokinetic data were collected in the Phase III Study YO40245 (hereafter referred to as "IMbrave150"), which was an open-label, randomized study to investigate the efficacy and safety of

atezolizumab in combination with bevacizumab compared with sorafenib for patients with previously untreated locally advanced or metastatic HCC.

Table 2: Number of PK samples and patients included or excluded in the atezolizumab analysis

	Number of patients in the dataset			Number of PK samples in the dataset			
Study / Arm	Total	No Eval PK	Eval	Total	Excl	Eval	BLQ
IMbrave150/ Atezo+Bev	325[a]	2	323 (99%)	1518[b]	30 (2%)	1189 (78%)	299 (20%)

Eval=patient or sample evaluable for popPK purpose; Excl=sample excluded (DV greater than 0); No Eval PK=patients without any evaluable PK sample; BLQ=number of BLQ concentrations, not used for the analysis.

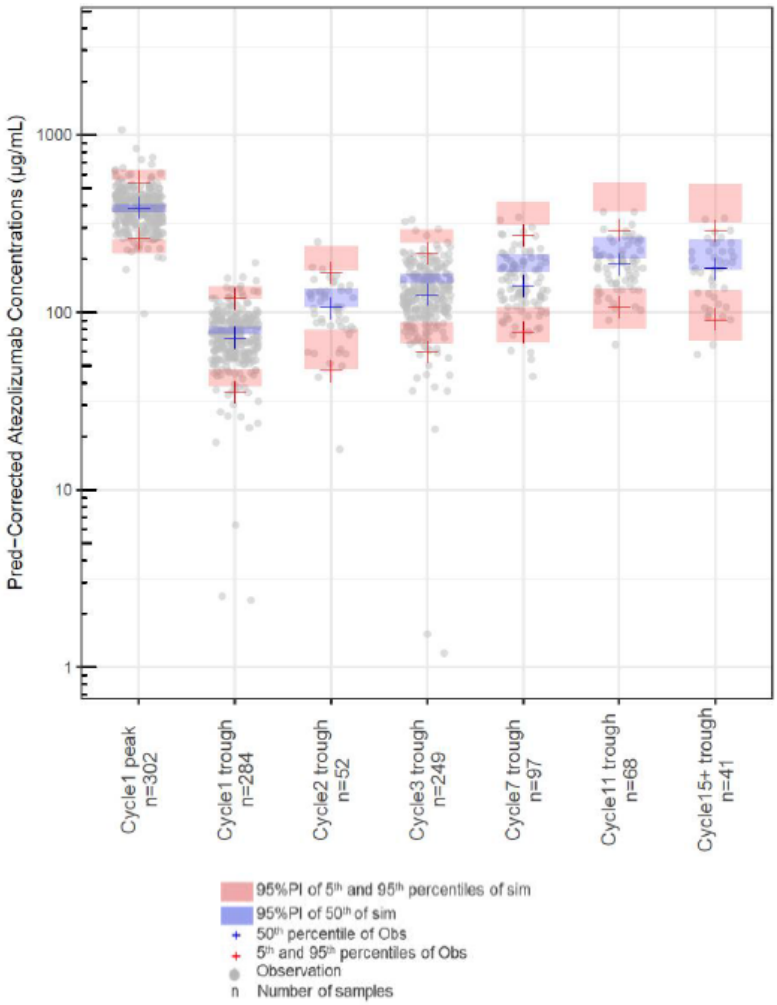
[a] Number of patients in "poppk_pooled_20191031_hcc.csv" file.

[b] sum of Exclusion+evaluable+BLQ.

Atezo + Bev Arm = Atezolizumab + Bevacizumab

PopPK analysis was performed using NONMEM, Version 7.4 and perl-speaks-NONMEM, Version 4.8.1 was used to evaluate/validate the popPK model using predictive checks. Data, exploration and visualisation of the data as well as descriptive statistics were performed using R V3.3.3 in addition to CRAN packages.

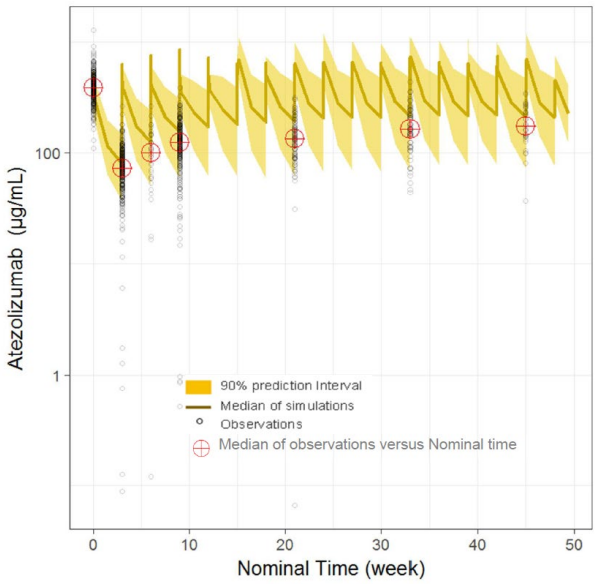
The Phase I popPK model PK parameter estimates were fixed to final estimates to perform a Bayesian post-hoc estimation based on IMbrave150 data and estimate patient-level random effect and PK parameters. The goodness-of fit plots suggest that the model was able to describe the PK profiles well and no trend was observed in goodness-of fit plots at the individual level. The pcVPC suggested that the median, 95th, and 5th percentiles of observed Cmax and Cmin were generally well within the prediction intervals of the Phase I popPK model, see Figure 1.



PI=prediction interval; popPK=population pharmacokinetics; VPC=visual predictive check.
Source: IMbrave150 PopPK Report No. 1099305, Figure 2

Figure 1: Prediction-corrected VPC of peaks and troughs of atezolizumab (all patients, semi-log scale) (study IMbrave150)

The effects of baseline body weight, albumin, tumour burden, ADA, and gender, indicated that the relationships estimated in the Phase I popPK model adequately described trends in IMbrave150 study. The positive correlation ($p<0.001$) between albumin and CL suggested a less steep relationship in IMbrave150 patients than the one estimated in the Phase I popPK model, and the positive correlation ($p<0.001$) between body weight and V2 appears to be a possible relationship specific for HCC. Age, race, number of metastatic sites, ECOG performance status, CRCL, eGFR, and platelet count did not appear to affect atezolizumab pharmacokinetics using IMbrave150 data. No covariate effect was related to liver function, i.e. ALT, AST, bilirubin, and LDH. No consistent trend in random effects was observed between hepatic impairment categories although there was an increasing trend in Eta. CL of patients with moderate hepatic impairment was lower than that of patients with either normal liver function or mild hepatic impairment. The number of patients with severe hepatic impairment (N = 2) was too small for comparison. There was no association between aetiology, macrovascular invasion, extrahepatic spread, alcohol use, or alpha-fetoprotein level (<400 ng/mL or ≥400 ng/mL) and atezolizumab PK.



Not all observed data are displayed; x-axis is truncated to 50 weeks.

Figure 2: 90% prediction interval of the PK profile using the Phase I PopPK model with IMbrave150 observed concentrations

The Phase I popPK model was used to derive the individual PK estimates for HCC patients, based on atezolizumab observed concentration-time profiles in IMbrave150.

Table 3: Summary statistics (geometric mean [Geometric Mean CV%]) of atezolizumab exposure metrics at Cycle 1 predicted using popPK model

Study (N)/Arm (N)	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC (µg.day/mL)	$t_{1/2}$ beta (day)*
IMbrave150, Atezo+Bev Arm (N=323)	380 [20.1]	70.8 [40.8]	2851 [22.6]	22.1 [7.13]

N = Number of patients; C_{max} = C_{max} at Cycle 1; C_{min} = C_{min} at Cycle 1; AUC = $AUC_{(0\text{-}21)}$ at Cycle 1; CV% = coefficient of variation; *$t_{1/2}$ beta is the terminal half-life based on post-hoc parameter estimates. For this parameter, harmonic mean and standard deviation are reported.

Atezo + Bev Arm=Atezolizumab + Bevacizumab

Table 4: Summary statistics (geometric mean [Geometric Mean CV%]) of atezolizumab exposure metrics at steady-state predicted using popPK model

Study (N)/Arm (N)	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)	$AUC_{,ss}$ (µg.day/mL)	Post-hoc accumulation ratio
IMbrave150, Atezo+Bev Arm (N=323)	554 [27.0]	163 [61.9]	5505 [40.4]	1.93 [19.6]

CV% = coefficient of variation; N = number of patients; $C_{max,ss}$ = C_{max} at steady-state; $C_{min,ss}$ = C_{min} at steady-state; $AUC_{,ss}$ = AUC at steady-state.

Accumulation ratio is derived as the ratio between AUC and AUC_{ss};
Atezo + Bev Arm : Atezolizumab + Bevacizumab

Absorption

Atezolizumab is administered as an IV infusion. There have been no clinical studies performed with other routes of administration.

Distribution

PopPK analysis indicate that V1 is 3.28 L and Vss is 6.91 L in the typical patient.

Elimination

PopPK analysis indicate that the typical CL of atezolizumab is 0.200 L/day and the typical terminal t1/2 is 27 days.

Dose proportionality and time dependencies

The previously developed popPK model estimated geometric mean accumulation ratio for Cmin, Cmax, and AUC was 2.75, 1.46, and 1.91-fold, respectively, following multiple dose administration of atezolizumab q3w days. The observed extent of accumulation is in close agreement with that predicted based on the popPK reported t1/2 of 27 days dosed q3w. Atezolizumab PK was linear over a dose range of 1 to 20 mg/kg of atezolizumab, including the fixed 1200 mg dose of atezolizumab.

Based on simulations, 90% of steady-state is attained after the following median (range) number of cycles: 3 cycles (1-6), 2 cycles (1-4), and 3 cycles (1-5) for Cmin, Cmax, and AUC, respectively.

The summary of the individual exposure metrics (IMbrave150) at cycle 1 and at steady-state based on the Phase 1 popPK Model is presented in the Tables below. The geometric mean accumulation ratio based on AUC was 2-fold. Cmin and Cmax accumulated 2.3- and 1.5-fold (geometric means), respectively.

Table 5: Summary Statistics (Geometric Mean [Geometric Mean CV%]) of Atezolizumab Exposure Metrics at Cycle 1 Predicted Using PopPK Model (Study IMbrave150)

Study, Arm (N)	C_{max} (µg/mL)	C_{min} (µg/mL)	AUC (µg.day/mL)	$t_{1/2}$ beta (day)*
IMbrave150, Atezo+Bev Arm (N=323)	380 [20.1]	70.8 [40.8]	2851 [22.6]	22.1 [7.13]

N=Number of patients; C_{max}=C_{max} at Cycle 1; C_{min}=C_{min} at Cycle 1; AUC=AUC(0-21) at Cycle 1; CV%=coefficient of variation

*t1/2 beta is the terminal half-life based on post-hoc parameter estimates. For this parameter, harmonic mean and standard deviation are reported.

Atezo+ Bev Arm=Atezolizumab+ Bevacizumab.

Table 6: Summary Statistics (Geometric Mean [Geometric Mean CV%]) of Atezolizumab Exposure Metrics at Steady-State Predicted Using PopPK Model (Study IMbrave150)

Study, Arm (N)	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)	$AUC_{,ss}$ (µg.day/mL)	Post-hoc accumulation ratio
IMbrave150, Atezo+Bev Arm (N=323)	554 [27.0]	163 [61.9]	5505 [40.4]	1.93 [19.6]

CV%=coefficient of variation; N=number of patients; $C_{max,ss}$=C_{max} at steady-state; $C_{min,ss}$=C_{min} at steady-state; $AUC_{,ss}$=AUC at steady-state.

Accumulation ratio is derived as the ratio between AUC and AUC_{ss};

Atezo + Bev Arm : Atezolizumab + Bevacizumab

Special populations

Atezolizumab concentrations after 1200 mg q3w across studies

Exposures of Atezo + Bev in IMbrave150 were consistent with those observed in prior studies in HCC patients which followed the same 1200 mg q3w regimen of atezolizumab, indicating that the addition of bevacizumab therapy did not affect the PK of atezolizumab.

Table 7: Mean (SD) Serum Atezolizumab PK Concentrations (µg/mL) by Study and Treatment Group Following Multiple IV Doses of Atezolizumab 1200 mg Given Every 3 Weeks

		NSCLC	mUC	HCC					
		OAK	IMvigor211	PCD4989g	YO29233	GO30140			IMbrave150
Nominal Time (day)	Dose Regimen PK Description	ATZ (N=561)	ATZ (N=423)	ATZ (N=14)	ATZ (N=21)	Arm A: ATZ+BEV (N=104)	Arm F1: ATZ+BEV (N=59)	Arm F2: ATZ (N=56)	ATZ+BEV (N=324)
0.02	C_{max} Dose 1	400 (127)	366 (125)	410 (140)	490 (140)	374 (84.0)	385 (NE)	NA	398 (131)
21	C_{min} Dose 1 (q3w)	83.2 (31.0)	73.9 (29.1)	82.1 (43.4)	90.5 (19.1)	74.4 (28.6)	81.6 (28.5)	93.6 (31.7)	79.6 (50.3)
42	C_{min} Dose 2 (q3w)	130 (55.8)	111 (46.5)	135 (83.4)	144 (45.3)	111 (41.8)	127 (43.6)	133 (49.9)	102 (55.8)
42.04	C_{max} Dose 3 (q3w)	NA	NA	447 (182)	NA	489 (113)	NA	NA	NA
63	C_{min} Dose 3 (q3w)	158 (66.4)	139 (56.9)	155 (73.9)	160 (44.7)	133 (56.9)	150 (47.4)	157 (54.0)	131 (64.4)
84	C_{min} dose 7 (q3w)	NA	NA	142 (32.5)	NA	NA	NA	NA	NA

ATZ=atezolizumab; BEV=bevacizumab; C_{min}=minimum serum concentration; C_{max}=maximum serum concentration; N=number used to calculate statistics; NA=not available; NE=not evaluable, only 1 value; SD=standard deviation.

2.3.3. Pharmacodynamics

Dose rationale

Both GO30140 (Arms A and F1) and IMbrave150 (Atezo + Bev) evaluated atezolizumab administered at a fixed dose of 1200 mg by IV infusion q3w in combination with 15 mg/kg of bevacizumab by IV q3w in patients with metastatic and/or unresectable HCC (see supportive studies).

Atezolizumab administered at a fixed dose of 1200 mg q3w (1200 mg on Day 1 of each 21-day cycle), is an approved dosage for atezolizumab. Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg q3w. In the Phase I Study GO27831 (PCD4989g, Report No. 1064914) the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg q3w (equivalent to an average body weight based dose of 15 mg/kg q3w) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical PK, efficacy, and safety data.

Bevacizumab administered at a fixed dose of 15 mg/kg q3w on Day 1 of each 21-day cycle is an approved dosage for bevacizumab (see Avastin approved label). The 15 mg/kg q3w dose of bevacizumab aligns with the atezolizumab dosing schedule (1200 mg q3w), and is also the dosage used in the GO30140 (Arms A and F1) and IMbrave150 studies (Atezo+Bev) in combination with atezolizumab. This dose was generally well-tolerated, the incidence and severity of bevacizumab AESIs with combination of Atezo+ Bev in the overall population of Arm A (N = 104) and Arm F1 (N = 60) of study GO30140, as well as in the IMbrave150 study was consistent with that reported in the bevacizumab label indicating that the addition of atezolizumab to bevacizumab does not exacerbate the incidence or severity of bevacizumab AESIs.

Mechanism of action

Atezolizumab targets human programmed death-ligand 1 (PD-L1) on tumor-infiltrating immune cells (ICs) and tumor cells (TCs), and inhibits its interaction with its receptors, PD-1 and B7.1 (CD80, B7-1). Both of these interactions are reported to provide inhibitory signals to T cells.

Bevacizumab targets vascular endothelial growth factor (VEGF). VEGF is a pleiotropic inflammatory factor that is normally associated with wound repair. VEGF and angiogenesis is an essential factor in the oncogenic process, and plays a role in pathogenesis. VEGF is associated with vascular density, tumor invasiveness and metastasis, and poor prognosis (Frenette 2012; Boige et al. 2012).

Primary and secondary pharmacology

Immunogenicity

- Study IMbrave150

Blood samples were collected to characterize atezolizumab PK and ADA incidence following atezolizumab treatment. Serum samples for PK and ADA analysis were obtained at multiple timepoints before, during, and after treatment with atezolizumab (Table 9).

Table 8: IMbrave150: Atezolizumab ADA and PK Sampling Schedule

Pre-Dose at Cycle C*x*, Day 1							Tx Disc Visit (≤30 days after last dose)
C1 [a]	C2	C3	C4	C8	C12	C16	
X	X	X	X	X	X	X	X

ADA=anti-drug antibody; Atezo=atezolizumab; Bev=bevacizumab; C=Cycle; CSR=Clinical Study Report; Disc=discontinuation; PK=pharmacokinetic; Tx=treatment.

[a] Samples for atezolizumab PK analysis were collected pre-dose and 30±10 minutes post-infusion C1D1. ADA sample was collected only pre-dose in C1 (i.e., not post-infusion C1).

Note: Each cycle in this study has a duration of 21 days. Samples apply to Atezo+Bev arm only.

Source: IMbrave150 Primary CSR (Report No. 1092943).

Atezolizumab Immunogenicity Rates

The incidence of treatment-emergent atezolizumab ADAs in the Atezo+Bev arm is within the range of treatment-emergent ADA-positive incidence rates observed across atezolizumab studies.

Table 9: IMbrave150: Baseline Prevalence and Post-Baseline Incidence of ADAs to Atezolizumab

	Atezo+Bev N=329
Baseline evaluable patients	**N=311**
No. of patients positive for ADA	7 (2.3%)
No. of patients negative for ADA	304
Post-baseline evaluable patients	**N=315**
No. of patients positive for ADA (treatment-emergent ADA-positive)	88 (27.9%)
Treatment-induced ADA	88
Treatment-enhanced ADA	0
No. of patients negative for ADA	227 (72.1%)
Treatment-unaffected ADA	7

ADA=anti-drug antibody; Atezo+Bev=atezolizumab+bevacizumab; CSR=Clinical Study Report.

Note: See Section 1.1 for further details on definitions of treatment-induced and treatment-enhanced ADA.

Data cutoff: 29 August 2019.

Atezolizumab pharmacokinetics by ADA status

Atezolizumab concentrations up to Cycle 16 Day 1 by ADA status are summarized in Table 11 for all PK-evaluable atezolizumab-treated patients. The arithmetic mean Cmax values at Cycle 1 were 408 and 372 µg/mL for ADA-negative and ADA-positive patients, respectively, a difference of 8.82% (Table 11). The corresponding Cmin values at Cycle 1, Day 21 (i.e., Predose Cycle 2), were 89.3 and 54.4 µg/mL, respectively, a difference of 39.1%. The vast majority of patients had Cmin above the target exposure of 6 µg/mL, regardless of ADA status.

Table 10: Summary Statistics for Atezolizumab Cmax and Cmin by Treatment-Emergent ADA Status Following Atezolizumab 1200 mg IV Given Every 3 Weeks (Study IMbrave150)

Visit / Timepoint	Nominal Time (Days)	N	AM (µg/mL)	AM SD (µg/mL)	AM (CV %)	GM (µg/mL)	GM (% CV)	Median (µg/mL)	Min (µg/mL)	Max (µg/mL)
Negative (227)										
Cycle 1 C_{max}/C1D1	0.06	210	408	133	32.7	388	32.7	395	111	1260
Cycle 1 C_{min}/Predose C2D1	21	212	89.3	54.5	61.0	77.5	74.0	81.6	0.0890	596
Cycle 2 C_{min}/Predose C3D1	42	26	125	51.3	41.2	114	47.2	118	37.8	263
Cycle 3 C_{min}/Predose C4D1	63	192	138	58.4	42.2	125	49.9	133	19.8	386
Cycle 7 C_{min}/Predose C8D1	147	67	153	61.2	40.1	141	40.8	138	60.9	319
Cycle 11 C_{min}/Predose C12D1	231	55	194	76.6	39.4	181	40.7	179	73.5	437
Cycle 15 C_{min}/Predose C16D1	315	30	196	75.4	38.4	182	42.3	183	81.5	345
Positive (88)										
Cycle 1 C_{max}/C1D1	0.06	84	372	119	32.0	356	30.9	354	130	915
Cycle 1 C_{min}/Predose C2D1	21	82	54.4	23.1	42.5	42.3	178.1	51.7	0.0300	109
Cycle 2 C_{min}/Predose C3D1	42	13	58.2	34.9	59.9	34.0	493.1	59.3	0.120	125
Cycle 3 C_{min}/Predose C4D1	63	71	111	75.3	68.2	82.6	138.2	104	0.518	540
Cycle 7 C_{min}/Predose C8D1	147	34	125	51.2	40.9	114	47.3	120	31.1	256
Cycle 11 C_{min}/Predose C12D1	231	19	124	55.2	44.6	110	56.5	148	44.1	215
Cycle 15 C_{min}/Predose C16D1	315	7	145	68.1	47.1	125	72.6	159	36.4	232

ADA=Anti-Drug Antibodies; C_{max}=maximum concentrations of atezolizumab in serum; C_{min}=minimum (trough) concentrations of atezolizumab in serum; CV=coefficient of variation.

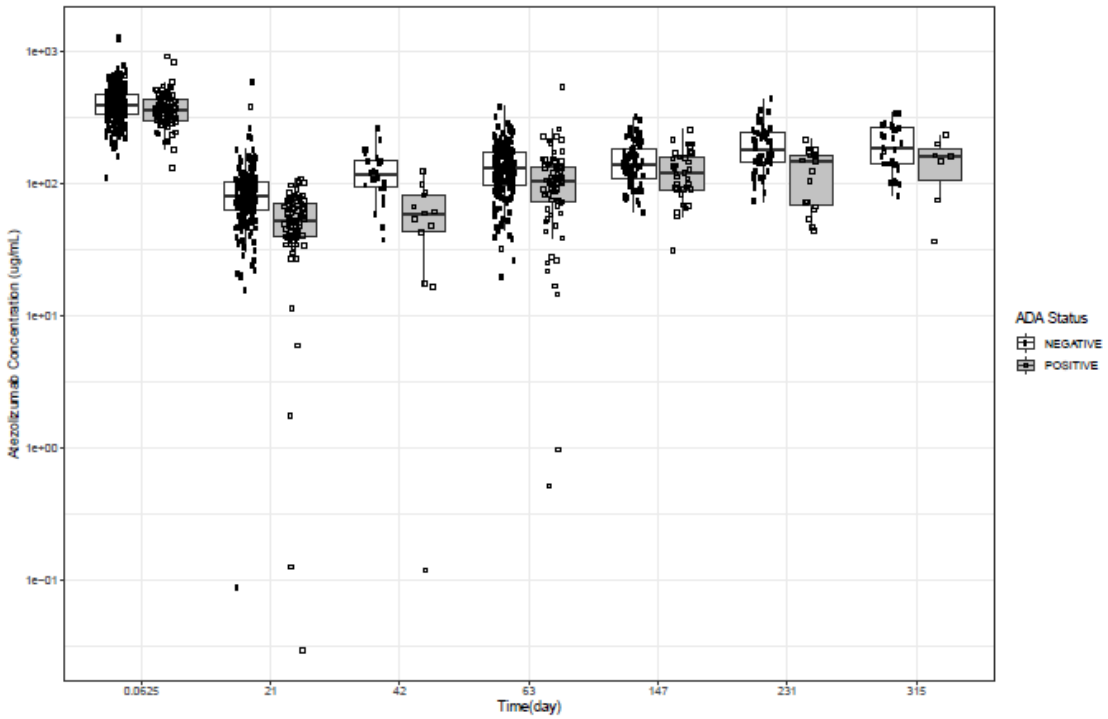
Six Records from 5 patients were excluded due to dose discrepancy, 2 Records from 2 patients were excluded due to anomalous collection date/time, 3 Records from 3 patients were excluded due to anomalous PK concentration

CxD21 (C_{min}) is the same as C(x+1)D1 Predose.

There were 14 patients with missing ADA status. Total number of patients=227+88+14=329.

Source: IMbrave150 CSR (Report No. 1092943), Table 57

A mean serum atezolizumab concentration-time plot (log scale) following multiple doses of atezolizumab 1200 mg q3w by ADA positivity is shown in Figure 4.



Data source: IMbrave150 (Report No. 1092943) CSR Figure 13

Figure 3: Box Plot of Atezolizumab Concentrations vs. Time by Treatment- Emergent ADA Status Following Multiple IV Doses of Atezolizumab (Study IMbrave150)

Table 11: Summary statistics (mean [SD]) and t-test on atezolizumab clearance and exposure metrics by ADA status

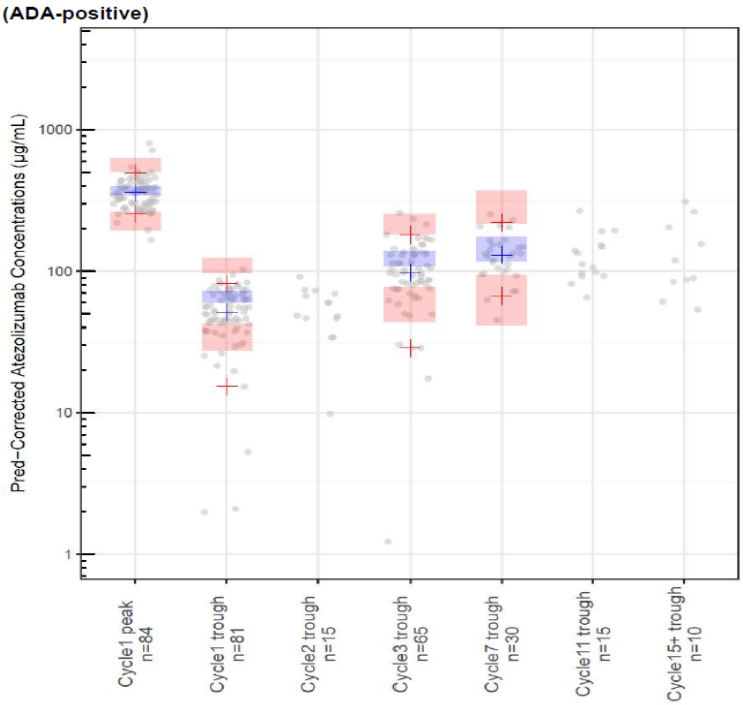
Variable (unit)	ADA Negative N=227	ADA Positive N=88	p-value	Mean Difference (95%CI)
Clearance (L/d)	0.208 (0.0862)	0.308 (0.121)	9.19E-11	-0.1 (-0.128,-0.0724)
C_{max}, Cycle 1 (µg/mL)	395 (83.2)	368 (70.1)	4.94E-03	26.4 (8.1,44.8)
C_{min}, Cycle 1 (µg/mL)	81.3 (23.8)	60.3 (19.6)	1.22E-13	21 (15.8,26.2)
AUC_{0-21}, Cycle 1 (µg.day/mL)	3060 (646)	2550 (496)	1.79E-12	512 (377,645)

C_{min} = Individual model-predicted minimum atezolizumab concentration at Cycle 1, C_{max}=Individual model-predicted maximum atezolizumab concentration at Cycle 1; AUC_{0-21} = Area under the curve from 0 to 21 days at Cycle 1 ;CV = coefficient of variation, SD=standard deviation; CI=confidence interval, The 95% CI for difference/ratio and t-test.

The two-sided p-value is from two-sample t-test.

N: number of patients in each ADA status group in the popPK population.

There was significant difference (p<0.001) between atezolizumab clearance in ADA positive patients and ADA negative patients. A substantial difference was also observed for other exposure metrics (i.e., Cmin and AUC0-21) with lower exposure in ADA positive patients compared to ADA negative patients, less pronounced for Cmax.



Note: Only the PK visits with at least 20 samples are displayed on the plot.
3 PRED-concentrations below 1 µg/mL are not displayed on this plot

Figure 4: Prediction-corrected VPC of peaks and troughs of atezolizumab by ADA status (semi-log scale) (study IMbrave150)

Incidence of ADAs across studies (GO30140, IMbrave150 and pooled analysis)

The pre-treatment ADA prevalence and post-treatment ADA incidence for atezolizumab is shown in Table 12 for IMbrave150 and GO30140. The ADA prevalence at baseline was 2.3% for atezolizumab-treated patients with a baseline ADA sample in IMbrave150, and 0%, 3.4%, and 3.4%, respectively for Arms A, F1, and F2 of GO30140.

Post-treatment, the atezolizumab ADA incidence rates were 27.9% in IMbrave150, and 23.8%, 37.9% and 29.8% in Arms A, F1, and F2, respectively, of GO30140 as shown in Table 12. These are within the range of treatment-emergent ADA incidence rates observed across atezolizumab studies. For Arm F2 of GO30140, ADA samples obtained post crossover were not used for ADA status derivation.

When pooled across the two studies evaluating atezolizumab plus bevacizumab treatment in HCC there were 134 of 474 ADA-evaluable patients who developed treatment-emergent ADAs to atezolizumab (incidence rate of 28.3%).

Table 12: Baseline Prevalence and Post-Baseline Incidence of ADAs to Atezolizumab

	IMbrave150	GO30140			Both Studies
	Atezo+Bev Treated Patients (N=329)	Arm A Atezo+Bev (N=104)	Arm F1 Atezo+Bev (N=60)	Arm F2 Atezo Monotherapy (N=58)	Combined Atezo+Bev (N=493)
Baseline evaluable patients	311	104	58	58	473
No. of patients positive for ADA	7 (2.3%)	0	2 (3.4%)	2 (3.4%)	9 (1.90%)
No. of patients negative for ADA	304	104	56	56	464
Post–baseline evaluable patients	315	101	58	57	474
No. of patients positive for ADA	88 (27.9%)	24 (23.8%)	22 (37.9%)	17 (29.8%)	134 (28.3%)
Treatment-induced ADA [a]	88	24	21	17	133
Treatment-enhanced ADA [b]	0	0	1	0	1
No. of patients negative for ADA	227	77	36	40	340
Treatment-unaffected ADA [c]	7	0	1	2	8

ADA=anti-drug antibodies, can also be referred to as ATA or anti–therapeutic antibodies

Note: See Shankar et al. 2014 for further details on the definition of treatment-induced and treatment-enhanced ADA.

[a] Treatment-induced ADAs=Patients who had a baseline-negative ADA result or were missing data who developed anti-drug antibodies at any time after initial drug administration.

[b] Treatment-enhanced ADA=Patients who had a baseline-positive ADA result in whom the assay result was enhanced (greater than baseline titer by ≥0.60 titer units) at any time after initial drug administration.

[c] Treatment-unaffected ADAs=Patients who had a baseline-positive ADA result in whom the assay result was not enhanced (not greater than baseline titer by ≥0.60 titer units) at any time after initial drug administration. These patients are considered post-baseline negative for ADAs.

Source=Table 52 of GO30140 CSR (Report No. 1091227), and Table 54 of IMbrave150 (YO40245) CSR (Report No. 1092943)

2.3.4. Discussion on clinical pharmacology

Samples received for determination of atezolizumab concentrations in serum from HCC patients were analysed within established sample storage stability using validated analytical methods. For the IMbrave150 Phase III study conducted in HCC patients, the in-study validation was acceptable and incurred sample reanalysis was performed and met the acceptance criteria. All analyses including assessment of immunogenicity were conducted with assays assessed in previous procedures.

The IMbrave150 study was an open-label, randomized study to investigate the efficacy and safety of atezolizumab in combination with bevacizumab compared with sorafenib for patients with previously untreated locally advanced or metastatic HCC. Pharmacokinetic data collected in IMbrave 150 was used for external validation of the Phase I PopPK model, with determination of individual Bayesian estimates for the HCC patients. The phase I PopPK model could reasonably well describe the atezolizumab concentrations of IMbrave150, although some overprediction was observed for C_{trough}. VPCs stratified for ADA status showed overprediction at Cycle 1 C_{trough} for ADA positives whereas the fit was acceptable for ADA negatives. Overprediction was also observed of $C_{troughs}$ for patients with mild hepatic impairment (NCI-ODWG Group B1+B2). The Phase 1 popPK model was used to estimate the exposure metrics after multiple injections of 1200 mg q3w atezolizumab. The predicted exposure of atezolizumab in IMbrave 150 was comparable to the exposure achieved in other studies with atezolizumab 1200 mg q3w dosing, with or without bevacizumab and across indications. Atezolizumab administered at a fixed dose of 1200 mg q3w is already approved hence the dose rationale for treatment of HCC patients is considered acceptable. The incidence of ADAs in the Atezo+Bev arm of IMbrave150 was 27.9% which is within what

has been observed in other atezolizumab indications. Atezolizumab clearance was significantly lower ($p<0.001$) in ADA positive patients as compared to ADA negative patients. NAb data for IMbrave150 were submitted and showed that 65 patients out of 313 evaluable patients had neutralising antibodies (88/315 patients were ADA positive).

2.3.5. Conclusions on clinical pharmacology

Overall atezolizumab PK is sufficiently described and no apparent differences are detected compared to the previous description of PK following 1200 mg q3w IV administered as monotherapy and in other indications.

The analysis of immunogenicity revealed that atezolizumab exposure and efficacy was lower in ADA-positive as compared to ADA-negative patients (see also 2.4.2. Main Study).

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No explicit dose response studies have been provided.

2.4.2. Main study

A Phase III, Open-label, Randomized Study of Atezolizumab in Combination with Bevacizumab Compared with Sorafenib in Patients with Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma.

Figure 5: Study design for IMbrave150

Methods

Study participants

Inclusion Criteria

General Inclusion Criteria

Patients had to meet all of the following criteria to be eligible for study entry:

- At least one measurable (per RECIST v1.1) untreated lesion
- ECOG Performance Status of 0 or 1 within 7 days prior to randomization
- Adequate hematologic and end organ function

Disease-Specific Inclusion Criteria

Patients had to meet all of the following criteria for study entry:

- Locally advanced or metastatic and/or unresectable HCC with diagnosis confirmed by histology/cytology or clinically by AASLD criteria (see details in Protocol) in cirrhotic patients

Patients without cirrhosis required histological confirmation of diagnosis.

- Disease that was not amenable to curative surgical and/or locoregional therapies, or progressive disease after surgical and/or locoregional therapies.
- No prior systemic therapy (including systemic investigational agents) for HCC Previous use of herbal therapies/traditional Chinese medicines with anti-cancer activity included in the label was allowed, provided that these medications were discontinued prior to randomization.
- Patients who received prior local therapy (e.g., radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound, transarterial chemoembolization, transarterial embolization, etc.) were eligible provided the target lesion(s) had not been previously treated with local therapy or the target lesion(s) within the field of local therapy had subsequently progressed in accordance with RECIST v1.1.
- Child-Pugh class A within 7 days prior to randomization
- Serum bilirubin ≤3xthe upper limit of normal (ULN)
- Serum albumin ≥28 g/L (2.8 g/dL) without transfusion
- For patients not receiving therapeutic anticoagulation: INR or a PTT ≤2xULN
- Documented virology status of hepatitis, as confirmed by screening HBV and HCV serology test
- For patients with active hepatitis B virus (HBV):

– HBV DNA <500 IU/mL obtained within 28 days prior to initiation of study treatment, and anti-HBV treatment (per local standard of care; e.g., entecavir) for a minimum of 14 days prior to study entry and willingness to continue treatment for the length of the study

Exclusion Criteria

General Exclusion Criteria

Patients who met any of the following criteria were excluded from study entry:

- History of malignancy other than HCC within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate >90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC
- Moderate or severe ascites
- History of hepatic encephalopathy
- Co-infection of HBV and HCV

Patients with a history of HCV infection who were negative for HCV RNA by PCR were considered non-infected with HCV.

- Untreated or incompletely treated esophageal and/or gastric varices with bleeding or high risk for bleeding

Patients had to undergo an esophagogastroduodenoscopy (EGD), and all size of varices (small to large) had to be assessed and treated per local standard of care prior to enrollment. Patients who had undergone an EGD within 6 months prior to initiation of study treatment did not need to repeat the procedure.

- A prior bleeding event due to esophageal and/or gastric varices within 6 months prior to initiation of study treatment

Exclusion Criteria Related to Medications

Patients who met any of the following criteria were excluded from study entry:

- Prior allogeneic stem cell or solid organ transplantation
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or bevacizumab formulation
- Treatment with strong CYP3A4 inducers within 14 days prior to initiation of study treatment, including rifampin (and its analogues) or St. John's wort
- Treatment with any agent that may interfere with the immunostimulatory nature of atezolizumab.

Exclusion Criteria Related to Bevacizumab

All patients had to meet several bevacizumab-specific criteria based on the known safety profile of this drug. These criteria excluded patients with evidence of or a possibility for bleeding issues, uncontrolled hypertension, and/or gastrointestinal perforations.

Treatments

Table 13: Study treatment regimens

Arm	Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)	Infusion Rate
Sorafenib	21 days	Sorafenib 400 mg BID, by mouth, continuously	Not applicable
Atezo+Bev [a]	21 days	Atezolizumab 1200 mg IV on Day 1	Over 60 (± 15) minutes (for the first infusion); 30 (± 10) minutes for subsequent infusions if tolerated
		Bevacizumab 15 mg/kg IV on Day 1	Over 90 (± 15) minutes (for the first infusion); shortening to 60 (± 10) then 30 (± 10) minutes for subsequent infusions if tolerated

[a] For patients randomized to the Atezo+Bev arm, on Day 1 of each cycle, atezolizumab was administered first, followed by bevacizumab, with a minimum of 5 minutes between dosing.
BID = twice per day.

Objectives

Primary Efficacy Objective

The primary efficacy objective of IMbrave150 is to evaluate the efficacy of the combination of atezolizumab and bevacizumab compared to sorafenib monotherapy administered to patients with locally advanced or metastatic HCC who have received no prior systemic treatment, as measured by:

- Overall Survival (OS), defined as the time from randomization to death from any cause
- Progression-free Survival (PFS), defined as the time from randomization to the first occurrence of disease progression as determined by an Independent Review Facility (IRF) according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, or death from any cause (whichever occurred first)

Secondary Efficacy Objectives

The secondary efficacy objectives of IMbrave150 are as follows:

Secondary Efficacy Objectives	Corresponding Endpoints
• To evaluate the efficacy of atezolizumab + bevacizumab compared with sorafenib	• Objective response rate (ORR), defined as a complete or partial response, as determined – by an IRF according to RECIST v1.1 – by an IRF according to HCC mRECIST – by the Investigator according to RECIST v1.1 • Duration of Response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first) as determined – by an IRF according to RECIST v1.1 – by an IRF according to HCC mRECIST – by the Investigator according to RECIST v1.1 • PFS as determined – by an IRF according to HCC mRECIST – by the Investigator according to RECIST v1.1 • Time to progression (TTP), defined as the time from randomization to the first occurrence of disease progression, as determined: – by an IRF according to RECIST v1.1 – by an IRF according to HCC mRECIST – by the Investigator according to RECIST v1.1
• To evaluate the association of pre-specified biomarkers with the efficacy of atezolizumab + bevacizumab compared with sorafenib	• PFS as determined by the Investigator and by an IRF according to RECIST v1.1 and overall survival (OS) by baseline serum AFP level (< 400 ng/mL vs. ≥ 400 ng/mL)
• To evaluate patient–reported outcomes (PROs) of disease/treatment-related symptoms, global health status/quality of life (GHS/QoL), and function experienced by patients on atezolizumab + bevacizumab versus sorafenib	• Time to Deterioration (TTD), defined as the time from randomization to first deterioration (decrease from baseline of ≥ 10 points), maintained for two consecutive assessments or one assessment followed by death from any cause within 3 weeks in the following EORTC QLQ-C30 subscales: – Physical functioning (PF) – Role functioning (RF) – Global health status/quality of life (GHS/QoL)

AFP = α–fetoprotein; EORTC = European Organisation for Research and Treatment of Cancer; HCC mRECIST = modified RECIST for HCC; IRF = independent review facility; PFS = progression-free survival; PRO = patient-reported outcome; QLQ-C30 = quality-of-life questionnaire for cancer; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1

Safety objectives

The safety objectives of IMbrave150 are to evaluate the safety and tolerability of atezolizumab administered in combination with bevacizumab compared with sorafenib monotherapy in patients with HCC as measured by the following endpoints:

- Incidence and severity of adverse events, with severity determined according to NCI CTCAE v4.0 (National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0)
- Vital signs
- Clinical laboratory test results

Pharmacokinetic objectives

The pharmacokinetic (PK) objectives of IMbrave150 are to characterize the PK profile of atezolizumab when given in combination with bevacizumab. The pharmacokinetics of bevacizumab was not investigated in this study.

Immunogenicity objectives

The immunogenicity objectives of IMbrave150 are to evaluate the immune response to atezolizumab as measured by the presence of anti-drug antibodies (ADAs) to atezolizumab during the study relative to the presence of ADAs at baseline.

Exploratory objectives

The exploratory objectives of IMbrave150 defined in the protocol and reported in this CSR are as follows:

- To evaluate the efficacy of atezolizumab administered in combination with bevacizumab compared to sorafenib monotherapy as measured by PFS, TTP, ORR, and DOR, as determined by the Investigator according to immune-modified RECIST
- To evaluate patient-reported outcomes (PROs) of disease/treatment-related symptoms (including abdominal pain and itching), global health status/quality of life, and function experienced by patients on atezolizumab+bevacizumab versus sorafenib, as measured by European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and European Organization for the Research and Treatment of Hepatocellular Carcinoma Questionnaire 18 (EORTC QLQ-HCC18)
- To evaluate potential effects of ADAs to atezolizumab on efficacy or safety, and on the pharmacokinetics of atezolizumab+bevacizumab
- To identify tissue or blood-based biomarkers that are associated with response to atezolizumab+bevacizumab versus sorafenib, or can increase the understanding of HCC disease evolution under atezolizumab+bevacizumab treatment

Outcomes/endpoints

Co-primary endpoint: OS and PFS by IRF

Table 14: Statistical analysis of primary, secondary and exploratory efficacy endpoints

Efficacy Variable	Analysis Method	Censoring / Sensitivity Analyses / Subgroup Analyses/Others
Primary Efficacy Endpoints		
OS: SAP Section 4.4.1.1 SAP Section 4.4.7	Kaplan-Meier methodology, stratified log-rank test, and stratified Cox proportional hazards model. Stratification factors for OS were the same as for PFS. Treatment comparisons were to be conducted at the two-sided significance level of 0.048. If the null hypotheses of the PFS and key secondary endpoints testing were all rejected at a two sided significance level of 0.002, OS was to be tested at a two-sided significance level of 0.05. Results from an unstratified analysis are also provided.	Censoring Data for patients who were alive at the time of the clinical cutoff date were censored at the last date they were known to be alive. Data for patients with no post-baseline information were censored at the date of randomization. Subgroup Analyses Examination of consistency of OS including, but not necessarily limited to, the following subgroups: • Demographics (age, sex, race, geographic region) • Baseline disease characteristics (MVI, EHS, AFP level ECOG, etiology, PD-L1 status, BCLC staging at the time of study entry) OS data including the unstratified HR estimated from a Cox proportional hazards model and Kaplan-Meier estimates of median OS are displayed for each subgroup in a Forest plot
PFS–IRF: • per RECIST v1.1 SAP Section 4.4.1.2 SAP Section 4.4.6 SAP Section 4.4.7	Kaplan-Meier methodology, stratified two-sided log-rank test, and stratified Cox proportional hazards model. Stratification factors (as per IxRS): • Geographic region (Asian excluding Japan vs. rest of world) • MVI and/or EHS (presence vs. absence) • Baseline AFP (< 400 vs. ≥ 400 ng/mL). Treatment comparisons were to be conducted at the two-sided significance level of 0.002. If the null hypothesis of the OS testing was rejected at a two-sided significance level of 0.048, PFS was to be tested at the two-sided significance level of 0.05. Results from an unstratified analysis are also provided.	Censoring Data for patients who were alive and had not experienced PD at the time of the clinical cutoff date were to be censored at the date of the last tumor assessment on or prior to the clinical cutoff date. Data for patients with no post-baseline tumor assessment were to be censored at the date of randomization. Sensitivity Analysis If > 5% of patients missed two or more consecutive tumor assessments scheduled immediately prior to the date of PD or death in any treatment arm, the following sensitivity analysis was planned to be performed using the same methodology as for the primary analysis: • Patients were censored at the last tumor assessment prior to the missed visits. Subgroup Analyses Examination of consistency of PFS by IRF per RECIST v1.1 including, but not necessarily limited to, the following subgroups: • Demographics (age, sex, race, geographic region) • Baseline disease characteristics (MVI, EHS, AFP level ECOG, etiology, PD-L1 status, BCLC staging at the time of study entry) PFS data including the unstratified HR estimated from a Cox proportional hazards model and Kaplan-Meier estimates of median PFS are displayed for each subgroup in a Forest plot

Secondary endpoints:

- ORR: defined as a complete or partial response, as determined
    - by an IRF according to RECIST v1.1
    - by an IRF according to HCC mRECIST
    - by the Investigator according to RECIST v1.1
- DOR: defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first) as determined
    - by an IRF according to RECIST v1.1
    - by an IRF according to HCC mRECIST
    - by the Investigator according to RECIST v1.1
- PFS as determined
    - by an IRF according to HCC mRECIST

    - by the Investigator according to RECIST v1.1
- Time to Deterioration (TTD), defined as the time from randomization to first deterioration (decrease from baseline of ≥ 10 points), maintained for two consecutive assessments or one assessment followed by death from any cause within 3 weeks in the following EORTC QLQC30 subscales:
    - Physical functioning (PF)
    - Role functioning (RF)
    - Global health status/quality of life (GHS/QoL)

Sample size

A total of approximately 480 patients was planned to be randomized in the global enrolment phase of this study, using a 2:1 randomization ratio to allocate patients to either the atezolizumab + bevacizumab arm (Arm A) or the sorafenib arm (Arm B).

The sample size of the study was determined based on the number of deaths required to demonstrate efficacy in terms of OS. To detect an improvement in OS using a log-rank test at a two-sided significance level of 0.048, approximately 312 deaths were considered to be required to achieve 80% overall power assuming a target HR of 0.71 (median OS improvement vs. control is 4.9 months).

Randomisation

IMbrave150 was a randomized study. After written informed consent had been obtained, all screening procedures and assessments had been completed, and eligibility had been established for a patient, the study site obtained the patient's identification number and treatment assignment from the interactive voice or web-based response system (IxRS). Patients were randomized to one of two treatment arms, Atezo+Bev or sorafenib, according to a 2:1 randomization ratio using a permuted-block randomization method.

Randomization was stratified according to the following stratification factors:

- Geographic region (Asia excluding Japan vs. rest of world)
- Macrovascular invasion and/or extrahepatic spread (presence vs. absence)
- Baseline AFP (<400 vs. ≥400 ng/mL)
- ECOG Performance Status (0 vs 1)

Blinding (masking)

The study was an open-label study.

Statistical methods

Co-primary Endpoint: Overall Survival

To detect an improvement in OS using a log-rank test at a two-sided significance level of 0.048., approximately 312 deaths were required at the final OS analysis to achieve an overall 80% power assuming a target hazard ratio (HR) of 0.71 (median OS improvement vs. control of 4.9 months). The minimum detectable difference (MDD) of OS is an HR of 0.783 (median OS improvement vs. control of 3.3 months). This analysis is expected to occur approximately 33 months after first-patient in (FPI). The

estimates of the number of events required to demonstrate efficacy in the ITT population with regard to OS were based on the following assumptions:

- Patients were to be randomized to the Atezo+Bev and Sorafenib arms in a 2:1 ratio
- OS followed a one-piece exponential distribution
- The median OS in the control arm was to be 12 months
- The stopping boundaries of two interim analyses and the final analysis of OS were to use the O'Brien-Fleming boundaries approximated using the Lan-DeMets method
- The dropout rate was to be 5% for the Atezo+Bev arm and 10% for the Sorafenib arm over 12 months for OS
- The recruitment of approximately 480 patients was to take place over approximately 10 months

Co-Primary Endpoint: Progression-Free Survival by IRF Assessment per RECIST v1.1

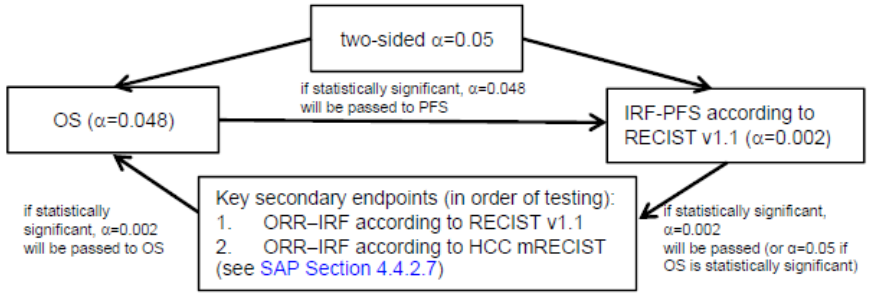
To detect an improvement in Progression-Free Survival per RECIST v1.1 by Independent Review Facility (IRF-PFS) using a log-rank test at a two-sided significance level of 0.002, approximately 308 events were required for the primary PFS analysis to achieve approximately 97% power with a target HR of 0.55 (median PFS improvement vs. control of 3.3 months). The MDD was a PFS HR of 0.688 (median PFS improvement vs. control of 1.8 months). The clinical cutoff date for this primary PFS analysis was expected to occur approximately 16 months after the first patient was enrolled in the study.

The estimates of the number of events required to demonstrate efficacy in the ITT population with regard to PFS were based on the following assumptions:

- Patients were to be randomized to the Atezo+Bev and Sorafenib arms in a 2:1 ratio
- PFS followed a one-piece exponential distribution
- The median PFS in the control arm was to be 4 months
- The dropout rate was to be 5% for the Atezo+Bev arm and 10% for the Sorafenib arm over 12 months for PFS
- The recruitment of approximately 480 patients was to take place over approximately 10 months

Overall Type I Error Control

The overall type I error rate for this study was controlled at a two-sided significance level of 0.05 by a graphical approach, i.e., alpha splitting and recycling. The overall two-sided significance level of 0.05 was split into a two-sided significance level of 0.048 for the testing of OS and a two-sided significance level of 0.002 for the testing of PFS initially. If OS was statistically significant, the allocated two-sided significance level of 0.048 could be recycled to PFS such that PFS could be tested at a two-sided significance level of 0.05 instead of 0.002. If the analysis of PFS was statistically significant, then the two-sided significance level of 0.002 (or 0.05 if OS was statistically significant) was to be recycled to key secondary endpoints (IRF-assessed ORR according to RECIST v1.1 and HCC mRECIST) to be formally tested in a hierarchical fashion. If PFS and both key secondary endpoints were statistically significant at a two-sided significance level of 0.002, then OS could be tested at a two-sided significance level of 0.05 instead of 0.048. An overview of the type I error rate control strategy for the co-primary and key secondary efficacy endpoints is shown in Figure 6.



HCC mRECIST = hepatocellular carcinoma-specific modified Response Evaluation Criteria in Solid Tumors; IRF = independent review facility; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; IRF-PFS = progression-free survival as assessed by Independent Review Facility; RECIST = Response Evaluation Criteria in Solid Tumors.

Figure 6: Overview of the type I error control for co-primary and key secondary endpoints

Multiplicity Control for Key Secondary Endpoints

If the co-primary endpoint of IRF-PFS according to RECIST v1.1 was statistically significant, then ORR-IRF (confirmation required) according to RECIST v1.1 and ORR-IRF (confirmation required) according to HCC mRECIST were to be hierarchically tested. Specifically, ORR-IRF per RECIST v1.1 was to be tested first and if it was statistically significant, ORR-IRF per HCC mRECIST was then to be tested. If ORR-IRF per RECIST v1.1 was not statistically significant, ORR-IRF per HCC mRECIST was not to be tested. Implementation of this ordered statistical testing procedure will strongly control the type I error at 5% (two-sided) among all key hypotheses. The key secondary endpoints (ORR-IRF per RECIST v1.1 and ORR-IRF per HCC mRECIST) were to be tested at a two-sided alpha of 0.002 if the co-primary endpoint PFS-IRF per RECIST v1.1 has reached statistical significance at a two-sided alpha of 0.002, but OS has not reached statistical significance at the first interim analysis that was to be conducted at the time of the primary PFS analysis. On the other hand, if both co-primary endpoints of PFS and OS have reached statistical significance at the specified two-sided alpha level at the time of the primary PFS analysis, key secondary endpoints were to be tested at a two-sided alpha of 0.05.

Analysis Timing

There were no interim analyses planned for the co-primary endpoint of IRF=PFS in this study. The primary analysis of IRF-PFS per RECIST v1.1 was to be conducted when approximately 308 PFS events had occurred in the ITT population. The clinical cutoff date for this primary PFS analysis was expected to occur approximately 16 months after the first patient was enrolled in the study.

Two interim analyses were planned to be conducted for OS. The first interim analysis was to be performed at the time of the primary PFS analysis. It was anticipated that at that time, approximately 172 deaths would have been observed. The respective MDD OS hazard ratio was 0.633 (median OS improvement vs. control of 6.9 months). The second OS interim analysis is planned to be conducted when approximately 243 deaths have been accumulated, estimated to occur approximately 24 months after the first patient was enrolled in the study. The respective MDD OS hazard ratio is 0.728 (median OS improvement vs. control of 4.6 months).

The respective MDD OS hazard ratio for the final OS analysis is 0.783 (median OS improvement vs. control of 3.3 months).

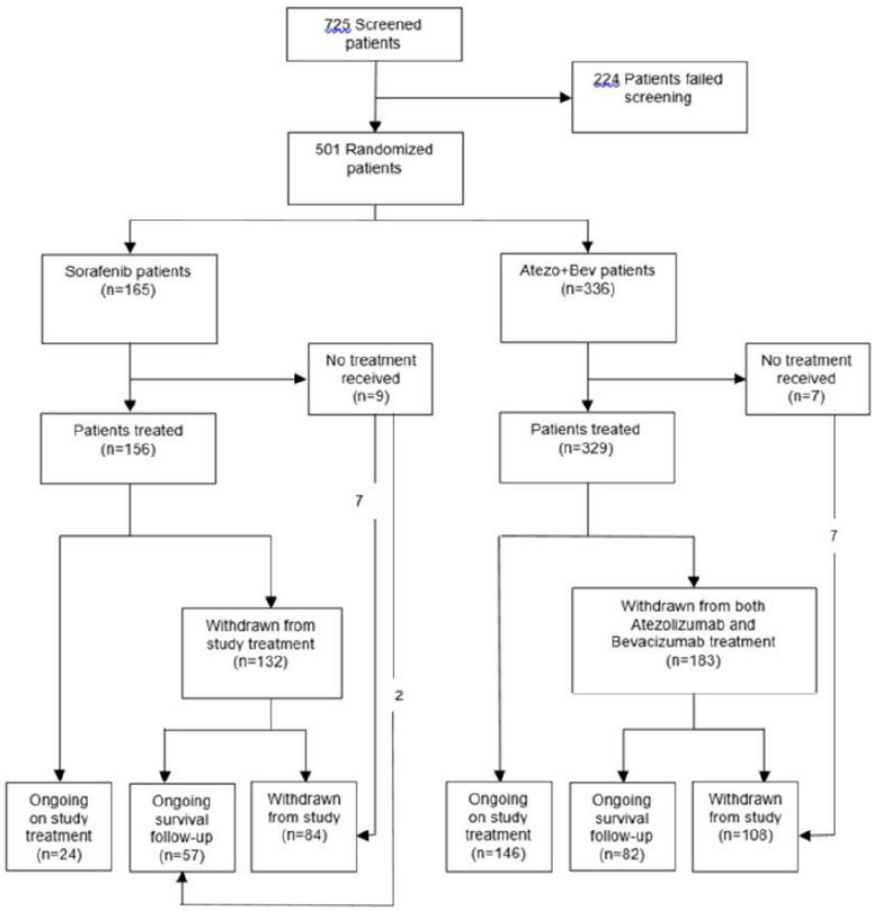
Results

Participant flow

In total, 725 patients were screened for entry into this study and 224 patients failed screening based on information collected on the IxRS. The most common specified reasons for screen failure included:

- inadequate hematologic and end-organ function (n=49)
- non-Child-Pugh Class A (n=29)
- withdrawal of consent (n=17)
- other (n=13; no additional information provided)
- active HBV with ≥500 IU/mL HBV DNA and/or no anti-HBV treatment as required (n=12)
- presence of untreated or incompletely treated oesophageal and/or gastric varices with bleeding or high-risk for bleeding (n=11), and
- presence of serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture (n=11).

As of the clinical cutoff date of 29 August 2019, 14.5% and 34.5% of patients in the Sorafenib arm and 43.5% and 24.4% of patients in the Atezo+Bev arm were continuing any study treatment or in survival follow-up, respectively.



As of the clinical cutoff date, for the Sorafenib arm, of the 9 patients who did not receive treatment, 7 patients withdrew from the study and 2 patients are ongoing in survival follow-up and for the Atezo+Bev arm, all 7 patients who did not receive any treatment withdrew from the study.

For both treatment arms, patients withdrawn from study treatment as well as patients who did not receive study treatment contribute to the numbers displayed for the categories "Ongoing survival follow-up" and "Withdrawn from study".

Atezo+Bev=atezolizumab plus bevacizumab

Figure 7: Disposition of patients – Imbrave150

Table 15: Reasons for Discontinuation from Study Treatment (Safety-Evaluable Population)

	Sorafenib (N=156)	Atezo+Bev (N=329)	
	Sorafenib	Atezolizumab	Bevacizumab
Received At Least One Study Treatment			
Yes	156 (100%)	329 (100%)	329 (100%)
Treatment Status			
Ongoing	24 (15.4%)	146 (44.4%)	137 (41.6%)
Withdrawn from treatment	132 (84.6%)	183 (55.6%)	192 (58.4%)
Withdrawn From Treatment Reason			
DEATH	7 (4.5%)	15 (4.6%)	16 (4.9%)
ADVERSE EVENT	16 (10.3%)	29 (8.8%)	49 (14.9%)
SYMPTOMATIC DETERIORATION	4 (2.6%)	10 (3.0%)	9 (2.7%)
PROGRESSIVE DISEASE	93 (59.6%)	111 (33.7%)	100 (30.4%)
PHYSICIAN DECISION	4 (2.6%)	3 (0.9%)	4 (1.2%)
WITHDRAWAL BY SUBJECT	7 (4.5%)	15 (4.6%)	14 (4.3%)
OTHER	1 (0.6%)	0	0

Table 16: Patient Disposition from Study (ITT Population)

	Sorafenib (N=165)	Atezo+Bev (N=336)	All Patients (N=501)
Received Treatment	156 (94.5%)	329 (97.9%)	485 (96.8%)
On study	81 (49.1%)	228 (67.9%)	309 (61.7%)
On Treatment	24 (14.5%)	146 (43.5%)	170 (33.9%)
In Follow-Up	57 (34.5%)	82 (24.4%)	139 (27.7%)
Discontinued study	84 (50.9%)	108 (32.1%)	192 (38.3%)
Death	65 (39.4%)	95 (28.3%)	160 (31.9%)
Progressive disease	0	1 (0.3%)	1 (0.2%)
Withdrawal by subject	19 (11.5%)	12 (3.6%)	31 (6.2%)

"On Treatment" indicates that the patient is still receiving at least one of the study treatments.

Recruitment

First patient enrolled: 15 March 2018, Last patient enrolled: 30 January 2019, Data cut-off: 29 August 2019

111 sites in 17 countries/regions. The number of patients enrolled and randomized per country/region, followed by the number of centers (in parentheses): China mainland 78 (15), United States 74 (19), Japan 61 (13), Republic of Korea 47 (6), France 42 (10), Taiwan 41 (5), Hong Kong 18 (2), Russian Federation 24 (2), Poland 23 (5), Italy 17 (6), Singapore 17 (2), Germany 16 (7), United Kingdom 13 (4), Spain 11 (5), Australia 9 (4), Canada 5 (4), Czech Republic 5 (2).

Conduct of the study

Changes in Conduct of Study

The first version of the protocol was issued on 18 October 2017 and was amended three times. The key changes to the protocol along with the rationale are summarised in Table 6.

Table 17: Summary of protocol amendments

Protocol Amendment (Date)	Key Changes and Rationale
Version 1 (18 Oct 2017)	Original protocol
Version 2 (14 March 2018)	First version under which patients were treated.
Version 3 (15 Sep 2018)	• The co-primary endpoints for the study were changed from Investigator-assessed ORR and OS to IRF-assessed PFS and OS, given that ORR for atezolizumab + bevacizumab was being extensively investigated in the Phase Ib study GO30140 • The eligibility criteria were updated to refine the patient population, with the intent to ensure the safety of the patients, considering the toxicity profile of the study drugs • The window for assessing ECOG performance status, Child-Pugh Class A, and adequate hematologic and end-organ function lab tests was shortened from 14 days to 7 days prior to randomization to ensure fit patients were enrolled and to exclude patients who could have progressively deteriorating liver function and overall health status • Immune-related nephritis was added as an important identified risk for atezolizumab along with management guidelines • The collection of additional atezolizumab ADA and PK samples was added to more fully characterize any ADA responses to atezolizumab
Version 4 (20 Feb 2019)	The protocol was amended primarily to modify the originally planned statistical analysis and to align with the SAP to include a second interim analysis for OS in anticipation of the changing HCC landscape. Other changes in the statistical analysis plan included: • The method used for control of the overall type I error rate was updated from using a group sequential weighted Holm procedure to using a graphical approach to strongly control the type I error at 5% (two-sided) • The secondary endpoint for PROs of TTD was amended to align with the co-primary endpoints of PFS and OS • PFS was added as the primary endpoint of the China subpopulation analysis to align with the global study analysis.

ADA = anti-drug antibody; HCC = hepatocellular carcinoma; INV = Investigator; IRF = independent review facility; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcome; PK = pharmacokinetic; TTD = time to deterioration.

Changes in Planned Analyses

Protocol deviations

As of the clinical cutoff date of 29 August 2019, 33.7% of all randomized patients had at least one major protocol deviation. The overall frequency and type of major protocol deviations were generally similar across the treatment arms.

Table 18: Major protocol deviations (ITT population)

Protocol Deviation Category Protocol Deviation Description	Sorafenib (N=165)	Atezo+Bev (N=336)	All Patients (N=501)
Total number of patient with at least one deviation	49 (29.7%)	120 (35.7%)	169 (33.7%)
Overall total number of deviations	70	224	294
EXCLUSION CRITERIA			
Total number of patient with at least one deviation	1 (0.6%)	5 (1.5%)	6 (1.2%)
Total number of events	1	5	6
Active or history of autoimmune disease or immune deficiency	1 (0.6%)	0	1 (0.2%)
Current or recent use of aspirin or trmt with dipyramidole, ticlopidine, clopidogrel, cilostazol	0	1 (0.3%)	1 (0.2%)
Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC	0	1 (0.3%)	1 (0.2%)
Major surgical procedure, open biopsy, significant traumatic injury w/in 28d prior to study start	0	1 (0.3%)	1 (0.2%)
Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of IP	0	1 (0.3%)	1 (0.2%)
chronic daily trmt w/ a non steroidal anti-inflammatory drug	0	1 (0.3%)	1 (0.2%)
INCLUSION CRITERIA			
Total number of patient with at least one deviation	6 (3.6%)	4 (1.2%)	10 (2.0%)
Total number of events	6	4	10
Adequate hematologic and end-organ function as defined in the protocol	3 (1.8%)	3 (0.9%)	6 (1.2%)
At least one measurable (per RECISTv1.1) untreated lesion	1 (0.6%)	0	1 (0.2%)
Child-Pugh class A	0	1 (0.3%)	1 (0.2%)
HBV DNA < 500 IU/ml w/in 28 days and antiHBV trmt for minimum of 14d and willing to continue trmt	1 (0.6%)	0	1 (0.2%)
no prior systemic treatment for HCC	1 (0.6%)	0	1 (0.2%)
MEDICATION			
Total number of patient with at least one deviation	9 (5.5%)	28 (8.3%)	37 (7.4%)
Total number of events	9	35	44
Received prohibited concomitant medication	2 (1.2%)	0	2 (0.4%)
Sig deviation from dose except AE management	2 (1.2%)	2 (0.6%)	4 (0.8%)
Sig deviation from scheduled drug admin visit	3 (1.8%)	12 (3.6%)	15 (3.0%)
Sig deviation from study med administration	1 (0.6%)	13 (3.9%)	14 (2.8%)
Use of protocol-prohibited therapy (Section 4.4.3)	1 (0.6%)	1 (0.3%)	2 (0.4%)
PROCEDURAL			
Total number of patient with at least one deviation	42 (25.5%)	105 (31.3%)	147 (29.3%)
Total number of events	54	180	234
Change in imaging modality impacting the primary endpoint	1 (0.6%)	0	1 (0.2%)
Deviation from reporting timelines SAEs	5 (3.0%)	10 (3.0%)	15 (3.0%)
Error with randomization	0	1 (0.3%)	1 (0.2%)
Error with stratification	9 (5.5%)	39 (11.6%)	48 (9.6%)
ICF not signed by patient or study personnel	0	2 (0.6%)	2 (0.4%)
Missing consent to updated ICF	2 (1.2%)	11 (3.3%)	13 (2.6%)
Missing or out of window assessment impact study integrity, safety	13 (7.9%)	33 (9.8%)	46 (9.2%)
No signed ICF for optional RBR	0	1 (0.3%)	1 (0.2%)
Omission of labs prior to drug administration	5 (3.0%)	24 (7.1%)	29 (5.8%)
Omission of tumor assessment	14 (8.5%)	31 (9.2%)	45 (9.0%)

A patient will be only counted once if received more than one deviation of the same type.

The percentage of patients with protocol deviations for each of the 5 categories of protocol deviations highlighted by CHMP is presented in the table below.

Table 19: Selected Categories of Protocol Deviations, Intent-to-Treat Population

Protocol Deviation Category[a]	Sorafenib (N=165)	Atezo + Bev (N=336)
Deviation from scheduled drug administration visit	3 (1.8%)	12 (3.6%)
Deviation from study medication administrations	1 (0.6%)	13 (3.9%)
Error with stratification	9 (5.5%)	39 (11.6%)
Missing or out of window assessment impact study integrity, safety	13 (7.9%)	33 (9.8%)
Omission of lab tests prior to drug administration	5 (3.0%)	24 (7.1%)

[a] A patient will be only counted once if received more than one deviation of the same type.

Many of the deviations that occurred in these categories in the Atezo + Bev arm were missed thyroid panels, missed urinalysis tests, or missed components of other lab panels.

Table 20: Stratification Factor Errors

Stratification Factor Error	Atezo + Bev (Arm A)	Sorafenib (Arm B)
Geographic Region	0	0
Macrovascular invasion and/or extrahepatic spread	31*	8
Baseline AFP	3	1
ECOG Status	6*	0
Total	40 errors	9 errors

AFP = Alpha Feto-Protein; ECOG = Eastern Cooperative Oncology Group.

* = one patient, randomized to Arm A, had 2 stratification errors; 1) macrovascular invasion and/or extrahepatic spread and 2) ECOG status

Baseline data

Table 21: Demographic and baseline disease characteristics

	Sorafenib (N=165)	Atezo+Bev (N=336)	All Patients (N=501)
Age (yr)			
n	165	336	501
Median	66.0	64.0	65.0
Age group (yr)			
n	165	336	501
18-40	7 (4.2%)	18 (5.4%)	25 (5.0%)
41-64	67 (40.6%)	157 (46.7%)	224 (44.7%)
>= 65	91 (55.2%)	161 (47.9%)	252 (50.3%)
Sex			
n	165	336	501
Male	137 (83.0%)	277 (82.4%)	414 (82.6%)
Race			
n	165	336	501
Asian	96 (58.2%)	188 (56.0%)	284 (56.7%)
White	52 (31.5%)	123 (36.6%)	175 (34.9%)
Geographic Region (eCRF)			
n	165	336	501
Asia (excluding Japan)	68 (41.2%)	133 (39.6%)	201 (40.1%)
Rest of World	97 (58.8%)	203 (60.4%)	300 (59.9%)
ECOG Performance Status at Screening (eCRF)			
n	165	336	501
0	103 (62.4%)	209 (62.2%)	312 (62.3%)
1	62 (37.6%)	127 (37.8%)	189 (37.7%)
PD-L1 Category 1			
n	58	124	182
TC and IC < 1%	25 (43.1%)	45 (36.3%)	70 (38.5%)
TC or IC >= 1%	33 (56.9%)	79 (63.7%)	112 (61.5%)
PD-L1 Category 2			
n	58	124	182
TC and IC < 5%	41 (70.7%)	78 (62.9%)	119 (65.4%)
TC or IC >= 5%	17 (29.3%)	46 (37.1%)	63 (34.6%)
PD-L1 Category 3			
n	58	124	182
TC and IC < 10%	53 (91.4%)	112 (90.3%)	165 (90.7%)
TC or IC >= 10%	5 (8.6%)	12 (9.7%)	17 (9.3%)

For patients whose cause of HCC was multifactorial as assessed by the Investigator, the viral cause was prioritized over non-viral causes to define the primary etiology of the patient.
[1] Partial Diagnosis date is imputed with 1st day of the month if the day is missing in the calculations of Time from Initial Diagnosis.
[2] A patient may have more than one cause of disease.

Table 22: Hepatocellular carcinoma history and disease characteristics (ITT population)

	Sorafenib (N=165)	Atezo+Bev (N=336)	All Patients (N=501)
BCLC Stage at Study Entry			
n	165	336	501
STAGE A1	3 (1.8%)	5 (1.5%)	8 (1.6%)
STAGE A4	3 (1.8%)	3 (0.9%)	6 (1.2%)
STAGE B	26 (15.8%)	52 (15.5%)	78 (15.6%)
STAGE C	133 (80.6%)	276 (82.1%)	409 (81.6%)
Etiology of HCC			
n	165	336	501
Hepatitis B	76 (46.1%)	164 (48.8%)	240 (47.9%)
Hepatitis C	36 (21.8%)	72 (21.4%)	108 (21.6%)
Non-viral	53 (32.1%)	100 (29.8%)	153 (30.5%)
Extrahepatic Spread (EHS) Present at Study Entry (eCRF)			
n	165	336	501
Yes	93 (56.4%)	212 (63.1%)	305 (60.9%)
Macro-Vascular Invasion (MVI) Present at Study Entry (eCRF)			
n	165	336	501
Yes	71 (43.0%)	129 (38.4%)	200 (39.9%)
EHS and/or MVI Present at Study Entry (eCRF)			
n	165	336	501
Yes	120 (72.7%)	258 (76.8%)	378 (75.4%)
Child Pugh Category			
n	165	334	499
A5	121 (73.3%)	239 (71.6%)	360 (72.1%)
A6	44 (26.7%)	94 (28.1%)	138 (27.7%)
B7	0	1 (0.3%)	1 (0.2%)
Baseline Sum of Target Lesion Diameter (mm) per INV			
n	164	336	500
Mean (SD)	92.32 (63.53)	84.51 (58.82)	87.08 (60.45)
Median	83.20	71.80	74.00
Min - Max	10.0 - 312.0	10.0 - 321.0	10.0 - 321.0
AFP Category at Screening (eCRF)			
n	165	336	501
<400 ng/mL	104 (63.0%)	210 (62.5%)	314 (62.7%)
>=400 ng/mL	61 (37.0%)	126 (37.5%)	187 (37.3%)
Varices at time of Enrollment			
n	165	336	501
Yes	43 (26.1%)	88 (26.2%)	131 (26.1%)
Type of Prior Local Therapy			
n	85	161	246
Radiofrequency Ablation (RFA)	24 (14.5%)	47 (14.0%)	71 (14.2%)
Transarterial Chemoembolization (TACE)	70 (42.4%)	130 (38.7%)	200 (39.9%)
Prior Cancer Radiotherapy			
n	165	336	501
Yes	17 (10.3%)	34 (10.1%)	51 (10.2%)

For patients whose cause of HCC was multifactorial as assessed by the Investigator, the viral cause was prioritized over non-viral causes to define the primary etiology of the patient.
[1] Partial Diagnosis date is imputed with 1st day of the month if the day is missing in the calculations of Time from Initial Diagnosis.
[2] A patient may have more than one cause of disease. 12OCT2019 4:48

Table 23: Prior local hepatocellular carcinoma treatment history (ITT population)

	Sorafenib (N=165)	Atezo+Bev (N=336)
Total number of patients with at least one treatment	85 (51.5%)	161 (47.9%)
Total number of treatments	296	548
Therapy Intent		
ADJUVANT	10 (6.1%)	14 (4.2%)
CURATIVE	44 (26.7%)	86 (25.6%)
NEO-ADJUVANT	4 (2.4%)	6 (1.8%)
PALLIATIVE	36 (21.8%)	61 (18.2%)
Other	3 (1.8%)	11 (3.3%)
Name of Therapy		
Percutaneous Ethanol Injection (PEI)	3 (1.8%)	12 (3.6%)
Radiofrequency Ablation (RFA)	24 (14.5%)	47 (14.0%)
Transarterial Embolization (TAE)	8 (4.8%)	12 (3.6%)
Transarterial Chemoembolization (TACE)	70 (42.4%)	130 (38.7%)
Drug Eluting Beads -Transarterial Chemoembolization (DEB-TACE)	1 (0.6%)	3 (0.9%)
Transcatheter Arterial Infusion (TAI)	2 (1.2%)	3 (0.9%)
Transarterial Radioembolization (TARE)	4 (2.4%)	8 (2.4%)
Other	7 (4.2%)	6 (1.8%)

Multiple cases within a specific therapy intent or name of therapy for a patient were counted once in the frequency for the therapy intent or name of therapy.

Table 24: Prior hepatocellular carcinoma radiation therapy (ITT population)

Therapy Setting Site	Sorafenib (N=165)	Atezo+Bev (N=336)
Total number of patients with at least one treatment	17 (10.3%)	34 (10.1%)
Total number of treatments	22	36
PALLIATIVE		
Total number of patients with at least one treatment	8 (4.8%)	24 (7.1%)
Total number of treatments	12	25
ABDOMINAL CAVITY	0	1 (0.3%)
BONE	2 (1.2%)	3 (0.9%)
BRAIN	1 (0.6%)	0
LIVER	4 (2.4%)	17 (5.1%)
LYMPH NODE	0	1 (0.3%)
PELVIS	0	1 (0.3%)
STOMACH	1 (0.6%)	0
OTHER	1 (0.6%)	1 (0.3%)
OTHER		
Total number of patients with at least one treatment	4 (2.4%)	3 (0.9%)
Total number of treatments	4	3
LIVER	4 (2.4%)	2 (0.6%)
MEDIASTINUM	0	1 (0.3%)
METASTATIC		
Total number of patients with at least one treatment	3 (1.8%)	3 (0.9%)
Total number of treatments	4	3
BONE	0	1 (0.3%)
LIVER	2 (1.2%)	1 (0.3%)
LUNG	1 (0.6%)	0
OTHER	0	1 (0.3%)
ADJUVANT		
Total number of patients with at least one treatment	2 (1.2%)	3 (0.9%)
Total number of treatments	2	3
LIVER	1 (0.6%)	3 (0.9%)
PROSTATE GLAND	1 (0.6%)	0
NEO-ADJUVANT		
Total number of patients with at least one treatment	0	2 (0.6%)
Total number of treatments	0	2
LIVER	0	2 (0.6%)

Multiple cases within a specific therapy setting for a patient were counted once in the frequency for the therapy setting.

Concomitant Treatments for HCC

During the study period, radiation therapy was given to a small number of patients for palliative reasons only: 1 patient in the Sorafenib arm and 5 patients in the Atezo+Bev arm. Radiation therapy to bone was the predominant radiotherapy site reported (5 patients), 1 patient received radiation therapy to liver and 1 patient to lung. During the study period, 3 patients in each treatment arm received cancer-related surgery.

Table 25: On-study Hepatocellular Carcinoma-Related Surgery

On-study Surgery On-study Surgery Location	Sorafenib (N=165)	Atezo+Bev (N=336)
Total number of patients with at least one treatment	3 (1.8%)	3 (0.9%)
Total number of treatments	6	4
PALLIATIVE		
Total number of patients with at least one treatment	3 (1.8%)	1 (0.3%)
Total number of treatments	6	1
BONE	0	1 (0.3%)
ESOPHAGUS	1 (0.6%)	0
LIVER	1 (0.6%)	0
OTHER	1 (0.6%)	0
CURATIVE		
Total number of patients with at least one treatment	0	1 (0.3%)
Total number of treatments	0	1
LIVER	0	1 (0.3%)
DIAGNOSTIC		
Total number of patients with at least one treatment	0	1 (0.3%)
Total number of treatments	0	2
LIVER	0	1 (0.3%)

Multiple cases of a specific surgery for a patient were counted once in frequency for the surgery.

Numbers analysed

Table 26: Analysis populations (all patients)

	Sorafenib	Atezo+Bev
All Randomized Intent-to-Treat Patients	165	336
All Safety Evaluable Patients	156	329
All PRO Evaluable Patients	145	309
All ADA Evaluable Patients	0	315
All PK Evaluable Patients	0	324

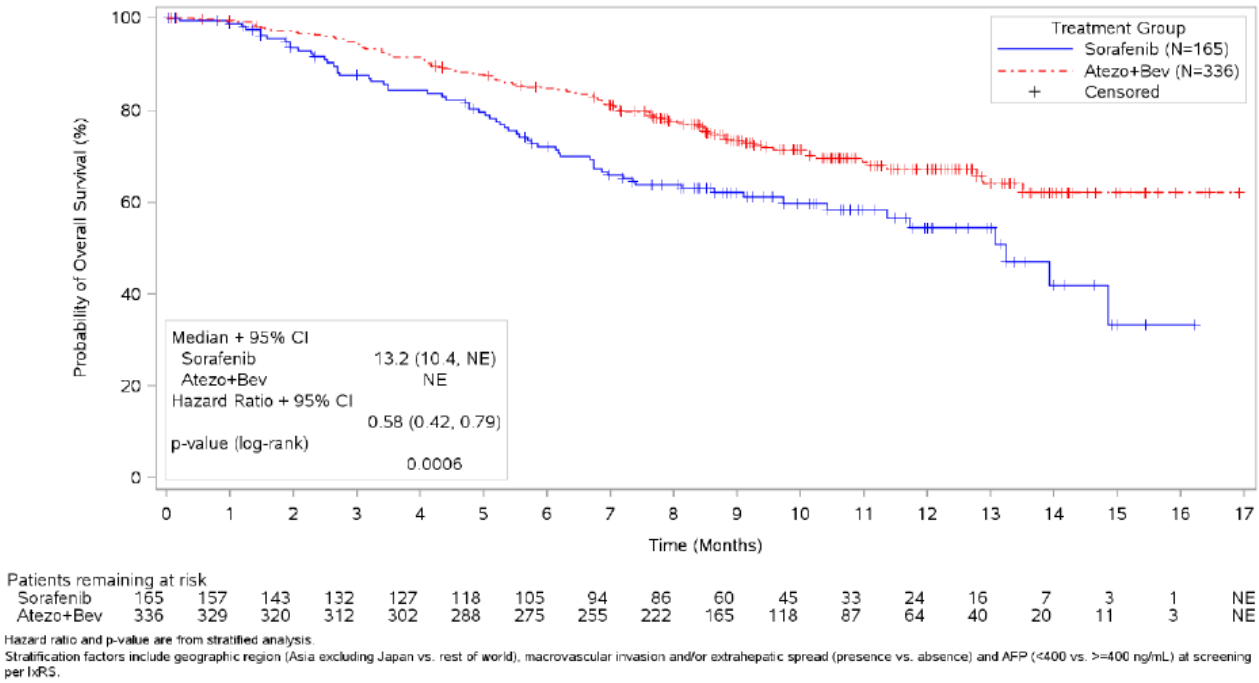
ADA = anti-drug antibodies; PRO = patient reported outcome, PK = Pharmacokinetic.
Safety, ADA and PK Evaluable populations are based on the actual treatment received. All other populations are based on the randomized treatment.

Outcomes and estimation

Co-primary endpoint - OS and PFS

Table 27: Overview of efficacy: co-primary and key secondary efficacy endpoints (ITT population)

	Sorafenib N = 165	Atezo + Bev N = 336
Co-Primary Endpoints		
Overall Survival		
No. (%) of patients with event	65 (39.4%)	96 (28.6%)
Median, months	13.24	NE
95% CI	(10.41, NE)	NE
Stratified hazard ratio (95% CI) [a]	0.58 (0.42, 0.79)	
p-value (log-rank)	0.0006	
6-month OS (%)	72.2%	84.8%
IRF-Assessed PFS per RECIST v1.1		
No. (%) of patients with event	109 (66.1%)	197 (58.6%)
Median, months	4.27	6.83
95% CI	(3.98, 5.55)	(5.75, 8.28)
Stratified hazard ratio (95% CI) [a]	0.59 (0.47, 0.76)	
p-value (log-rank)	<0.0001	
6-month PFS (%)	37.2%	54.5%



Hazard ratio and p-value are from stratified analysis.
Stratification factors include geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence) and AFP (<400 vs. >=400 ng/mL) at screening per IxRS.

Figure 8: Kaplan-Meier plot of overall survival (ITT population) – cut-off date: 29 August 2019

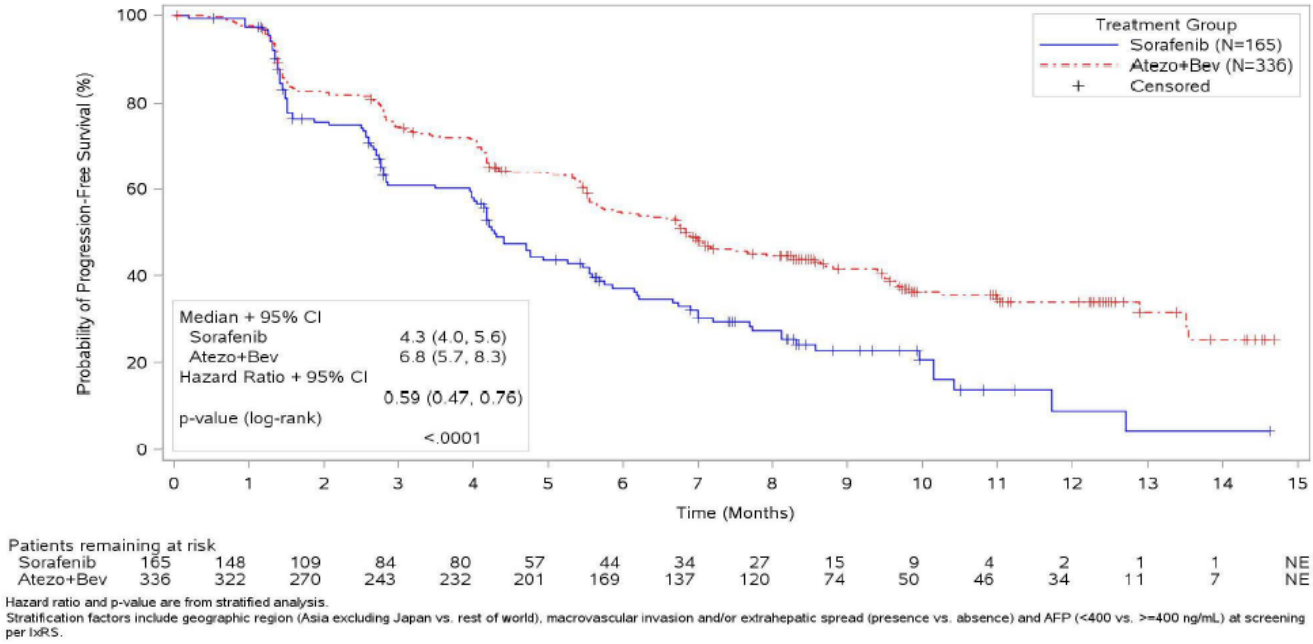


Figure 9: Kaplan-Meier plot of progression-free survival based on IRF-assessment per RECIST v1.1 (ITT population) – cut-off date: 29 August 2019

The MAH has computed adjusted p-values for all efficacy endpoints that were formally tested (co-primary endpoints: OS and IRF-assessed PFS per RECIST version 1.1; key secondary endpoints: IRF-assessed ORR per RECIST v1.1 and per HCC modified RECIST) using the method described in Bretz et al. 2009. These adjusted p-values adjust for multiplicity of the co-primary and key secondary efficacy endpoints, in the context of the group-sequential design of OS (as described in the protocol), and therefore are to be compared with the overall two-sided alpha of 0.05. Table 31 lists the unadjusted observed p-values as reported in the IMbrave150 CSR (versus the respective multiplicity adjusted alpha boundaries) and the respective adjusted p-values (versus alpha boundary of 0.05, two-sided) for the co-primary and key secondary efficacy endpoints that were formally tested in IMbrave150. All p-values, confidence intervals, alpha boundaries in Table 31 are two sided. The statistical testing conclusions remain the same after the adjustment.

Table 28: Adjusted and Unadjusted P-values for Co-Primary and Key Secondary Efficacy Endpoints in IMbrave150

Endpoint	Unadjusted Observed P-value vs multiplicity adjusted Alpha Boundary	Adjusted P-value vs Alpha Boundary of 0.05	Comments
OS	0.0006 vs 0.0033	0.0006 vs 0.05	Boundary is crossed
PFS (IRF-RECIST v1.1)	<0.0001 vs 0.02	0.0005 vs 0.05	Boundary is crossed
ORR (IRF- RECIST v1.1)	<0.0001 vs 0.02	0.0006 vs 0.05	Boundary is crossed
ORR (IRF- HCC mRECIST)	<0.0001 vs 0.02	0.0006 vs 0.05	Boundary is crossed

IRF = Independent Review Facility; mRECIST = modified RECIST; ORR = objective response rate; OS=overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors.

Key secondary endpoints

Table 29: Confirmed objective response rate based on IRF-assessment per RECIST v1.1 (ITT population with measurable disease at baseline)

	Sorafenib (N=159)		Atezo+Bev (N=326)
Responders 95% CI	19 (11.9%) (7.35, 18.03)		89 (27.3%) (22.54, 32.48)
Stratified Analysis Difference in Overall Response Rates (95% CI) p-value (Cochran-Mantel-Haenszel) Odds Ratio for Overall Response (95% CI)		15.35 (7.90, 22.81) <.0001 2.90 (1.68, 5.01)	
Complete Response (CR) 95% CI	0 (0.00, 2.29)		18 (5.5%) (3.30, 8.59)
Partial Response (PR) 95% CI	19 (11.9%) (7.35, 18.03)		71 (21.8%) (17.42, 26.66)
Stable Disease (SD) 95% CI	69 (43.4%) (35.57, 51.48)		151 (46.3%) (40.81, 51.90)
Progressive Disease (PD) 95% CI	39 (24.5%) (18.06, 31.97)		64 (19.6%) (15.46, 24.37)
Not Evaluable (NE) Missing	14 (8.8%) 18 (11.3%)		8 (2.5%) 14 (4.3%)

Patients were classified as missing or not evaluable if no post-baseline response assessments were available or all post-baseline response assessments were not evaluable.
Responders refer to all patients with <CR/PR>. A window of 28 days is used for the confirmation of CR/PR.
95% CI for rates were constructed using the Clopper Pearson method. Wald is the normal approximation for 95% CI of difference in rates. Odds ratios were estimated by logistic regression.
Stratification factors include geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence) and AFP (<400 vs. >=400 ng/mL) at screening per IxRS.

Table 30: Confirmed objective response rate based on IRF-assessment per HCC mRECIST (ITT population with measurable disease at baseline)

	Sorafenib (N=158)		Atezo+Bev (N=325)
Responders 95% CI	21 (13.3%) (8.42, 19.60)		108 (33.2%) (28.13, 38.64)
Stratified Analysis Difference in Overall Response Rates (95% CI) p-value (Cochran-Mantel-Haenszel) Odds Ratio for Overall Response (95% CI)		19.94 (12.10, 27.78) <.0001 3.39 (2.02, 5.71)	
Complete Response (CR) 95% CI	3 (1.9%) (0.39, 5.45)		33 (10.2%) (7.09, 13.96)
Partial Response (PR) 95% CI	18 (11.4%) (6.89, 17.41)		75 (23.1%) (18.61, 28.05)
Stable Disease (SD) 95% CI	66 (41.8%) (33.99, 49.87)		127 (39.1%) (33.74, 44.62)
Progressive Disease (PD) 95% CI	40 (25.3%) (18.74, 32.84)		66 (20.3%) (16.07, 25.10)
Not Evaluable (NE) Missing	14 (8.9%) 17 (10.8%)		10 (3.1%) 14 (4.3%)

Patients were classified as missing or not evaluable if no post-baseline response assessments were available or all post-baseline response assessments were not evaluable.
Responders refer to all patients with <CR/PR>. A window of 28 days is used for the confirmation of CR/PR.
95% CI for rates were constructed using the Clopper Pearson method. Wald is the normal approximation for 95% CI of difference in rates. Odds ratios were estimated by logistic regression.
Stratification factors include geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence) and AFP (<400 vs. >=400 ng/mL) at screening per IxRS.

Table 31: Duration of confirmed response based on IRF-assessment per RECIST v1.1 (confirmed responders population)

	Sorafenib (N=159)		Atezo+Bev (N=326)
Patients included in analysis(%)	19 (100%)		89 (100%)
Patients with event (%)	6 (31.6%)		12 (13.5%)
Earliest contributing event			
Death	1		5
Disease Progression	5		7
Patients without event (%)	13 (68.4%)		77 (86.5%)
Time to Event (Months)			
Median	6.28		NE
95% CI	(4.67, NE)		NE
25% and 75%-ile	4.67, NE		
Range	1.4+ to 9.1+		1.3+ to 13.4+
Stratified Analysis			
p-value (log-rank)		0.0051	
Hazard Ratio		0.23	
95% CI		(0.08, 0.70)	
Unstratified Analysis			
p-value (log-rank)		0.0067	
Hazard Ratio		0.27	
95% CI		(0.10, 0.74)	
Time Point Analysis			
6 Months			
Patients remaining at risk	6		43
Event Free Rate (%)	59.09		87.61
95% CI	(31.33, 86.85)		(79.89, 95.33)
1 Year			
Patients remaining at risk	NE		5
Event Free Rate (%)	NE		79.22
95% CI	NE		(67.68, 90.77)

+ Censored, ^ Censored and event, NE = Not estimable.
Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.
Stratification factors include geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence) and AFP (<400 vs. >=400 ng/mL) at screening per IxRS.

Table 32: Duration of confirmed response based on IRF-assessment per HCC mRECIST (confirmed responders population)

	Sorafenib (N=156)		Atezo+Bev (N=325)
Patients included in analysis (%)	21 (100%)		108 (100%)
Patients with event (%)	8 (38.1%)		24 (22.2%)
Earliest contributing event			
Death	1		8
Disease Progression	7		16
Patients without event (%)	13 (61.9%)		84 (77.8%)
Time to Event (Months)			
Median	6.28		NE
95% CI	(4.86, NE)		NE
25% and 75%-ile	4.86, NE		8.15, NE
Range	1.4* to 9.1*		1.3* to 13.4*
Stratified Analysis			
p-value (log-rank)		0.0048	
Hazard Ratio		0.30	
95% CI		(0.12, 0.73)	
Unstratified Analysis			
p-value (log-rank)		0.0293	
Hazard Ratio		0.42	
95% CI		(0.18, 0.94)	
Time Point Analysis			
6 Months			
Patients remaining at risk	8		51
Event Free Rate (%)	62.50		82.25
95% CI	(38.34, 86.66)		(74.31, 90.20)
1 Year			
Patients remaining at risk	NE		5
Event Free Rate (%)	NE		65.29
95% CI	NE		(52.84, 77.75)

* Censored, ^ Censored and event, NE = Not estimable.
Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.
Stratification factors include geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence) and AFP (<400 vs. >=400 ng/mL) at screening per IxRS.

PRO

Table 33: Summary of the PRO secondary efficacy endpoints (ITT population)

Endpoint/Scale	Sorafenib N = 165	Atezo+Bev N = 336
	TTD: Median (95% CI) Time to Event (Months)	
Physical Functioning per EORTC-QLQ-C30		
No. (%) of patients with events	64 (38.8%)	114 (33.9%)
Median (95% CI) time to event, months	4.86 (3.48, 6.24)	13.14 (9.69, NE)
Stratified hazard ratio (95% CI) [a]	0.53 (0.39, 0.73)	
Role Functioning per EORTC-QLQ-C30		
No. (%) of patients with events	69 (41.8%)	136 (40.5%)
Median (95% CI) time to event, months	3.58 (2.20, 5.98)	9.13 (6.51, NE)
Stratified hazard ratio (95% CI) [a]	0.62 (0.46, 0.84)	
GHS/QoL per EORTC-QLQ-C30		
No. (%) of patients with events	66 (40.0%)	132 (39.3%)
Median (95% CI) time to event, months	3.58 (3.02, 6.97)	11.24 (5.98, NE)
Stratified hazard ratio (95% CI) [a]	0.63 (0.46, 0.85)	

CI = confidence interval; GHS/QoL = global health status/quality of life; HCC = hepatocellular carcinoma; N = number; TTD = time to deterioration

[a] Stratification factors include geographic region (Asia [excluding Japan] vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence) and AFP (<400 vs. ≥400 ng/mL) at screening per IxRS

Ancillary analyses

Sensitivity analysis

The impact of missing scheduled tumour assessments on the co-primary efficacy endpoint of PFS based on IRF-assessment per RECIST v1.1 was assessed. In this analysis, patients who missed two or more consecutive tumor assessments scheduled immediately prior to the date of PD or death in any treatment arm were censored at the last tumor assessment prior to the missed visit.

Table 34: Sensitivity analysis for PFS based on IRF-assessment per RECIST v1.1 censored for missing visits (ITT population)

Cut off date: 2019-08-29

	Sorafenib (N=165)		Atezo+Bev (N=336)
Patients with event (%)	100 (60.6%)		190 (56.5%)
Earliest contributing event			
Death	21		28
Disease Progression	79		162
Patients without event (%)	65 (39.4%)		146 (43.5%)
Time to Event (Months)			
Median	4.21		6.87
95% CI	(3.94, 5.55)		(5.68, 8.57)
25% and 75%-ile	2.07, 8.57		2.92, NE
Range	0.0* to 14.6*		0.0* to 14.7*
Stratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.60	
95% CI		(0.47, 0.77)	
Unstratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.60	
95% CI		(0.47, 0.77)	
Time Point Analysis			
6 Months			
Patients remaining at risk	39		163
Event Free Rate (%)	36.29		54.14
95% CI	(27.87, 44.72)		(48.63, 59.64)
1 Year			
Patients remaining at risk	2		33
Event Free Rate (%)	15.38		35.00
95% CI	(5.77, 24.99)		(28.80, 41.19)

* Censored, ^ Censored and event, NE = Not estimable.
Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.
Stratification factors include geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence) and AFP (<400 vs. >=400 ng/mL) at screening per IxRS.
Patients who missed two or more consecutive tumor assessments scheduled immediately prior to the date of disease progression by IRF-assessment per RECIST v1.1 or death were censored at the last tumor assessment prior to the missed visits.

The MAH has conducted the two requested sensitivity analyses for the co-primary endpoint of PFS as assessed by IRF per RECIST version 1.1.

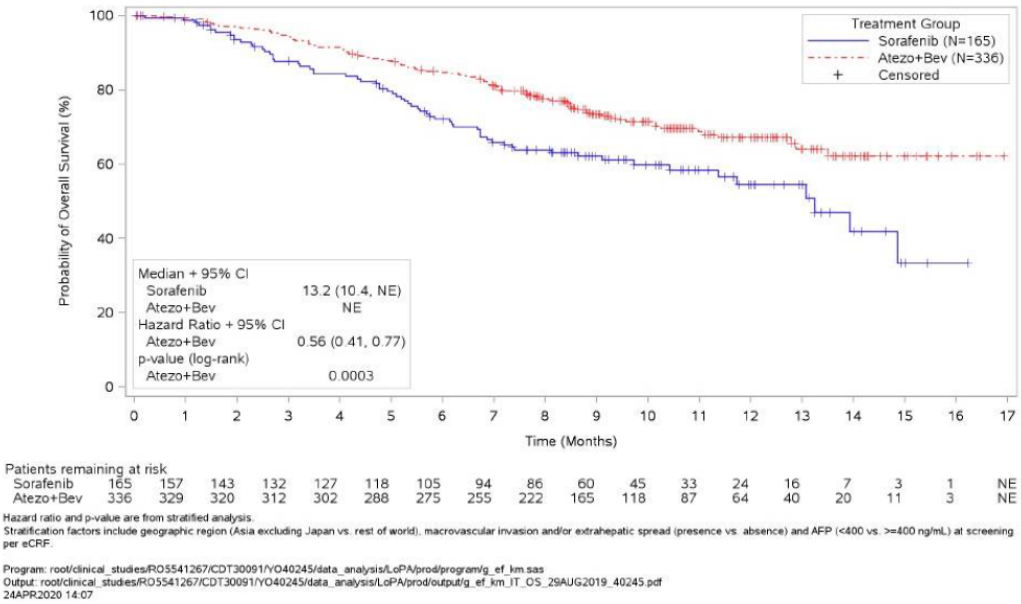
Sensitivity Analysis 1: Patients who missed ≥ 1 consecutive tumor assessments immediately prior to progressive disease (PD) or death are counted as event at the last tumor assessment prior to the missed visit;

Sensitivity Analysis 2: Patients who missed ≥ 2 consecutive tumor assessments immediately prior to PD or death are counted as event at the last tumor assessment prior to the missed visit.

Table 35: IRF-assessed PFS per RECIST v1.1, Primary and Sensitivity Analyses

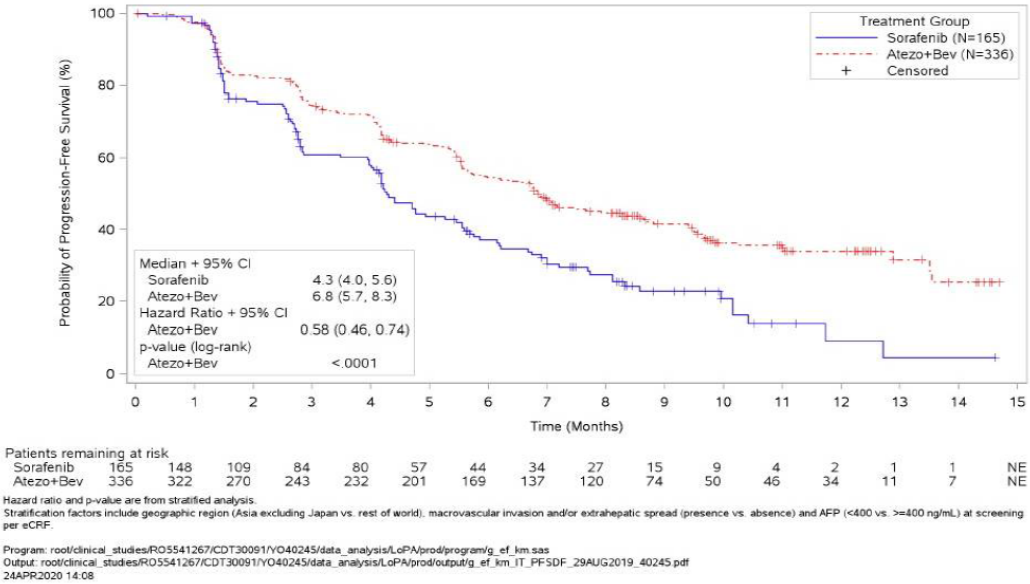
	Sorafenib N = 165	Atezo + Bev N = 336
IRF-PFS Primary Analysis reported in the CSR		
No. (%) of patients with event	109 (66.1%)	197 (58.6%)
Median, months	4.3	6.8
95% CI	(4.0, 5.6)	(5.7, 8.3)
Stratified hazard ratio (95% CI)	0.59 (0.47, 0.76)	
IRF-PFS Sensitivity Analysis 1		
No. (%) of patients with event	109 (66.1%)	197 (58.6%)
Median, months	4.0	6.8
95% CI	(2.8, 4.2)	(5.6, 7.7)
Stratified hazard ratio (95% CI)	0.56 (0.44, 0.72)	
IRF-PFS Sensitivity Analysis 2		
No. (%) of patients with event	109 (66.1%)	197 (58.6%)
Median, months	4.2	6.8
95% CI	(2.8, 4.7)	(5.6, 7.9)
Stratified hazard ratio (95% CI)	0.57 (0.45, 0.72)	

Atezo = atezolizumab ; Bev = Bevacizumab ; CI = confidence interval; IRF = Independent Review Facility; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors.
Stratification factors include geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence) and baseline AFP (<400 vs. >=400 ng/mL) per IxRS.



Atezo+Bev=atezolizumab+bevacizumab; N=number of patients; NE=not estimable

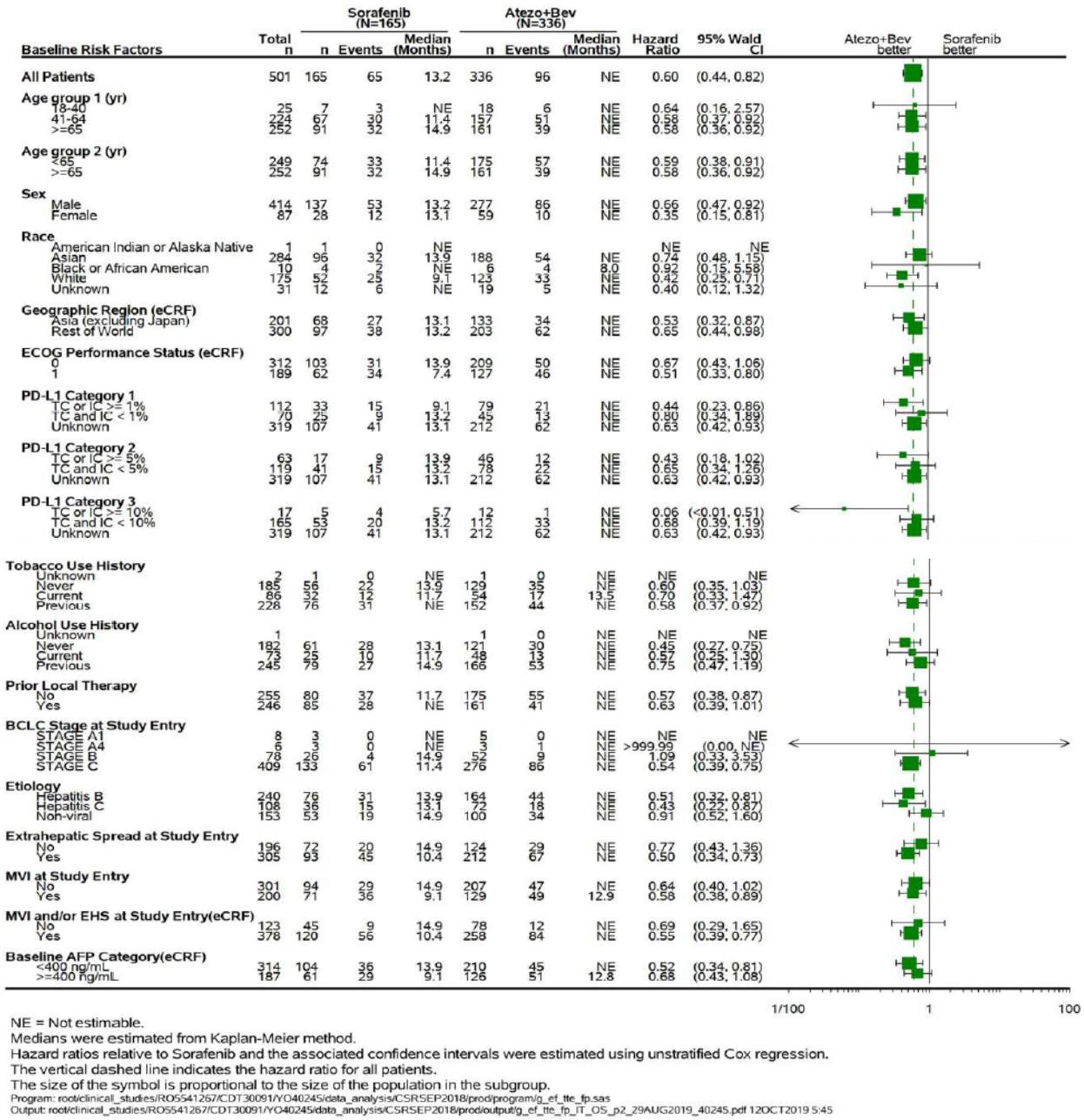
Figure 10: Kaplan-Meier plot of overall survival, ITT population (sensitivity analysis incorporating stratification factor information based on eCRF) – cut-off date: 29 August 2019



Atezo + Bev = atezolizumab + bevacizumab; CI = confidence interval; N = number of patients

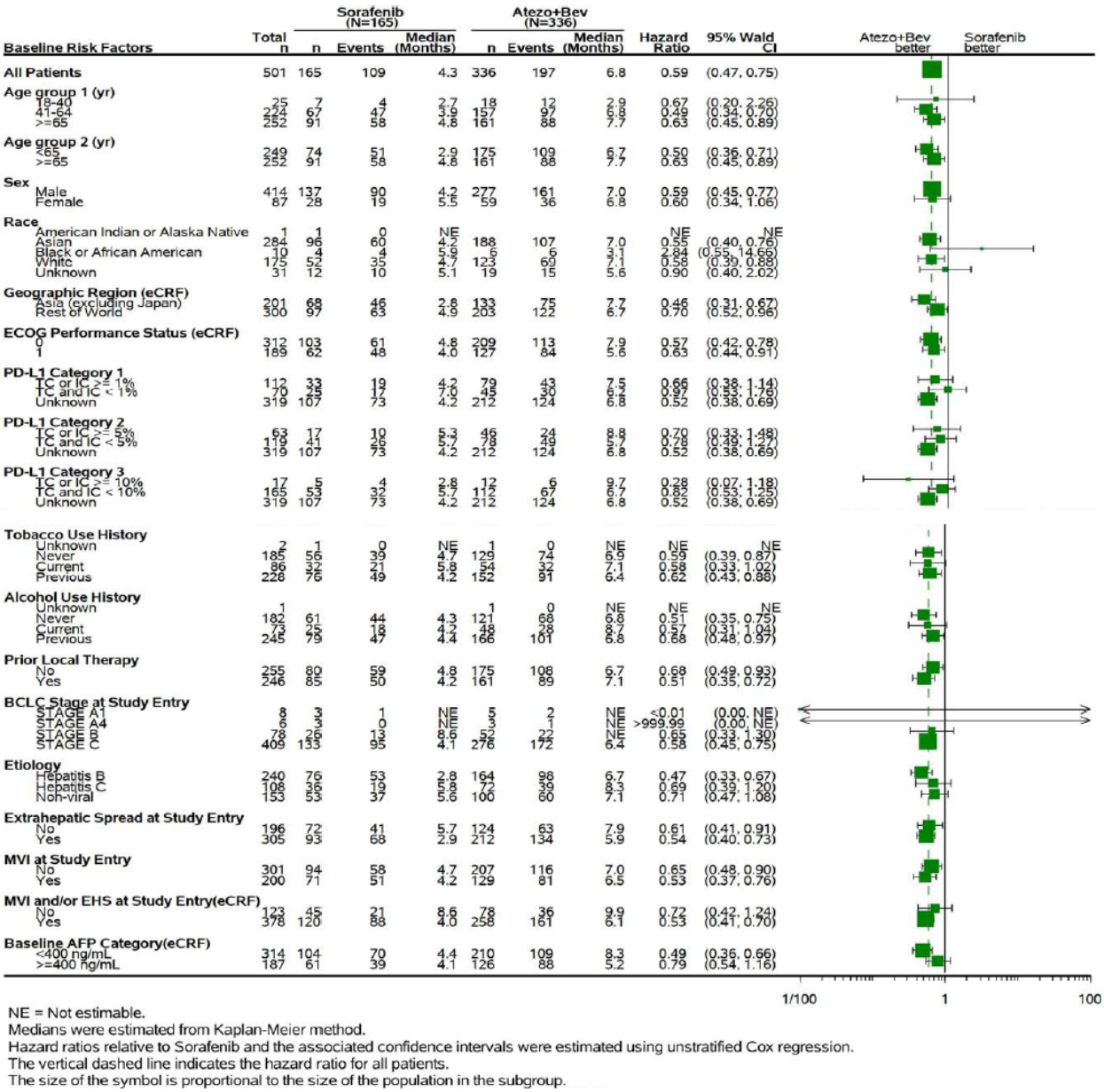
Figure 11: Kaplan-Meier plot of progression-free survival based on IRF-assessment per RECIST v1.1, ITT population (sensitivity analysis incorporating stratification factor information based on eCRF) – cut-off date: 29 August 2019

Subgroup analysis



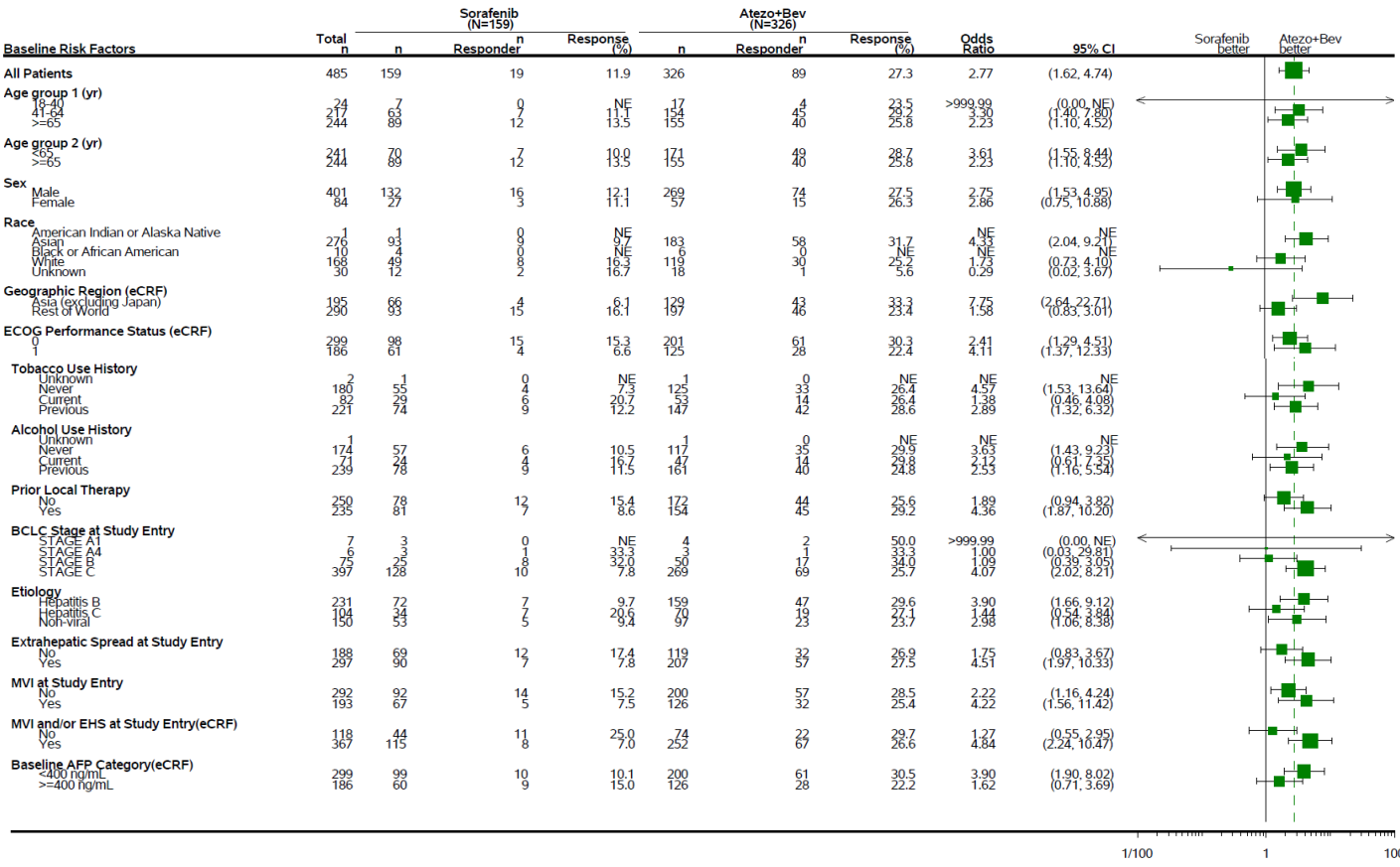
NE = Not estimable.
Medians were estimated from Kaplan-Meier method.
Hazard ratios relative to Sorafenib and the associated confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
Program: root/clinicall_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018/prod/program/g_ef_tte_fp.sas
Output: root/clinicall_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018/prod/output/g_ef_tte_fp_IT_OS_p2_29AUG2019_40245.pdf 12OCT2019 5:45

Figure 12: Subgroup Analyses of overall survival (ITT population)



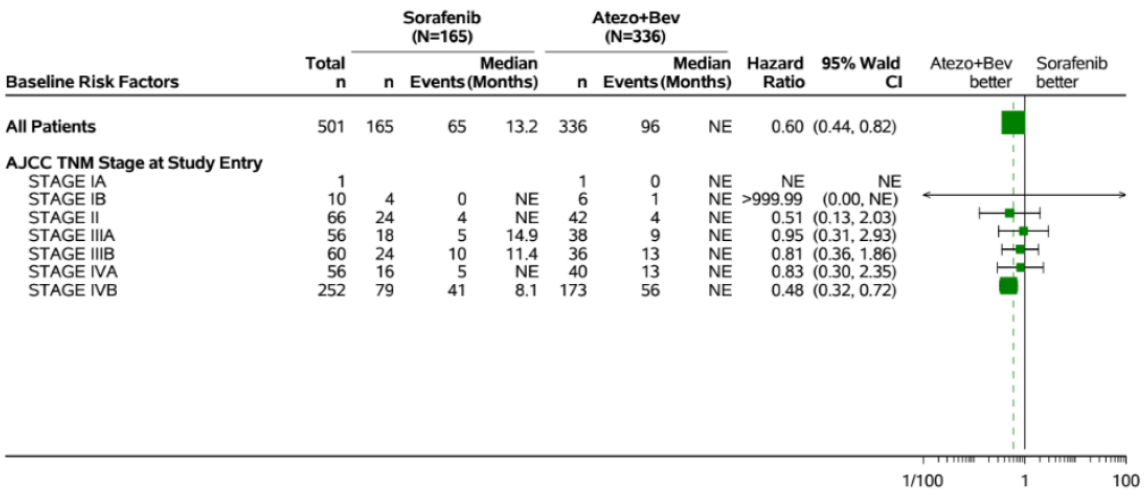
NE = Not estimable.
Medians were estimated from Kaplan-Meier method.
Hazard ratios relative to Sorafenib and the associated confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.

Figure 13: Subgroup Analyses of progression-free survival Based on IRF-Assessment per RECIST v1.1



Responders refer to all patients with <CR/PR>. A window of 28 days is used for the confirmation of CR/PR.
Odds ratios relative to Sorafenib and the associated Wald confidence intervals were estimated using unstratified logistic regression.
The vertical dashed line indicates the odds ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.

Figure 14: Subgroup Analyses of Confirmed ORR Based on IRF-Assessment per RECIST v1.1 - excerpt



NE = Not estimable.
Medians were estimated from Kaplan-Meier method.
Hazard ratios relative to Sorafenib and the associated confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.

Figure 15: Forest-plot – subgroup analysis of overall survival, ITT population (cut-off date: 29 August 2019)

Table 36: Overall Survival and Progression-Free Survival Based on IRF-Assessment per RECIST v1.1 in Child-Pugh Score A5 and A6 subgroups, Intent to Treat Population (IMbrave150)

	Child-Pugh A5		Child-Pugh A6		Overall Population	
	Sorafenib	Atezo + Bev	Sorafenib	Atezo + Bev	Sorafenib	Atezo + Bev
OS						
n	121	239	44	94	165	336
Events	39 (32.2%)	52 (21.8%)	26 (59.1%)	42 (44.7%)	65 (39.4%)	96 (28.6%)
Median (months)	13.9	NE	6.7	12.8	13.2	NE
HR (95% CI)	0.57 (0.38, 0.86)		0.57 (0.35, 0.92)		0.60 (0.44, 0.82)	
IRF-PFS per RECIST v1.1						
n	121	239	44	94	165	336
Events	75 (62.0%)	135 (56.5%)	34 (77.3%)	60 (63.8%)	109 (66.1%)	197 (58.6%)
Median (months)	4.8	7.1	2.8	5.7	4.3	6.8
HR (95% CI)	0.61 (0.46, 0.82)		0.52 (0.34, 0.80)		0.59 (0.47, 0.75)	

CI = confidence interval; HR = hazard ratio; IRF = Independent Review Facility; NE = Not Evaluable; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; OS = overall survival.
The results presented are from unstratified analyses.

Table 37: Overall Survival and Progression-Free Survival Based on IRF-Assessment per RECIST v1.1 in Subgroups by Age (<75 vs. ≥75), Intent to Treat Population (IMbrave150)

	< 75 Age Group		≥ 75 Age Group		Overall Population	
	Sorafenib	Atezo + Bev	Sorafenib	Atezo + Bev	Sorafenib	Atezo + Bev
OS						
n	137	281	28	55	165	336
Events	55 (40.1%)	82 (29.2%)	10 (35.7%)	14 (25.5%)	65 (39.4%)	96 (28.6%)
Median (months)	13.2	NE	NE	NE	13.2	NE
HR (95% CI)	0.61 (0.43, 0.86)		0.54 (0.24, 1.21)		0.60 (0.44, 0.82)	
IRF-PFS per RECIST v1.1						
n	137	281	28	55	165	336
Events	92 (67.2%)	168 (59.8%)	17 (60.7%)	29 (52.7%)	109 (66.1%)	197 (58.6%)
Median (months)	4.3	6.8	4.3	7.7	4.3	6.8
HR (95% CI)	0.59 (0.45, 0.76)		0.60 (0.33, 1.10)		0.59 (0.47, 0.75)	

Atezo = atezolizumab; Bev = bevacizumab; CI = confidence interval; HR = hazard ratio; IRF = Independent Review Facility; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; OS = overall survival;
The results presented are from unstratified analyses.

Table 38: Overview of efficacy (ITT population): Co-primary and key secondary efficacy endpoints in the China subpopulation and the global population

Endpoint	China Subpopulation		Global Population	
	Sorafenib N = 61	Atezo + Bev N = 133	Sorafenib N = 165	Atezo + Bev N = 336
Co-Primary Endpoints				
Overall Survival				
No. (%) of patients with events	25 (41.0%)	26 (19.5%)	65 (39.4%)	96 (28.6%)
Median, months	11.4	NE	13.2	NE
Stratified hazard ratio (95% CI) [a]	0.44 (0.25, 0.76)		0.58 (0.42, 0.79)	
IRF-Assessed Progression-Free Survival per RECIST v1.1				
No. (%) of patients with events	38 (62.3%)	75 (56.4%)	109 (66.1%)	197 (58.6%)
Median, months	3.2	5.7	4.3	6.8
Stratified hazard ratio (95% CI) [a]	0.60 (0.40, 0.90)		0.59 (0.47, 0.76)	
Key Secondary Endpoints				
IRF- Assessed Confirmed Objective Response Rate per RECIST v1.1				
No. of evaluable patients	60	130	159	326
ORR, N (%)	4 (6.7%)	32 (24.6%)	19 (11.9%)	89 (27.3%)
Difference in Confirmed ORR, % (95% CI)	17.9% (7.0, 28.9)		15.4% (7.9, 22.8)	
IRF- Assessed Confirmed Objective Response Rate per HCC mRECIST				
No. of evaluable patients	59	128	158	325
ORR, N (%)	5 (8.5%)	38 (29.7%)	21 (13.3%)	108 (33.2%)
Difference in Confirmed ORR, % (95% CI)	21.2% (9.3, 33.1)		19.9% (12.1, 27.8)	

Atezo = atezolizumab; Bev = bevacizumab; CI = confidence interval; HCC = hepatocellular carcinoma; IRF = Independent Research Facility; mRECIST = modified RECIST; NE = not estimable; No. = number; ORR = objective response rate; RECIST = Response Evaluation Criteria in Solid Tumors

[a] Stratification factors include geographic region (Asia excluding Japan vs. Rest of World – Global population only), macrovascular invasion and/or extrahepatic spread (presence vs. absence) and AFP (<400 vs. ≥400 ng/mL) at screening per IxRS

Sources: t_ef_tte01_IT_OS, t_ef_tte01_IT_PFSDF, t_ef_rsp01_IT_MDF_CBORDF, t_ef_rsp01_IT_HMDF_hcbordf (China Topline Report)

Clinical outcomes by PD-L1 expression status

Table 39: Overall Survival, IRF-Progression-Free Survival per RECIST v1.1, and IRF-assessed Best Confirmed Overall Response per RECIST v1.1 in Subgroups by PD-L1 Category 1 (TC or IC ≥ 1% vs. TC and IC < 1%), Intent to Treat Population (IMbrave150)

	TC or IC ≥ 1%		TC and IC < 1%		Overall Population	
	Sorafenib	Atezo + Bev	Sorafenib	Atezo + Bev	Sorafenib	Atezo + Bev
OS						
n	36	86	28	49	165	336
Events	16	24	11	13	65	96
Median (months)	9.1	NE	13.2	NE	13.2	NE
HR (95% CI)[a]	0.48 (0.25, 0.90)		0.70 (0.31, 1.58)		0.60 (0.44, 0.82)	
IRF-PFS per RECIST v1.1						
n	36	86	28	49	165	336
Events	21	48	20	31	109	197
Median (months)	4.4	7.0	7.0	6.7	4.3	6.8
HR (95% CI)[a]	0.67 (0.40, 1.13)		0.89 (0.50, 1.58)		0.59 (0.47, 0.75)	
IRF-ORR per RECIST v1.1						
n	35	85	27	49	159	326
Responders (n)	6	29	4	11	19	89
Response (%)	17.1	34.1	14.8	22.4	11.9	27.3
OR (95% CI)[b]	2.50 (0.93, 6.71)		1.66 (0.47, 5.84)		2.77 (1.62, 4.74)	

HR = hazard ratio; IRF = Independent Review Facility; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; OR = odds ratio; ORR = objective response rate; OS = overall survival; PD-L1 = Programmed death-ligand 1.

[a] = Hazard ratios relative to Sorafenib and the associated confidence intervals were estimated using unstratified Cox regression.

[b] = Odds ratios relative to Sorafenib with their associated Wald confidence intervals

See also "Supportive studies" for clinical outcomes by PD-L1 expression status in Phase Ib Study GO30140.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial **YO40245 (IMbrave150)**

Title: Phase III, open-label, randomized study of atezolizumab in combination with bevacizumab compared with sorafenib in patients with untreated locally advanced or metastatic hepatocellular carcinoma.			
Study identifier	YO40245 (IMbrave150); EudraCT: 2017-003691-31		
Design	Phase III, open-label, multicenter, global, randomized, two-arm study designed to evaluate the efficacy and safety of atezolizumab + bevacizumab versus sorafenib in patients with locally advanced or metastatic hepatocellular carcinoma who had not received prior systemic treatment.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	15 March 2018 (FPI) to 29 August 2019 (CCOD) not applicable not applicable	
Hypothesis	Superiority		
Treatments groups	Atezolizumab and Bevacizumab (Atezo + Bev)		Atezolizumab: Intravenous (IV), 1200 mg on Day 1 of each 21-day cycle (every three weeks) until investigator-assessed unacceptable toxicity or loss of clinical benefit. Bevacizumab: Intravenous (IV), 15 mg/kg on Day 1 of each 21-day cycle. N = 336 randomised patients.
	Sorafenib		400 mg (2x200 mg tablets), PO, BID, starting on Day 1 of Cycle 1. N = 165 randomised patients.
Endpoints and definitions	Co-Primary endpoints	OS, PFS by IRF per RECIST 1.1	-Overall Survival, defined as time from randomization to death due to any cause. -PFS, defined as time from randomization to the first documented disease progression as determined by an IRF according to RECIST Version 1.1, or death from any cause (whichever occurred first).
	Key Secondary endpoints	ORR by IRF, DOR by IRF	-Objective response, defined as a complete or partial response, by IRF per RECIST v1.1 and HCC mRECIST. -Duration of response, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), by IRF per RECIST v1.1 and HCC mRECIST.
Database lock	Clinical cut-off date: 29 August 2019		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to Treat (ITT) Population CCOD of 29 August 2019		
Descriptive statistics and estimate variability	Treatment group	Sorafenib	Atezo + Bev
	Number of subject	165	336
	OS (median (months))	13.2	NE
	95% CI	10.4; NE	NE
	PFS by IRF per RECIST v1.1 (median (months))	4.3	6.8
	95% CI	4.0; 5.6	5.7; 8.3
	ORR by IRF per RECIST v1.1 (n, (%))	No. of evaluable patients: 159 19 (11.9%)	No. of evaluable patients: 326 89 (27.3%)

	95% CI	7.4; 18.0	22.5; 32.5
	ORR by IRF per HCC mRECIST (n, (%))	No. of evaluable patients: 158 21 (13.3%)	No. of evaluable patients: 325 108 (33.2%)
	95% CI	8.4; 19.6	28.1; 38.6
	DOR by IRF per RECIST v1.1 (median (months))	No. of evaluable patients: 19 6.3	No. of evaluable patients: 89 NE
	95% CI	4.7; NE	
	DOR by IRF per HCC mRECIST (median (months))	No. of evaluable patients: 21 6.3	No. of evaluable patients: 108 NE
	95% CI	4.9; NE	
Effect estimate per comparison	OS	Comparison groups	Atezo + Bev vs. Sorafenib
		HR	0.58
		95% CI	0.42; 0.79
		P-value	0.0006
	PFS by IRF per RECIST v1.1 (median (months))	Comparison groups	Atezo + Bev vs. Sorafenib
		HR	0.59
		95% CI	0.47; 0.76
		P-value	<0.0001

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

- **Immunogenicity of bevacizumab**

Study GO30140

The treatment-emergent ADA incidence rate for bevacizumab in study GO30140 was low, ranging between **2.1%-3.8%** for the two atezolizumab plus bevacizumab arms. This is in line with ADA incidence rates for bevacizumab that have been reported in other clinical studies across indications.

Study IMbrave150

No sampling for bevacizumab ADAs was conducted in study IMbrave150 due to the low post-treatment incidence of bevacizumab ADAs observed across earlier studies in combination with atezolizumab.

- **Immunogenicity of atezolizumab**

The treatment-emergent atezolizumab ADA incidence rate was **27.9%** in IMbrave150 and ranged from 23.8% to 37.9% across all HCC studies (studies GO30140, PCD4989g, and YO29233). The median time to onset of ADA in IMbrave150 was 3.14 weeks.

Table 40: Baseline Prevalence and Post-Baseline Incidence of ADAs to Atezolizumab in Studies IMbrave150, GO30140 and Both Studies combined

	IMbrave150	GO30140			Both Studies
	Atezo+Bev Treated Patients (N=329)	Arm A Atezo+Bev (N=104)	Arm F1 Atezo+Bev (N=60)	Arm F2 Atezo Monotherapy (N=58)	Combined Atezo+Bev (N=493)
Baseline evaluable patients	311	104	58	58	473
No. of patients positive for ADA	7 (2.3%)	0	2 (3.4%)	2 (3.4%)	9 (1.90%)
No. of patients negative for ADA	304	104	56	56	464
Post−baseline evaluable patients	315	101	58	57	474
No. of patients positive for ADA	88 (27.9%)	24 (23.8%)	22 (37.9%)	17 (29.8%)	134 (28.3%)
Treatment-induced ADA [a]	88	24	21	17	133
Treatment-enhanced ADA [b]	0	0	1	0	1
No. of patients negative for ADA	227	77	36	40	340
Treatment-unaffected ADA [c]	7	0	1	2	8

ADA=anti-drug antibodies, can also be referred to as ATA or anti−therapeutic antibodies

Note: See Shankar et al. 2014 for further details on the definition of treatment-induced and treatment-enhanced ADA.

[a] Treatment-induced ADAs=Patients who had a baseline-negative ADA result or were missing data who developed anti-drug antibodies at any time after initial drug administration.

[b] Treatment-enhanced ADA=Patients who had a baseline-positive ADA result in whom the assay result was enhanced (greater than baseline titer by ≥0.60 titer units) at any time after initial drug administration.

[c] Treatment-unaffected ADAs=Patients who had a baseline-positive ADA result in whom the assay result was not enhanced (not greater than baseline titer by ≥0.60 titer units) at any time after initial drug administration. These patients are considered post-baseline negative for ADAs.

Demographic and baseline characteristics by atezolizumab ADA status in IMbrave150

Differences in baseline factors (≥ 5% absolute difference in categorical variables or ≥10% relative difference in continuous variables) were observed between ADA-positive and -negative subgroups (data not shown).

Subgroup Analyses of Efficacy Endpoints by Atezolizumab ADA Status in IMbrave150

Table 41: IMbrave150: Overview of Efficacy by Treatment-Emergent ADA Status without Landmark

	Atezo+Bev	
Parameter	ADA-Negative N=227	ADA-Positive N=88
Co-Primary Endpoints		
Overall Survival		
No. (%) of patients with event	47 (20.7%)	36 (40.9%)
Median, months	NE	12.78
95% CI	NE	(10.15, NE)
Progression-Free Survival (IRF per RECIST v1.1)		
No. (%) of patients with event	123 (54.2%)	60 (68.2%)
Median, months	7.16	5.59
95% CI	(6.74, 9.66)	(4.34, 8.57)
Secondary Endpoints		
Objective Response Rate (IRF per RECIST v1.1)		
No. of evaluable patients	217	88
Confirmed ORR, N (%)	64 (29.5%)	24 (27.3%)
95% CI	(23.51%, 36.04%)	(18.32%, 37.81%)

ADA=anti-drug antibody; Atezo+Bev=atezolizumab+bevacizumab; CI=confidence interval; CSR=Clinical Study Report; IRF=Independent Review Facility; NE=not estimable; ORR=objective response rate; RECIST=Response Evaluation Criteria in Solid Tumors.

Data cutoff: 29 August 2019.

Efficacy by landmark ADA status in IMbrave150

A separate immunogenicity report for study IMbrave150 was provided, where additional analyses were presented to account for imbalances in baseline demographics and prognostic factors between ADA subgroups that could confound the estimation of treatment effect compared with control (data not shown).

Supportive studies

Phase Ib Study GO30140

Study GO30140 is an ongoing open-label, multi-center, global Phase Ib study with non-randomized and randomized arms evaluating the safety, efficacy, and pharmacokinetics of atezolizumab when administered with bevacizumab and/or other treatments in patients with different solid tumours.

Arm A of Study GO30140 was a non-randomized single-arm cohort designed to evaluate the efficacy and safety of Atezo + Bev in patients with advanced or metastatic and/or unresectable HCC who had not received prior systemic therapy (n=104). The primary efficacy endpoint of Arm A was confirmed ORR by IRF per RECIST v1.1. No statistical testing was applied in Arm A of GO30140.

Arm F of Study GO30140 randomized 119 patients open-label in a 1:1 ratio to the combination treatment of Atezo + Bev (Arm F1) or atezolizumab monotherapy (Arm F2) to characterize the single agent contribution to the combination treatment effect in advanced or metastatic and/or unresectable HCC patients without prior systemic therapy. The primary efficacy endpoint of Arm F was PFS by IRF per RECIST v1.1. Arm F was statistically-powered at a two-sided significance level of 0.2 for the primary efficacy endpoint.

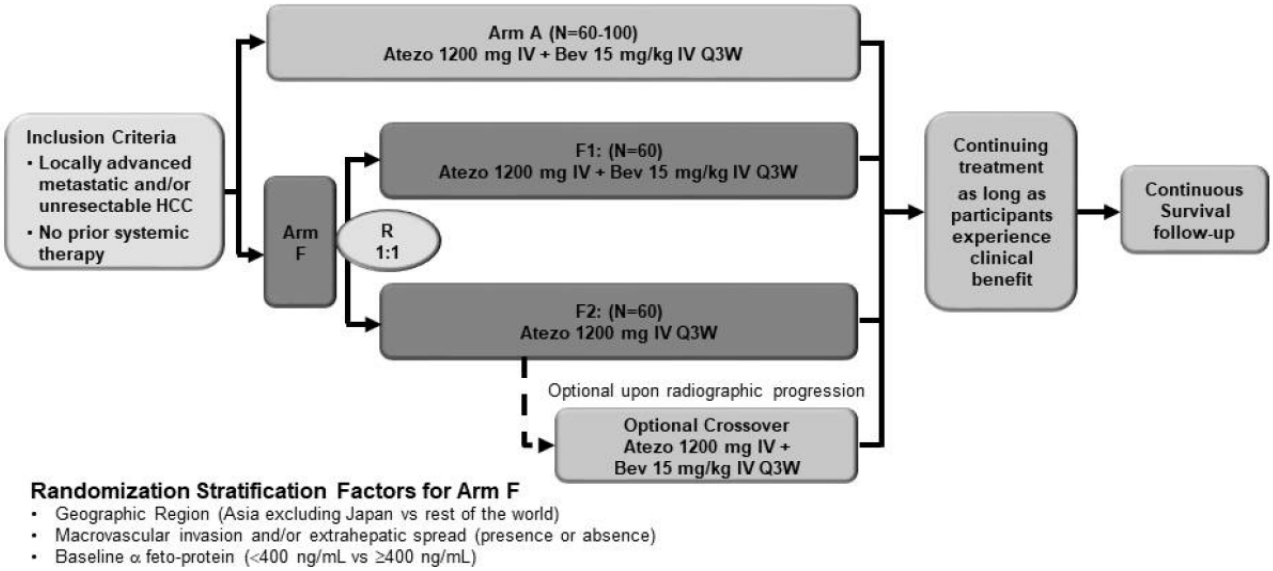


Figure 16: Overview of Study Design for GO30140

Eligibility criteria

Patients with locally advanced or metastatic and/or unresectable HCC who had received no prior systemic therapy were included. At baseline, patients had documented virology status of hepatitis, at least one measurable untreated lesion (per RECIST v1.1), ECOG PS score of 0 or 1, and adequate hematologic and end-organ function. Both studies excluded patients who had co-infection of hepatitis B virus (HBV) and hepatitis C virus (HCV), or with untreated or incompletely treated oesophageal and/or gastric varices with bleeding or high-risk for bleeding. Patients with vascular invasion of the portal or hepatic veins were eligible for both studies. In Arm F of GO30140, patients with Child-Pugh A were

eligible; Arm A allowed enrolment of patients with Child-Pugh score up to B7. Eligibility criteria regarding life expectancy were only included in GO30140 Arm F, with patients being eligible for the study only if their life expectancy status was determined by the Investigator as ≥ 3 months.

Schedule of Tumour Assessments

In study GO30140 tumour assessments were done at baseline, then every 8 (± 1) weeks for the first 12 months, and every 12 (± 3) weeks thereafter (as opposed to IMbrave150 with more frequent assessments every 6 (± 1) weeks for the first 54 weeks and 9 (± 1) weeks thereafter).

Patient disposition

Table 42: Discontinuation from Study (Enrolled Patients) – study GO30140

	Arm A Atezo + Bev (N=104)	Arm F1 Atezo + Bev (N=60)	Arm F2 Atezo (N=59)	Arm F2-Crossover Atezo + Bev (N=26)
Received Treatment	104 (100.0%)	60 (100.0%)	58 (98.3%)	26 (100.0%)
Still On-study	55 (52.9%)	43 (71.7%)	39 (66.1%)	18 (69.2%)
On Treatment	26 (25.0%)	25 (41.7%)	29 (49.2%)	15 (57.7%)
In Survival Follow-up	29 (27.9%)	18 (30.0%)	10 (16.9%)	3 (11.5%)
Discontinued Study	49 (47.1%)	17 (28.3%)	20 (33.9%)	8 (30.8%)
Death	47 (45.2%)	16 (26.7%)	18 (30.5%)	8 (30.8%)
Withdrawal By Subject	2 (1.9%)	1 (1.7%)	2 (3.4%)	0

For combination treatments, "On Treatment" refers to patients on any component of the combination treatment. Note that for every row, except the 'On Treatment' row, the number of patients in the F2 crossover arm are included in the respective Arm F2 column. The row of "On Treatment" for Arm F2 column includes 15 patients on the crossover treatment of Atezo + Bev in addition to 14 patients still on Atezo monotherapy.
Data Extraction Date: 31JUL2019; Data Cut Date: 14JUN2019

Table 43: Reasons for Discontinuation from Study Treatment (Safety Evaluable Patients) – study GO30140

	Arm A Atezo + Bev (N=104)		Arm F1 Atezo + Bev (N=60)		Arm F2 Atezo (N=58)	Arm F2-Crossover Atezo + Bev (N=26)	
	Atezolizumab	Bevacizumab	Atezolizumab	Bevacizumab	Atezolizumab	Atezolizumab	Bevacizumab
Received at least one dose of study treatment							
Yes	104 (100.0%)	104 (100.0%)	60 (100.0%)	60 (100.0%)	58 (100.0%)	26 (100.0%)	26 (100.0%)
Treatment Status							
Ongoing	26 (25.0%)	24 (23.1%)	25 (41.7%)	25 (41.7%)	14 (24.1%)	15 (57.7%)	15 (57.7%)
Withdrawn from treatment	78 (75.0%)	80 (76.9%)	35 (58.3%)	35 (58.3%)	44 (75.9%)	11 (42.3%)	11 (42.3%)
Reason for Treatment Discontinuation							
DEATH	3 (2.9%)	3 (2.9%)	0	0	0	0	0
ADVERSE EVENT	12 (11.5%)	18 (17.3%)	3 (5.0%)	5 (8.3%)	1 (1.7%)	1 (3.8%)	1 (3.8%)
SYMPTOMATIC DETERIORATION	5 (4.8%)	4 (3.8%)	3 (5.0%)	4 (6.7%)	0	0	0
PROGRESSIVE DISEASE	52 (50.0%)	50 (48.1%)	26 (43.3%)	23 (38.3%)	40 (69.0%)	9 (34.6%)	9 (34.6%)
PHYSICIAN DECISION	0	0	2 (3.3%)	2 (3.3%)	0	0	0
WITHDRAWAL BY SUBJECT	5 (4.8%)	4 (3.8%)	1 (1.7%)	1 (1.7%)	3 (5.2%)	1 (3.8%)	1 (3.8%)
OTHER	1 (1.0%)	1 (1.0%)	0	0	0	0	0

Data Extraction Date: 31JUL2019; Data Cut Date: 14JUN2019

Baseline data

Table 44: Summary of Key Demographic Characteristics for IMbrave150 and GO30140

	IMbrave150		GO30140		
	Sorafenib (N=165)	**Atezo+Bev (N=336)**	**Arm A (Atezo+Bev) (N=104)**	**Arm F (Atezo+Bev) (N=60)**	**Arm F Atezo Mono (N=59)**
Age≥65 (years), n (%)	91 (55.2%)	161 (47.9%)	37 (35.6%)	21 (35.0%)	25 (42.4%)
Median	66	64	62.0	59.5	63.0
Sex: Males, n (%)	137 (83.0%)	277 (82.4%)	84 (80.8%)	54 (90.0%)	49 (83.1%)
Race, n (%)					
White	52 (31.5%)	123 (36.6%)	20 (19.2%)	14 (23.3%)	9 (15.3%)
Asian	96 (58.2%)	188 (56.0%)	75 (72.1%)	45 (75.0%)	47 (79.7%)
ECOG PS 1, n (%)	62 (37.6%)	127 (37.8%)	52 (50.0%)	33 (55.0%)	34 (57.6%)
Region, n (%)					
Asia (excluding Japan)	68 (41.2%)	133 (39.6%)	59 (56.7%)	39 (65.0%)	39 (66.1%)
RoW	97 (58.8%)	203 (60.4%)	45 (43.3%)	21 (35.0%)	20 (33.9%)
PD-L1 (SP263), n (%) ‡	N=58	N=124	N=86	N=43	N=52
TC<1% and IC<1%	25 (43.1%)	45 (36.3%)	25 (29.1%)	15 (34.9%)	18 (34.6%)
TC≥1% or IC≥1%	33 (56.9%)	79 (63.7%)	61 (70.9%)	28 (65.1%)	34 (65.4%)
TC≥5% or IC≥5%	17 (29.3%)	46 (37.1%)	37 (43.0%)	8 (18.6%)	16 (30.8%)
TC≥10% or IC≥10%	5 (8.6%)	12 (9.7%)	30 (34.9%)	5 (11.6%)	6 (11.5%)

ECOG=Eastern Cooperative Oncology Group; IC=tumor-infiltrating immune cell; RoW=Rest of the World; PD-L1=programmed death-ligand 1, TC=tumor cells

‡ Pre-treatment tissue sample collection was optional in IMbrave150

Table 45: Summary of Key Baseline Disease Characteristics for IMbrave150 and GO30140

	IMbrave150		GO30140		
			Arm A	Arm F1	Arm F2
	Sorafenib (N=165)	Atezo+Bev (N=336)	Atezo+Bev (N=104)	Atezo+Bev (N=60)	Atezo Mono (N=59)
HCC Etiology, n (%)					
HBV-positive	76 (46.1%)	164 (48.8%)	51 (49.0%)	34 (56.7%)	32 (54.2%)
HCV-positive	36 (21.8%)	72 (21.4%)	31 (29.8%)	11 (18.3%)	10 (16.9%)
Non-viral *	53 (32.1%)	100 (29.8%)	22 (21.2%)	15 (25.0%)	17 (28.8%)
Child-Pugh Class, n (%)					
A5	121 (73.3%)	239 (71.6%)	77 (74.0%)	43 (71.7%)	42 (71.2%)
A6	44 (26.7%)	94 (28.1%)	21 (20.2%)	17 (28.3%)	17 (28.8%)
B7	0	1 (0.3%)	6 (5.8%)	0	0
Time from initial Diagnosis					
Median (months)	5.84	6.37	7.43	10.17	8.79
BCLC Stage at Study Entry, n (%)					
Stage A1	3 (1.8%)	5 (1.5%)	NA	NA	NA
Stage A4	3 (1.8%)	3 (0.9%)	0	0	2 (3.4%)
Stage B	26 (15.8%)	52 (15.5%)	10 (9.6%)	6 (10.0%)	4 (6.8%)
Stage C	133 (80.6%)	276 (82.1%)	94 (90.4%)	54 (90.0%)	53 (89.8%)
MVI, EHS at study Entry, n (%)					
MVI Present	71 (43.0%)	129 (38.4%)	55 (52.9%)	20 (33.3%)	25 (42.4%)
EHS Present	93 (56.4%)	212 (63.1%)	74 (71.2%)	40 (66.7%)	39 (66.1%)
EHS and/or MVI Present	120 (72.7%)	258 (76.8%)	91 (87.5%)	47 (78.3%)	50 (84.7%)
AFP at Baseline ≥400, n (%) ^	61 (37.0%)	126 (37.5%)	37 (35.6%)	18 (30.0%)	19 (32.2%)
Prior Cancer Radiotherapy, n (%)					
Yes	17 (10.3%)	34 (10.1%)	20 (19.2%)	21 (35.0%)	15 (25.4%)
Prior HCC Local Therapy, n (%)					
TACE	70 (42.4%)	130 (38.7%)	56 (53.8%)	32 (53.3%)	28 (47.5%)
RFA	24 (14.5%)	47 (14.0%)	21 (20.2%)	10 (16.7%)	7 (11.9%)

AFP=Alpha Fetoprotein; BCLC=Barcelona Clinic Liver Cancer; EHS=extrahepatic Spread; HBV=hepatitis B virus; HCC=hepatocellular carcinoma; HCV=hepatitis C virus; MVI=macrovascular invasion; NA=not applicable; RFA=radiofrequency ablation; TACE=transarterial chemoembolization;

* Non-viral HCC etiology includes alcohol, non-Alcoholic Related Liver Damage, and unknown cause.

^ Data obtained from eCRF instead of IxRS

Source: IMbrave150 and GO30140 CSRs.

Outcomes and estimation

The timing (clinical cutoff date of 14 June 2019) for the analyses presented was driven by the event requirements for the primary PFS analysis in Arm F of GO30140, which were met with 74 PFS events observed across both treatment arms. The primary analysis of Arm A was conducted at the same time as the primary analysis of Arm F.

The primary analysis for Arm A was performed approximately 10.5 months after the last patient was enrolled in Arm A. The median duration of survival follow-up was 12.4 months (range 0.7-34.3) in Arm A.

The primary analysis for Arm F was performed approximately 3 months after the last patient was randomized into Arm F. The median duration of survival follow-up was 6.6 months (range 1.0-11.9) in Arm F1 and 6.7 months (range 0.5-11.4) in Arm F2.

- Efficacy in Arm A

Table 46: Overview of the Primary Efficacy and Selected Secondary Efficacy Endpoints in Arm A

Key Efficacy Endpoints	Arm A (Atezo + Bev) (N = 104)		
	IRF-assessed per RECIST v1.1	IRF-assessed per HCC mRECIST	Investigator-assessed per RECIST v1.1
Objective Response Rate [a b]	37 (35.6%)	41 (39.4%)	34 (32.7%)
95% CI	(26.4, 45.6)	(30.0, 49.5)	(23.8, 42.6)
Complete Response (CR)	12 (11.5%)	16 (15.4%)	3 (2.9%)
95% CI	(6.11, 19.29)	(9.06, 23.78)	(0.60, 8.20)
Partial Response (PR)	25 (24.0%)	25 (24.0%)	31 (29.8%)
95% CI	(16.20, 33.41)	(16.20, 33.41)	(21.23, 39.57)
Duration of Response [b]			
Number of responders	n = 37	n = 41	n = 34
Ongoing response, n (%)	28 (75.7%)	28 (68.3%)	24 (70.6%)
Median (months), (95% CI)	NE (11.8, NE)	NE (11.8, NE)	NE (11.7, NE)
(Range)	(1.6* - 31.0*)	(1.6* - 31.0*)	(3.5 - 31.0*)
Progression-Free Survival			
Number of events (%)	69 (66.3%)	69 (66.3%)	75 (72.1%)
Median, months (95% CI)	7.3 (5.4 – 9.9)	7.3 (5.4 – 9.9)	7.4 (5.6 – 10.7)
6-month PFS Rate (%)	54%	55%	56%
12-month PFS Rate (%)	35%	35%	38%
Overall Survival			
Number of deaths (%)		47 (45.2%)	
Median, months (95% CI)		17.1 (13.8, NE)	
6-month OS Rate (%)		82%	
12-month OS Rate (%)		63%	

CI = confidence interval; HCC = hepatocellular carcinoma; IRF = independent review facility; mRECIST = modified RECIST; NE = not estimable, OS=overall survival; PFS=progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors.

* censored.

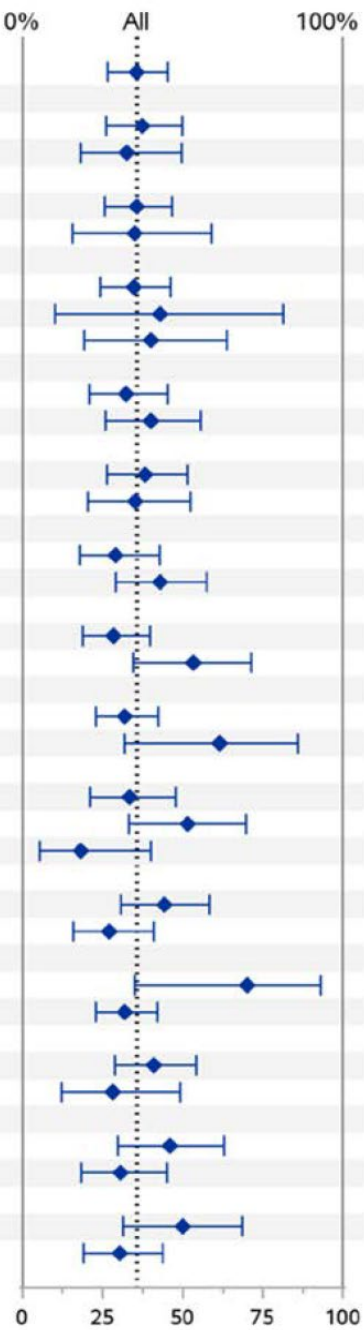
[a] Primary efficacy endpoint; ORR per IRF-assessed RECIST v1.1.

[b] Only confirmed responders were included in the analysis.

Clinical cutoff date of 14 June 2019.

Subgroup Analyses

Name / Level	Patients n (%)	Response n	ORR (95% CI)
All	104 (100.0)	37	35.6 (26.4-45.6)
Age Group			
< 65	67 (64.4)	25	37.3 (25.8-50.0)
>= 65	37 (35.6)	12	32.4 (18.0-49.8)
Sex			
Male	84 (80.8)	30	35.7 (25.6-46.9)
Female	20 (19.2)	7	35.0 (15.4-59.2)
Race			
Asian	75 (72.1)	26	34.7 (24.0-46.5)
Black or African American	7 (6.7)	3	42.9 (9.9-81.6)
White	20 (19.2)	8	40.0 (19.1-63.9)
Geographic Region			
Asia Excluding Japan	59 (56.7)	19	32.2 (20.6-45.6)
ROW	45 (43.3)	18	40.0 (25.7-55.7)
AFP Categories (ng/mL)			
<400	60 (57.7)	23	38.3 (26.1-51.8)
>=400	37 (35.6)	13	35.1 (20.2-52.5)
Macro-Vascular Invasion (MVI) Present			
Yes	55 (52.9)	16	29.1 (17.6-42.9)
No	49 (47.1)	21	42.9 (28.8-57.8)
Extrahepatic Spread (EHS)			
Yes	74 (71.2)	21	28.4 (18.5-40.1)
No	30 (28.8)	16	53.3 (34.3-71.7)
MVI and/or EHS present			
Yes	91 (87.5)	29	31.9 (22.5-42.5)
No	13 (12.5)	8	61.5 (31.6-86.1)
HCC Etiology			
Hepatitis B	51 (49.0)	17	33.3 (20.8-47.9)
Hepatitis C	31 (29.8)	16	51.6 (33.1-69.8)
Non-viral	22 (21.2)	4	18.2 (5.2-40.3)
ECOG Performance Score			
0	52 (50.0)	23	44.2 (30.5-58.7)
1	52 (50.0)	14	26.9 (15.6-41.0)
BCLC Staging at Study Entry			
Stage B	10 (9.6)	7	70.0 (34.8-93.3)
Stage C	94 (90.4)	30	31.9 (22.7-42.3)
PD-L1 (IHC SP263) Status (1% cut-off)			
TC or IC >= 1%	61 (58.7)	25	41.0 (28.6-54.3)
TC and IC < 1%	25 (24.0)	7	28.0 (12.1-49.4)
PD-L1 (IHC SP263) Status (5% cut-off)			
TC or IC >= 5%	37 (35.6)	17	45.9 (29.5-63.1)
TC and IC < 5%	49 (47.1)	15	30.6 (18.3-45.4)
PD-L1 (IHC SP263) Status (10% cut-off)			
TC or IC >= 10%	30 (28.8)	15	50.0 (31.3-68.7)
TC and IC < 10%	56 (53.8)	17	30.4 (18.8-44.1)



ROW: Rest of the world refers to the USA, Australia, New Zealand and Japan. Non-viral HCC etiology includes unknown non-hepatitis B and C cause. Responses refer to either a (confirmed) CR or PR per RECIST v1.1. 95% CI for rates were constructed using Clopper Pearson method.
Data Extraction Date: 31JUL2019; Data Cut Date: 14JUN2019

Figure 17: Subgroup Analyses of Confirmed OR Based on IRF-Assessment per RECIST v1.1 in Arm A

- Updated OS results are based on an updated data cut (CCOD 15 October 2019) which provides approximately 4 months of additional follow-up for patients as compared to the primary analysis. At the updated CCOD, 54 (51.9%) of the 104 efficacy evaluable patients in Arm A had died.

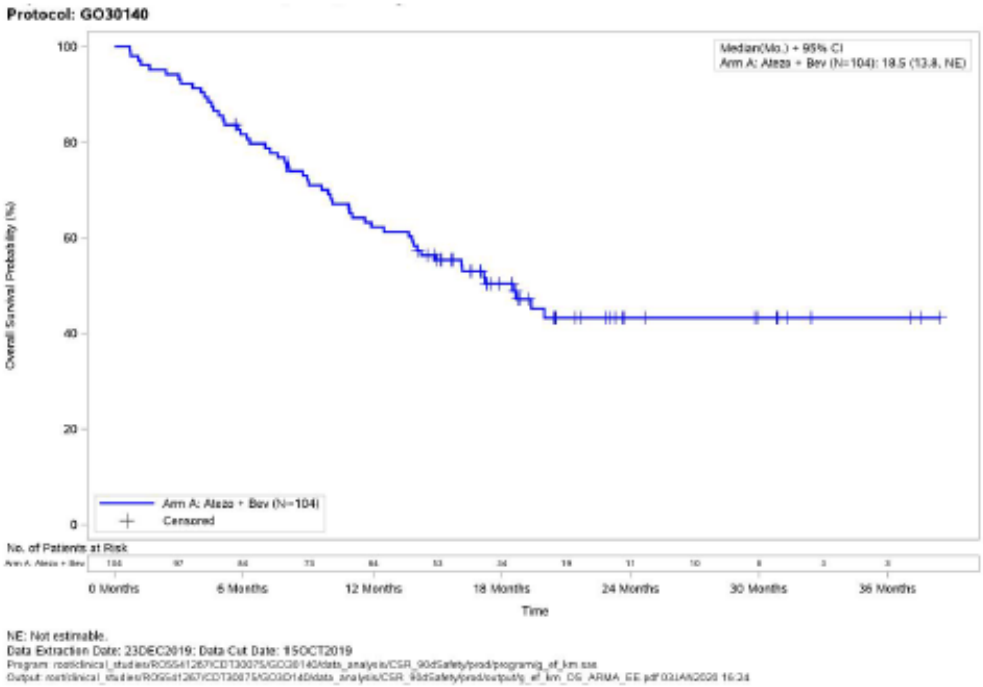


Figure 18: Kaplan-Meier plot of OS, Arm A, efficacy evaluable patients (updated data, CCOD 15 October 2019)

Table 47: Summary of overall Survival in Arm A, Efficacy Evaluable Patients

	Primary Analysis CCOD (14 June 2019) (reported in GO30140 CSR) Arm A Atezo + Bev (N = 104)	Updated CCOD (15 October 2019) Arm A Atezo + Bev (N = 104)
Patients with event (%)	47 (45.2%)	54 (51.9%)
Time to event (months)		
Median	17.1	18.5
95% CI for the median	(13.8, NE)	(13.8, NE)
Time point analysis		
6months		
Patients remaining at risk	84	84
Event free probability	0.82	0.82
95% CI	(0.74, 0.89)	(0.74, 0.89)
1 year		
Patients remaining at risk	54	64
Event free probability	0.63	0.62
95% CI	(0.53, 0.72)	(0.53, 0.72)

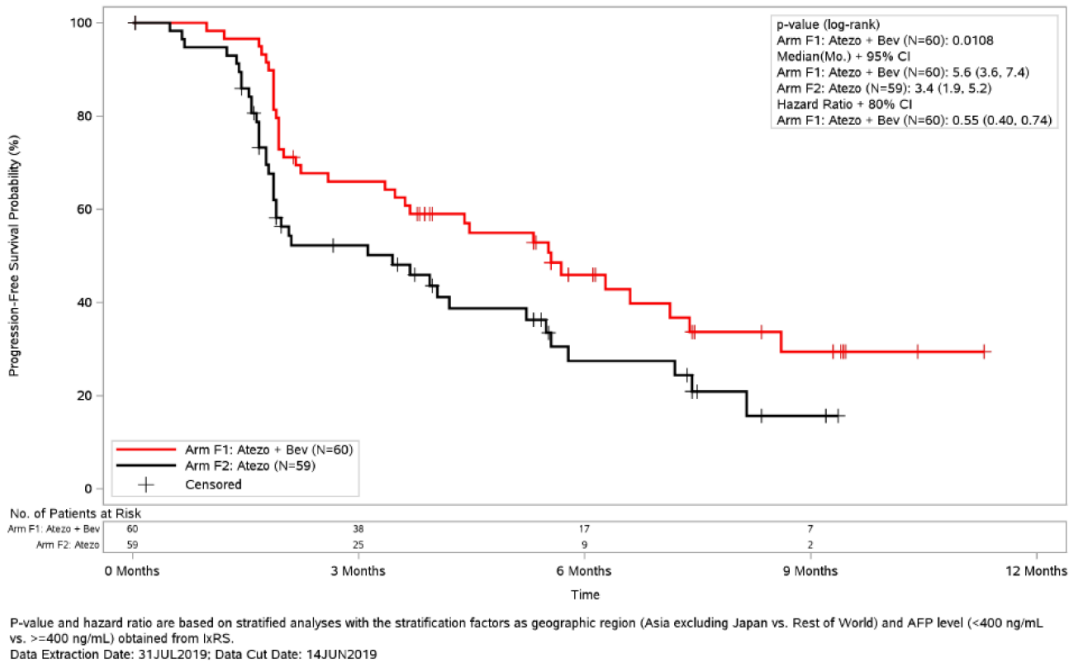
Atezo = atezolizumab; Bev = bevacizumab; CCOD = clinical cutoff date; CI = confidence interval; NE = not estimable.

- Efficacy in Arm F

Table 48: Overview of the Primary Efficacy and Selected Secondary Efficacy Endpoints in Arm F

	IRF-assessed per RECIST v1.1		IRF-assessed per HCC mRECIST		Investigator-assessed per RECIST v1.1	
Key Efficacy Endpoints	**Atezo + Bev (N=60)**	**Atezo (N=59)**	**Atezo + Bev (N=60)**	**Atezo (N=59)**	**Atezo + Bev (N=60)**	**Atezo (N=59)**
Progression-Free Survival [a]						
Number of events (%)	35 (58.3%)	39 (66.1%)	34 (56.7%)	39 (66.1%)	35 (58.3%)	44 (74.6%)
Median, months (95% CI)	5.6 (3.6 – 7.4)	3.4 (1.9 – 5.2)	5.6 (3.6 – 7.4)	3.4 (1.9 – 5.2)	5.7 (3.5 – 9.3)	2.0 (1.9 – 3.7)
Stratified HR* (80% CI)	0.55 (0.40, 0.74)		0.54 (0.40, 0.74)		0.44 (0.33, 0.60)	
Log-rank p-value*	0.0108		-		-	
Objective Response Rate [b]	12 (20.0%)	10 (16.9%)	16 (26.7%)	10 (16.9%)	8 (13.3%)	5 (8.5%)
95% CI for Response Rates	(10.8, 32.3)	(8.4, 29.0)	(16.1, 39.7)	(8.4, 29.0)	(5.9, 24.6)	(2.8, 18.7)
CR	1 (1.7%)	3 (5.1%)	3 (5.0%)	3 (5.1%)	0	0
PR	11 (18.3)	7 (11.9%)	13 (21.7%)	7 (11.9%)	8 (13.3%)	5 (8.5%)
Difference in ORR (80% CI)	3.1% (-7.7, 13.8)		9.7% (-1.6, 21.0)		4.9% (-4.1, 13.8)	
SD	28 (46.7%)	19 (32.2%)	25 (41.7%)	19 (32.2%)	33 (55.0%)	20 (33.9%)
Non-CR/Non-PD	0	1 (1.7%)	0	1 (1.7%)	0	0
PD	17 (28.3%)	25 (42.4%)	16 (26.7%)	25 (42.4%)	17 (28.3%)	31 (52.5%)
Missing/Unevaluable	3 (5.0%)	4 (6.8%)	3 (5.0%)	4 (6.8%)	2 (3.3%)	3 (5.1%)
Disease Control Rate	40 (66.7%)	29 (49.2%)	41 (68.3%)	29 (49.2%)	41 (68.3%)	25 (42.4%)

CI = confidence interval; CR = complete response; HCC = hepatocellular carcinoma; IRF = independent review facility; mRECIST=modified RECIST; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.
* Stratification factors included in the analysis were geographic region (Asia excluding Japan vs. Rest of World) and AFP level (<400 ng/mL vs. ≥400 ng/mL at baseline obtained from IxRS.
[a] Primary efficacy endpoint; PFS per IRF-assessed RECIST v1.1.
[b] Only confirmed responders were included in analysis.
Clinical cutoff date of 14 June 2019.



P-value and hazard ratio are based on stratified analyses with the stratification factors as geographic region (Asia excluding Japan vs. Rest of World) and AFP level (<400 ng/mL vs. >=400 ng/mL) obtained from IxRS.
Data Extraction Date: 31JUL2019; Data Cut Date: 14JUN2019

Figure 19: KM plot of IRF-Assessed PFS per RECIST v1.1 in GO30140 (Arm F, ITT Population)

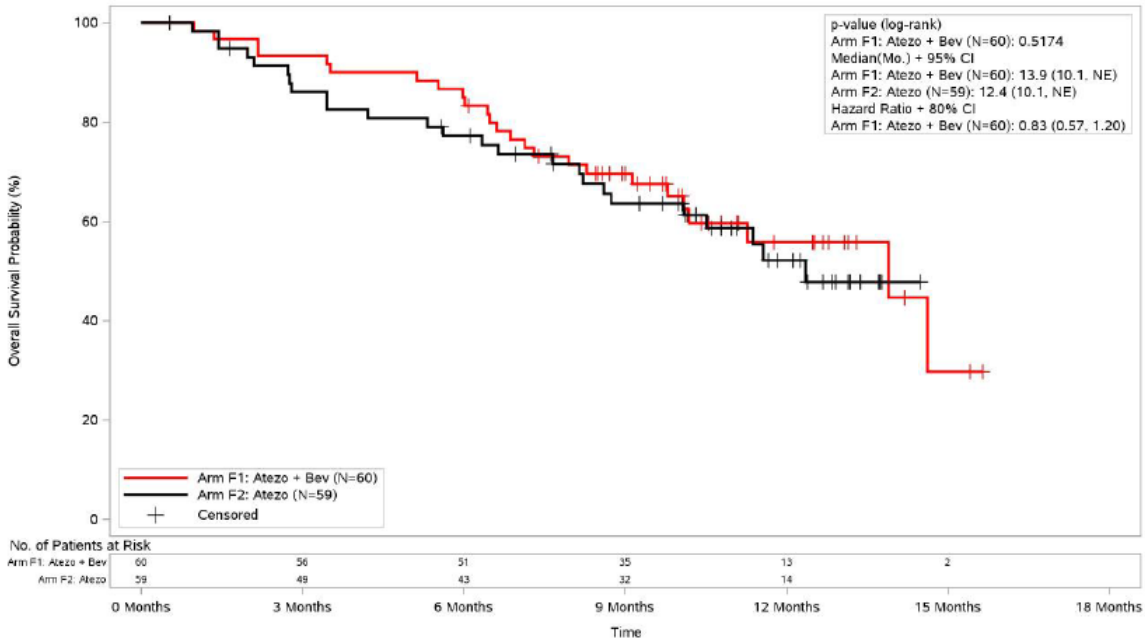
The median duration of response could not be estimated at the time of the clinical data cutoff date. As of that date, all of the 12 responders in the Atezo+Bev arm and 8 of the 10 responders in the Atezo monotherapy arm were ongoing.

Overall survival results were not mature at the time of the primary PFS analysis, 16 patients (26.7%) in the Atezo+Bev arm and 18 patients (30.5%) in the Atezo monotherapy arm had died. This resulted

in a stratified HR of 0.78 (80% CI: 0.50, 1.21). The 6-month OS rate was 88% for the Atezo+Bev patients and 76% for the patients in the Atezo monotherapy arm.

Intra-study crossover was allowed from Atezolizumab monotherapy to the combination treatment (26 patients crossed over from Atezo monotherapy (Arm F2) to treatment with Atezo + Bev after Investigator-assessed disease progression.

- Updated OS results based on a CCOD of 15 October 2019 provide approximately 4 months of additional follow-up for patients as compared to the primary analysis. At the updated CCOD for Arm F, 25 patients (41.7%) of 60 ITT patients in the Atezo + Bev arm and 25 patients (42.4%) of 59 ITT patients in the Atezo monotherapy arm had died.



NE: Not estimable.
P-value and hazard ratio are based on stratified analyses with the stratification factors as geographic region (Asia excluding Japan vs. Rest of World) and AFP level (<400 ng/mL vs. >=400 ng/mL) obtained from IxRS.
Data Extraction Date: 23DEC2019; Data Cut Date: 15OCT2019
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Output: root/clinical_studies/RO5541267/CDT30075/GO30140/data_analysis/CSR_90dSafety/prod/output/g_ef_km_OS_ARMF_EE.pdf 03JAN2020 16:32

Figure 20: Kaplan-Meier plot of overall survival, Arm F, efficacy evaluable patients (updated data, CCOD 15 October 2019)

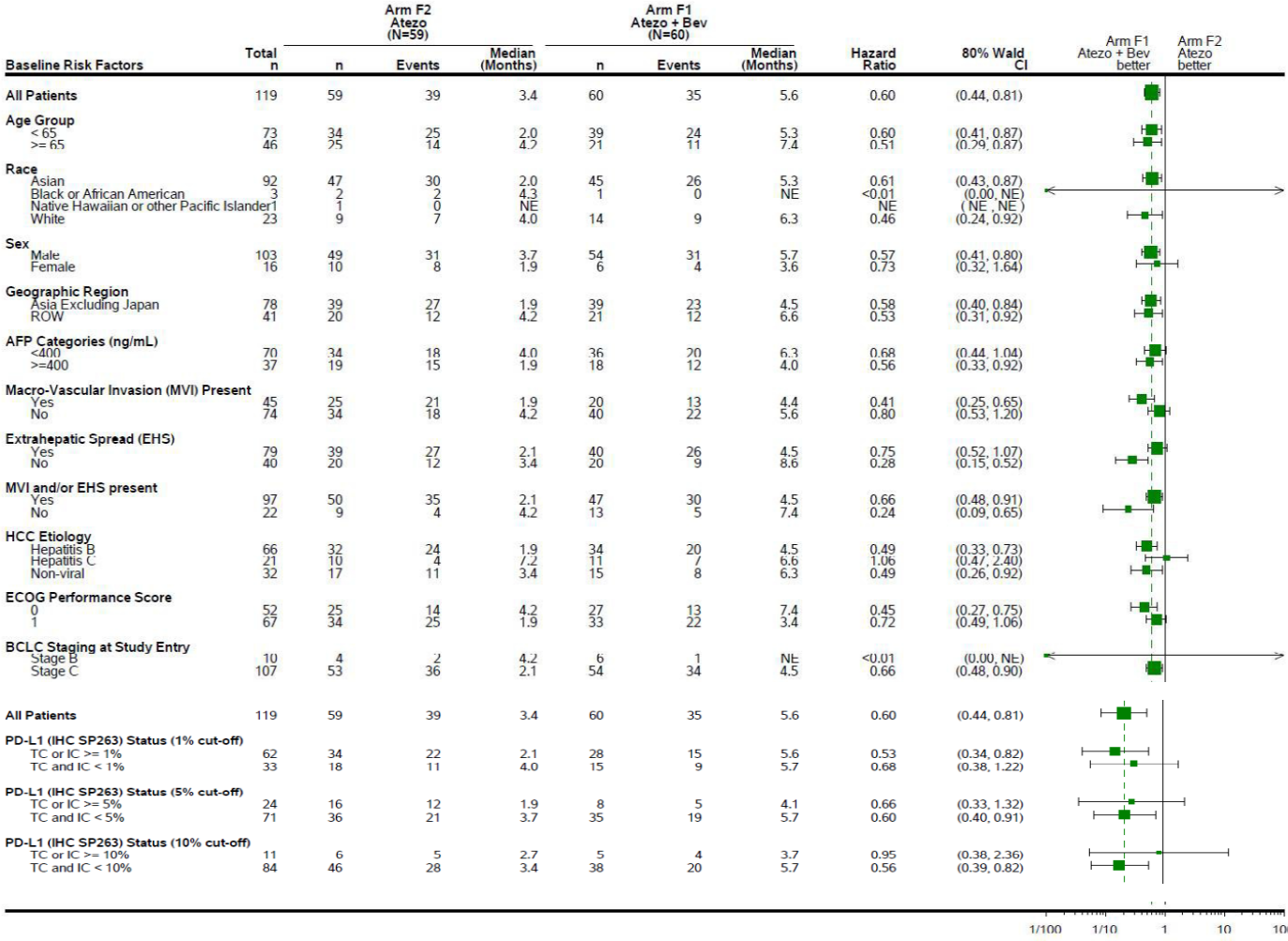
Table 49: Summary of overall survival in arm F1 and arm F2, efficacy evaluable patients

	Primary Analysis CCOD (14 June 2019) (reported in GO30140 CSR)		Updated CCOD (15 October 2019)	
	Arm F1 Atezo + Bev (N = 60)	Arm F2 Atezo (N = 59)	Arm F1 Atezo + Bev (N=60)	Arm F2 Atezo (N = 59)
Patients with event (%)	16 (26.7%)	18 (30.5%)	25 (41.7%)	25 (42.4%)
Death	16	18	25	25
Time to event (months)				
Median	NE	NE	13.9	12.4
95% CI for the median	(8.3, NE)	(8.2, NE)	10.1, NE)	(10.1, NE)
Stratified Analysis[a]				
Hazard ratio (80% CI)	0.78 (0.50, 1.21)		0.83 (0.57, 1.20)	
Time point analysis				
6months				
Patients remaining at risk	37	33	51	43
Event free probability (95% CI)	0.88 (0.79, 0.96)	0.76 (0.65, 0.88)	0.85 (0.76, 0.94)	0.77 (0.66, 0.88)
1 year				
Patients remaining at risk	NE	NE	13	14
Event free probability (95% CI)	NE	NE	0.56 (0.41, 0.70)	0.52 (0.37, 0.67)

Atezo = atezolizumab; Bev = bevacizumab; CCOD = clinical cutoff date; CI = confidence interval; NE = not estimable.

[a] Stratified analysis included geographic region (Asia excluding Japan vs. Rest of World) and AFP level (< 400 ng/mL vs ≥ 400 ng/mL) at baseline obtained from IxRS as the stratification factors.

Subgroup Analyses



Baseline Risk Factors	Total n	Arm F2 Atezo (N=59) n	Events	Median (Months)	Arm F1 Atezo + Bev (N=60) n	Events	Median (Months)	Hazard Ratio	80% Wald CI
All Patients	119	59	39	3.4	60	35	5.6	0.60	(0.44, 0.81)
Age Group									
< 65	73	34	25	2.0	39	24	5.3	0.60	(0.41, 0.87)
>= 65	46	25	14	4.2	21	11	7.4	0.51	(0.29, 0.87)
Race									
Asian	92	47	30	2.0	45	26	5.3	0.61	(0.43, 0.87)
Black or African American	3	2	2	4.3	1	0	NE	<0.01	(0.00, NE)
Native Hawaiian or other Pacific Islander	1	1	0	NE				NE	(NE , NE)
White	23	9	7	4.0	14	9	6.3	0.46	(0.24, 0.92)
Sex									
Male	103	49	31	3.7	54	31	5.7	0.57	(0.41, 0.80)
Female	16	10	8	1.9	6	4	3.6	0.73	(0.32, 1.64)
Geographic Region									
Asia Excluding Japan	78	39	27	1.9	39	23	4.5	0.58	(0.40, 0.84)
ROW	41	20	12	4.2	21	12	6.6	0.53	(0.31, 0.92)
AFP Categories (ng/mL)									
<400	70	34	18	4.0	36	20	6.3	0.68	(0.44, 1.04)
>=400	37	19	15	1.9	18	12	4.0	0.56	(0.33, 0.92)
Macro-Vascular Invasion (MVI) Present									
Yes	45	25	21	1.9	20	13	4.4	0.41	(0.25, 0.65)
No	74	34	18	4.2	40	22	5.6	0.80	(0.53, 1.20)
Extrahepatic Spread (EHS)									
Yes	79	39	27	2.1	40	26	4.5	0.75	(0.52, 1.07)
No	40	20	12	3.4	20	9	8.6	0.28	(0.15, 0.52)
MVI and/or EHS present									
Yes	97	50	35	2.1	47	30	4.5	0.66	(0.48, 0.91)
No	22	9	4	4.2	13	5	7.4	0.24	(0.09, 0.65)
HCC Etiology									
Hepatitis B	66	32	24	1.9	34	20	4.5	0.49	(0.33, 0.73)
Hepatitis C	21	10	4	7.2	11	7	6.6	1.06	(0.47, 2.40)
Non-viral	32	17	11	3.4	15	8	6.3	0.49	(0.26, 0.92)
ECOG Performance Score									
0	52	25	14	4.2	27	13	7.4	0.45	(0.27, 0.75)
1	67	34	25	1.9	33	22	3.4	0.72	(0.49, 1.06)
BCLC Staging at Study Entry									
Stage B	10	4	2	4.2	6	1	NE	<0.01	(0.00, NE)
Stage C	107	53	36	2.1	54	34	4.5	0.66	(0.48, 0.90)
All Patients	119	59	39	3.4	60	35	5.6	0.60	(0.44, 0.81)
PD-L1 (IHC SP263) Status (1% cut-off)									
TC or IC >= 1%	62	34	22	2.1	28	15	5.6	0.53	(0.34, 0.82)
TC and IC < 1%	33	18	11	4.0	15	9	5.7	0.68	(0.38, 1.22)
PD-L1 (IHC SP263) Status (5% cut-off)									
TC or IC >= 5%	24	16	12	1.9	8	5	4.1	0.66	(0.33, 1.32)
TC and IC < 5%	71	36	21	3.7	35	19	5.7	0.60	(0.40, 0.91)
PD-L1 (IHC SP263) Status (10% cut-off)									
TC or IC >= 10%	11	6	5	2.7	5	4	3.7	0.95	(0.38, 2.36)
TC and IC < 10%	84	46	28	3.4	38	20	5.7	0.56	(0.39, 0.82)

Hazard ratios were estimated by unstratified Cox regression. Arm F2 is the reference. NE: Not estimable.
ROW: Rest of the world refers to the USA, Australia, New Zealand and Japan. Non-viral HCC etiology includes unknown non-hepatitis B and C cause.
Data Extraction Date: 31JUL2019; Data Cut Date: 14JUN2019

Figure 21: Subgroup Analyses of PFS Based on IRF-Assessment per RECIST v1.1 in Arms F

- Clinical outcomes by PD-L1 expression status

Study GO30140 – Arm A (Atezo+Bev)

Name / Level	Patients n (%)	Response n	ORR (95% CI)
All	104 (100.0)	37	35.6 (26.4-45.6)
PD-L1 (IHC SP263) Status (1% cut-off)			
TC or IC >= 1%	61 (58.7)	25	41.0 (28.6-54.3)
TC and IC < 1%	25 (24.0)	7	28.0 (12.1-49.4)
PD-L1 (IHC SP263) Status (5% cut-off)			
TC or IC >= 5%	37 (35.6)	17	45.9 (29.5-63.1)
TC and IC < 5%	49 (47.1)	15	30.6 (18.3-45.4)
PD-L1 (IHC SP263) Status (10% cut-off)			
TC or IC >= 10%	30 (28.8)	15	50.0 (31.3-68.7)
TC and IC < 10%	56 (53.8)	17	30.4 (18.8-44.1)

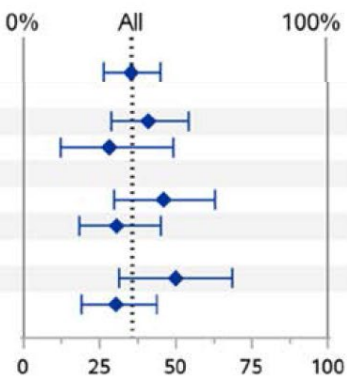


Figure 22: ORR by PD-L1 expression - excerpt from subgroup analyses of confirmed IRF-assessed ORR per RECIST v1.1 in Arm A of GO30140

- Comparison of efficacy results between IMbrave150 and G030140

	IMbrave150		GO30140		
			Arm A	Arm F1	Arm F2
	Sorafenib (N = 165)	Atezo + Bev (N = 336)	Atezo + Bev (N = 104)	Atezo + Bev (N = 60)	Atezo (N = 59)
Duration of Survival Follow-up					
Median, months (Min-Max)	8.1 (0.0 - 16.2)	8.9 (0.1 - 16.9)	12.4 (0.7 - 34.3)	6.6 (1.0 - 11.9)	6. 7 (0.5 - 11.4)
Overall Survival					
No. (%) of patients with event	65 (39.4%)	96 (28.6%)	47 (45.2%)	16 (26.7%)	18 (30.5%)
Median, months (95% CI)	13.2 (10.4, NE)	NE (NE, NE)	17.1 (13.8, NE)	NE (8.3, NE)	NE (8.2, NE)
Stratified hazard ratio (CI), p-value *	0.58 (0.42, 0.79) [a], 0.0006		-	0.78 (0.50, 1.21) [b], -	
6-Month OS rate (%) (95% CI)	72% (65, 79)	85% (81, 89)	82% (74, 89)	88% (79, 96)	76% (65, 88)
Progression-Free Survival: IRF-Assessed per RECIST v1.1					
No. (%) of patients with event	109 (66.1%)	197 (58.6%)	69 (66.3%)	35 (58.3%)	39 (66.1%)
Median, months (95% CI)	4.3 (4.0, 5.6)	6.8 (5.8, 8.3)	7.3 (5.4, 9.9)	5.6 (3.6, 7.4)	3.4 (1.9, 5.2)
Stratified hazard ratio (CI), p-value *	0.59 (0.47, 0.76) [a], <0.0001		-	0.55 (0.40, 0.74) [b], 0.0108	
6-Month PFS rate (%) (95% CI)	37% (29, 45)	55% (49, 60)	54% (45, 64)	46% (32, 59)	27% (14, 41)
Confirmed Objective Response Rate: IRF-Assessed per RECIST v1.1					
No. of evaluable patients	159	326	104	60	59
Confirmed ORR, N (%)[a] (95% CI)	19 (11.9%) (7.35, 18.03)	89 (27.3%) (22.54, 32.48)	37 (35.6%) (26.43, 45.57)	12 (20.0%) (10.78, 32.33)	10 (16.9%) (8.44, 28.97)
Difference in ORR, (%), (CI), p-value	15.4%, (7.9, 22.8), <0.0001 [b]		-	3.1%, (-7.7, 13.8) [c], -	
Disease Control Rate: IRF-Assessed per RECIST v1.1					
DCR (%)	55.3%	73.6%	71.2%	66.7%	49.2%
Duration of Confirmed Response: IRF-Assessed per RECIST v1.1 *					
No. of evaluable patients	19	89	37	12	10
No. (%) of patients with event	6 (31.6%)	12 (13.5%)	9 (24.3%)	0	2 (20.0%)
Patients with ongoing response N (%)	13 (68.4%)	77 (86.5%)	28 (75.7%)	12 (100.0%)	8 (80.0%)
Median time to event (months) (95% CI)	6.3 (4.67, NE)	NE	NE (11.8, NE)	NE	NE (3.7, NE)
6-Month event-free rate (%)	59%	88%	81%	100%	75%

CI = confidence interval; DCR = disease control rate; IRF = independent review facility; NE = Not estimable; ORR = objective response rate; RECIST v1.1 = response evaluation criteria in solid tumors version 1.1.

[a] Responses refer to either a (confirmed) CR or PR per RECIST v1.1.

[b] Two-sided 95% confidence interval is shown. P-value was based on stratified Cochran-Mantel-Haenszel test.

[c] Two-sided 80% confidence interval is shown.

CI = confidence interval; IRF = independent review facility; NE = Not estimable; OS = overall survival; PFS = progression-free survival; RECIST v1.1 = response evaluation criteria in solid tumors version 1.1

[a] Stratification factors included geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence) and baseline AFP levels (<400 vs. ≥400 ng/mL) per IxRS. Sorafenib is the reference. Two-sided 95% confidence interval is shown.

[b] Stratification factors included geographic region (Asia excluding Japan vs. rest of world) and baseline AFP levels (<400 vs. ≥400 ng/mL) per IxRS. Arm F2 is the reference. Two-sided 80% confidence interval is shown.

*. Based on stratified log-rank test, with stratification factors for IMbrave150 and GO30140 Arm F as outlined in footnotes a and b, respectively.

Additional studies

Table 50: Summary of Additional Studies

	Atezo Monotherapy		Bev Monotherapy	
	PCD4989g (GO27831)	YO29233 (China PK)	Boige et al., 2012	Siegel et al., 2008
Study Phase	Ia	I	II	II
Treatment Line	1L+	1L+	1L+	1L+
Study Design	Open-label, multicenter, multi-cohort, single-arm, non-randomized, dose-escalation	Open-label, multicenter, multi-cohort, single-arm, non-randomized	Single center, single-arm	Single center, single-arm
Population	Patients with HCC	Patients with HCC	Patients with HCC	Patients with HCC
No. of Patients Evaluable for Efficacy	n = 15 (1L = 5; 2L+ = 10)	n = 21 (1L = 7; 2L+ = 14)	n = 43	n = 46
Dose, Route, and Regimen	Atezo: IV, 1200 mg Q3W		Bev: 5 mg/kg or 10 mg/kg Q2W	
Data Cutoff Date	Last Patient Last Visit: 30 September 2018	Data cutoff date: 19 November 2018	Publications referenced	

1L = First Line treatment; 2L = Second-Line treatment; IV = Intravenous infusion; Q2W = dosed every two weeks; Q3W = dosed every three weeks.
Source: Supplemental Results Reports PCD4989g and YO29233, Boige et al., 2012, Siegel et al. 2008.

Atezolizumab Monotherapy

Atezolizumab administered as single-agent for the treatment of HCC has been assessed in PCD4989g and YO29233 multi-cohort Phase I studies.

- Study PCD4989g

As of the last patient last visit (LPLV) of 30 September 2018, there were 15 patients with HCC treated with atezolizumab in PCD4989g (n=5 1L patients, n=10 2L+ patients). None (95% CI: 0.0, 21.8) of the patients with HCC had a confirmed objective response as assessed by the Investigator per RECIST v1.1, two 1L patients achieved SD. Of note, two out of five 1L patients (40%) were alive by the time of the LPLV based on a median duration of survival follow-up of 23.7 months (range 2.2 to 31) for 1L HCC patients.

- Study YO29233

In the analysis of Study YO29233 based on a CCOD of 19 November 2018, there were 20 patients from the HCC expansion cohort, and 1 patient from the PK cohort treated with Atezo. All patients were Chinese, and were reported to have HBV as a cause of HCC disease. Among those patients, 7 received atezolizumab as 1L treatment and 14 as 2L+ treatment. 2 1L HCC patients (28.6%) had a confirmed Investigator-assessed PR per RECIST v1.1. One of those responses was ongoing (DOR of 14.0+ months) while the other responder had discontinued treatment due to disease progression (DOR of 6.9 months). No 2L+ HCC patients achieved a confirmed response.

Bevacizumab Monotherapy

Bevacizumab as a single-agent for the treatment of HCC has been assessed in the Investigator-sponsored trials of Siegel et al. 2008 and Boige et al 2012.

- Phase II Study of Bevacizumab in Unresectable HCC **Siegel et al., J Clin Oncol. 2008; 26(18)*

In the study conducted by Siegel et al. 2008, 46 adult patients (15 [33%] 1L, 31 [67%] 2L) with organ-confined HCC, ECOG PS of 0-2, and compensated liver function (Child-Pugh A or B7), received bevacizumab 5 mg/kg or 10 mg/kg Q2W until disease progression or treatment-limiting toxicity. Of note, patients with MVI, EHS, or greater than 50% tumor involvement in the liver were excluded.

The primary objective was to determine whether bevacizumab improved the 6-month progression-free survival (PFS) rate from 40% to 60%.

Forty-six patents were enrolled between February 2003 and September 2006. The median age was 58 years. Eighty-three percent of patients were male, and 95% had an ECOG PS of 0 or 1. One third of patients had received no prior therapy.

Overall, there were 6 objective responses (13%; 95% CI: 3%, 23%), including one complete response and five partial responses and 65% (95% CI: 51%, 79%) of patients were progression-free at 6 months. Median PFS was 6.9 (95% CI: 6.5, 9.1) months and median OS was 12.4 (95% CI: 9.4, 19.9) months.

- Phase II Study of Bevacizumab in Advanced HCC *_Boige et al., The Oncologist 2012; 17_*

In the study conducted by Boige et al. 2012, 43 patients (22 (51.2%) 1L, 21 [48.8%] 2L) with histologically confirmed advanced HCC not amenable to curative-intent therapies (e.g., resection, liver transplantation, or percutaneous ablation) received bevacizumab 5 mg/kg or 10 mg/kg Q2W until disease progression or unacceptable toxicity. Patients enrolled from May 2005 to December 2007 had ECOG PS ≤2 and compensated liver function (Child-Pugh A or B7) with no more than one prior systemic therapy. More than half of the patients had extrahepatic metastases, (91%) were classified as BCLC stage C.

The primary objective of the study was to assess disease control rate at 16 weeks (16W-DCR) defined as the proportion of patients with a CR, PR, or SD at 16 weeks after study entry, as measured by the Investigator and reviewed by an independent radiologist according to RECIST v1.0. All tumor measurements were performed by the Investigator. At the end of the study, tumor measurements were reviewed by an independent radiologist who was blinded to the clinical and biological data.

Among the 38 patients evaluable for radiologic response, 6 patients achieved a PR (ITT ORR, 14% [95% CI: 4%, 24%]) and the median DOR was 148 days (4.9 months, range 55-362 days). Eighteen patients had SD, including 12 patients who experienced SD for ≥ 16 weeks. The 16W-DCR was 42% (95% CI: 27%, 57%) in the overall population. The median PFS was 3 months (95% CI: 2, 4 months) and the median OS was 8 months (95% CI: 4, 9 months) after a median duration of follow-up of 27 months. The 6- months PFS and OS rates were 33% (95% CI, 20%–47%) and 63% (95% CI, 48%–76%), respectively.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH has provided study IMbrave150, a Phase III, open-label, randomized Study of atezolizumab in combination with bevacizumab compared with sorafenib in Patients with untreated locally advanced or metastatic Hepatocellular Carcinoma. Study GO30140 provided supportive data in 1L HCC patients; Arm F used a randomized design to compare the combination treatment against atezolizumab monotherapy, whereas Arm A evaluated Atezo+Bev as single treatment option.

This pivotal study is overall well-designed and well-conducted. No major concerns have been identified. The study design has previously been discussed with the CHMP and endorsed as such (EMEA/H/SA/2522/16/2017/II). Sorafenib is SoC in this patient population. There is no atezo mono arm in this study in order to determine its contribution; however, based on available data from single arm studies and from the supportive study GO30140, it can be assumed that atezolizumab as monotherapy would not be superior to sorafenib. The use of bevacizumab has also previously been investigated in 1L and 2L HCC, showing limited efficacy (Siegel et al. 2008). However, the combination of atezolizumab and bevacizumab in the supportive study (Arm A) led to clinically encouraging results. These have now been confirmed in study IMbrave150.

The inclusion and exclusion criteria clearly define a patient population with locally advanced or metastatic and/or unresectable HCC not amenable to curative therapy, with no prior systemic treatments, Child-Pugh Class A, no other malignancies for the last 5 years, other types of liver cancer or co-infection with HBV/HCV. This is clearly reflected in section 5.1 of the SmPC.

Efficacy data and additional analyses

The study met its co-primary endpoint by showing statistically significant PFS gain, with a median PFS of 6.83 vs 4.27 months in atezo+bev and sorafenib arms respectively. The HR is 0.58, (0.47, 0.76), p<0.0001. These results are deemed clinically meaningful in this patients' population with a dismal prognosis.

The OS data from the 1st IA show a statistically significant HR of 0.58 (0.42, 0.79) with a p-value of 0.0006. At the time of the 1st IA, the OS data were not mature yet with 161 deaths out of 312 deaths per the pre-specified OS analyses were observed. The MAH will submit updated overall survival (OS) data from the IMbrave150 study post-approval, providing 12 months of additional follow-up and the final OS data (after approximately 312 deaths have occurred (Recommendations)).

The key secondary endpoints showed statistically significant and clinically meaningful differences in favour of atezo+bev. ORR by IRF per RECIST 1.1 showed 27.3% vs 11.9%, ORR by IRF per HCC mRECIST showed 33.2% vs. 13.3%. DOR was also considerably longer in the atezo+bev arm.

The effect of ADA on efficacy and safety has long been a concern. In the unresectable hepatocellular carcinoma study (IMbrave150), 27.9% of patients tested positive for ADAs at one or more post-dose time points. These patients generally had poorer health and disease characteristics at baseline compared to patients who only tested negative for ADA. The MAH has been requested to provide analyses of OS and PFS comparing ADA- and ADA+, adjusting for multiple baseline covariates to assess the effect of ADAs on efficacy; these exploratory analyses on OS showed that patients who were ADA-positive by week 6 (20.1%) appeared to have similar OS compared to sorafenib-treated patients, whereas ADA-negative patients by week 6 had an increased OS benefit compared to sorafenib-treated patients. These OS results were inconclusive due to the low number of events in ADA subgroups. Exploratory analyses on PFS suggested treatment benefit with atezolizumab + bevacizumab over sorafenib regardless of ADA status by week 6. It is not possible to draw any firm conclusion regarding the clinical relevance of the impact of ADA on efficacy given that ADA is a post-randomization variable.

Overall, subgroup analyses showed that results are consistent with the overall OS and PFS estimates.

Available data suggest a small benefit of Atezo+Bev compared to sorafenib in the subgroup of patients with negative PD-L1 expression (applying a cutoff of <1%). Considering, that TC and IC expression of <1% was reported in nearly 40% of patients evaluable for PD-L1 expression (70/182) the lack of comprehensive PD-L1 –expression data is regarded as limitation of IMbrave 150. However, current data seem to indicate a treatment benefit in all-comers.

2.4.4. Conclusions on the clinical efficacy

Overall, study IMbrave150 met one of its co-primary endpoints, PFS, showing a statistically significant and clinically relevant difference in favour of atezo+bev, and thus considered a positive study. These results are supported by the 1st IA of OS and key secondary endpoints.

2.5. Clinical safety

Introduction

The assessment of safety is based on the pivotal study IMbrave 150.

Patient exposure

Table 51: Extent of study drug exposure (safety-evaluable population)

	Sorafenib (N=156)	Atezo+Bev (N=329)	
	Sorafenib	Atezolizumab	Bevacizumab
Treatment duration (months)			
n	156	329	329
Mean (SD)	4.1 (3.5)	6.8 (4.1)	6.5 (4.0)
Median	2.8	7.4	6.9
Min - Max	0 - 16	0 - 16	0 - 16
Treatment duration (months)			
n	156	329	329
<3	89 (57.1%)	75 (22.8%)	78 (23.7%)
3 to <6	22 (14.1%)	48 (14.6%)	58 (17.6%)
6 to <9	28 (17.9%)	100 (30.4%)	97 (29.5%)
9 to <12	12 (7.7%)	76 (23.1%)	69 (21.0%)
>=12	5 (3.2%)	30 (9.1%)	27 (8.2%)
Dose Intensity (%)			
n	156	329	329
Mean (SD)	83.8 (20.1)	95.1 (6.9)	93.3 (9.6)
Median	96.0	98.0	97.0
Min - Max	27 - 100	54 - 104	44 - 104
Number of doses received			
n	156	329	329
Mean (SD)	215.1 (194.6)	10.4 (5.8)	9.8 (5.5)
Median	149.0	11.0	10.0
Min - Max	6 - 908	1 - 24	1 - 23
Total cumulative dose (mg)			
n	156	329	329
Mean (SD)	84784.6 (76639.8)	12440.3 (6917.4)	10485.1 (6467.4)
Median	64100.0	13200.0	10543.5
Min - Max	2400 - 362800	1200 - 28800	723 - 30510

Adverse events

Common AEs

Table 52: Adverse events with an incidence rate of at least 10% in any treatment arm by system organ class and preferred term (safety-evaluable population)

MedDRA System Organ Class MedDRA Preferred Term	Sorafenib (N=156)	Atezo+Bev (N=329)
Total number of patients with at least one adverse event	154 (98.7%)	323 (98.2%)
Overall total number of events	1299	3058
Gastrointestinal disorders		
Total number of patients with at least one adverse event	118 (75.6%)	193 (58.7%)
Total number of events	293	525
Diarrhoea	77 (49.4%)	62 (18.8%)
Abdominal pain	27 (17.3%)	40 (12.2%)
Constipation	22 (14.1%)	44 (13.4%)
Nausea	25 (16.0%)	40 (12.2%)
Vomiting	13 (8.3%)	33 (10.0%)
General disorders and administration site conditions		
Total number of patients with at least one adverse event	77 (49.4%)	166 (50.5%)
Total number of events	105	278
Fatigue	29 (18.6%)	67 (20.4%)
Pyrexia	15 (9.6%)	59 (17.9%)
Asthenia	21 (13.5%)	22 (6.7%)
Skin and subcutaneous tissue disorders		
Total number of patients with at least one adverse event	107 (68.6%)	123 (37.4%)
Total number of events	187	197
Pruritus	15 (9.6%)	64 (19.5%)
Palmar-plantar erythrodysaesthesia syndrome	75 (48.1%)	3 (0.9%)
Rash	27 (17.3%)	41 (12.5%)
Alopecia	22 (14.1%)	4 (1.2%)
Investigations		
Total number of patients with at least one adverse event	68 (43.6%)	159 (48.3%)
Total number of events	223	518
Aspartate aminotransferase increased	26 (16.7%)	64 (19.5%)
Blood bilirubin increased	22 (14.1%)	43 (13.1%)
Alanine aminotransferase increased	14 (9.0%)	46 (14.0%)
Platelet count decreased	18 (11.5%)	35 (10.6%)
Weight decreased	15 (9.6%)	37 (11.2%)
Metabolism and nutrition disorders		
Total number of patients with at least one adverse event	66 (42.3%)	129 (39.2%)
Total number of events	118	214
Decreased appetite	38 (24.4%)	58 (17.6%)
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	47 (30.1%)	130 (39.5%)
Total number of events	71	219
Cough	15 (9.6%)	39 (11.9%)
Epistaxis	7 (4.5%)	34 (10.3%)
Vascular disorders		
Total number of patients with at least one adverse event	42 (26.9%)	108 (32.8%)
Total number of events	52	160
Hypertension	38 (24.4%)	98 (29.8%)
Renal and urinary disorders		
Total number of patients with at least one adverse event	20 (12.8%)	86 (26.1%)
Total number of events	24	120
Proteinuria	11 (7.1%)	66 (20.1%)
Injury, poisoning and procedural complications		
Total number of patients with at least one adverse event	6 (3.8%)	46 (14.0%)
Total number of events	7	61
Infusion related reaction	0	37 (11.2%)

Includes AEs with onset date on or after the date of the first dose of study drug up to the data cutoff date.
Investigator text for AEs are encoded using MedDRA version 22.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Table 53: Adverse events with a difference of at least 5% between treatment arms by system organ class (safety-evaluable population)

MedDRA System Organ Class MedDRA Preferred Term	Sorafenib (N=156)	Atezo+Bev (N=329)
Total number of patients with at least one adverse event	154 (98.7%)	323 (98.2%)
Overall total number of events	1299	3058
Gastrointestinal disorders		
Total number of patients with at least one adverse event	118 (75.6%)	193 (58.7%)
Total number of events	293	525
Diarrhoea	77 (49.4%)	62 (18.8%)
Abdominal pain	27 (17.3%)	40 (12.2%)
General disorders and administration site conditions		
Total number of patients with at least one adverse event	77 (49.4%)	166 (50.5%)
Total number of events	105	278
Pyrexia	15 (9.6%)	59 (17.9%)
Asthenia	21 (13.5%)	22 (6.7%)
Oedema peripheral	5 (3.2%)	29 (8.8%)
Skin and subcutaneous tissue disorders		
Total number of patients with at least one adverse event	107 (68.6%)	123 (37.4%)
Total number of events	187	197
Pruritus	15 (9.6%)	64 (19.5%)
Palmar-plantar erythrodysaesthesia syndrome	75 (48.1%)	3 (0.9%)
Alopecia	22 (14.1%)	4 (1.2%)
Investigations		
Total number of patients with at least one adverse event	68 (43.6%)	159 (48.3%)
Total number of events	223	518
Alanine aminotransferase increased	14 (9.0%)	46 (14.0%)
Metabolism and nutrition disorders		
Total number of patients with at least one adverse event	66 (42.3%)	129 (39.2%)
Total number of events	118	214
Decreased appetite	38 (24.4%)	58 (17.6%)
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	47 (30.1%)	130 (39.5%)
Total number of events	71	219
Epistaxis	7 (4.5%)	34 (10.3%)
Vascular disorders		
Total number of patients with at least one adverse event	42 (26.9%)	108 (32.8%)
Total number of events	52	160
Hypertension	38 (24.4%)	98 (29.8%)
Musculoskeletal and connective tissue disorders		
Total number of patients with at least one adverse event	34 (21.8%)	100 (30.4%)
Total number of events	44	150
Musculoskeletal pain	3 (1.9%)	24 (7.3%)
Renal and urinary disorders		
Total number of patients with at least one adverse event	20 (12.8%)	86 (26.1%)
Total number of events	24	120
Proteinuria	11 (7.1%)	66 (20.1%)
Injury, poisoning and procedural complications		
Total number of patients with at least one adverse event	6 (3.8%)	46 (14.0%)
Total number of events	7	61
Infusion related reaction	0	37 (11.2%)
Endocrine disorders		
Total number of patients with at least one adverse event	5 (3.2%)	39 (11.9%)
Total number of events	5	47
Hypothyroidism	3 (1.9%)	29 (8.8%)

Includes AEs with onset date on or after the date of the first dose of study drug up to the data cutoff date.
Investigator text for AEs are encoded using MedDRA version 22.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Treatment-related AEs

Table 54: Adverse events related to study treatment with an incidence rate of at least 5% in any treatment arm by system organ class and preferred term (safety-evaluable population)

	Sorafenib (N=156)	Atezo+Bev (N=329)		
MedDRA System Organ Class MedDRA Preferred Term	Sorafenib	Atezo	Bev	Any treatment
Total number of patients with at least one adverse event	147 (94.2%)	252 (76.6%)	241 (73.3%)	276 (83.9%)
Overall total number of events	790	1259	1136	1505
Skin and subcutaneous tissue disorders				
Total number of patients with at least one adverse event	107 (68.6%)	82 (24.9%)	42 (12.8%)	85 (25.8%)
Total number of events	175	123	53	127
Palmar-plantar erythrodysaesthesia syndrome	75 (48.1%)	1 (0.3%)	1 (0.3%)	2 (0.6%)
Pruritus	13 (8.3%)	43 (13.1%)	17 (5.2%)	43 (13.1%)
Rash	26 (16.7%)	29 (8.8%)	14 (4.3%)	29 (8.8%)
Alopecia	21 (13.5%)	3 (0.9%)	2 (0.6%)	3 (0.9%)
Gastrointestinal disorders				
Total number of patients with at least one adverse event	91 (58.3%)	83 (25.2%)	81 (24.6%)	97 (29.5%)
Total number of events	178	153	148	180
Diarrhoea	67 (42.9%)	34 (10.3%)	22 (6.7%)	34 (10.3%)
Nausea	20 (12.8%)	19 (5.8%)	19 (5.8%)	21 (6.4%)
Vomiting	8 (5.1%)	13 (4.0%)	13 (4.0%)	13 (4.0%)
Constipation	8 (5.1%)	6 (1.8%)	8 (2.4%)	8 (2.4%)
Abdominal pain	8 (5.1%)	3 (0.9%)	3 (0.9%)	3 (0.9%)
Investigations				
Total number of patients with at least one adverse event	45 (28.8%)	107 (32.5%)	88 (26.7%)	111 (33.7%)
Total number of events	124	341	266	357
Aspartate aminotransferase increased	11 (7.1%)	45 (13.7%)	29 (8.8%)	46 (14.0%)
Platelet count decreased	15 (9.6%)	23 (7.0%)	24 (7.3%)	27 (8.2%)
Alanine aminotransferase increased	4 (2.6%)	34 (10.3%)	18 (5.5%)	34 (10.3%)
Blood bilirubin increased	9 (5.8%)	27 (8.2%)	20 (6.1%)	27 (8.2%)
Weight decreased	8 (5.1%)	12 (3.6%)	12 (3.6%)	13 (4.0%)
General disorders and administration site conditions				
Total number of patients with at least one adverse event	58 (37.2%)	91 (27.7%)	80 (24.3%)	97 (29.5%)
Total number of events	71	121	105	132
Fatigue	24 (15.4%)	49 (14.9%)	40 (12.2%)	50 (15.2%)
Pyrexia	8 (5.1%)	27 (8.2%)	25 (7.6%)	30 (9.1%)

Asthenia	16 (10.3%)	10 (3.0%)	8 (2.4%)	11 (3.3%)
Vascular disorders				
Total number of patients with at least one adverse event	32 (20.5%)	21 (6.4%)	81 (24.6%)	84 (25.5%)
Total number of events	35	31	102	105
Hypertension	31 (19.9%)	17 (5.2%)	78 (23.7%)	78 (23.7%)
Metabolism and nutrition disorders				
Total number of patients with at least one adverse event	45 (28.8%)	58 (17.6%)	50 (15.2%)	63 (19.1%)
Total number of events	69	86	74	92
Decreased appetite	31 (19.9%)	29 (8.8%)	26 (7.9%)	33 (10.0%)
Respiratory, thoracic and mediastinal disorders				
Total number of patients with at least one adverse event	25 (16.0%)	42 (12.8%)	58 (17.6%)	65 (19.8%)
Total number of events	29	51	73	85
Dysphonia	10 (6.4%)	15 (4.6%)	20 (6.1%)	22 (6.7%)
Epistaxis	3 (1.9%)	4 (1.2%)	24 (7.3%)	24 (7.3%)
Renal and urinary disorders				
Total number of patients with at least one adverse event	8 (5.1%)	33 (10.0%)	68 (20.7%)	69 (21.0%)
Total number of events	8	49	95	96
Proteinuria	7 (4.5%)	27 (8.2%)	62 (18.8%)	62 (18.8%)
Blood and lymphatic system disorders				
Total number of patients with at least one adverse event	18 (11.5%)	41 (12.5%)	35 (10.6%)	43 (13.1%)
Total number of events	32	89	78	92
Anaemia	8 (5.1%)	9 (2.7%)	8 (2.4%)	9 (2.7%)
Endocrine disorders				
Total number of patients with at least one adverse event	4 (2.6%)	35 (10.6%)	15 (4.6%)	36 (10.9%)
Total number of events	4	42	17	43
Hypothyroidism	2 (1.3%)	25 (7.6%)	14 (4.3%)	26 (7.9%)
Injury, poisoning and procedural complications				
Total number of patients with at least one adverse event	0	33 (10.0%)	10 (3.0%)	37 (11.2%)
Total number of events	0	40	13	46
Infusion related reaction	0	32 (9.7%)	10 (3.0%)	36 (10.9%)

Includes AEs with onset date on or after the date of the first dose of study drug up to the data cutoff date.
Investigator text for AEs are encoded using MedDRA version 22.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Grade ≥3 AEs

Table 55: Adverse events with highest NCI CTCAE grade categories 3-4 and 5 with a difference of at least 2% between treatment arms by system organ class and preferred term (safety-evaluable population)

MedDRA System Organ Class MedDRA Preferred Term	Sorafenib (N=156)		Atezo+Bev (N=329)	
	Grade 3-4	Grade 5	Grade 3-4	Grade 5
Total number of patients with at least one adverse event	86 (55.1%)	9 (5.8%)	186 (56.5%)	15 (4.6%)
Investigations				
Total number of patients with at least one adverse event	25 (16.0%)	0	61 (18.5%)	0
Blood bilirubin increased	10 (6.4%)	0	8 (2.4%)	0
Alanine aminotransferase increased	2 (1.3%)	0	12 (3.6%)	0
Platelet count decreased	2 (1.3%)	0	11 (3.3%)	0
Gastrointestinal disorders				
Total number of patients with at least one adverse event	27 (17.3%)	1 (0.6%)	48 (14.6%)	5 (1.5%)
Diarrhoea	8 (5.1%)	0	6 (1.8%)	0
Vascular disorders				
Total number of patients with at least one adverse event	21 (13.5%)	0	53 (16.1%)	0
Hypertension	19 (12.2%)	0	50 (15.2%)	0
Metabolism and nutrition disorders				
Total number of patients with at least one adverse event	21 (13.5%)	0	30 (9.1%)	0
Decreased appetite	6 (3.8%)	0	4 (1.2%)	0
Hypophosphataemia	6 (3.8%)	0	2 (0.6%)	0
General disorders and administration site conditions				
Total number of patients with at least one adverse event	12 (7.7%)	3 (1.9%)	14 (4.3%)	1 (0.3%)
Asthenia	4 (2.6%)	0	1 (0.3%)	0
Skin and subcutaneous tissue disorders				
Total number of patients with at least one adverse event	21 (13.5%)	0	2 (0.6%)	0
Palmar-plantar erythrodysaesthesia syndrome	13 (8.3%)	0	0	0
Rash	4 (2.6%)	0	0	0
Renal and urinary disorders				
Total number of patients with at least one adverse event	6 (3.8%)	0	14 (4.3%)	0
Proteinuria	1 (0.6%)	0	10 (3.0%)	0
Injury, poisoning and procedural complications				
Total number of patients with at least one adverse event	2 (1.3%)	0	13 (4.0%)	0
Infusion related reaction	0	0	8 (2.4%)	0

Includes AEs with onset date on or after the date of the first dose of study drug up to the data cutoff date.
Investigator text for AEs are encoded using MedDRA version 22.0. All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this preferred term.
To the SOC Overall row counts, a patient contributes once for each grade category for which at least one AE with the corresponding highest grade is reported.

Adverse Events of Special Interest

Table 56: Overview of adverse events of special interest for atezolizumab (safety-evaluable population)

	Sorafenib (N=156)	Atezo+Bev (N=329)
Total number of patients with at least one AESI	128 (82.1%)	226 (68.7%)
Total number of events	411	866
Total number of patients with at least one		
AESI Related to any Study Treatment	115 (73.7%)	173 (52.6%)
Grade 3/4 AESI	47 (30.1%)	85 (25.8%)
Treatment-related Grade 3/4 AESI	39 (25.0%)	49 (14.9%)
Grade 5 AESI	2 (1.3%)	3 (0.9%)
Treatment-related Grade 5 AESI	1 (0.6%)	2 (0.6%)
Serious AESI	17 (10.9%)	45 (13.7%)
Treatment-related Serious AESI	13 (8.3%)	20 (6.1%)
AESI Leading to Withdrawal from any Study Treatment	9 (5.8%)	20 (6.1%)
AESI Leading to Dose Interruption/Modification of any Study Treatment	56 (35.9%)	66 (20.1%)
AESI Medical Concepts: patients with at least one		
Identified risks for Atezolizumab		
Immune-Mediated Hepatitis (Diagnosis and Lab Abnormalities)	62 (39.7%)	142 (43.2%)
Immune-Mediated Hepatitis (Lab Abnormalities)	54 (34.6%)	126 (38.3%)
Immune-Mediated Rash	96 (61.5%)	64 (19.5%)
Immune-Mediated Hepatitis (Diagnosis)	20 (12.8%)	43 (13.1%)
Immune-Mediated Hypothyroidism	4 (2.6%)	36 (10.9%)
Infusion-Related Reactions	0	36 (10.9%)
Immune-Mediated Hyperthyroidism	0	15 (4.6%)
Immune-Mediated Pancreatitis	6 (3.8%)	9 (2.7%)
Immune-Mediated Diabetes Mellitus	0	8 (2.4%)
Immune-Mediated Colitis	1 (0.6%)	6 (1.8%)
Immune-Mediated Pneumonitis	0	4 (1.2%)
Immune-Mediated Nephritis	0	3 (0.9%)
Immune-Mediated Adrenal Insufficiency	0	1 (0.3%)
Potential risks for Atezolizumab		
Immune-Mediated Severe Cutaneous Reactions	1 (0.6%)	0
Immune-Mediated Ocular Inflammatory Toxicity	0	1 (0.3%)
Autoimmune Hemolytic Anemia	0	1 (0.3%)
Immune-Mediated Vasculitis	0	1 (0.3%)
Systemic Immune Activation	0	1 (0.3%)

Includes AEs with onset date on or after the date of the first dose of study drug up to the data cutoff date.
Investigator text for AEs are encoded using MedDRA version 22.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Sponsor-defined Adverse Events of Special Interest that have not occurred in any HCC patient enrolled in the safety analysis population for this output are not displayed.

Table 57: Overview of adverse events of special interest for bevacizumab (safety-evaluable population)

	Sorafenib (N=156)	Atezo+Bev (N=329)
Total number of patients with at least one AESI	76 (48.7%)	190 (57.8%)
Total number of events	106	388
Total number of patients with at least one		
AESI Related to any Study Treatment	52 (33.3%)	146 (44.4%)
Grade 3/4 AESI	29 (18.6%)	76 (23.1%)
Treatment-related Grade 3/4 AESI	21 (13.5%)	53 (16.1%)
Grade 5 AESI	2 (1.3%)	6 (1.8%)
Treatment-related Grade 5 AESI	0	3 (0.9%)
Serious AESI	15 (9.6%)	40 (12.2%)
Treatment-related Serious AESI	6 (3.8%)	21 (6.4%)
AESI Leading to Withdrawal from any Study Treatment	1 (0.6%)	26 (7.9%)
AESI Leading to Dose Interruption/Modification of any Study Treatment	15 (9.6%)	56 (17.0%)
AESI Medical Concepts: patients with at least one		
Hypertension	40 (25.6%)	102 (31.0%)
Bleeding / Haemorrhage	27 (17.3%)	83 (25.2%)
Proteinuria	13 (8.3%)	70 (21.3%)
Thromboembolic Event - Venous	5 (3.2%)	10 (3.0%)
Thromboembolic Event - Arterial	2 (1.3%)	9 (2.7%)
Congestive Heart Failure	2 (1.3%)	1 (0.3%)
Wound Healing Complications	0	2 (0.6%)
Fistula/Abscess (Non GI)	1 (0.6%)	0
Gastrointestinal Perforation	0	1 (0.3%)

Includes AEs with onset date on or after the date of the first dose of study drug up to the data cutoff date.
Investigator text for AEs are encoded using MedDRA version 22.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Sponsor-defined Adverse Events of Special Interest that have not occurred in any HCC patient enrolled in the safety analysis population for this output are not displayed.

Diabetes mellitus occurred in 2.0% (10/493) of HCC patients who received atezolizumab in combination with bevacizumab. The median time to onset was 4.4 months (range: 1.2 months - 8.3 months). No events of diabetes mellitus led to atezolizumab withdrawal.

Adverse drug reactions

The table below reflects the adverse drug reactions related of Tecentriq as identified in the pooled safety dataset for atezolizumab monotherapy (n=3568) and in combination therapy (n=4,371).

Atezolizumab monotherapy (n=3568)		System Organ Class	Atezolizumab in combination therapy (n=4371)	
Frequency (All Grades)	Incidence % (All Grades)		Frequency (All Grades)	Incidence % (All Grades)
Infections and infestations				
very common	467 (13.1%)	Urinary tract infection[a]	-	-
-	-	Lung infection[b]	very common	564 (12.9%)
-	-	Sepsis[aj]	common	91 (2.1%)
Blood and lymphatic system disorders				
-	-	Anaemia	very common	1608 (36.8%)
common	131 (3.7%)	Thrombocytopenia[d]	very common	1211 (27.7%)
-	-	Neutropenia[e]	very common	1565 (35.8%)
-	-	Leukopenia[f]	very common	571 (13.1%)
-	-	Lymphopenia[g]	common	145 (3.3%)
Immune system disorders				
common	46 (1.3%)	Infusion-related reaction[h]	common	157 (3.6%)
Endocrine disorders				
common	214 (6.0%)	Hypothyroidism[i]	very common	586 (13.4%)
uncommon	47 (1.3%)	Hyperthyroidism[j]	common	193 (4.4%)
uncommon	11 (0.3%)	Diabetes mellitus[k]	-	-
uncommon	12 (0.3%)	Adrenal insufficiency[l]	-	-
rare	3 (<0.1%)	Hypophysitis[m]	-	-
Metabolism and nutrition disorders				

very common	855 (24.0%)	Decreased appetite	very common	1091 (25.0%)
common	154 (4.3%)	Hypokalaemia[ae]	common	296 (6.8%)
common	174 (4.9%)	Hyponatraemia[af]	common	235 (5.4%)
common	120 (3.4%)	Hyperglycaemia	-	-
-	-	Hypomagnesaemia[n]	common	403 (9.2%)
Nervous system disorders				
very common	388 (10.9%)	Headache	very common	612 (14.0%)
uncommon	5 (0.1%)	Guillain-Barré syndrome[p]	-	-
uncommon	14 (0.4%)	Meningoencephalitis[q]	-	-
rare	1 (<0.1%)	Myasthenic syndrome[r]	-	-
-	-	Peripheral neuropathy[o]	very common	1007 (23.0%)
-	-	Syncope	common	68 (1.6%)
-	-	Dizziness	common	408 (9.3%)
Eye Disorders				
rare	3 (<0.1%)	Uveitis	-	-
Cardiac disorders				
rare	0	Myocarditis[s]	-	-
Vascular disorders				
common	108 (3.0%)	Hypotension	-	-
-	-	Hypertension[ai]	very common	611 (14.0%)
Respiratory, thoracic, and mediastinal disorders				
very common	707 (19.8%)	Cough	very common	783 (17.9%)
very common	678 (19.0%)	Dyspnoea	very common	695 (15.9%)
common	99 (2.8%)	Pneumonitis[t]	-	-
common	75 (2.1%)	Hypoxia[ag]	-	-
common	110 (3.1%)	Nasal congestion	-	-
common	160 (4.5%)	Nasopharyngitis	-	-
-		Dysphonia	common	236 (5.4%)
Gastrointestinal disorders				
very common	799 (22.4%)	Nausea	very common	1504 (34.4%)
very common	504 (14.1%)	Vomiting	very common	808 (18.5%)
very common	710 (19.9%)	Diarrhoea[u]	very common	1185 (27.1%)
common	299 (8.4%)	Abdominal pain	-	-
common	43 (1.2%)	Colitis[v]	-	-
common	86 (2.4%)	Dysphagia	-	-
common	143 (4.0%)	Oropharyngeal pain[w]	-	-
uncommon	27 (0.8%)	Pancreatitis[x]	-	-
-	-	Constipation	very common	1123 (25.7%)
-	-	Stomatitis	common	351 (8.0%)
-	-	Dysgeusia	common	269 (6.2%)
Hepatobiliary disorders				
common	200 (5.6%)	AST increased	common	390 (8.9%)
common	191 (5.4%)	ALT increased	common	392 (9.0%)
common	66 (1.8%)	Hepatitis[y]	-	-
Skin and subcutaneous tissue disorders				
very common	705 (19.8%)	Rash[z]	very common	1189 (27.2%)
very common	498 (14.0%)	Pruritus	very common	573 (13.1%)
common	216 (6.1%)	Dry skin	-	-
uncommon	18 (0.5%)	Psoriasis	uncommon	24 (0.5%)
-	-	Alopecia[ah]	very common	1152 (26.4%)
Musculoskeletal and connective tissue disorders				
very common	485 (13.6%)	Arthralgia	very common	729 (16.7%)
very common	513 (14.4%)	Back pain	very common	522 (11.9%)
very common	525 (14.7%)	Musculoskeletal pain[aa]	very common	815 (18.6%)
uncommon	15 (0.4%)	Myositis[ab]	-	-
Renal and urinary disorders				
common	210 (5.9%)	Blood creatinine increased[c]	common	255 (5.8%)
rare	8 (0.2%)	Nephritis[ad]	-	-
-	-	Proteinuria[ac]	common	359 (8.2%)
General disorders and administration site conditions				
very common	717 (20.1%)	Pyrexia	very common	786 (18.0%)
very common	1231 (34.5%)	Fatigue	very common	1442 (33.0%)
very common	497 (13.9%)	Asthenia	very common	780 (17.8%)
common	205 (5.7%)	Influenza like illness	-	-
common	230 (6.4%)	Chills	-	-
-	-	Oedema peripheral	very common	451 (10.3%)

Investigations				
-	-	Blood alkaline phosphatase increased	common	200 (4.6%)

[a] Includes reports of urinary tract infection, cystitis, pyelonephritis, escherichia urinary tract infection, urinary tract infection bacterial, kidney infection, pyelonephritis acute, urinary tract infection fungal, urinary tract infection pseudomonal.
[b] Includes reports of pneumonia, bronchitis, lung infection, lower respiratory tract infection, infective exacerbation of COPD, infectious pleural effusion, tracheobronchitis, atypical pneumonia, lung abscess, paracancerous pneumonia, pyopneumothorax, pleural infection.
[c] Includes reports of blood creatinine increased, hypercreatininaemia.
[d] Includes reports of thrombocytopenia, platelet count decreased.
[e] Includes reports of neutropenia, neutrophil count decreased, febrile neutropenia, neutropenic sepsis, granulocytopenia.
[f] Includes reports of white blood cell count decreased, leukopenia.
[g] Includes reports of lymphopenia, lymphocyte count decreased
[h] Includes reports of infusion related reaction
[i] Includes reports of autoimmune hypothyroidism, autoimmune thyroiditis, blood thyroid stimulating hormone abnormal, blood thyroid stimulating hormone decreased, blood thyroid stimulating hormone increased, euthyroid sick syndrome, goitre, hypothyroidism, myxoedema coma, thyroid disorder, thyroid function test abnormal, thyroiditis, thyroxine decreased, thyroxine free decreased, thyroxine free increased, thyroxine increased, tri-iodothyronine decreased, tri-iodothyronine free abnormal, tri-iodothyronine free decreased, tri-iodothyronine free increased, silent thyroiditis, thyroiditis chronic.
[j] Includes reports of hyperthyroidism, Basedow's disease, endocrine ophthalmopathy, exophthalmos.
[k] Includes reports of diabetes mellitus, type 1 diabetes mellitus, diabetic ketoacidosis, ketoacidosis.
[l] Includes reports of adrenal insufficiency, primary adrenal insufficiency.
[m] Incudes reports of hypophysitis, temperature regulation disorder.
[n] Includes reports of hypomagnesaemia, blood magnesium decreased.
[o] Includes reports of neuropathy peripheral, autoimmune neuropathy, peripheral sensory neuropathy, polyneuropathy, herpes zoster, peripheral motor neuropathy, neuralgic amyotrophy, peripheral sensorimotor neuropathy, toxic neuropathy, axonal neuropathy, lumbosacral plexopathy, neuropathic arthropathy, peripheral nerve infection.
[p] Includes reports of Guillain-Barré syndrome, demyelinating polyneuropathy.
[q] Includes reports of encephalitis, meningitis, photophobia.
[r] Incudes reports of myasthenia gravis.
[s] Reported in studies outside the pooled dataset. The frequency is based on the program wide exposure.
[t] Includes reports of pneumonitis, lung infiltration, bronchiolitis, interstitial lung disease, radiation pneumonitis.
[u] Includes reports of diarrhoea, defaecation urgency, frequent bowel movements, diarrhoea haemorrhagic.
[v] Includes reports of colitis, autoimmune colitis, colitis ischaemic, colitis microscopic, colitis ulcerative.
[w] Includes reports of oropharyngeal pain, oropharyngeal discomfort, throat irritation.
[x] Includes reports of autoimmune pancreatitis, pancreatitis, pancreatitis acute, lipase increased, amylase increased.
[y] Includes reports of ascites, autoimmune hepatitis, hepatocellular injury, hepatitis, hepatitis acute, hepatotoxicity, liver disorder, drug-induced liver injury, hepatic failure, hepatic steatosis, hepatic lesion, oesophageal varices haemorrhage, varices oesophageal.
[z] Includes reports of acne, acne pustular, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis exfoliative generalised, drug eruption, eczema, eczema infected, erythema, erythema multiforme, erythema of eyelid, exfoliative rash, folliculitis, furuncle, palmar-plantar erythrodysaesthesia syndrome, rash , rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, seborrhoeic dermatitis, skin exfoliation, skin toxicity, skin ulcer, toxic epidermal necrolysis, toxic skin eruption.
[aa] Includes reports of musculoskeletal pain, myalgia, bone pain.
[ab] Includes reports of myositis, rhabdomyolysis, polymyalgia rheumatica, dermatomyositis, muscle abscess, myoglobin urine present.
[ac] Includes reports of proteinuria, protein urine present, haemoglobinurea, urine abnormality, nephrotic syndrome, albuminuria.
[ad] Includes report of nephritis, Henoch-Schonlein Purpura nephritis.
[ae] Includes report of hypokalaemia, blood potassium decreased.
[af] Includes report of hyponatraemia, blood sodium decreased.
[ag] Includes report of hypoxia, oxygen saturation decreased.
[ah] Includes report of alopecia, madarosis, alopecia areata, alopecia totalis, hypotrichosis.
[ai] Includes reports of hypertension, blood pressure increased, hypertensive crisis, blood pressure systolic increased, diastolic hypertension, blood pressure inadequately controlled, retinopathy hypertensive, hypertensive nephropathy, essential hypertension.
[aj] Includes reports of sepsis, septic shock, urosepsis, neutropenic sepsis, pulmonary sepsis, bacterial sepsis, klebsiella sepsis, abdominal sepsis, candida sepsis, escherichia sepsis, pseudomonal sepsis, staphylococcal sepsis.

Serious adverse event/deaths/other significant events

Deaths

Table 58: Deaths and causes of death (safety-evaluable population)

	Sorafenib (N=156)	Atezo+Bev (N=329)	All Patients (N=485)
All Death			
n	64	93	157
<= 30 days after last dose	14 (9.0%)	11 (3.3%)	25 (5.2%)
> 30 days after last dose	50 (32.1%)	82 (24.9%)	132 (27.2%)
Primary Cause of Death			
n	64	93	157
Adverse Event	9 (5.8%)	15 (4.6%)	24 (4.9%)
Progressive Disease	51 (32.7%)	71 (21.6%)	122 (25.2%)
Other[a]	4 (2.6%)	7 (2.1%)	11 (2.3%)
n	4	7	11
Death Due To Cardio Pulmonary Arrest	0	1 (0.3%)	1 (0.2%)
Death Due To GI Bleed	1 (0.6%)	0	1 (0.2%)
Death Due To Heart Attack	1 (0.6%)	0	1 (0.2%)
Death Due To Post Study Reporting Of Death	1 (0.6%)	4 (1.2%)	5 (1.0%)
Death Due To Unknown	1 (0.6%)	2 (0.6%)	3 (0.6%)

Program: root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018/prod/program/t_dd.sas
Output: root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018/prod/output/t_dd_SE_29AUG2019_40245.out
12OCT2019 6:15

a = All deaths that were not attributed to disease progression and occurred either after the adverse event reporting period (see details in Section 3.9.5.2) or from public records, were reported as "other".

Table 59: Adverse events leading to death (Safety-evaluable population)

MedDRA System Organ Class MedDRA Preferred Term	Sorafenib (N=156)	Atezo+Bev (N=329)
Total number of patients with at least one adverse event	9 (5.8%)	15 (4.6%)
Overall total number of events	9	15
Gastrointestinal disorders		
Total number of patients with at least one adverse event	1 (0.6%)	5 (1.5%)
Total number of events	1	5
Gastrointestinal haemorrhage	0	3 (0.9%)
Gastric ulcer perforation	0	1 (0.3%)
Oesophageal varices haemorrhage	0	1 (0.3%)
Peritoneal haemorrhage	1 (0.6%)	0
Infections and infestations		
Total number of patients with at least one adverse event	1 (0.6%)	4 (1.2%)
Total number of events	1	4
Pneumonia	0	2 (0.6%)
Empyema	0	1 (0.3%)
Hepatitis E	1 (0.6%)	0
Sepsis	0	1 (0.3%)
General disorders and administration site conditions		
Total number of patients with at least one adverse event	3 (1.9%)	1 (0.3%)
Total number of events	3	1
Death[a]	2 (1.3%)	0
General physical health deterioration	1 (0.6%)	0
Multiple organ dysfunction syndrome	0	1 (0.3%)
Hepatobiliary disorders		
Total number of patients with at least one adverse event	2 (1.3%)	2 (0.6%)
Total number of events	2	2
Hepatic cirrhosis	2 (1.3%)	0
Hepatic function abnormal	0	1 (0.3%)
Liver injury	0	1 (0.3%)
Cardiac disorders		
Total number of patients with at least one adverse event	2 (1.3%)	1 (0.3%)
Total number of events	2	1
Cardiac arrest	1 (0.6%)	1 (0.3%)
Cardiac failure	1 (0.6%)	0
Nervous system disorders		
Total number of patients with at least one adverse event	0	1 (0.3%)
Total number of events	0	1
Subarachnoid haemorrhage	0	1 (0.3%)
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	0	1 (0.3%)
Total number of events	0	1
Respiratory distress	0	1 (0.3%)

Includes AEs with onset date on or after the date of the first dose of study drug up to the data cutoff date.
Investigator text for AEs are encoded using MedDRA version 22.0.

Program: root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018/prod/program/t_ae.sas
Output: root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018/prod/output/t_ae_SE_grade5_29AUG2019_40245.out
12OCT2019 6:16

a = The investigator reported the event as 'death' when the patient died suddenly and no autopsy result was avalilable.

Treatment-Related Fatal Adverse Events

In the SE population, 1 treatment-related Grade 5 AE occurred in the Sorafenib arm (hepatic cirrhosis) and 6 treatment-related Grade 5 AEs occurred in the Atezo+Bev arm. In the Atezo+Bev arm, the treatment-related Grade 5 AEs were pneumonia, subarachnoid hemorrhage, liver injury, hepatic function abnormal, gastric ulcer perforation, and gastrointestinal hemorrhage; and each of them occurred in 1 patient.

Summaries of the treatment-related Grade 5 AEs reported in the both arms are provided below.

Hepatic cirrhosis

This 47-year-old male patient had hepatic cirrhosis, esophageal varices and splenomegaly. No confirmed signs of disease progression were noted prior to the event of decompensated liver cirrhosis. The last dose of sorafenib was administered on Study Day 132. On the same day, the patient experienced ascites and a general condition of swelling of the legs. Relevant laboratory work-up showed AST 55 U/L, ALT 27 U/L, total

bilirubin 28.2 mmol/ L, and albumin 29 g/l. He was diagnosed with a Grade 2 decompensated liver cirrhosis. The patient received diuretic therapy and correction of water and electrolyte disorders. Sorafenib was discontinued due to the event of decompensated liver cirrhosis. The patient's condition worsened and he died due to decompensated liver cirrhosis on Study Day 223. The investigator considered this event as related to sorafenib and also as related to the concurrent condition of hepatic cirrhosis.

Pneumonia

This 71-year old male patient had no relevant concurrent condition reported and received the most recent dose of atezolizumab and bevacizumab prior to the event on Study Day 225. Prior to event onset, no confirmed disease progression was noticed. The patient developed severe lung infection and was admitted for septic shock on Study Day 231, which subsequently led to multi-organ impairment (kidney, heart, lung). The CT scan showed consolidation in the lungs. The patient died due to pneumonia on Study Day 240. The investigator considered the event as related to both atezolizumab and bevacizumab.

Subarachnoid hemorrhage

This 88-year-old male patient had a medical history of hypertension that was controlled under treatment. He received the most recent dose of atezolizumab and bevacizumab prior to the event on Study Day 126. The patient developed acute diffuse subarachnoid hemorrhage and was admitted to the intensive care unit on Study Day 147. The patient's blood pressure was 190/78 mm/Hg. CT head showed bilateral acute subarachnoid hemorrhage. Carotid duplex showed less than 50% stenosis of bilateral internal carotid arteries and greater than 50% stenosis of the bilateral external carotid arteries. The patient died due to subarachnoid hemorrhage on Study Day 152. The event was assessed as related to bevacizumab and disease under study but not related to atezolizumab by the investigator.

Liver injury

This 61-year-old male patient with hepatic cirrhosis and esophageal and gastric varices at baseline received the most recent dose of atezolizumab and bevacizumab prior to the event on Study Day 85. Prior to event onset, no confirmed disease progression was noticed. On Study Day 94, a laboratory work-up showed increased levels of total bilirubin of 9.35 mg/dl, ALT of 202 U/L, AST of 367 U/L, ALP of 298 U/L and the patient was diagnosed with Grade 2 liver injury. Liver biopsy result revealed bilirubinostasis and the conventional histological picture for toxic damage under the mentioned therapy. Both atezolizumab and bevacizumab were interrupted due to the event. The event did not improve after treatment with steroids and immunosuppressive agents (mycophenolate mofetil and tacrolimus). The patient died due to liver injury on Study Day 121. The event of liver injury was considered as related to atezolizumab and disease under study but not related to bevacizumab by the investigator.

Hepatic function abnormal

This 74-year-old male patient with hepatic fibrosis at baseline received the most recent dose of atezolizumab and bevacizumab prior to event on Study Day 22. The patient discontinued both study treatments on Study Day 43 due to disease progression. On Study Day 73, a laboratory work-up showed increased levels of AST of 806 U/L and ALT of 735 U/L. He developed Grade 4 hepatic function abnormal on Study Day 77, which was assessed as related to atezolizumab, and started treatment with steroids. On Study Day 86, a CT scan revealed hepatic atrophy which suggested that the patient developed liver failure and plasma exchange was started. The event did not improve and the patient died due to hepatic function abnormal on Study Day 90. The autopsy result revealed remarkable liver atrophy. There was also a necrosis of the ascending and transverse colon due to the direct invasion by HCC. The AE of hepatic function abnormal was assessed as related to atezolizumab, disease under study, and concurrent illness but not related to bevacizumab by the investigator.

Gastric ulcer perforation

This 76-year-old male patient had concurrent condition of duodenal ulcer and received the most recent dose of atezolizumab and bevacizumab prior to the event on Study Day 43. Prior to event onset no confirmed disease progression was noticed. On Study Day 64, a gastric penetration was identified on computer tomography (CT). The upper gastrointestinal series revealed no leakage of the contrast medium from the stomach. Gastroscopy revealed an ulcer on the stomach's anterior wall. The patient's Hemoglobin

was 6.4 g/dl and he received blood transfusion, omeprazole, and paracetamol for the event. The patient developed a gastric perforation despite treatment. Atezolizumab and bevacizumab were both discontinued due to gastric ulcer perforation. The patient developed peritonitis on Study Day 87. He died on Study Day 190 from deterioration of his nutritional condition due to the gastric ulcer perforation. The event of gastric ulcer perforation was assessed as related to bevacizumab by the investigator.

Gastrointestinal hemorrhage

This 58-year-old male patient was positive for macro-vascular invasion with portal vein tumor thrombosis in the first-order branches of the portal vein (VP3) and had hepatic cirrhosis at baseline. He received the most recent dose of atezolizumab and bevacizumab prior to the event on Study Day 44. The patient vomited blood at home on Study Day 62 and died at home on the next day. His last tumor assessment indicated stable disease. The Grade 5 AE of gastrointestinal hemorrhage was assessed as related to both atezolizumab and bevacizumab and also related to disease under study by the investigator.

Serious AEs

Table 60: Serious adverse events with an incidence rate of at least 1% in any treatment arm by system organ class and preferred term (safety-evaluable population)

MedDRA System Organ Class MedDRA Preferred Term	Sorafenib (N=156)	Atezo+Bev (N=329)
Total number of patients with at least one adverse event	48 (30.8%)	125 (38.0%)
Overall total number of events	83	221
Gastrointestinal disorders		
Total number of patients with at least one adverse event	18 (11.5%)	49 (14.9%)
Total number of events	22	58
Gastrointestinal haemorrhage	3 (1.9%)	8 (2.4%)
Oesophageal varices haemorrhage	1 (0.6%)	8 (2.4%)
Ascites	1 (0.6%)	5 (1.5%)
Abdominal pain	2 (1.3%)	2 (0.6%)
Upper gastrointestinal haemorrhage	2 (1.3%)	2 (0.6%)
Pancreatitis	2 (1.3%)	1 (0.3%)
Peritoneal haemorrhage	2 (1.3%)	0
Infections and infestations		
Total number of patients with at least one adverse event	3 (1.9%)	24 (7.3%)
Total number of events	3	28
Sepsis	0	5 (1.5%)
Hepatobiliary disorders		
Total number of patients with at least one adverse event	9 (5.8%)	16 (4.9%)
Total number of events	9	19
Cholangitis	1 (0.6%)	4 (1.2%)
Hepatic cirrhosis	2 (1.3%)	0
Hepatic failure	2 (1.3%)	0
Respiratory, thoracic and mediastinal disorders		
Total number of patients with at least one adverse event	7 (4.5%)	15 (4.6%)
Total number of events	9	16
Dyspnoea	2 (1.3%)	3 (0.9%)
Pulmonary embolism	2 (1.3%)	3 (0.9%)
General disorders and administration site conditions		
Total number of patients with at least one adverse event	5 (3.2%)	10 (3.0%)
Total number of events	5	10
Pyrexia	2 (1.3%)	7 (2.1%)
Death	2 (1.3%)	0
Nervous system disorders		
Total number of patients with at least one adverse event	5 (3.2%)	10 (3.0%)
Total number of events	5	10
Hepatic encephalopathy	3 (1.9%)	2 (0.6%)

Metabolism and nutrition disorders		
Total number of patients with at least one adverse event	4 (2.6%)	10 (3.0%)
Total number of events	5	11
Hyponatraemia	2 (1.3%)	0
Investigations		
Total number of patients with at least one adverse event	4 (2.6%)	9 (2.7%)
Total number of events	6	10
Blood bilirubin increased	2 (1.3%)	4 (1.2%)
Blood and lymphatic system disorders		
Total number of patients with at least one adverse event	4 (2.6%)	6 (1.8%)
Total number of events	4	10
Anaemia	2 (1.3%)	4 (1.2%)
Thrombocytopenia	2 (1.3%)	2 (0.6%)
Injury, poisoning and procedural complications		
Total number of patients with at least one adverse event	2 (1.3%)	7 (2.1%)
Total number of events	2	8
Infusion related reaction	0	4 (1.2%)
Renal and urinary disorders		
Total number of patients with at least one adverse event	3 (1.9%)	3 (0.9%)
Total number of events	3	3
Acute kidney injury	2 (1.3%)	2 (0.6%)

Includes AEs with onset date on or after the date of the first dose of study drug up to the data cutoff date.
Investigator text for AEs are encoded using MedDRA version 22.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Laboratory findings

Table 61: Clinically relevant laboratory safety test shifts from baseline (NCI CTCAE Grade 0-2 to Grade 3-4) (Safety-evaluable population)

	Sorafenib (N=156)	Atezo + Bev (N=329)	All patients (N=485)
Hematology			
Hemoglobin (High)	0	0	0
Hemoglobin (Low)	6 (3.9%)	10 (3.1%)	16 (3.4%)
Lymphocytes Abs (High)	0	0	0
Lymphocytes Abs (Low)	8 (9.1%)	28 (12.7%)	36 (11.7%)
Platelet (Low)	7 (4.6%)	21 (6.5%)	28 (5.9%)
Neutrophils, Total, Abs (Low)	1 (1.1%)	5 (2.3%)	6 (1.9%)
Total Leukocyte Count (High)	0	0	0
Total Leukocyte Count (Low)	2 (1.3%)	11 (3.4%)	13 (2.7%)
Coagulation			
International Normalized Ratio (High)	1 (0.7%)	1 (0.3%)	2 (0.4%)
Activated Partial Thromboplastin Time (High)	1 (0.7%)	0	1 (0.2%)
Chemistry			
Albumin (Low)	1 (0.7%)	5 (1.5%)	6 (1.3%)
Alkaline Phosphatase (High)	7 (4.6%)	14 (4.3%)	21 (4.4%)
SGPT/ALT (High)	7 (4.6%)	24 (7.5%)	31 (6.5%)
SGOT/AST (High)	23 (15.1%)	50 (15.6%)	73 (15.4%)
Bilirubin (High)	20 (13.2%)	25 (7.7%)	45 (9.5%)
Calcium (High)	0	1 (0.3%)	1 (0.2%)
Calcium (Low)	2 (1.3%)	1 (0.3%)	3 (0.6%)
Creatinine (High)	4 (2.6%)	3 (0.9%)	7 (1.5%)
Glucose (High)	5 (3.4%)	25 (7.9%)	30 (6.5%)
Glucose (Low)	1 (0.7%)	4 (1.2%)	5 (1.1%)
Magnesium (High)	2 (1.3%)	2 (0.6%)	4 (0.9%)
Magnesium (Low)	0	0	0
Phosphorus (Low)	23 (15.3%)	14 (4.4%)	37 (7.9%)
Potassium (High)	3 (2.0%)	6 (1.9%)	9 (1.9%)
Potassium (Low)	9 (5.9%)	4 (1.2%)	13 (2.7%)
Sodium (High)	0	1 (0.3%)	1 (0.2%)
Sodium (Low)	14 (9.2%)	40 (12.5%)	54 (11.4%)

Note: A clinically relevant shift is defined as a shift from Grade 0, 1 or 2 at baseline to Grade 3 or 4 post-baseline.

The proportion of patients who had normal TSH at baseline and treatment-emergent TSH abnormalities (high TSH) was lower in the Sorafenib arm (16.7%) compared to the Atezo+Bev arm (28.0%). The proportion of patients who had normal TSH at baseline and treatment-emergent TSH abnormalities (low TSH) was numerically lower on Sorafenib (2.6%) compared to the Atezo+ Bev arm (8.2%). There were patients with both treatment-emergent TSH high and TSH low laboratory values in the Atezo+Bev arm.

Table 62: TSH Shift Table of post-baseline changes – safety-evaluable population (cut-off date 29 Aug 2019)

Laboratory Test: Thyroid-Stimulating Hormone (mU/L)

Treatment Group	Baseline Reference Range Indicator	Post-Baseline Low	Post-Baseline Normal	Post-Baseline High
Sorafenib (N=156)	Low	0	0	0
	Normal	4 (2.6%)	135 (86.5%)	26 (16.7%)
	High	1 (0.6%)	6 (3.8%)	18 (11.5%)
	Missing	0	2 (1.3%)	1 (0.6%)
Atezo + Bev (N=329)	Low	9 (2.7%)	7 (2.1%)	0
	Normal	27 (8.2%)	284 (86.3%)	92 (28.0%)
	High	4 (1.2%)	13 (4.0%)	31 (9.4%)
	Missing	0	4 (1.2%)	1 (0.3%)

Patients with both missing and non-missing baseline Thyroid Stimulating Hormone(TSH) labs are included.
If one patient has one post-baseline measurement of high and the other as low, then both measurements contribute to this table.
Elevated TSH were patients with an increase from baseline and the post baseline value is above upper limit reference. Decreased TSH were patients with a decrease from baseline and the post baseline value is below lower limit reference.
Local lab reference ranges are used to assess the out of range values.

An overview of safety in the safety-evaluable population with moderate hepatic impairment is provided in the table below.

Table 63: Overall Summary of Adverse Events in patients with moderate hepatic impairment (Safety Evaluable Population)

	Patients with Moderate Hepatic Impairment		All Patients Population	
	Sorafenib N=18	Atezo + Bev N=28	Sorafenib N=156	Atezo + Bev N=329
Total number of patients with at least one AE	18 (100%)	27 (96.4%)	154 (98.7%)	323 (98.2%)
Total number of patients with at least one:				
AE Related to any Study Treatment	17 (94.4%)	22 (78.6%)	147 (94.2%)	276 (83.9%)
AE Related to Atezolizumab	0	21 (75.0%)	0	252 (76.6%)
AE Related to Bevacizumab	0	18 (64.3%)	0	241 (73.3%)
Grade 3–4 AE	11 (61.1%)	16 (57.1%)	86 (55.1%)	186 (56.5%)
Treatment-related Grade 3–4 AE	9 (50.0%)	9 (32.1%)	71 (45.5%)	117 (35.6%)
Grade 5 AE	1 (5.6%)	2 (7.1%)	9 (5.8%)	15 (4.6%)
Treatment-related Grade 5 AE	0	0	1 (0.6%)	6 (1.8%)
Serious AE	6 (33.3%)	14 (50.0%)	48 (30.8%)	125 (38.0%)
Related Serious AE	4 (22.2%)	6 (21.4%)	24 (15.4%)	56 (17.0%)
AE Leading to Withdrawal from any Study Treatment	2 (11.1%)	5 (17.9%)	16 (10.3%)	51 (15.5%)
AE Leading to Withdrawal from Atezolizumab	0	3 (10.7%)	0	28 (8.5%)
AE Leading to Withdrawal from Bevacizumab	0	5 (17.9%)	0	48 (14.6%)
AE Leading to Withdrawal from Both Atezolizumab and Bevacizumab	0	3 (10.7%)	0	23 (7.0%)
AE Leading to Dose Modification/Interruption of any Study Treatment	11 (61.1%)	14 (50.0%)	95 (60.9%)	163 (49.5%)
AE Leading to Dose Interruption of any Study Treatment	10 (55.6%)	14 (50.0%)	64 (41.0%)	163 (49.5%)
AE Leading to Dose Reduction of Sorafenib	6 (33.3%)	0	58 (37.2%)	0

Note: Includes AEs with onset date on or after the date of the first dose of study drug up to the data cutoff date. Investigator text for AEs are encoded using MedDRA version 22.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately. Grade 3-4 AE and Treatment-Related Grade 3-4 AE refer to highest grade experienced.

Table 64: **Summary of Adverse Events of Special Interest for Atezolizumab (Safety-Evaluable Population)**

	Patients with Moderate Hepatic Impairment		All Patients Population	
	Sorafenib N=18	**Atezo+Bev N=28**	**Sorafenib N=156**	**Atezo+Bev N=329**
Total number of patients with at least one:				
Atezolizumab AESI				
Immune-Mediated Hepatitis (Diagnosis and Lab Abnormalities)	12 (66.7%)	22 (78.6%)	62 (39.7%)	142 (43.2%)
Immune-Mediated Hepatitis (Lab Abnormalities)	11 (61.1%)	18 (64.3%)	54 (34.6%)	126 (38.3%)
Immune-Mediated Hepatitis (Diagnosis)	2 (11.1%)	9 (32.1%)	20 (12.8%)	43 (13.1%)
Immune-Mediated Rash	12 (66.7%)	3 (10.7%)	96 (61.5%)	64 (19.5%)
Immune-Mediated Hypothyroidism	0	4 (14.3%)	4 (2.6%)	36 (10.9%)
Infusion-Related Reactions	0	6 (21.4%)	0	36 (10.9%)
Immune-Mediated Hyperthyroidism	0	1 (3.6%)	0	15 (4.6%)
Immune-Mediated Pancreatitis	0	3 (10.7%)	6 (3.8%)	9 (2.7%)
Immune-Mediated Diabetes Mellitus	0	2 (7.1%)	0	8 (2.4%)
Immune-Mediated Colitis	0	1 (3.6%)	1 (0.6%)	6 (1.8%)
Immune-Mediated Pneumonitis	0	0	0	4 (1.2%)
Immune-Mediated Nephritis	0	0	0	3 (0.9%)
Autoimmune Hemolytic Anemia	0	0	0	1 (0.3%)
Immune-Mediated Adrenal Insufficiency	0	0	0	1 (0.3%)
Immune-Mediated Ocular Inflammatory Toxicity	0	0	0	1 (0.3%)
Immune-Mediated Severe Cutaneous Reactions	1 (5.6%)	0	1 (0.6%)	0
Immune-Mediated Vasculitis	0	1 (3.6%)	0	1 (0.3%)
Systemic Immune Activation	0	0	0	1 (0.3%)
Bevacizumab AESI				
Hypertension	4 (22.2%)	5 (17.9%)	40 (25.6%)	102 (31.0%)
Bleeding / Haemorrhage	3 (16.7%)	7 (25.0%)	27 (17.3%)	83 (25.2%)
Proteinuria	0	7 (25.0%)	13 (8.3%)	70 (21.3%)
Thromboembolic Event - Venous	0	1 (3.6%)	5 (3.2%)	10 (3.0%)
Thromboembolic Event - Arterial	0	1 (3.6%)	2 (1.3%)	9 (2.7%)
Congestive Heart Failure	1 (5.6%)	0	2 (1.3%)	1 (0.3%)
Wound Healing Complications	0	0	0	2 (0.6%)
Fistula/Abscess (Non GI)	1 (5.6%)	0	1 (0.6%)	0
Gastrointestinal Perforation	0	0	0	1 (0.3%)

AESIs=adverse events of special interest
Note: Includes AEs with onset date on or after the date of the first dose of study drug up to the data cutoff date.

Hy's Law Analysis

Potential Hy's law cases were defined in the study protocol as ALT or AST increases above 3xfold the baseline with concomitant total bilirubin increases above 2xfold the ULN within 7 days.

Following detailed review, 24 of the 26 potential Hy's law cases (13 in the Sorafenib and 11 in the Atezo+Bev arm) did not qualify as true Hy's law cases due to the following reasons:

- Patients had liver function test abnormalities in the context of investigator-assessed progressive disease (9 cases in the Sorafenib arm and 6 cases in the Atezo+Bev arm)
- The liver function abnormalities could be attributed to alternate etiologies, including cholangitis or disease under study (4 cases in the Sorafenib arm and 5 cases in the Atezo+Bev arm).

The 2 remaining potential Hy's law cases (1 patient in each treatment arm) were classified as true Hy's law cases due to the lack of alternate etiology. The patient in the Sorafenib arm experienced Grade 3 blood bilirubin increased on Study Day 22. Sorafenib was interrupted due to the event and the Grade 3 blood bilirubin increased resolved on Study Day 29. On Study Day 50, the patient experienced elevated liver function tests in the Hy's law range with a corresponding Grade 4 liver function test increased and Grade 3 blood bilirubin increased. Sorafenib was permanently discontinued due to these events and the

event resolved on Study Day 78. The event was assessed as related to Sorafenib. Due to the lack of alternate etiology and the positive re-challenge, this case met the criteria for Hy's law.

The patient in the Atezo+Bev arm experienced Grade 4 hepatobiliary disease on Study Day 9 prior to elevated liver function tests in the Hy's law range on Study Day 36. The event led to both atezolizumab and bevacizumab discontinuation. The patient received mycophenolate mofetil and methylprednisolone for the event. Hepatobiliary disease resolved. The event was assessed as related to both study treatments.

Table 65: Summary for potential Hy's law analysis (safety-evaluable population)

	Sorafenib (N=156)	Atezo+Bev (N=329)	All Patients (N=485)
Hy's Law Criteria Met	14 (9.0%)	12 (3.6%)	26 (5.4%)

Patients who met Hy's Law Criteria reported at least one TBILI > 2 x ULN within 7 days after latest ALT or AST > 3 x baseline.
Reference Range of Local Labs are used.
ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase, TBILI = Bilirubin, Normalized scores are the reported scores divided by ULN. ULN = Upper Limit Normal.

Safety in special populations

Intrinsic factors: age, safety in elderly

Overall, the safety profile of Atezo+Bev was generally comparable across all age groups.

The majority of patients across all age groups reported at least one AE. The distribution of AE categories was comparable between the < 65 years and ≥ 65 years age subgroups).

The smaller sample size for the subgroups of 75-84 years (n = 66) and ≥ 85 years (n = 7) limits meaningful conclusions in these two subgroups.

While there were some numerical differences in certain atezolizumab AESI categories between patients aged < 65 years (n = 277) and ≥ 65 years (n = 216), the overall atezolizumab AESI profiles were also similar between the two groups.

Table 66: Overview of AE by Age between Atezo+Bev and sorafenib population (<65 vs. ≥65 years)

	Sorafenib HCC (N=156)		Atezo+Bev HCC (N=493)	
	< 65 (N=69)	>= 65 (N=87)	< 65 (N=277)	>= 65 (N=216)
Total number of patients with at least one AE	67 (97.1%)	87 (100%)	266 (96.0%)	214 (99.1%)
Total number of events	519	780	2661	2038
Total number of patients with at least one				
Treatment-related AE	63 (91.3%)	84 (96.6%)	226 (81.6%)	182 (84.3%)
Atezo-related AE	0	0	202 (72.9%)	166 (76.9%)
Grade 3-4 AE	35 (50.7%)	51 (58.6%)	140 (50.5%)	123 (56.9%)
Treatment-related Grade 3-4 AE	26 (37.7%)	45 (51.7%)	87 (31.4%)	83 (38.4%)
Atezo-related Grade 3-4 AE	0	0	67 (24.2%)	50 (23.1%)
Grade 5 AE	3 (4.3%)	6 (6.9%)	10 (3.6%)	12 (5.6%)
Treatment-related Grade 5 AE	1 (1.4%)	0	3 (1.1%)	6 (2.8%)
Atezo-related Grade 5 AE	0	0	3 (1.1%)	4 (1.9%)
Serious AE	16 (23.2%)	32 (36.8%)	101 (36.5%)	85 (39.4%)
Treatment-related serious AE	8 (11.6%)	16 (18.4%)	46 (16.6%)	42 (19.4%)
Atezo-related serious AE	0	0	34 (12.3%)	31 (14.4%)
AE leading to any Study Treatment withdrawal	3 (4.3%)	13 (14.9%)	33 (11.9%)	42 (19.4%)
AE leading to Atezo withdrawal	0	0	19 (6.9%)	23 (10.6%)
AE leading to any Dose modification or Study Treatment interruption	40 (58.0%)	55 (63.2%)	113 (40.8%)	109 (50.5%)
AE leading to Atezo interruption	0	0	80 (28.9%)	85 (39.4%)

Atezo=Atezolizumab Bev=Bevacizumab. Sorafenib HCC: YO40245(Arm B). Atezo+Bev HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. All treatment emergent AEs are included.
Clinical cut-off dates: YO40245:29AUG2019, GO30140:14JUN2019.

Table 67: Overview of AE by Age between Atezo+Bev and sorafenib population (≥65 years)

	Sorafenib HCC (N=156)			Atezo+Bev HCC (N=493)		
	65 - 74 (N=63)	75 - 84 (N=23)	>=85 (N=1)	65 - 74 (N=143)	75 - 84 (N=66)	>=85 (N=7)
Total number of patients with at least one AE	63 (100%)	23 (100%)	1 (100%)	141 (98.6%)	66 (100%)	7 (100%)
Total number of events	606	166	8	1306	652	80
Total number of patients with at least one						
Treatment-related AE	61 (96.8%)	22 (95.7%)	1 (100%)	119 (83.2%)	59 (89.4%)	4 (57.1%)
Atezo-related AE	0	0	0	108 (75.5%)	55 (83.3%)	3 (42.9%)
Grade 3-4 AE	39 (61.9%)	11 (47.8%)	1 (100%)	76 (53.1%)	42 (63.6%)	5 (71.4%)
Treatment-related Grade 3-4 AE	33 (52.4%)	11 (47.8%)	1 (100%)	50 (35.0%)	31 (47.0%)	2 (28.6%)
Atezo-related Grade 3-4 AE	0	0	0	25 (17.5%)	24 (36.4%)	1 (14.3%)
Grade 5 AE	4 (6.3%)	2 (8.7%)	0	7 (4.9%)	4 (6.1%)	1 (14.3%)
Treatment-related Grade 5 AE	0	0	0	3 (2.1%)	2 (3.0%)	1 (14.3%)
Atezo-related Grade 5 AE	0	0	0	3 (2.1%)	1 (1.5%)	0
Serious AE	23 (36.5%)	8 (34.8%)	1 (100%)	50 (35.0%)	31 (47.0%)	4 (57.1%)
Treatment-related serious AE	13 (20.6%)	2 (8.7%)	1 (100%)	22 (15.4%)	19 (28.8%)	1 (14.3%)
Atezo-related serious AE	0	0	0	15 (10.5%)	16 (24.2%)	0
AE leading to any Study Treatment withdrawal	9 (14.3%)	4 (17.4%)	0	25 (17.5%)	16 (24.2%)	1 (14.3%)
AE leading to Atezo withdrawal	0	0	0	11 (7.7%)	11 (16.7%)	1 (14.3%)
AE leading to any Dose modification or Study Treatment interruption	39 (61.9%)	15 (65.2%)	1 (100%)	68 (47.6%)	37 (56.1%)	4 (57.1%)
AE leading to Atezo interruption	0	0	0	53 (37.1%)	28 (42.4%)	4 (57.1%)

Atezo=Atezolizumab Bev=Bevacizumab. Sorafenib HCC: YO40245(Arm B). Atezo+Bev HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. All treatment emergent AEs are included.
Clinical cut-off dates: YO40245:29AUG2019, GO30140:14JUN2019.

Table 68: Overview AESI for Atezo by Atezolizumab, by Age Categories (Years)

	Atezo+Bev HCC (N=493)				
	< 65 (N=277)	>= 65 (N=216)	65 - 74 (N=143)	75 - 84 (N=66)	>=85 (N=7)
Total number of patients with at least one AE of Special Interest	187 (67.5%)	133 (61.6%)	86 (60.1%)	44 (66.7%)	3 (42.9%)
Total number of events	439	314	205	103	6
Total number of patients with at least one					
Treatment-related AE of Special Interest	143 (51.6%)	97 (44.9%)	61 (42.7%)	34 (51.5%)	2 (28.6%)
Atezo-related AE of Special Interest	138 (49.8%)	91 (42.1%)	57 (39.9%)	33 (50.0%)	1 (14.3%)
Grade 3-4 AE of Special Interest	66 (23.8%)	49 (22.7%)	32 (22.4%)	15 (22.7%)	2 (28.6%)
Treatment-related Grade 3-4 AE of Special Interest	33 (11.9%)	31 (14.4%)	17 (11.9%)	13 (19.7%)	1 (14.3%)
Atezo-related Grade 3-4 AE of Special Interest	32 (11.6%)	27 (12.5%)	14 (9.8%)	12 (18.2%)	1 (14.3%)
Grade 5 AE of Special Interest	2 (0.7%)	4 (1.9%)	2 (1.4%)	2 (3.0%)	0
Treatment-related Grade 5 AE of Special Interest	2 (0.7%)	3 (1.4%)	2 (1.4%)	1 (1.5%)	0
Atezo-related Grade 5 AE of Special Interest	2 (0.7%)	3 (1.4%)	2 (1.4%)	1 (1.5%)	0
Serious AE of Special Interest	29 (10.5%)	37 (17.1%)	23 (16.1%)	13 (19.7%)	1 (14.3%)
Treatment-related Serious AE of Special Interest	13 (4.7%)	21 (9.7%)	11 (7.7%)	10 (15.2%)	0
Atezo-related Serious AE of Special Interest	12 (4.3%)	18 (8.3%)	9 (6.3%)	9 (13.6%)	0
AE of Special Interest leading to any Study Treatment withdrawal	12 (4.3%)	17 (7.9%)	13 (9.1%)	4 (6.1%)	0
AE of Special Interest leading to Atezo withdrawal	10 (3.6%)	12 (5.6%)	8 (5.6%)	4 (6.1%)	0
AE of Special Interest leading to any Dose modification or Study Treatment interruption	42 (15.2%)	39 (18.1%)	26 (18.2%)	11 (16.7%)	2 (28.6%)
AE of Special Interest leading to Atezo interruption	37 (13.4%)	33 (15.3%)	24 (16.8%)	7 (10.6%)	2 (28.6%)
AE of Special Interest Requiring the Use of Systemic Corticosteroids	25 (9.0%)	35 (16.2%)	15 (10.5%)	18 (27.3%)	2 (28.6%)

Intrinsic factor: sex

Consistent with the disease demographics for HCC, the majority of patients were men (82.8%). The overall safety profile of Atezo+Bev was comparable between men and women with the following exceptions: a numerically higher percentage of men experienced Grade 5 AEs (5.1% vs 1.2%) and treatment-related Grade 5 AEs (2.2% vs. 0). Due to the relatively smaller number of female patients compared with the male patients, these differences should be interpreted with caution.

Table 69: Overview of Adverse Events by Sex (safety-evaluable population)

	Sorafenib HCC (N=156)		Atezo+Bev HCC (N=493)	
	Female (N=27)	Male (N=129)	Female (N=85)	Male (N=408)
Total number of patients with at least one AE	27 (100%)	127 (98.4%)	83 (97.6%)	397 (97.3%)
Total number of events	218	1081	796	3903
Total number of patients with at least one				
Treatment-related AE	27 (100%)	120 (93.0%)	70 (82.4%)	338 (82.8%)
Atezo-related AE	0	0	62 (72.9%)	306 (75.0%)
Grade 3-4 AE	16 (59.3%)	70 (54.3%)	46 (54.1%)	217 (53.2%)
Treatment-related Grade 3-4 AE	12 (44.4%)	59 (45.7%)	29 (34.1%)	141 (34.6%)
Atezo-related Grade 3-4 AE	0	0	22 (25.9%)	95 (23.3%)
Grade 5 AE	0	9 (7.0%)	1 (1.2%)	21 (5.1%)
Treatment-related Grade 5 AE	0	1 (0.8%)	0	9 (2.2%)
Atezo-related Grade 5 AE	0	0	0	7 (1.7%)
Serious AE	7 (25.9%)	41 (31.8%)	32 (37.6%)	154 (37.7%)
Treatment-related serious AE	3 (11.1%)	21 (16.3%)	16 (18.8%)	72 (17.6%)
Atezo-related serious AE	0	0	12 (14.1%)	53 (13.0%)
AE leading to any Study Treatment withdrawal	5 (18.5%)	11 (8.5%)	13 (15.3%)	62 (15.2%)
AE leading to Atezo withdrawal	0	0	8 (9.4%)	34 (8.3%)
AE leading to any Dose modification or Study Treatment interruption	15 (55.6%)	80 (62.0%)	42 (49.4%)	180 (44.1%)
AE leading to Atezo interruption	0	0	29 (34.1%)	136 (33.3%)

Atezo=Atezolizumab Bev=Bevacizumab. Sorafenib HCC: YO40245(Arm B). Atezo+Bev HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. All treatment emergent AEs are included.
Clinical cut-off dates: YO40245:29AUG2019, GO30140:14JUN2019.

Table 70: Overview AESI for Atezo by Sex

	Atezo+Bev HCC (N=493)	
	Female (N=85)	Male (N=408)
Total number of patients with at least one AE of Special Interest	53 (62.4%)	267 (65.4%)
Total number of events	104	649
Total number of patients with at least one		
Treatment-related AE of Special Interest	39 (45.9%)	201 (49.3%)
Atezo-related AE of Special Interest	38 (44.7%)	191 (46.8%)
Grade 3-4 AE of Special Interest	18 (21.2%)	97 (23.8%)
Treatment-related Grade 3-4 AE of Special Interest	11 (12.9%)	53 (13.0%)
Atezo-related Grade 3-4 AE of Special Interest	11 (12.9%)	48 (11.8%)
Grade 5 AE of Special Interest	0	6 (1.5%)
Treatment-related Grade 5 AE of Special Interest	0	5 (1.2%)
Atezo-related Grade 5 AE of Special Interest	0	5 (1.2%)
Serious AE of Special Interest	10 (11.8%)	56 (13.7%)
Treatment-related Serious AE of Special Interest	5 (5.9%)	29 (7.1%)
Atezo-related Serious AE of Special Interest	5 (5.9%)	25 (6.1%)
AE of Special Interest leading to any Study Treatment withdrawal	4 (4.7%)	25 (6.1%)
AE of Special Interest leading to Atezo withdrawal	4 (4.7%)	18 (4.4%)
AE of Special Interest leading to any Dose modification or Study Treatment interruption	11 (12.9%)	70 (17.2%)
AE of Special Interest leading to Atezo interruption	9 (10.6%)	61 (15.0%)
AE of Special Interest Requiring the Use of Systemic Corticosteroids	11 (12.9%)	49 (12.0%)
Special Interest AE Medical Concepts: patients with at least one		
Immune-Mediated Hepatitis (Diagnosis and Lab Abnormalities)	24 (28.2%)	167 (40.9%)
Immune-Mediated Hepatitis (Lab Abnormalities)	23 (27.1%)	148 (36.3%)
Immune-Mediated Rash	20 (23.5%)	89 (21.8%)
Immune-Mediated Hepatitis (Diagnosis)	6 (7.1%)	54 (13.2%)
Immune-Mediated Hypothyroidism	5 (5.9%)	44 (10.8%)
Infusion-Related Reactions	10 (11.8%)	33 (8.1%)
Immune-Mediated Hyperthyroidism	3 (3.5%)	13 (3.2%)
Immune-Mediated Pancreatitis	3 (3.5%)	8 (2.0%)
Immune-Mediated Diabetes Mellitus	3 (3.5%)	7 (1.7%)
Immune-Mediated Colitis	2 (2.4%)	7 (1.7%)
Immune-Mediated Pneumonitis	1 (1.2%)	6 (1.5%)
Immune-Mediated Nephritis	1 (1.2%)	2 (0.5%)
Immune-Mediated Myositis (Myositis+Rhabdomyolysis)	0	3 (0.7%)
Immune-Mediated Adrenal Insufficiency	0	2 (0.5%)
Rhabdomyolysis	0	2 (0.5%)
Special Interest AE Medical Concepts: patients with at least one		
Autoimmune Hemolytic Anemia	0	2 (0.5%)
Immune-Mediated Meningoencephalitis	0	1 (0.2%)
Immune-Mediated Myositis	0	1 (0.2%)
Systemic Immune Activation	0	1 (0.2%)
Immune-Mediated Ocular Inflammatory Toxicity	0	1 (0.2%)
Immune-Mediated Myocarditis	0	1 (0.2%)
Immune-Mediated Guillain-Barre Syndrome	0	1 (0.2%)
Immune-Mediated Encephalitis	0	1 (0.2%)
Immune-Mediated Vasculitis	0	1 (0.2%)

Intrinsic factor: Race

Overall, the highest frequency in AE grade 3-4 were reported Hypertension, AST increased, Proteinuria blood bilirubin increased, platelet count decreased, ALT increased and Hyponatraemia in all subgroups.

However, the majority of patients in the Atezo+Bev population were Asians (62.1%), with Whites accounting for 31.0%. Given the relatively small sample sizes in "Black" (n=13) and "Other" (n=21) subgroups, the safety analyses by race is presented for the Asian and White subgroups only.

While there was a numerical increase in incidence of events in AE categories in White patients when compared to Asian patients, these increases were not driven by any specific SOC or PT.

Table 71: Overview of Adverse Events in Atezo+Bev and Sorafenib HCC Patients by Race (Safety Evaluable Patients)

	Sorafenib HCC (N=156)		Atezo+Bev HCC (N=493)	
	White (N=51)	Black (N=4)	White (N=153)	Black (N=13)
Total number of patients with at least one AE	51 (100%)	4 (100%)	152 (99.3%)	13 (100%)
Total number of events	437	20	1605	194
Total number of patients with at least one				
Treatment-related AE	48 (94.1%)	4 (100%)	134 (87.6%)	11 (84.6%)
Atezo-related AE	0	0	120 (78.4%)	10 (76.9%)
Grade 3-4 AE	29 (56.9%)	2 (50.0%)	87 (56.9%)	9 (69.2%)
Treatment-related Grade 3-4 AE	21 (41.2%)	2 (50.0%)	55 (35.9%)	4 (30.8%)
Atezo-related Grade 3-4 AE	0	0	38 (24.8%)	3 (23.1%)
Grade 5 AE	5 (9.8%)	0	8 (5.2%)	1 (7.7%)
Treatment-related Grade 5 AE	1 (2.0%)	0	2 (1.3%)	0
Atezo-related Grade 5 AE	0	0	2 (1.3%)	0
Serious AE	24 (47.1%)	0	63 (41.2%)	7 (53.8%)
Treatment-related serious AE	10 (19.6%)	0	29 (19.0%)	3 (23.1%)
Atezo-related serious AE	0	0	21 (13.7%)	1 (7.7%)
AE leading to any Study Treatment withdrawal	6 (11.8%)	0	31 (20.3%)	2 (15.4%)
AE leading to Atezo withdrawal	0	0	16 (10.5%)	2 (15.4%)
AE leading to any Dose modification or Study Treatment interruption	34 (66.7%)	2 (50.0%)	82 (53.6%)	8 (61.5%)
AE leading to Atezo interruption	0	0	71 (46.4%)	5 (38.5%)

	Sorafenib HCC (N=156)		Atezo+Bev HCC (N=493)	
	Asian (N=88)	Other (N=13)	Asian (N=306)	Other (N=21)
Total number of patients with at least one AE	86 (97.7%)	13 (100%)	294 (96.1%)	21 (100%)
Total number of events	726	116	2621	279
Total number of patients with at least one				
Treatment-related AE	82 (93.2%)	13 (100%)	247 (80.7%)	16 (76.2%)
Atezo-related AE	0	0	222 (72.5%)	16 (76.2%)
Grade 3-4 AE	49 (55.7%)	6 (46.2%)	152 (49.7%)	15 (71.4%)
Treatment-related Grade 3-4 AE	40 (45.5%)	8 (61.5%)	105 (34.3%)	6 (28.6%)
Atezo-related Grade 3-4 AE	0	0	71 (23.2%)	5 (23.8%)
Grade 5 AE	1 (1.1%)	3 (23.1%)	11 (3.6%)	2 (9.5%)
Treatment-related Grade 5 AE	0	0	7 (2.3%)	0
Atezo-related Grade 5 AE	0	0	5 (1.6%)	0
Serious AE	16 (18.2%)	8 (61.5%)	104 (34.0%)	12 (57.1%)
Treatment-related serious AE	8 (9.1%)	6 (46.2%)	51 (16.7%)	5 (23.8%)
Atezo-related serious AE	0	0	38 (12.4%)	5 (23.8%)
AE leading to any Study Treatment withdrawal	5 (5.7%)	5 (38.5%)	37 (12.1%)	5 (23.8%)
AE leading to Atezo withdrawal	0	0	20 (6.5%)	4 (19.0%)
AE leading to any Dose modification or Study Treatment interruption	51 (58.0%)	8 (61.5%)	119 (38.9%)	13 (61.9%)
AE leading to Atezo interruption	0	0	78 (25.5%)	11 (52.4%)

Atezo=Atezolizumab Bev=Bevacizumab. Sorafenib HCC: YO40245(Arm B). Atezo+Bev HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. All treatment emergent AEs are included.
Clinical cut-off dates: YO40245:29AUG2019, GO30140:14JUN2019.

Extrinsic factors HCC: Etiology

Approximately half of Atezo + Bev and Sorafenib treated HCC patients had the etiology of hepatitis B virus (HBV) infection (Atezo + Bev: 50.1%, Sorafenib: 45.5%), followed by non-viral etiologies (Atezo + Bev: 27.4%, Sorafenib: 33.3%) and hepatitis C virus (HCV) infection (Atezo + Bev: 22.5%, Sorafenib: 21.2%).

Table 72: Overview AE by HCC Etiology (safety-evaluable population)

	Sorafenib HCC (N=156)			Atezo+Bev HCC (N=493)		
	Hepatitis B (N=71)	Hepatitis C (N=33)	Non-viral (N=52)	Hepatitis B (N=247)	Hepatitis C (N=111)	Non-viral (N=135)
Total number of patients with at least one AE	69 (97.2%)	33 (100%)	52 (100%)	235 (95.1%)	111 (100%)	134 (99.3%)
Total number of events	548	291	460	2103	1277	1319
Total number of patients with at least one						
Treatment-related AE	67 (94.4%)	33 (100%)	47 (90.4%)	189 (76.5%)	104 (93.7%)	115 (85.2%)
Atezo-related AE	0	0	0	166 (67.2%)	95 (85.6%)	107 (79.3%)
Grade 3-4 AE	34 (47.9%)	26 (78.8%)	26 (50.0%)	116 (47.0%)	72 (64.9%)	75 (55.6%)
Treatment-related Grade 3-4 AE	28 (39.4%)	20 (60.6%)	23 (44.2%)	77 (31.2%)	52 (46.8%)	41 (30.4%)
Atezo-related Grade 3-4 AE	0	0	0	53 (21.5%)	34 (30.6%)	30 (22.2%)
Grade 5 AE	3 (4.2%)	1 (3.0%)	5 (9.6%)	5 (2.0%)	6 (5.4%)	11 (8.1%)
Treatment-related Grade 5 AE	1 (1.4%)	0	0	2 (0.8%)	2 (1.8%)	5 (3.7%)
Atezo-related Grade 5 AE	0	0	0	2 (0.8%)	2 (1.8%)	3 (2.2%)
Serious AE	10 (14.1%)	14 (42.4%)	24 (46.2%)	81 (32.8%)	48 (43.2%)	57 (42.2%)
Treatment-related serious AE	5 (7.0%)	5 (15.2%)	14 (26.9%)	33 (13.4%)	26 (23.4%)	29 (21.5%)
Atezo-related serious AE	0	0	0	25 (10.1%)	16 (14.4%)	24 (17.8%)
AE leading to any Study Treatment withdrawal	3 (4.2%)	3 (9.1%)	10 (19.2%)	31 (12.6%)	20 (18.0%)	24 (17.8%)
AE leading to Atezo withdrawal	0	0	0	15 (6.1%)	10 (9.0%)	17 (12.6%)
AE leading to any Dose modification or Study Treatment interruption	37 (52.1%)	26 (78.8%)	32 (61.5%)	86 (34.8%)	66 (59.5%)	70 (51.9%)
AE leading to Atezo interruption	0	0	0	59 (23.9%)	50 (45.0%)	56 (41.5%)

Atezo=Atezolizumab Bev=Bevacizumab. Sorafenib HCC: YO40245(Arm B). Atezo+Bev HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. All treatment emergent AEs are included.
Clinical cut-off dates: YO40245:29AUG2019, GO30140:14JUN2019.

Table 73: AE grade 3-4 PT by HCC Etiology (Atezo+Bev population)

	Atezo+Bev HCC (N=493)		
MedDRA Preferred Term	Hepatitis B (N=247)	Hepatitis C (N=111)	Non-viral (N=135)
HYPERTENSION	27 (10.9%)	21 (18.9%)	20 (14.8%)
ASPARTATE AMINOTRANSFERASE INCREASED	12 (4.9%)	12 (10.8%)	6 (4.4%)
PROTEINURIA	8 (3.2%)	8 (7.2%)	4 (3.0%)
BLOOD BILIRUBIN INCREASED	7 (2.8%)	4 (3.6%)	5 (3.7%)
PLATELET COUNT DECREASED	9 (3.6%)	2 (1.8%)	5 (3.7%)
ALANINE AMINOTRANSFERASE INCREASED	9 (3.6%)	5 (4.5%)	1 (0.7%)
HYPONATRAEMIA	6 (2.4%)	4 (3.6%)	5 (3.7%)
ANAEMIA	8 (3.2%)	2 (1.8%)	3 (2.2%)
DIARRHOEA	4 (1.6%)	2 (1.8%)	4 (3.0%)
ASCITES	5 (2.0%)	3 (2.7%)	1 (0.7%)
DYSPNOEA	1 (0.4%)	2 (1.8%)	6 (4.4%)
FATIGUE	4 (1.6%)	3 (2.7%)	2 (1.5%)
NEUTROPHIL COUNT DECREASED	5 (2.0%)	2 (1.8%)	2 (1.5%)
ABDOMINAL PAIN	3 (1.2%)	3 (2.7%)	2 (1.5%)
CHOLANGITIS	5 (2.0%)	1 (0.9%)	2 (1.5%)
INFUSION RELATED REACTION	4 (1.6%)	0	4 (3.0%)
OESOPHAGEAL VARICES HAEMORRHAGE	4 (1.6%)	1 (0.9%)	3 (2.2%)
PYREXIA	4 (1.6%)	1 (0.9%)	2 (1.5%)
BLOOD ALKALINE PHOSPHATASE INCREASED	1 (0.4%)	2 (1.8%)	3 (2.2%)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	5 (2.0%)	1 (0.9%)	0
HYPERBILIRUBINAEMIA	2 (0.8%)	3 (2.7%)	1 (0.7%)
PNEUMONIA	3 (1.2%)	1 (0.9%)	2 (1.5%)
THROMBOCYTOPENIA	4 (1.6%)	2 (1.8%)	0
DECREASED APPETITE	1 (0.4%)	3 (2.7%)	1 (0.7%)
GASTROINTESTINAL HAEMORRHAGE	2 (0.8%)	1 (0.9%)	2 (1.5%)
HEPATIC ENCEPHALOPATHY	2 (0.8%)	2 (1.8%)	1 (0.7%)
HYPERKALAEMIA	1 (0.4%)	3 (2.7%)	1 (0.7%)
SEPSIS	1 (0.4%)	1 (0.9%)	3 (2.2%)
CONFUSIONAL STATE	1 (0.4%)	1 (0.9%)	2 (1.5%)
HYPERGLYCAEMIA	1 (0.4%)	2 (1.8%)	1 (0.7%)
HYPOALBUMINAEMIA	1 (0.4%)	1 (0.9%)	2 (1.5%)
HYPOGLYCAEMIA	2 (0.8%)	0	2 (1.5%)
LYMPHOCYTE COUNT DECREASED	3 (1.2%)	1 (0.9%)	0
PULMONARY EMBOLISM	1 (0.4%)	0	3 (2.2%)
STOMATITIS	2 (0.8%)	2 (1.8%)	0
UPPER GASTROINTESTINAL HAEMORRHAGE	4 (1.6%)	0	0

SAE by HCC etiology

Table 74: SAE by HCC etiology (Atezo+Bev population)

MedDRA System Organ Class MedDRA Preferred Term	Grade	Atezo+Bev HCC (N=493) Hepatitis B (N=247)	Hepatitis C (N=111)	Non-viral (N=135)
- Any adverse events -	- Any Grade -	81 (32.8%)	48 (43.2%)	57 (42.2%)
	1	3 (1.2%)	2 (1.8%)	1 (0.7%)
	2	12 (4.9%)	4 (3.6%)	5 (3.7%)
	3	53 (21.5%)	30 (27.0%)	34 (25.2%)
	4	8 (3.2%)	6 (5.4%)	6 (4.4%)
	5	5 (2.0%)	6 (5.4%)	11 (8.1%)
GASTROINTESTINAL DISORDERS				
- Overall -	- Any Grade -	33 (13.4%)	17 (15.3%)	20 (14.8%)
	1	0	0	1 (0.7%)
	2	6 (2.4%)	2 (1.8%)	1 (0.7%)
	3	24 (9.7%)	14 (12.6%)	14 (10.4%)
	4	1 (0.4%)	0	1 (0.7%)
	5	2 (0.8%)	1 (0.9%)	3 (2.2%)
OESOPHAGEAL VARICES HAEMORRHAGE	- Any Grade -	5 (2.0%)	1 (0.9%)	4 (3.0%)
	2	1 (0.4%)	0	0
	3	4 (1.6%)	1 (0.9%)	3 (2.2%)
	5	0	0	1 (0.7%)
GASTROINTESTINAL HAEMORRHAGE	- Any Grade -	4 (1.6%)	2 (1.8%)	3 (2.2%)
	2	0	1 (0.9%)	0
	3	1 (0.4%)	1 (0.9%)	2 (1.5%)
	4	1 (0.4%)	0	0
	5	2 (0.8%)	0	1 (0.7%)
ASCITES	- Any Grade -	3 (1.2%)	1 (0.9%)	2 (1.5%)
	2	0	0	1 (0.7%)
	3	3 (1.2%)	1 (0.9%)	1 (0.7%)
DIARRHOEA	- Any Grade -	1 (0.4%)	2 (1.8%)	2 (1.5%)
	3	1 (0.4%)	2 (1.8%)	2 (1.5%)
UPPER GASTROINTESTINAL HAEMORRHAGE	- Any Grade -	4 (1.6%)	1 (0.9%)	0
	3	4 (1.6%)	0	0
	5	0	1 (0.9%)	0
INFECTIONS AND INFESTATIONS				
- Overall -	- Any Grade -	12 (4.9%)	9 (8.1%)	16 (11.9%)
	2	2 (0.8%)	1 (0.9%)	1 (0.7%)
	3	7 (2.8%)	6 (5.4%)	10 (7.4%)
	4	1 (0.4%)	1 (0.9%)	2 (1.5%)
	5	2 (0.8%)	1 (0.9%)	3 (2.2%)
PNEUMONIA	- Any Grade -	2 (0.8%)	2 (1.8%)	2 (1.5%)
	2	1 (0.4%)	0	0
	3	1 (0.4%)	1 (0.9%)	1 (0.7%)
	5	0	1 (0.9%)	1 (0.7%)
SEPSIS	- Any Grade -	3 (1.2%)	0	3 (2.2%)
	2	1 (0.4%)	0	0
	3	0	0	3 (2.2%)
	4	1 (0.4%)	0	0
	5	1 (0.4%)	0	0
URINARY TRACT INFECTION	- Any Grade -	0	1 (0.9%)	2 (1.5%)
	2	0	0	1 (0.7%)
	3	0	1 (0.9%)	1 (0.7%)
BACTERAEMIA	- Any Grade -	1 (0.4%)	0	0
	5	1 (0.4%)	0	0
HEPATOBILIARY DISORDERS				
- Overall -	- Any Grade -	12 (4.9%)	7 (6.3%)	8 (5.9%)
	1	1 (0.4%)	0	0
	2	0	1 (0.9%)	0
	3	8 (3.2%)	3 (2.7%)	3 (2.2%)
	4	2 (0.8%)	2 (1.8%)	3 (2.2%)
	5	1 (0.4%)	1 (0.9%)	2 (1.5%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
- Overall -	- Any Grade -	7 (2.8%)	4 (3.6%)	12 (8.9%)
	2	4 (1.6%)	1 (0.9%)	1 (0.7%)
	3	3 (1.2%)	2 (1.8%)	9 (6.7%)
	4	0	0	1 (0.7%)
	5	0	1 (0.9%)	1 (0.7%)

RESPIRATORY DISTRESS	- Any Grade -	0	0	1 (0.7%)
	5	0	0	1 (0.7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
- Overall -	- Any Grade -	8 (3.2%)	3 (2.7%)	6 (4.4%)
	1	2 (0.8%)	2 (1.8%)	1 (0.7%)
	2	2 (0.8%)	0	0
	3	4 (1.6%)	1 (0.9%)	4 (3.0%)
	5	0	0	1 (0.7%)
PYREXIA	- Any Grade -	7 (2.8%)	3 (2.7%)	3 (2.2%)
	1	2 (0.8%)	2 (1.8%)	1 (0.7%)
	2	2 (0.8%)	0	0
	3	3 (1.2%)	1 (0.9%)	2 (1.5%)
FATIGUE	- Any Grade -	1 (0.4%)	0	1 (0.7%)
	3	1 (0.4%)	0	1 (0.7%)
ASTHENIA	- Any Grade -	0	0	1 (0.7%)
	3	0	0	1 (0.7%)
MULTIPLE ORGAN DYSFUNCTION SYNDROME	- Any Grade -	0	0	1 (0.7%)
	5	0	0	1 (0.7%)
NERVOUS SYSTEM DISORDERS				
- Overall -	- Any Grade -	7 (2.8%)	4 (3.6%)	6 (4.4%)
	2	1 (0.4%)	0	0
	3	6 (2.4%)	4 (3.6%)	3 (2.2%)
	4	0	0	2 (1.5%)
	5	0	0	1 (0.7%)
CEREBRAL INFARCTION	- Any Grade -	1 (0.4%)	0	2 (1.5%)
	3	1 (0.4%)	0	1 (0.7%)
	4	0	0	1 (0.7%)
HEPATIC ENCEPHALOPATHY	- Any Grade -	2 (0.8%)	0	1 (0.7%)
	3	2 (0.8%)	0	0
	4	0	0	1 (0.7%)
SUBARACHNOID HAEMORRHAGE	- Any Grade -	1 (0.4%)	0	1 (0.7%)
	3	1 (0.4%)	0	0
	5	0	0	1 (0.7%)
METABOLISM AND NUTRITION DISORDERS				
- Overall -	- Any Grade -	4 (1.6%)	3 (2.7%)	6 (4.4%)
	2	3 (1.2%)	0	0
	3	0	2 (1.8%)	2 (1.5%)
	4	1 (0.4%)	1 (0.9%)	4 (3.0%)
INVESTIGATIONS				
- Overall -	- Any Grade -	7 (2.8%)	2 (1.8%)	3 (2.2%)
	3	6 (2.4%)	1 (0.9%)	2 (1.5%)
	4	1 (0.4%)	1 (0.9%)	1 (0.7%)
VASCULAR DISORDERS				
- Overall -	- Any Grade -	3 (1.2%)	5 (4.5%)	2 (1.5%)
	2	1 (0.4%)	1 (0.9%)	1 (0.7%)
	3	2 (0.8%)	3 (2.7%)	1 (0.7%)
	4	0	1 (0.9%)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
- Overall -	- Any Grade -	4 (1.6%)	1 (0.9%)	3 (2.2%)
	2	1 (0.4%)	0	0
	3	2 (0.8%)	1 (0.9%)	2 (1.5%)
	4	1 (0.4%)	0	1 (0.7%)
CARDIAC DISORDERS				
- Overall -	- Any Grade -	2 (0.8%)	2 (1.8%)	3 (2.2%)
	1	0	0	1 (0.7%)
	2	0	0	1 (0.7%)
	3	1 (0.4%)	0	0
	4	1 (0.4%)	0	1 (0.7%)
	5	0	2 (1.8%)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
- Overall -	- Any Grade -	1 (0.4%)	0	6 (4.4%)
	2	0	0	2 (1.5%)
	3	1 (0.4%)	0	4 (3.0%)
INFUSION RELATED REACTION	- Any Grade -	1 (0.4%)	0	3 (2.2%)
	2	0	0	2 (1.5%)
	3	1 (0.4%)	0	1 (0.7%)
PSYCHIATRIC DISORDERS				
- Overall -	- Any Grade -	2 (0.8%)	3 (2.7%)	2 (1.5%)
	1	1 (0.4%)	0	0
	2	0	1 (0.9%)	1 (0.7%)
	3	1 (0.4%)	2 (1.8%)	0
	4	0	0	1 (0.7%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
- Overall -	- Any Grade -	2 (0.8%)	1 (0.9%)	3 (2.2%)
	2	0	0	1 (0.7%)
	3	2 (0.8%)	1 (0.9%)	1 (0.7%)
	4	0	0	1 (0.7%)

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)				
- Overall -	- Any Grade -	5 (2.0%)	1 (0.9%)	0
	1	1 (0.4%)	1 (0.9%)	0
	2	3 (1.2%)	0	0
	3	1 (0.4%)	0	0
RENAL AND URINARY DISORDERS				
- Overall -	- Any Grade -	2 (0.8%)	1 (0.9%)	1 (0.7%)
	2	0	0	1 (0.7%)
	3	2 (0.8%)	1 (0.9%)	0
IMMUNE SYSTEM DISORDERS				
- Overall -	- Any Grade -	1 (0.4%)	0	2 (1.5%)
	2	0	0	1 (0.7%)
	4	1 (0.4%)	0	1 (0.7%)
ANAPHYLACTIC REACTION	- Any Grade -	0	0	1 (0.7%)
	4	0	0	1 (0.7%)
CYTOKINE RELEASE SYNDROME	- Any Grade -	1 (0.4%)	0	0
	4	1 (0.4%)	0	0
HYPERSENSITIVITY	- Any Grade -	0	0	1 (0.7%)
	2	0	0	1 (0.7%)
ENDOCRINE DISORDERS				
- Overall -	- Any Grade -	0	0	2 (1.5%)
	2	0	0	1 (0.7%)
	3	0	0	1 (0.7%)
ADRENAL INSUFFICIENCY	- Any Grade -	0	0	2 (1.5%)
	2	0	0	1 (0.7%)
	3	0	0	1 (0.7%)

Extrinsic Factors by Region

Region

The majority of patients treated with Atezo + Bev and Sorafenib were from Asia-Pacific (Atezo + Bev: n = 279, Sorafenib: n = 86), followed by North America (Atezo + Bev: n = 102, Sorafenib: n = 21), and Europe and Middle East (Atezo + Bev: n=99, Sorafenib: n=48).

Table 75: Overview of AEs in Atezo+Bev and Sorafenib HCC patients by region (safety-evaluable patients)

	Sorafenib HCC (N=156)		Atezo+Bev HCC (N=493)	
	Europe and Middle East (N=48)	North America (N=21)	Europe and Middle East (N=99)	North America (N=102)
Total number of patients with at least one AE	48 (100%)	21 (100%)	99 (100%)	100 (98.0%)
Total number of events	376	223	836	1360
Total number of patients with at least one				
Treatment-related AE	45 (93.8%)	20 (95.2%)	84 (84.8%)	88 (86.3%)
Atezo-related AE	0	0	74 (74.7%)	84 (82.4%)
Grade 3-4 AE	24 (50.0%)	14 (66.7%)	53 (53.5%)	61 (59.8%)
Treatment-related Grade 3-4 AE	22 (45.8%)	9 (42.9%)	31 (31.3%)	39 (38.2%)
Atezo-related Grade 3-4 AE	0	0	23 (23.2%)	25 (24.5%)
Grade 5 AE	8 (16.7%)	0	6 (6.1%)	8 (7.8%)
Treatment-related Grade 5 AE	1 (2.1%)	0	1 (1.0%)	2 (2.0%)
Atezo-related Grade 5 AE	0	0	1 (1.0%)	1 (1.0%)
Serious AE	23 (47.9%)	10 (47.6%)	44 (44.4%)	42 (41.2%)
Treatment-related serious AE	12 (25.0%)	4 (19.0%)	20 (20.2%)	18 (17.6%)
Atezo-related serious AE	0	0	15 (15.2%)	11 (10.8%)
AE leading to any Study Treatment withdrawal	9 (18.8%)	1 (4.8%)	22 (22.2%)	19 (18.6%)
AE leading to Atezo withdrawal	0	0	13 (13.1%)	13 (12.7%)
AE leading to any Dose modification or Study Treatment interruption	30 (62.5%)	15 (71.4%)	58 (58.6%)	47 (46.1%)
AE leading to Atezo interruption	0	0	52 (52.5%)	33 (32.4%)

	Sorafenib HCC (N=156)		Atezo+Bev HCC (N=493)	
	Asia-Pacific (N=86)	Australia (N=1)	Asia-Pacific (N=279)	Australia (N=13)
Total number of patients with at least one AE	84 (97.7%)	1 (100%)	269 (96.4%)	12 (92.3%)
Total number of events	694	6	2377	126
Total number of patients with at least one				
Treatment-related AE	81 (94.2%)	1 (100%)	227 (81.4%)	9 (69.2%)
Atezo-related AE	0	0	203 (72.8%)	7 (53.8%)
Grade 3-4 AE	47 (54.7%)	1 (100%)	138 (49.5%)	11 (84.6%)
Treatment-related Grade 3-4 AE	39 (45.3%)	1 (100%)	97 (34.8%)	3 (23.1%)
Atezo-related Grade 3-4 AE	0	0	67 (24.0%)	2 (15.4%)
Grade 5 AE	1 (1.2%)	0	8 (2.9%)	0
Treatment-related Grade 5 AE	0	0	6 (2.2%)	0
Atezo-related Grade 5 AE	0	0	5 (1.8%)	0
Serious AE	15 (17.4%)	0	92 (33.0%)	8 (61.5%)
Treatment-related serious AE	8 (9.3%)	0	48 (17.2%)	2 (15.4%)
Atezo-related serious AE	0	0	37 (13.3%)	2 (15.4%)
AE leading to any Study Treatment withdrawal	5 (5.8%)	1 (100%)	32 (11.5%)	2 (15.4%)
AE leading to Atezo withdrawal	0	0	15 (5.4%)	1 (7.7%)
AE leading to any Dose modification or Study Treatment interruption	50 (58.1%)	0	111 (39.8%)	6 (46.2%)
AE leading to Atezo interruption	0	0	74 (26.5%)	6 (46.2%)

Atezo=Atezolizumab Bev=Bevacizumab. Sorafenib HCC: YO40245(Arm B). Atezo+Bev HCC: YO40245(Arm A) + GO30140(Arm A+F1).
Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. Multiple occurrences of th
same AE in one individual are counted only once except for "Total number of events" rows, multiple occurrences of the same AE in an
individual are counted separately. All treatment emergent AEs are included.
Clinical cut-off dates: YO40245:29AUG2019, GO30140:14JUN2019.

The overall distribution of AESIs was comparable across patients in Asia-Pacific, Europe and Middle East, and North America with the following exception: a higher proportion (≥10% differences) of patients experienced Grade 3-4 atezolizumab AESIs in Europe and Middle East when compared to patients in Asia-Pacific.

Table 76: SAE Highest NCI CTCAE Grades and by SOC and Preferred Term, by Region [excerpt]

MedDRA System Organ Class MedDRA Preferred Term	Grade	Atezo+Bev HCC (N=493) Asia-Pacific (N=279)	Australia (N=13)	Europe and Middle East (N=99)	North America (N=102)
- Any adverse events -	- Any Grade -	92 (33.0%)	8 (61.5%)	44 (44.4%)	42 (41.2%)
	1	3 (1.1%)	0	1 (1.0%)	2 (2.0%)
	2	13 (4.7%)	0	5 (5.1%)	3 (2.9%)
	3	62 (22.2%)	7 (53.8%)	25 (25.3%)	23 (22.5%)
	4	6 (2.2%)	1 (7.7%)	7 (7.1%)	6 (5.9%)
	5	8 (2.9%)	0	6 (6.1%)	8 (7.8%)
GASTROINTESTINAL DISORDERS					
- Overall -	- Any Grade -	32 (11.5%)	4 (30.8%)	13 (13.1%)	21 (20.6%)
	1	0	0	0	1 (1.0%)
	2	5 (1.8%)	0	3 (3.0%)	1 (1.0%)
	3	23 (8.2%)	4 (30.8%)	8 (8.1%)	17 (16.7%)
	4	2 (0.7%)	0	0	0
	5	2 (0.7%)	0	2 (2.0%)	2 (2.0%)
OESOPHAGEAL VARICES HAEMORRHAGE	- Any Grade -	5 (1.8%)	1 (7.7%)	3 (3.0%)	1 (1.0%)
	2	0	0	1 (1.0%)	0
	3	5 (1.8%)	1 (7.7%)	1 (1.0%)	1 (1.0%)
	5	0	0	1 (1.0%)	0
GASTROINTESTINAL HAEMORRHAGE	- Any Grade -	2 (0.7%)	0	5 (5.1%)	2 (2.0%)
	2	0	0	1 (1.0%)	0
	3	0	0	3 (3.0%)	1 (1.0%)
	4	1 (0.4%)	0	0	0
	5	1 (0.4%)	0	1 (1.0%)	1 (1.0%)

Table 77: Overview of Adverse Events of Special Interest for Atezolizumab, by Region

	Atezo+Bev HCC (N=493) Asia-Pacific (N=279)	Australia (N=13)	Europe and Middle East (N=99)	North America (N=102)
Total number of patients with at least one AE of Special Interest	170 (60.9%)	5 (38.5%)	71 (71.7%)	74 (72.5%)
Total number of events	429	12	142	170
Total number of patients with at least one				
Treatment-related AE of Special Interest	136 (48.7%)	3 (23.1%)	54 (54.5%)	47 (46.1%)
Atezo-related AE of Special Interest	131 (47.0%)	3 (23.1%)	49 (49.5%)	46 (45.1%)
Grade 3-4 AE of Special Interest	53 (19.0%)	4 (30.8%)	29 (29.3%)	29 (28.4%)
Treatment-related Grade 3-4 AE of Special Interest	31 (11.1%)	2 (15.4%)	19 (19.2%)	12 (11.8%)
Atezo-related Grade 3-4 AE of Special Interest	28 (10.0%)	2 (15.4%)	17 (17.2%)	12 (11.8%)
Grade 5 AE of Special Interest	3 (1.1%)	0	2 (2.0%)	1 (1.0%)
Treatment-related Grade 5 AE of Special Interest	3 (1.1%)	0	1 (1.0%)	1 (1.0%)
Atezo-related Grade 5 AE of Special Interest	3 (1.1%)	0	1 (1.0%)	1 (1.0%)
Serious AE of Special Interest	28 (10.0%)	3 (23.1%)	19 (19.2%)	16 (15.7%)
Treatment-related Serious AE of Special Interest	16 (5.7%)	1 (7.7%)	11 (11.1%)	6 (5.9%)
Atezo-related Serious AE of Special Interest	13 (4.7%)	1 (7.7%)	10 (10.1%)	6 (5.9%)
AE of Special Interest leading to any Study Treatment withdrawal	11 (3.9%)	2 (15.4%)	11 (11.1%)	5 (4.9%)
AE of Special Interest leading to Atezo withdrawal	7 (2.5%)	1 (7.7%)	9 (9.1%)	5 (4.9%)
AE of Special Interest leading to any Dose modification or Study Treatment interruption	34 (12.2%)	1 (7.7%)	29 (29.3%)	17 (16.7%)
AE of Special Interest leading to Atezo interruption	30 (10.8%)	1 (7.7%)	26 (26.3%)	13 (12.7%)
AE of Special Interest Requiring the Use of Systemic Corticosteroids	25 (9.0%)	3 (23.1%)	19 (19.2%)	13 (12.7%)

Table 78: AESI for Atezolizumab by Medical Concept and Preferred Term, by Region (Excerpt)

Medical Concept MedDRA Preferred Term	Atezo+Bev HCC (N=493) Asia-Pacific (N=279)	Australia (N=13)	Europe and Middle East (N=99)	North America (N=102)
Total number of patients with at least one adverse event	170 (60.9%)	5 (38.5%)	71 (71.7%)	74 (72.5%)
Immune-Mediated Hepatitis (Diagnosis and Lab Abnormalities)				
Total number of patients with at least one adverse event	99 (35.5%)	3 (23.1%)	42 (42.4%)	47 (46.1%)
ASPARTATE AMINOTRANSFERASE INCREASED	47 (16.8%)	0	17 (17.2%)	19 (18.6%)
ALANINE AMINOTRANSFERASE INCREASED	37 (13.3%)	0	10 (10.1%)	14 (13.7%)
BLOOD BILIRUBIN INCREASED	33 (11.8%)	0	11 (11.1%)	17 (16.7%)
ASCITES	14 (5.0%)	0	10 (10.1%)	10 (9.8%)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	10 (3.6%)	0	0	0
Immune-Mediated Hepatitis (Lab Abnormalities)				
Total number of patients with at least one adverse event	90 (32.3%)	1 (7.7%)	36 (36.4%)	44 (43.1%)
ASPARTATE AMINOTRANSFERASE INCREASED	47 (16.8%)	0	17 (17.2%)	19 (18.6%)
ALANINE AMINOTRANSFERASE INCREASED	37 (13.3%)	0	10 (10.1%)	14 (13.7%)
BLOOD BILIRUBIN INCREASED	33 (11.8%)	0	11 (11.1%)	17 (16.7%)
ASCITES	14 (5.0%)	0	10 (10.1%)	10 (9.8%)

Immune-Mediated Rash				
Total number of patients with at least one adverse event	60 (21.5%)	2 (15.4%)	16 (16.2%)	31 (30.4%)
RASH	43 (15.4%)	0	9 (9.1%)	25 (24.5%)
RASH MACULO-PAPULAR	8 (2.9%)	1 (7.7%)	0	5 (4.9%)
Immune-Mediated Hepatitis (Diagnosis)				
Total number of patients with at least one adverse event	26 (9.3%)	2 (15.4%)	18 (18.2%)	14 (13.7%)
ASCITES	14 (5.0%)	0	10 (10.1%)	10 (9.8%)
HEPATIC ENCEPHALOPATHY	5 (1.8%)	1 (7.7%)	1 (1.0%)	3 (2.9%)
OESOPHAGEAL VARICES HAEMORRHAGE	5 (1.8%)	1 (7.7%)	3 (3.0%)	1 (1.0%)
Immune-Mediated Hypothyroidism				
Total number of patients with at least one adverse event	32 (11.5%)	0	10 (10.1%)	7 (6.9%)
HYPOTHYROIDISM	26 (9.3%)	0	10 (10.1%)	5 (4.9%)
BLOOD THYROID STIMULATING HORMONE INCREASED	6 (2.2%)	0	1 (1.0%)	2 (2.0%)
Infusion-Related Reactions				
Total number of patients with at least one adverse event	24 (8.6%)	2 (15.4%)	10 (10.1%)	7 (6.9%)
INFUSION RELATED REACTION	24 (8.6%)	2 (15.4%)	10 (10.1%)	7 (6.9%)
Immune-Mediated Hyperthyroidism				
Total number of patients with at least one adverse event	7 (2.5%)	0	8 (8.1%)	1 (1.0%)
HYPERTHYROIDISM	7 (2.5%)	0	8 (8.1%)	1 (1.0%)
Immune-Mediated Pancreatitis				
Total number of patients with at least one adverse event	4 (1.4%)	1 (7.7%)	1 (1.0%)	5 (4.9%)

Subgroup Analyses of Safety by Anti-Drug Antibody Status

The impact of atezolizumab ADA status on safety was evaluated. No analysis was done for the impact of bevacizumab ADA status on safety due to the very low bevacizumab ADA positive rate in general.

Pooled Analysis IMbrave150 and GO31040

Among ADA-evaluable patients, atezolizumab ADA-negative and ADA-positive patients received a median number of 11.0 and 10.0 cycles of atezolizumab, respectively.

An overview of safety by ADA status is shown in Table 1. Numerical differences were observed in treatment related (Atezo-related) AEs specially Grade 3-4 AEs, SAEs AEs and AEs leading to discontinuation of treatment. Several PTs in the All AEs output showed a difference in frequency of more than 5% in the ADA-positive group, but no specific pattern was identified and the majority of the events were commonly reported events in cancer patients. No significant differences were observed in potentially immune related AEs, and no significant difference between groups was seen among SAEs. The incidence of AESIs of any grade by ADA status was comparable (60.8% ADA-negative vs. 61.5% ADA-positive).

Table 79: Overview of Adverse Events by atezolizumab ADA status

ADA Evaluable Patients Protocols: IMbrave150 (YO40245), GO30140	Atezo+Bev HCC (N=474) ADA- (N=340)	 ADA+ (N=134)
Total number of patients with at least one AE	331 (97.4%)	131 (97.8%)
Total number of events	3245	1294
Total number of patients with at least one:		
Treatment-related AE	280 (82.4%)	114 (85.1%)
Atezo-related AE	250 (73.5%)	105 (78.4%)
Grade 3-4 AE	170 (50.0%)	79 (59.0%)
Treatment-related Grade 3-4 AE	111 (32.6%)	50 (37.3%)
Atezo-related Grade 3-4 AE	73 (21.5%)	35 (26.1%)
Grade 5 AE	11 (3.2%)	9 (6.7%)
Treatment-related Grade 5 AE	4 (1.2%)	4 (3.0%)
Atezo-related Grade 5 AE	3 (0.9%)	3 (2.2%)
Serious AE	107 (31.5%)	67 (50.0%)
Treatment-related serious AE	47 (13.8%)	36 (26.9%)
Atezo-related serious AE	37 (10.9%)	23 (17.2%)
AE leading to any Study Treatment withdrawal	47 (13.8%)	24 (17.9%)
AE leading to Atezo withdrawal	24 (7.1%)	14 (10.4%)
AE leading to any Dose modification or Study Treatment interuption	143 (42.1%)	73 (54.5%)
AE leading to Atezo interruption	106 (31.2%)	55 (41.0%)

ADA=Anti-Drug Antibodies, -=Negative, +=Positive
Atezo=Atezolizumab Bev=Bevacizumab. Atezo+Bev HCC: IMbrave150 (YO40245) (Atezo+Bev)+GO30140 (Arm A+F1).
Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. All treatment emergent AEs are included.
Clinical cut-off dates: Study IMbrave150 (YO40245) (29 August 2019), GO30140 (14 June 2019).

The incidences of AEs are shown in Table 5.5.1.8.13 for terms where a ≥5% difference was seen between the two ADA subgroups. There were numerical differences by ADA status with most incidences higher in ADA-positive patients.

Table 80: Adverse Events by ADA status with 5% difference between ADA subgroups

ADA Evaluable Patients Protocols: IMbrave150 (YO40245), GO30140	Atezo+Bev HCC (N=474)	
MedDRA Preferred Term	ADA- (N=340)	ADA+ (N=134)
Proteinuria	88 (25.9%)	27 (20.1%)
Fatigue	71 (20.9%)	35 (26.1%)
Decreased Appetite	76 (22.4%)	20 (14.9%)
Pyrexia	52 (15.3%)	31 (23.1%)
Constipation	41 (12.1%)	27 (20.1%)
Anaemia	26 (7.6%)	17 (12.7%)
Infusion Related Reaction	23 (6.8%)	20 (14.9%)

ADA=Anti-Drug Antibodies, -=Negative, +=Positive.
Atezo=Atezolizumab Bev=Bevacizumab. Atezo+Bev HCC: IMbrave150 (YO40245) (Atezo+Bev)+GO30140(Arm A+F1).
Investigator text for AEs encoded using MedDRA v22.0. All counts represent patients.
Multiple occurrences of the same AE in one individual are counted once. All treatment emergent AEs are included.
Clinical cut-off dates: Study IMbrave150 (YO40245) (29 August 2019), Study GO30140 (14 June 2019).

The incidence of Grade 1-2 events was higher in the ADA-negative compared with the ADA-positive subgroup (44.1% vs. 32.1%) whereas Grade 3-4 AEs (50.0% vs. 59.0%) and Grade 5 AEs (3.2% vs. 6.7%) occurred at a higher incidence in the ADA-positive subgroup.

The most common SOCs in which Grade 3-4 AEs were reported with a differential ≥5% between ADA-negative and ADA-positive patients included:

- Investigations (15.0% vs. 23.9%), most common AEs were increased AST (5.3% vs. 6.7%), increased ALT (3.2% vs. 3.0%), increased bilirubin (2.9% vs. 3.7%), increased platelets (2.4% vs. 6%) and increased blood alkaline phosphatase (0% vs. 4.9%).
- Hepatobiliary Disorders (4.4% vs. 9.7%), most common AE was cholangitis (1.2% vs. 3.1%).

Other commonly reported Grade 3-4 AEs included proteinuria (ADA-negative: 4.1%; ADA-positive: 3.7%), anemia (ADA-negative: 2.1%; ADA-positive: 3.7%) and IRRs (ADA-negative: 0.9%; ADA-positive: 3.0%).

The most common SOCs in which Grade 5 AEs were reported included Gastrointestinal Disorders (ADA-negative subgroup: 2 patients, 0.6%; ADA-positive subgroup: 4 patients, 3.0%) and Infections and Infestations (ADA-negative subgroup: 5 patients, 1.5%; ADA-positive subgroup: 0 patients).

The most frequent Grade 5 AE was pneumonia (PT) among ADA-negative patients (2 patients, 0.6%) and gastrointestinal haemorrhage (PT) among ADA-positive patients (3 patients, 2.2%).

Table 81: Grade 5 Events by ADA Status

ADA Evaluable Patients Protocols: IMbrave150 (YO40245), GO30140	ADA-Negative N=340	ADA-Positive N=134
Total Number of Grade 5 AEs	11 (3%)	9 (6.7%)
Gastrointestinal disorders	**2 (0.6%)**	**4 (3.0%)**
Gastrointestinal haemorrhage	0 (0%)	3 (2%)
Gastric ulcer perforation	1 (<1%)	0 (0%)
Upper gastrointestinal haemorrhage	0 (0%)	1 (0.7%)
Oesophageal varices haemorhage	1 (<1%)	0 (0%)
General disorders and administration site Conditions	**0**	**1 (0.7%)**
Multi organ dysfunction syndrome	0 (0%)	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	**1 (0.3%)**	**0 (0%)**
Respiratory distress	1 (0.3%)	0 (0%)
Infections and infestations	**5 (1.5%)**	**0**
Pneumonia	2 (1%)	0 (0%)
Bacteraemia	1 (0.3%)	0 (0%)
Empyema	1 (0.3%)	0 (0%)
Peritonitis bacterial	1 (0.3%)	0 (0%)
Nervous system disorders	**0**	**1 (0.7%)**
Subarachnoid haemorrhage	0 (0%)	1 (0.7%)
Hepatobiliary Disorders	**2 (0.6%)**	**2 (1.5%)**
Abnormal hepatic function	1 (0.7%)	1 (1%)
Hepatic cirrhosis	1 (0.3%)	0 (0%)
Liver injury	0 (0%)	1 (0.7%)
Cardiac disorders	**1 (0.3%)**	**1 (0.7%)**
Cardiac arrest	1 (0.3%)	1 (0.7%)

AE= adverse event; ADA= anti-drug antibody

Data source: t_ae_ctc_H2A_A_byada_29AUG2019_40245P.

The incidence of AEs reported as serious was higher in the ADA-positive subgroup (50.0%) compared with the ADA-negative subgroup (31.5%). The most common serious AEs by preferred term are shown in Table 92. Gastrointestinal hemorrhage was the only SAE with a ≥ 2% difference between ADA-negative and -positive patients (0.9% vs. 4.5%). All other serious AEs were reported at a low incidence.

Table 82: Common (≥1% in any Arm) Serious Adverse Events by ADA Status (ADA Evaluable Population)

ADA Evaluable Patients Protocols: IMbrave150 (YO40245), GO30140	Atezo+Bev HCC (N=474)	
MedDRA System Organ Class MedDRA Preferred Term	ADA- (N=340)	ADA+ (N=134)
- Any adverse events -	107 (31.5%)	67 (50.0%)
Gastrointestinal Haemorrhage	3 (0.9%)	6 (4.5%)
Upper Gastrointestinal Haemorrhage	2 (0.6%)	3 (2.2%)
Varices Oesophageal	0	2 (1.5%)
Ascites	4 (1.2%)	1 (0.7%)
Oesophageal Varices Haemorrhage	9 (2.6%)	1 (0.7%)
Colitis	4 (1.2%)	0
Diarrhoea	5 (1.5%)	0
Pneumonia	3 (0.9%)	3 (2.2%)
Cholangitis	4 (1.2%)	3 (2.2%)
Autoimmune Hepatitis	0	2 (1.5%)
Hyperbilirubinaemia	1 (0.3%)	2 (1.5%)
Pyrexia	7 (2.1%)	4 (3.0%)
Epistaxis	0	2 (1.5%)
Infusion Related Reaction	1 (0.3%)	2 (1.5%)

ADA=Anti-Drug Antibodies, -=Negative, +=Positive.

Atezo=Atezolizumab Bev=Bevacizumab. Atezo+Bev HCC: IMbrave150 (YO40245) (Atezo+Bev)+GO30140(Arm A+F1).

Investigator text for AEs encoded using MedDRA v22.0. All counts represent patients.

Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient. To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC. Percentages are based on N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: Study IMbrave150 (YO40245) (29 August 2019), Study GO30140 (14 June 2019).

The incidence of AESIs was generally comparable across the majority of safety categories with the exception of Grade 3-4 AESIs (19.1% ADA-negative vs. 30.6% ADA-positive) (Table 5.5.1.8.16). The difference in Grade 3-4 AESIs was mainly driven by more events of hepatitis laboratory abnormalities in the ADA-positive subgroup.

By medical concept, the most common (≥10% in either ADA-negative or ADA-positive) AESIs were hepatitis (diagnosis and laboratory abnormalities), rash, hypothyroidism and IRR. The frequency of most AESIs was similar between the ADA subgroups except for hepatitis laboratory abnormalities (32.1% ADA-negative vs. 37.3% ADA-positive) and IRRs (6.5% vs. 14.9%).

- Hepatitis laboratory abnormalities were mainly of Grade 1-2 severity in the ADA-negative group (Grade 1-2: 20.0% vs. Grade 3-4: 11.8%) whereas in the ADA-positive group, Grade 3-4 events were more common (Grade 3-4: 20.2% vs. Grade 1-2: 16.4%).
- IRRs were mainly Grade 1-2 in both ADA subgroups (ADA-negative: 5.5% vs. ADA-positive: 12.0%) and the overall incidence of Grade 3 IRRs was low (ADA-negative: 0.9% vs. ADA-positive: 3.0%). There were no Grade 4 or Grade 5 IRRs. There were no events of hypersensitivity or anaphylaxis in the ADA-positive subgroup;

There was one case of Grade 4 cytokine release syndrome in this subgroup.

Table 83: Overview of Adverse Events of Special Interest for Atezolizumab by ADA Status

ADA Evaluable Patients Protocols: IMbrave150 (YO40245), GO30140	Atezo+Bev HCC (N=474)	
	ADA- (N=340)	ADA+ (N=134)
Total number of patients with at least one AE of Special Interest	219 (64.4%)	88 (65.7%)
Total number of events	520	199
Total number of patients with at least one:		
Treatment-related AE of Special Interest	162 (47.6%)	68 (50.7%)
Atezo-related AE of Special Interest	156 (45.9%)	63 (47.0%)
Grade 3-4 AE of Special Interest	65 (19.1%)	41 (30.6%)
Treatment-related Grade 3-4 AE of Special Interest	35 (10.3%)	23 (17.2%)
Atezo-related Grade 3-4 AE of Special Interest	31 (9.1%)	22 (16.4%)
Grade 5 AE of Special Interest	3 (0.9%)	2 (1.5%)
Treatment-related Grade 5 AE of Special Interest	2 (0.6%)	2 (1.5%)
Atezo-related Grade 5 AE of Special Interest	2 (0.6%)	2 (1.5%)
Serious AE of Special Interest	40 (11.8%)	21 (15.7%)
Treatment-related Serious AE of Special Interest	20 (5.9%)	12 (9.0%)
Atezo-related Serious AE of Special Interest	17 (5.0%)	11 (8.2%)
AE of Special Interest leading to any Study Treatment withdrawal	20 (5.9%)	8 (6.0%)
AE of Special Interest leading to Atezo withdrawal	13 (3.8%)	8 (6.0%)
AE of Special Interest leading to any Dose modification or Study Treatment interruption	53 (15.6%)	26 (19.4%)
AE of Special Interest leading to Atezo interruption	48 (14.1%)	21 (15.7%)
AE of Special Interest Requiring the Use of Systemic Corticosteroids	35 (10.3%)	18 (13.4%)
Special Interest AE Medical Concepts: patients with at least one:		
Immune-Mediated Hepatitis (Diagnosis and Lab Abnormalities)	124 (36.5%)	55 (41.0%)
Immune-Mediated Hepatitis (Lab Abnormalities)	109 (32.1%)	50 (37.3%)
Immune-Mediated Rash	81 (23.8%)	26 (19.4%)
Immune-Mediated Hepatitis (Diagnosis)	39 (11.5%)	19 (14.2%)
Immune-Mediated Hypothyroidism	35 (10.3%)	12 (9.0%)
Infusion-Related Reactions	22 (6.5%)	20 (14.9%)
Immune-Mediated Hyperthyroidism	12 (3.5%)	4 (3.0%)
Immune-Mediated Pancreatitis	8 (2.4%)	3 (2.2%)
Immune-Mediated Diabetes Mellitus	7 (2.1%)	3 (2.2%)
Immune-Mediated Colitis	8 (2.4%)	1 (0.7%)
Immune-Mediated Pneumonitis	4 (1.2%)	2 (1.5%)
Immune-Mediated Nephritis	2 (0.6%)	1 (0.7%)
Immune-Mediated Myositis (Myositis+Rhabdomyolysis)	1 (0.3%)	2 (1.5%)
Immune-Mediated Adrenal Insufficiency	2 (0.6%)	0
Rhabdomyolysis	0	2 (1.5%)
Autoimmune Hemolytic Anemia	1 (0.3%)	1 (0.7%)
Immune-Mediated Meningoencephalitis	1 (0.3%)	0
Immune-Mediated Myositis	1 (0.3%)	0
Systemic Immune Activation	0	1 (0.7%)
Immune-Mediated Ocular Inflammatory Toxicity	1 (0.3%)	0
Immune-Mediated Guillain-Barre Syndrome	0	1 (0.7%)
Immune-Mediated Encephalitis	1 (0.3%)	0
Immune-Mediated Vasculitis	1 (0.3%)	0

ADA=Anti-Drug Antibodies, -=Negative, +=Positive.
Atezo=Atezolizumab Bev=Bevacizumab. Atezo+Bev HCC: IMbrave150 (YO40245) (Atezo+Bev)+GO30140(Arm A+F1).
Investigator text for AEs encoded using MedDRA v22.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. All treatment emergent AEs are included.
Clinical cut-off dates: Study IMbrave150 (YO40245) (29 August 2019), Study GO30140 (14 June 2019).

Safety related to drug-drug interactions and other interactions

No drug-drug interaction studies have been submitted with this application.

Discontinuation due to adverse events

Table 84: Adverse events reported in ≥1% of patients in any treatment arm leading to withdrawal of study treatment (Safety-evaluable population)

	Sorafenib (N=156)	Atezo+Bev (N=329)		
MedDRA System Organ Class MedDRA Preferred Term	Sorafenib	Atezo	Bev	Any treatment
Total number of patients with at least one adverse event	16 (10.3%)	28 (8.5%)	48 (14.6%)	51 (15.5%)
Overall total number of events	17	30	49	55
Gastrointestinal disorders				
Total number of patients with at least one adverse event	2 (1.3%)	6 (1.8%)	18 (5.5%)	18 (5.5%)
Total number of events	2	6	18	18
Oesophageal varices haemorrhage	0	0	4 (1.2%)	4 (1.2%)

Includes AEs with onset date on or after the date of the first dose of study drug up to the data cutoff date.
Investigator text for AEs are encoded using MedDRA version 22.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

AEs leading to dose modification/interruption

AEs that led to dose reduction were reported in 37.2% of patients in the Sorafenib arm. Dose reductions for any reason were not permitted in the Atezo+Bev arm. A numerically lower proportion of patients in the Sorafenib arm (41.0%) experienced AEs that led to dose interruption compared to the Atezo + Bev arm (49.5%). The most common AEs (> 2% of patients) leading to dose reduction/interruption of sorafenib in the Sorafenib arm were palmar-plantar erythrodysaesthesia syndrome (17.3%), diarrhea (10.9%), blood bilirubin increased (5.1%), fatigue (4.5%), decreased appetite (4.5%), hypertension (3.8%), platelet count decreased (3.2%), pyrexia (3.2%), vomiting (3.2%), rash (3.2%), aspartate aminotransferase increased

(3.2%), ascites (2.6%), nausea (2.6%), abdominal pain (2.6%), alanine aminotransferase increased (2.6%), and asthenia (2.6%). The most common AEs (> 2% of patients) leading to dose interruption of any treatment in the Atezo+Bev arm were proteinuria (6.7%), hypertension (6.1%), aspartate aminotransferase increased (5.2%), alanine aminotransferase increased (3.3%), hyperthyroidism (2.7%), platelet count decreased (2.4%), and pyrexia (2.4%).

Post marketing experience

Since the International Birth Date (18 May 2016) through 17 May 2019, an estimated cumulative total of 46,699 patients have received atezolizumab from marketing experience (US n=29,044; EU n=8,253; Japan n=3,796; Rest of the World n=5,605). No new or unexpected safety findings were identified in the post-marketing setting for atezolizumab used as a monotherapy or in the approved combination therapies.

Safety in Patients developing ADA

Table 85: Safety summary profile by atezolizumab ADA status (ADA-evaluable atezolizumab patients in safety-evaluable population) (IMbrave150 study)

	ADA - (N=227)	ADA + (N=88)
Total number of patients with at least one AE	224 (98.7%)	86 (97.7%)
Total number of AEs	2123	858
Total number of patients with at least one		
AE Related to any Study Treatment	191 (84.1%)	76 (86.4%)
AE Related to Atezolizumab	170 (74.9%)	73 (83.0%)
AE Related to Bevacizumab	169 (74.4%)	65 (73.9%)
Grade 3/4 AE	120 (52.9%)	56 (63.6%)
Treatment-related Grade 3/4 AE	77 (33.9%)	33 (37.5%)
Grade 5 AE	7 (3.1%)	7 (8.0%)
Treatment-related Grade 5 AE	3 (1.3%)	3 (3.4%)
Serious AE	72 (31.7%)	46 (52.3%)
Related Serious AE	30 (13.2%)	23 (26.1%)
AE Leading to Withdrawal from any Study Treatment	34 (15.0%)	15 (17.0%)
AE Leading to Withdrawal from Atezolizumab	16 (7.0%)	10 (11.4%)
AE Leading to Withdrawal from Bevacizumab	33 (14.5%)	13 (14.8%)
AE Leading to Withdrawal from Both Atezolizumab and Bevacizumab	14 (6.2%)	7 (8.0%)
AE Leading to Dose Modification/Interruption of any Study Treatment	104 (45.8%)	54 (61.4%)
AE Leading to Dose Interruption of any Study Treatment	104 (45.8%)	54 (61.4%)
AE Leading to Dose Reduction of Sorafenib	0	0

Includes AEs with onset date on or after the date of the first dose of study drug up to the data cutoff date.
Investigator text for AEs are encoded using MedDRA version 22.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Grade 3-4 AE and Treatment-Related Grade 3-4 AE refer to highest grade experienced.

Table 86: Grade 3 or Grade 4 adverse events by MedDRA preferred term by ADA status with a >2% difference between ADA-negative and ADA-positive patients (ADA-evaluable atezolizumab patients in safety-evaluable population) (IMbrave150 study)

		ADA- (N=227)	ADA+ (N=88)
MedDRA Preferred Term	Grade		
AST increased	3	11 (4.8%)	8 (9.1%)
Hyponatremia	3	4 (1.8%)	5 (5.7%)
Infusion-related reaction	3	3 (1.3%)	4 (4.5%)
Blood ALP increased	3	0	4 (4.5%)
Hyperbilirubinemia	3	0	2 (2.3%)
Varices esophageal	3	0	2 (2.3%)
Proteinuria	3	9 (4.0%)	1 (1.1%)
Fatigue	3	7 (3.1%)	1 (1.1%)

AST=aspartate aminotransferase; ALP=alkaline phosphatase.

Source: t_ae_ctc_IMM_teada

No >2% Difference in Grade 4 AEs were identified

Table 87: Serious adverse events by MedDRA preferred term by ADA status with a >2% (>1 patient) difference between ADA-negative and ADA-positive patients (ADA-evaluable atezolizumab patients in safety-evaluable population) (IMbrave150 study)

	ADA- (N=227)	ADA+ (N=88)
MedDRA Preferred Term		
Gastrointestinal hemorrhage	3 (1.3%)	5 (5.7%)
Blood bilirubin increased	1 (0.4%)	3 (3.4%)
Varices esophageal	0	2 (2.3%)
Autoimmune hepatitis	0	2 (2.3%)
Hyperbilirubinemia	0	2 (2.3%)
Esophageal varices haemorrhage	7 (3.1%)	1 (1.1%)

Table 88: Common (≥1% in any Arm) Serious Adverse Events by ADA Status (ADA Evaluable Population)

ADA Evaluable Patients Protocols: IMbrave150 (YO40245), GO30140	**Atezo+Bev HCC (N=474)**	
MedDRA System Organ Class MedDRA Preferred Term	ADA- (N=340)	ADA+ (N=134)
- Any adverse events -	107 (31.5%)	67 (50.0%)
Gastrointestinal Haemorrhage	3 (0.9%)	6 (4.5%)
Upper Gastrointestinal Haemorrhage	2 (0.6%)	3 (2.2%)
Varices Oesophageal	0	2 (1.5%)
Ascites	4 (1.2%)	1 (0.7%)
Oesophageal Varices Haemorrhage	9 (2.6%)	1 (0.7%)
Colitis	4 (1.2%)	0
Diarrhoea	5 (1.5%)	0
Pneumonia	3 (0.9%)	3 (2.2%)
Cholangitis	4 (1.2%)	3 (2.2%)
Autoimmune Hepatitis	0	2 (1.5%)
Hyperbilirubinaemia	1 (0.3%)	2 (1.5%)
Pyrexia	7 (2.1%)	4 (3.0%)
Epistaxis	0	2 (1.5%)
Infusion Related Reaction	1 (0.3%)	2 (1.5%)

ADA=Anti-Drug Antibodies, -=Negative, +=Positive.

Atezo=Atezolizumab Bev=Bevacizumab. Atezo+Bev HCC: IMbrave150 (YO40245) (Atezo+Bev)+GO30140(Arm A+F1).

Investigator text for AEs encoded using MedDRA v22.0. All counts represent patients.

Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient. To the SOC Overall row counts, a patient contributes only with the AE occurring with the highest grade within the SOC. Percentages are based on N in the column headings. All treatment emergent AEs are included.

Clinical cut-off dates: Study IMbrave150 (YO40245) (29 August 2019), Study GO30140 (14 June 2019).

2.5.1. Discussion on clinical safety

The analysis of safety is based on the findings in the pivotal study IMbrave150, where a sufficient number of patients have been exposed to atezo+bev for a sufficient period of time. The safety database should allow a thorough assessment of the safety profile of atezo+bev.

Overall, the observed AEs reflect the known safety profile of sorafenib, atezo and bev. These AEs are well-known by clinicians, and the majority of them are manageable in the clinically setting with supportive therapy, etc.

The incidence of Grade 3-4 and Grade 5 AEs is similar between the two treatment arms. Looking at Grade 3-4, higher incidences in atezo+bev arm are seen in terms of ALT increase, decreased platelet count, hypertension, proteinuria and IRR. There were more deaths in the sorafenib arm, both due to AEs and disease progression. In the sorafenib arm, 9 (5.8%) patients died due to AEs compared to 15 (4.6%) patients in the atezo+bev arm. Six patients in the atezo+bev arm died due to fatal bleedings, and 3 of them were deemed related to bevacizumab by the investigators. Precautionary measures are reflected in section 4.4 of the SmPC.

A higher incidence of SAEs is observed in the atezo+bev arm, and the main differences are seen in terms of gastrointestinal disorder, including bleedings (14.9% vs. 11.5%) and infections (7.3% vs 1.9%).

A higher incidence of fatal infections is seen in the atezo+bev arm. Although "infections" is reflected in section 4.8, and "sepsis" is mentioned in footnote "e", the MAH was requested to clearly reflect the risk of sepsis in table 2 of section 4.8 of the SmPC.

HCC patients are at higher risk of esophageal/gastric varices due to the underlying disease. Despite attempts to exclude all patients with prior bleeding due to esophageal and/or gastric varices within 6 months prior to study treatment, and perform esophagogastroduodenoscopy (EGD) on all patients in order to treat all size varices, a considerable number of patients experienced gastrointestinal bleedings in the atezo+bev arm.

Dose modifications were not allowed in the atezo+bev arm. Overall, a higher incidence of discontinuation was observed in the atezo+bev arm, 15.6% vs. 10.3%. approximately 1/3 of discontinuations were due to gastrointestinal bleeding. Bevacizumab was discontinued due to AEs much more often than atezo, 14.6% vs 8.5%. This clearly reflects that bevacizumab is less well tolerated than atezo.

A higher number of patients needed a dose interruption in the atezo+bev arm, and the most common AEs leading to dose interruption were proteinuria (6.7%), hypertension (6.1%), ALT/AST increase (5.2%), hyperthyroidism (2.7%), thrombocytopenia (2.4%) and pyrexia (2.4%). Again, it is clearly seen that the majority of dose interruptions were due to AEs related to the use of bevacizumab.

Finally, the MAH provided an analysis of safety depending on the ADA status. ADA+ patients overall experience more AEs, Grade 3-4 AEs, Grade 5 AEs, SAEs, and AEs leading to discontinuation of treatment or dose interruption. Looking at Grade 3-4 AEs and SAEs, patients with ADA+ status experienced more gastrointestinal bleedings and liver toxicity.

Data in HCC patients with Child-Pugh B liver disease treated with atezolizumab in combination with bevacizumab are very limited and there are currently no data available in HCC patients with Child-Pugh C liver disease.

Patients treated with bevacizumab have an increased risk of haemorrhage, and cases of severe gastrointestinal haemorrhage, including fatal events, were reported in patients with hepatocellular carcinoma (HCC) treated with atezolizumab in combination with bevacizumab. In patients with HCC, screening for and subsequent treatment of oesophageal varices should be performed as per clinical practice prior to starting treatment with the combination of atezolizumab and bevacizumab.

Bevacizumab should be permanently discontinued in patients who experience Grade 3 or 4 bleeding with the combination treatment.

Diabetes mellitus can occur during treatment with atezolizumab in combination with bevacizumab. Physicians should monitor blood glucose levels prior to and periodically during treatment with atezolizumab in combination with bevacizumab as clinically indicated (see section 4.4 of the SmPC).

2.5.2. Conclusions on clinical safety

The incidence of Grade 3-4 and Grade 5 AEs is similar between the atezo+bev and sorafenib arms. Despite attempts to exclude all patients at risk for gastrointestinal bleeding from the study higher incidences of bleeding, including fatal bleedings, infections, discontinuations and dose interruptions due to AEs were seen in the atezo+bev arm. The use of bevacizumab in patients with HCC is challenging, because many of these patients have a higher risk of bleeding due to their underlying disease and adequate information has been reflected in section 4.4 of the SmPC.

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 MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 13.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 13.1 with the following content:

Safety concerns

Table 78: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Immune-related hepatitis Immune-related pneumonitis Immune-related colitis Immune-related pancreatitis Immune-related endocrinopathies (diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency and hypophysitis) Immune-related neuropathies (Guillain-Barré syndrome, and myasthenic syndrome / myasthenia gravis) Immune-related meningoencephalitis Infusion-related reactions Immune-related myocarditis Immune-related nephritis

Summary of safety concerns	
	Immune-related myositis
Important potential risks	Anti-drug antibodies Embryo-fetal toxicity
Missing information	Concomitant use with other immuno-modulatory drugs Long term use Concomitant or sequential use of atezolizumab with intra-vesical Bacillus Calmette-Guérin vaccine for the treatment of urothelial carcinoma

Pharmacovigilance plan

Table 79: On-going and planned additional pharmacovigilance activities

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
There are no Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
There are no Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Category 3 - Required additional pharmacovigilance activities				
GO29322: A Phase IB Study of the Safety and Pharmacology of atezolizumab Administered with Ipilimumab or Interferon-Alpha in Patients with Locally Advanced or Metastatic Solid Tumors Ongoing	To evaluate the safety and tolerability of atezolizumab and ipilimumab in combination in patients with advanced or metastatic NSCLC or melanoma. To evaluate the safety and tolerability of atezolizumab and interferon alfa-2b in combination in patients with advanced or metastatic RCC or melanoma	Concomitant use with other immunomodulatory drugs	Final CSR	November 2020
WO29635: A Phase IB/II, Open-Label Study of the Safety and Pharmacology of Atezolizumab Administered with or without Bacille Calmette-Guérin in Patients with High Risk Non Muscle-Invasive Bladder Cancer Ongoing	To evaluate the safety and tolerability of atezolizumab as a single agent and in combination with BCG. To identify the DLTs and to determine the MTD or tolerability at the MAD of BCG in combination with atezolizumab	Concomitant or sequential use of atezolizumab with intra-vesical BCG vaccine for the treatment of urothelial carcinoma	Final CSR	June 2022
MO39171 (TAIL): Single-Arm Long-Term Safety and Efficacy Study of	To evaluate the long-term safety of atezolizumab on the bases of the following	Long-term use	Final CSR	May 2022

atezolizumab in previously treated NSCLC Patients Ongoing	endpoints: The incidence of all serious adverse events (SAEs) related to atezolizumab treatment and the incidence of immune-related adverse events (irAEs) related to atezolizumab treatment			
MO29983: An Open-Label, Single Arm, Multicenter, Safety Study of atezolizumab in Locally Advanced or Metastatic Urothelial or Non-Urothelial Carcinoma of the Urinary Tract Ongoing	To evaluate the safety of atezolizumab based on the following endpoints: Nature, severity, duration, frequency and timing of adverse events (AEs) and changes in vital signs, physical findings, and clinical laboratory results during and following atezolizumab administration.	Long-term use	Final CSR	Q1 2023
WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions Ongoing	The overall objective is to evaluate the effectiveness of the HCP brochure designed to mitigate important immune-related risks in patients receiving atezolizumab in the European Union. Data from HCP surveys and reporting rates for the important identified immune related risks will be collected and analyzed to evaluate effectiveness of the HCP brochure	Immune-related hepatitis Immune-related pneumonitis Immune-related colitis Immune-related pancreatitis Immune-related endocrinopathies (diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, and hypophysitis) Immune-related neuropathies (Guillain-Barré syndrome, and myasthenic syndrome / myasthenia gravis) Immune related meningoencephalitis Infusion-related reactions Immune-related myocarditis Immune-related nephritis	Protocol submission Interim report Final Report	February 2018 December 2020 December 2022

ADAs = anti-drug antibodies; BCG = bacillus Calmette-Guerin; CSR = Clinical Study Report; DLT = dose-limiting toxicity; HCP=healthcare professional; MAD = maximum administered dose; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; OS = overall survival; RCC = renal cell carcinoma; TBD=to be determined.

Risk minimisation measures

Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
Immune-Related Hepatitis	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects **Additional risk minimization measures:** • Educational materials for HCPs • Patient alert cards	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.
Immune-Related Pneumonitis	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects **Additional risk minimization measures:** • Educational materials	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	for HCPs • Patient alert cards	Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.
Immune-Related Colitis	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects **Additional risk minimization measures:** • Educational materials for HCPs • Patient alert cards	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.
Immune-Related Pancreatitis	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects **Additional risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Educational materials for HCPs • Patient alert cards	immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.
Immune-Related Endocrinopathies (Diabetes Mellitus, Hypothyroidism, Hyperthryroidism, Adrenal Insufficiency, and Hypophysitis)	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects **Additional risk minimization measures:** • Educational materials for HCPs • Patient alert cards	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis and infusion-related reactions.
Immune-Related Neuropathies (Guillain-Barre Syndrome and Myasthenia Gravis)	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects **Additional risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Educational materials for HCPs • Patient alert cards	immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.
Immune-Related Meningoencephalitis	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects **Additional risk minimization measures:** • Educational materials for HCPs • Patient alert cards	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis and infusion-related reactions.
Infusion-Related Reactions	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects **Additional risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition and intervention of the following important

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Educational materials for HCPs • Patient alert cards	immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.
Immune-Related Myocarditis	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects **Additional risk minimization measures:** • Educational materials for HCPs • Patient alert cards	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition of and intervention in the following important immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.
Immune-related nephritis	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 –Undesirable effects **Additional risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** WO40486 (Observational Study) Evaluation of the effectiveness of HCP educational materials which aims to facilitate early recognition of and intervention in the following important

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Educational materials for HCPs Patient alert cards	immune-related risks: Pneumonitis, hepatitis, colitis, pancreatitis, endocrinopathies, neuropathies, meningoencephalitis, myocarditis, nephritis, and infusion-related reactions.
Immune-related myositis	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 Undesirable effects **Additional risk minimization measures:** • Educational materials for HCPs • Patient alert cards	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Anti-drug Antibodies	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.8 Undesirable effects **No additional risk minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Embryo-fetal toxicity	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.6 Fertility, pregnancy	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	and lactation Section 5.3 Preclinical safety data **No additional risk minimization measures**	None
Concomitant use with other immuno-modulatory agents	**Routine risk minimization measures:** This safety concern considered as missing information is mentioned as one of the exclusion criteria within the Warnings and Precautions and description of studies included in the E.U. SmPC. **No Additional risk minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study GO29322
Long-term use	**Routine risk minimization measures:** Proposed text in E.U. SmPC: None **No Additional risk minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Studies: • MO29983 • MO39171
Concomitant or sequential use of atezolizumab with intra-vesical Bacillus Calmette-Guérin vaccine for the treatment of urothelial carcinoma.	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.4 Special Warnings and Precautions for Use: Includes language that patients who were administered a live attenuated vaccine with 28 days	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study WO29635

Safety concern	Risk minimization measures	Pharmacovigilance activities
	prior to enrolment were excluded from clinical trials **No Additional risk minimization measures**	

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 SmPC have been updated. Particularly, a new warning with regard to the very limited data in HCC patients with Child-Pugh B liver disease and the absence of data in HCC patients with Child-Pugh C liver disease. A new warning has also been included to reflect patients excluded from the clinical trials in HCC.

The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current QRD template, which were reviewed and accepted by the CHMP.

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 MAH and has been found acceptable for the following reasons:

- No significant changes impacting the readability of the package leaflet are made. In particular, key safety messages are not affected by this extension. The new additions follow the same structure and use similar descriptions and terminology as used in the approved package leaflet.
- The posology proposed in this application is the same as for the currently approved indications.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. It occurs in patients with chronic liver inflammation due to HBV, HCV, excessive alcohol intake or other toxins such as aflatoxin. Furthermore, haemochromatosis, alpha 1-antitrypsin deficiency, metabolic syndrome and NASH increase the risk of HCC.

The Applicant seeks approval for:

"Tecentriq, in combination with bevacizumab, is indicated for the treatment of adult patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy (see section 5.1)."

3.1.2. Available therapies and unmet medical need

Sorafenib remains the global standard of care for treatment of patients with unresectable HCC based on two multicenter, randomized, double–blind, placebo-controlled Phase III trials: the SHARP trial in Western regions and a trial conducted in the Asia-Pacific region (Asia-Pacific Trial). Both studies demonstrated a survival benefit of sorafenib vs. placebo. Sorafenib is often poorly tolerated, and dose reductions or drug discontinuations due to AEs are common (Nexavar EPAR).

Recently, treatment with lenvatinib, a multi-targeted receptor tyrosine kinase inhibitor, was shown to be non-inferior to sorafenib in terms of the primary efficacy endpoint of OS (lenvatinib vs. sorafenib: median OS 13.6 months vs. 12.3 months; hazard ratio [HR]=0.92, 95% confidence interval [CI]: 0.79, 1.06; non-inferiority margin = 1.08) though a statistically significant improvement in OS was not observed (REFLECT) (Lenvima II/11/G EPAR).

Despite available treatment options, there is a still a high unmet need for effective treatment options in these patients, who have a dismal prognosis.

3.1.3. Main clinical studies

The MAH has provided Study IMbrave150, a phase III, open-label, randomized study of atezolizumab in combination with bevacizumab compared with sorafenib in patients with untreated locally advanced or metastatic hepatocellular carcinoma.

3.2. Favourable effects

The study met its co-primary endpoint by showing statistically significant PFS gain, with a median PFS of 6.83 vs 4.27 months in atezo+bev and sorafenib arms respectively. The HR is 0.59 (0.47, 0.76), p<0.0001.

The OS data from the 1st IA show a statistically significant HR of 0.58 (0.42, 0.79) with a p-value of 0.0006.

The key secondary endpoints showed statistically significant and clinically meaningful differences in favour of atezo+bev. ORR by IRF per RECIST 1.1 showed 27.3% vs 11.9%, ORR by IRF per HCC mRECIST showed 33.2% vs. 13.3%. DOR was also considerably longer in the atezo+bev arm.

3.3. Uncertainties and limitations about favourable effects

The OS and DOR data are not mature yet. More mature data will be provided post approval (recommendation).

There seems to be a trend showing a negative impact of ADA on OS and PFS, however data should be interpreted with caution, because of differences in baseline disease characteristics between ADA- and ADA+ patients and immature OS data in the ADA subgroups. The MAH provided analyses of OS and PFS comparing ADA- and ADA+, adjusting for multiple baseline covariates that indicated similar OS results between the ADA+ population and sorafenib, whereas an OS benefit was shown for the ADA- subgroup compared to sorafenib. It is not possible to draw any firm conclusion regarding the clinical relevance of the impact of ADA on efficacy given that ADA is a post-randomization variable.

Although no reliable conclusions can be drawn from the exploratory PD-L1 expression analyses of available samples in only 40% of the study population, efficacy outcomes appear to be associated with PD-L1 expression status, with a larger benefit for the PD-L1 positive subgroup (PD-L1 TC/IC≥ 1%).

However, available data suggest a small overall survival benefit for Atezo + Bev compared to Sorafenib also in the PD-L1 negative subgroup without detrimental effects with regard to PFS or response status. Efficacy data by PD-L1 expression status should be provided with updated OS data post approval.

3.4. Unfavourable effects

Higher incidences of Grade 3-4 AEs are seen in the atezo+bev arm in terms of ALT increase, decreased platelet count, hypertension, proteinuria and IRR.

Six patients in the atezo+bev arm died due to fatal bleedings. Furthermore, a higher incidence of fatal infections is seen in the atezo+bev arm.

A higher incidence of SAEs is observed in the atezo+bev arm, and the main differences are seen in terms of gastrointestinal disorder, including bleedings (14.9% vs. 11.5%) and infections (7.3% vs 1.9%).

Dose modifications were not allowed in the atezo+bev arm. Overall, a higher incidence of discontinuation was observed in the atezo+bev arm, 15.6% vs. 10.3%. approximately 1/3 of discontinuations were due to gastrointestinal bleeding. Bevacizumab was discontinued due to AEs much more often than atezo, 14.6% vs 8.5%.

A higher number of patients needed a dose interruption in the atezo+bev arm, and the most common AEs leading to dose interruption were proteinuria (6.7%), hypertension (6.1%), ALT/AST increase (5.2%), hyperthyroidism (2.7%), thrombocytopenia (2.4%) and pyrexia (2.4%).

3.5. Uncertainties and limitations about unfavourable effects

An analysis of safety as function of ADA status seems to show that ADA+ patients overall experience more AEs, Grade 3-4 AEs, Grade 5 AEs, SAEs, and AEs leading to discontinuation of treatment or dose interruption. Looking at Grade 3-4 AEs and SAEs, patients with ADA+ status experienced more gastrointestinal bleedings and liver toxicity.

3.6. Effects Table

Table 89: Effects Table for Tecentriq in combination with bevacizumab for 1L HCC (IMbrave150; data cut-off: 29 August 2019)

Effect	Short description	Unit	Atezo+Bev	Sorafenib	Uncertainties / Strength of evidence
Favourable Effects					
OS		Months	NA	13.3	OS data immature (IA OS, 32% event rate, median follow-up 8.6 months)
		HR (95%CI)	0.58 (0.42, 0.79)		
PFS	IRF-assessed per RECIST v1.1	Months	6.8	4.3	Only data for patients with well-preserved liver function
		HR (95%CI)	0.59 (0.47, 0.76)		
ORR	Confirmed, IRF-assessed per RECIST v1.1	%	27	12	
ORR	Confirmed, IRF-assessed per mRECIST	%	33	13	
Unfavourable Effects					
	AEs	%	98.2	98.7	
	G3/4 AEs	%	56.5	55.1	•Higher percentage of SAEs in

Effect	Short description	Unit	Atezo+Bev	Sorafenib	Uncertainties / Strength of evidence
	Related G3/4 AEs	%	35.6	45.5	Atezo+Bev driven by gastrointestinal bleeding AEs •Higher incidences in hyperthyroidism and diabetes mellitus.
	Serious AEs	%	38.0	30.8	
	AESIs	%	60.5	72.0	
	G5 AEs	% (n)	1.8 (6)	0.6 (1)	
	AEs leading to treatment discontinuation	%	15.5	10.	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Patients with HCC have a dismal prognosis with a relatively short median OS, as seen in the control arm. Thus, there is a high unmet need for new effective treatment options that can prolong OS in these patients. Atezolizumab in combination with bevacizumab seems to prolong both PFS and OS. These findings are further supported by an increase in ORR and DOR.

Efficacy results appear to be associated with PD-L1 expression status based on exploratory analysis in only 40% of the study population. Available data suggest a small overall survival benefit for Atezo + Bev compared to Sorafenib also in the PD-L1 negative subgroup. Considering also the safety profiles of both treatment arms and the fact that biopsies are often not part of the routine clinical management, a favourable benefit-risk assessment is accepted in an all-comer population.

Atezolizumab in combination with bevacizumab gives rise to considerably more bleeding episodes, including fatal bleeding, compared to sorafenib. Despite attempts to exclude all patients at risk for gastrointestinal bleeding from the study, a higher incidence of bleeding, including fatal bleeding, infections, discontinuations and dose interruptions due to AEs were seen in the atezo+bev arm. Overall the incidence of Grade 3-4 and Grade 5 AEs is similar between the two treatment arms.

3.7.2. Balance of benefits and risks

The demonstrated benefit in the overall study population is considered clinically relevant and there are no major safety concerns apart from a higher risk of gastrointestinal bleeding, which is clearly reflected in the SmPC, where precautionary measures are also reflected. The benefits of atezolizumab in combination with bevacizumab outweigh the safety concerns in the target population.

3.7.3. Additional considerations on the benefit-risk balance

Raising ADA development as a concern is difficult since developing ADAs is a risk and cannot be determined *a priori*.

3.8. Conclusions

The overall B/R of atezolizumab in combination with bevacizumab is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends 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 and IIIB

Extension of Indication to include, in combination with with bevacizumab, the treatment of patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy, based on the results of the pivotal study YO40245 (IMbrave150) as well as data from Arms A and F of the supportive Phase Ib study GO30140. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the Tecentriq 1200mg concentrate for solution for infusion SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.1.

An updated RMP version 13.1 was agreed during the procedure.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Tecentriq EMEA/H/C/004143/II/0039.

Attachments

1. EN PI (changes highlighted) as adopted by the CHMP on 17 September 2020.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 06 October 2020. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf.

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. The MAH is reminded that, at the same time as the submission on the eCTD closing sequence mentioned above, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

4. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.