15 December 2022
EMA/42902/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imfinzi

International non-proprietary name: durvalumab

Procedure No. EMEA/H/C/004771/II/0045

Note

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

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List of abbreviations

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AFP	Alpha-fetoprotein
ALBI	Albumin-bilirubin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the serum concentration-time curve
$AUC_{0\text{-}inf}$	Area under the serum concentration-time curve from 0 to infinity
BCLC	Barcelona Clinic Liver Cancer
BICR	Blinded Independent Central Review
BOR	Best objective response
CD	Cluster of differentiation
CI	Confidence interval
C_{max}	Maximum serum concentration
C_{min}	Minimum serum concentration
$C_{min,1}$	Minimum serum concentration after the first dose
CR	Complete response
CRF	Case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events (version 4.03)
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
D	Durvalumab 1500 mg (20 mg/kg) Q4W
DCO	Data cut-off
DCR	Disease control rate
DCR-16w	Disease control rate at 16 weeks
DCR-24w	Disease control rate at 24 weeks
DoR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EHS	Extrahepatic spread
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FA	Final analysis
FAS	Full analysis set
FDA	United States Food and Drug Administration
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HR	Hazard ratio
HRQoL	Health-related quality of life
IA	Interim analysis
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICI	Immune checkpoint inhibitor
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
imAE	Immune-mediated adverse event
IO	Immuno-oncology
IV	Intravenous
mAb	Monoclonal antibody
MTP	Multiple testing procedure
MVI	Macrovascular invasion
nAb	Neutralizing antibody
NCCN	National Comprehensive Cancer Network
NI	Noninferiority
NSCLC	Non-small cell lung cancer

Abbreviation or special term	Explanation
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand-1
PD-L2	Programmed cell death ligand-2
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetics
PR	Partial response
PRO	Patient Reported Outcome
PS	Performance status
PT	Preferred term
QLQ-HCC18	18-item hepatocellular cancer health-related quality of life questionnaire
QoL	Quality of life
QxW	Every x weeks
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
S	Sorafenib 400 mg twice daily
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA query
SoC	Standard of care
T	Tremelimumab 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W
T300+D	Tremelimumab 300 mg (4 mg/kg) for a single priming dose and durvalumab 1500 mg (20 mg/kg) Q4W
T75+D	Tremelimumab 75 mg (1 mg/kg) Q4W × 4 doses and durvalumab 1500 mg (20 mg/kg) Q4W
TKI	Tyrosine kinase inhibitor
TTR	Time to onset of objective response
UC	Urothelial carcinoma
US	United States
VEGFR	Vascular endothelial growth factor receptor

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 5 April 2022 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 IMFINZI in combination with tremelimumab for the treatment of adults with unresectable hepatocellular carcinoma (uHCC), based on final results from Study D419CC00002 (HIMALAYA); This was a randomized, open-label, multi-center phase III study of durvalumab and tremelimumab as first-line treatment in patients with unresectable hepatocellular carcinoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and Package Leaflet. Version 6.1 of the RMP has also been submitted.

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/0106/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

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 received Scientific advice from the CHMP on 18 May 2017 (EMEA/H/SA/3558/1/2017/II). The Scientific advice pertained to the clinical aspects of the dossier, such as the principles of the statistical analyses of the Himalaya study and the design of the supportive study 22.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Aaron Sosa Mejia Co-Rapporteur: <N/A>

Timetable	Actual dates
Submission date	5 April 2022
Start of procedure:	23 April 2022
CHMP Rapporteur Assessment Report	16 June 2022
PRAC Rapporteur Assessment Report	22 June 2022
PRAC members comments	29 June 2022
PRAC Outcome	7 July 2022
CHMP members comments	11 July 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	13 July 2022
Request for supplementary information (RSI)	21 July 2022
CHMP Rapporteur Assessment Report	18 October 2022
PRAC Rapporteur Assessment Report	14 October 2022
PRAC members comments	19 October 2022
PRAC Outcome	27 October 2022
CHMP members comments	28 October 2022
Updated CHMP Rapporteur Assessment Report	3 November 2022
Request for supplementary information (RSI)	10 November 2022
CHMP and PRAC Rapporteurs Joint AR (JAR)	02 December 2022
Comments from PRAC and CHMP	05 December 2022
Opinion	15 December 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Unresectable hepatocellular carcinoma (uHCC) regardless of tumoral PD-L1 expression.

State the claimed therapeutic indication

The initially claimed new therapeutic indication in section 4.1 of the SmPC was:

Durvalumab in combination with tremelimumab is indicated for the treatment of patients with unresectable hepatocellular carcinoma.

The indication was updated during the procedure to:

IMFINZI in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).

Epidemiology and risk factors

The incidence of HCC increases progressively with advancing age in all populations, reaching a peak at 70 years (El-Serag 2012, White et al 2017). Rates of both incidence and mortality are 2 to 3 times higher among men than among women in most regions (Sung et al 2021).

The main risk factors for HCC are chronic infection with HBV or HCV, aflatoxin-contaminated foods, heavy alcohol intake, excess body weight, type 2 diabetes, and smoking. The major risk factors vary from region to region, which is reflected in the incidence of HCC across geographic regions (Sung et al 2021). The highest incidence rates are seen in East Asia and Sub-Saharan Africa, while lower rates are seen in Europe and North America (WHO 2019).

Worldwide, HBV causes an estimated 75% to 80% of HCC cases, while HCV causes 10% to 20% of cases (Perz et al 2006). HCV infection (particularly in the US, Japan, and Egypt [Mak et al 2018, McGlynn et al 2015]), excessive alcohol consumption, and non-alcoholic fatty liver disease (linked to the growing prevalence of obesity and type 2 diabetes) represent the main risk factors for HCC (Vogel et al 2019).

Biologic features

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

Moreover, increased expression of immunosuppressive cell populations, such as regulatory T cells and myeloid derived suppressor cells, and inhibitory signalling molecules, such as CTLA 4 and PD 1, have

been observed in HCC (Gao et al 2009, Hato et al 2014, Pardee and Butterfield 2012) and is additionally associated with HBV and HCV infection. This upregulation contributes to the immunosuppressive environment for HCC and highlights the importance of the PD-(L)1 and CTLA-4 pathways in HCC (Golden-Mason et al 2007, Pardee and Butterfield 2012, Peng et al 2008).

Clinical presentation, diagnosis and stage/prognosis

The HCC prognosis and treatment depend on factors such as tumour burden, degree of liver dysfunction, and clinical performance status (PS) (Marrero et al 2018, Vogel et al 2019). Hepatocellular carcinoma classically develops and grows in silent fashion, making its discovery challenging prior to the development of later stage disease (Bialecki and Di Bisceglie 2005), which usually leads to a late diagnosis, with a median survival following diagnosis of approximately 6 to 20 months (McGlynn et al 2015). Hepatocellular carcinoma is a medically complex and difficult to treat disease as the majority of patients have underlying cirrhosis requiring management of both the malignancy and underlying liver disease. Hence, the 5-year survival rate for HCC is less than 20% (Sarveazad et al 2019, Villanueva 2019). Unresectable HCC remains a difficult to treat disease, and the majority of patients will ultimately die of either HCC or complications of liver disease.

Management

Sorafenib, an oral TKI targeting multiple kinases, including VEGFR-1, -2, and -3 and BRAF, has been the standard of care (SOC) for advanced HCC in the first-line setting since its approval in 2007, which was based on improvement compared to placebo, establishing a median OS of 10.7 months (vs 7.9 months for placebo [Llovet et al 2008]). Subsequent studies have demonstrated a median OS ranging from 10.7 to 13.4 months (Finn et al 2021, Llovet et al 2008, Yamashita et al 2020). In 2018, lenvatinib, another multiple kinase inhibitor against VEGFR-1, -2, and -3 and fibroblast growth factor receptor-1, -2, -3, and -4, was approved as first-line treatment for advanced HCC in patients without main portal vein invasion and ECOG PS 0 to 1. Lenvatinib demonstrated non-inferiority to sorafenib in a Phase III study, with a median OS of 13.6 months vs 12.3 months with sorafenib (Kudo et al 2018). Atezolizumab (a PD-L1 inhibitor) in combination with bevacizumab (an angiogenesis inhibitor targeting vascular endothelial growth factor A) has also been approved in the first-line setting, after the Phase III IMbrave150 study showed improvements in OS and PFS compared to sorafenib (Finn et al 2020b, Finn et al 2021). The NCCN, ESMO, and Japanese Society of Hepatology guidelines were updated in 2020 to recommend atezolizumab in combination with bevacizumab as the preferred option to treat first-line HCC (NCCN Guidelines 2021, JSH 2021; Vogel and Martinelli 2021 [ie, ESMO Guidelines 2021]).

Regorafenib and cabozantinib (both multitargeted TKIs) have been approved for patients with advanced HCC, who have tolerated and progressed on sorafenib (Abou-Alfa et al 2018, Bruix et al 2017). Another approved second-line therapy is ramucirumab (a monoclonal antibody against VEGFR 2), which has improved survival in patients with serum AFP $\geq$ 400 ng/mL and previous treatment with sorafenib (Zhu et al 2019). In addition, nivolumab (an anti-PD-1 mAb) in combination with ipilimumab (an anti CTLA-4 mAb) has recently received accelerated approval from the FDA for patients previously treated with sorafenib, due to results from the CheckMate 040 study, a Phase II study in which nivolumab (1 mg/kg, Q3W) plus ipilimumab (3 mg/kg Q3W × 4) (N=50; 28/50 [56%] with HBV) achieved a 32% ORR (Yau et al 2020).

Unmet medical need

Despite recent advances in treatment options, patients with uHCC continue to have a low life expectancy and the underlying liver disease and portal vein hypertension increase the risk of gastrointestinal

bleeding in patients with advanced HCC, which can be potentially life-threatening (Boregowda et al 2019). Currently available therapies provide only a modest improvement in survival with safety profiles that require management due to adverse events such as diarrhoea, hypertension, and palmar-plantar erythrodysaesthesia (PPE)(Cheng et al 2009, Lencioni et al 2014, Llovet et al 2008). Treatment with atezolizumab plus bevacizumab also carries a higher incidence of bleeding, including fatal bleeding, despite attempts to exclude patients at risk for gastrointestinal bleeding from the pivotal study (NCCN Guidelines 2021). Moreover, the underlying liver cirrhosis may result in moderate liver dysfunction, which may exacerbate the toxicity of systemic therapies such as TKIs (Cheng et al 2020). Hence, additional therapeutic options are needed, including options for patients with uHCC who are at higher risk of bleeding events, so there exist an unmet medical need for better and tolerable treatment options for patients with uHCC.

2.1.2. About the product

Durvalumab binds to programmed cell death ligand-1 (PD-L1) (but not programmed cell death ligand-2) and thus blocks its interaction with programmed cell death 1 (PD-1) on T-lymphocytes (T-cells) and cluster of differentiation (CD) 80 (B7.1) on immune cells (ICs) and is engineered to reduce antibody-dependent cell-mediated cytotoxicity (ADCC). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses and may result in tumour regressions including objective responses based on tumour cell reduction as well as in stable disease due to tumour growth control. This mechanism of action may elicit eventually delay of progression and extension of survival.

Durvalumab is approved for the treatment of locally advanced, unresectable, NSCLC in adult patients whose tumours express PD L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy (EMEA/H/C/004771/0000). Durvalumab is also approved in combination with standard-of-care platinum-based chemotherapy as 1L treatment of extensive stage small cell lung cancer (ES SCLC; EMEA/H/C/004771/II/0014/G).

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

Table 1. Summary of EMA Regulatory Interactions and Correspondence Specific to the HIMALAYA Study

Date	Type of interaction	Summary of outcome
17 March 2017 – 22 May 2017	Pre-Phase III Scientific Advice	EMA agreed with the principles of the statistical analysis and commented that the proposed interim analysis may lack power and/or maturity when investigating all subgroups (including patients with low expression of PD-L1 in whom prognosis may be better and treatment efficacy less pronounced). The design of Study 22 is appropriate, but contribution of components is dependent on results and could be driven by PD-L1 expression.
19 Jan 2022	Joint Pre-submission Meeting	AstraZeneca held a joint pre-submission meeting with the Rapporteur and Co-Rapporteur to review the planned submission of tremelimumab in combination with durvalumab for the treatment of adults with unresectable hepatocellular carcinoma. The Rapporteur acknowledged that HIMALAYA was well-designed to evaluate contribution of components. It was noted, however, that the added benefit of tremelimumab relative to the safety profile of the combination would be a key consideration in the review. Additionally, study integrity will be a key consideration for the Agency during their review. The Rapporteur sought assurance to support that study integrity was maintained, as the non-inferiority margin was adopted without prior agency feedback during the conduct of the study.

Abbreviations: EMA, European Medicines Agency; HIMALAYA, Study D419CC00002; PD-L1, programmed cell death ligand 1; Study 22, Study D4190C00022.

The Scientific advice given by the EMA was generally followed.

2.1.4. General comments on compliance with GCP

N/A

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

Durvalumab is an IgG1 monoclonal antibody, a protein being extensively degraded in the patient's body by regular proteolytic mechanisms before excretion. Durvalumab 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 corr2), durvalumab 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 have been submitted in this application, which is considered acceptable.

Durvalumab is human monoclonal antibody of the IgG1 kappa subclass. Antibodies are considered naturally occurring proteins, which are not expected to remain either stable or biologically active in the environment for any significant period. The justification for not performing any ERA studies is accepted.

2.3. Clinical aspects

2.3.1. Introduction

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 2. Listing of clinical studies

Study	Phase	Objectives of study	Study design and type of control	Route of administration and dosage regimen	
Pivotal study					
HIMALAYA (D419CC00002) Randomized, Open-label, Multi-center Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients with Advanced Hepatocellular Carcinoma (HIMALAYA)	III	Efficacy and safety of durvalumab and tremelimumab in combination versus durvalumab alone and sorafenib as SoC	Randomized, open-label	Durvalumab 1500 mg Q4W	
				Durvalumab 1500 mg Q4W Tremelimumab 300 mg single dose	
				Durvalumab 1500 mg Q4W Tremelimumab 75 mg 4 doses	
				Sorafenib (SoC) 400 mg BID	
Supporting studies					
Study 22 (D4190C00022) A study of safety, tolerability, and	I/II	Safety, tolerability, efficacy, PK, and immunogenicity	Open-label, multiple-arm, randomized	*Part 1*	Tremelimumab 75 mg (1 mg/kg) × 4 doses Durvalumab 1500 mg (20 mg/kg) Q4W

clinical activity of durvalumab and tremelimumab administered as monotherapy, or durvalumab in combination with tremelimumab or bevacizumab in subjects with advanced unresectable HCC				*Part 2A & China Cohort*	Durvalumab monotherapy 1500 mg (20 mg/kg) Q4W Tremelimumab monotherapy 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W Tremelimumab 75 mg (1 mg/kg) × 4 doses + Durvalumab IV 1500 mg (20 mg/kg) Q4W
				Part 2B	Tremelimumab IV 300 mg (4 mg/kg) × 1 dose + Durvalumab IV 1500 mg (20 mg/kg) Q4W
				Part 3	Durvalumab monotherapy 1500 mg (20 mg/kg) Q4W Tremelimumab monotherapy 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W Tremelimumab 75 mg (1 mg/kg) × 4 doses + Durvalumab 1500 mg (20 mg/kg) Q4W Tremelimumab 300 mg (4 mg/kg) × 1 dose + Durvalumab 1500 mg (20 mg/kg) Q4W
				Part 4	Durvalumab 1120 mg (15 mg/kg) + Bevacizumab 15 mg/kg Q3W
Study 11 (D4190C00011) Phase I multicenter, open-label, doseexploration, and dose-expansion study of Durvalumab in combination with Tremelimumab in subjects with recurrent or metastatic SCCHN	I	Evaluate safety, tolerability, and efficacy of Durvalumab in combination with Tremelimumab	Non-randomized, open-label	*Dose exploration*	
				Cohort 1	Durvalumab 15 mg/kg Q4W Tremelimumab 3 mg/kg Q4W
				Cohort 2	Durvalumab 10 mg/kg Q2W Tremelimumab 1 mg/kg Q4W
				Cohort 3	Durvalumab 20 mg/kg Q4W Tremelimumab 1 mg/kg Q4W
				Cohort 4	Durvalumab 20 mg/kg Q2W Tremelimumab 3 mg/kg Q4W
				Dose exploration	
				Cohort A PD-L1 High	Durvalumab 20 mg/kg Q4W Tremelimumab 1 mg/kg Q4W then Durvalumab 10 mg/kg Q2W
				Cohort B PD-L1 Low or Negative	Durvalumab 20 mg/kg Q4W Tremelimumab 1 mg/kg Q4W

					then Durvalumab 10 mg/kg Q2W
				Cohort C prior IMT treatment	Durvalumab 20 mg/kg Q4W Tremelimumab 1 mg/kg Q4W then Durvalumab 10 mg/kg Q2W
HAWK (D4193C00001) Phase II, multicenter, single-arm, global study of Durvalumab monotherapy in SCCHN	II	Efficacy of durvalumab monotherapy and health-related quality of life	Open-label, single-arm	Durvalumab IV 10 mg/kg Q2W for 12 months or until progression of disease	
Study 21 (D4190C00021) Phase Ib/II study to evaluate the safety, tolerability, and clinical activity of durvalumab in combination with tremelimumab, of durvalumab monotherapy, and of tremelimumab monotherapy in second- and third-line subjects with metastatic or recurrent gastric or gastroesophageal junction adenocarcinoma	Ib/II	Evaluate the safety, antitumor activity, PK, and immunogenicity of Durvalumab in combination with Tremelimumab, of Durvalumab monotherapy, and of Tremelimumab monotherapy	Randomized, multicenter, open-label, comparative study	*Phase 1b*	Durvalumab 20 mg/kg + Tremelimumab 1 mg/kg
				Phase 2	
				Arm A	Durvalumab 20 mg/kg + Tremelimumab 1 mg/kg
				Arm B	Durvalumab 10 mg/kg
				Arm C	Tremelimumab 10 mg/kg
				Arm D	Durvalumab 20 mg/kg + Tremelimumab 1 mg/kg
				Arm E	Durvalumab 20 mg/kg + Tremelimumab 1 mg/kg
Study 1108 (CD-ON-MEDI4736-1108) Phase I/II study to evaluate the safety, tolerability, and pharmacokinetics of MEDI4736 in subjects with advanced solid tumors	I/II	Safety, tolerability, efficacy, PK, and immunogenicity	Open-label, multiple-arm, nonrandomized	*Dose-escalation phase*	
				Durvalumab 0.1, 0.3, 1, 3, 10 mg/kg Q2W + 15 mg/kg Q3W for up to 12 months or until PD	
				Dose-exploration phase	
				Durvalumab 20 mg/kg Q4W for up to 12 months	
				Dose-expansion phase	
				Durvalumab 10 mg/kg Q2W up to 12 months	
Study 06 (D4190C00006) Phase Ib open-label study to evaluate the	Ib	Safety, tolerability, and efficacy of durvalumab in	Open-label	*Dose-escalation phase - combination*	

safety and tolerability of durvalumab (MEDI4736) in combination with tremelimumab in subjects with advanced NSCLC [a]		combination with tremelimumab		Durvalumab IV 3-20 mg/kg Q4W or 10 mg/kg Q2W + Tremelimumab IV 1-10 mg/kg Q4W for 6 doses, then Q12W for 3 doses
				Dose-expansion phase - combination
				Durvalumab 20 mg/kg Q4W for 4 doses then IV 20 mg/kg Q4W for 9 doses + Tremelimumab 1 mg/kg Q4W for 4 doses
Japan Study 02 (D4190C00002) A Phase I, open-label, multicenter study to evaluate the safety, tolerability, and PK of MEDI4736 in patients with advanced solid tumors	I	Safety and tolerability of durvalumab monotherapy or in combination with tremelimumab	Open-label, Non-randomized	Durvalumab monotherapy *Dose-escalation phase* Durvalumab IV 1, 3, 10 mg/kg Q2W; 15 mg/kg Q3W; 20 mg/kg Q4W Dose-expansion phase Durvalumab IV 10 mg/kg Q2W
				Combination therapy *Dose-expansion phase* Durvalumab IV 20 mg/kg Q4W for 4 doses then IV 20 mg/kg Q4W + Tremelimumab IV 1 mg/kg Q4W for 4 doses
Study 10 (D4190C00010) Phase I study of MEDI4736 (anti-PD-L1 antibody) in combination with tremelimumab (anti-CTLA-4 antibody) in subjects with advanced solid tumors	I	Safety, tolerability, and efficacy of the combination of durvalumab and tremelimumab	Open-label	Combination therapy *Dose-exploration phase* Durvalumab IV at 20 mg/kg Q4W for 12 months AND Tremelimumab IV 1 mg/kg Q4W (7 doses) then Q12W (2 doses) OR Durvalumab IV 10 mg/kg Q2W for 12 months AND Tremelimumab 3 mg/kg Q4W (7 doses) then Q12W (2 doses) Dose-expansion phase – combination therapy Durvalumab IV 20 mg/kg Q4W for 4 doses then IV 10 mg/kg Q2W + Tremelimumab IV 1 mg/kg Q4W for 4 doses
DANUBE (D419BC00001) Phase III study of Durvalumab alone and in combination with Tremelimumab in patients with unresectable stage IV urothelial cancer	III	Efficacy and safety of Durvalumab monotherapy and in combination with Tremelimumab versus SoC	Randomized, open-label, controlled (SoC), multicenter	Durvalumab 1500 mg Q4W alone
				Durvalumab 1500 mg Q4W + Tremelimumab 75 mg Q4W for 4 doses
				SoC
KESTREL (D419LC00001) Phase III study of Durvalumab alone and	III	Efficacy and safety of Durvalumab	Randomized, open-label, multi-center, global study	Durvalumab 1500 mg Q4W alone

in combination with Tremelimumab in patients with metastatic SCCHN		monotherapy and in combination with Tremelimumab versus SoC		Durvalumab 1500 mg Q4W + Tremelimumab 75 mg Q4W for 4 doses
				SoC
POSEIDON (D419MC00004) Phase III, randomized, global study to determine the efficacy of durvalumab or durvalumab and tremelimumab in combination with platinum-based chemotherapy for first-line treatment in patients with metastatic NSCLC	III	Efficacy, PK, immunogenicity, safety, and tolerability versus SoC	Randomized, multi-center, open-label, comparative active comparator	Durvalumab 1500 mg Q3W for 4 doses + SoC, then Durvalumab 1500 mg Q4W until PD
				Durvalumab 1500 mg Q3W for 4 doses + SoC, then Durvalumab 1500 mg Q4W until PD Tremelimumab 75 mg Q3W for 4 doses + 1 dose at week 16
				SoC (abraxane + carboplatin, pemetrexed + cisplatin or carboplatin, or gemcitabine + cisplatin or carboplatin)
ATLANTIC (D4191C00003) Phase II non-comparative, open-label, multicenter, international study of MEDI4736 in patients with locally advanced or metastatic NSCLC (Stage IIIB-IV) who have received at least 2 prior systemic treatment regimens including one platinum-based chemotherapy regimen	II	Efficacy, safety, tolerability, PK, and immunogenicity	Open-label, single-arm, non-randomized	Durvalumab 10 mg/kg Q2W for up to 12 months
PACIFIC (D4191C00001) Phase III, randomized, double-blind, placebo-controlled, multicenter, international study of durvalumab as sequential therapy in patients with locally advanced, unresectable NSCLC (Stage III) who have not progressed following definitive, platinum-based concurrent chemoradiation therapy	III	Efficacy, safety, tolerability, PK, immunogenicity, and health-related quality of life versus SoC	Randomized, double-blind, placebocontrolled	Durvalumab 10 mg/kg Q2W for up to 12 months

MYSTIC (D419AC00001) Phase III, randomized, open-label, multicenter, global study of durvalumab monotherapy and durvalumab in combination with tremelimumab compared to SoC in patients with advanced or metastatic NSCLC	III	Efficacy versus SoC	Open-label, randomized, active comparator	*Durvalumab monotherapy* Durvalumab IV 20 mg/kg Q4W
				Combination therapy Durvalumab IV 20 mg/kg Q4W for 4 doses then IV 20 mg/kg Q4W until PD AND Tremelimumab IV 1 mg/kg Q4W for 4 doses
NEPTUNE (D419AC00003) Phase III randomized, open-label, multicenter, global study of MEDI4736 in combination with tremelimumab therapy versus standard of care platinum-based chemotherapy in first line treatment of patients with advanced or metastatic NSCLC	III	Efficacy, PK, immunogenicity, safety, and tolerability versus SoC	Open-label, randomized, active comparator	*Combination therapy* Durvalumab IV 20 mg/kg Q4W for 4 doses then IV 20 mg/kg Q4W AND Tremelimumab IV 1 mg/kg Q4W for 4 doses
ARCTIC (D4191C00004) Phase III, open-label, randomized, multicenter, international study of durvalumab, given as monotherapy or in combination with tremelimumab, determined by PD-L1 expression, versus SoC in patients with locally advanced or metastatic NSCLC (Stage IIIB-IV) who have received at least 2 prior systemic treatment regimens including one platinum-based chemotherapy regimen and do not have known EGFR TK activating mutations or ALK rearrangements	III	Efficacy, safety, tolerability, PK, and immunogenicity versus SoC	Open-label, randomized, active comparator	*Durvalumab monotherapy* Durvalumab IV 10 mg/kg Q2W for up to 12 months
				Tremelimumab monotherapy Tremelimumab IV 10 mg/kg IV Q4W for 24 weeks followed by 10 mg/kg IV Q12W for 24 weeks

				Combination therapy Durvalumab IV 20 mg/kg Q4W for 12 weeks then IV 10 mg/kg Q2W for 34 weeks + Tremelimumab IV 1 mg/kg Q4W for 12 weeks (maximum of 22 doses of durvalumab + 4 doses of tremelimumab)
CASPIAN (D419QC00001) Phase III, randomized, multicenter, open-label, comparative study to determine the efficacy of durvalumab or durvalumab and tremelimumab in combination with platinum-based chemotherapy for the first-line treatment in patients with extensive disease SCLC	III	Efficacy, PK, immunogenicity, safety, and tolerability versus SoC	Open-label, randomized, active comparator	Durvalumab IV 1500 mg Q3W for 4 doses then durvalumab IV 1500 mg Q4W until PD + EP for 4 cycles
				Combination therapy (D + T + EP) Durvalumab IV 1500 mg Q3W for 4 doses then Durvalumab IV 1500 mg Q4W until PD + Tremelimumab IV 75 mg Q3W for 4 doses + EP for 4 cycles
				SoC EP for up to 6 cycles [b]
CONDOR (D4193C00003) Phase II, randomized, open-label, multi-center, global study of durvalumab monotherapy, tremelimumab monotherapy, and durvalumab in combination with tremelimumab in patients with recurrent or metastatic SCCHN	II	Efficacy of durvalumab in combination with tremelimumab and health-related quality of life	Open-label, randomized	*Durvalumab monotherapy* Durvalumab IV 10 mg/kg Q2W for up to 12 months
				Tremelimumab monotherapy Tremelimumab IV 10 mg/kg Q4W for 7 doses then Q12W for 2 doses for up to 12 months
				Combination therapy Durvalumab IV 20 mg/kg Q4W for 4 doses then IV 10 mg/kg Q2W to complete 12 months of treatment + Tremelimumab IV 1 mg/kg Q4W for 4 doses

EAGLE (D4193C00002) Phase III, randomized, open-label, multicenter, global study of durvalumab monotherapy and durvalumab in combination with tremelimumab versus SoC in patients with recurrent or metastatic SCCHN	III	Efficacy of durvalumab monotherapy and durvalumab in combination with tremelimumab versus SoC	Open-label, randomized	*Durvalumab monotherapy* Durvalumab IV 10 mg/kg Q2W
				Combination therapy Durvalumab IV 20 mg/kg Q4W for 4 doses then IV 10 mg/kg Q2W for 12 months or until PD + Tremelimumab IV 1 mg/kg Q4W for 4 doses
D4884C00001 Phase II multicenter, open-label study of tremelimumab monotherapy in patients with advanced solid tumors	II	Efficacy and safety	Open-label	*Durvalumab monotherapy* Durvalumab IV 1500 mg Q4W for up to 12 months
				Tremelimumab monotherapy Tremelimumab IV 750 mg Q4W for 7 doses then Q12W for 2 doses
				Combination therapy Durvalumab IV 1500 mg Q4W for 4 doses + Tremelimumab IV 75 mg/kg Q4W for 4 doses then Durvalumab IV 1500 mg Q4W for up to 8 months
DETERMINE (D4880C00003) Phase IIb, randomized, double-blind study comparing tremelimumab to placebo in second- or third-line treatment of subjects with unresectable pleural or peritoneal malignant mesothelioma	IIb	Efficacy and safety	Randomized, double-blind, placebocontrolled	*Tremelimumab monotherapy* Tremelimumab IV 10 mg/kg Q4W for 7 doses (6 months) then Q12W

[a] For Study 06, an NCA was done for an interim dataset (DCO 28 February 2017). As the final dataset (DCO 19 November 2019) only had 343 additional samples (all in the dose-expansion phase) compared to the interim, it was determined that an additional NCA for the final dataset was not required. This was supported by the sparse sampling in the dose-expansion phase patients (~2 samples per patient per treatment), which would contribute little to no value to a NCA, which typically relies on intense sampling in order to accurately estimate key PK parameters such as half-life and AUC. Therefore, only the results of the interim NCA are presented.
[b] Patients in the EP alone group were permitted an additional 2 cycles of EP (up to 6 cycles total) per the Investigator's discretion.
Abbreviations; ALK, anaplastic lymphoma kinase; AUC, area under the serum concentration-time curve; CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; D, durvalumab; DCO, data cutoff; EGFR, epidermal growth factor receptor; EP, etoposide and either carboplatin or cisplatin; IV, intravenous; NCA, noncompartmental analysis; NSCLC, non-small cell lung cancer; PD, progression of disease; PD-L1, programmed cell death ligand-1; PK, pharmacokinetics; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q12W, every 12 weeks; SCCHN, head and neck squamous cell carcinoma; SoC, standard of care; T, tremelimumab; TK, tyrosine kinase.

Durvalumab and tremelimumab are both human monoclonal antibodies (mAb) that act as checkpoint inhibitors with distinct yet complementary mechanisms of action with respect to enhancing the antitumor immune response.

The clinical pharmacological data are derived from 1 pivotal study (HIMALAYA) and 20 supportive durvalumab studies and 17 supportive tremelimumab studies.

All studies included male and female patients aged 18 years and older with advanced solid tumors. No PK data has been obtained from healthy volunteers.

The clinical pharmacology studies that support this proposed indication are summarized in Table 2.

2.3.2. Pharmacokinetics

Durvalumab population PK analysis

The primary objectives of the PopPK analysis were (1) to characterize the PK of durvalumab, using HIMALAYA and Study 22 data combined with data from previous clinical trials that studies durvalumab in various indications (CD-ON-MEDI4736-1108, ATLANTIC, PACIFIC, CASPIAN and POSEIDON), (2) to assess the impact of pre-defined covariates on individual post-hoc PK parameters and (3) to derive individual predicted exposure metrics (AUC, dose1, Cmax, dose1, Cmin, dose1, AUC0-inf, AUCss, Cmax,ss, Cmin,ss) of durvalumab for patients based on individual Empirical Bayes Estimates (EBEs) from the population PK models.

The population PK analysis of durvalumab was derived from a total dataset of 4043 patients, of which 2827 patients were from the previous dataset and 295 were from Study 22 and 928 were from HIMALAYA. 216 BLQ samples (1.45%) were excluded from the analysis of which 83 of those samples were from Study 22 and HIMALAYA. 49 samples (1.5%) from Study 22 and HIMALAYA were also excluded from the analysis due to incorrect PK sample time. Eventually, 14760 serum PK samples from 4043 patients treated with durvalumab were available in the final dataset for analysis.

Previously, durvalumab population PK (Population PK and Exposure-Response Report (MS-2021)) was described by a two-compartment distribution model with time-dependent CL. IIV was included on CL, V1 and Tmax. Residuals were described by a combined additive and proportional error model. The previous model included several statistically significant covariate effects on CL: WT, ALB, combination therapy, sex, CrCL, LDH, and ECOG; and on V1: WT and sex.

The updated model was re-evaluated based on the current data and previous developed model structure. From full covariate model, backward elimination was considered to find a statistically parsimonious model. Significance levels of 0.001 was employed. After backward elimination, the full model was explored by graphical inspection of all covariate effects (plots and correlation coefficients of empirical Bayes estimates of individual random effects from the full model vs. covariates). Results suggested that all previous covariates were important as the objective function value (OFV) increased by $\geq$ 12 points when excluding either of them. Race, region and tumour type (NSCLC, bladder and HCC) were also tested on CL and V1. These analyses re-confirmed race and region were not significant covariate for durvalumab, while tumour type was considered significant on CL of durvalumab and therefore included in the model.

The following model was chosen as the final model for durvalumab: a two-compartment distribution model with time-dependent CL. IIV on CL, V1 and Tmax. Residuals were described by a combined proportional and additive error model. The final model included several statistically significant covariate effects on CL: WT, ALB, combination therapy, sex, CrCL, LDH, ECOG and tumour type (NSCLC, bladder and HCC); and on V1: WT and sex.

The relationships between the covariates and the model parameters are described in the following equations:

$$CL_{cat.cov} = 1_{comb=0} \cdot (1 - 0.0459_{comb=1}) \cdot (1 - 0.0417_{comb=2}) \cdot 1_{ECOGbin=0} \cdot (1 - 0.516_{ECOGbin=1}) \cdot 1_{male} \cdot (1 - 0.149_{female}) \cdot 1_{tumtyp=0} \cdot (1 - 0.0393_{tumtyp=1}) \cdot (1 + 0.0622_{tumtyp=2}) \cdot (1 + 0.0472_{tumtyp=3})$$

$$CL_{cont.cov} = \left(\frac{alb_i}{39}\right)^{-0.659} \cdot \left(\frac{CrCL_i}{85.66}\right)^{0.121} \cdot \left(\frac{LDH_i}{247}\right)^{0.0442} \cdot \left(\frac{WT_i}{69.4}\right)^{0.376}$$

$$CL_{T,i} = 0.277 \cdot CL_{cat.cov}. CL_{cont.cov} \cdot exp\left(\frac{T_{max} \cdot t}{TC_{50} + t}\right) \cdot \exp(\eta_i)$$

where CLcat.cov, CLcont.cov and CLT,i represent the impact of categorical and continuous covariates and the individual total CL including the time-dependent decrease of CL respectively.

$$V_{c,i} = 3.45 \cdot \left(\frac{WT_i}{69.4}\right)^{0.499} \cdot 1_{male} \cdot (1 - 0.140_{female})$$

Note: albi=Albumin concentration at baseline, CrCLi=Creatinine clearance at baseline, LDHi=Lactate dehydrogenase at baseline, WTi=Bodyweight at baseline

PK parameter estimates of the final durvalumab model along with percent relative standard error (%RSE), results of non-parametric bootstrap analysis and shrinkage can be seen in Table 3. GOF plots of DV vs. PRED, DV vs. IPRED, CWRES vs. PRED and CWRES vs. time after dose can be seen in Figure 1. A pcVPC of the final model for HIMALAYA is shown in Figure 2.

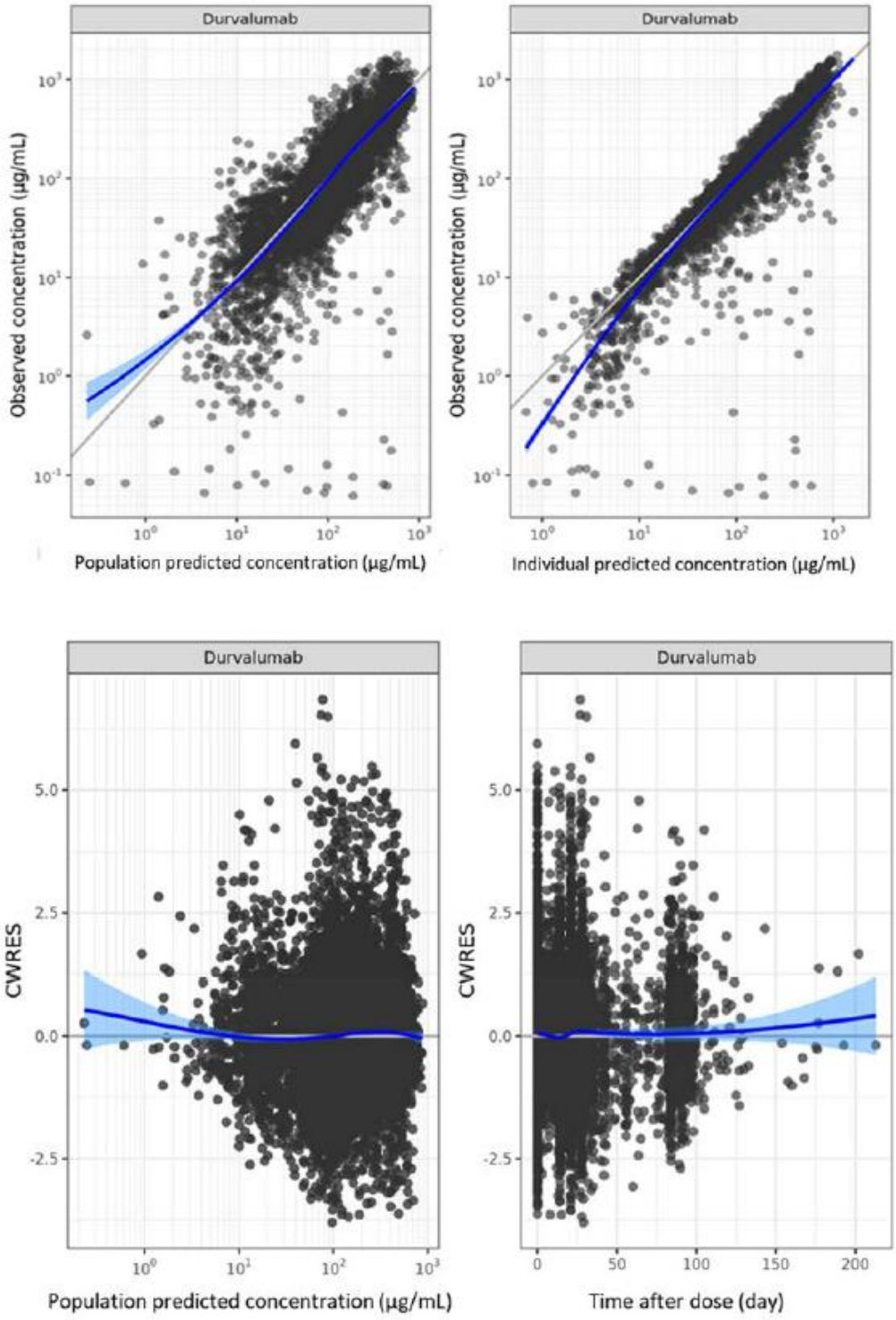
The durvalumab population PK model was updated with sparse data from HIMALAYA and Study 22 and pooled with the previous dataset (Studies CASPIAN, PACIFIC, ATLANTIC, POSEIDON and CD-ON-MEDIA-4736-1108).

The final model included the following covariate effects on CL: WT, ALB, combination therapy, sex, CrCL, LDH, ECOG and tumour type (solid, NSCLC, bladder and HCC); and on V1: WT and sex. The final model was evaluated by means of non-parametric bootstrap analysis, RSEs, GOF-plots and pcVPCs.

Table 3. Population PK Model Parameter Estimates durvalumab (Final Model)

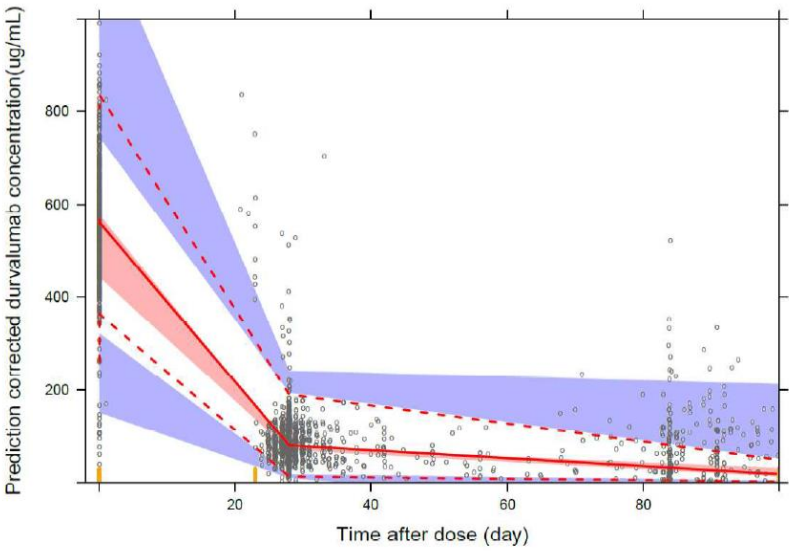
Parameter	Estimate	RSE (%)	bootstrap 95%CI	Shrinkage (%)	Unit
Population Parameter					
CL	0.277	2.01	[0.263 ; 0.292]	--	L/day
V1	3.45	0.807	[3.40 ; 3.49]	--	L
V2	2.13	2.02	[1.98 ; 2.29]	--	L
Q	0.469	5.15	[0.411 ; 0.535]	--	L/day
Tmax	-0.372	4.99	[-0.419 ; -0.327]	--	L/day
TC_{50}	88.7	9.92	[58.3 ; 150]	--	day
LAM	1.00	--	--	--	-
Covariate					
Albumin on CL	-0.659	2.87	[-0.834 ; -0.506]	--	--
Creatinine clearance on CL	0.121	15.6	[0.0800 ; 0.162]	--	--
ECOG status on CL	-0.0516	20.7	[-0.0720 ; -0.0278]	--	--
LDH on CL	0.0442	23.3	[0.0208 ; 0.0642]	--	--
Sex on CL	-0.149	7.95	[-0.172 ; -0.126]	--	--
COMB1 on CL	-0.0459	27.0	[-0.0688 ; -0.0195]	--	--
COMB2 on CL	-0.0417	43.2	[-0.0886 ; 0.00746]	--	--
Body weight on CL	0.376	8.32	[0.317 ; 0.443]	--	--
Tumor type 1 on CL	-0.0393	46.1	[-0.0750 ; -0.00306]	--	--
Tumor type 2 on CL	0.0622	55.8	[-0.0131 ; 0.137]	--	--
Tumor type 3 on CL	0.0472	46.1	[0.00497 ; 0.0932]	--	--
Sex on V1	-0.140	7.60	[-0.163 ; -0.118]	--	--
Body weight on V1	0.499	5.01	[0.449 ; 0.549]	--	--
Interindividual Variability					
ETA CL	0.0896	2.85	[0.0803 ; 0.0982]	17.6	--
Cov CL-V1	0.0389	5.34	[0.0338 ; 0.0441]	-	--
ETA V1	0.0524	3.32	[0.0451 ; 0.0598]	29.9	--
ETA T_{max}	0.0665	9.03	[0.0436 ; 0.109]	59.3	--
Residual Variability					
Proportional component	0.250	0.541	[0.241 ; 0.258]	15.0	--
Additive component	4.28	6.70	[3.39 ; 5.29]	15.0	µg/mL

Figure 1: Final Durvalumab PopPK Model – Basic GOF



Note: The blue line is a trend line through the data points, and the blue area is the 95% CI around it.
Source: Figure 2, Population PK and Exposure-Response Report, Module 5.3.3.5.
CI, confidence interval; CWRES=conditional weighted residuals.

Figure 2. pcVPC of the final model vs time after dose - HIMALAYA Study



Note: The solid and dashed lines represent the median, 5th, and 95th percentiles of the observations; the shaded red and blue areas represent the 95% confidence interval of the median, 5th, and 95th percentiles predicted by the model.
Abbreviations: CI=confidence interval, pcVPC=prediction-corrected visual predictive check
Source: /projects/qcp/QCP_MODELING/ONC/durvalumab/poppk_20210729_himalaya/Scripts/s04_vpc.R

Durvalumab and tremelimumab exposure-Response modelling analysis (MS-2021-02)

The ER analysis for both efficacy and safety was based on patients from HIMALAYA study administered 1500 mg Q4W durvalumab and a 300 mg single dose tremelimumab IV. 388 and 397 patients were included in the ER analysis for durvalumab and tremelimumab, respectively. The final durvalumab/tremelimumab PopPK models were used to obtains EBEs of individual PK parameters.

Exposure-efficacy:

The exposure-efficacy relationships in the HIMALAYA study were explored by Kaplan-Meier plots stratified by durvalumab and tremelimumab exposure quartiles. Several exposure metrics for tremelimumab and durvalumab were derived. For both efficacy outcomes, OS and PFS, Cox Proportional Hazard (CPH) models were developed and a stepwise covariate selection was performed (α = 1% and 0.1%). No significant exposure-efficacy relationships were identified for durvalumab or tremelimumab. The CPH models for OS suggested that AST and NLR were associated with shorter survival in T300+D arm as they were identified as statistically significant covariates. Maximum concentration following the first dose (Cmax, dose 1) for tremelimumab was also identified as a marginally statistically significant exposure metric (LRT: 11.92 > 10.83) but was removed due to non-significance in the Wald test (p = 0.199), the standard error of coefficient (β) being large and the 95% CI of β containing the null. The removal of this covariate in the CPH model is considered appropriate. Likewise, trough concentration following the first dose (Cmin, dose 1) for tremelimumab was also identified as a marginally significant covariate within PFS based on the LRT but was removed for the same reasons. No other covariates were identified to be significant with PFS.

Exposure-safety:

Logistic regression modelling did not identify any significant impact of durvalumab or tremelimumab exposure on the incidence of adverse effects.

QTcF modelling analysis

Linear mixed-effects exposure-response modelling with an intercept was conducted to characterize the relationship of change from baseline of QTcF (ΔQTcF) with durvalumab or tremelimumab serum concentrations. The concentration-ΔQTcF analysis population consisted of 293 observations from 67 patients administered durvalumab and 254 observations from 66 patients administered tremelimumab from Study 06. Unscheduled concentration-QTcF observations and non-central ECG records were excluded from the analysis.

For durvalumab, the slope for the relationship of ΔQTcF to durvalumab concentration was 0.0048 ms per µg/mL (p = 0.112), with a mean intercept of 0.082 ms (p = 0.950; 90% CI: -2.07, 2.24 ms; Table 4).

The slope for the relationship of ΔQTcF to tremelimumab concentration was -0.012 ms per µg/mL (p = 0.531), and the mean intercept was 0.581 ms (p = 0.629; 90% CI: -1.41, 2.57 ms; Table 5).

The slope or the intercept for tremelimumab and durvalumab were not significantly different from zero.

Table 4: Parameter estimates of durvalumab PK-ΔQTcF relationship

Parameter estimates						
Parameter	**Estimate**	**Standard error**	***p*- value**	**90% confidence limits**		**Gradient**
Intercept (ms)	0.08205	1.2916	0.9495	-2.0726	2.2367	0.000012
Slope (ms/µg/mL)	0.004841	0.003007	0.1123	-0.00018	0.009858	0.003814
Inter individual variability on intercept	7.8721	0.8472	<.0001	6.4588	9.2855	0.000021
Model error	9.4501	0.4275	<.0001	8.7369	10.1633	-8.91E-6

PK pharmacokinetic

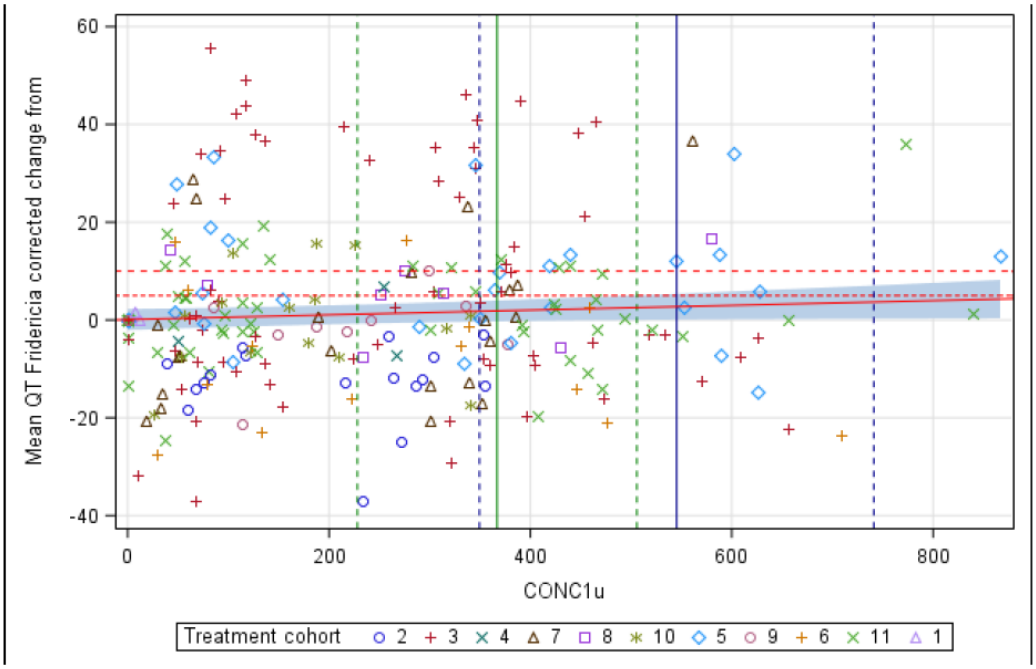
Table 5: Parameter estimates of Tremelimumab PK-ΔQTcF relationship

Parameter estimates						
Parameter	**Estimate**	**Standard error**	***p*- value**	**90% confidence limits**		**Gradient**
Intercept (ms)	0.5806	1.1952	0.6288	-1.4137	2.5749	-1.01E-6
Slope (ms/ µg/mL)	-0.01225	0.01945	0.5312	-0.04470	0.02021	-0.00007
Inter individual variability on intercept	7.5385	0.8414	<.0001	6.1345	8.9425	-2.99E-6
Model error	9.2338	0.4544	<.0001	8.4755	9.9921	4.764E-6

PK pharmacokinetic

The upper bound of the 90% 2-sided CI for ΔQTcF was less than 10 ms, and the highest observed concentration of durvalumab and tremelimumab had a predicted mean ΔQTcF of less than 5 ms (Figure 3, Figure 4 and Table 6).

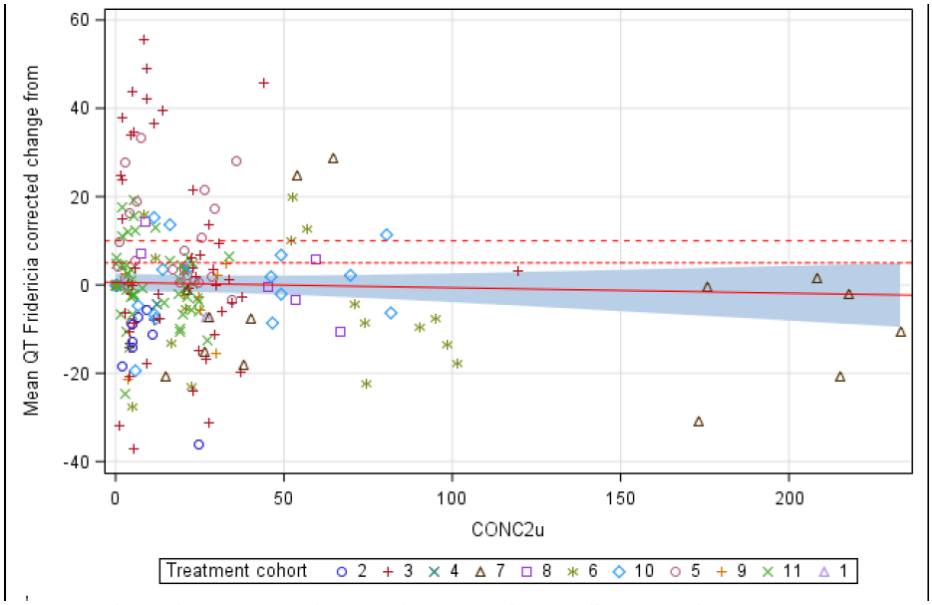
Figure 3. QTcF (change from baseline) versus concentration of durvalumab on intercept full data



Cmax,ss maximum plasma concentration at steady state; IQR interquartile range; IV intravenous; Q2W every 2 weeks; Q4W every 4 weeks

Note: Red line is the linear regression line and the shaded area is the 90% CI based on the linear mixed-effects model prediction. Red short dashed horizontal line is 5 msec change from baseline identity line. Red long dashed horizontal line is 10 msec change from baseline identity line. Green dashed vertical lines are observed median +/- IQR predicted Cmax,ss for a 10 mg/kg Q2W IV durvalumab dosing. Green solid line is median predicted Cmax,ss for a 10 mg/kg Q2W IV durvalumab dosing. Blue dashed vertical lines are observed median +/- IQR(interquartile range) predicted Cmax,ss for a 20 mg/kg Q4W IV durvalumab dosing. Blue solid line is median predicted Cmax,ss for a 20 mg/kg Q4W IV durvalumab dosing. Treatment cohorts are 1: 3 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab; 2: 10 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab;3: 15 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab; 4: 10 mg/kg durvalumab (Q4W) + 3 mg/kg Tremelimumab; 5: 20 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab; 6: 15 mg/kg durvalumab (Q4W) + 3 mg/kg Tremelimumab; 7: 15 mg/kg durvalumab (Q4W) + 10 mg/kg

Figure 4. QTcF (change from baseline) versus concentration of tremelimumab on intercept full data



Cmax,ss maximum plasma concentration at steady state; IQR interquartile range; IV intravenous; Q2W every 2 weeks; Q4W every 4 weeks

Note: Red line is the linear regression line and the shaded area is the 90% CI based on the linear mixed-effects model prediction. Red short dashed horizontal line is 5 msec change from baseline identity line. Red long dashed horizontal line is 10 msec change from baseline identity line. Treatment cohorts are 1: 3 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab; 2: 10 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab;3: 15 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab; 4: 10 mg/kg durvalumab (Q4W) + 3 mg/kg Tremelimumab; 5: 20 mg/kg durvalumab (Q4W) + 1 mg/kg Tremelimumab; 6: 15 mg/kg durvalumab (Q4W) + 3 mg/kg Tremelimumab; 7: 15 mg/kg durvalumab (Q4W) + 10 mg/kg Tremelimumab; 8: 20 mg/kg durvalumab (Q4W) + 3 mg/kg Tremelimumab; 9: 10 mg/kg durvalumab (Q2W) + 1 mg/kg Tremelimumab; 10: 10 mg/kg durvalumab (Q2W) + 3 mg/kg Tremelimumab; 11: 20 mg/kg durvalumab (Q4W) + 1 mg/kg tremelimumab (Q4W)/ 20 mg/kg durvalumab (Q4W)

Table 6. Summary of maximum observed durvalumab or Tremelimumab serum concentration and predicted mean and CI of ΔQTcF

	Observed Cmax (µg/mL)	Cohort	Dosing regimen	Predicted mean ΔQTcF (ms)	90% CI of predicted mean ΔQTcF (ms)
Durvalumab	866.6	10	20mg/kg durvalumab, 1mg/kg tremelimumab	4.28	(0.36, 8.20)
Tremelimumab	233	4	10mg/kg durvalumab, 15mg/kg tremelimumab	-2.27	(-9.49, 4.96)

ΔQTcF change from baseline of QTcF; CI confidence interval; Cmax maximum plasma concentration; QTcF Fridericia's heart rate corrected QT interval.

Absorption

Durvalumab is administered intravenously and the bioavailability is 100 %.

Distribution

Distribution studies have not been conducted for durvalumab in the context of this application.

In an analysis that included data from HIMALAYA, the typical CL and central volume of distribution for durvalumab were 0.277 L/day and 3.45 L, respectively. The values differ less than 10% from the values

derived for the model reported previously. The time-dependent clearance suggests that clearance could decrease by a maximum of 31%, which is also similar to the 39% in the previous model.

Elimination

No studies regarding durvalumab metabolism have been conducted.

No new data has been provided from HIMALAYA on elimination.

Dose proportionality and time dependencies

Based on the final Population PK model, time-dependent CL was identified for durvalumab in combination with tremelimumab.

A faster clearance was observed in the low dose cohorts for durvalumab. A dose-proportional increase in Cmax over the dose range of 0.1 to 20 mg/kg was observed following the first IV dose.

Durvalumab clearance has been shown to decrease over time.

For the durvalumab population PK model, estimates of inter-individual variability (CV%) were 29.9% on CL, 22.9% on V1 and 25.8% on T_{max}.

Intra- and inter-individual variability

For the tremelimumab population PK model, estimates of inter-individual variability (CV%) were 32.9% on CL, 24.9% on V1, 46.0% on V2 and 119.2% on T_{max}.

For the durvalumab population PK model, estimates of inter-individual variability (CV%) were 29.9% on CL, 22.9% on V1 and 25.8% on T_{max}.

Special populations

The effect of intrinsic factors (i.e., race, age, renal impairment, hepatic impairment, sex, and body weight) on the PK of durvalumab has not been studied in specific dedicated studies.

Based on pop PK analyses, albumin levels (ALB), creatinine clearance, ECOG status, LDH, gender, body weight, tumor types, and combination therapy were identified as statistically significant covariates on clearance. Body weight and gender had a statistically significant impact on central volume of distribution. However, none of the covariates were considered as clinically relevant, i.e. impact on durvalumab PK was less than or about 20% in univariate testing. Accordingly, no dose adjustment seems required in these special populations.

Pharmacokinetic interaction studies

No formal drug-drug interaction studies have been conducted with durvalumab or tremelimumab.

PK drug-drug interaction of durvalumab or tremelimumab with other therapeutics is not anticipated given that durvalumab and tremelimumab are not primarily cleared via hepatic or renal pathways; instead, the primary elimination pathways are protein catabolism via reticuloendothelial system (RES) or target-mediated disposition. Durvalumab and tremelimumab are not expected to induce or inhibit the major drug metabolizing cytochrome P450 pathways.

Pharmacokinetics using human biomaterials

No in vitro permeability, in vitro metabolism, or in vitro metabolic drug-drug interaction studies that used human biomaterials have been performed.

Immunogenicity

In HIMALAYA, immunogenicity data were available from 684 durvalumab ADA-evaluable patients, ie, those patients who had non-missing baseline and at least 1 non-missing post-baseline ADA result for durvalumab.

Table 7: Summary of ADA responses to durvalumab (safety analysis set)

Parameter	D (N = 388)	T300+D (N = 388)	T75+D (N = 152)
Durvalumab ADA evaluable patients	282 (72.7%)	294 (75.8%)	108 (71.1%)
ADA positive at any visit (ADA prevalence) [a]	20 (7.1%)	24 (8.2%)	8 (7.4%)
Treatment-emergent ADA positive (ADA incidence) [b]	8 (2.8%)	9 (3.1%)	5 (4.6%)
Treatment-boosted ADA [c]	1 (0.4%)	0	0
Treatment-induced ADA (positive post-baseline only)	7 (2.5%)	9 (3.1%)	5 (4.6%)
ADA positive at baseline only	12 (4.3%)	13 (4.4%)	3 (2.8%)
ADA positive post-baseline and positive at baseline	1 (0.4%)	2 (0.7%)	0
Persistently positive [d]	8 (2.8%)	9 (3.1%)	4 (3.7%)
Transiently positive [e]	0	2 (0.7%)	1 (0.9%)
nAb positive at any time	2 (0.7%)	5 (1.7%)	0

[a] ADA prevalence is defined as the proportion of patients with a positive ADA result at any time, baseline or post-baseline in the ADA-evaluable.

[b] ADA incidence is the proportion of treatment-emergent patients (sum of treatment-induced ADA and treatment-boosted ADA) in the ADA-evaluable population.

[c] Treatment-boosted ADA is defined as baseline positive ADA titer that was boosted to ≥ 4-fold during the study period.

[d] Persistently positive is having at least 2 post-baseline ADA-positive measurements with at least 16 weeks (112 days) between the first and last positive measurements, or an ADA-positive result at the last available assessment. The category may include patients meeting these criteria who were ADA-positive at baseline.

[e] Transiently positive is ADA-positive as baseline and having at least 1 post-baseline ADA-positive measurement and not fulfilling the conditions for persistently positive.

2.3.3. Pharmacodynamics

Mechanism of action

Durvalumab is a human IgG1k mAb that binds to programmed cell death ligand-1 (PD-L1) and blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Expression of PD-L1 can be induced by inflammatory signals and can be expressed on both tumor cells and tumor-associated immune cells in the tumor microenvironment. PD-L1 blocks T-cell function and activation through interactions with PD-1 and CD80 (B7.1). By binding to its receptors PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production. Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, without inducing antibody-dependent cell-mediated cytotoxicity (ADCC).

Tremelimumab is a human IgG2 mAb directed against cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). CTLA-4 is a critical regulatory signal for T-cell expansion and activation following an immune response, and it serves as a natural braking mechanism that maintains T-cell homeostasis. During T-cell

activation, T cells upregulate CTLA-4, which binds to CD80 and CD86 ligands on antigen-presenting cells, sending an inhibitory signal and preventing CD28-mediated T-cell co-stimulation, thus limiting T-cell activation. Tremelimumab blocks these events, leading to prolongation and enhancement of T-cell activation and expansion.

Durvalumab and tremelimumab are checkpoint inhibitors with distinct yet complementary mechanisms of action with respect to enhancing the antitumor immune response triggered by chemotherapy. Tremelimumab mediated blockade of CTLA-4 functions early in the immune response, lowering the threshold for T cell activation, allowing more T cells to be activated and increasing the diversity of the T cell population. This increases the probability that a T cell recognizing a tumor neoantigen can become activated. Durvalumab blockade of PD-L1 is expected to function mainly during the effector phase of T cell function, once T cells enter the tumor, where it acts to block local suppression of T-cell function by PD-L1, enhancing the ability of activated anti-tumor T cells to target and kill tumor cells.

Primary and secondary pharmacology

Primary pharmacology

In Study 06, Study 10, and Study 22, circulating lymphocytes (T, B, and NK cells) and proliferating (Ki67+) T cell subsets were quantified.

The data for Study 06 and Study 10 demonstrated that 15 or 20 mg/kg Q4W durvalumab (combined with doses as low as 1 mg/kg Q4W of tremelimumab) result in significant elevations in proliferating CD4 + Ki67 + T cell quantities, demonstrating a pharmacodynamic effect consistent with the proposed mechanisms of action of both durvalumab and tremelimumab. The elevations in CD4 + Ki67 + T cell quantities were dose-proportional to tremelimumab. Additionally, CD8 + Ki67 + T cells were elevated above pre-treatment levels.

In Study 22, substantial and consistent increases in CD4 + Ki67 + T cells were observed in the T300 + D, T, and T75 + D treatment arms that were associated with increasing tremelimumab dose. Increases in CD8 + Ki67 + T cells were observed in all treatment arms and peaked on Day 15. Findings indicated a potential saturable pharmacodynamic effect on this lymphocyte population, because equivalent elevation magnitudes were observed in the T300 + D and T arms. Among all monitored lymphocyte populations, median CD8 + Ki67 + T cell counts from patients with complete or partial response were elevated at the highest levels above those of stable disease and PD patients. Pairwise analysis using the Wilcoxon method revealed significant differences between median CD8 + Ki67 + T cell counts in patients with complete or partial response vs stable disease or PD patients ($p < 0.01$).

In Study 1108, target engagement was assessed by measuring the reduction of free sPD-L1 in serum before and following durvalumab administration. sPD-L1 data were available from 851 patients in the dose-escalation, dose-exploration, and dose-expansion cohorts following administration of durvalumab 0.1 to 10 mg/kg Q2W, 15 mg/kg Q3W, and 20 mg/kg Q4W, respectively.

Mean baseline sPD-L1 was approximately 137 pg/mL (range: 67 to 681 pg/mL). Following administration of 0.1 to 20 mg/kg durvalumab, sPD-L1 concentrations were maximally suppressed at Day 14 (or after the first dose) for all doses except 0.1 mg/kg. The extent and duration of the suppression was dose-dependent. Complete sPD-L1 suppression was observed around the dose levels at ≥0.3 mg/kg. Following 10 mg/kg Q2W, approximately 97% of patients demonstrated complete sPD-L1 suppression throughout the dosing interval.

Suppression of free sPD-L1 was similar among 10 mg/kg Q2W, 15 mg/kg Q3W, and 20 mg/kg Q4W cohorts.

Similar results were observed in Japan Study 02, where sPD-L1 was completely suppressed in all patients following administration of durvalumab 1, 3, 10 mg/kg Q2W; 15 mg/kg Q3W; and 20 mg/kg Q4W.

Likewise, suppression of free sPD-L1 was observed following treatment with the durvalumab and tremelimumab combination in all study groups in Study 10 and in all but 3 patients in Study 06.

Secondary pharmacology

Overall, concentration-QTc-analysis did not identify a significant linear relationship between tremelimumab or durvalumab serum concentrations and ΔQTcF. The predicted mean ΔQTcF and upper 90% CI at the maximum observed concentration for tremelimumab or durvalumab in the dataset were below the threshold of clinical concern. See section QTcF modelling analysis under section 2.3.2

Exposure-response-relationships

Assessment of an exposure-efficacy relationship was conducted using overall survival (OS) and progression-free survival (PFS) as efficacy parameters in patients from HIMALAYA, for whom the different exposure metrics could be calculated.

For the exposure-response analysis for efficacy (OS and PFS), only the T300 + D cohort was used, but with the SoC cohort as a comparator in some of the analyses. The exposure-response Cox proportional-hazards (CPH model) for OS and PFS was developed based on durvalumab and tremelimumab-treated patients in the HIMALAYA study. Simulated durvalumab and tremelimumab serum concentration-time PK profiles, based on individual post-hoc PK parameters, were used as a measure of exposure after T300 + D.

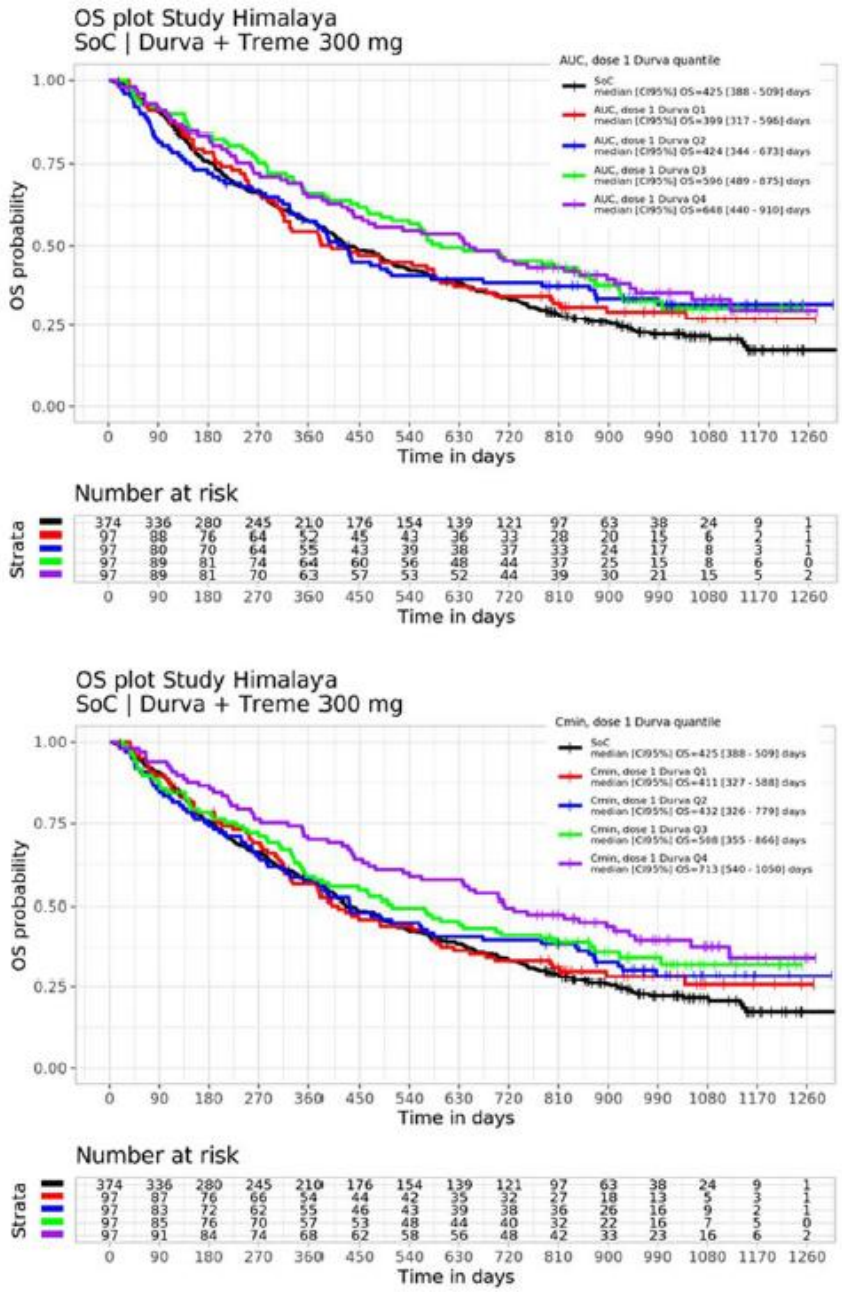
Exposure-efficacy relationship

Overall survival (OS)

The data for OS were stratified by model-predicted exposures metrics and overlaid with data from patients in the SoC arm. There were 6 exposure metrics used for durvalumab ($AUC_{dose\ 1}$, $C_{min,dose\ 1}$, $C_{max,dose\ 1}$, AUC_{ss}, $C_{min,ss}$, and $C_{max,ss}$).

Figure 5 and Figure 6 shows the OS Kaplan-Meier (KM) plots for exposure metrics of durvalumab. The number of patients at risk is indicated below each plot. The KM plots indicated that there was no clear relationship between efficacy and exposure to durvalumab with all quartiles overlapping each other.

Figure 5: OS Kaplan-Meier plots for durvalumab exposure metrics by quartiles at dose 1



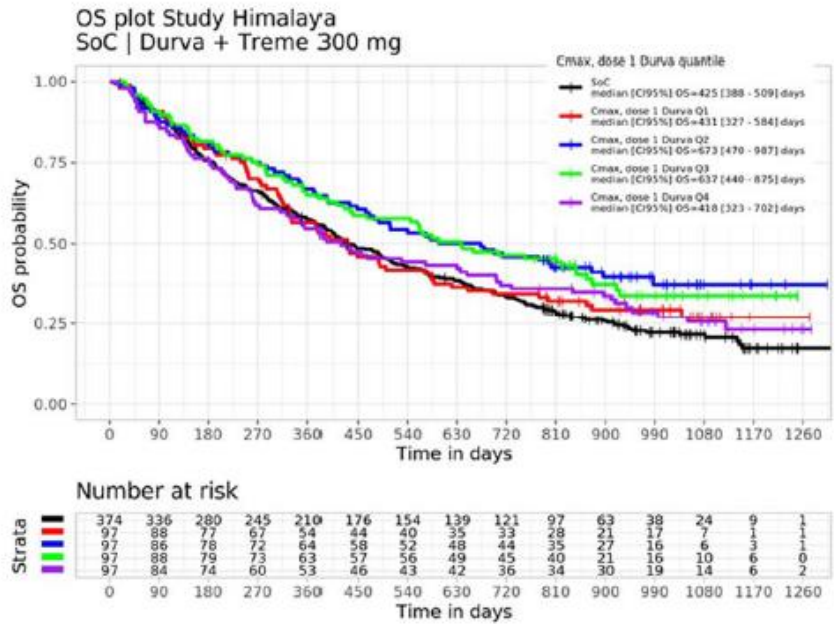
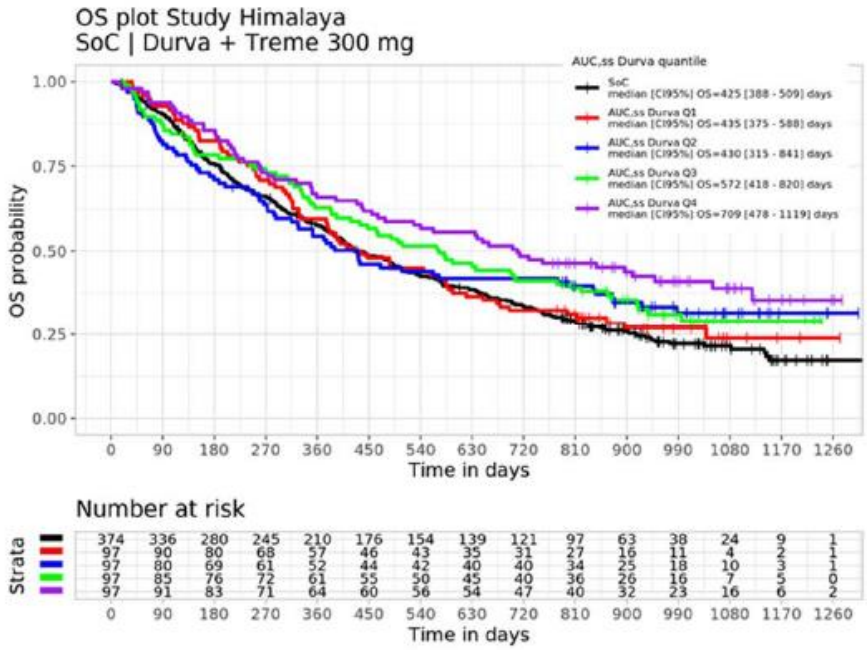
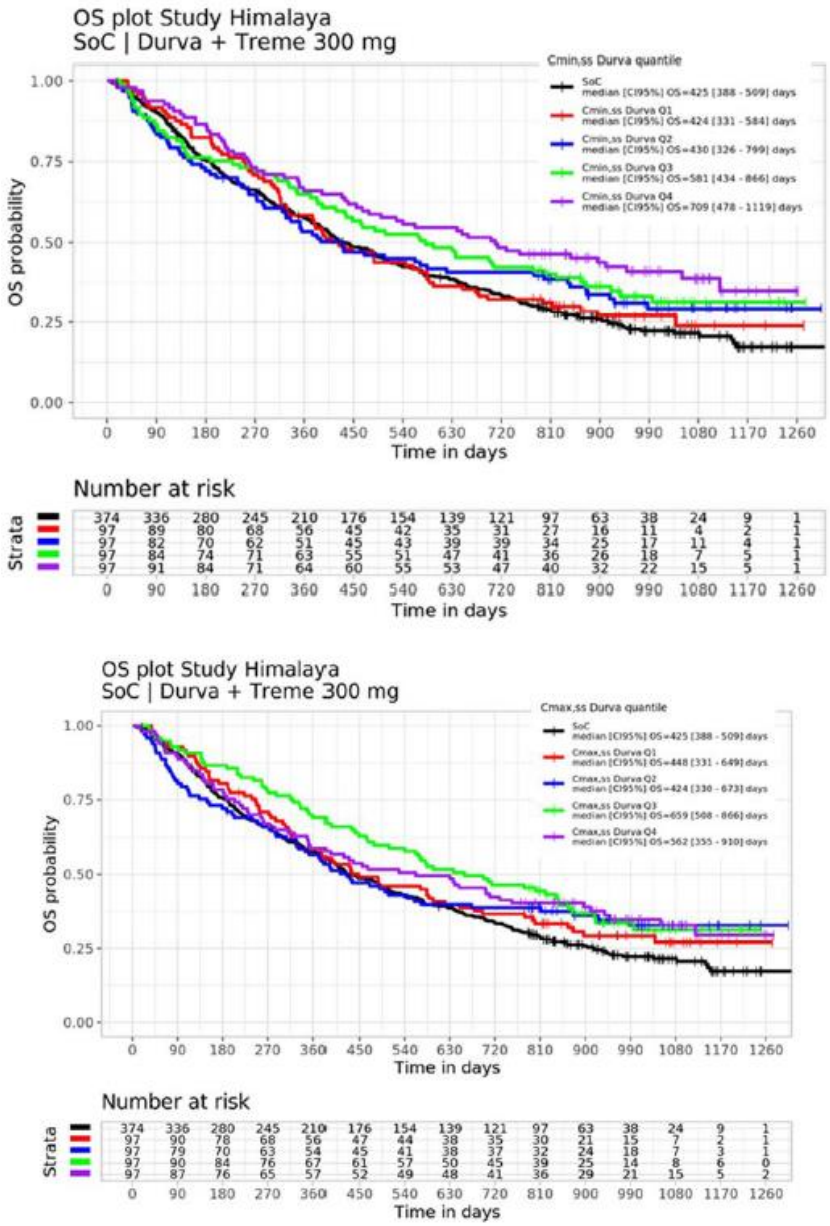


Figure 6: OS Kaplan-Meier plots for durvalumab exposure metrics by quartiles at Steady State





The covariates, aspartate aminotransferase (AST) and neutrophil-to-lymphocyte ratio (NLR) were identified as significant in the final model. Higher AST and NLR were associated with shorter survival in T300 + D arm, suggesting they are prognostic factors for OS. The OS Kaplan Meier plot stratified by these 2 significant covariates can be found in Figure 7. A Forest plot of the final CPH model for OS is showed in Figure 8.

Figure 7: OS Kaplan Meier plots stratified by significant covariates

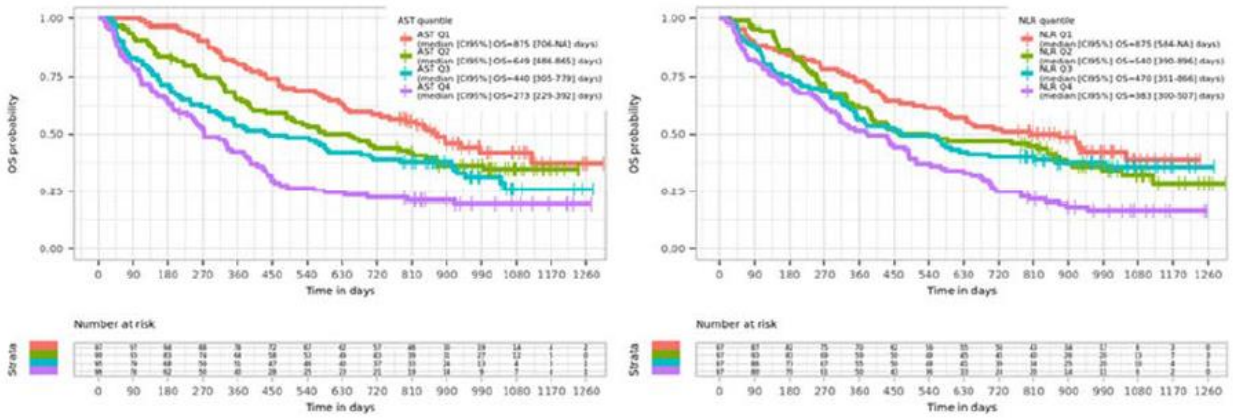
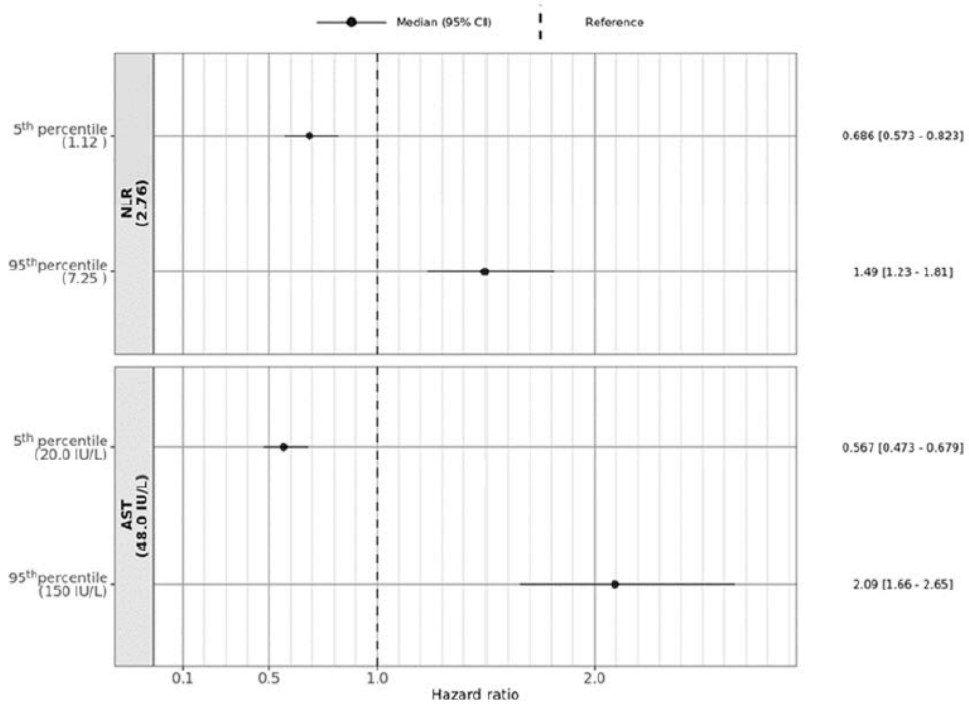


Figure 8. Forest plot of the final Cox proportional-hazards model for OS



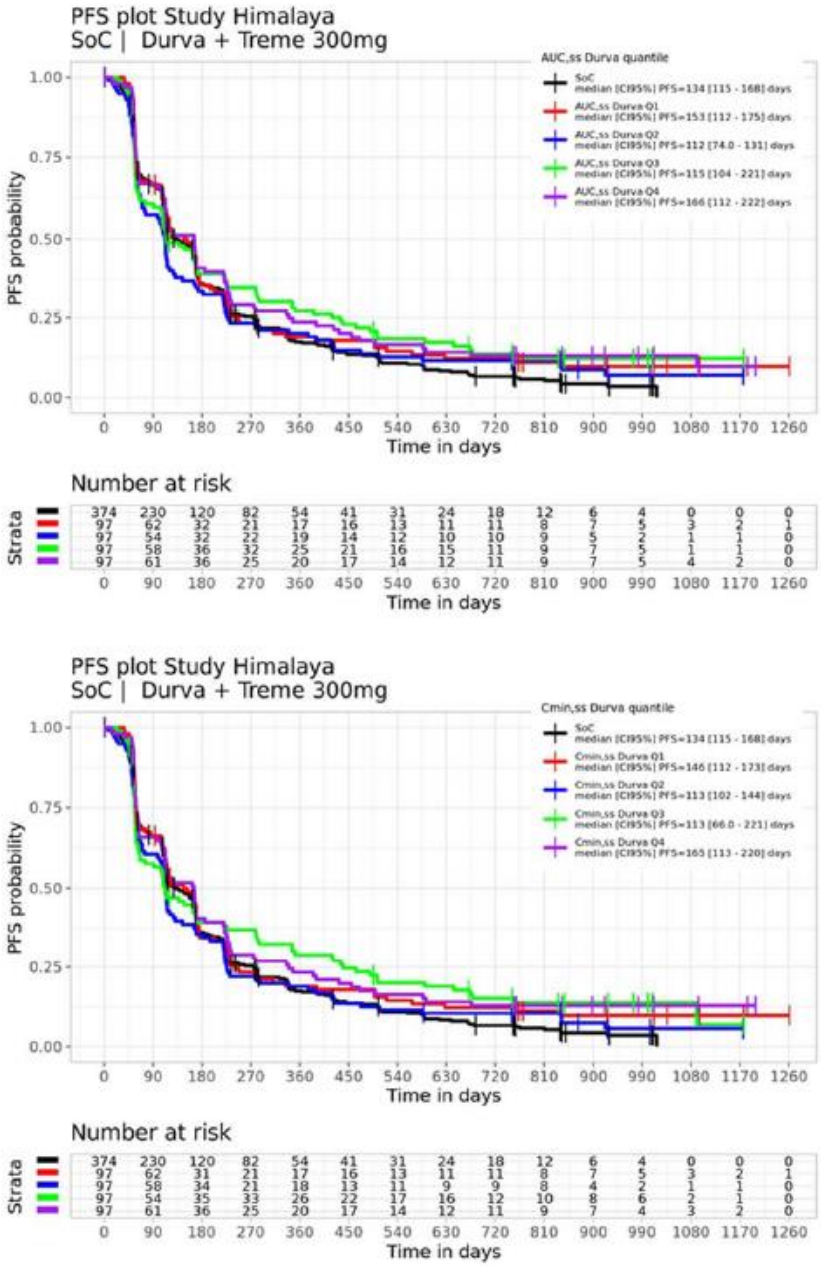
Note: Numbers at the right of the graph are the predicted HR and associated 95% CI.

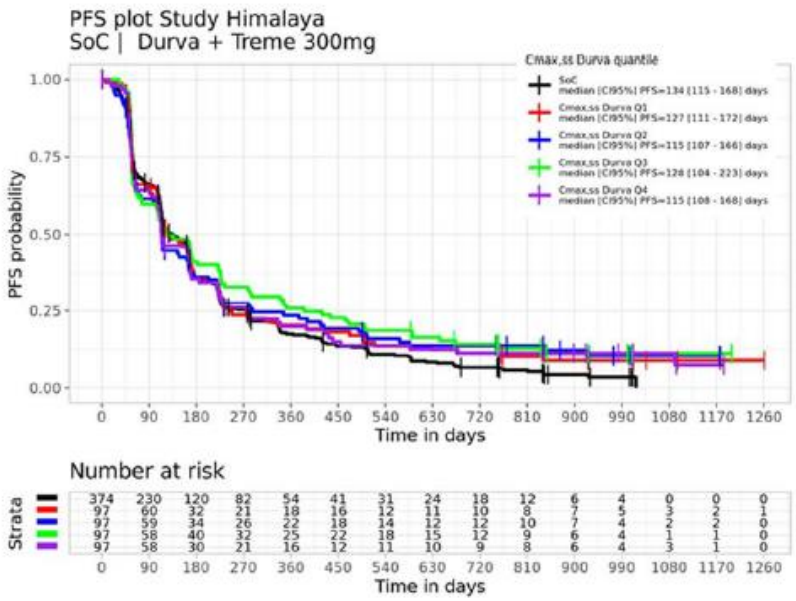
Progression-free survival (PFS)

Figure 9 shows PFS Kaplan-Meier curves for patients receiving durvalumab in combination with tremelimumab AUC_{ss}, $C_{min,ss}$, $C_{max,ss}$ for durvalumab), data stratified by model-predicted exposures metrics and overlaid with data from patients in the SoC arm. The number of patients at risk is indicated below the plot.

The plot indicated no clear efficacy relationship to durvalumab exposure with all quartiles overlapping each other.

Figure 9: PFS Kaplan-Meier plots for durvalumab exposure metrics by quartiles at Steady State





Note: Shaded areas are the 95% CI around the Kaplan-Meier curves. Vertical ticks represent the right censoring. AUC_{ss}, area under the serum concentration-time curve at steady state; CI, confidence interval; C_{max}, maximum concentration, C_{min}, minimum concentration; SoC, standard of care.

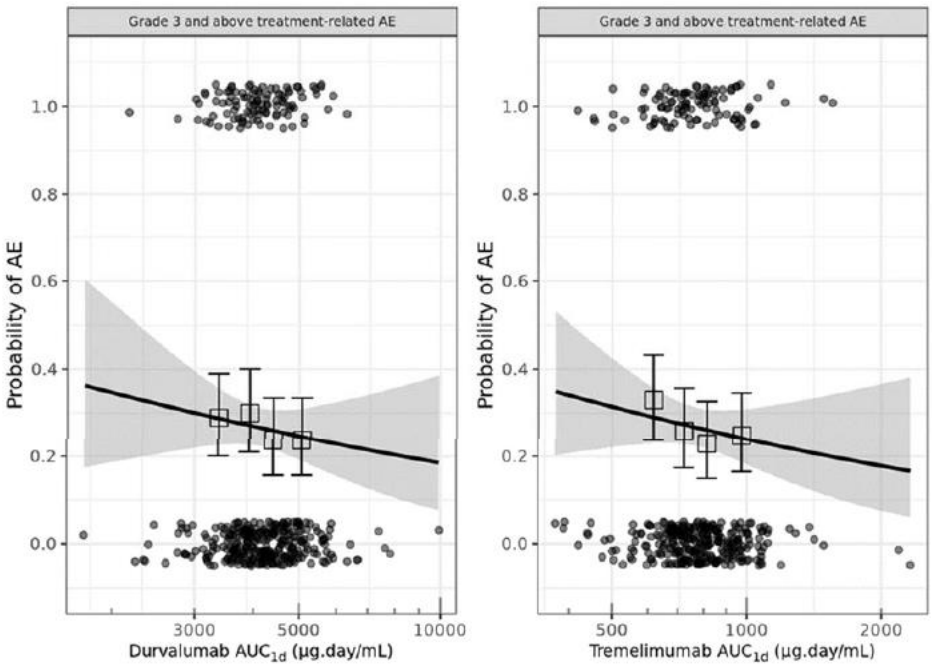
Exposure-safety relationship

For assessment of an exposure-safety relationship, the evaluated safety endpoints were Grade 3 and above treatment-related AEs from HIMALAYA, Grade 3 and above AESIs, and AEs leading to durvalumab treatment discontinuation.

Grade 3 and above treatment-related AEs

The probability of AEs calculated in quartiles of the $AUC_{dose\ 1}$ exposure metrics for durvalumab and tremelimumab is shown in Figure 10. This figure summarizes the logistic regression results assessing the impact of exposure on the probability of AEs. The p-values associated with exposure effects were relatively large, indicating that the relationship was not statistically significant.

Figure 10. Relationship between the probability of having Grade 3 and above treatment-related AEs and $AUC_{dose\ 1}$ for durvalumab and tremelimumab



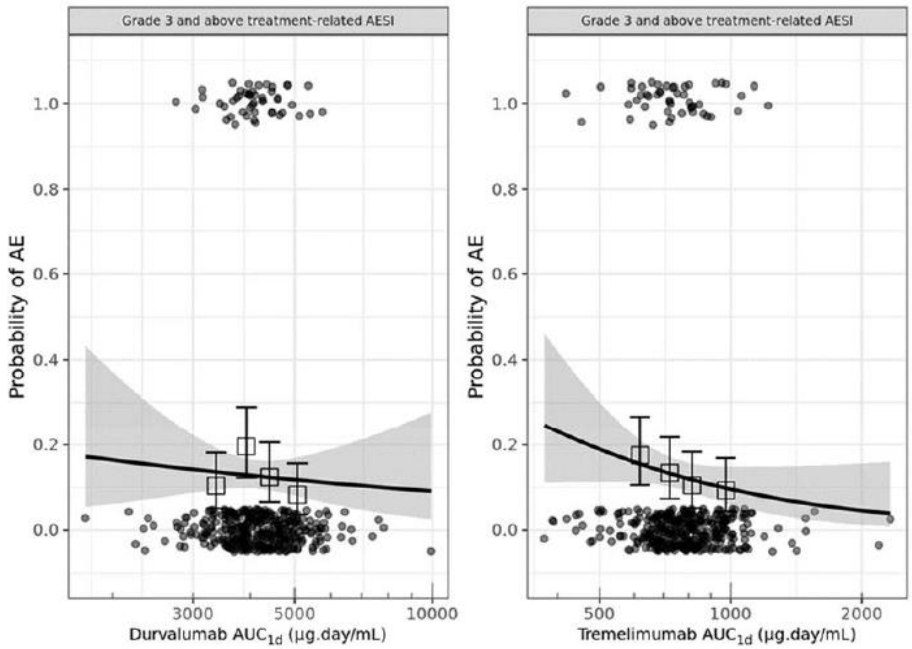
Note: The black solid circles are the observed AE, and the open squares with error bars are the observed probability of response at each exposure quartile. The black lines are the logistic regression between two variables, and the gray area represents the associated confidence interval.
AE, adverse event; AUC, area under the serum concentration-time curve.

Grade 3 and Above Treatment-related AESIs

The probability of AESIs calculated in quartiles of the $AUC_{dose\ 1}$ exposure metrics for durvalumab and tremelimumab is shown in Figure 11.

The p-values associated with exposure effects were relatively large, indicating that the relationship was not statistically significant.

Figure 11. Relationship between the probability of having Grade 3 and above treatment-related AESIs and AUC$_{dose\ 1}$ for durvalumab and tremelimumab



Note: The black solid circles are the observed AEs, and the open squares with error bars are the observed probability of response at each exposure quartile. The black lines are the logistic regression between two variables, and the gray area represents the associated confidence interval.
Abbreviations: AE, adverse event; AUC, area under the serum concentration-time curve.

2.3.4. Discussion on clinical pharmacology

Durvalumab and tremelimumab are checkpoint inhibitors with distinct yet complementary mechanisms of action with respect to enhancing the antitumor immune response. Tremelimumab mediated blockade of CTLA-4 functions early in the immune response, lowering the threshold for T cell activation, allowing more T cells to be activated and increasing the diversity of the T cell population. This increases the probability that a T cell recognizing a tumor neoantigen can become activated. Durvalumab blockade of PD-L1 is expected to function mainly during the effector phase of T cell function, once T cells enter the tumor, where it acts to block local suppression of T-cell function by PD-L1, enhancing the ability of activated anti-tumor T cells to target and kill tumor cells.

Durvalumab (Imfinzi) was approved in 2018 in the EU for treatment of adults with locally advanced, unresectable NSCLC, whose disease has not progressed following platinum-based chemoradiation therapy.

The clinical pharmacology of durvalumab as monotherapy has previously been described adequately.

The Applicant is currently seeking marketing approval for the use of a durvalumab (IMFINZI) in combination with a single, priming dose of tremelimumab for the treatment of patients with unresectable hepatocellular carcinoma (uHCC).

The purpose of the present application is to update the product information for durvalumab administered in combination with tremelimumab for this indication.

The clinical pharmacological data are derived from 1 pivotal study (HIMALAYA) and 20 supportive durvalumab studies and 17 supportive tremelimumab studies.

All studies included male and female patients aged 18 years and older with advanced solid tumors. No PK data has been obtained from healthy volunteers.

The clinical pharmacology programme in special populations is considered adequate and typical for a protein drug product being administered intravenously.

The effect of hepatic and renal impairment was not formally tested in dedicated clinical trials; this is acceptable since durvalumab is a human IgG antibody, which is expected to be degraded into small peptides and amino acids via catabolic pathways in the same way as endogenous IgG.

Assessment of an exposure-efficacy relationship was conducted using OS and PFS as efficacy parameters in patients from HIMALAYA, for whom the different exposure metrics could be calculated.

OS and PFS were explored by Kaplan-Meier (KM) estimates and analyzed by Cox proportional-hazards models.

For OS the KM plots indicated that there was no clear relationship between efficacy and exposure to durvalumab with all quartiles overlapping each other.

The covariates, aspartate aminotransferase (AST) and neutrophil-to-lymphocyte ratio (NLR) were identified as significant in the final model. Higher AST and NLR were associated with shorter survival in T300 + D arm, suggesting they are prognostic factors for OS.

For PFS the KM plots indicated no clear efficacy relationship to durvalumab exposure with all quartiles overlapping each other. Overall, no covariate was identified to be related with PFS in this analysis.

Additional explorative analyses of the covariates, body weight, and ADA status for durvalumab exposure (data not shown) did not indicate any clear trend between OS or PFS and body weight or ADA status. However, the small number of ADA-positive patients after durvalumab treatment mean that the Kaplan-Meier plots for ADA status should be interpreted with caution.

For assessment of exposure-safety relationship, the evaluated safety endpoints were Grade 3 and above treatment-related adverse events (AEs) from HIMALAYA, Grade 3 and above Adverse event of special interest (AESIs) and AEs leading to durvalumab treatment discontinuation.

None of the tremelimumab or durvalumab exposure metrics in a logistic regression analysis were identified to have an influence on safety events.

A body weight-AE analysis did not identify any clear trend between the probability of AEs and increasing or decreasing body weight.

Both the ADA incidence and prevalence were similar across treatment arms (D, T300+D and T75+D), it is agreed that the presence of tremelimumab did not have an apparent effect on the immunogenicity of durvalumab.

2.3.5. Conclusions on clinical pharmacology

The clinical pharmacology of durvalumab in combination with tremelimumab has overall been adequately described.

2.4. Clinical efficacy

This extension of indication for durvalumab is based on efficacy data from HIMALAYA, a randomised, open-label, multicentre Phase III study in patients with unresectable hepatocellular carcinoma (HCC) not

eligible for locoregional therapy and with no prior systemic therapy for HCC. Additional supportive evidence of clinical efficacy is provided from study 22, a randomised, phase I/II, open-label study.

Table 8. Overview of Studies in the Clinical Development Program for Durvalumab in Combination With Tremelimumab and Durvalumab Monotherapy in Patients With uHCC

Study number and acronym	Study title	Study design	Objective	DCO date(s)	Location in Module 5
Pivotal Study					
D419CC00002 **HIMALAYA**	A Randomized, Open-label, Multicenter Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients With Advanced Hepatocellular Carcinoma (HIMALAYA)	Phase III, randomized, open-label, sponsor-blind, multicenter, global study	To assess the efficacy and safety of T300+D vs S and D vs S	**FA:** 27 August 2021	5.3.5.1
Supportive Study					
D4190C00022 **Study 22**	A Study of Safety, Tolerability, and Clinical Activity of Durvalumab and Tremelimumab Administered as Monotherapy, or Durvalumab in Combination With Tremelimumab or Bevacizumab in Subjects with Advanced Hepatocellular Carcinoma	Phase I/II, randomized, open-label, multicenter, international study	Parts 2 and 3: To assess the safety, tolerability, and clinical activity of T300+D, D, and T.	**FA:** 06 November 2020	5.3.5.2

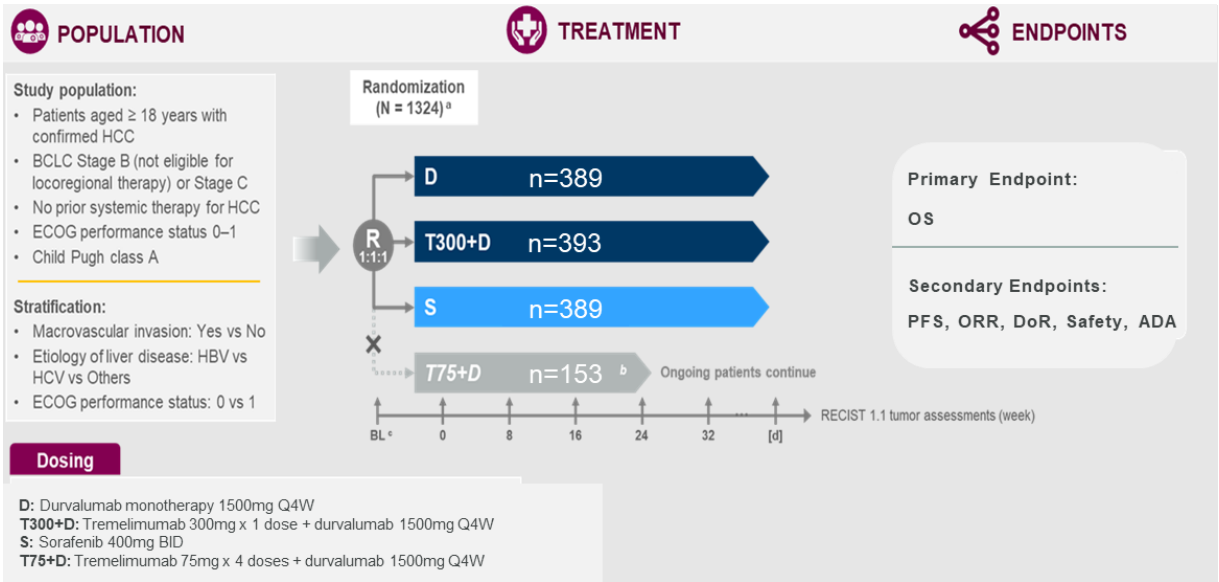
Abbreviations: D = durvalumab 1500 mg (20 mg/kg) Q4W; DCO = data cut-off; FA = Final Analysis; Q4W = every 4 weeks; Q12W = every 12 weeks; T = tremelimumab 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W; T300+D = tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) Q4W; uHCC = unresectable hepatocellular carcinoma.

2.4.1. Main study

A Randomized, Open-label, Multicenter Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients With Advanced Hepatocellular Carcinoma (HIMALAYA)

Study design for the pivotal trial is illustrated in Figure 12.

Figure 12. HIMALAYA: Study Design



Patient numbers shown correspond to the actual enrollment.

Enrollment into the T75+D arm was closed following protocol edition 4.0 (29 November 2018). Patients randomized to T75+D prior to protocol amendment 3 could continue on their assigned study treatment, provided the Investigator and patient agreed this was in the patient's best interest. Patients randomized to T75+D arm who had not completed or started all 4 doses of tremelimumab could either complete the full schedule or continue with durvalumab monotherapy only

Methods

Study participants

Patients were enrolled at 181 sites and randomized at 170 study centers in 16 countries: Brazil (13 centers), Canada (9), France (14), Germany (10), Hong Kong (5), India (10), Italy (8), Japan (27), South Korea (8), Russian Federation (10), Spain (6), Taiwan (9), Thailand (9), Ukraine (8), United States of America (21), and Vietnam (3).

Inclusion Criteria

For inclusion in the study, patients had to fulfill all of the following criteria:

1. Age ≥ 18 years at the time of screening.

2. Body weight > 30 kg.

3. Written informed consent and any locally required authorization obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

4. Confirmed HCC based on histopathological findings from tumor tissues.

5. Must not have received prior systemic therapy for HCC.

6. Ineligible for locoregional therapy for unresectable HCC. For patients who progressed after locoregional therapy for HCC, locoregional therapy must have been completed ≥ 28 days prior to the baseline scan for the current study.

7. BCLC stage B (ie, not eligible for locoregional therapy) or stage C.

8. Child-Pugh score class A.

9. ECOG performance status of 0 or 1 at enrollment.

10. Patients with HBV infection, characterized by positive HBsAg and/or anti-HBcAb with detectable HBV DNA (≥ 10 IU/mL or above the limit of detection per local or central laboratory standard), must be treated with antiviral therapy, per institutional practice, to ensure adequate viral suppression (HBV DNA ≤ 2000 IU/mL) prior to enrollment. Patients were to remain on antiviral therapy for the study duration and for 6 months after the last dose of study treatment. Patients who tested positive for HBc with undetectable HBV DNA (< 10 IU/mL or under the limit of detection per local or central laboratory standard) did not require antiviral therapy prior to enrollment. These patients were tested at every cycle to monitor HBV DNA levels and antiviral therapy initiated if HBV DNA was detected (≥ 10 IU/mL or above the limit of detection per local or central laboratory standard). HBV DNA detectable patients were to initiate and remain on antiviral therapy for the study duration and for 6 months after the last dose of study treatment.

11. Patients with HCV infection: Confirmed diagnosis of HCV characterized by the presence of detectable HCV RNA or anti-HCV antibody upon enrollment.

12. At least 1 measurable lesion, not previously irradiated, that could be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes, which must have a short axis ≥ 15 mm) with CT or MRI, and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines. A

lesion which progressed after previous ablation or transarterial chemoablation could be measurable if it met these criteria.

13. Adequate organ and marrow function, as defined below. Criteria "a", "b," "c," and "f" could not be met with transfusions, infusions, or growth factor support administered within 14 days of starting the first dose.

a. Hemoglobin $\geq$ 9 g/dL

b. Absolute neutrophil count $\geq$ 1000/μL

c. Platelet count $\geq$ 75000/μL

d. TBL $\leq$ 2.0 $\times$ ULN

e. AST and ALT $\leq$ 5 $\times$ ULN

f. Albumin $\geq$ 2.8 g/dL

g. INR $\leq$ 1.6. Note: INR prolongation due to anticoagulants for prophylaxis (eg, atrial fibrillation) in patients without liver cirrhosis could be an exception

h. Calculated creatinine clearance $\geq$ 50 mL/min as determined by Cockcroft-Gault (using actual body weight) or 24 h urine creatinine clearance

14. Evidence of postmenopausal status or negative urinary or serum pregnancy test for female premenopausal patients.

15. Life expectancy of at least 12 weeks.

Exclusion Criteria

Any of the following was regarded as a criterion for exclusion from the study:

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

2. Previous study treatment (s) assignment in the present study.

3. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.

4. Received an IP within 28 days prior to the first dose of study treatment.

5. Any unresolved toxicity NCI CTCAE Grade $\geq$ 2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria:

- Patients with Grade $\geq$ 2 neuropathy were evaluated on a case-by-case basis after consultation with the Study Physician
- Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab could be included only after consultation with the Study Physician.

6. Any concurrent chemotherapy, study treatment, or biologic or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) was acceptable.

7. Known allergy or hypersensitivity to any of the study treatments or any of the study treatment excipients.

8. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 28 days of the first dose of study treatment.

9. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of study treatments. Note: Local surgery of isolated lesions for palliative intent was acceptable.

10. History of allogeneic organ transplantation (eg, liver transplant).

11. History of hepatic encephalopathy within the past 12 months or requirement for medications to prevent or control encephalopathy (eg, no lactulose, rifaximin, etc if used for purposes of hepatic encephalopathy).

12. Clinically meaningful ascites, defined as any ascites requiring non-pharmacologic intervention (eg, paracentesis) to maintain symptomatic control, within 6 months prior to the first scheduled dose. Patients on stable doses of diuretics for ascites for $\geq$ 2 months were eligible.

13. Patients with main portal vein thrombosis (ie, thrombosis in the main trunk of the portal vein, with or without blood flow) on baseline imaging.

14. Active or prior documented GI bleeding (eg, esophageal varices or ulcer bleeding) within 12 months. Note: For patients with a history of GI bleeding for more than 12 months or assessed as high risk for esophageal varices by the Investigator, adequate endoscopic therapy according to institutional standards was required).

15. Current symptomatic or uncontrolled hypertension defined as DBP > 90 mmHg or SBP > 140 mmHg.

16. Any condition interfering with swallowing pills, uncontrolled diarrhea, or other contraindication to oral therapy.

17. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). Patients without active disease in the last 5 years were excluded unless discussed with the Study Physician and considered appropriate for study participation.

The following were exceptions to this criterion:

- Vitiligo or alopecia
- Hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
- Any chronic skin condition not requiring systemic therapy
- Patients with celiac disease controlled by diet alone

18. Co-infection with HBV and HCV or HBV and HDV. HBV positive (presence of HBsAg and/or anti-HBcAb with detectable HBV DNA); HCV positive (presence of anti-HCV antibodies); or HDV positive (presence of anti-HDV antibodies).

19. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, ILD, serious chronic GI conditions associated with diarrhea, inferior vena cava thrombosis, or psychiatric illness/social situations that would limit compliance with study requirements, substantially increase the risk of incurring AEs, or compromise the ability of the patient to give written informed consent.

20. History of another primary malignancy except for:

- Malignancy treated with curative intent and with no known active disease ≥ 5 years before the first dose of study treatment and of low potential risk for recurrence
- Patients with a history of prostate cancer of stage ≤ T2cN0M0 without biochemical recurrence or progression and who, in the opinion of the Investigator, are not deemed to require active intervention
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated carcinoma in situ without evidence of disease

21. History of leptomeningeal carcinomatosis.

22. History of, or current, brain metastases or spinal cord compression. Patients with suspected brain metastases at screening should have an MRI (preferred) or CT, each preferably with IV contrast of the brain prior to study entry.

23. Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC.

24. History of active primary immunodeficiency.

25. Active infection including TB (clinical evaluation that included clinical history, physical examination and radiographic findings, and TB testing in line with local practice), or HIV (positive HIV1/2 antibodies)

26. Current or prior use of immunosuppressive medication within 14 days before the first dose of study treatment, with the exception of the following:

- Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection)
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent
- Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)

27. Receipt of live attenuated vaccine within 30 days prior to the first dose of study treatment. Note: Patients, if enrolled, should not receive live vaccine while receiving study treatment and up to 30 days after the last dose of study treatment.

28. Female patients who were pregnant or breastfeeding, or male or female patients of reproductive potential who were not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab plus tremelimumab combination therapy. Not engaging in sexual activity, as per the patient's preferred and usual lifestyle, for the total duration of the treatment and washout periods was an acceptable practice.

29. Prior randomization or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.

30. Patients who had received anti-PD-1, anti-PD-L1, or anti-CTLA-4 prior to the first dose of study treatment.

Treatments

Table 9. Study Treatments

Treatment arm	Description
D	Durvalumab monotherapy 1500 mg Q4W until confirmed PD, unacceptable toxicity, or any discontinuation criteria were met
T75+D	Tremelimumab (75 mg) × 4 doses + durvalumab (1500 mg) Q4W followed by durvalumab monotherapy (1500 mg) Q4W until confirmed PD, unacceptable toxicity, or any discontinuation criteria were met. [a]
T300+D	Tremelimumab (300 mg) × 1 dose + durvalumab (1500 mg) Q4W, followed by durvalumab 1500 mg monotherapy Q4W until confirmed PD, unacceptable toxicity, or any discontinuation criteria were met
S	Sorafenib 400 mg (2 × 200 mg tablets) orally BID, until confirmed PD at the Investigator's discretion, unacceptable toxicity, or any discontinuation criteria were met. (Suspected sorafenib-related toxicities were managed based on the approved product label for each country). [b]

[a] Following protocol amendment 3, enrollment into the T75+D arm was closed. Patients randomized to T75+D prior to protocol amendment 3 could continue on assigned study treatment (provided the Investigator and patient agreed it was in the best interest of the patient) until confirmed PD or any other discontinuation criteria were met. If a patient assigned to T75+D had not completed or started all 4 doses of tremelimumab, the patient was able to continue to complete the full schedule or continue with durvalumab monotherapy only.

[b] In countries where sorafenib was not approved, the following modification was followed: sorafenib dose may be reduced to 400 mg (2 × 200 mg tablets) orally once daily. If additional dose reduction was required, the sorafenib dose could be reduced to a single 400 mg dose (2 × 200-mg tablets) orally every other day.

BID, twice daily; CSP, Clinical Study Protocol; Q4W, every 4 weeks; PD, disease progression.

The proposed dosing regimen for the relevant arm for this procedure (T300+D, arm C) is new and encompasses one single initial dose of tremelimumab 300 mg in combination with durvalumab 1500 mg and thereafter, durvalumab monotherapy iv Q4W until PD or unacceptable toxicity.

The relevant comparator arm for the current procedure was the standard of care arm (SOC, arm D), which contains sorafenib 400 mg orally twice daily as standardly dosed, and treatment should have also been given until PD or unacceptable toxicity. No cross-over was allowed.

The two other treatment arms with D (durvalumab 1500 mg Q4W, arm A) and T75+D (tremelimumab 75 mg Q4W × 4 doses + durvalumab 1500 mg Q4W, followed by durvalumab 1500 mg Q4W, arm B) are not of relevance for this procedure.

It is noted that although the combination of a CTLA-4 inhibitor, such as tremelimumab, and an immunecheckpoint inhibitor such as durvalumab is not new, it is the first time that the anti-CTLA-4 is given only as an induction dose and then monotherapy with durvalumab is continued until PD. Moreover, the already approved combination therapy with ipilimumab + nivolumab differs as nivolumab is PD-1 inhibitor, while durvalumab is a PD-L1 inhibitor.

The Applicant claims that pharmacodynamic results reported for tremelimumab and durvalumab in Study 006 suggest that the pharmacodynamic effects of anti-CTLA-4 are mainly associated with the first dosing cycle and subside in subsequent cycles regardless of dose. Moreover, these results led to the hypothesis that a single dose of tremelimumab might accomplish similar pharmacodynamic effects as seen in Study 006 and also seen for ipilimumab, while also limiting the toxicity associated with the second (and subsequent) anti-CTLA-4 dosing cycles.

Objectives

Table 10. Study Objectives and Endpoints

Objective	Outcome measure
Primary objective:	**Primary endpoint/variables:**
To assess the efficacy of T300+D vs S (for superiority)	• OS
Key secondary objectives:	**Key secondary endpoint/variables:**
To assess the efficacy of D vs S (for non-inferiority)	• OS
To assess the efficacy of D vs S (for superiority)	• OS
Secondary objectives:	**Secondary endpoint/variables:**
To assess the efficacy of D vs S and T300+D vs S	• OS18, OS24, and OS36 • PFS, TTP, ORR, DCR, DCR-16w, DCR-24w, and DoR, according to RECIST 1.1 using Investigator assessments
To assess the efficacy of D and T300+D in patients with an opportunity for 32 weeks of follow-up	• ORR, BOR, and DoR according to RECIST1.1 and mRECIST by BICR
To assess the efficacy of D vs S and T300+D vs S by PD-L1 expression	• OS • PFS, TTP, ORR, DCR, DCR-16w, DCR-24w, and DoR according to RECIST 1.1 using Investigator assessments
To assess disease-related symptoms, impacts, and HRQoL in D vs S and T300+D vs S	• EORTC QLQ-C30: Time to deterioration in global health status/QoL, functioning (physical), multi-term symptom (fatigue), single-item symptoms (appetite loss, nausea) • EORTC QLQ-HCC18: Time to deterioration in single-item symptoms (shoulder pain, abdominal pain, abdominal swelling)
To investigate the immunogenicity of D and T300+D	• Presence of ADA for durvalumab and tremelimumab
To evaluate the population PK and pharmacodynamics in D and T300+D	• Durvalumab and tremelimumab concentrations and PK parameters in individual arms
Safety objectives:	**Safety endpoint/variables:**
To assess the safety and tolerability profile across all treatment arms	• AEs and laboratory findings [a]
Exploratory objectives:	**Exploratory endpoint/variables:**
To assess PFS from rechallenge in the T300+D arm and to assess PFS from first post-discontinuation therapy in D, T300+D, and S [b]	• PFSFR and PFSNT using Investigator assessments

Objective	Outcome measure
To assess the efficacy of D vs S and T300+D vs S using irRECIST and mRECIST for HCC [b]	• PFS, TTP, ORR, DCR, DCR-16w, DCR-24w, and DoR according to irRECIST and mRECIST and by BICR, if performed
To investigate the relationship between the progressive changes in AFP level and efficacy parameters [b]	• Association of AFP expression level with: ○ OS ○ PFS, TTP, ORR, DoR, DCR, DCR-16w, and DCR-24w according to RECIST 1.1 using Investigator assessments
To investigate the efficacy of D vs S and T300+D vs S by baseline gene expression [b]	• Association of interferon-gamma and immune-related gene expression, as measured by mRNA levels from baseline tumor biopsies and blood, with ○ OS ○ PFS, TTP, ORR, DoR, DCR, DCR-16w, and DCR-24w according to RECIST 1.1 using Investigator assessments
To investigate the efficacy of D vs S and T300+D vs S by candidate biomarkers that may correlate with drug activity or identify patients likely to respond to treatment [b]	• Association of intratumoral immune cell numbers (specifically CD8+ T cells), ctDNA, and/or tumor mutations with: ○ OS ○ PFS, TTP, ORR, DoR, DCR, DCR-16w and DCR-24w according to RECIST 1.1 using Investigator assessments
To investigate the efficacy of D vs S in patients who are at low risk of early mortality based on baseline characteristics [b]	• OS
To assess the efficacy of D vs T300+D in the overall population and in the population defined by PD-L1 expression [b]	• OS • PFS, TTP, ORR, DCR, DCR-16w, DCR-24w and DoR, by according to RECIST 1.1 using Investigator assessments
To assess patient-reported treatment tolerability directly using specific items of the PRO-CTCAE questionnaire in D vs S and T300+D vs S	• PRO-CTCAE symptoms (11 items)
Healthcare resource utilization	• EQ-5D-5L • Hospital admission form
To assess physician-reported patient outcome in D vs S and T300+D vs S	• ECOG performance status
To assess the efficacy of the discontinued immunotherapy arm (T75+D) for descriptive purposes	• OS • PFS, TTP, ORR, DCR, DCR-16w, DCR-24w, and DoR according to RECIST 1.1 using Investigator assessments

Outcomes/endpoints

Please refer to Table 10 above regarding the objectives and endpoints for the pivotal study Himalaya.

Sample size

This study was planned to screen approximately 1650 patients, with no prior systemic therapy for hepatocellular carcinoma (HCC) and not eligible for locoregional therapy, in order to randomize approximately 1310 patients. (This included 1155 patients randomized to Arms A (Durvalumab monotherapy), C (T300+D), D (S) with 385 per arm; and approximately 155 patients in Arm B (T75+D), randomized prior to the closure of this arm). **The study was sized to characterize the OS benefit of Arm C vs. Arm D (T300+D vs S).**

The sample size estimation assumed an exponentially distributed OS and a 2-month delay in separation of the OS curves for Arm C vs. Arm D. A non-uniform accrual of patients with a duration of 22 months was assumed when estimating the analysis times.

For the efficacy comparisons, the median OS for sorafenib (Arm D) was assumed to be 11.5 months, with an 18-month OS rate of 33.8%.

Durvalumab 1500 mg plus tremelimumab 300 mg × 1 dose (Arm C) versus sorafenib 400 mg BID (Arm D) (OS in FAS [ITT])

The assumed OS treatment effect was an average HR of 0.70 for Arm C versus Arm D. This translates to an increase in median OS from 11.5 months to 16.5 months, and in the 18-month OS rate from 33.8% to 46.8% in Arm C versus Arm D. Final analysis of OS was planned to be performed when approximately 515 events in Arm C and Arm D combined (~67% maturity) have occurred. This number of OS events was foreseen to provide 97% power to demonstrate a statistically significant difference in OS at a 2-sided 4.25% significance level. The smallest treatment difference that could be observed as statistically significant at the final analysis was foreseen to be an average HR of 0.84 (an increase in median OS from 11.5 months to 13.7 months in Arm C versus Arm D).

No formal sample size calculations were associated with the analyses planned for IA1. However, global enrollment was required to be completed prior to the DCO for IA1.

There were 2 IAs and a FA planned for HIMALAYA. Any major changes to the planned analyses were addressed in protocol amendments finalized prior to the date of the first DCO for Interim analysis 1 for ORR (02 September 2019). These changes were informed by the open-label Study 22 and study read-outs from external studies in the same disease area, including KEYNOTE-240 and CheckMate-459. No HIMALAYA data were available for use to modify the protocol design or statistical analysis plan.

The sample size calculations were updated several times while the study was ongoing. Major changes were implemented in the Protocol version 4 (29 Nov 2018) and in Protocol version 6 (20 Aug 2019). In protocol version 4, the arm durvalumab + tremelimumab 75 mg was closed due to unfavourable results obtained in the supportive Study 22. At this point, the sample size for the remaining arms was increased to 385 and the number of required events at the second interim analysis and at the final analysis was changed. In protocol version 6, the median OS and 18-month OS rate for sorafenib was increased from 10 months and 28.7 % to 11.5 months and 33.8 %, respectively. The required number of events at the second interim analysis and at the final analysis were also changed.

The Applicant claimed that the changes made in the protocol and SAP were solely informed by external data including Study 22 and KEYNOTE-240 and CheckMate-459. Nevertheless, changes in the sample size while the study is ongoing can jeopardize the interpretation of the results since they may alter the behavior of study participants and personnel. The changes were implemented between 1 and 2 years from study start, and one month before the first interim analysis (2 Sep 2019). Therefore, the sample size calculations are not considered relevant and the study results were assessed based on the size of the confidence intervals.

Randomisation

Subjects were planned to be randomized in a 1:1:1:1 ratio to one of the following 4 arms:

1) Arm A: Durvalumab 1500 mg monotherapy

2) Arm B: Tremelimumab 75 mg × 4 doses plus Durvalumab 1500 mg combination therapy

3) Arm C: Tremelimumab 300 mg × 1 dose plus Durvalumab 1500 mg combination therapy

4) Arm D: Sorafenib 400 mg BID.

Protocol amendment 4 closed enrolment to Arm B. As a result of protocol amendment 4, subjects were randomized in a 1:1:1 ratio to Arm A, Arm C and Arm D. Subjects randomized to Arm B prior to amendment 4 could have remained on study as planned until discontinuation criteria were met at the discretion of the investigator.

Randomization was foreseen to be stratified according to macrovascular invasion (yes versus no), etiology of liver disease (hepatitis B virus [confirmed HBV] versus hepatitis C virus [confirmed HCV] versus others), and ECOG PS (0 versus 1).

A randomization list was produced for each of the randomization stratum. A blocked randomization was generated, and all centers used the same list in order to minimize any imbalance in the number of patients assigned to each treatment arm.

Blinding (masking)

The study was open-label. The Study Team, responsible for the conduct of the study, was blinded to randomized treatment assignment until formal study unblinding occured at Interim Analysis 2 (IA2) or the Final Analysis (FA). The Study Team members were not planned to have access to any information regarding the interim analysis results. If a Study Team member was needed to join the Submission Team, this member was not allowed to re-join the Study Team until the Study Team and Study Database are formally unblinded at IA2 or FA. This study used an external IDMC that comprised independent therapeutic area experts and biostatisticians to assess ongoing safety as well as the interim efficacy analyses. The IDMC remit was to report to the Sponsor and if applicable recommend changes to study conduct.

Measures were in place to ensure that the Study team was blinded to treatment assignment and results from the interim analyses. An IDMC assessed safety data ongoing and performed the interim analyses.

Statistical methods

Full analysis set

The full analysis set (FAS) was planned to include all randomized patients, including patients who were randomized in error. The FAS was planned to be used for all efficacy analyses (including PROs). Treatment arms were to be compared on the basis of randomized study drug(s), regardless of the study drug(s) actually received. Patients who were randomized but did not subsequently go on to receive study drug(s) were included in the analysis in the treatment arm to which they were randomized.

For IA1 an additional analysis set was planned to be defined: FAS subjects with an opportunity for 32 weeks of follow up at the time of IA1 (FAS-32w, i.e., randomized ≥ 32 weeks prior to IA1 DCO).

The primary analysis was performed using the FAS, which includes all randomized patients. For the first IA, only subjects who had the opportunity to attend at least 32 weeks of follow-up were included. The results of the first IA are not related to the primary objectives of the study.

Statistical analyses

Table 11. Formal Statistical Analyses to be Conducted and Pre-planned Sensitivity

Endpoint	Analysis
Overall survival (OS)	Primary analysis: Stratified log-rank test (for p-value), HR from Cox model (with 95% CI) Sensitivity analyses: - Attrition bias. Kaplan-Meier plot of time-to-censoring where the censoring indicator of the primary analysis is reversed. - Exploratory analysis using max-combo test. - Impact of COVID19. OS analysis will be repeated but subjects who died from COVID-19 Infection will be censored at their COVID infection death date.
Progression Free Survival (PFS)	Primary analysis: Stratified log-rank test using Investigator assessments per RECIST 1.1 (for p-value), HR from Cox model (with 95% CI)
Time to progression (TTP)	Primary analysis: Stratified log-rank test using Investigator assessments per RECIST 1.1 (for p-value), HR from Cox model (with 95% CI)

Endpoint	Analysis
Objective response rate (ORR)	IA1: Exact confidence intervals; IA2 and FA: Logistic regression using Investigator assessments per RECIST 1.1 (odds ratio with 95% CI and p-value)
Best Objective Response (BoR)	Descriptive statistics
Duration of response (DoR)	Descriptive statistics including KM plot
Disease control rate (DCR, DCR-16w, DCR-24w)	Descriptive statistics
Proportion of subjects alive at 18m (OS18)	KM estimates of OS at 18 months
Proportion of subjects alive at 24m (OS24)	KM estimates of OS at 24 months
Proportion of subjects alive at 36m (OS36)	KM estimates of OS at 36 months Stratified chi-square test of difference in KM estimators at a fixed time point (36 months) (for p-value)
PFS from rechallenge	Summarized by treatment arm using Investigator assessments per RECIST 1.1.
PFS on next treatment	Summarized by treatment arm
Time to deterioration (EORTC QLQ-C30 and EORTC QLQ-HCC18)	Stratified log-rank test (for p-value), HR from Cox model (with 95% CI), KM plot
EORTC QLQ-C30, EORTC QLQ-HCC18	Average change from baseline using an MMRM analysis, Summary statistics
Improvement based best overall response (EORTC QLQ-C30, EORTC QLQ-HCC18)	Logistic regression with odds ratio, 95% CI and p-value
EQ-5D-5L, PGIC, PRO-CTCAE	Summary statistics

EORTC European Organisation for Research and Treatment of Cancer; EQ-5D-5L EuroQoL 5-Dimension, 5-Level health state utility index; MMRM Mixed effect model repeat measurement; OS overall survival; QLQ-C30 30-item core quality of life questionnaire; QLQ-HCC18 18-item hepatocellular cancer health-related quality of life questionnaire.

Overall survival

The primary OS endpoint was to be analysed using a stratified log-rank tests adjusting for etiology of liver disease (confirmed HBV versus confirmed HCV versus others), ECOG (0 versus 1), and macrovascular invasion (yes versus no) for generation of the p-value and using rank tests for association

as the testing approach, which corresponds to Cox regression with the Breslow approach for handling ties (Breslow, 1974).

The effect of Arm C vs. Arm D treatment was to be estimated by the HR from stratified Cox proportional hazards model (with ties=Efron and stratification variables as listed above) together with its corresponding 95% confidence interval (CI) calculated using a profile likelihood approach. The stratification variable used the values recorded in the randomization system (IWRS).

If there is >10% discordance in stratification factors as recorded in IWRS versus the Case Report Form (CRF), then a sensitivity analysis of the primary endpoint OS was to be performed using CRF based stratification factors.

Secondary OS analyses were to be performed using the same methodology as for primary analysis described above.

Censoring rules for OS

Any subject not known to have died at the time of analysis was planned to be censored based on the last recorded date on which the subject was known to be alive.

Assumptions of Proportionality

The assumption of proportionality of hazard was to be assessed first by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time-dependent covariate to assess the extent to which this represents random variation. If a lack of proportionality of hazard is evident, the variation in treatment effect was to be described by presenting piecewise HR calculated over distinct time periods. The Grambsch-Therneau test and Schoenfeld residuals may have also been used to check violation of the proportional hazards assumption. As a lack of proportionality was expected (due to delayed effect in IO agents), a three-component stratified MaxCombo test was planned to be used as a sensitivity analysis with the same stratification factors as the primary analysis. The Restricted Mean Survival Time (RMST) was also to be analysed up to the minimum of the largest observed event time in each of the two arms and /or suitable clinically relevant timepoint. In addition, an area-under-the-curve approach (Kaplan-Meier method) and Royston-Parmar model (Royston and Parmar 2011, 2013) may also have been used.

Sensitivity analysis

- Censoring patterns: A sensitivity analysis for OS was planned to examine the censoring patterns to rule out attrition bias, achieved by a Kaplan-Meier plot of time-to-censoring where the censoring indicator of OS was reversed.
- Impact of switching (crossover outside of this study) to other immunotherapies (or other potentially active investigational agents) on OS analyses: Exploratory analyses of OS adjusting for the impact of subsequent switching of immunotherapy or the investigational treatment may have been performed, if a sufficient proportion of subjects switched.
- Effect of COVID-19: A sensitivity analysis was planned to be conducted to assess for the potential impact of COVID deaths on OS. This was to be assessed by repeating the OS analysis except that any subject who had a death with primary/secondary cause as COVID-19 Infection was to be censored at their COVID infection death date.
- Effect of covariates on the HR estimate: Cox proportional hazards modelling was to be employed to assess the effect of pre-specified covariates on the HR estimate for the primary OS treatment comparisons. As an exploratory analysis, the covariates from the model in the primary analysis and the model containing additional covariates may have been presented.

OS12, OS18, OS24, and OS36

OS12, OS18, OS24, and OS36 were to be defined as the Kaplan-Meier estimate of OS at 12 months, 18 months, 24 months, and 36 months. OS12, OS18, OS24, and OS36, along with their 95% CI, were to be summarized (using the Kaplan- Meier curve) and presented by treatment arm. An analysis of OS36 was to be performed to compare Arm C vs. Arm D using a stratified chisquare test for the difference in KM estimators (cloglog transformed) for Arms C and D at a fixed time point (36 months). The test was to be conducted using the methods described in (Klein et al., 2007), including cloglog transformation on KM estimators, with randomization stratification factors (macrovascular invasion, etiology of liver disease, and ECOG). Note that the adjustment for the stratification factors was planned to be applied only if there were sufficient number of events and subjects at risk available in each strata at 36 months. Otherwise, an unstratified chisquare test was to be used to compare the difference in KM estimators at 36 months.

OS was analysed using a stratified log-rank tests adjusting for the factors used at randomization: etiology of liver disease (confirmed HBV versus confirmed HCV versus others), ECOG (0 versus 1), and macrovascular invasion (yes versus no). The HR was to be estimated using a stratified Cox model. The fulfilment of the proportional hazard assumption was investigated using a graphical approach and a maxcombo test. Sensitivity analyses were planned to explore the impact of treatment switch, covid 19 and effect of covariates. Censoring patterns were examined using the reverse Kaplan-Meier method. Patients not known to have died were censored at the last observation date.

The statistical method implemented to analysis OS is overall endorsed. The Applicant has clarified that the concordance rate between stratification factors entered in the IWRS vs eCRF at screening and baseline is high and due to <10% discordance rate, the threshold for triggering the sensitivity analysis was not met. Hence, no sensitivity analysis for primary efficacy analysis of OS adjusted for eCRF stratification factors at baseline has been conducted, which is acceptable.

Objective response rate based on Investigator assessment (ORR)

Data obtained up until progression, or the last evaluable assessment in the absence of progression, was planned to be included in the assessment of ORR. Subjects who went off treatment without progression, received a subsequent therapy, and then responded were planned not be included as responders in the ORR. ORR based on at least one confirmed response will also be derived and reported in CSR.

Logistic regression models adjusting for the same factors as the primary endpoint (etiology of liver disease, ECOG, and macrovascular invasion) was planned to be fitted. The results of the analysis were planned to be presented in terms of an odds ratio together with its associated profile likelihood 95% CI (e.g. using the option 'LRCI' in SAS procedure GENMOD) and p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

Additionally, at IA2 and FA a stratified Cochran Mantel–Haenszel (CMH) test was planned to be performed using randomization stratification factors (macrovascular invasion, etiology of liver disease, and ECOG). CMH test results were foreseen to include odds ratios and p-values.

Progression Free Survival by Investigator (PFS)

Analysis of PFS (time to first progression) was planned to be performed to compare Arm C vs. Arm D and Arm A vs. Arm D using the same methodology as for OS. Exploratory analyses compared Arm A vs. Arm C.

Table 12. Censoring rules for PFS

Assessment	Outcome	Date of Progression or Censoring
No baseline assessments or no evaluable response visits (excluding deaths within 2 visits of baseline)	Censored	Randomization date
No baseline or evaluable tumor assessments and death within 2 visits of baseline	Progressed	Date of death
Progression documented between scheduled visits	Progressed	Date of assessment of progression
No progression (or death) at time of analysis	Censored	Date of last evaluable tumor assessment
Death between assessment visits	Progressed	Date of death
Death or progression after 2 or more missed visits	Censored	Date of last evaluable tumor assessment prior to the 2 missed visits

PFS Progression-free survival.

Interim analyses

Two interim analyses and a final analysis were planned as described below:

Interim Analysis 1 (IA1): The first interim analysis was planned to be performed after approximately 100 subjects per treatment arm have had the opportunity for 32 weeks of follow-up and not prior to the last subject enrolled. The objective was to evaluate the efficacy of Arm A and Arm C in terms of ORR and DoR. The analysis set for ORR and DoR were the FAS-32wA. BICR of radiological scans were to be performed on all subjects included in IA1 who have been randomized and have had the opportunity for at least 32 weeks follow-up. Both Investigator (using RECIST 1.1) and BICR (using RECIST 1.1 and mRECIST) assessments were planned for IA1. Therefore, ORR and DoR (for both confirmed and unconfirmed responses) according to both Investigator using RECIST 1.1 and BICR using RECIST 1.1 and mRECIST were reported for IA1.

Interim Analysis 2 (IA2): The second interim analysis was planned to be performed when approximately 404 OS events in Arm C and Arm D combined (~52% maturity), approximately 30 months after the first subject was randomized. The goal was to evaluate the efficacy of Arm C vs. Arm D (for superiority) and then Arm A vs. Arm D (for non-inferiority, then superiority) in terms of OS. It is anticipated that approximately 453 OS events would have occurred across Arms A and D combined (~59% maturity) at the time of the DCO for IA2.

Final Analysis (FA): The final analysis was expected to be performed when approximately 515 OS events in Arm C and Arm D combined (~67% maturity), approximately 37.5 months after the first subject was randomized. The primary objective was to assess the efficacy of Arm C vs. Arm D in terms of OS for superiority. The key secondary objectives were to assess the efficacy of Arm A vs. Arm D in terms of OS (for non-inferiority, then superiority). It was anticipated that approximately 560 OS events would have occurred across Arms A and D combined (~73% maturity) at the time of the DCO for the final analysis. Efficacy data for Arm B (which was closed for enrollment with Amendment 4) were planned to be summarized descriptively, however were not be formally analysed.

Multiplicity

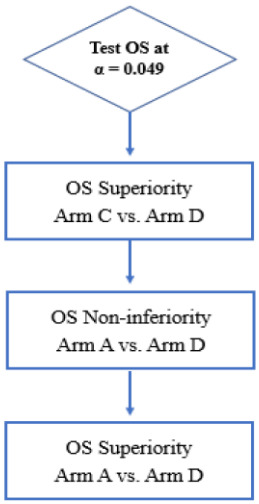
To strongly control the familywise error rate (FWER) at the 5% level (2-sided), an alpha level of 0.1% was planned to be spent on the interim ORR analysis (IA1) while the remaining 4.9% alpha level were

planned to be spent on all OS analyses. The primary objective of OS was to be tested (H1: Arm C vs. Arm D) with 4.9% for this comparison.

Since two analyses of OS were planned (Interim Analysis, Final Analysis), the Lan DeMets approach (Lan and DeMets 1983) that approximates the O'Brien and Fleming spending function was planned to be used to maintain an overall 2-sided 4.9% type I error across the two planned analyses of OS (Interim and Final) for the primary comparison (H1: Arm C vs. Arm D).

If all the OS analyses (H1, H2, and H3) were considered successful (superiority tests were statistically significant and non-inferiority was achieved), the 4.9% alpha level were to be passed to test the difference in the three-year survival rates (OS36) between Arm C and Arm D; otherwise, the test would not have been conducted. The study was to be considered positive (a success) if the primary OS analysis result was statistically significant at either IA2 or FA. If significance was achieved at IA2, it did not need to be tested again at FA.

Figure 13. Multiple testing strategy



The MAH planned to perform 2 interim and 1 final analyses. The first interim analysis was planned to be performed after 100 subjects per treatment arm have had the opportunity for 32 weeks of follow-up. The objective is to evaluate the efficacy of Arm A and Arm C in terms of ORR and DoR. This analysis was not related to the primary objective of the study. The second interim analysis was related to OS and planned to be performed after 404 OS events were observed (~52% maturity). The final OS analysis was planned to be performed after 515 OS events (~67% maturity) had been observed. The MAH implemented a hierarchical approach to protect the type I error due to multiple hypotheses being tested (OS superiority for T300+D vs S, OS non-inferiority for D vs S, OS superiority D vs S). An inflation of the type I error due to multiple looks was avoided using an alpha spending function.

The implemented strategy to control the type I error is endorsed. Of note, the results presented in the CSR corresponds to the final analysis for OS.

Changes to Planned Analyses

Changes to the statistical analyses planned are shown in Table 13. The AstraZeneca study team was responsible for all changes to the planned statistical analyses. All major changes were made prior to the DBL for the final analysis (DCO: 27 August 2021) (data not shown). Minor changes to the algorithms for counting the number of dose delays for S and for determination of analysis windows for T and D were made after the SAP was finalized.

Table 13. Changes to Planned Analyses

Key Details of Change (Section of Report Affected)	Reason for Change
Two additional efficacy endpoints that were not detailed in the CSP were calculated: time to response and time from randomization to first subsequent therapy or death. Neither endpoint is reported in the CSR	To support the payer analysis
Section 6.5 of the CSP (see Appendix 16.1.1) does not define or provide instructions for determining AEPIs. The latest list of PTs was used to determine both AESIs and AEPIs (Section 9.8.6.2)	For completeness
The following details of the non-inferiority approach were added to the SAP (see Sections 1.3 and 4.2.2.1 of Appendix 16.1.9) to supplement the information provided on the non-inferiority margin in Sections 8.2 and 8.5 of the CSP (see Appendix 16.1.1): • results of the 3 studies used to determine the non-inferiority margin • clarification that the assumed HR for the comparison of D vs S is based on the results in Checkmate 459 for nivolumab vs sorafenib in the same population (Yau et al 2019) • results from 4 other studies that were designed with non-inferiority to a sorafenib control in first-line HCC Section 4.2.2.1 also specifies that for the interim and final analyses of the primary OS and key secondary analyses (including non-inferiority), adjusted alpha levels are derived based on the exact number of OS events using the Lan and DeMets approach that approximates the O'Brien Fleming spending function. Section 4.2.2.1 clarifies that the primary analysis method (log-rank test) will be used to assess non-inferiority and superiority for the OS comparisons of D vs S	Provision of additional details and sources for the chosen statistical analysis methods
The CSP indicated that details of the China cohort and the corresponding analysis plan would be outlined in a China-specific amendment and SAP. As no patients were enrolled in the China cohort, a China-specific SAP was not prepared	No longer required
A test of the 3-year overall survival rate (OS36) between T300+D and S was added to the MTP in SAP Section 4.2.1. The test is described in SAP Section 4.2.3.7. Section 4.2.1 clarifies that only in the case that all OS analyses were statistically significant and non-inferiority was achieved for D vs S, would the 4.9% alpha level be passed to test the difference in the 3-year survival rates (OS36) between T300 +D and S. Section 4.2.3.7 provides the details of the test for OS36; the test would be performed using the stratified method described in (Klein et al 2007), using stratification factors collected at randomization (macrovascular invasion, etiology of liver disease, and ECOG). The adjustment for stratification factors would be applied only if there are sufficient number of events and number of subjects at risk available in each stratum at 36 months, otherwise unstratified methods from (Klein et al 2007) would be used.	To further assess efficacy between T300+D and S

AEPI, adverse event of possible interest; AESI, adverse event of special interest; CSP, clinical study protocol; CSR, clinical study report; D, durvalumab monotherapy 1500 mg Q4W; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival; OS36, OS at 36 months; PT, preferred term; S, sorafenib 400 mg twice daily; SAP, statistical analysis plan; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

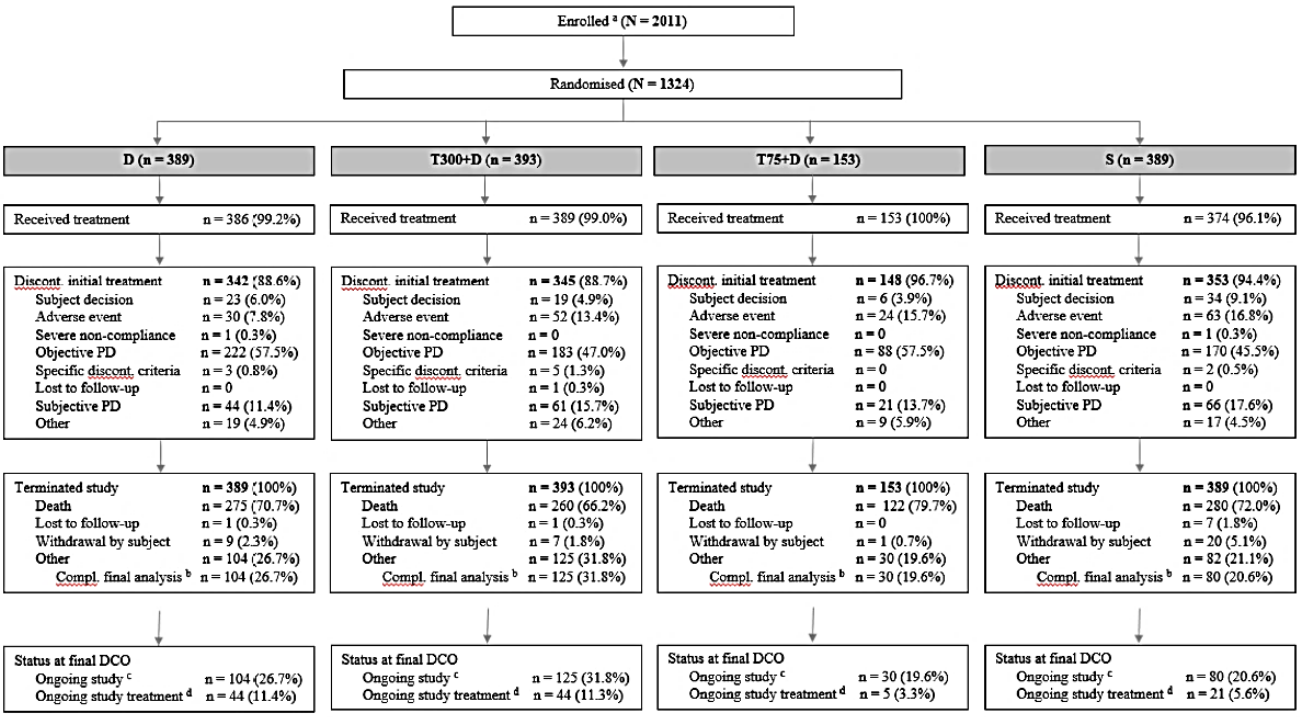
Key details of amendment (section of this report affected)	Reason for amendment
No major updates	Released to correct administrative errors noted in CSP version 4.0
Protocol amendment 5, Protocol version 6.0 (20 August 2019)	
Statistical analysis methods revised to change dual primary objectives to hierarchical approach with a single primary objective (T300+D vs S for superiority) and 2 key secondary objectives (D vs S for non-inferiority, then D vs S for superiority) of OS (Section 9.8): • The multiple testing strategy was updated to reflect the procedure for controlling the type 1 error given the update from dual primary objectives to a hierarchical approach with a single primary objective and 2 key secondary objectives of OS • ORR and PRO endpoints were removed from the MTP • The number of events, maturity, power and 2-sided significance levels for these analyses were updated	An IA of the ongoing Study 22 suggested that the best clinical benefit (in terms of ORR and OS) was observed in patients who received the T300+D combination when compared to durvalumab monotherapy, tremelimumab monotherapy, or T75+D. As a result, the primary analysis for the current study was revised
Efficacy assessments in IA1, ie, RECIST 1.1 and mRECIST analyses (ORR, BOR, DoR) by BICR for the IA1 set of patients with an opportunity for 32 weeks of follow-up were added as a secondary objective. It was also clarified that enrollment had to be completed before IA1 could be performed (Section 8)	To clarify analyses in IA1
The order of hypotheses for superiority was changed: H1: T300+D vs S and H3: D vs S. A new hypothesis was added - H2: for non-inferiority D vs S (Section 9.8)	To align with revised objectives

There are 4 versions of the SAP: SAP edition 1 (25 Oct 2017), SAP edition 2 (23 Aug 2019), SAP edition 3 (15 May 2020), and SAP edition 4 (30 July 2021). Several amendments were done to the study protocol throughout the study and the SAP was therefore updated. Major changes to the study design were made in Protocol version 5 (20 Aug 2019) where the objectives of the study, primary endpoints and the testing hierarchy were modified.

Results

Participant flow

Figure 14. Patient Disposition



[a] Informed consent received. The reported value of 2011 includes 61 rescreened subjects who each received a new subject ID code during the rescreening phase per protocol. The actual number of subjects enrolled was 1950.

[b] Patients confirmed alive in follow-up or on active study treatment at the time of final analysis reported 'study completion' on the disposition eCRF.

[c] Patients ongoing in study are the same as patients who completed the final analysis.

[d] Percentages are calculated from the number of patients who received treatment in the Global Study. For combination therapy patients durvalumab reason is reported.

Compl., completed; D, durvalumab monotherapy 1500 mg Q4W; DCO, data cutoff; Discont., discontinued or discontinuation; PD, disease progression; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W

Source: Table 14.1.1

Table 14. Subject Disposition (All subjects, DCO 27 Aug 2021)

	Number (%) of subjects				
	Durva 1500 mg	Treme 300 mg x1 dose + Durva 1500 mg	Treme 75 mg x4 doses + Durva 1500 mg	Sora 400 mg BID	Total
Subjects enrolled[a]					2011
Subjects randomized	389	393	153	389	1324
Subjects who were not randomized[b]					687
Eligibility criteria not fulfilled					654 (95.2)
Other					33 (4.8)
Subjects who received treatment	386 (99.2)	389 (99.0)	153 (100)	374 (96.1)	1302 (98.3)
Subjects who did not receive treatment	3 (0.8)	4 (1.0)	0	15 (3.9)	22 (1.7)
Subjects ongoing study treatment at data cut-off[c]	44 (11.4)	44 (11.3)	5 (3.3)	21 (5.6)	114 (8.8)
Subjects who discontinued initial study treatment[cd]	342 (88.6)	345 (88.7)	148 (96.7)	353 (94.4)	1188 (91.2)
Subject decision	23 (6.0)	19 (4.9)	6 (3.9)	34 (9.1)	82 (6.3)
Adverse event	30 (7.8)	52 (13.4)	24 (15.7)	63 (16.8)	169 (13.0)
Severe non-compliance to protocol	1 (0.3)	0	0	1 (0.3)	2 (0.2)
Objective disease progression	222 (57.5)	183 (47.0)	88 (57.5)	170 (45.5)	663 (50.9)
Development of study specific discontinuation criteria	3 (0.8)	5 (1.3)	0	2 (0.5)	10 (0.8)
Subject lost to follow-up	0	1 (0.3)	0	0	1 (0.1)
Subjective disease progression	44 (11.4)	61 (15.7)	21 (13.7)	66 (17.6)	192 (14.7)
Other	19 (4.9)	24 (6.2)	9 (5.9)	17 (4.5)	69 (5.3)
Subjects ongoing study[ef]	0	0	0	0	0
Subjects who terminated study[e]	389 (100)	393 (100)	153 (100)	389 (100)	1324 (100)
Death	275 (70.7)	260 (66.2)	122 (79.7)	280 (72.0)	937 (70.8)
Lost to follow-up	1 (0.3)	1 (0.3)	0	7 (1.8)	9 (0.7)
Screen failure	0	0	0	0	0
Withdrawal by subject	9 (2.3)	7 (1.8)	1 (0.7)	20 (5.1)	37 (2.8)
Other	104 (26.7)	125 (31.8)	30 (19.6)	82 (21.1)	341 (25.8)
Completed final analysis[f]	104 (26.7)	125 (31.8)	30 (19.6)	80 (20.6)	339 (25.6)

[a] Informed consent received.
[b] Percentages are calculated from the number of not randomized subjects.
[c] Percentages are calculated from the number of subjects who received treatment in the Global Study. For combination therapy subjects durvalumab reason is reported.
[d] Initial study treatment refers to originally assigned treatment and does not include rechallenge with tremelimumab.
[e] Percentages are calculated from the number of subjects randomized into the Global Study.
[f] Subjects confirmed alive in follow-up or on active study treatment at the time of final analysis reported 'study completion' on the disposition CRF.
Subjects are summarized using the planned treatment arm in this table.
The reported value of 2011 includes 61 rescreened subjects who each received a new subject ID code during the rescreening phase per protocol. The actual number of subjects enrolled was 1950.

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No study sites were terminated or paused due to the COVID-19 pandemic. Patient enrollment was completed prior to the start of the pandemic. A total of 107 patients were impacted by visit, procedure, or treatment delays due to the pandemic, resulting in 281 protocol deviations (Table 15).

Table 15. Important Protocol Deviations (FAS)

Important protocol deviations [a]	N (%) of patients				
	D (N = 389)	T300+D (N = 393)	T75+D (N = 153)	S (N = 389)	Total (N = 1324)
Number of subjects with at least 1 important deviation	3 (0.8)	9 (2.3)	3 (2.0)	21 (5.4)	36 (2.7)
Active or prior documented autoimmune or inflammatory disorders [b]	0	0	0	1 (0.3)	1 (0.1)
Additional investigational systemic anticancer therapy concurrent with those under investigation in this study (as specified in CSP Section 7.7)	0	1 (0.3)	0	0	1 (0.1)
Baseline tumor assessments (RECIST1.1) performed more than 28 days before the first dose of study treatment	0	0	0	2 (0.5)	2 (0.2)
Child-Pugh score was not class A	0	1 (0.3)	1 (0.7)	3 (0.8)	5 (0.4)
Concurrent chemotherapy, radiotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment other than those under investigation in this study while the patient is on study treatment(s)	0	1 (0.3)	1 (0.7)	0	2 (0.2)
Patient randomized but did not receive study treatment	3 (0.8)	4 (1.0)	0	15 (3.9)	22 (1.7)
Patient received / used incorrect medication (ie, expired medication, incorrect kit ID, incorrect dose, alternative study treatment to what which they were randomized)	0	2 (0.5)	0	0	2 (0.2)
Patients co-infected with HBV and HCV, or co-infected with HBV and hepatitis D virus (HDV). [c]	0	1 (0.3)	0	0	1 (0.1)
Patients with main portal vein tumor thrombosis (Vp4)	0	1 (0.3)	1 (0.7)	0	2 (0.2)

[a] The same patient may have had more than 1 important protocol deviation.

[b] Includes inflammatory bowel disease (eg, colitis or Crohn's disease), diverticulitis (with the exception of diverticulosis), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.). Active disease (outside of the allowed exceptions) in the last 5 years that has not been discussed with the Study Physician and considered appropriate for study participation

[c] HBV positive (presence of HbsAg and/or anti-HbcAb with detectable HBV DNA); HCV positive (presence of anti-HCV antibodies); HDV positive (presence of anti-HDV antibodies)

Table 16. Not randomized patients with "other" reason for screening failure

Reason for screening failure	Number of patients
Because it was possible that selection criterion 12 would not be satisfied.	1
Eligibility was not able to be verified within 28 days so patient was reconsented with a new screening id: [redacted]	1
Exceeded screening time (new screening number [redacted])	1
Incorrect activation of the patient	1
Issue due to sorafenib shipment	1
Not recorded	7
Patient died due to progression disease, before randomization.	1
Patient doesn't meet inclusion criteria 3, as patient withdrew informed consent	1
Patient was withdrawal	1
Screen fail due to insurance reasons	1
Screen failure	2
Screening assessment could not be completed during screening date	1
Screening assessments were not completed during screening.	2
Screening period was greater than 28 days because some examinations was missing	1
Sf due to death	1
Subject does not come to site	1
Subject fell out of screening window.	1
Subject was unable to provide tumor sample	1
Subject withdrawn in the middle of screening	1
Time for screening was exceeded.	1
Screening assessments were not completed during screening.	1
Unable to be randomized within 28 days of icf	1
Unable to submit tumor sample	1
Withdrawal during screening	2

Of 1950 patients enrolled in the pivotal study, 61 were rescreened and 1324 were randomized to 1 of the 4 original treatment arms. The Applicant has clarified that of the 687 non-randomized patients, 654 did not fulfil eligibility criteria and 33 were not randomized due to other reasons. The screen failure reasons of these 33 patients as collected as free text field in CRF are summarized in Table 16: 10/33 patients were not randomized due to inability to complete screening procedures within the 28-day window, 6/33 withdrew informed consent or failed to return to clinic, 2/33 were unable to provide the required tumor tissue sample, and 2/33 died prior to randomization. In addition, 9/33 did not report more specific screen failure reasons. Other reasons were reported in 1 patient each and included insurance coverage issues, incorrect screening, inability to verify eligibility, or local issues with sorafenib supply. The clarification is accepted, and the screen failure reasons are in line with what could be expected for a clinical trial with the targeted patient population.

Recruitment

The first patient was enrolled on 11 October 2017 and the last patient on 19 June 2019. The median follow-up for OS at DCO (27 August 2021) was ~33 months in the T300+D arm and ~32 months in the S arm.

Conduct of the study

Table 17. Protocol Amendments and Other Significant Changes to Study Conduct

Key details of amendment (section of this report affected)	Reason for amendment
Protocol amendment 1, Protocol version 2.0 (20 December 2017)	
Updated descriptions of risks for durvalumab, tremelimumab, and the combination of durvalumab with tremelimumab (Section 12.2.4). Toxicity Management Guidelines replaced with new version from 01 November 2017.	To align with updates across the clinical program and Investigator's Brochure
Inclusion of the exploratory objective: to assess PFS from rechallenge in the durvalumab plus tremelimumab combination arms only, and to assess PFS from first post-IP discontinuation therapy in all arms	Additional exploratory objective of interest
Section 9.3 • IC10 amended to clarify treatment of patients with HBV infection with antiviral therapy to ensure adequate viral suppression prior to enrollment, and to further clarify that patients who test positive for HBc with undetectable HBV DNA (< 10 IU/ml) do not require antiviral therapy prior to enrollment. These patients were to be tested at every cycle to monitor HBV DNA levels and initiate antiviral therapy if HBV DNA was detected (≥ 10 IU/ml). HBV DNA detectable patients were to initiate and remain on antiviral therapy for the study duration and for 6 months after the last dose of IP • New IC15 requiring patients to have a life expectancy of at least 12 weeks • EC12 amended to specify "clinically meaningful ascites (defined as ascites requiring non-pharmacologic intervention eg, paracentesis or escalation in pharmacologic intervention to maintain symptomatic control), within 6 months prior to the first scheduled dose", rather than "ascites that require ongoing paracentesis, within 6 weeks prior to the first scheduled dose to control symptoms." The amended EC12 also indicates patients on stable doses of diuretics for ascites for ≥ 2 months are eligible • EC22 qualified to indicate that a history of, or current, brain metastases was an exclusion	• IC10: to ensure patients receive antiviral medication as clinically indicated • IC15: for compliance with new CSP template • EC12: to clarify protocol definition of clinically meaningful ascites • EC22: to ensure patient safety
Updated AESI terminology (Section 12.2.4)	To align with updates across the clinical program
Protocol amendment 2, Protocol version 3.0 (23 January 2018)	
No major updates	Released to correct errors noted in CSP version 2.0
Protocol amendment 3, Protocol version 4.0 (29 November 2018)	

Key details of amendment (section of this report affected)	Reason for amendment
Enrollment into the T75+D arm was closed, based on results from a pre-planned IA evaluating tolerability and clinical activity in Study D419CC00022. All other arms were unchanged (Section 9.1)	In the ongoing Study 22, safety data showed that the T75+D regimen was tolerable with no new safety signals. However, efficacy data for the T75+D regimen did not differentiate it from the durvalumab monotherapy arm. Thus, there was insufficient clinical activity observed to warrant continuing enrollment in the T75+D arm in the current study
Following closure of enrollment in the T75+D arm, the primary and secondary objectives were re-aligned: The original primary objective of OS for T75+D vs S was replaced with D vs S and T300+D vs S for OS. Other supportive endpoints were clarified for consistency across the CSP, and a new endpoint (DCR-16w) was added (Section 8)	To align with study design changes
The multiple testing strategy was updated to reflect the procedure for controlling the type 1 error as a result of the changes to the primary and secondary objectives. PRO endpoints were added to the MTP (Section 9.8.3)	To align with study design changes
Update such that IA1 was performed after approximately 100 patients per treatment arm had the opportunity for 32 rather than 24 weeks of follow-up (Section 9.8.9)	To ensure 24 weeks of imaging follow-up, the baseline scan needs to be 8 weeks prior to the first follow-up scan, ie, a total of 32 weeks
The sample size was updated to align with closure of enrollment in the T75+D arm. The number of events, maturity, power and 2-sided significance levels for these analyses were updated accordingly and the MTP was updated to reflect the revised procedure for controlling the type 1 error. No changes were made to the assumed HRs, timelines, or median OS. The statistical methods were revised to indicate the T75+D arm would be summarized descriptively, but not formally analyzed (Section 9.8.1)	To align with study design changes
Patients in the T75+D arm could continue to receive their assigned treatment according to the CSP (Section 9.4)	To align with study design changes
Patients in the T75+D arm who were eligible for rechallenge could be rechallenged with either 75 mg tremelimumab × 4 doses or 300 mg tremelimumab × 1 dose in combination with durvalumab 1500 mg (with prior approval from the AstraZeneca clinical team) (Section 9.4.1.5)	To align with study design changes
EC19 amended to include "inferior vena cava thrombosis" (Section9.3.2)	Patients with inferior vena cava thrombosis were excluded due to the risk of pulmonary embolism and sudden death
Protocol amendment 4, Protocol version 5.0 (17 December 2018)	

No major updates	Released to correct administrative errors noted in CSP version 4.0
Protocol amendment 5, Protocol version 6.0 (20 August 2019)	
Statistical analysis methods revised to change dual primary objectives to hierarchical approach with a single primary objective (T300+D vs S for superiority) and 2 key secondary objectives (D vs S for non-inferiority, then D vs S for superiority) of OS (Section 9.8): • The multiple testing strategy was updated to reflect the procedure for controlling the type 1 error given the update from dual primary objectives to a hierarchical approach with a single primary objective and 2 key secondary objectives of OS • ORR and PRO endpoints were removed from the MTP • The number of events, maturity, power and 2-sided significance levels for these analyses were updated	An IA of the ongoing Study 22 suggested that the best clinical benefit (in terms of ORR and OS) was observed in patients who received the T300+D combination when compared to durvalumab monotherapy, tremelimumab monotherapy, or T75+D. As a result, the primary analysis for the current study was revised
Efficacy assessments in IA1, ie, RECIST 1.1 and mRECIST analyses (ORR, BOR, DoR) by BICR for the IA1 set of patients with an opportunity for 32 weeks of follow-up were added as a secondary objective. It was also clarified that enrollment had to be completed before IA1 could be performed (Section 8)	To clarify analyses in IA1
The order of hypotheses for superiority was changed: H1: T300+D vs S and H3: D vs S. A new hypothesis was added - H2: for non-inferiority D vs S (Section 9.8)	To align with revised objectives
The assessment of efficacy for the comparison of D vs T300+D in the overall population and in the population defined by PD-L1 expression was changed from a secondary to an exploratory objective (Section 8)	Archival tissue up to 3 years of age was allowed for the HIMALAYA study. Data suggest that sample age may affect PD-L1 expression status (eg, PD-L1 expression measured in an older sample might be lower than PD-L1 expression at the current time for a patient). Therefore, it was decided to change the assessment of efficacy by PD-L1 expression to an exploratory objective
An exploratory objective relating to patients with early mortality risk was added (Section 8)	This was an exploratory objective of interest
Protocol amendment 6, Protocol version 7.0 (22 September 2021)	

Key details of amendment (section of this report affected)	Reason for amendment
The OS at 36 months (OS36) was added to the secondary objectives (proportion of patients alive at 36 months after randomization [OS36]). The OS36 was defined as the KM estimate of OS at 36 months after randomization (Section 9.8.4.1). Clarified that patients in all treatment arms, not just durvalumab, may continue to receive treatment following the final primary analysis DCO. Added that long-term follow-up data may be collected in eCRFs post final primary analysis for approximately 3 years and defined end of study, if long-term follow-up is collected post final primary analysis, as the last visit of the last patient in the study.	To further assess efficacy

AESI, adverse event of special interest; BICR, blinded independent central review; BOR, best overall response; CSP, Clinical Study Protocol; D, durvalumab monotherapy 1500 mg Q4W; DCO, data cut-off; DCR-16w, disease control rate at 16 weeks; DNA, deoxyribonucleic acid; DoR, duration of response; EC, exclusion criterion; HBc, hepatitis B core; HBV, hepatitis B virus; HR, hazard ratio; IA1, interim analysis 1; IC, inclusion criterion; IP, investigational product; KM, Kaplan-Meier; mRECIST, modified Response Evaluation Criteria in Solid Tumors; MTP, multiple testing procedure; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PRO, patient-reported outcome; Q4W, every 4 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; S, sorafenib 400 mg twice daily; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Table 18. Summary of Overall Survival: T300+D Versus Sorafenib and D Versus Sorafenib (PD-L1 Analysis Set)

Subgroup	Treatment	Number of Patients	Events (%)	Median (months) (95% CI)	Hazard Ratio (95% CI)
PD-L1 Evaluable patients[a]	T300+D	337	229 (68.0)	16.00 (13.11, 19.58)	0.84 (0.70, 1.00)
	D	344	248 (72.1)	16.46 (13.83, 19.12)	0.90 (0.76, 1.08)
	Sorafenib	329	248 (75.4)	14.55 (12.75, 16.85)	
TIP <1%[b]	T300+D	189	128 (67.7)	14.26 (11.43, 21.29)	0.83 (0.65, 1.05)
	D	190	141 (74.2)	15.06 (12.68, 18.53)	0.93 (0.73, 1.17)
	Sorafenib	181	138 (76.2)	13.93 (12.39, 16.69)	
TIP ≥1%[b]	T300+D	148	101 (68.2)	17.35 (13.50, 23.03)	0.85 (0.65, 1.11)
	D	154	107 (69.5)	17.22 (12.29, 24.38)	0.87 (0.66, 1.13)
	Sorafenib	148	110 (74.3)	15.93 (10.68, 21.72)	-

The analysis was performed using stratified log-rank test adjusting for treatment, aetiology of liver disease (HBV versus HCV versus others), ECOG PS (0 versus 1), and macro-vascular invasion (yes versus no). The values of the stratification factors were obtained from the interactive web response system.
Unstratified analyses.

CI = confidence interval; D = durvalumab 1500 mg Q4W; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; HCV = hepatitis C virus; PD-L1 = programmed cell death ligand 1; PS = performance status; QxW = every X weeks; T300+D = tremelimumab 300 mg for a single dose and durvalumab 1500 mg Q4W; TIP = Tumour and Immune Cell Positivity. Source:CSR table 14.2.1.3

Baseline data

Table 19. Demographic and Baseline Patient Characteristics in HIMALAYA (Pivotal Study) and Study 22 (Supportive Study)

Study Analysis set (DCO)	HIMALAYA FAS (Final Analysis)			Study 22 (Parts 2 and 3) FAS (Final Analysis)	
	D (N = 389)	T300+D (N = 393)	S (N = 389)	D (N = 104)	T300+D (N = 75)
Age (years)					
Mean	62.6	63.0	63.5	64.0	64.4
SD	11.47	11.65	11.12	10.81	11.24
Median	64.0	65.0	64.0	64.5	66.0
Min	20	22	18	32	26
Max	86	86	88	89	86
Age group (years), n (%)					
< 65	203 (52.2)	195 (49.6)	195 (50.1)	52 (50.0)	34 (45.3)
≥ 65 – < 75	130 (33.4)	145 (36.9)	137 (35.2)	33 (31.7)	31 (41.3)
≥ 75	56 (14.4)	53 (13.5)	57 (14.7)	19 (18.3)	10 (13.3)
Sex, n (%)					
Male	323 (83.0)	327 (83.2)	337 (86.6)	92 (88.5)	65 (86.7)
Female	66 (17.0)	66 (16.8)	52 (13.4)	12 (11.5)	10 (13.3)
Region group, n (%)					
Asia (excl. Japan)	167 (42.9)	156 (39.7)	156 (40.1)	47 (45.2)	31 (41.3)
Rest of World (incl. Japan)	222 (57.1)	237 (60.3)	233 (59.9)	57 (54.8)	44 (58.7)
Race, n (%)					
White	160 (41.1)	182 (46.3)	179 (46.0)	35 (33.7)	27 (36.0)
Black or African American	2 (0.5)	7 (1.8)	10 (2.6)	10 (9.6)	4 (5.3)
Asian	212 (54.5)	195 (49.6)	189 (48.6)	55 (52.9)	44 (58.7)
Native Hawaiian or other Pacific Islander	0	1 (0.3)	0	2 (1.9)	0
American Indian or Alaska Native	0	0	0	1 (1.0)	0
Other	15 (3.9)	7 (1.8)	5 (1.3)	1 (1.0)	0
Ethnic group, n (%)					
Hispanic or Latino	13 (3.3)	21 (5.3)	21 (5.4)	5 (4.8)	4 (5.3)
Not Hispanic or Latino	376 (96.7)	372 (94.7)	362 (93.1)	99 (95.2)	71 (94.7)
Weight group (kg), n (%)					
< 70	218 (56.0)	190 (48.3)	202 (51.9)	47 (45.2)	49 (65.3)
≥ 70 – < 90	130 (33.4)	158 (40.2)	137 (35.2)	41 (39.4)	20 (26.7)
≥ 90	41 (10.5)	45 (11.5)	50 (12.9)	15 (14.4)	5 (6.7)

Table 19. Demographic and Baseline Patient Characteristics in HIMALAYA (Pivotal Study) and Study 22 (Supportive Study)

Study Analysis set (DCO)	HIMALAYA FAS (Final Analysis)			Study 22 (Parts 2 and 3) FAS (Final Analysis)	
	D (N = 389)	T300+D (N = 393)	S (N = 389)	D (N = 104)	T300+D (N = 75)
BMI group (kg/m^2), n (%)					
Underweight (< 18.5)	15 (3.9)	19 (4.8)	17 (4.4)	7 (6.7)	4 (5.3)
Normal (≥ 18.5 – < 25.0)	210 (54.0)	188 (47.8)	195 (50.1)	47 (45.2)	47 (62.7)
Overweight (≥ 25.0 – < 30.0)	114 (29.3)	128 (32.6)	125 (32.1)	32 (30.8)	17 (22.7)
Obese (≥ 30.0)	47 (12.1)	56 (14.2)	48 (12.3)	17 (16.3)	6 (8.0)
Alcohol use, n (%) [a]					
Never	150 (38.6)	162 (41.2)	147 (37.8)	NA	NA
Current	62 (15.9)	54 (13.7)	60 (15.4)	NA	NA
Former	176 (45.2)	176 (44.8)	182 (46.8)	NA	NA
Missing	1 (0.3)	1 (0.3)	0	NA	NA

[a] Alcohol use was not captured in the Study 22 eCRF.

Baseline is the last assessment prior to the intake of the first dose of any study drug; for patients not treated, the last assessment on or prior to treatment allocation (Study 22 Part 2B) or randomization (HIMALAYA and Study 22 Parts 2A and 3) was used.

Abbreviations: BMI = body mass index; DCO = data cut-off; eCRF = electronic case report form; Excl. = excluding; FAS = full analysis set; Max = maximum; Min = minimum; N = total number of patients; n = number of patients in a treatment arm; NA = not applicable; SD = standard deviation.

Table 20. Disease Characteristics at Screening in HIMALAYA (Pivotal Study) and Study 22 (Supportive Study)

Study Analysis set (DCO)	HIMALAYA FAS (Final Analysis)			Study 22 (Parts 2 and 3) FAS (Final Analysis)	
	D (N = 389)	T300+D (N = 393)	S (N = 389)	D (N = 104)	T300+D (N = 75)
ECOG performance status, n (%)					
0	244 (62.7)	246 (62.6)	239 (61.4)	52 (50.0)	46 (61.3)
1	145 (37.3)	147 (37.4)	148 (38.0)	52 (50.0)	29 (38.7)
BCLC stage, n (%) [a]					
Early (A)	NA	NA	NA	1 (1.0)	1 (1.3)
Intermediate (B)	80 (20.6)	77 (19.6)	66 (17.0)	9 (8.7)	13 (17.3)
Advanced (C)	309 (79.4)	316 (80.4)	323 (83.0)	80 (76.9)	58 (77.3)
Etiology of liver disease, n (%)					
HBV-positive	119 (30.6)	122 (31.0)	119 (30.6)	40 (38.5)	27 (36.0)
HCV-positive	107 (27.5)	110 (28.0)	104 (26.7)	29 (27.9)	21 (28.0)
Others	163 (41.9)	161 (41.0)	166 (42.7)	35 (33.7)	27 (36.0)
MVI and/or EHS, n (%)					
MVI = Yes and/or EHS = Yes [b]	255 (65.6)	263 (66.9)	251 (64.5)	72 (69.2)	58 (77.3)

Table 20. Disease Characteristics at Screening in HIMALAYA (Pivotal Study) and Study 22 (Supportive Study)

Study Analysis set (DCO)	HIMALAYA FAS (Final Analysis)			Study 22 (Parts 2 and 3) FAS (Final Analysis)	
	D (N = 389)	T300+D (N = 393)	S (N = 389)	D (N = 104)	T300+D (N = 75)
MVI = No and EHS=No	133 (34.2)	128 (32.6)	137 (35.2)	12 (11.5)	13 (17.3)
Child-Pugh score, n (%)					
A/5	284 (73.0)	295 (75.1)	277 (71.2)	79 (76.0)	51 (68.0)
A/6	96 (24.7)	92 (23.4)	102 (26.2)	23 (22.1)	23 (30.7)
B/7	1 (0.3)	2 (0.5)	10 (2.6)	2 (1.9)	1 (1.3)
Alpha-fetoprotein, n (%)					
< 400 ng/ml	247 (63.5)	243 (61.8)	256 (65.8)	62 (59.6)	39 (52.0)
≥ 400 ng/ml	137 (35.2)	145 (36.9)	124 (31.9)	39 (37.5)	35 (46.7)
Missing	5 (1.3)	5 (1.3)	9 (2.3)	3 (2.9)	1 (1.3)
ALBI score					
1	198 (50.9)	217 (55.2)	203 (52.2)	NA	NA
2	189 (48.6)	174 (44.3)	185 (47.6)	NA	NA
3	2 (0.5)	1 (0.3)	1 (0.3)	NA	NA
Missing	0	1 (0.3)	0	NA	NA
PD-L1 expression level, n (%) [c]					
Positive (TIP ≥ 1%)	154 (39.6)	148 (37.7)	148 (38.0)	55 (52.9)	27 (36.0)
Negative (TIP < 1%)	190 (48.8)	189 (48.1)	181 (46.5)	35 (33.7)	38 (50.7)
Missing	42 (10.8)	52 (13.2)	45 (11.6)	14 (13.5)	10 (13.3)
Prior treatment with sorafenib/VEGFR TKI, n (%) [d]					
Yes	NA	NA	NA	66 (63.5)	55 (73.3)
No	NA	NA	NA	38 (36.5)	20 (26.7)

[a] In HIMALAYA, patients were enrolled only if they had BCLC Stage B (not eligible for locoregional therapy) or Stage C. In Study 22, BCLC Stage was not specified in the inclusion criteria and collection of BCLC scores was not mandated at screening until protocol amendment 3 (20 July 2017); as a result, baseline BCLC scores were missing for some patients in Part 2A (see Section 9.2.2, Study 22 CSR, Module 5.3.5.2).

[b] Includes all patients with "MVI = Yes and EHS = No/Missing," "MVI = No/Missing and EHS = Yes," and "MVI = Yes and EHS = Yes."

[c] PD-L1 expression level was defined as "Positive" if PD-L1 staining of any intensity in tumor cell membranes and/or tumor-associated immune cells covered ≥ 1% of tumor area (TIP ≥ 1%), and "Negative" if PD-L1 staining of any intensity in tumor cell membranes and/or tumor-associated immune cells covered < 1% of tumor area (TIP < 1%).

[d] Per inclusion criteria, no patients in HIMALAYA received prior systemic therapy for HCC (first-line setting only). In Study 22, patients were required to be immunotherapy-naïve and had either progressed on, were intolerant to, or have refused treatment with sorafenib or another approved VEGFR TKI (first-line and second-line settings).

Abbreviations: BCLC = Barcelona Clinic Liver Cancer; eCRF = electronic case report form; DCO = data cut-off; ECOG = Eastern Cooperative Oncology Group; EHS = extrahepatic spread; FAS = full analysis set; HBV = hepatitis B virus; HCV = hepatitis C virus; MVI = macrovascular invasion; N = total number of patients; n = number of patients in a treatment arm; NA, not applicable; PD-L1 = programmed cell death ligand-1; TIP = tumor immune percentage; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.

Prior cancer therapy

Per inclusion criteria, no patients in HIMALAYA received prior systemic therapy for HCC (first-line setting only). Overall, the most common disease-related medical procedures prior to study entry, including ablative therapy, therapeutic embolization, regional chemotherapy, and HCC-related surgery, were similar across treatment arms and consistent with that typically seen in the target patient population.

In study 22, the prior anticancer treatment modalities reported were prior treatment with sorafenib/VEGFR TKI (55/75 patients, 73.3%). Most patients had undergone prior TACE or RFA Per protocol, all patients were immunotherapy-naïve.

Post-IP Discontinuation Anticancer Systemic Therapy

Table 21. Post- Discontinuation Anticancer Systemic Therapy

	Number (%) of patients				
Anticancer therapy [a]	D (N = 389)	T300+D (N = 393)	T75+D (N = 153)	S (N = 389)	Total (N = 1324)
Total number of subjects	168 (43.2)	160 (40.7)	67 (43.8)	175 (45.0)	570 (43.1)
Immunotherapy	20 (5.1)	15 (3.8)	5 (3.3)	89 (22.9)	129 (9.7)
Atezolizumab	11 (2.8)	6 (1.5)	1 (0.7)	14 (3.6)	32 (2.4)
Avelumab	0	0	0	1 (0.3)	1 (0.1)
Cancer Vaccines	0	0	0	1 (0.3)	1 (0.1)
Durvalumab	0	0	0	2 (0.5)	2 (0.2)
Immunotherapy	0	0	0	4 (1.0)	4 (0.3)
Investigational Immunotherapy	1 (0.3)	0	0	0	1 (0.1)
Ipilimumab	2 (0.5)	0	0	2 (0.5)	4 (0.3)
Mgd 013	0	2 (0.5)	0	2 (0.5)	4 (0.3)
Monoclonal Antibodies	3 (0.8)	2 (0.5)	1 (0.7)	7 (1.8)	13 (1.0)
Nivolumab	5 (1.3)	5 (1.3)	3 (2.0)	47 (12.1)	60 (4.5)
Pembrolizumab	1 (0.3)	0	0	17 (4.4)	18 (1.4)
Spartalizumab	0	0	0	1 (0.3)	1 (0.1)
Tremelimumab	0	0	0	2 (0.5)	2 (0.2)
Cytotoxic chemotherapy	18 (4.6)	20 (5.1)	7 (4.6)	25 (6.4)	70 (5.3)
Capecitabine	5 (1.3)	3 (0.8)	1 (0.7)	4 (1.0)	13 (1.0)
Capecitabine;oxaliplatin	1 (0.3)	0	0	0	1 (0.1)
Carboplatin	0	0	0	1 (0.3)	1 (0.1)
Carboplatin;etoposide	0	1 (0.3)	0	0	1 (0.1)
Cisplatin[b]	9 (2.3)	6 (1.5)	5 (3.3)	5 (1.3)	25 (1.9)
Cisplatin;doxorubicin	0	2 (0.5)	0	0	2 (0.2)
Cisplatin;fluorouracil	0	1 (0.3)	0	2 (0.5)	3 (0.2)
Cyclophosphamide	1 (0.3)	0	0	1 (0.3)	2 (0.2)
Doxorubicin	0	4 (1.0)	1 (0.7)	7 (1.8)	12 (0.9)
Fluorouracil	5 (1.3)	5 (1.3)	3 (2.0)	7 (1.8)	20 (1.5)
Folfox	0	4 (1.0)	0	2 (0.5)	6 (0.5)
Gemcitabine	3 (0.8)	1 (0.3)	0	2 (0.5)	6 (0.5)
Gemcitabine;oxaliplatin	0	0	0	1 (0.3)	1 (0.1)

Anticancer therapy [a]	Number (%) of patients				
	D (N = 389)	T300+D (N = 393)	T75+D (N = 153)	S (N = 389)	Total (N = 1324)
Irinotecan	1 (0.3)	0	0	1 (0.3)	2 (0.2)
Oxaliplatin[b]	7 (1.8)	2 (0.5)	1 (0.7)	8 (2.1)	18 (1.4)
Tegafur	0	0	0	1 (0.3)	1 (0.1)
Uracil	0	0	0	1 (0.3)	1 (0.1)
Vinorelbine	0	1 (0.3)	0	0	1 (0.1)
Targeted therapy	155 (39.8)	147 (37.4)	64 (41.8)	108 (27.8)	474 (35.8)
Cabozantinib	20 (5.1)	24 (6.1)	6 (3.9)	26 (6.7)	76 (5.7)
Capmatinib	0	0	0	1 (0.3)	1 (0.1)
H3b 6527	0	1 (0.3)	0	0	1 (0.1)
Lenvatinib	68 (17.5)	55 (14.0)	23 (15.0)	32 (8.2)	178 (13.4)
Olaparib	1 (0.3)	0	0	0	1 (0.1)
Pegargiminase	1 (0.3)	1 (0.3)	0	1 (0.3)	3 (0.2)
Regorafenib	26 (6.7)	29 (7.4)	17 (11.1)	62 (15.9)	134 (10.1)
Sorafenib	98 (25.2)	105 (26.7)	51 (33.3)	12 (3.1)	266 (20.1)
Tyrosine Kinase Inhibitors	0	2 (0.5)	0	0	2 (0.2)
Antiangiogenic therapy	20 (5.1)	11 (2.8)	9 (5.9)	19 (4.9)	59 (4.5)
Bevacizumab	12 (3.1)	6 (1.5)	1 (0.7)	16 (4.1)	35 (2.6)
Ramucirumab	8 (2.1)	7 (1.8)	7 (4.6)	3 (0.8)	25 (1.9)
Thalidomide	2 (0.5)	0	1 (0.7)	0	3 (0.2)
Homeopathic therapy	1 (0.3)	0	0	2 (0.5)	3 (0.2)
Herbal anticancer remedies	1 (0.3)	0	0	2 (0.5)	3 (0.2)
Other	1 (0.3)	3 (0.8)	0	9 (2.3)	13 (1.0)
Fenbendazole	0	0	0	1 (0.3)	1 (0.1)
Folinic Acid	1 (0.3)	1 (0.3)	0	3 (0.8)	5 (0.4)
Investigational Antineoplastic Drugs	0	2 (0.5)	0	3 (0.8)	5 (0.4)
Investigational Drug	0	0	0	2 (0.5)	2 (0.2)

[a] Therapies taken following discontinuation of IP.

[b] Includes intra-arterial administrations.

Patients may have received more than 1 post-IP discontinuation therapy.

D, durvalumab monotherapy 1500 mg Q4W; FAS, Full Analysis Set; N, number of patients in treatment group; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Source: Table 14.1.17.

Numbers analysed

Table 22. Analysis sets

	Durva 1500 mg	Treme 300 mg x1 dose + Durva 1500 mg	Treme 75 mg x4 doses + Durva 1500 mg	Sora 400 mg BID	Total
Subjects randomized	389	393	153	389	1324
Subjects included in full analysis set	389	393	153	389	1324
Subjects included in safety analysis set	388	388	152	374	1302
Subjects excluded from safety analysis set	3	4	0	15	22
Did not receive treatment	3	4	0	15	22
Subjects included in Durvalumab PK analysis set	357	348	142		847
Subjects excluded from Durvalumab PK analysis set[a]	34	44	10		88
Did not receive treatment	3	4	0		7
No post-dose data available	31	40	10		81
Subjects included in Tremelimumab PK analysis set		386	142		528
Subjects excluded from Tremelimumab PK analysis set[b]		6	12		18
Did not receive treatment		4	2		6
No post-dose data available		2	10		12

Full analysis set - all randomized subjects analysed on an ITT basis.
Safety analysis set - all subjects who received at least one dose of study treatment.
PK analysis sets - all subjects who received at least 1 dose of study drugs and for whom any postdose data are available.
ADA evaluable sets - all subjects who have non-missing baseline ADA and at least one non-missing post-baseline ADA result.
Results in categories 'Subjects included in safety analysis set', 'Subjects included in PK analysis set' and 'Subjects included in ADA evaluable set' are calculated on basis of actual arm , in other categories on basis of planned arm.
[a] Subjects excluded from the Durvalumab PK analysis are either not part of the safety analysis set or belong to the safety analysis set but are missing a Durvalumab postdose PK assessment.
[b] Subjects excluded from the Tremelimumab PK analysis are either not part of the safety analysis set or belong to the safety analysis set but are missing a Tremelimumab postdose PK assessment.

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Outcomes and estimation

Primary endpoint: Overall survival

Table 23. Overall Survival in HIMALAYA (Pivotal Study)

Study **Analysis set (DCO)**	**HIMALAYA** **FAS (Final Analysis)**		
	D **(N = 389)**	**T300+D** **(N = 393)**	**S** **(N = 389)**
HR (compared to sorafenib) [a]	**0.86**	**0.78**	-
95% CI [a]	0.73 - 1.02	0.66 - 0.92	-
96.02% CI for HR (T300+D vs S) [a, b]	-	0.65 - 0.93	**-**
2-sided p-value (T300+D vs S)	**-**	**0.0035**	-
95.67% CI for HR (D vs S) [a, c]	0.73 - 1.03	-	**-**
2-sided p-value (D vs S) [d]	**0.0674**	-	-
Median OS (months) [e]	**16.56**	**16.43**	**13.77**
95% CI for median OS [e]	**14.06 - 19.12**	**14.16 - 19.58**	**12.25 - 16.13**
OS rate at 12 months, % [e]	59.3	60.2	56.2
OS rate at 18 months, % [e]	47.4	48.7	41.5
OS rate at 24 months, % [e]	39.6	40.5	32.6
OS rate at 36 months, % [e]	24.7	30.7	20.2
Deaths, n (%)	280 (72.0)	262 (66.7)	293 (75.3)
Censored patients, n (%)	109 (28.0)	131 (33.3)	96 (24.7)
Still in survival follow-up at DCO [f]	104 (26.7)	125 (31.8)	79 (20.3)
Terminated prior to death [g]	109 (28.0)	131 (33.3)	96 (24.7)
Lost to follow-up	1 (0.3)	1 (0.3)	7 (1.8)
Withdrawn consent	4 (1.0)	5 (1.3)	10 (2.6)
Median (range) duration of follow-up in censored patients (months) [h]	31.61 (1.91 – 45.70)	32.36 (6.18 – 42.84)	30.36 (0.03 – 43.60)
Median (95% CI) duration of follow-up in all patients (months) [i]	32.56 (31.57 – 33.71)	33.18 (31.74 – 34.53)	32.23 (30.42 – 33.71)

[a] The HR was calculated using a Cox proportional hazards model adjusting for treatment arm, etiology of liver disease (HBV vs HCV vs all others), ECOG (0 vs 1), and MVI (yes vs no). An HR < 1 favors either the T300+D arm or the D arm compared with the S arm in terms of being associated with a longer OS.

[b] T300+D vs S (primary objective in HIMALAYA). Statistical significance for T300+D vs S was based on a 2-sided interim $p < 0.0419$ (overall alpha 4.9%), as defined in the MTP.

[c] D vs S (key secondary objective in HIMALAYA). The non-inferiority margin for D vs S was 1.08, as defined in the MTP.

[d] The analysis was performed using a stratified log-rank test adjusting for treatment arm, etiology of liver disease (HBV vs HCV vs all others), ECOG (0 vs 1), and MVI (yes vs no).

[e] Calculated using the Kaplan-Meier method.

[f] Patients confirmed alive in follow-up or on active study treatment at the time of final analysis reported "study completion" on the disposition CRF.

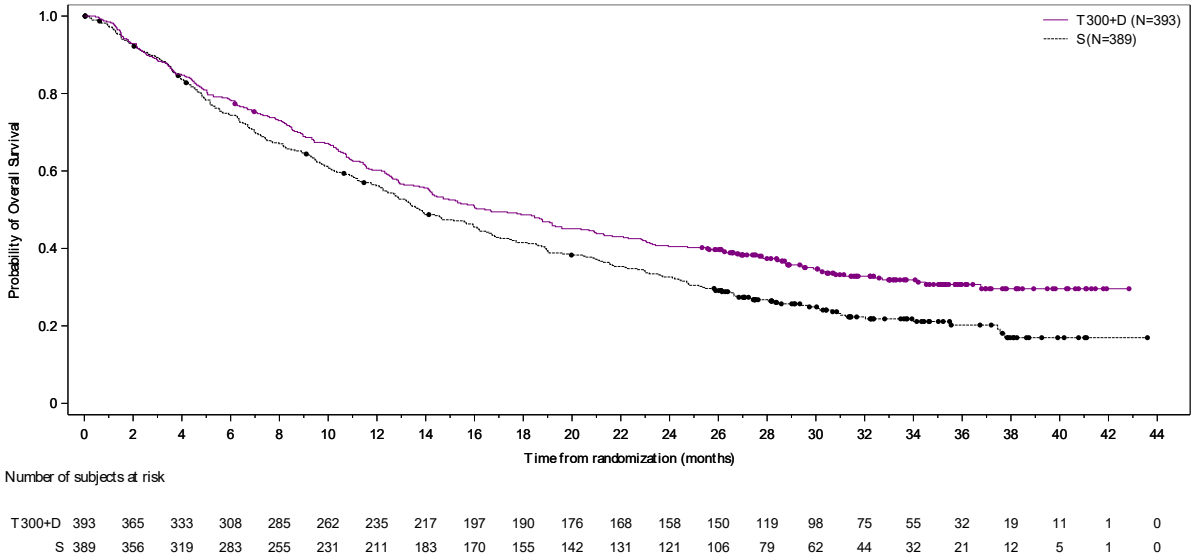
[g] Includes patients with unknown survival status or patients who were lost to follow-up.

[h] Median for duration of follow-up is the arithmetic median.

[i] Calculated using the reverse Kaplan-Meier technique (with censor indicator reversed).

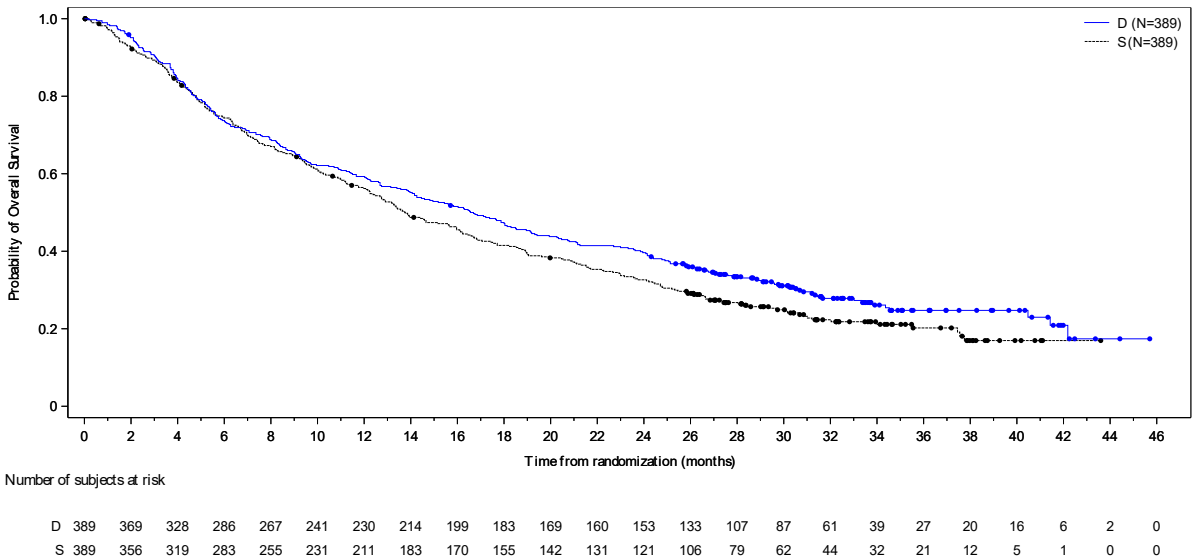
Abbreviations: CI = confidence interval; CRF = case report form; DCO = data cut-off; FAS = full analysis set; HR = hazard ratio; IA = interim analysis; OS = overall survival.

Figure 15. Kaplan-Meier Plot of Overall Survival in the T300+D and S Arms in HIMALAYA, FAS (Final Analysis)



Abbreviations: FAS = Full Analysis Set; Q4W = every 4 weeks; S = sorafenib 400 mg twice daily; T300+D = tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Figure 16. Kaplan-Meier Plot of Overall Survival in the D and S Arms in HIMALAYA, FAS (Final Analysis)



Abbreviations: D = durvalumab monotherapy 1500 mg Q4W; FAS = Full Analysis Set; Q4W = every 4 weeks; S = sorafenib 400 mg twice daily

Secondary endpoints:

Progression-free survival (PFS)

Table 24. Progression-free Survival by Investigator Assessment According to RECIST 1.1 (FAS)

	Number (%) of patients		
	D (N = 389)	**T300+D (N = 393)**	**S (N = 389)**
Hazard ratio (D vs S and T300+D vs S)	1.02	0.90	-
95% CI for hazard ratio	0.88 - 1.19	0.77 - 1.05	-
2-sided p-value	0.7736	0.1625	-
Median PFS (months) [a]	3.65	3.78	4.07
95% CI for median PFS [a]	3.19 - 3.75	3.68 - 5.32	3.75 - 5.49
Total PFS events, n (%) [b]	345 (88.7)	335 (85.2)	327 (84.1)
Median (range) duration of follow-up in all patients (months)	3.61 (0.03 - 44.02)	3.75 (0.03 - 41.46)	3.75 (0.03 - 33.41)
Median (range) duration of follow-up in censored patients (months)	27.63 (0.03 - 44.02)	27.55 (0.03 - 41.46)	1.95 (0.03 - 33.18)

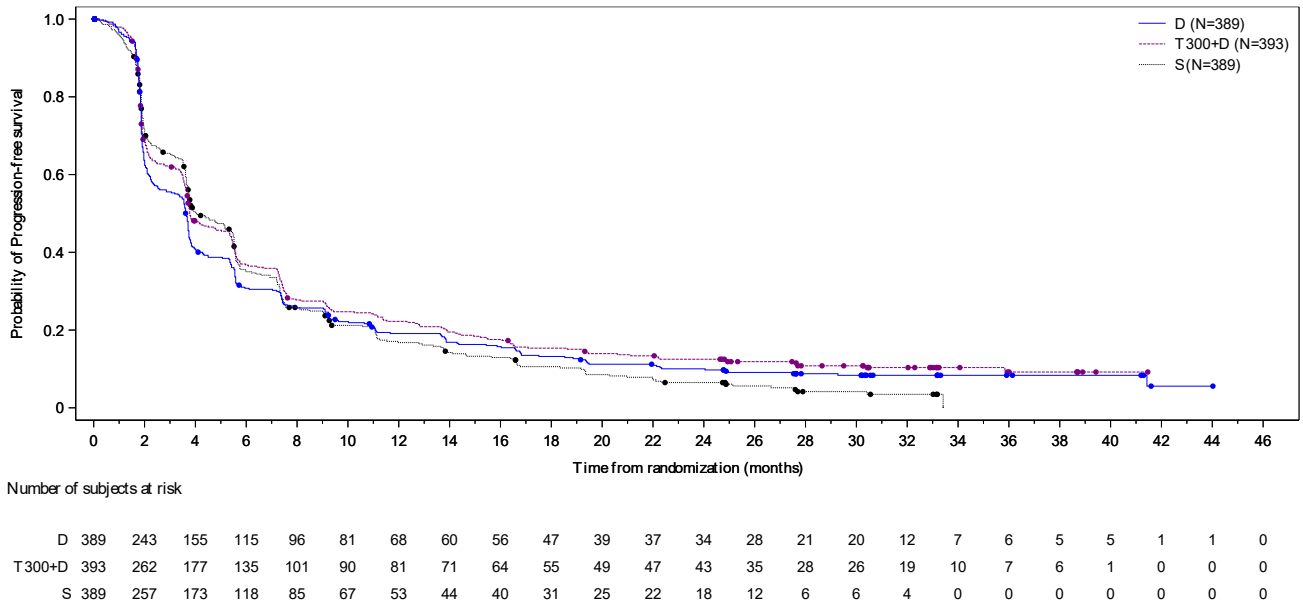
- Calculated using the Kaplan-Meier technique.
- Patients who had not progressed or died, or who progressed or died after 2 or more missed visits, were censored at the latest evaluable RECIST 1.1 assessment, or Day 1 if there were no evaluable visits. Patients who have no evaluable visits or baseline data were censored at Day 1 unless they died within 2 visits of baseline. Patients who die without tumor progression will be censored at the time of death.

Progression determined by Investigator assessment. Lost to follow-up is defined as patients who have no RECIST 1.1 progression or death at the time of the DCO and have a termination status of 'Lost to follow-up' from the Disposition module. Withdrawn consent is defined as patients who have no RECIST 1.1 progression or death at the time of DCO and whose termination status is 'Withdrawn consent' on the Disposition module. The analysis methods used to obtain the hazard ratio, confidence interval, and 2-sided p-value are the same as for the primary OS analysis.

A hazard ratio of < 1 favours IO treatment arms to be associated with a longer progression-free survival than sorafenib.

Abbreviations: CI = confidence interval; D = durvalumab monotherapy 1500 mg; Q4W; DCO = data cut-off; ECOG PS, Eastern Cooperative Oncology Group performance status; FAS = Full Analysis Set; IO = immuno-oncology; HBV, hepatitis B virus; HCV, hepatitis C virus; N = total number of patients; n = number of PFS events; PFS = progression-free survival; Q4W = every 4 weeks; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; S = sorafenib 400 mg twice daily; T75+D = tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D = tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Figure 17. Kaplan-Meier Plot for Progression-free Survival by Investigator Assessment According to RECIST 1.1 (FAS)



Abbreviations: D = durvalumab monotherapy 1500 mg; Q4W; FAS = Full Analysis Set; Q4W = every 4 weeks; N = total number of patients; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; S = sorafenib 400 mg twice daily; T75+D = tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D = tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Table 25: Progression-free survival (FAS 32w FUP) based on BICR assessments per RECIST 1.1 (DCO 27-AUG-2021)

	Number (%) of subjects			
	Durva 1500 mg (N=236)	Treme 300 mg x1 dose + Durva 1500 mg (N=234)	Treme 75 mg x4 doses + Durva 1500 mg (N=153)	Sora 400 mg BID (N=236)
Total events[a], n (%)	194 (82.2)	172 (73.5)		163 (69.1)
RECIST progression	175 (74.2)	148 (63.2)		137 (58.1)
Target Lesions[b]	106 (44.9)	81 (34.6)		76 (32.2)
Non Target Lesions[b]	101 (42.8)	74 (31.6)		68 (28.8)
New Lesions[b]	50 (21.2)	53 (22.6)		45 (19.1)
Death in the absence of progression	19 (8.1)	24 (10.3)		26 (11.0)
Censored subjects, n (%)	42 (17.8)	62 (26.5)		73 (30.9)
Censored RECIST progression[c]	0	0		1 (0.4)
Censored death[d]	11 (4.7)	17 (7.3)		44 (18.6)
Progression-free at time of analysis	0	0		0
Lost to follow-up	0	0		2 (0.8)
Withdrawn consent	0	0		2 (0.8)
Study completion[e]	31 (13.1)	45 (19.2)		24 (10.2)
Median progression-free survival (months)[f]	3.48	3.65		3.78
95% CI for median progression-free survival[f]	2.17 - 3.68	3.52 - 3.94		3.68 - 5.32
Hazard ratio	1.19	0.96		
95% CI for hazard ratio	0.97 - 1.47	0.77 - 1.19		
2-sided p-value	0.0971	0.6668		
Median (range) duration of follow-up in all subjects (months)	3.07 (0.03 - 19.42)	3.61 (0.03 - 16.59)		3.61 (0.03 - 16.43)
Median (range) duration of follow-up in censored subjects (months)	8.99 (0.03 - 19.42)	9.33 (0.03 - 16.59)		5.49 (0.03 - 13.96)

Progression is determined by BICR, RECIST 1.1. CI=Confidence interval. NR = Not reached. FAS 32w FUP = Full analysis set with opportunity for 32 weeks of follow-up at IA1 DCO.
Lost to follow up is defined as subjects whom have no RECIST 1.1 progression or death at the time of the data cutoff and have a termination status of 'Lost to follow-up' from the Disposition module.
Withdrawn consent is defined as all subjects whom have no RECIST 1.1 progression or death at the time of data cut off and whose termination Status is 'Withdrawn consent' on the Disposition module.
[a] Subjects who have not progressed or died, or who progress or die after two or more missed visits, are censored at the latest evaluable RECIST assessment, or day 1 if there are no evaluable visits. Subjects who have no evaluable visits or do not have baseline data will be censored at study day 1 unless they die within 2 visits of baseline.
[b] Target Lesions, Non Target Lesions and New Lesions are not necessarily mutually exclusive categories. [c] RECIST progression event occurred after 2 or more missed visits after last evaluable RECIST assessment (or randomization).
[d] Death occurred after 2 or more missed visits after last evaluable RECIST assessment (or randomization).
[e] Other recorded on disposition eCRF with specified status of 'Study terminated by sponsor. [f] Calculated using the Kaplan-Meier technique.
The analysis methods used to obtain the hazard ratio, confidence interval and 2-sided p-value are the same as for the primary OS analysis. A hazard ratio < 1 favours IO treatment arms to be associated with a longer progression-free survival than sorafenib.
root/cdar/d419/d419cc00002/ar/csr/restricted_tlf/prod/program/eff004.sas eff004hfa.rtf 08NOV2021:16:24 kwxd463

PFS by BICR by mRECIST was also performed in the FAS 32w FUP (not shown), and this did not show a statistically significant difference of PFS between the three arms (D vs T300+D vs S) either.

Overall response rate (ORR) and best objective response

Table 26. Objective Response Rate Based on Investigator Assessment (Confirmed Responses) According to RECIST 1.1 (FAS)

Treatment arm	N	Number of patients with response [a]	Response rate (%)	Comparison between arms		
				Odds ratio [b]	95% CI	2-sided p-value
D	389	66	17.0	3.80	2.29, 6.57	<0.0001
T300+D	393	79	20.1	4.69	2.85, 8.04	<0.0001
S	389	20	5.1	-	-	-

[a] Responses include only confirmed responses. [b] Comparator arm for the odds ratio is S.

The analysis was performed using a logistic regression model adjusted for treatment with factors for etiology of liver disease, ECOG PS, and MVI. An odds ratio of > 1 favors IO treatment arms.

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; FAS = Full Analysis Set; IO = immuno-oncology; MVI = macrovascular invasion; Q4W = every 4 weeks; S = sorafenib 400 mg twice daily; T300+D = tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Table 27. Best Objective Response Based on Investigator Assessment (Confirmed Response) According to RECIST 1.1 (FAS)

Response status	BOR	Number (%) of patients		
		D (N = 389)	T300+D (N = 393)	S (N = 389)
Response	Total	66 (17.0)	79 (20.1)	20 (5.1)
	Complete response	6 (1.5)	12 (3.1)	0
	Partial response	60 (15.4)	67 (17.0)	20 (5.1)
Non-response	Total	323 (83.0)	314 (79.9)	369 (94.9)
	Stable disease	147 (37.8)	157 (39.9)	216 (55.5)
	Progression	160 (41.1)	141 (35.9)	118 (30.3)
	RECIST progression	143 (36.8)	117 (29.8)	91 (23.4)
	Death	17 (4.4)	24 (6.1)	27 (6.9)
	Not evaluable	16 (4.1)	16 (4.1)	35 (9.0)

Abbreviations: BOR = best objective response; D = durvalumab monotherapy 1500 mg; Q4W; FAS = Full Analysis Set; N = total number of patients; Q4W = every 4 weeks; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors Version 1.1; S = sorafenib 400 mg twice daily; T300+D = tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Table 28. Objective response rate based on BICR assessment (confirmed response) according to RECIST 1.1 (FAS 32w FUP) – DCO 27 AUG 2021

	Durva 1500 mg (N=236)	Treme 300 mg x1 dose + Durva 1500 mg (N=234)	Treme 75 mg x4 doses + Durva 1500 mg (N=153)	Sora 400 mg BID (N=236)
Subjects with Objective response, n (%)	36 (15.3)	44 (18.8)		12 (5.1)
Objective response rate (%)	15.3	18.8		5.1
95% exact CI	10.92, 20.49	14.01, 24.41		2.65, 8.71

CI=Confidence interval.
RECIST version 1.1.
Lost to follow up and withdrawn consent are defined as subjects who have no RECIST 1.1 progression or death at the time of the DCO and have a termination status of 'Lost to follow-up' or 'Withdrawn consent,' respectively in the Disposition module. FAS 32w FUP = Full analysis set with opportunity for 32 weeks of follow-up at IA1 DCO.

Table 29. Disagreements between investigator and BICR of RECIST progression per RECIST 1.1 (FAS 32w FUP) – DCO 27 AUG 2021

	Number (%) of subjects				Difference	
	Durva 1500 mg (N=236)	Treme 300 mg x1 dose + Durva 1500 mg (N=234)	Treme 75 mg x4 doses + Durva 1500 mg (N=153)	Sora 400 mg BID (N=236)	Durva 1500 mg - Sora 400 mg BID	Treme 300 mg x1 dose + Durva 1500 mg - Sora 400 mg BID
RECIST progression[a] declared by:						
Investigator and central review	160 (67.8)	138 (59.0)		123 (52.1)		
Progression date agreement (within 2 weeks)	90 (38.1)	61 (26.1)		63 (26.7)		
Progression date >=2 weeks earlier by central review than by Investigator	47 (19.9)	61 (26.1)		46 (19.5)		
Progression date >=2 weeks earlier by Investigator than by central review	23 (9.7)	16 (6.8)		14 (5.9)		
Investigator but not central review	26 (11.0)	36 (15.4)		45 (19.1)		
Central review but not Investigator	15 (6.4)	10 (4.3)		14 (5.9)		
No Progression by both	35 (14.8)	50 (21.4)		54 (22.9)		
Early Discrepancy Rate (EDR)[b]	0.26	0.30		0.35	-0.09	-0.05
Late Discrepancy Rate (LDR)[c]	0.56	0.58		0.50	0.05	0.07

[a] Progression events that do not occur within two visits of the last evaluable assessment (or randomization) are censored.
[b] EDR is the frequency of Investigator declared progressions before central review as a proportion of all Investigator progressions.
[c] LDR is the frequency of Investigator declared progressions after central review as a proportion of all discrepancies.
RECIST version 1.1.

Duration of response and time to response

Table 30. Duration of Response and Time to Onset of Objective Response in HIMALAYA (Final Analysis) According to Investigator Assessment per RECIST 1.1 (FAS)

Study Analysis set (DCO)	**HIMALAYA** **FAS (Final Analysis)**		
Response assessment	**Investigator per RECIST 1.1 [a]**		
	D **(N = 66)**	**T300+D** **(N = 79)**	**S** **(N = 20)**
Patients with objective response, n (%)	38	44	13
DoR from onset of response (months) [b, c]			
25th percentile	7.43	8.54	6.51
Median	16.82	22.34	18.43
75th percentile	NR	NR	25.99
Percentage remaining in response [c]			
At 6 months	81.8	82.3	78.9
At 12 months	57.8	65.8	63.2
TTR from randomization (months)			
25th percentile	1.87	1.84	1.89
Median	2.09	2.17	3.78
75th percentile	3.98	3.98	8.44

[a] Confirmed responses only.

[b] DoR is the time from the first documentation of CR/PR until the date of progression, death, or the last evaluable RECIST assessment for patients who do not progress.

[c] Calculated using the Kaplan-Meier method.

Abbreviations: CR = complete response; DCO = data cut-off; DoR = duration of response; FAS = full analysis set; N = total number of patients; n = number of patients in a treatment arm; NR = not reached; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; TTR = time to onset of objective response.

Patient-reported outcomes (PROs)

Patient-reported symptoms, function, and health-related quality of life (HRQoL) were collected in the HIMALAYA study using the EORTC QLQ C30 and its HCC module (EORTC QLQ HCC18). At baseline,

patient-reported symptoms, functioning, and HRQoL scores were comparable between the HIMALAYA study arms.

Table 31. Summary of Change from Baseline Using MMRM in EORTC QLQ-30 (FAS)

Symptom Scale Item	Statistic	Number (%) of patients			
		D (N = 389)	T300+D (N = 393)	T75+D (N = 153)	S (N = 389)
GHS/QoL					
GHS/QoL	n	282	249	116	254
	Adjusted mean (SE)	-1.8 (1.26)	-5.8 (1.29)	-6.2 (2.04)	NE
	95% CI	-4.30, 0.65	-8.37, -3.32	-10.22, -2.21	NE
	Estimated difference	NE	NE	-	-
	95% CI for difference	NE	NE	-	-
	p-value	NE	NE	-	-
Function					
Physical functioning	n	282	249	116	254
	Adjusted mean (SE)	-0.9 (1.16)	-2.7 (1.19)	-4.4 (1.87)	NE
	95% CI	-3.18, 1.37	-5.05, -0.39	-8.05, -0.71	NE
	Estimated difference	NE	NE	-	-
	95% CI for difference	NE	NE	-	-
	p-value	NE	NE	-	-
Symptoms					
Fatigue	n	282	249	116	254
	Adjusted mean (SE)	1.7 (1.40)	1.9 (1.43)	4.3 (2.27)	NE
	95% CI	-1.09, 4.43	-0.91, 4.72	-0.14, 8.75	NE
	Estimated difference	NE	NE	-	-
	95% CI for difference	NE	NE	-	-
	p-value	NE	NE	-	-
Appetite loss	n	282	249	116	254
	Adjusted mean (SE)	3.8 (1.62)	1.7 (1.65)	2.8 (2.63)	NE
	95% CI	0.64, 7.00	-1.58, 4.91	-2.36, 7.97	NE
	Estimated difference	NE	NE	-	-
	95% CI for difference	NE	NE	-	-
	p-value	NE	NE	-	-
Nausea	n	282	249	116	254
	Adjusted mean (SE)	1.2 (1.18)	0.7 (1.20)	3.1 (1.91)	NE
	95% CI	-1.16, 3.47	-1.64, 3.08	-0.61, 6.87	NE
	Estimated difference	NE	NE	-	-
	95% CI for difference	NE	NE	-	-
	p-value	NE	NE	-	-
Diarrhea	n	282	249	116	254
	Adjusted mean (SE)	1.2 (1.43)	-1.0 (1.45)	5.7 (2.31)	NE
	95% CI	-1.62, 3.97	-3.83, 1.86	1.20, 10.28	NE
	Estimated difference	NE	NE	-	-
	95% CI for difference	NE	NE	-	-
	p-value	NE	NE	-	-

The analysis set includes a subset of the FAS with an evaluable baseline assessment and at least 1 evaluable post-baseline assessment. Change from baseline is derived using a MMRM analysis of all the post-baseline scores for each visit. The model includes treatment, visit, and treatment by visit interaction as explanatory variables and the baseline score as a covariate.

All scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. A high score for functional scales (physical, role, emotional, cognitive, social) and global health status/QoL represents a high functioning/QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems.

Adjusted mean: adjusted mean change from baseline.

95% CI: 95% CI for adjusted mean change.

Estimated difference: overall estimate of the treatment difference between D (monotherapy or combination therapy) and S.

CI, confidence interval; D, durvalumab monotherapy 1500 mg; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer 30-item core quality of life questionnaire; FAS, Full Analysis Set; MMRM, mixed-effect model for repeated measurement; N, number of patients in treatment arm; NE, not evaluable; QoL, Quality of Life; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; SE, standard error; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Table 32. Summary of Change from Baseline in EORTC QLQ-HCC18 Symptoms (FAS)

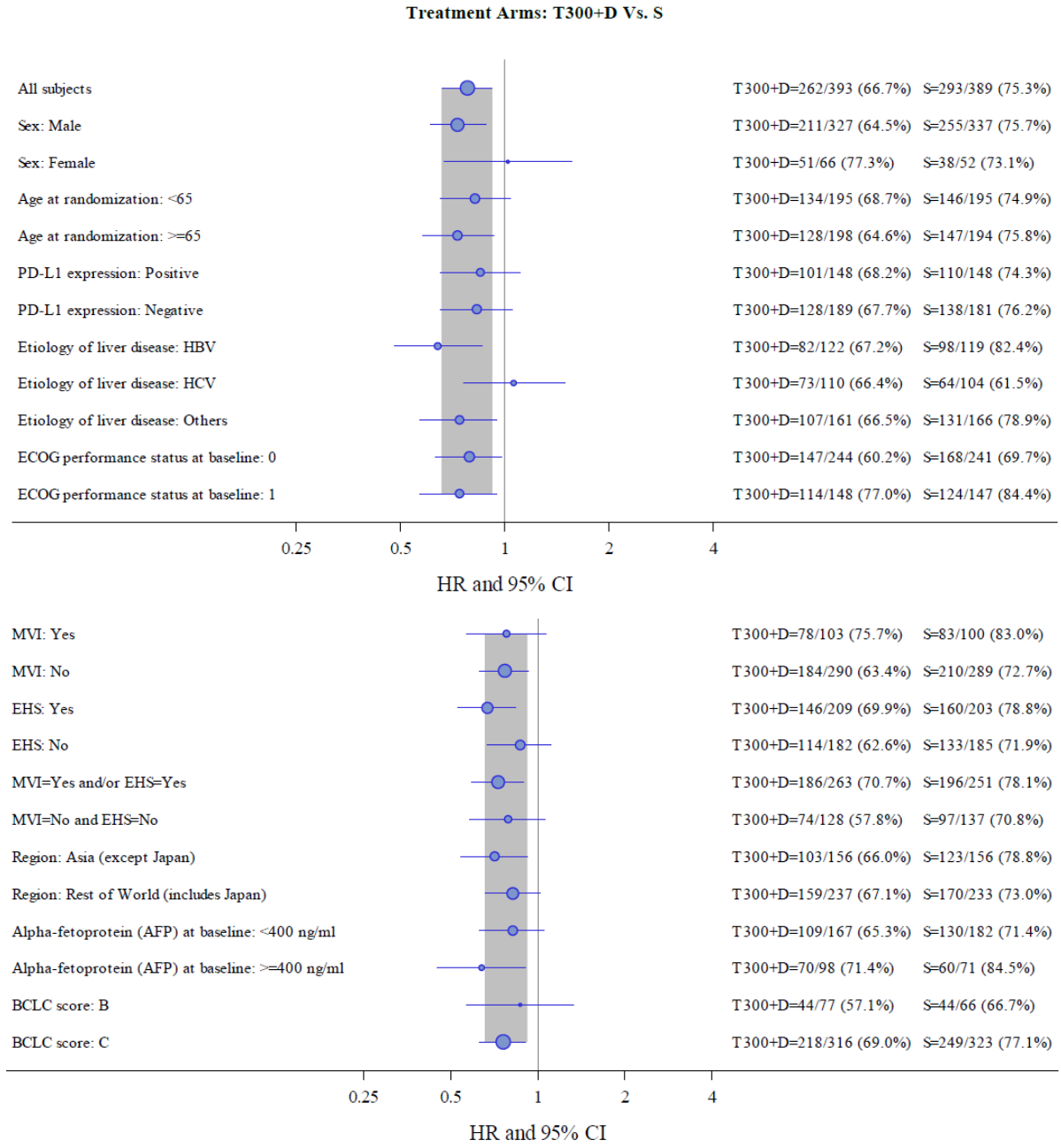
Symptom Scale Item	Statistic	Number (%) of patients			
		D (N= 389)	T300+D (N= 393)	T75+D (N = 153)	S (N= 389)
Abdominal swelling	n	280	238	112	253
	Adjusted mean (SE)	1.0 (1.32)	-0.1 (1.37)	-0.7 (2.15)	NE
	95% CI	-1.64, 3.56	-2.84, 2.55	-4.93, 3.52	NE
	Estimated difference	NE	NE	-	-
	95% CI for difference	NE	NE	-	-
	p-value	NE	NE	-	-
Abdominal pain	n	280	238	112	253
	Adjusted mean (SE)	0.6 (1.49)	-1.4 (1.54)	-0.5 (2.42)	NE
	95% CI	-2.30, 3.53	-4.41, 1.62	-5.29, 4.20	NE
	Estimated difference	NE	NE	-	-
	95% CI for difference	NE	NE	-	-
	p-value	NE	NE	-	-
Shoulder pain	n	280	238	112	253
	Adjusted mean (SE)	-2.4 (1.51)	-1.7 (1.56)	-4.8 (2.46)	NE
	95% CI	-5.35, 0.59	-4.75, 1.35	-9.66, 0.01	NE
	Estimated difference	NE	NE	-	-
	95% CI for difference	NE	NE	-	-
	p-value	NE	NE	-	-

EORTC Score Interpretation: All scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. A high score for functional scales (physical, role, emotional, cognitive, social) and global health status/QoL represents a high functioning/QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems.
CI, confidence interval; D, durvalumab monotherapy 1500 mg; EORTC QLQ-HCC18, European Organization for Research and Treatment of Cancer 18-item hepatocellular cancer health-related quality of life questionnaire; FAS, Full Analysis Set; N, number of patients in treatment arm; NE, not evaluable; QoL, Quality of Life; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; SE, standard error; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.
Source: Table 14.2.9.1.

Ancillary analyses

Subgroup analyses

Figure 18. Forest plots of Overall survival, subgroup analysis, FAS, DCO 27 AUG 2021



Hazard ratio and 95% CI.
A hazard ratio <1 implies a lower risk of death for the Treme 300 mg x 1 dose + Durva 1500 mg treatment arm.
For analysis methods, refer to Table 14.2.1.3.
Subgroup analyses for stratification factors, etiology of liver disease (HBV versus HCV versus others) and macro-vascular invasion (yes versus no) are performed using values collected from the pathology at screening eCRF. Others (for etiology of liver disease) is defined as no active viral hepatitis identified.
Values of ECOG are obtained from performance status eCRF.
Size of circle is proportional to the number of events.
Grey band represents the 95% confidence interval for the overall (all subjects) hazard ratio.
D = Durva 1500 mg,T300+D = Treme 300 mg x1 dose + Durva 1500 mg, S = Sora 400 mg BID
root/cdar/d419/d419cc00002/ar/csr/restricted_tlf/prod/program/eff003.sas eff003fa.rtf 08NOV2021:16:24 kwxd463

Abbreviations: AFP = alpha-fetoprotein; BCLC = Barcelona Clinic Liver Cancer; ECOG = Eastern Cooperative Oncology Group; EHS = extrahepatic spread; FAS = full analysis set; HBV = hepatitis B virus; HCV = hepatitis C virus; HR = hazard ratio; MVI = macrovascular invasion; OS = overall survival; PD-L1 = programmed cell death ligand-1; TIP = tumor immune percentage.

Table 33. Subgroup Analysis of Overall Survival by PD-L1 Expression Level, HIMALAYA (FAS)

PD-L1 expression subgroup	Treatment arm	N	Number (%) of events	Comparison to S	
				HR [a]	95% CI
Positive: TIP ≥ 1% [b]	D	154	107 (69.5)	0.87	0.66, 1.13
	T300+D	148	101 (68.2)	0.85	0.65, 1.11
	S	148	110 (74.3)	–	–
Negative: TIP < 1% [b]	D	190	141 (74.2)	0.93	0.73, 1.17
	T300+D	189	128 (67.7)	0.83	0.65, 1.05
	S	181	138 (76.2)	–	–
Positive: TIP ≥ 5% [c]	D	70	47 (67.1)	0.90	0.59, 1.38
	T300+D	67	44 (65.7)	0.94	0.60, 1.47
	S	66	46 (69.7)	–	–
Negative: TIP < 5% [c]	D	274	201 (73.4)	0.92	0.75, 1.12
	T300+D	270	185 (68.5)	0.84	0.69, 1.03
	S	263	202 (76.8)	–	–
Positive: TIP ≥ 10% [c]	D	37	26 (70.3)	0.88	0.47, 1.66
	T300+D	34	21 (61.8)	0.88	0.44, 1.79
	S	33	21 (63.6)	–	–
Negative: TIP < 10% [c]	D	307	222 (72.3)	0.89	0.74, 1.08
	T300+D	303	208 (68.6)	0.83	0.69, 1.01
	S	296	227 (76.7)	–	–

[a] HR < 1 favors the IO treatment arm.

[b] HR and 95% CI were estimated from an unstratified Cox proportional hazards model with treatment as the only covariate and using the Efron method to control for ties.

[c] HR and 95% CI were estimated from a Cox proportional hazards model adjusting for treatment, etiology of liver disease (HBV vs HCV vs others), ECOG performance status (0 vs 1), and MVI (yes vs no).

PD-L1 expression level is based on the TIP score method as: PD-L1 Positive (TIP ≥ 1%) or PD-L1 Negative (TIP < 1%). The TIP 1% cut-off is the only validated cut-off at which HIMALAYA patient samples were read. Additional PD-L1 TIP cut-offs of 5% and 10% should be interpreted in an exploratory manner.

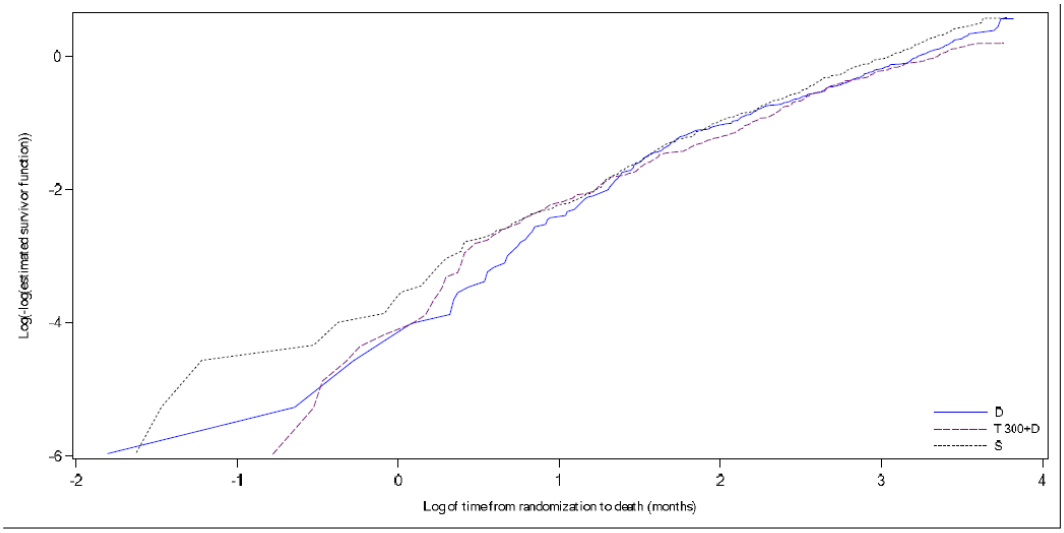
Abbreviations: CI = confidence interval; D = durvalumab monotherapy 1500 mg Q4W; ECOG = Eastern Cooperative Oncology Group; FAS = Full Analysis Set; HR = hazard ratio; IO, immuno-oncology; MVI = macrovascular invasion; PD-L1 = programmed cell death ligand 1; Q4W = every 4 weeks; S = sorafenib 400 mg twice daily; T300+D = tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TIP = tumor and immune cell positivity.

Sensitivity analyses

Non-proportional hazards

Some evidence of delayed treatment effect was observed as illustrated by the lack of parallel lines in the log-log(survival) against log(time from randomization to death) for the individual treatment arms (Figure 19). This was also noted in the survival curves with D vs S (separation at 9 months) and T300+D vs S (separation at 4 months). This finding is expected, as IO agents have illustrated delayed treatment effects in clinical settings. The assumption of non-proportionality was rigorously assessed with a post hoc analysis performed to test the linear interaction between treatment and time, and no significant interaction was found (T300+D vs S: nominal p = 0.094, D vs S: nominal p = 0.34).

Figure 19. Complementary Log-log(event) vs Log(time) to Assess Assumptions of Proportionality of Hazards for OS (FAS)



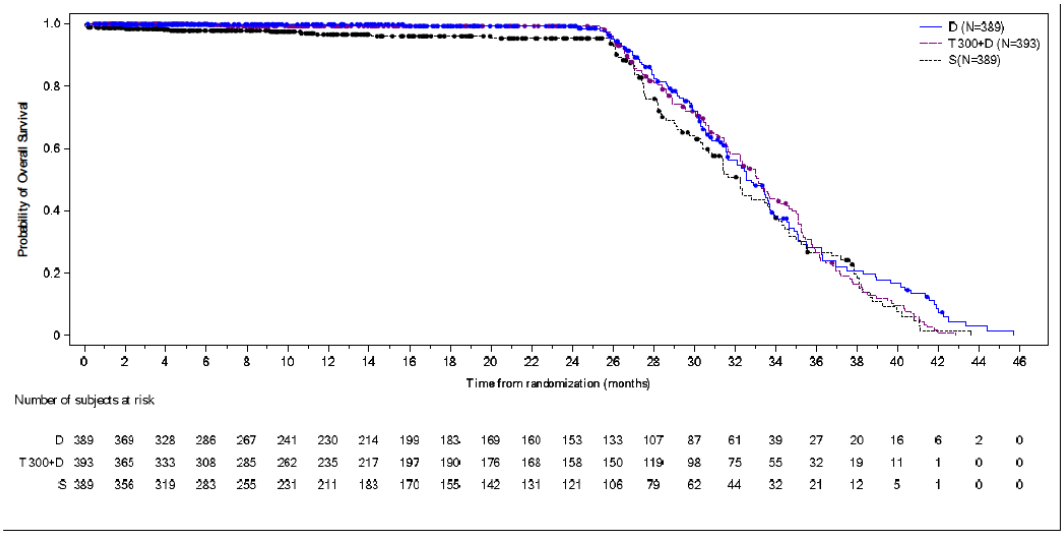
D, durvalumab monotherapy 1500 mg Q4W; FAS, Full Analysis Set; Q4W, every 4 weeks; OS, Overall Survival; S, sorafenib 400 mg twice daily; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Source: Figure 14.2.1.9.

Inversed Censoring

The reverse KM survival curve shown in Figure 20 is constructed by reversing the "censor" and "event" of the standard KM curve (data not shown). Figure 20 shows that the curves for arms D, T300+D and S remain close to 1 for the first 26 months post randomization, indicating nearly complete follow-up for this period of time. No meaningful difference in the length of follow-up among arms D, T300+D and S can be seen in the figure, which is also evidenced by similar median follow-up times in censored patients (D: 31.61 months, T300+D: 32.36 months, and S: 30.36 months).

Figure 20. Overall Survival, Sensitivity Analysis, KM Plot with Inversed Censoring Indicators (FAS)



D, durvalumab monotherapy 1500 mg Q4W; FAS, Full Analysis Set; KM, Kaplan Meier; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Source: Figure 14.2.1.1.3.

Contribution of components

Table 34. Data From HIMALAYA (Pivotal Study) and Study 22 (Supportive Study) Relevant to the Recommended T300+D Regimen in Patients with uHCC

Study Analysis set	**HIMALAYA** **FAS (Final Analysis)**		**Study 22 (Parts 2 and 3)** **FAS (Final Analysis)**		
	D **(N = 389)**	**T300+D** **(N = 393)**	**D** **(N = 104)**	**T300+D** **(N = 75)**	**T** **(N = 69)**
Median OS (months) [a]	16.56	16.43	12.91	17.05	17.05
95% CI for median OS	14.06, 19.12	14.16, 19.58	8.74, 16.79	10.55, 22.83	11.33, 20.24
HR (95% CI) for T300+D vs D	0.90 (0.76, 1.07)		–	–	–
OS rate at 12 months, % [a]	59.3	60.2	50.4	57.6	59.8
OS rate at 18 months, % [a]	47.4	48.7	34.0	47.8	43.3
OS rate at 24 months, % [a]	39.6	40.5	26.2	38.3	30.9
OS rate at 36 months, % [a]	24.7	30.7	–	–	–
Tumor response assessment	**Investigator assessment per RECIST 1.1**		**BICR per RECIST 1.1**		
	D **(N = 389)**	**T300+D** **(N = 393)**	**D** **(N = 104)**	**T300+D** **(N = 75)**	**T** **(N = 69)**
Median PFS [a]	3.65	3.78	2.07	2.17	2.69
95% CI for median PFS	3.19, 3.75	3.68, 5.32	1.84, 2.86	1.91, 5.42	1.87, 5.29
Progression-free at DCO n (%)	32 (8.2)	49 (12.5)	8 (7.7)	11 (14.7)	4 (5.8)
ORR (%) [b]	17.0	20.1	11.5	24.0	7.2
Complete Response [b]	6 (1.5)	12 (3.1)	0	1 (1.3)	0
Partial Response [b]	60 (15.4)	67 (17.0)	12 (11.5)	17 (22.7)	5 (7.2)
DCR (%) [c]	54.8 [d]	60.1 [d]	37.5 [b]	45.3 [b]	49.3 [b]
Median DoR (months) [d, e]	16.82	22.34	14.95	18.43	23.95
Median TTR (months) [d, f]	2.09	2.17	3.65	2.28	1.81

[a] Calculated using the Kaplan-Meier method.

[b] Confirmed responses only.

- Disease control = complete response + partial response + stable disease.

[d] Response did not require confirmation.

[e] DoR is the time from the first documentation of CR/PR until the date of progression, death, or the last evaluable RECIST assessment for subjects that do not progress.

[f] TTR is the time to onset of confirmed response from from randomization (HIMALAYA; Study 22 Parts 2A and 3) or from treatment allocation (Study 22 Part 2B).

Abbreviations: BICR = blinded independent central review; CI = confidence interval; CR = complete response; DCO = data cut-off; DCR = disease control rate; DoR = duration of response; FAS = Full Analysis Set; HR = hazard ratio; ORR = objective response rate; OS = overall survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; TTR = time to onset of objective response; uHCC = unresectable hepatocellular carcinoma.

Additional sensitivity analyses following inaccurate survival information at site 6208

GCP findings from the PMDA concerning the HIMALAYA trial, indicated that survival information was inaccurate for 4 subjects at site 6208. Following question regarding this issue, the supplementary analysis of OS with the corrected data was provided.

In total the site 6208 enrolled 14 patients in HIMALAYA study. Overall survival data for 4/14 enrolled patients was affected, and no discrepancies in survival information were identified for the remaining 10/14 patients after onsite review.

Table 35. **Overall survival data for affected 4/14 enrolled patients at site 6208**

Subject Number	Randomization Date (mm/dd/yyyy)	Treatment Arm	Survival Status/Date of Death (mm/dd/yyyy)				Variance (days): CRF vs death certificate
			CRF	Source document / medical record	Local oncology registry	Death certificate	
[redacted]	01/26/2018	S	03/05/2018	N/A	03/04/2018	03/04/2018	1
	04/05/2018	S	Alive on 09/03/2021	Alive on 09/03/2021	08/12/2021	08/12/2021	22
	07/15/2019	T300+D	08/05/2019	08/05/2019	07/25/2019	07/25/2019	11
	07/16/2019	D	04/23/2020	04/23/2020	07/23/2019	07/23/2019	275

D = durvalumab 1500 mg Q4W; N/A = not applicable; Q4W = every 4 weeks; S = sorafenib 400 mg twice daily; T300+D = tremelimumab 300 mg for a single dose and durvalumab 400 mg Q4W; T75+D = tremelimumab 75 mg Q4W × 4 doses and durvalumab 1500 mg Q4W.

Table 36. Sensitivity Analysis of OS by Removing Site 6208 (Full Analysis Set)

	Number (%) of subjects			
	D (N=385)	T300+D (N=391)	T75 +D (N=151)	S (N=383)
Deaths, n (%)	277 (71.9)	260 (66.5)	121 (80.1)	288 (75.2)
Censored subjects, n (%)	108 (28.1)	131 (33.5)	30 (19.9)	95 (24.8)
Median overall survival (months)[a]	16.56	16.66	16.56	13.77
95% CI for median overall survival[a]	14.06 - 19.12	14.19 – 20.37	12.71 - 19.78	12.25 - 16.13
Hazard ratio[b]	0.87	0.77		-
95% CI for hazard ratio[b]	0.73 - 1.02	0.65 - 0.91		-

Calculated using the Kaplan-Meier technique.
The analysis was performed using a Cox proportional hazards model adjusting for treatment, etiology of liver disease (hepatitis B virus vs. hepatitis C virus vs. others), Eastern Cooperative Oncology Group performance status (0 vs. 1), and macro-vascular invasion (yes vs. no). Values of the variables used for adjustment were obtained from the Interactive Voice Response System.
Note: Table does not include subjects from Russian site 6208. A hazard ratio < 1 favors IO treatment arms to be associated with a longer overall survival than sorafenib. A hazard ratio < 1 favors IO treatment arms to be associated with a longer overall survival than sorafenib.
CI = confidence interval; D = durvalumab 1500 mg Q4W; IO = immuno-oncology; NR = not reached; Q4W = every 4 weeks; S = sorafenib 400 mg twice daily; T300+D = tremelimumab 300 mg for a single dose and durvalumab 400 mg Q4W; T75+D = tremelimumab 75 mg Q4W × 4 doses and durvalumab 1500 mg Q4W.

Figure 21. KM Plot of OS by Removing Site 6208 (Full Analysis Set)

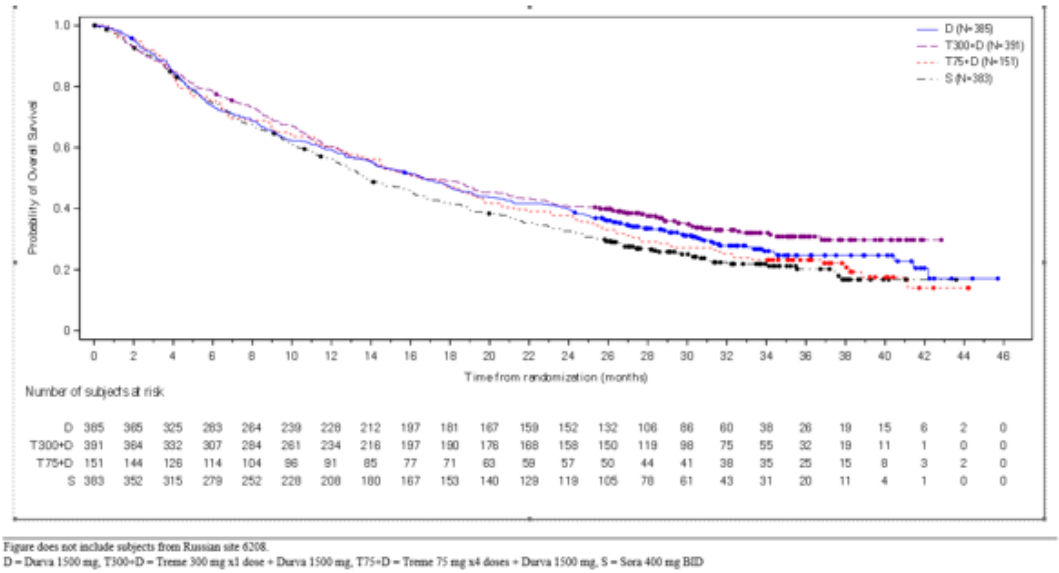


Figure does not include subjects from Russian site 6208.
D = Durva 1500 mg, T300+D = Treme 300 mg x1 dose + Durva 1500 mg, T75+D = Treme 75 mg x4 doses + Durva 1500 mg, S = Sora 400 mg BID

The Applicant has provided the requested sensitivity analysis, using the most conservative approach by removing all 14 patients enrolled at this site and this showed that the OS HR was of 0.77 (95%CI: 0.65, 0.91) for T300+D vs. S comparison, which is the main scope of the current procedure. There is overall consistency between the sensitivity analysis and the primary analysis, which is considered reassuring.

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).

Table 37: **Summary of Efficacy for trial HIMALAYA**

Title: A Randomized, Open-label, Multi-center Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients with Advanced Hepatocellular Carcinoma (HIMALAYA)		
Study identifier	EudraCT number: 2016-005126-11, NCT number: NCT03298451	
Design	Randomized, open-label, multicentre Phase III study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Not applicable Not applicable Not applicable
Hypothesis	Superiority for T300+D vs S	
	D	Durvalumab 1500 mg Q4W until PD or unacceptable toxicity, N=389
	T300+D	Tremelimumab 300 mg as single dose plus durvalumab 1500 mg Q4W followed by durvalumab monotherapy 1500 mg Q4W until PD or unacceptable toxicity, N=393
	S	Sorafenib monotherapy 400 mg twice daily until PD or unacceptable toxicity, N=389

Title: A Randomized, Open-label, Multi-center Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients with Advanced Hepatocellular Carcinoma (HIMALAYA)			
Study identifier	EudraCT number: 2016-005126-11, NCT number: NCT03298451		
	T75+D		Tremelimumab 75 mg Q4W × 4 doses + durvalumab 1500 mg Q4W, followed by durvalumab monotherapy 1500 mg Q4W. Arm closed prematurely, results not shown.
Endpoints and definitions	Primary endpoint	OS	OS of T300+D vs S
	Key Secondary endpoints	OS	Non-Inferiority of D vs S and superiority of D vs S.
	Other secondary endpoints	PFS, ORR, DoR	Progression-free survival, overall response rate and duration of response
Database lock	27 August 2021		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat, final analysis			
Descriptive statistics and estimate variability	Treatment group	D	T300+D	S
	Number of subjects	389	393	389
	OS (Months)	16.56	16.43	13.77
	95%CI	14.06; 19.12	14.16; 19.58	12.25; 16.13
	PFS by INV (months)	3.65	3.78	4.07
	95%CI	3.19; 3.75	3.68; 5.32	3.75; 5.49
	ORR (%)	17	20.1	5.1
	DoR (%)	16.82	22.34	18.43

Effect estimate per comparison	Primary endpoint OS	Comparison groups	T300+D vs S
		Stratified HR	0.78
		95% CI	0.66, 0.92
		P-value	0.0035
	Secondary endpoint OS	Comparison groups	D vs S (non-inferior)
		Stratified HR	0.86
		95.67% CI	0.73; 1.03*
		P-value	NA
	Secondary endpoint OS	Comparison groups	D vs S (superior)
		Stratified HR	0.86
		95.67% CI	0.73; 1.03
		P-value	0.0674 (NS)
Notes	*below prespecified clinical NI (non-inferiority) margin of 1.08		

Clinical studies in special populations

Table 38. Patient Counts by Age Category –Controlled Trial Versus Non-controlled Trial (Full Analysis Set)

Age	**Controlled trials** (N=1324)	**Non-controlled trials (N=332)**
< 65	667 (50.4)	175 (52.7)
65-74	467 (35.3)	108 (32.5)
75-84	181 (13.7)	46 (13.9)
85+	9 (0.7)	3 (0.9)

Note: Controlled trial includes only HIMALAYA and non-controlled trail includes only Study 22.

In vitro biomarker test for patient selection for efficacy

PD-L1 testing

The relationship between PD-L1 expression level and clinical outcomes (eg, OS, PFS, and ORR) was investigated, and the results are presented by treatment arm.

PD-L1 expression was determined by the analytically validated VENTANA PD-L1 (SP263) assay using the TIP score method. The TIP score was defined as the total percentage of the tumor area covered by tumor cells with PD-L1 membrane staining at any intensity and/or tumor-associated immune cells with any pattern of PD-L1 staining at any intensity. Two PD-L1 expression subgroups were defined:

- PD-L1 TIP ≥ 1% (Positive): PD-L1 staining of any intensity in tumour cell membranes and/or tumour-associated immune cells covering ≥ 1% of the tumor area
- PD-L1 TIP < 1% (Negative): PD-L1 staining of any intensity in tumour cell membranes and/or tumour-associated immune cells covering < 1% of the tumor area.

Collection of patient samples for analysis of PD-L1 expression

Patients were strongly encouraged to provide a fresh tissue biopsy for the purpose of PD-L1 expression analyses at screening. The tumour specimen submitted to the central laboratory for PD-L1 expression analysis should be of sufficient quantity and quality (with pathology quality control) to allow for PD-L1 immunohistochemical (IHC) analyses. Newly acquired or archived specimens with limited tumour content and fine needle aspirates were not acceptable for defining tumour PD-L1 expression.

- MANDATORY: Provision of a tumour biopsy, formalin fixed and embedded in paraffin, for the purpose of PD-L1 expression analyses (and for enabling exploratory analyses as described in the proceeding section). A newly acquired tumor biopsy (<3 months) was strongly preferred; however, if not feasible with an acceptable clinical risk, an archival sample taken ≤3 years prior to screening could have been submitted. Note: the tumor biopsy was optional for the China cohort.
- Samples should have been collected via an image-guided core needle (at least 18 gauge) or an excisional archival tumour biopsy sample. Where institutional practice, in this setting, uses a smaller gauge needle, samples should have been submitted with tissue adequate to ensure that a valid result can be achieved (ie, total tissue quantity submitted should have been similar to core needle or excisional biopsy requirements).
- When fresh tissue was obtained, 2 cores should have been placed in formalin and processed to a single paraffin-embedded block. It was anticipated that 4 passes of an 18 gauge core needle would provide sufficient tissue for both PD-L1 analyses and exploratory analyses as described below. Tumour lesions used for fresh biopsies should not have been the same lesions used as

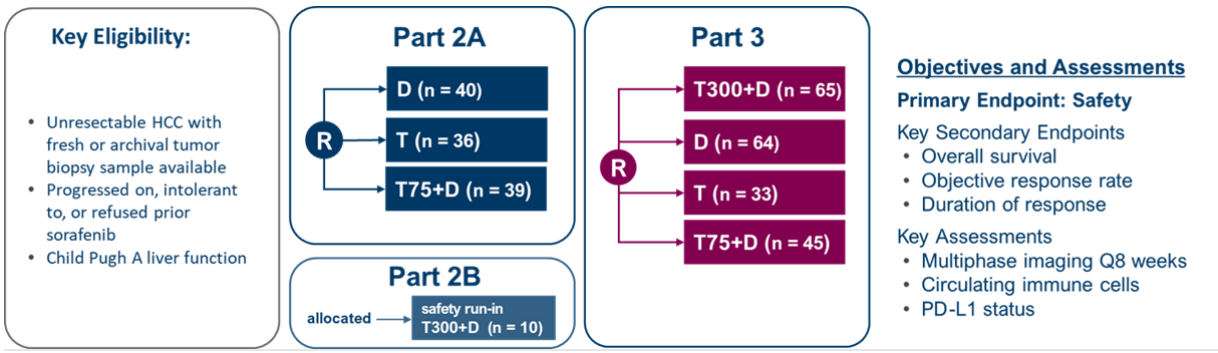
RECIST 1.1 TLs, unless there were no other lesions suitable for biopsy, and in this instance, only core needle (not excisional/incisional) biopsy was allowed. For patients with a single TL, if screening biopsy was collected prior to screening imaging for baseline tumour assessment, allowed approximately 2 weeks before imaging scans were acquired.

- OPTIONAL: Additional archived tumour tissue block (formalin fixed and paraffin embedded), where such samples exist in a quantity sufficient to allow for analysis. Tumour tissue block was preferred. If a tissue block was unavailable, unstained sections from the tissue block may be submitted.
- OPTIONAL: Tumour biopsy at the time of progression was requested
- OPTIONAL: Additional tumour biopsies collected as part of clinical care (eg, for mixed responses or upon PD) could have been submitted for further analysis.
- Additional archived tissue not intended for PD-L1 testing, and optional biopsies obtained at the time of progression or part of clinical care were not to be collected in China. Additionally, China study sites were not to submit tumour tissue blocks and only unstained sections from the tissue block were to be submitted for analysis.
- The Ventana SP263 IHC assay was to be used to determine PD-L1 expression in all available specimens. To meet the requirement of the United States Food and Drug Administration for approval of a companion diagnostic, sections of the tumour were to be retained at Ventana and/or at the Investigation Use only testing laboratory for potential additional studies to support potential test approval.

The Ventana SP163 PD-L1 assay was validated as an appropriate method for the selection of patients who would obtain benefit from durvalumab monotherapy in the PACIFIC trial, whose outcome led to the PD-L1 restricted indication of this anti-PD-L1 product in the locally advanced unresectable NSCLC setting after chemoradiotherapy. Thus, the choice of PD-L1 assay is acceptable.

Supportive study

Figure 22. Study 22: Study Design



Following protocol amendment 5, enrollment into the T75+D arm in Part 3 was closed. Patients already randomized to T75+D could continue on assigned study treatment (provided the Investigator and patient thought it in the best interests of the patient) until confirmed progressive disease or any other discontinuation criteria were met. Weight-based dosing regimen was used in Parts 2A; fixed-dosing regimens were used in Part 2B and Part 3 (durvalumab only).

Abbreviations: D = durvalumab 1500 mg (20 mg/kg) Q4W; DoR, duration of response; HCC = hepatocellular carcinoma; n = number of subjects in a treatment arm; PD-L1 = programmed cell death ligand-1; OS, overall survival; ORR, objective response rate; Q8W, every 8 weeks; Q4W = every 4 weeks; Q8 = every 8 weeks; Q12W = every 12 weeks; T = tremelimumab 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W; T300+D = tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) Q4W; T75+D = tremelimumab 75 mg (1 mg/kg) Q4W × 4 doses + durvalumab 1500 mg (20 mg/kg) Q4W, followed by durvalumab 1500 mg (20 mg/kg) Q4W.

Study 22 was a randomized, multicenter, international, open-label, multipart study designed to evaluate the safety, tolerability, and clinical activity of durvalumab and tremelimumab administered as monotherapy, and durvalumab in combination with tremelimumab or bevacizumab, in patients with advanced HCC. The study was comprised of multiple parts but only Parts 2 and 3 of Study 22 are relevant for this procedure.

The primary objectives of Parts 2 and 3 were to:

- Assess the safety and tolerability of durvalumab and tremelimumab administered as monotherapy and durvalumab administered in combination with tremelimumab to subjects with advanced HCC.

The secondary objectives were to:

- Evaluate the efficacy of durvalumab and tremelimumab administered as monotherapy and durvalumab in combination with tremelimumab in subjects with advanced HCC.
- Evaluate the relationship between baseline and pharmacodynamic biomarkers and measures of clinical outcomes of durvalumab and tremelimumab administered as monotherapy, and durvalumab in combination with tremelimumab in subjects with advanced HCC.

The final analysis of data in all study parts was performed 12 months after the first dose of investigational product was given to the last patient enrolled in the study (DCO: 06 November 2020).

Patient population

In Study 22, eligible patients were aged ≥ 18 years (≥ 20 years for Japanese patients) with advanced HCC confirmed pathologically or with non-invasive methods. This study enrolled immunotherapy-naïve patients who progressed on, were intolerant to, or refused treatment with sorafenib or another approved VEGFR TKI. Patients with co-infection of viral hepatitis B and hepatitis C, active or prior documented GI bleeding within 12 months, ascites requiring non-pharmacologic intervention within 6 months, hepatic encephalopathy within 12 months before the start of treatment, and active or prior documented autoimmune or inflammatory disorders were excluded.

In Part 2A of Study 22, eligible patients were randomized in a 1:1:1 ratio to each of the following 3 treatment arms: D: Durvalumab 20 mg/kg Q4W; T: Tremelimumab 10 mg/kg Q4W × 7 doses followed by Q12W; T75+D: Tremelimumab 1 mg/kg Q4W × 4 doses + durvalumab 20 mg/kg Q4W, followed by durvalumab 20 mg/kg Q4W

Part 2B was a safety run-in for the combination regimen consisting of a single, priming dose of tremelimumab (300 mg) added to durvalumab Q4W. Part 3 was a dose expansion cohort of patients enrolled in Parts 2A and B. Eligible patients were randomized in a 2:2:1:2 ratio to each of the following 4 treatment arms: D: Durvalumab 1500 mg (20 mg/kg) Q4W; T300+D: Tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) Q4W; T: Tremelimumab 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W; T75+D: Tremelimumab 75 mg (1 mg/kg) Q4W× 4 doses + durvalumab 1500 mg (20 mg/kg) Q4W, followed by durvalumab 1500 mg (20 mg/kg) Q4W.

In Part 2A, patients were stratified based on viral status (uninfected, HCV infected, or HBV infected) and PD-L1 expression (positive, negative, or non-evaluable). In Part 3, patients were stratified based on viral status (uninfected, HCV infected, or HBV infected) and sorafenib-based therapy (refusers or all others).

Table 39. Previous Disease-related Treatment Modalities in Parts 2 and 3 (FAS)

	Number (%) of patients				
	D (N = 104)	T300+D (N = 75)	T (N = 69)	T75+D (N = 84)	Total (N = 332)
Systemic therapy [a]	66 (63.5)	55 (73.3)	44 (63.8)	55 (65.5)	220 (66.3)
Carotuximab	1 (1.0)	0	0	0	1 (0.3)
Regorafenib	1 (1.0)	0	0	0	1 (0.3)
Sorafenib	66 (63.5)	55 (73.3)	44 (63.8)	55 (65.5)	220 (66.3)
Radiotherapy	16 (15.4)	22 (29.3)	15 (21.7)	22 (26.2)	75 (22.6)
Cancer-related surgery	37 (35.6)	34 (45.3)	23 (33.3)	37 (44.0)	131 (39.5)
Other	49 (47.1)	25 (33.3)	31 (44.9)	39 (46.4)	144 (43.4)

[a] Based on World Health Organization Drug Global B3-format (September 2020).

D, durvalumab monotherapy 1500 mg (20 mg/kg) Q4W; FAS, Full Analysis Set; Q4W, every 4 weeks; T, tremelimumab monotherapy 750 mg (10 mg/kg) Q4W × 7 doses followed by every 12 weeks; T75+D, tremelimumab 75 mg (1 mg/kg) × 4 doses + durvalumab 1500 mg (20 mg/kg) Q4W; T300+D, tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) Q4W.

Results

A total of 326 (98.2%) patients in the FAS of Parts 2 and 3 received study treatment. At the final DCO, 93.3% of patients across all treatment arms discontinued study treatment. The most frequently reported reason for discontinuing study treatment was HCC disease progression in 66.6% of patients; 11% of patients discontinued due to AEs. The rate of study treatment discontinuation due to PD or AEs was similar across the T300+D and D treatment arms.

The number of patients in Parts 2 and 3 with important protocol deviations with the potential to affect the analyses was low (13 patients overall [3.9%]).

For patient demographics and disease characteristics, please refer to Table 19 and Table 20 in the Results section above**Error! Reference source not found.**.

Table 40. Overall Survival in Parts 2 and 3 (FAS)

	D (N = 104)	T300+D (N = 75)	T (N = 69)	T75+D (N = 84)
Median OS (months) [a]	12.91	17.05	17.05	11.30
95% CI for median OS [a]	8.74-16.79	10.55-22.83	11.33-20.24	8.38-14.95
Deaths, n (%)	78 (75.0)	49 (65.3)	55 (79.7)	64 (76.2)
Censored patients, n (%)	26 (25.0)	26 (34.7)	14 (20.3)	20 (23.8)
Still in survival follow-up [b]	20 (19.2)	23 (30.7)	12 (17.4)	15 (17.9)
Terminated prior to death [c]	6 (5.8)	3 (4.0)	2 (2.9)	5 (6.0)
Lost to follow-up	0	1 (1.3)	0	2 (2.4)
Withdrawn consent	3 (2.9)	2 (2.7)	2 (2.9)	2 (2.4)
Other	3 (2.9) [d]	0	0	1 (1.2) [e]
OS rate at 12 months, % [a]	50.4	57.6	59.8	49.4
95% CI for OS rate at 12 months [a]	40.3-59.7	45.5-68.0	47.1-70.4	38.1-59.7
OS rate at 18 months, % [a]	34.0	47.8	43.3	35.5
95% CI for OS rate at 18 months [a]	24.9-43.3	35.9-58.7	31.3-54.7	25.2-45.9
OS rate at 24 months, % [a]	26.2	38.3	30.9	30.3
95% CI for OS rate at 24 months [a]	17.9-35.3	26.9-49.6	20.3-42.2	20.7-40.6
Duration of follow-up in censored patients (months), median (range) [f]	23.18 (1.84-44.29)	24.61 (0.95-35.58)	31.03 (1.81-44.02)	29.82 (0.03-43.14)

[a] Calculated using the Kaplan-Meier technique.

[b] Includes patients known to be alive at the data cut-off.

[c] Includes patients with unknown survival status who terminated study participation and patients who were lost to follow-up.

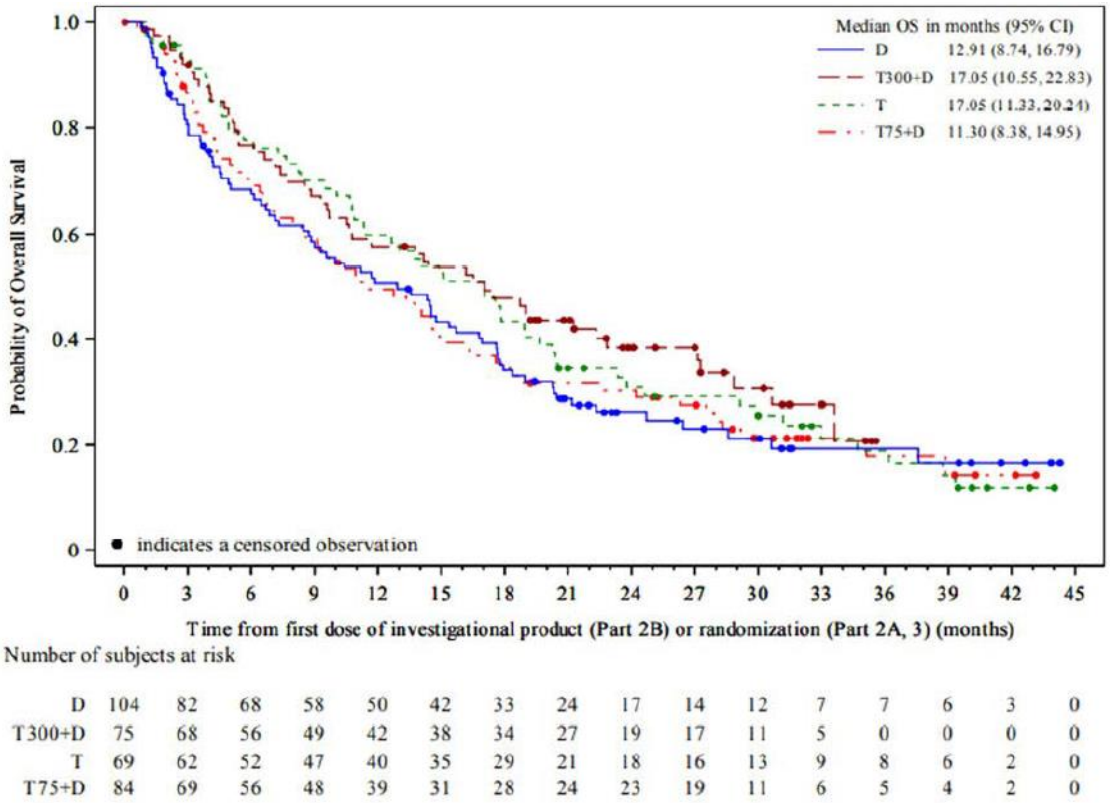
[d] 'Other' reasons (1 patient each): psychiatric issues and study compliance, adverse event, and patient did not receive treatment.

[e] 'Other' reason: patient did not receive treatment.

[f] Median for duration of follow-up is the arithmetic median. Duration of follow-up was calculated from date of randomization (Part 2A, Part 3) or date of first study treatment dose (Part 2B).

CI, confidence interval; D, durvalumab monotherapy 1500 mg (20 mg/kg) Q4W; FAS, Full Analysis Set; OS, overall survival; Q4W, every 4 weeks; T, tremelimumab monotherapy 750 mg (10 mg/kg) Q4W × 7 doses followed by every 12 weeks; T75+D, tremelimumab 75 mg (1 mg/kg) × 4 doses + durvalumab 1500 mg (20 mg/kg) Q4W; T300+D, tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) Q4W.

Figure 23. Kaplan-Meier Plot of Overall Survival in Parts 2 and 3 (FAS)



CI, confidence interval; D, durvalumab monotherapy 1500 mg (20 mg/kg) Q4W; FAS, full analysis set; OS, overall survival; Q4W, every 4 weeks; T, tremelimumab monotherapy 750 mg (10 mg/kg) Q4W × 7 doses followed by every 12 weeks; T75+D, tremelimumab 75 mg (1 mg/kg) × 4 doses + durvalumab 1500 mg (20 mg/kg) Q4W; T300+D, tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) Q4W.
Source: Figure 14.2.1.

Table 41. Confirmed Objective Response Rate in Parts 2 and 3 Based on BICR According to RECIST 1.1 (FAS)

	D (N = 104)	T300+D (N = 75)	T (N = 69)	T75+D (N = 84)
Patients with objective response, n (%) [a]	12 (11.5)	18 (24.0)	5 (7.2)	8 (9.5)
ORR (%)	11.5	24.0	7.2	9.5
95% exact CI	6.1, 19.3	14.9, 35.3	2.4, 16.1	4.2, 17.9

[a] Patients with confirmed complete response or confirmed partial response.

BICR, blinded independent central review; CI, confidence interval; D, durvalumab monotherapy 1500 mg (20 mg/kg) Q4W; FAS, Full Analysis Set; ORR, objective response rate; Q4W, every 4 weeks; RECIST 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1; T, tremelimumab monotherapy 750 mg (10 mg/kg) Q4W × 7 doses followed by every 12 weeks; T75+D, tremelimumab 75 mg (1 mg/kg) × 4 doses + durvalumab 1500 mg (20 mg/kg) Q4W; T300+D, tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) Q4W.

Table 42. Duration and Onset of Objective Response in Patients with Confirmed Objective Response in Parts 2 and 3 Based on BICR According to RECIST 1.1 (FAS)

	D (N = 104)	T300+D (N = 75)	T (N = 69)	T75+D (N = 84)
Number of patients with objective response, n (%)	12 (11.5)	18 (24.0)	5 (7.2)	8 (9.5)
Number of responders who subsequently progressed or died, n	6	9	3	4
Duration of response from onset of response (months) [a, b]				
Median	14.95	18.43	23.95	13.21
25th, 75th percentile	8.54, NR	5.59, 23.95	4.07, NR	10.15, NR
Percentage remaining in response [b]				
6 months	83.3	71.8	60.0	87.5
12 months	56.3	64.6	60.0	58.3
Time to onset of response from randomization (Parts 2A and 3)/treatment allocation (Part 2B) (months)				
Median	3.65	2.28	1.81	2.86
25th, 75th percentile	2.71, 5.59	1.81, 3.68	1.81, 1.84	1.84, 3.83

[a] Duration of response is the time from the first documentation of a confirmed complete response/partial response until the date of progression, death, or the last evaluable RECIST assessment.

[b] Calculated using the Kaplan-Meier technique.

BICR, blinded independent central review; D, durvalumab monotherapy 1500 mg (20 mg/kg) Q4W; FAS, Full Analysis Set; NR, not reached; Q4W, every 4 weeks; RECIST 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1; T, tremelimumab monotherapy 750 mg (10 mg/kg) Q4W × 7 doses followed by every 12 weeks; T75+D, tremelimumab 75 mg (1 mg/kg) × 4 doses + durvalumab 1500 mg (20 mg/kg) Q4W; T300+D, tremelimumab 300 mg (4 mg/kg) × 1 dose + durvalumab 1500 mg (20 mg/kg) Q4W.

Overall Survival (Part 2 Only)

A total of 125 patients were randomized/allocated to treatment in Part 2: 40 in the D arm, 10 in the T300+D arm, 36 in the T arm, and 39 in the T75+D arm. At the final DCO, 81.6% of patients in part 2 had died (FAS): 80.0% in the D arm, 70.0% in the T300+D arm, 80.6% in the T arm, and 87.2% in the T75+D arm. The percentage of patients alive at the final DCO and in survival follow-up (including those still receiving study treatment) was highest in the T300+D arm (30.0%) compared to the other 3 arms (10.3% to 17.5%).

The Kaplan-Meier estimate of median OS was highest for patients receiving T300+D (28.06 months) compared to patients receiving D (11.78 months), T (17.05 months), or T75+D (13.34 months).

Overall Survival (Part 3 Only)

Part 3 included the following number of patients per treatment arm: 64 in D arm; 65 in T300+D arm; 33 in T arm; 45 in T75+D arm. Median OS was higher for patients in the T300+D (16.16 months) and T arms (17.54 arms) compared to D (13.57 months) and T75+D (11.30 months).

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of the new active substance, tremelimumab (T), in combination with the already approved PD-L1 inhibitor durvalumab (D) for the treatment of unresectable hepatocellular carcinoma (uHCC) is primarily based on the pivotal Himalaya study. This was a randomised, open-label, multicentre Phase III study in patients with uHCC not eligible for locoregional therapy. Patients were recruited from 181 sites across 16 countries, mostly from countries with an EU-like population. No prior systemic therapy was allowed and only patients with mild or no symptoms pertaining to the HCC and/or liver cirrhosis were

eligible, which is not considered reflective of the general patient population with uHCC. However, the inclusion and exclusion criteria are reflected in the SmPC section 5.1, so this is acceptable. 1324 patients were randomised to 4 arms, durvalumab monotherapy (D, n=389); tremelimumab single dose 300 mg + durvalumab (T300+D, n=393); Tremelimumab 75 mg x 4 + durvalumab (T75+D, n=153); and sorafenib (S, n=389). Randomization was stratified according to macrovascular invasion (yes versus no), etiology of liver disease (hepatitis B virus [confirmed HBV] versus hepatitis C virus [confirmed HCV] versus others), and ECOG PS (0 versus 1). The stratification factors are considered clinically relevant as they are important prognostic factors for the outcome of uHCC. Other important prognostic factors could have been added, such as AFP levels; however, considering the size of the pivotal trial, it is considered appropriate to limit the number of stratification factors to three. Additional supportive evidence of clinical efficacy was provided from study 22, a randomised, phase I/II, open-label study.

The overall design of the pivotal Himalaya study is endorsed as it allows to assess the efficacy of the proposed dosing of tremelimumab single dose 300 mg + durvalumab 1500 mg iv followed by durvalumab monotherapy 1500 mg iv Q4W (T300+D) versus standard of care (Sorafenib - S) in the proposed first-line setting. Moreover, the Applicant included a durvalumab monotherapy arm and an arm with another combination regimen of T75+D, which was abolished after some time.

Baseline characteristics for patients included in the Himalaya study showed that the median age in the relevant arms (T300+D vs the S arm vs the T300+D arm of study 22) were 65 vs 64 vs 66 years of age; however, approximately half of the patients were <65 years of age and the vast majority of the patients were male (83.2% vs 86.6% vs 86.7%) and of white (46.3% vs 46% vs 36%) or Asian (49.6% vs 48.6% vs 58.7%) race. Alcohol use was only registered in the pivotal Himalaya study and it is noted that a large proportion was never users (~40%) or former users (~45%). The baseline characteristics are well balanced between the arms, but only approximately 46% of the study population are considered EU like according to region and race characteristics. Moreover, the alcohol use in the study population is considered lower than for the EU population.

Disease characteristics showed that most patients were ECOG PS 0 (~60%) and of advanced Barcelona Clinic Liver Cancer (BCLC) stage C (~80%). Additionally, macrovascular invasion and/or extrahepatic spread was observed for many (~65%). However, the poor prognostic factor of AFP >400 ng/ml was observed in approximately a third of the patients, which is also reflected by the distribution of the Child-Pugh score categories, showing that many of the included patients have a favourable prognosis.

It is noted that only a third of the included patients had tumours that were PD-L1 positive (TIP≥1%) and that there were ~13% of the patients in the D+T containing arms, who had missing data on PD-L1 status. Overall, the important disease characteristics are well distributed between the treatment arms. Regarding the level of poor prognostic factors, it is considered that these are lower than expected for the targeted patient population, which should be kept in mind when interpreting the results of the studies.

The primary objective of the pivotal Himalaya study was to assess superiority of efficacy of T300+D vs standard of care (sorafenib) regarding OS for the ITT population. The two key secondary objectives of the trial were to assess non-inferiority of the efficacy of durvalumab monotherapy versus SoC (sorafenib) regarding OS and superiority of the efficacy of durvalumab monotherapy versus SoC (sorafenib) regarding OS. Other important secondary endpoints are PFS and overall response rate plus duration of response. The current MAA for tremelimumab is based on efficacy results from the primary objective of the pivotal study. The primary objective and key secondary objectives pertain to overall survival, and this is endorsed, considering the targeted patient population and the robustness of OS as an endpoint.

Although it does not preclude a benefit/risk assessment, the overall conduct of the study is considered suboptimal due to the changes in primary endpoints and sample size especially considering the open

label design. Additionally, interpretation of radiological assessments of tumour response is hindered because of the lack of blinded central review of the assessments in the final analysis.

Efficacy data and additional analyses

The pivotal Himalaya study:

The primary objective was met as treatment with T300+D showed a statistically significant and clinically relevant improvement in **OS** compared to standard of care, sorafenib. Median OS was improved from 13.77 months to 16.43 months, HR 0.78 (96.02% CI: 0.65, 0.92). The analysis was performed after ~33 months of follow up and 66.7% of events in the T300+D arm and 75.3% events in the S arm, respectively, so the OS data are considered mature. The KM curves begin to separate after 4 months of therapy and stay separated.

It is acknowledged that Himalaya was primarily designed to demonstrate superiority of T300+D vs S in terms of OS and was amended to demonstrate non-inferiority of D vs S for OS as the next analysis in the hierarchical testing. Moreover, the study design allowed for assessment of the contribution of tremelimumab to the combination regimen, through prespecified exploratory analyses of T300+D vs D, which showed an HR of 0.90 (95%CI: 0.76, 1.07) for OS, which was 16.43 months vs 16.56 months, respectively. The Applicant has further argued that due to the complementary mechanisms of action of tremelimumab and durvalumab, the reduction in risk of death, more patients achieving a BOR of CR plus more durable responses in the T300+D arm that the addition of tremelimumab is justified. Additionally, a post-hoc analysis calculating piecewise constant treatment effects favoured T300+D independent of selected time interval when compared to either S or D, further illustrating the OS benefit offered by T300+D compared with D. However, there are remaining uncertainties regarding the optimal dosing regimen e.g. would more than one single dose of tremelimumab have had a significant contribution to added efficacy compared to T300+D and is 300 mg the optimal dose or could the same efficacy and maybe a better safety profile have been obtained with several but lower doses of tremelimumab.

The secondary endpoint of **ORR** by investigator was 20.1% for the T300+D arm compared to 5.1% in the sorafenib arm, while 3.1% of the patients in the T300+D arm had a complete response (CR) vs no patients in the S arm. Confirmed ORR by BIRC was slightly lower in the T300+D arm (18.8%), but this is not directly comparable with ORR by Investigator, since the evaluation was only done in a subset of patients. The improvement of the response rate both by INV and by BIRC is considered borderline clinically meaningful in its magnitude; however, the responders in the T300+D arm (n=79) had durable responses with a median **DoR** of 22.34 months.

The **PFS** analyses were not in the testing hierarchy, so they are not controlled for multiplicity. PFS by investigator was not clinically significantly improved, since the median PFS was 3.78 months in the T300+D arm versus 4.07 months in the S arm; HR 0.90 (95%CI: 0.77, 1.05). The PFS analyses are mature with 85.2% and 84.1% events in the T300+D and S arms, respectively and the KM curves do not clearly separate at any time. This finding is considered consistent with the pattern of efficacy generally observed for immunotherapy, where PFS benefit is often lacking or of a small magnitude, while OS is often clinically significantly improved. Hence, this could be considered an acceptable result as the primary endpoint was OS, and that an OS benefit has been shown for the proposed treatment regimen T300+D vs S.

However, there are uncertainties when interpreting PFS and ORR considering that the final analysis in an open label setting was done by investigators. Additionally, assessments were performed using RECIST 1.1. although in the immunotherapy setting, irRECIST may have been more appropriate/more informative. Nevertheless, rate of possible pseudoprogression of HCC with CTLA-4/PD-L1 inhibition is currently unknown, which creates uncertainty around PFS and ORR data, since patients with confirmed

PD (according to RECIST 1.1) were discontinued from IP. Confirmation of PD required a follow-up scan evaluated by Confirmation of Radiological Progression criteria preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD. In the HIMALAYA study, confirmation of PD was not mandatory as RECIST 1.1 used for final analysis does not require confirmation of progression and therefore was not done in the study. The lack of data on potential pseudoprogression is of concern as patients could be denied potentially beneficial treatment. This issue remains to be answered in clinical practice.

Additionally, assessments by BICR were performed only on a subset of patients evaluable for 32 weeks of follow up (for interim analysis 1), and included RECIST 1.1, irRECIST, and mRECIST. Following interim analysis 1, no further BICR assessments were performed. In view of the robustness of the primary endpoint (OS) the Applicant's approach regarding PFS can be accepted.

The study design of Himalaya allowed for assessment of the contribution of tremelimumab to the combination regimen, through prespecified exploratory analyses of T300+D vs D, which showed an HR of 0.90 (95%CI: 0.76, 1.07) for OS, which was 16.43 months vs 16.56 months, respectively. The Applicant has also provided a rationale for the addition of tremelimumab to durvalumab for the HCC indication, which is primarily based on the following: the combined blockade of CTLA-4 and PD-(L)1 to increase effector T-cell response through two distinct yet complementary mechanisms of action and an approximately 10% reduction in the average risk of death was observed with T300+D versus D. Moreover, while the objective response rates with T300+D and D were similar in HIMALAYA (20.1% vs. 17.0%), twice as many BORs of CR were observed in HIMALAYA with T300+D (12 [3.1%]) compared to D (6 [1.5%]).

The provided arguments are acknowledged and it is accepted that the Applicant seeks an approval for the T300+D regimen. However, there remains to be unanswered questions to what would have been the optimal dosing regimen e.g. would more than one single dose of tremelimumab have had a significant contribution to added efficacy compared to T300+D and is 300 mg the optimal dose or could the same efficacy and maybe a better safety profile have been obtained with several but lower doses of tremelimumab.

PRO data was collected as a secondary endpoint. Since the pivotal study was open-label and PRO endpoints were not multiplicity-protected, clinical meaningfulness of PRO data is not considered relevant and the Applicant has agreed to delete them from the SmPC.

No additional information on changes in AFP were provided as these data were not collected in the HIMALAYA study.

Relevant **subgroup analyses** of the primary endpoint of OS show that the benefit of T300+D vs S is maintained across important subgroups of age of less than or ≥ 65 years, HBV or other reasons for liver disease, ECOG performance status, macrovascular invasion (MVI), AFP at baseline and BCLB score C.

<u>The supportive Study 22:</u>

The supportive study 22 was a randomized, multicentre, open-label, multipart study designed to evaluate the safety and efficacy of durvalumab and/or tremelimumab in patients with advanced HCC in the 2L+ setting. The study was comprised of multiple parts, but the results from the T300+D arm is considered of most relevance for the proposed indication (n=75), although the study randomised patients to 4 treatment arms. Patients were immunotherapy-naïve patients with advanced HCC, who had progressed on, were intolerant to, or refused treatment with sorafenib or another approved Vascular endothelial growth factor receptor (VEGFR) TKI. Due to different stratification factors in Parts 2A and 3 and lack of randomisation altogether in Part 2B, pooling of efficacy data is inappropriate. Fortunately, OS data from

Part 2 and 3 is available separately as well. Although there were no interim analyses planned in the Original Protocol (09 April 2015), in the end 6 interim analyses were performed (and added through Protocol Amendments).

Baseline data for the T300+D arm showed that the median age was 66 years and the vast majority of the patients were male (86.7%) and of white (36%) or Asian (58.7%) race. Disease characteristics show that the vast majority of patients were ECOC PS 0 (61.3%) and disease of advanced BCLC stage C (77.3%) plus macrovascular invasion and/or extrahepatic spread (77.3%).

In conclusion, Study 22 is an early phase, exploratory study that was amended several times. The primary objective of the study was to assess the safety and tolerability, whereas efficacy was a secondary objective and there was no hierarchical testing procedure or correction for multiplicity. The efficacy data quality should be viewed in this light. Moreover, out of the 75 patients in Study 22, who were treated with T300+D, only 55 patients had received prior treatment with sorafenib and were thus truly 'second line'. Due to the lack of a SoC comparator arm in Study 22, there is no benchmark for the results of the T300+D study arm, as there is insufficient understanding of the relevance of the efficacy as observed in the other study arms. In addition, the exploratory design of Study 22 and in particular the lack of a SAP that would provide for formal comparisons between the study arms, hampers both the contextualisation and interpretation of the efficacy results obtained in these 55 patients. As a consequence, the time-to-event endpoints cannot be interpreted adequately. It is noted that the ORR in these 55 patients was only 20%, which cannot be considered dramatic (EMA/CHMP/205/95 Rev.5).

The final analysis showed a median OS of 17 months (65.3% events) for patients who received the proposed dosing regimen of T300+D, while the ORR was 24% and the duration of response (DoR) was 18 months. The Applicant compares this result to durvalumab monotherapy; however, this is not approved for or is standard of care (SOC) in the 2L+ setting, so this comparison is not considered relevant for the current application. Since none of the arms of Study 22 contained any SOC, the results for the T300+D arm are considered supportive of efficacy for the proposed dosing regimen in the first-line setting.

2.4.3. Conclusions on the clinical efficacy

The results from the pivotal Himalaya study show a statistically significant and clinically relevant OS benefit over standard of care in the first-line setting of unresectable HCC.

2.5. Clinical safety

Introduction

Table 43. Summary of Clinical Studies Included in the Submission Package

Study Name (Study Number) Status DCO	**Phase Study Design**	**Patient Population**	**No. of patients Assigned and Treated (Treatment group)**
Studies in HCC			
HIMALAYA (D419CC00002) Ongoing 27 Aug 2021	Phase III Randomized, open-label, comparative, multicenter	Advanced HCC with no prior systemic therapy for HCC	1324 (total) **393 (T300+D)** 389 (D) 389 (Sorafenib) 153 (T75+D)

Table 43. Summary of Clinical Studies Included in the Submission Package

Study Name (Study Number) Status DCO	Phase Study Design	Patient Population	No. of patients Assigned and Treated (Treatment group)
Study 22 (D4190C00022) Complete 06 Nov 2020	Phase II Randomized, open-label, comparative, multicenter	Advanced unresectable HCC	326 (total) **74 (T300+D)** 101 (D) 82 (T75+D) 69 (T)

HCC-tumor Pools

The pivotal safety dataset used to characterize the safety profile of durvalumab in combination with tremelimumab in the proposed indication was derived from pooled data from HIMALAYA and Study 22. The populations in the HCC-tumor pools are described below:

- **HCC T300+D pool:** This population consists of all patients who have received at least 1 dose of durvalumab given at a dose of 1500mg IV Q4W (or equivalent) in combination with tremelimumab 300 mg IV x 1 dose (or equivalent) for HCC.
- **HCC D pool:** This population consists of all patients who have received at least 1 dose of durvalumab monotherapy given at a dose of 20 mg/kg Q4W IV (or equivalent) for HCC.

Patient exposure

Table 44. Summary of Study Treatment Exposure (Safety Analysis Set)

	HCC-tumor pool		Pan-tumor pool		
	T300+D	**D**	**D**	**T75+D**	**T750**
	(N = 462)	**(N = 492)**	**(N = 4045)**	**(N = 3319)**	**(N = 643)**
Total treatment duration (weeks) [a]					
n	462	492	4045	3319	643
Mean (SD)	41.9 (44.34)	38.0 (41.49)	28.9 (32.18)	30.1 (37.06)	17.1 (18.46)
Median (min, max)	20.0 (2, 185)	19.9 (1, 193)	16.1 (0, 220)	16.0 (1, 222)	12.0 (1, 176)
Total treatment years	370.6	358.6	2240.4	1912.2	210.5
Total treatment duration (weeks); n (%)					
≥ 24	222 (48.1)	225 (45.7)	1671 (41.3)	1219 (36.7)	129 (20.1)
≥ 52	131 (28.4)	120 (24.4)	793 (19.6)	590 (17.8)	36 (5.6)
≥ 76	92 (19.9)	82 (16.7)	246 (6.1)	292 (8.8)	14 (2.2)
≥ 104	66 (14.3)	53 (10.8)	179 (4.4)	219 (6.6)	6 (0.9)

Table 45. Duration of Exposure (Safety Analysis Set)

		D (N = 388)	T300+D (N = 388)			T75+D (N = 152)			S (N = 374)
			Tremelimumab		Durvalumab	Tremelimumab		Durvalumab	
		Total study [a]	Initial treatment [b]	Rechallenge	Total study [a]	Initial treatment [b]	Rechallenge	Total study [a]	
Total treatment duration [c] (months)	N	388	388	30	388	152	12	152	374
	Mean (SD)	9.7 (10.16)	0.9 (0.04)	0.9 (0.00)	10.6 (10.82)	3.0 (1.14)	2.2 (1.27)	9.3 (10.38)	7.5 (8.48)
	Median (min, max)	5.5 (0.2, 44.4)	0.9 (0.4, 0.9)	0.9 (0.9, 0.9)	5.5 (0.4, 42.7)	3.6 (0.7, 5.6)	1.9 (0.9, 3.7)	4.6 (0.7, 44.2)	4.1 (0.1, 38.6)
	Total treatment years	312.7	29.6	2.3	341.7	38.6	2.2	118.0	234.9
Actual treatment duration [d] (months)	N	388	388	30	388	152	12	152	374
	Mean (SD)	9.3 (9.84)	0.9 (0.04)	0.9 (0.00)	10.1 (10.47)	2.9 (1.02)	2.1 (1.26)	8.9 (9.98)	7.2 (8.35)
	Median (min, max)	4.6 (0.2, 44.4)	0.9 (0.4, 0.9)	0.9 (0.9, 0.9)	5.5 (0.4, 42.6)	3.6 (0.7, 3.7)	1.8 (0.9, 3.7)	4.6 (0.7, 41.9)	3.7 (0.1, 38.6)
	Total treatment years	301.4	29.6	2.3	326.2	36.6	2.1	112.7	224.5
Total duration of cycle delays – total study (months)	N	180	0		194	60		88	182
	Mean (SD)	0.7 (1.22)	NA		1.0 (1.28)	0.4 (0.54)		0.7 (0.95)	0.7 (0.69)
	Median (min, max)	0.3 (0.0, 10.3)	NA		0.5 (0.0, 94)	0.1 (0.0, 1.9)		0.3 (0.0, 5.4)	0.5 (0.0, 3.7)

[a] Total study exposure includes initial treatment and rechallenge phase, where rechallenge occurred.

[b] Initial treatment phase includes the start of study treatment to last treatment or last treatment prior to rechallenge, where rechallenge occurred.

[c] Total treatment duration for immunotherapies = (last dose date + 27 days or date of death or DCO, whichever occurred earlier − first dose date + 1)/(365.25/12). Total treatment duration for S = (last dose date or date of death or DCO, whichever occurred earlier − first dose date + 1)/(365.25/12).

[d] Actual treatment duration = (intended exposure – total duration of dose delays)/(365.25/12).

Patients who took infusion earlier than planned were set to 0 for calculation.

D, durvalumab monotherapy 1500 mg Q4W; DCO, data cut-off; max, maximum; min, minimum; NA, not applicable; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; SD, standard deviation; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Source: Table 14.3.1.1.

Adverse events

Table 46. Overview of AEs in the HIMALAYA T300+D and S Arms and the HCC T300+D Pool (Safety Analysis Set)

	Number (%) of patients [a]		
	HCC T300+D pool	HIMALAYA T300+D arm	HIMALAYA S arm
AE category	**(N = 462)**	**(N = 388)**	**(N = 374)**
Any AE	451 (97.6)	378 (97.4)	357 (95.5)
Any AE possibly related to any study treatment [b]	355 (76.8)	294 (75.8)	317 (84.8)
Any AE possibly related to durvalumab [b]	349 (75.5)	288 (74.2)	NA
Any AE possibly related to tremelimumab [b]	224 (48.5)	175 (45.1)	NA
Any AE possibly related to sorafenib [b]	NA	NA	317 (84.8)
Any AE of CTCAE Grade 3 or 4 [c]	240 (51.9)	196 (50.5)	196 (52.4)
Any AE of CTCAE Grade 3 or 4 [c] possibly related to any study treatment [b]	127 (27.5)	100 (25.8)	138 (36.9)
Any AE with outcome of death	34 (7.4)	30 (7.7)	27 (7.2)
Any SAE (including events with outcome of death) [d]	189 (40.9)	157 (40.5)	111 (29.7)
Any AE leading to discontinuation of any study treatment	63 (13.6)	53 (13.7)	63 (16.8)
Any AE leading to discontinuation of any study treatment, possibly related to any study treatment [b]	41 (8.9)	32 (8.2)	41 (11.0)
Any AE leading to dose delay or interruption of any study treatment [e]	149 (32.3)	134 (34.5)	178 (47.6)
Any AE leading to dose delay or interruption of any study treatment [e], possibly related to any study treatment [b]	NE	83 (21.4)	144 (38.5)

[a] Patients with multiple events in the same category are counted only once in that category; patients with events in more than 1 category are counted once in each of those categories.

[b] As assessed by the investigator. Missing responses are counted as related.

[c] All CTCAE grades per patient, not just the maximum, are considered when identifying whether there is a Grade 3 or 4.

[d] Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.

[e] Includes AEs on the AE CRF form with action taken indicating dose delay or dose interruption, and AEs meeting study level dose delay definitions, where applicable.

Note: Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study treatment or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

AE, adverse event; CRF, case report form; CSR, Clinical Study Report; CTCAE, Common Terminology Criteria for Adverse Events (version 4.03); HCC, hepatocellular carcinoma; HCC T300+D pool, all patients from HIMALAYA and Study 22 who have received at least 1 dose of durvalumab given at a dose of 1500 mg IV Q4W (or equivalent) in combination with tremelimumab 300 mg IV × 1 dose (or equivalent) for HCC for any line of therapy; IV, intravenous; NA, not applicable; NE, not evaluated; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; SAE, serious adverse event; T300+D, tremelimumab 300 mg (4 mg/kg) for a single priming dose and durvalumab 1500 mg (20 mg/kg) Q4W.

Common adverse events

Table 47. Adverse Events by Preferred Term Occurring in ≥10% of Patients in Any Treatment Arm (Safety Analysis Set)

System organ class MedDRA preferred term	Number (%) of patients [a] D (N = 388)	 T300+D (N = 388)	 T75+D (N = 152)	 S (N = 374)
Patients with any AE	345 (88.9)	378 (97.4)	145 (95.4)	357 (95.5)
Gastrointestinal disorders	195 (50.3)	236 (60.8)	79 (52.0)	265 (70.9)
Diarrhoea	58 (14.9)	103 (26.5)	32 (21.1)	167 (44.7)
Constipation	42 (10.8)	36 (9.3)	12 (7.9)	35 (9.4)
Abdominal pain	37 (9.5)	46 (11.9)	26 (17.1)	63 (16.8)
Nausea	37 (9.5)	47 (12.1)	14 (9.2)	53 (14.2)
Skin and subcutaneous tissue disorders	135 (34.8)	198 (51.0)	70 (46.1)	243 (65.0)
Pruritus	56 (14.4)	89 (22.9)	27 (17.8)	24 (6.4)
Rash	40 (10.3)	87 (22.4)	27 (17.8)	51 (13.6)
Alopecia	5 (1.3)	2 (0.5)	1 (0.7)	53 (14.2)
Palmar-plantar erythrodysaesthesia syndrome	1 (0.3)	3 (0.8)	3 (2.0)	174 (46.5)
Investigations	123 (31.7)	155 (39.9)	50 (32.9)	122 (32.6)
Aspartate aminotransferase increased	56 (14.4)	48 (12.4)	16 (10.5)	24 (6.4)
Alanine aminotransferase increased	44 (11.3)	36 (9.3)	10 (6.6)	20 (5.3)
Metabolism and nutrition disorders	101 (26.0)	145 (37.4)	42 (27.6)	123 (32.9)
Decreased appetite	53 (13.7)	66 (17.0)	25 (16.4)	67 (17.9)
General disorders and administration site conditions	149 (38.4)	180 (46.4)	73 (48.0)	174 (46.5)
Asthenia	49 (12.6)	39 (10.1)	20 (13.2)	44 (11.8)
Fatigue	38 (9.8)	66 (17.0)	25 (16.4)	71 (19.0)
Pyrexia	36 (9.3)	50 (12.9)	16 (10.5)	33 (8.8)
Oedema peripheral	24 (6.2)	33 (8.5)	16 (10.5)	19 (5.1)
Respiratory, thoracic and mediastinal disorders	73 (18.8)	90 (23.2)	34 (22.4)	95 (25.4)
Cough	31 (8.0)	30 (7.7)	17 (11.2)	22 (5.9)
Psychiatric disorders	41 (10.6)	57 (14.7)	14 (9.2)	26 (7.0)
Insomnia	21 (5.4)	40 (10.3)	10 (6.6)	16 (4.3)
Endocrine disorders	41 (10.6)	92 (23.7)	32 (21.1)	20 (5.3)
Hypothyroidism	19 (4.9)	47 (12.1)	20 (13.2)	16 (4.3)
Vascular disorders	31 (8.0)	48 (12.4)	12 (7.9)	73 (19.5)
Hypertension	17 (4.4)	23 (5.9)	6 (3.9)	68 (18.2)

[a] Each patient has only been represented with the maximum reported CTCAE grade for each system organ class/preferred term.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurred first).

Preferred terms are ordered by decreasing frequency in the D arm.

Patients with an AE of maximum CTCAE Grade 5 after the DCO have been reset to 'unknown' at the DCO. This affected 0 patients in the D arm, 0 patients in the T300+D arm, 0 patients in the T75+D arm, and 0 patients in the S arm.

MedDRA version 23.1. CTCAE version 4.03.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; D, durvalumab monotherapy 1500 mg Q4W; DCO, data cut-off; IP, investigational product; MedDRA, Medical Dictionary for Regulatory Activities; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Table 48. Adverse Events and Event Rate Occurring in ≥ 10% of Patients in Any Treatment Group by Preferred Term (Safety Analysis Set)

MedDRA preferred term	HCC-tumor pool				Pan-tumor pool					
	T300+D		D		D		T75+D		T750	
	(N = 462)		(N = 492)		(N = 4045)		(N = 3319)		(N = 643)	
	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]	Number (%) of patients [a]	Event rate (per 100 pt years) [b]
Patients with any AE	451 (97.6)	121.7	443 (90.0)	123.5	3825 (94.6)	170.7	3151 (94.9)	164.8	609 (94.7)	289.3
Pruritus	118 (25.5)	31.8	76 (15.4)	21.2	463 (11.4)	20.7	623 (18.8)	32.6	173 (26.9)	82.2
Diarrhoea	117 (25.3)	31.6	78 (15.9)	21.7	650 (16.1)	29.0	780 (23.5)	40.8	257 (40.0)	122.1
Rash	115 (24.9)	31.0	53 (10.8)	14.8	395 (9.8)	17.6	442 (13.3)	23.1	128 (19.9)	60.8
Fatigue	83 (18.0)	22.4	62 (12.6)	17.3	997 (24.6)	44.5	775 (23.4)	40.5	150 (23.3)	71.3
Decreased appetite	76 (16.5)	20.5	68 (13.8)	19.0	769 (19.0)	34.3	687 (20.7)	35.9	166 (25.8)	78.9
Aspartate aminotransferase increased	71 (15.4)	19.2	85 (17.3)	23.7	277 (6.8)	12.4	268 (8.1)	14.0	35 (5.4)	16.6
Pyrexia	64 (13.9)	17.3	44 (8.9)	12.3	525 (13.0)	23.4	494 (14.9)	25.8	100 (15.6)	47.5
Abdominal pain	58 (12.6)	15.7	54 (11.0)	15.1	318 (7.9)	14.2	307 (9.2)	16.1	84 (13.1)	39.9
Nausea	57 (12.3)	15.4	49 (10.0)	13.7	678 (16.8)	30.3	625 (18.8)	32.7	166 (25.8)	78.9
Hypothyroidism	55 (11.9)	14.8	33 (6.7)	9.2	380 (9.4)	17.0	378 (11.4)	19.8	29 (4.5)	13.8
Alanine aminotransferase increased	53 (11.5)	14.3	70 (14.2)	19.5	256 (6.3)	11.4	242 (7.3)	12.7	31 (4.8)	14.7
Lipase increased	46 (10.0)	12.4	28 (5.7)	7.8	87 (2.2)	3.9	212 (6.4)	11.1	37 (5.8)	17.6
Constipation	45 (9.7)	12.1	54 (11.0)	15.1	652 (16.1)	29.1	571 (17.2)	29.9	103 (16.0)	48.9
Cough	45 (9.7)	12.1	43 (8.7)	12.0	643 (15.9)	28.7	435 (13.1)	22.7	102 (15.9)	48.5
Anaemia	43 (9.3)	11.6	36 (7.3)	10.0	509 (12.6)	22.7	532 (16.0)	27.8	96 (14.9)	45.6
Arthralgia	43 (9.3)	11.6	45 (9.1)	12.5	559 (13.8)	25.0	376 (11.3)	19.7	54 (8.4)	25.7
Asthenia	42 (9.1)	11.3	52 (10.6)	14.5	463 (11.4)	20.7	437 (13.2)	22.9	77 (12.0)	36.6
Vomiting	34 (7.4)	9.2	23 (4.7)	6.4	423 (10.5)	18.9	405 (12.2)	21.2	107 (16.6)	50.8
Weight decreased	32 (6.9)	8.6	15 (3.0)	4.2	285 (7.0)	12.7	349 (10.5)	18.3	71 (11.0)	33.7
Back pain	30 (6.5)	8.1	50 (10.2)	13.9	448 (11.1)	20.0	329 (9.9)	17.2	41 (6.4)	19.5
Dyspnoea	28 (6.1)	7.6	26 (5.3)	7.2	598 (14.8)	26.7	456 (13.7)	23.8	151 (23.5)	71.7

[a]Number (%) of patients with AEs, sorted in decreasing frequency of preferred term (HCC-tumor pool T300+D column).

[b]Number of patients with AEs divided by the total duration of treatment across all patients in given group, multiplied by 100.

Patients with multiple AEs are counted once for each preferred term.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Disease progression AEs reported in Study 1108, Study 6, Study 10, and Study 11 are not included in this summary.MedDRA version 23.1.

AE, adverse event; D, durvalumab 1500 mg (or equivalent); HCC, hepatocellular carcinoma; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; pt, patient; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg Q4W; T75+D, durvalumab given at a dose of 20 mg/kg Q4W (or equivalent) IV in combination with tremelimumab 1 mg/kg Q4W (or equivalent), for any line of therapy (across tumor types); T750, tremelimumab monotherapy 10 mg/kg Q4W (or equivalent) for any line of therapy (across tumor types). Source: Table 2.7.4.2.5, Pooled Safety Outputs, Module 5.3.5.3.

Table 49. Adverse Events of Maximum CTCAE Grade 3 or 4 by System Organ Class and Preferred Term (Frequency ≥5% in Any Treatment Arm) (Safety Analysis Set)

System organ class MedDRA preferred term	Number (%) of patients [a]			
	D (N = 388)	T300+D (N = 388)	T75+D (N = 152)	S (N = 374)
Patients with AE of maximum CTCAE Grade 3 or 4	144 (37.1)	196 (50.5)	60 (39.5)	196 (52.4)
Investigations	56 (14.4)	69 (17.8)	27 (17.8)	53 (14.2)
Aspartate aminotransferase increased	26 (6.7)	20 (5.2)	10 (6.6)	12 (3.2)
Lipase increased	16 (4.1)	24 (6.2)	5 (3.3)	11 (2.9)
Vascular disorders	5 (1.3)	11 (2.8)	5 (3.3)	23 (6.1)
Hypertension	4 (1.0)	7 (1.8)	3 (2.0)	23 (6.1)
Skin and subcutaneous tissue disorders	1 (0.3)	15 (3.9)	4 (2.6)	49 (13.1)
Palmar-plantar erthyrodysaesthesia syndrome	0	0	1 (0.7)	34 (9.1)

[a] Each patient is only represented with the maximum reported CTCAE grade for each system organ class / preferred term.

Preferred terms are ordered by decreasing frequency in the D arm.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurred first).

MedDRA version 23.1. CTCAE version 4.03.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; D, durvalumab monotherapy 1500 mg Q4W; DCO, data cut-off; IP, investigational product; MedDRA, Medical Dictionary for Regulatory Activities; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Table 50. Adverse Events of Maximum CTCAE Grade 3 or 4 by Preferred Term (≥ 5% of Patients in Any Treatment Group) (Safety Analysis Set)

MedDRA preferred term	Number (%) of patients [a]				
	HCC-tumor pool		Pan-tumor pool		
	T300+D	D	D	T75+D	T750
	(N = 462)	(N = 492)	(N = 4045)	(N = 3319)	(N = 643)
Patients with any AE of maximum CTCAE Grade 3 or 4	222 (48.1)	188 (38.2)	1600 (39.6)	1642 (49.5)	344 (53.5)
Aspartate aminotransferase increased	34 (7.4)	36 (7.3)	83 (2.1)	73 (2.2)	15 (2.3)
Lipase increased	33 (7.1)	17 (3.5)	51 (1.3)	143 (4.3)	20 (3.1)
Diarrhoea	18 (3.9)	8 (1.6)	34 (0.8)	92 (2.8)	81 (12.6)
Anaemia	13 (2.8)	11 (2.2)	177 (4.4)	169 (5.1)	20 (3.1)
Colitis	10 (2.2)	0	10 (0.2)	44 (1.3)	32 (5.0)
Dyspnoea	3 (0.6)	4 (0.8)	126 (3.1)	93 (2.8)	40 (6.2)

[a]Number (%) of patients with AEs, sorted in decreasing frequency of preferred term (HCC-tumor pool T300+D column).

Patients with multiple AEs are counted once for each preferred term.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication, or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Disease progression AEs reported in Study 1108, Study 6, Study 10, and Study 11 are not included in this summary.

MedDRA version 23.1.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events (version 4.03); D, durvalumab 1500 mg (or equivalent); HCC, hepatocellular carcinoma; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg Q4W; T75+D, durvalumab given at a dose of 20 mg/kg Q4W (or equivalent) IV in combination with tremelimumab 1 mg/kg Q4W (or equivalent), for any line of therapy (across tumor types); T750, tremelimumab monotherapy 10 mg/kg Q4W (or equivalent) for any line of therapy (across tumor types).

Table 51. Adverse Events with CTCAE Grade 3 or 4, Possibly Related to Investigational Product (Frequency of ≥ 2%) by System Organ Class, Preferred Term and Maximum Reported CTCAE Grade (HCC Pool; Safety Analysis Set)

System organ class / MedDRA Preferred term	Maximum reported CTCAE grade	Number (%) of patients [a] HCC-tumor pool T300 + D (N = 462)	D (N = 492)
Patients with any treatment-related AE	Total	57 (12.3)	27 (5.5)
	Grade 3	50 (10.8)	24 (4.9)
	Grade 4	7 (1.5)	3 (0.6)
Gastrointestinal disorders	Total	14 (3.0)	6 (1.2)
	Grade 3	14 (3.0)	6 (1.2)
Diarrhoea	Total	14 (3.0)	6 (1.2)
	Grade 3	14 (3.0)	6 (1.2)
Investigations	Total	44 (9.5)	22 (4.5)
	Grade 3	37 (8.0)	19 (3.9)
	Grade 4	7 (1.5)	3 (0.6)
Amylase increased	Total	15 (3.2)	3 (0.6)
	Grade 3	14 (3.0)	2 (0.4)
	Grade 4	1 (0.2)	1 (0.2)
Aspartate aminotransferase increased	Total	18 (3.9)	12 (2.4)
	Grade 3	18 (3.9)	11 (2.2)
	Grade 4	0	1 (0.2)
Lipase increased	Total	22 (4.8)	8 (1.6)
	Grade 3	16 (3.5)	7 (1.4)
	Grade 4	6 (1.3)	1 (0.2)

Each patient has only been represented with the maximum reported CTCAE grade for each system organ class / preferred term.
Number (%) of patients with AEs, sorted by international SOC order and alphabetical PT and then maximum grade.
Table includes events occurring in greater than or equal to 2% of patients in either group.
Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Possibly related to treatment, as assessed by the investigator. Missing responses are counted as related.
MedDRA version 23.1.
CTCAE (version 4.03).
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; D = durvalumab 1500 mg Q4W; HCC = hepatocellular carcinoma; PT = preferred term; MedDRA = Medical Dictionary for Regulatory Activities; QxW = every X weeks; SOC = System Organ Class; T300+D = tremelimumab 300 mg for single dose and durvalumab 1500 mg Q4W.

Adverse drug reactions (ADRs)

Table 52: Adverse reactions in patients with HCC treated with durvalumab in combination with tremelimumab 300 mg

	Durvalumab in combination with tremelimumab 300 mg (n=462)			
Adverse Reaction	**Frequency of any Grade**		**Frequency of Grade 3-4**	
Infections and infestations				
Upper respiratory tract infections[a]	Common	39 (8.4%)		
Pneumonia[b]	Common	20 (4.3%)	Common	6 (1.3%)
Influenza	Common	10 (2.2%)		
Dental and oral soft tissue infections[c]	Common	6 (1.3%)		
Oral candidiasis	Uncommon	3 (0.6%)		
Blood and lymphatic system disorders				
Immune thrombocytopenia[d]	Not known			
Endocrine disorders				

	Durvalumab in combination with tremelimumab 300 mg (n=462)			
Adverse Reaction	**Frequency of any Grade**		**Frequency of Grade 3-4**	
Hypothyroidism[e]	Very common	60 (13.0%)		
Hyperthyroidism[f]	Common	44 (9.5%)	Uncommon	1 (0.2%)
Thyroiditis[g]	Common	8 (1.7%)		
Adrenal insufficiency	Common	6 (1.3%)	Uncommon	1 (0.2%)
Hypopituitarism/Hypophysitis	Uncommon	4 (0.9%)		
Diabetes insipidus[d]	Not known			
Type 1 diabetes mellitus[d]	Not known			
Nervous system disorders				
Myasthenia gravis	Uncommon	2 (0.4%)		
Meningitis	Uncommon	1 (0.2%)	Uncommon	1 (0.2%)
Guillain-Barré syndrome[d]	Not known			
Encephalitis[d]	Not known			
Cardiac disorders				
Myocarditis	Uncommon	2 (0.4%)		
Respiratory, thoracic and mediastinal disorders				
Cough/Productive cough	Very common	50 (10.8%)	Uncommon	1 (0.2%)
Pneumonitis[h]	Common	11 (2.4%)	Uncommon	1 (0.2%)
Dysphonia	Uncommon	4 (0.9%)		
Interstitial lung disease	Uncommon	1 (0.2%)		
Gastrointestinal disorders				
Diarrhoea	Very common	117 (25.3%)	Common	18 (3.9%)
Abdominal pain[i]	Very common	91 (19.7%)	Common	10 (2.2%)
Lipase increased	Common	46 (10.0%)	Common	33 (7.1%)
Amylase increased	Common	41 (8.9%)	Common	20 (4.3%)
Colitis[j]	Common	16 (3.5%)	Common	12 (2.6%)
Pancreatitis[k]	Common	6 (1.3%)	Uncommon	3 (0.6%)
Intestinal perforation[d]	Not known			
Large intestine perforation[d]	Not known			
Hepatobiliary disorders				
Aspartate aminotransferase increased/Alanine aminotransferase increased[l]	Very common	83 (18.0%)	Common	41 (8.9%)
Hepatitis[m]	Common	23 (5.0%)	Common	8 (1.7%)
Skin and subcutaneous tissue disorders				
Rash[n]	Very common	150 (32.5%)	Common	14 (3.0%)
Pruritus	Very common	118 (25.5%)		
Dermatitis[o]	Common	6 (1.3%)		
Night sweats	Common	6 (1.3%)		
Pemphigoid	Uncommon	1 (0.2%)		
Musculoskeletal and connective tissue disorders				
Myalgia	Common	16 (3.5%)	Uncommon	1 (0.2%)
Myositis	Uncommon	3 (0.6%)	Uncommon	1 (0.2%)
Polymyositis	Uncommon	1 (0.2%)	Uncommon	1 (0.2%)
Renal and urinary disorders				
Blood creatinine increased	Common	21 (4.5%)	Uncommon	2 (0.4%)
Dysuria	Common	7 (1.5%)		
Nephritis[p]	Uncommon	3 (0.6%)	Uncommon	2 (0.4%)
Cystitis noninfective[d]	Not known			
General disorders and administration site conditions				
Pyrexia	Very common	64 (13.9%)	Uncommon	1 (0.2%)
Oedema peripheral[q]	Very common	48 (10.4%)	Uncommon	2 (0.4%)
Injury, poisoning and procedural complications				

	Durvalumab in combination with tremelimumab 300 mg (n=462)			
Adverse Reaction	**Frequency of any Grade**		**Frequency of Grade 3-4**	
Infusion-related reaction[r]	Common	6 (1.3%)		

[a] Includes nasopharyngitis, pharyngitis, rhinitis, tracheobronchitis and upper respiratory tract infection.

[b] Includes pneumocystis jirovecii pneumonia and pneumonia.

[c] Includes periodontitis, pulpitis dental, tooth abscess and tooth infection.

[d] Adverse reaction was not observed in the HCC pool, but was reported in patients treated with durvalumab or durvalumab + tremelimumab in AstraZeneca-sponsored clinical studies.

[e] Includes blood thyroid stimulating hormone increased, hypothyroidism and immune-mediated hypothyroidism.

[f] Includes blood thyroid stimulating hormone decreased and hyperthyroidism.

[g] Includes autoimmune thyroiditis, immune-mediated thyroiditis, thyroiditis and thyroiditis subacute.

[h] Includes immune-mediated pneumonitis and pneumonitis.

[i] Includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.

[j] Includes colitis, enteritis and enterocolitis.

[k] Includes pancreatitis and pancreatitis acute.

[l] Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased.

[m] Includes autoimmune hepatitis, hepatitis, hepatocellular injury, hepatotoxicity and immune-mediated hepatitis.

[n] Includes eczema, erythema, rash, rash macular, rash maculo-papular, rash papular and rash pruritic.

[o] Includes dermatitis and immune-mediated dermatitis.

[p] Includes autoimmune nephritis and immune-mediated nephritis.

[q] Includes oedema peripheral and peripheral swelling.

[r] Includes infusion-related reaction and urticaria.

Adverse events of special interest

Table 53. Overview of imAEs in the HIMALAYA T300+D and S Arms and the HCC T300+D Pool (Safety Analysis Set)

	Number (%) of patients [a]		
	HCC T300+D pool	**HIMALAYA T300+D arm**	**HIMALAYA S arm**
AE category	**(N = 462)**	**(N = 388)**	**(N = 374)**
Any AE	167 (36.1)	142 (36.6)	28 (7.5)
Any AE of CTCAE Grade 3 or 4	62 (13.4)	51 (13.1)	9 (2.4)
Any SAE (including AEs with outcome of death) [b]	47 (10.2)	40 (10.3)	4 (1.1)
Any AE with outcome of death	6 (1.3)	6 (1.5)	0
Received systemic corticosteroids	119 (25.8)	97 (25.0)	15 (4.0)
Received high dose corticosteroids	94 (20.3)	78 (20.1)	7 (1.9)
Received endocrine therapy	69 (14.9)	65 (16.8)	13 (3.5)
Received other immunosuppressants	15 (3.2)	15 (3.9)	0
Any AE leading to discontinuation of study treatment	26 (5.6)	22 (5.7)	6 (1.6)

[f] Patients with multiple events in the same category are counted only once in that category; patients with events in more than 1 category are counted once in each of those categories.

[g] Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.

Note: Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study treatment or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

AE, adverse event; CSR, Clinical Study Report; CTCAE, Common Terminology Criteria for Adverse Events (version 4.03); HCC, hepatocellular carcinoma; HCC T300+D pool, all patients from HIMALAYA and Study 22 who have received at least 1 dose of durvalumab given at a dose of 1500 mg IV Q4W (or equivalent) in combination with tremelimumab 300 mg IV × 1 dose (or equivalent) for HCC for any line of therapy; IV, intravenous; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; SAE, serious adverse event; T300+D, tremelimumab 300 mg (4 mg/kg) for a single priming dose and durvalumab 1500 mg (20 mg/kg) Q4W.

Table 54. Immune-Mediated Adverse Events Categories Reported for > 2% of Patients in the HCC Pool (Safety Analysis Set)

	Number (%) of patients [a]			
	HCC T300+D Pool (N = 462)		HCC D Pool (N = 492)	
imAE category	**Any Grade**	**CTCAE Grade 3 or 4**	**Any Grade**	**CTCAE Grade 3 or 4**
Any imAE	167 (36.1)	62 (13.4)	81 (16.5)	31 (6.3)
Hypothyroid events	45 (9.7)	0	25 (5.1)	0
Hepatic events	34 (7.4)	23 (5.0)	31 (6.3)	21 (4.3)
Diarrhoea/colitis	30 (6.5)	17 (3.7)	7 (1.4)	3 (0.6)
Dermatitis/rash	26 (5.6)	9 (1.9)	4 (0.8)	1 (0.2)
Hyperthyroid	21 (4.5)	1 (0.2)	6 (1.2)	0
Other rare/ miscellaneous	10 (2.2)	2 (0.4)	2 (0.4)	0

[h] Patients with multiple events in the same category are counted only once in that category; patients with events in more than one category are counted once in each of those categories.

Includes AEs with an onset date on or after the date of first date or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study treatment or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events (version 4.03); D, durvalumab 1500 mg (20 mg/kg) Q4W; HCC, hepatocellular carcinoma; imAE, immune-mediated adverse event; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg (4 mg/kg) for a single priming dose and durvalumab 1500 mg (20 mg/kg) Q4W.

In the HCC pool (n=462), the following immune mediated adverse drug reactions have been reported:

- immune-mediated pneumonitis occurred in 6 (1.3%) patients, including Grade 3 in 1 (0.2%) patient and Grade 5 (fatal) in 1 (0.2%) patient. The median time to onset was 29 days (range: 5-774 days). Six patients received systemic corticosteroids, and 5 of the 6 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient also received other immunosuppressants. Treatment was discontinued in 2 patients. Resolution occurred in 3 patients.

- immune-mediated hepatitis occurred in 34 (7.4%) patients, including Grade 3 in 20 (4.3%) patients, Grade 4 in 1 (0.2%) patient and Grade 5 (fatal) in 3 (0.6%) patients. The median time to onset was 29 days (range: 13-313 days). All patients received systemic corticosteroids, and 32 of the 34 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Nine patients also received other immunosuppressants. Treatment was discontinued in 10 patients. Resolution occurred in 13 patients.

- immune-mediated colitis or diarrhoea occurred in 31 (6.7%) patients, including Grade 3 in 17 (3.7%) patients. The median time to onset was 23 days (range: 2-479 days). All patients received systemic corticosteroids, and 28 of the 31 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Four patients also received other immunosuppressants. Treatment was discontinued in 5 patients. Resolution occurred in 29 patients.

Intestinal perforation was observed in patients receiving Imfinzi in combination with tremelimumab (rare) in studies outside of the HCC pool.

- immune-mediated hypothyroidism occurred in 46 (10.0%) patients. The median time to onset was 85 days (range: 26-763 days). One patient received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). All patients required other therapy including hormone

replacement therapy. Resolution occurred in 6 patients. Immune-mediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 4 patients.

- immune-mediated hyperthyroidism occurred in 21 (4.5%) patients, including Grade 3 in 1 (0.2%) patient. The median time to onset was 30 days (range: 13-60 days). Four patients received systemic corticosteriods, and all of the four patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Twenty patients required other therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker). One patient discontinued treatment due to hyperthyroidism. Resolution occurred in 17 patients.

- immune-mediated thyroiditis occurred in 6 (1.3%) patients. The median time to onset was 56 days (range: 7-84 days). Two patients received systemic corticosteroids, and 1 of the 2 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). All patients required other therapy including hormone replacement therapy. Resolution occurred in 2 patients.

- immune-mediated adrenal insufficiency occurred in 6 (1.3%) patients, including Grade 3 in 1 (0.2%) patient. The median time to onset was 64 days (range: 43-504 days). All patients received systemic corticosteroids, and 1 of the 6 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Resolution occurred in 2 patients.

- immune-mediated hypophysitis/hypopituitarism occurred in 5 (1.1%) patients. The median time to onset for the events was 149 days (range: 27-242 days). Four patients received systemic corticosteroids, and 1 of the 4 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Three patients also required endocrine therapy. Resolution occurred in 2 patients.

- immune-mediated nephritis occurred in 4 (0.9%) patients, including Grade 3 in 2 (0.4%) patients. The median time to onset was 53 days (range: 26-242 days). All patients received systemic corticosteroids, and 3 of the 4 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in 2 patients. Resolution occurred in 3 patients.

- immune-mediated rash or dermatitis (including pemphigoid) occurred in 26 (5.6%) patients, including Grade 3 in 9 (1.9%) patients and Grade 4 in 1 (0.2%) patient. The median time to onset was 25 days (range: 2-933 days). All patients received systemic corticosteroids and 14 of the 26 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient received other immunosuppressants. Treatment was discontinued in 3 patients. Resolution occurred in 19 patients.

Immune-mediated type 1 diabetes mellitus was observed in patients receiving Imfinzi in combination with tremelimumab (uncommon) in studies outside of the HCC pool.

Serious adverse event/deaths/other significant events

Table 55. Serious Adverse Events by System Organ Class and Preferred Term (≥ 2% Patients in Any Treatment Arm; Safety Analysis Set)

System Organ Class MedDRA Preferred Term	Number (%) of patients [a]			
	D (N = 388)	T300+D (N = 388)	T75+D (N = 152)	S (N = 374)
Patients with any SAE	115 (29.6)	157 (40.5)	52 (34.2)	111 (29.7)
Gastrointestinal disorders	22 (5.7)	48 (12.4)	14 (9.2)	35 (9.4)
Oesophageal varices haemorrhage	4 (1.0)	1 (0.3)	3 (2.0)	2 (0.5)
Diarrhoea	2 (0.5)	9 (2.3)	4 (2.6)	6 (1.6)
Infections and infestations	21 (5.4)	43 (11.1)	10 (6.6)	23 (6.1)
Sepsis	4 (1.0)	8 (2.1)	2 (1.3)	0
Pneumonia	3 (0.8)	7 (1.8)	6 (3.9)	8 (2.1)
General disorders and administration site conditions	18 (4.6)	11 (2.8)	7 (4.6)	9 (2.4)
Death	8 (2.1)	4 (1.0)	5 (3.3)	5 (1.3)
Hepatobiliary disorders	16 (4.1)	14 (3.6)	8 (5.3)	15 (4.0)
Hepatitis	1 (0.3)	3 (0.8)	4 (2.6)	0
Respiratory, thoracic, and mediastinal disorders	11 (2.8)	9 (2.3)	6 (3.9)	9 (2.4)
Pneumonitis	2 (0.5)	4 (1.0)	3 (2.0)	1 (0.3)
Blood and lymphatic system disorders	2 (0.5)	6 (1.5)	4 (2.6)	3 (0.8)
Anaemia	1 (0.3)	5 (1.3)	3 (2.0)	2 (0.5)

[a] Each patient has only been represented with the maximum reported CTCAE grade for each system organ class/preferred term.

Preferred terms are ordered by decreasing frequency in the D arm.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurred first).

Patients with an AE of maximum CTCAE Grade 5 after the DCO have been reset to 'unknown' at the DCO. This affected 0 patients in the D arm, 0 patients in the T300+D arm, 0 patients in the T75+D arm, and 0 patients in the S arm.

MedDRA version 23.1. CTCAE version 4.03.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; D, durvalumab monotherapy 1500 mg Q4W; DCO, data cut-off; IP, investigational product; MedDRA, Medical Dictionary for Regulatory Activities; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Treatment-related Serious Adverse Events

In the Safety Analysis Set, treatment-related SAEs were reported for more patients in the tremelimumab-containing arms than in the D and S arms (D, 8.2%; T300+D, 17.5%; T75+D, 18.4%; S, 9.4% patients). There were no treatment-related SAEs by PT reported by ≥ 5% patients. As with all SAEs, the majority of treatment-related SAEs occurred in the CTCAE Grade 3 or 4 category within every SOC. The frequency of treatment-related CTCAE Grade 3 or 4 SAEs was 24 patients (6.2%) in arm D, 44 patients (11.3%) in arm T300+D, 19 patients (12.5%) in arm T75+D, and 22 patients (5.9%) in arm S. Few treatment-related SAEs resulted in death.

17.5% of the SAEs (40.5%) in the T300+D arm were treatment-related. The below table describes treatment-related SAEs for the T300+D and S arms of the Himalaya study and the HCC pool (frequency more than 1%).

Table 56. Time to Onset, Discontinuation, Resolution and Duration of Treatment related Serious Adverse Events (Frequency of ≥ 1%) by Preferred Term

Preferred term	Parameters (days)	Descriptive statistics	HIMALAYA			HCC-tumour pool	
			T300 + D (N = 388)	D (N = 388)	S (N = 374)	T300 + D (N = 462)	D (N = 492)
Colitis	Time to onset	n	6	2	0	9	2
		Mean	219.5	104.0		228.2	104.0
		Minimum	8	11		8	11
		Median	21.5	104.0		25.0	104.0
		Maximum	815	197		815	197
	Duration of events	n	6	2	0	9	2
		Mean	54.2	39.5		50.3	39.5
		Minimum	7	36		7	36
		Median	51.0	39.5		43.0	39.5
		Maximum	99	43		99	43
	Time to discontinuation	n	2	1	0	2	1
		Mean	1.0	1.0		1.0	1.0
		Minimum	1	1		1	1
		Median	1.0	1.0		1.0	1.0
		Maximum	1	1		1	1
	Time to resolution	n	6	1	0	9	1
		Mean	54.2	43.0		50.3	43.0
		Minimum	7	43		7	43
		Median	51.0	43.0		43.0	43.0
		Maximum	99	43		99	43
Diarrhoea	Time to onset	n	7	1	6	9	2
		Mean	24.1	63.0	78.7	37.8	39.5
		Minimum	2	63	25	2	16
		Median	14.0	63.0	67.5	24.0	39.5
		Maximum	66	63	162	115	63
	Duration of events	n	7	1	6	9	2
		Mean	37.3	82.0	22.3	34.6	43.5
		Minimum	7	82	1	7	5
		Median	52.0	82.0	4.5	25.0	43.5
		Maximum	72	82	112	72	82
	Time to discontinuation	n	0	0	1	0	1
		Mean			102.0		1.0
		Minimum			102		1
		Median			102.0		1.0
		Maximum			102		1
	Time to resolution	n	7	0	5	9	1
		Mean	37.3		4.4	34.6	5.0
		Minimum	7		1	7	5
		Median	52.0		4.0	25.0	5.0
		Maximum	72		8	72	5
Hepatic function abnormal	Time to onset	n	1	5	1	2	9
		Mean	36.0	119.2	7.0	257.0	115.1
		Minimum	36	15	7	36	15
		Median	36.0	29.0	7.0	257.0	43.0
		Maximum	36	467	7	478	467
	Duration of events	n	1	5	1	2	9
		Mean	141.0	133.8	37.0	169.5	124.2
		Minimum	141	13	37	141	9
		Median	141.0	92.0	37.0	169.5	57.0
		Maximum	141	413	37	198	413
	Time to discontinuation	n	1	0	0	2	3
		Mean	29.0			200.5	112.0
		Minimum	29			29	1
		Median	29.0			200.5	57.0
		Maximum	29			372	278
	Time to resolution	n	1	3	1	1	4
		Mean	141.0	66.3	37.0	141.0	52.0
		Minimum	141	13	37	141	9
		Median	141.0	92.0	37.0	141.0	52.5
		Maximum	141	94	37	141	94

Note: Table includes events occurring in ≥ 1% of patients in either group.

D = durvalumab 1500 mg Q4W; HCC = hepatocellular carcinoma; QxW = every X weeks; S = sorafenib 400 mg twice daily; T300+D = tremelimumab 300 mg for single dose and durvalumab 1500 mg Q4W.

Deaths

Table 57. All Deaths (Full Analysis Set) – DCO: 27 AUG 2021

Category	Number (%) of subjects			
	Durva 1500 mg (N=389)	Treme 300 mg x1 dose + Durva 1500 mg (N=393)	Treme 75 mg x4 doses + Durva 1500 mg (N=153)	Sora 400 mg BID (N=389)
Total number of deaths	280 (72.0)	262 (66.7)	123 (80.4)	293 (75.3)
Death related to disease under investigation only	245 (63.0)	221 (56.2)	103 (67.3)	256 (65.8)
AE with outcome of death only	19 (4.9)	24 (6.1)	9 (5.9)	20 (5.1)
AE with outcome of death only (AE start date falling after 90 days follow up period)	2 (0.5)	3 (0.8)	1 (0.7)	0
Number of subjects with death related to disease progression and an AE with outcome of death	6 (1.5)	8 (2.0)	4 (2.6)	7 (1.8)
Other deaths[a]	8 (2.1)	6 (1.5)	6 (3.9)	10 (2.6)

[a] Subjects who died and are not captured in the earlier categories.
Death related to disease under investigation is determined by the investigator.
Rows are mutually exclusive, subjects are only reported in one category.

Table 58. Adverse Events with Outcome of Death by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term	Number (%) of patients [a]			
	D (N = 388)	T300+D (N = 388)	T75+D (N = 152)	S (N = 374)
Immune-mediated hepatitis	0	2 (0.5)	0	0
Internal haemorrhage	0	1 (0.3)	0	0
Myocarditis	0	1 (0.3)	0	0
Liver abscess	0	0	0	1 (0.3)
Peritonitis	0	0	0	1 (0.3)
Pneumonia	0	0	2 (1.3)	2 (0.5)
Sepsis	0	1 (0.3)	1 (0.7)	0
Cerebral haematoma	0	0	0	1 (0.3)
Cerebral haemorrhage	0	1 (0.3)	0	0
Haemorrhage intracranial	0	2 (0.5)	0	0
Hepatic encephalopathy	0	0	0	1 (0.3)
Myasthenia gravis	0	1 (0.3)	0	0
Nervous system disorder	0	1 (0.3)	0	0
Thrombocytopenia	0	1 (0.3)	0	0
Haematuria	0	0	0	1 (0.3)
Acute respiratory distress syndrome	0	1 (0.3)	0	0
Dyspnoea	0	0	0	1 (0.3)
Epistaxis	0	0	0	1 (0.3)
Pneumonitis	0	2 (0.5)	0	0
Pulmonary embolism	0	1 (0.3)	0	1 (0.3)
Respiratory failure	0	0	0	1 (0.3)

[a] Each patient has only been represented with the maximum reported CTCAE grade for each preferred term.
Preferred terms are ordered by decreasing frequency in the D arm.
Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurred first).
Patients with an AE of maximum CTCAE Grade 5 after the DCO have been reset to 'unknown' at the DCO. This affected 0 patients in the D arm, 0 patients in the T300+D arm, 0 patients in the T75+D arm, and 0 patients in the S arm.
MedDRA version 23.1. CTCAE version 4.03.

Below is the table of the treatment-related (as assessed by the investigator) AEs leading to death.

Table 59. Adverse Events with outcome of death, possibility related to investigational product by system organ class, preferred term and maximum reported CTCAE grade (Safety Analysis Set)

System organ class / MedDRA Preferred term	Maximum reported CTCAE grade	Number (%) of subjects[a]			
		Durva 1500 mg (N=388)	Treme 300 mg x1 dose + Durva 1500 mg (N=388)	Treme 75 mg x4 doses + Durva 1500 mg (N=152)	Sora 400 mg BID (N=374)
Subjects with any AE	Grade 5	0	9 (2.3)	2 (1.3)	3 (0.8)
Infections and infestations	Grade 5	0	0	1 (0.7)	0
Septic shock	Grade 5	0	0	1 (0.7)	0
Nervous system disorders	Grade 5	0	2 (0.5)	0	1 (0.3)
Cerebral haematoma	Grade 5	0	0	0	1 (0.3)
Myasthenia gravis	Grade 5	0	1 (0.3)	0	0
Nervous system disorder	Grade 5	0	1 (0.3)	0	0
Cardiac disorders	Grade 5	0	1 (0.3)	0	0
Myocarditis	Grade 5	0	1 (0.3)	0	0
Respiratory, thoracic and mediastinal disorders	Grade 5	0	2 (0.5)	0	0
Acute respiratory distress syndrome	Grade 5	0	1 (0.3)	0	0
Pneumonitis	Grade 5	0	1 (0.3)	0	0
Hepatobiliary disorders	Grade 5	0	4 (1.0)	1 (0.7)	1 (0.3)
Hepatic failure	Grade 5	0	1 (0.3)	1 (0.7)	1 (0.3)
Hepatitis	Grade 5	0	1 (0.3)	0	0
Immune-mediated hepatitis	Grade 5	0	2 (0.5)	0	0
Renal and urinary disorders	Grade 5	0	0	0	1 (0.3)
Haematuria	Grade 5	0	0	0	1 (0.3)
General disorders and administration site conditions	Grade 5	0	0	1 (0.7)	0
Multiple organ dysfunction syndrome	Grade 5	0	0	1 (0.7)	0

[a] Each subject has only been represented with the maximum reported CTCAE grade for each system organ class / preferred term.
Number (%) of subjects with AEs, sorted by international SOC order and alphabetical PT and then maximum grade.
Includes adverse events with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).
Subjects who have a maximum CTCAE grade 5 post the DCO, have been reset to unknown at the DCO. This affects 0 subjects in group 'Durva 1500 mg' and 0 subjects in group 'Treme 300 mg x1 dose + Durva 1500 mg' and 0 subjects in group 'Treme 75 mg x4 doses + Durva 1500 mg' and 0 subjects in group 'Sora 400 mg BID'.
Possibly related to treatment, as assessed by the investigator. Missing responses are counted as related.
MedDRA version 23.1.
CTCAE = Common Terminology Criteria for Adverse Events (version 4.03).
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Laboratory findings

Haematology

Table 60. Clinically important changes in haematology and clinical chemistry parameters (Safety Analysis set) – DCO: 27 AUG 2021

	n/N# (%) of subjects											
	Durva 1500 mg (N=388)			Treme 300 mg x1 dose + Durva 1500 mg (N=388)			Treme 75 mg x4 doses + Durva 1500 mg (N=152)			Sora 400 mg BID (N=374)		
Parameter	>= 1 CTCAE grade changes	>= 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	>= 1 CTCAE grade changes	>= 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	>= 1 CTCAE grade changes	>= 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	>= 1 CTCAE grade changes	>= 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
B-Hemoglobin	158/ 373 (42.4)	24/ 373 (6.4)	18/ 373 (4.8)	195/ 378 (51.6)	26/ 378 (6.9)	18/ 378 (4.8)	61/ 148 (41.2)	14/ 148 (9.5)	8/ 148 (5.4)	142/ 352 (40.3)	25/ 352 (7.1)	21/ 352 (6.0)
B-Leukocytes	112/ 370 (30.3)	11/ 370 (3.0)	5/ 370 (1.4)	76/ 376 (20.2)	8/ 376 (2.1)	3/ 376 (0.8)	35/ 147 (23.8)	2/ 147 (1.4)	2/ 147 (1.4)	106/ 352 (30.1)	11/ 352 (3.1)	4/ 352 (1.1)
B-Lymphocytes	160/ 371 (43.1)	64/ 371 (17.3)	32/ 371 (8.6)	156/ 377 (41.4)	78/ 377 (20.7)	42/ 377 (11.1)	62/ 147 (42.2)	25/ 147 (17.0)	19/ 147 (12.9)	138/ 351 (39.3)	68/ 351 (19.4)	35/ 351 (10.0)
B-Neutrophils	58/ 372 (15.6)	20/ 372 (5.4)	5/ 372 (1.3)	48/ 378 (12.7)	15/ 378 (4.0)	3/ 378 (0.8)	22/ 148 (14.9)	7/ 148 (4.7)	2/ 148 (1.4)	48/ 351 (13.7)	21/ 351 (6.0)	7/ 351 (2.0)
B-Platelets	108/ 372 (29.0)	12/ 372 (3.2)	8/ 372 (2.2)	109/ 378 (28.8)	14/ 378 (3.7)	6/ 378 (1.6)	41/ 148 (27.7)	7/ 148 (4.7)	5/ 148 (3.4)	122/ 352 (34.7)	16/ 352 (4.5)	11/ 352 (3.1)

Table 61. Clinically Important Changes in Haematology Parameters (Safety Analysis Set)

	n/N (%) of patients									
	HCC-tumor pool				Pan-tumor pool					
	T300+D (N = 462)		D (N = 492)		D (N = 4045)		T75+D (N = 3319)		T750 (N = 643)	
Parameter	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
Hemoglobin	31/452 (6.9)	22/452 (4.9)	31/476 (6.5)	23/476 (4.8)	209/3868 (5.4)	193/3868 (5.0)	195/3162 (6.2)	178/3162 (5.6)	28/538 (5.2)	25/538 (4.6)
Leukocytes	14/450 (3.1)	5/450 (1.1)	15/473 (3.2)	6/473 (1.3)	75/3868 (1.9)	22/3868 (0.6)	59/3158 (1.9)	16/3158 (0.5)	11/585 (1.9)	4/585 (0.7)
Lymphocytes - Low	86/431 (20.0)	51/431 (11.8)	81/450 (18.0)	38/450 (8.7)	738/3828 (19.3)	506/3828 (13.2)	617/3126 (19.7)	418/3126 (13.4)	48/513 (9.4)	37/513 (7.2)
Neutrophils	19/431 (4.4)	4/431 (0.9)	24/451 (5.3)	6/451 (1.3)	119/3833 (3.1)	37/3833 (1.0)	87/3104 (2.8)	18/3104 (0.6)	15/544 (2.8)	5/544 (0.9)
Platelets	14/452 (3.1)	6/452 (1.3)	16/475 (3.4)	14/475 (2.9)	64/3865 (1.7)	44/3865 (1.1)	59/3154 (1.9)	36/3154 (1.1)	14/585 (2.4)	9/585 (1.5)

Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of study medication or until the initiation of the first subsequent therapy (whichever occurred first).

Patient's worst (highest CTCAE grade) changes from baseline are used.

Percentages had been calculated using the number of patients with a baseline value and a post baseline value.

CTCAE, Common Terminology Criteria for Adverse Events (version 4.03); D, durvalumab 1500 mg (or equivalent); HCC, hepatocellular carcinoma; IV, intravenous; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg Q4W; T75+D, durvalumab given at a dose of 20 mg/kg Q4W (or equivalent) IV in combination with tremelimumab 1 mg/kg Q4W (or equivalent), for any line of therapy (across tumor types); T750, tremelimumab monotherapy 10 mg/kg Q4W (or equivalent) for any line of therapy (across tumor types).

Source: Table 2.7.4.10.2, Pooled Safety Outputs, Module 5.3.5.3.

Clinical chemistry

Table 62. Clinically Important Changes in Clinical Chemistry Parameters (Safety Analysis Set)

Clinical chemistry parameter	n/N [a] (%) of patients											
	D (N = 388)			T300+D (N = 388)			T75+D (N = 152)			S (N = 374)		
	≥ 1 CTCAE grade changes	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 1 CTCAE grade changes	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 1 CTCAE grade changes	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 1 CTCAE grade changes	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
ALT	194/374 (51.9)	52/374 (13.9)	49/374 (13.1)	212/377 (56.2)	71/377 (18.8)	67/377 (17.8)	76/148 (51.4)	24/148 (16.2)	22/148 (14.9)	185/352 (52.6)	41/352 (11.6)	43/352 (12.2)
Albumin	89/370 (24.1)	62/370 (16.8)	2/370 (0.5)	116/371 (31.3)	66/371 (17.8)	2/371 (0.5)	42/147 (28.6)	26/147 (17.7)	1/147 (0.7)	130/350 (37.1)	81/350 (23.1)	6/350 (1.7)
ALP	145/371 (39.1)	22/371 (5.9)	30/371 (8.1)	154/374 (41.2)	34/374 (9.1)	31/374 (8.3)	70/148 (47.3)	11/148 (7.4)	18/148 (12.2)	156/351 (44.4)	17/351 (4.8)	19/351 (5.4)
AST	205/373 (55.0)	65/373 (17.4)	86/373 (23.1)	238/377 (63.1)	87/377 (23.1)	101/377 (26.8)	80/148 (54.1)	28/148 (18.9)	40/148 (27.0)	191/350 (54.6)	48/350 (13.7)	74/350 (21.1)
Bilirubin	153/374 (40.9)	62/374 (16.6)	28/374 (7.5)	156/377 (41.4)	76/377 (20.2)	31/377 (8.2)	64/147 (43.5)	22/147 (15.0)	14/147 (9.5)	167/352 (47.4)	71/352 (20.2)	37/352 (10.5)
Calcium increased	16/367 (4.4)	9/367 (2.5)	6/367 (1.6)	11/367 (3.0)	2/367 (0.5)	2/367 (0.5)	4/146 (2.7)	1/146 (0.7)	0/146	8/344 (2.3)	3/344 (0.9)	2/344 (0.6)
Calcium decreased	130/367 (35.4)	1/367 (0.3)	1/367 (0.3)	123/367 (33.5)	5/367 (1.4)	0/367	50/146 (34.2)	2/146 (1.4)	0/146	148/344 (43.0)	3/344 (0.9)	1/344 (0.3)
Creatinine	70/372 (18.8)	6/372 (1.6)	1/372 (0.3)	78/374 (20.9)	10/374 (2.7)	5/374 (1.3)	25/148 (16.9)	7/148 (4.7)	0/148	52/352 (14.8)	11/352 (3.1)	3/352 (0.9)
Glucose increased	142/368 (38.6)	63/368 (17.1)	31/368 (8.4)	144/370 (38.9)	70/370 (18.9)	50/370 (13.5)	55/145 (37.9)	22/145 (15.2)	21/145 (14.5)	101/347 (29.1)	43/347 (12.4)	13/347 (3.7)
Glucose decreased	16/368 (4.3)	6/368 (1.6)	3/368 (0.8)	22/370 (5.9)	12/370 (3.2)	4/370 (1.1)	5/145 (3.4)	3/145 (2.1)	2/145 (1.4)	19/347 (5.5)	8/347 (2.3)	3/347 (0.9)
Magnesium increased	0/12	0/12	0/12	0/18	0/18	0/18	0/9	0/9	0/9	0/5	0/5	0/5
Magnesium decreased	0/12	0/12	0/12	2/18 (11.1)	1/18 (5.6)	0/18	0/9	0/9	0/9	1/5 (20.0)	0/5	0/5
Potassium increased	94/369 (25.5)	27/369 (7.3)	17/369 (4.6)	105/370 (28.4)	31/370 (8.4)	14/370 (3.8)	35/147 (23.8)	9/147 (6.1)	4/147 (2.7)	75/352 (21.3)	24/352 (6.8)	9/352 (2.6)
Potassium decreased	35/369 (9.5)	5/369 (1.4)	5/369 (1.4)	57/370 (15.4)	11/370 (3.0)	11/370 (3.0)	25/147 (17.0)	4/147 (2.7)	4/147 (2.7)	46/352 (13.1)	10/352 (2.8)	10/352 (2.8)
Sodium increased	17/371 (4.6)	0/371	0/371	19/372 (5.1)	2/372 (0.5)	1/372 (0.3)	13/147 (8.8)	0/147	0/147	23/352 (6.5)	3/352 (0.9)	1/352 (0.3)
Sodium decreased	139/371 (37.5)	23/371 (6.2)	25/371 (6.7)	171/372 (46.0)	57/372 (15.3)	57/372 (15.3)	70/147 (47.6)	15/147 (10.2)	15/147 (10.2)	140/352 (39.8)	39/352 (11.1)	39/352 (11.1)

[a] N corresponds to the number of patients with baseline value recorded.

Only worsening of CTCAE grades are presented.

Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of study treatment or until the initiation of the first subsequent therapy (whichever occurred first).

CTCAE version 4.03.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; D, durvalumab monotherapy 1500 mg Q4W; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Source: Table 14.3.7.1.2.2.

Table 63. Clinically Important Changes in Clinical Chemistry Parameters (Safety Analysis Set)

Parameter	HCC-tumor pool			
	T300+D (N = 462)		D (N = 492)	
	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
AST	101/451 (22.4)	121/451 (26.8)	87/476 (18.3)	112/476 (23.5)
Alkaline phosphatase	38/448 (16.0)	35/448 (7.8)	30/474 (6.3)	44/474 (9.3)
ALT	85/451 (18.8)	80/451 (17.7)	62/477 (13.0)	56/477 (11.7)
Albumin	71/445 (16.0%)	2/445 (0.4)	74/473 (15.6)	7/473 (1.5)
Total bilirubin	91/451 (20.2%)	35/451 (7.8)	81/477 (17.0)	40/477 (8.4)
Creatinine	22/448 (4.9)	8/448 (1.8)	19/475 (4.0)	3/475 (0.6)
GGT	9/93 (9.7)	20/93 (21.5)	8/116 (6.9)	20/116 (17.2)
Lipase	117/423 (27.7)	101/423 (23.9)	75/460 (16.3)	54/460 (11.7)
Amylase	81/426 (19.0)	63/426 (14.8)	37/459 (8.1)	32/459 (7.0)
Glucose (high)	86/444 (19.4)	65/444 (14.6)	75/471 (15.9)	39/471 (8.3)
Potassium (high)	36/444 (8.1)	17/444 (3.8)	38/471 (8.1)	21/471 (4.5)
Sodium (low)	64/446 (14.3)	64/446 (14.3)	35/474 (7.4)	37/474 (7.8)
Corrected Calcium (low)	5/367 (1.4)	0/367 (0)	1/367 (0.3)	1/367 (0.3)

Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of study medication or until the initiation of the first subsequent therapy (whichever occurred first).Patient's worst (highest CTCAE grade) changes from baseline are used. Percentages had been calculated using the number of patients with a baseline value and a post baseline value. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events (version 4.03); D, durvalumab 1500 mg (or equivalent); GGT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; IV, intravenous; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg Q4W; T75+D, durvalumab given at a dose of 20 mg/kg Q4W (or equivalent) IV in combination with tremelimumab 1 mg/kg Q4W (or equivalent), for any line of therapy (across tumor types); T750, tremelimumab monotherapy 10 mg/kg Q4W (or equivalent) for any line of therapy (across tumor types).

Table 64. Hyperglycaemia/new Onset Diabetes Mellitus SMQ AEs in the HCC T300+D Tumour Pool

					Received intervention					Event outcome		
SMQ Category/ MedDRA Preferred Term	Any AE	Any SAE[a]	CTCAE Grade 3-4	CTCAE Grade ≥ 3	Systemic Cortico-Steroids	High Dose Steroid	Other Immuno Suppre-ssants	Requires Endocrine Therapy	Leading to Dis-contin-uation of Study Drug	Resul-ted in Death	Not Resol-ved	Resol-ved
Hyperglycaemia/new onset diabetes mellitus	39 (8.4)	8 (1.7)	16 (3.5)	16 (3.5)	0	0	0	0	2 (0.4)	0	18 (3.9)	21 (4.5)
Diabetes mellitus	11 (2.4)	4 (0.9)	4 (0.9)	4 (0.9)	0	0	0	0	0	0	7 (1.5)	4 (0.9)
Diabetes mellitus inadequate control	2 (0.4)	0	0	0	0	0	0	0	0	0	0	2 (0.4)
Diabetic ketoacidosis	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0	0	0	0	0	1 (0.2)
Hyperglycaemia	22 (4.8)	2 (0.4)	10 (2.2)	10 (2.2)	0	0	0	0	1 (0.2)	0	7 (1.5)	15 (3.2)
Type 2 diabetes mellitus	6 (1.3)	2 (0.4)	2 (0.4)	2 (0.4)	0	0	0	0	1 (0.2)	0	4 (0.9)	2 (0.4)

[a] As assessed by the investigator.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after date of first dose up to and including 90 days following the date of last dose of study medication, or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

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AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; HCC = hepatocellular carcinoma; Q4W = every 4 weeks; SAE = serious adverse event; T300+D = tremelimumab 300 mg for a single dose and durvalumab 1500 mg Q4W; SMQ = Standardised MedDRA Query.

Source: IEMT 0316.2b0.

Liver chemistry

Table 65. Proportion of Patients with Elevated ALT or AST (≥3 x ULN), and Elevated Total Bilirubin (≥ 2 x ULN; Safety Analysis Set)

	Number (%) of patients			
Category	D (N = 388)	T300+D (N = 388)	T75+D (N = 152)	S (N = 374)
ALT or AST ≥ 3 × ULN and BILI > 2 × ULN [a]	46 (11.9)	51 (13.1)	17 (11.2)	47 (12.6)
ALT or AST ≥ 3 × ULN and BILI > 2 × ULN and no ALP ≥ 2 × ULN [a]	19 (4.9)	15 (3.9)	3 (2.0)	23 (6.1)

[a] The onset date of ALT or AST elevation occurred within 14 days prior to or on the date of total bilirubin elevation.

Percentages were calculated based on the number of patients with measurements.

Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of IP or until initiation of the first subsequent therapy (whichever occurred first).

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, total bilirubin; D, durvalumab monotherapy 1500 mg Q4W; Q4W, every 4 weeks; IP, investigational product; S, sorafenib 400 mg twice daily; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; ULN upper limit of normal.

Source: Table 14.3.7.1.4.

Table 66. Liver Function Abnormalities (Safety Analysis Set)

	Number (%) of patients				
	HCC-tumor pool		Pan-tumor pool		
Category	T300+D (N = 462)	D (N = 492)	D (N = 4045)	T75+D (N = 3319)	T750 (N = 643)
ALT or AST					
≥ 3 × to ≤ 5 × ULN	93 (20.1)	84 (17.1)	242 (6.0)	217 (6.5)	27 (4.2)
> 5 × to ≤ 8 × ULN	65 (14.1)	56 (11.4)	127 (3.1)	111 (3.3)	16 (2.5)
> 8 × to ≤ 10 × ULN	26 (5.6)	31 (6.3)	57 (1.4)	28 (0.8)	7 (1.1)
> 10 × to ≤ 20 × ULN	39 (8.4)	33 (6.7)	67 (1.7)	66 (2.0)	4 (0.6)

Category	Number (%) of patients				
	HCC-tumor pool		Pan-tumor pool		
	T300+D (N = 462)	D (N = 492)	D (N = 4045)	T75+D (N = 3319)	T750 (N = 643)
> 20 × ULN	14 (3.0)	11 (2.2)	29 (0.7)	36 (1.1)	5 (0.8)
TBL					
≥ 2 × to ≤ 3 × ULN	29 (6.3)	41 (8.3)	67 (1.7)	39 (1.2)	6 (0.9)
> 3 × to ≤ 5 × ULN	16 (3.5)	18 (3.7)	48 (1.2)	33 (1.0)	1 (0.2)
> 5 × ULN	19 (4.1)	22 (4.5)	56 (1.4)	32 (1.0)	7 (1.1)
Potential Hy's law [a]	57 (12.3)	65 (13.2)	131 (3.2)	85 (2.6)	7 (1.1)

[a] The onset date of ALT or AST elevation should be prior to or on the date of TBL elevation.

Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of study medication or until the initiation of the first subsequent therapy (whichever occurred first).

Patients were counted only once in the worst reported subcategory.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, durvalumab 1500 mg (or equivalent); HCC, hepatocellular carcinoma; IV, intravenous; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg Q4W; T75+D, durvalumab given at a dose of 20 mg/kg Q4W (or equivalent) IV in combination with tremelimumab 1 mg/kg Q4W (or equivalent), for any line of therapy (across tumor types); T750, tremelimumab monotherapy 10 mg/kg Q4W (or equivalent) for any line of therapy (across tumor types); TBL, total bilirubin; ULN, upper limit of normal.

The number of probable DILI or immune-related hepatitis cases were as follows: 2 patients in the D arm ([redacted] and [redacted]); 4 patients in the T300+D arm ([redacted], [redacted], [redacted], and [redacted]); 3 patients for the T75+D arm ([redacted], [redacted], and [redacted]); and 3 patients for the S arm ([redacted], [redacted], and [redacted]).

Four patients in Study 22 had liver function test abnormalities meeting the criteria for Hy's Law for whom the role of durvalumab and/or tremelimumab could not be completely excluded. In the HIMALAYA study, 2 patients in the D arm, 4 patients in the T300+D arm, and 3 patients in the T75+D arm had liver function test abnormalities meeting the criteria for Hy's Law for whom the role of durvalumab and/or tremelimumab could not be completely excluded. Narratives for the 4 patients, who met the Hy's law criteria in the T300+D arm have been provided and has not given rise to any concerns

Thyroid function

Table 67. Abnormal Thyroid Function (Safety Analysis Set)

Category	Number (%) of patients			
	D (N = 388)	T300+D (N = 388)	T75+D (N = 152)	S (N = 374)
Elevated TSH > ULN	150 (38.7)	157 (40.5)	67 (44.1)	178 (47.6)
Elevated TSH > ULN with TSH ≤ ULN at baseline	94 (24.2)	107 (27.6)	47 (30.9)	114 (30.5)
Elevated TSH > 3 × ULN	40 (10.3)	66 (17.0)	28 (18.4)	30 (8.0)
Elevated TSH > 3 × ULN with TSH ≤ ULN at baseline	21 (5.4)	42 (10.8)	18 (11.8)	4 (1.1)
Elevated TSH > 10 × ULN	15 (3.9)	37 (9.5)	13 (8.6)	6 (1.6)
Elevated TSH > 10 × ULN with TSH ≤ ULN at baseline	8 (2.1)	25 (6.4)	11 (7.2)	1 (0.3)
Low TSH < LLN	66 (17.0)	129 (33.2)	43 (28.3)	35 (9.4)
Low TSH < LLN with TSH ≥ LLN at baseline	60 (15.5)	114 (29.4)	39 (25.7)	31 (8.3)

Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of investigational product or until initiation of the first subsequent therapy (whichever occurred first).

D, durvalumab monotherapy 1500 mg Q4W; Q4W, every 4 weeks; LLN, lower limit of normal; S, sorafenib 400 mg twice daily; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

Source: Table 14.3.7.1.6.

Table 68. Abnormal On-Treatment Thyroid Tests (Safety Analysis Set)

Category	Number (%) of patients				
	HCC-tumor pool		Pan-tumor pool		
	T300+D (N = 462)	D (N = 492)	D (N = 4045)	T75+D (N = 3319)	T750 (N = 643)
On-treatment elevated TSH > ULN	180 (39.0)	180 (36.6)	1269 (31.4)	1152 (34.7)	127 (19.8)
On-treatment elevated TSH > ULN with TSH ≤ ULN at baseline *	124	116	780	697	76
with at least one T3 free/T4 free < LLN [a]	73 (58.9)	68 (58.6)	456 (58.5)	420 (60.3)	21 (27.6)
with all other T3 free/T4 free ≥ LLN [a]	41 (33.1)	38 (32.8)	270 (34.6)	216 (31.0)	19 (25.0)
with T3 free/T4 free missing [a]	10 (8.1)	10 (8.6)	54 (6.9)	61 (8.8)	36 (47.4)
On-treatment low TSH < LLN	154 (33.3)	82 (16.7)	880 (21.8)	896 (27.0)	86 (13.4)
On-treatment low TSH < LLN with TSH ≥ LLN at baseline *	136	74	709	778	66
with at least one T3 free/T4 free > ULN [a]	72 (52.9)	28 (37.8)	310 (43.7)	364 (46.8)	11 (16.7)
with all other T3 free/T4 free ≤ ULN [a]	57 (41.9)	36 (48.6)	348 (49.1)	353 (45.4)	19 (28.8)
with T3 free/T4 free missing [a]	7 (5.1)	10 (13.5)	51 (7.2)	61 (7.8)	36 (54.5)
Number of patients with at least one baseline and post-baseline TSH result *	437	464	3679	3028	543
On-treatment elevated TSH > ULN and above baseline [a]	165 (37.8)	162 (34.9)	1108 (30.1)	1011 (33.4)	106 (19.5)

Category	Number (%) of patients				
	HCC-tumor pool		Pan-tumor pool		
	T300+D (N = 462)	D (N = 492)	D (N = 4045)	T75+D (N = 3319)	T750 (N = 643)
On-treatment decreased TSH < LLN and below baseline [a]	148 (33.9)	80 (17.2)	816 (22.2)	848 (28.0)	76 (14.0)

[a] Percentage is based on number of patients in the main category above denoted with a *.

Baseline is defined as the last result obtained prior to the start of study treatment.

Derived from laboratory assessments between the start of treatment and up to and including 90 days following the date of last dose of study medication or until the initiation of the first subsequent therapy (whichever occurred first).

D, durvalumab 1500 mg (or equivalent); HCC, hepatocellular carcinoma; IV, intravenous; LLN, lower limit of normal; Q4W, every 4 weeks; T3, free triiodothyronine; T300+D, tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg Q4W; T4, free thyroxine; T75+D, durvalumab given at a dose of 20 mg/kg Q4W (or equivalent) IV in combination with tremelimumab 1 mg/kg Q4W (or equivalent), for any line of therapy (across tumor types); T750, tremelimumab monotherapy 10 mg/kg Q4W (or equivalent) for any line of therapy (across tumor types); TSH, thyroid stimulating hormone; ULN, upper limit of normal.

45 patients (9.7%) in the HCC pool had imAEs of hypothyroid events and no grade 3, 4, or 5 events were reported. 1 patient needed high-dose corticosteroid treatment and the median time to onset for the imAE of hypothyroid event was 85 days (range: 26 to 763 days).

21 patients (4.5%) in the HCC pool had imAEs of hyperthyroid events. Grade 3 or 4 events were reported in 1 patient (0.2%) and no grade 5 events were reported. 4 patients (0.9%) received high dose corticosteroid treatment and one patient (0.2%) discontinued study treatment. The median time to onset for the imAE of hyperthyroid events was 30 days (range: 13 to 60 days).

Safety in special populations

Intrinsic factors

Age

Table 69. Adverse Events in any Category – Patient Level by Age Group

AE category	Number (%) of patients [a]				
	HCC-tumor pool		Pan-tumor pool		
	T300+D (N1 = 226) (N2 = 173) (N3 = 63)	D (N1 = 254) (N2 = 163) (N3 = 75)	D (N1 = 2250) (N2 = 1356) (N3 = 439)	T75+D (N1 = 1852) (N2 = 1126) (N3 = 341)	T750 (N1 = 315) (N2 = 253) (N3 = 75)
Any AE possibly related to any study treatment [b]					
< 65 years	163 (72.1)	132 (52.0)	1287 (57.2)	1223 (66.0)	214 (67.9)
≥ 65 to < 75 years	138 (79.8)	93 (57.1)	804 (59.3)	781 (69.4)	182 (71.9)
≥ 75 years	54 (85.7)	42 (56.0)	248 (56.5)	249 (73.0)	64 (85.3)
Any AE possibly related to durvalumab [b]					
< 65 years	162 (71.7)	132 (52.0)	1283 (57.0)	1201 (64.8)	0
≥ 65 to < 75 years	136 (78.6)	93 (57.1)	801 (59.1)	770 (68.4)	0
≥ 75 years	51 (81.0)	42 (56.0)	248 (56.5)	244 (71.6)	1 (1.3)
Any AE possibly related to tremelimumab [b]					

Table 69. Adverse Events in any Category – Patient Level by Age Group

AE category	Number (%) of patients [a]				
	HCC-tumor pool		Pan-tumor pool		
	T300+D (N1 = 226) (N2 = 173) (N3 = 63)	D (N1 = 254) (N2 = 163) (N3 = 75)	D (N1 = 2250) (N2 = 1356) (N3 = 439)	T75+D (N1 = 1852) (N2 = 1126) (N3 = 341)	T750 (N1 = 315) (N2 = 253) (N3 = 75)
< 65 years	102 (45.1)	0	0	1137 (61.4)	208 (66.0)
≥ 65 to < 75 years	87 (50.3)	0	0	720 (63.9)	180 (71.1)
≥ 75 years	35 (55.6)	0	0	231 (67.7)	64 (85.3)
Any AE with outcome of death					
< 65 years	9 (4.0)	11 (4.3)	112 (5.0)	110 (5.9)	19 (6.0)
≥ 65 to < 75 years	19 (11.0)	13 (8.0)	90 (6.6)	80 (7.1)	20 (7.9)
≥ 75 years	6 (9.5)	6 (8.0)	29 (6.6)	39 (11.4)	5 (6.7)
Any AE leading to discontinuation of any study treatment					
< 65 years	19 (8.4)	19 (7.5)	188 (8.4)	261 (14.1)	62 (19.7)
≥ 65 to < 75 years	29 (16.8)	19 (11.7)	156 (11.5)	200 (17.8)	69 (27.3)
≥ 75 years	15 (23.8)	9 (12.0)	53 (12.1)	89 (26.1)	24 (32.0)
Any AE leading to discontinuation of durvalumab					
< 65 years	19 (8.4)	19 (7.5)	183 (8.1)	235 (12.7)	0
≥ 65 to < 75 years	29 (16.8)	19 (11.7)	151 (11.1)	189 (16.8)	0
≥ 75 years	15 (23.8)	9 (12.0)	53 (12.1)	77 (22.6)	0
Any AE leading to discontinuation of tremelimumab					
< 65 years	2 (0.9)	0	0	166 (9.0)	62 (19.7)
≥ 65 to < 75 years	3 (1.7)	0	0	128 (11.4)	68 (26.9)
≥ 75 years	2 (3.2)	0	0	58 (17.0)	24 (32.0)

[i] Patients with multiple events in the same category are counted only once in that category. patients with events in more than 1 category are counted once in each of those categories.

[j] As assessed by the investigator. Missing responses are counted as related.

Percentages are calculated from N1, N2, and N3 for < 65 years, ≥ 65 to < 75 years, and ≥ 75 years, respectively.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Disease progression AEs reported in Study 1108, Study 6, Study 10, and Study 11 are not included in this summary.

AE, adverse event; D, durvalumab 1500 mg (or equivalent); HCC, hepatocellular carcinoma; IV, intravenous; N1, total number of < 65 years patients, N2, total number of ≥ 65 to < 75 years patients, N3, total number of ≥ 75 years patients; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg Q4W; T75+D, durvalumab given at a dose of 20 mg/kg Q4W (or equivalent) IV in combination with tremelimumab 1 mg/kg Q4W (or equivalent), for any line of therapy (across tumor types); T750, tremelimumab monotherapy 10 mg/kg Q4W (or equivalent) for any line of therapy (across tumor types).

Table 70. Adverse Events by Age Category in the HCC T300+D Tumour Pool

AE Category or System Organ Class	Number (%) of patients		
	< 65 years (N = 226)	≥ 65 - < 75 years (N = 173)	≥ 75 years (N = 63)
Any AE	218 (96.5)	170 (98.3)	63 (100.0)
Any SAE	91 (40.3)	72 (41.6)	26 (41.3)

AE Category or System Organ Class	Number (%) of patients		
	< 65 years (N = 226)	≥ 65 - < 75 years (N = 173)	≥ 75 years (N = 63)
Hospitalization/prolong existing hospitalization	88 (38.9)	66 (38.2)	25 (39.7)
Life-threatening	14 (6.2)	18 (10.4)	9 (14.3)
Disability/incapacity	3 (1.3)	11 (6.4)	1 (1.6)
Other (medically significant)	23 (10.2)	29 (16.8)	8 (12.7)
Any AE with outcome of death	9 (4.0)	19 (11.0)	6 (19.5)
Any AE leading to discontinuation of study treatment	19 (8.4)	29 (16.8)	15 (23.8)
Psychiatric disorders	24 (10.6)	28 (16.2)	10 (15.9)
Nervous system disorders	30 (13.3)	39 (22.5)	12 (19.0)
Injuries, poisoning, and procedural complications	9 (4.0)	15 (8.7)	11 (17.5)
Cardiac disorders	7 (3.1)	11 (6.4)	5 (7.9)
Vascular disorders	18 (8.0)	28 (16.2)	8 (12.7)
Cerebrovascular disorders	0	0	0
Infections and infestations	824 (36.6)	550 (40.6)	167 (38.0)
Cholinergic syndrome	0	0	0
Sum of selected AEs (e.g. postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures, etc) [b]	5 (2.2)	13 (7.5)	5 (7.9)
Anticholinergic syndrome	0	0	0
Ataxia	0	0	0
Dizziness	4 (1.8)	9 (5.2)	2 (3.2)
Fall	1 (0.4)	2 (1.2)	2 (3.2)
Hand fracture	0	0	0
Multiple fractures	0	0	0
Orthostatic hypotension	0	0	0
Spinal fracture	0	0	0
Syncope	1 (0.4)	2 (1.2)	1 (1.6)
Other AEs appearing more frequently in older patients [c]			
Anaemia	14 (6.2)	17 (9.8)	12 (19.0)
Hypothyroidism	21 (9.3)	23 (13.3)	11 (17.5)
Hyperkalaemia	7 (3.1)	9 (5.2)	6 (9.5)
Pneumonitis	1 (0.4)	4 (2.3)	5 (7.9)
Abdominal pain	35 (15.5)	17 (9.8)	6 (9.5)
Constipation	24 (10.6)	18 (10.4)	3 (4.8)
Diarrhoea	55 (24.3)	48 (27.7)	14 (22.2)
Nausea	24 (10.6)	19 (11.0)	14 (22.2)
Pruritus	51 (22.6)	54 (31.2)	13 (20.6)

AE Category or System Organ Class	Number (%) of patients		
	< 65 years (N = 226)	≥ 65 - < 75 years (N = 173)	≥ 75 years (N = 63)
Rash	58 (25.7)	44 (25.4)	13 (20.6)
Fatigue	33 (14.6)	33 (19.1)	17 (27.0)
Oedema peripheral	14 (6.2)	24 (13.9)	7 (11.1)

AE = adverse event; HCC = hepatocellular carcinoma; Q4W = every 4 weeks; SAE = serious adverse event; T300+D = tremelimumab 300 mg for a single dose and durvalumab 1500 mg Q4W.

[a] The details of each SAE and the criteria met individually are found in the patient narratives

[b] Patients with multiple AEs are counted once for each category and sub-category.

[c] >5% difference between the <65, 65 to 74, and ≥75 age categories.

Body weight

In the HCC D pool, a slight increasing trend for Grade 3 to 4 AEs was observed for patients with **body weight** ≥ 90 kg (N=55), compared to patients < 70 kg (54.5% vs 36.2%), and similarly for SAEs (49.1% vs 29.4%). A similar trend was observed in the Pan-tumor D pool.

ECOG performance status

In both of the HCC-tumor pools, patients with a **baseline ECOG status** of 1 experienced a higher incidence of Grade 3 to 4 AEs (T300+D pool: 56.6% vs 49.1%) and AEs leading to death (T300+D pool: 10.3% vs 5.6%). In the HCC-tumor pools, no other clinically meaningful differences were observed in the safety profile of T300+D versus D alone with respect to performance status.

Extrinsic factors

Geographical region

In the HCC tumor pools, the Applicant claimed that there were no clinically meaningful differences in the safety profile of the T300+D pool compared with the D pool with respect to **geographical region**.

Immunological events

Table 71. Adverse Events in any Category, by ADA Category to Durvalumab (Safety Analysis Set)

AE category [a]	Number (%) of patients											
	D (N = 388)				T300+D (N = 388)				T75+D (N = 152)			
	TE-ADA+ [b]	nAb+	ADA+ [c]	ADA- [d]	TE-ADA+ [b]	nAb+	ADA+ [c]	ADA- [d]	TE-ADA+ [b]	nAb+	ADA+ [c]	ADA- [d]
Number of durvalumab ADA evaluable patients in the category	8	2	20	262	9	5	24	270	5	0	8	100
Any AE	6 (75.0)	2 (100)	18 (90.0)	235 (89.7)	9 (100)	5 (100)	23 (95.8)	264 (97.8)	5 (100)	0	8 (100)	97 (97.0)
Any AE possibly related to treatment [e]	4 (50.0)	0	9 (45.0)	148 (56.5)	5 (55.6)	3 (60.0)	17 (70.8)	213 (78.9)	4 (80.0)	0	5 (62.5)	76 (76.0)
Any AE of CTCAE Grade 3 or 4	2 (25.0)	0	9 (45.0)	89 (34.0)	5 (55.6)	3 (60.0)	10 (41.7)	135 (50.0)	2 (40.0)	0	2 (25.0)	40 (40.0)
Any AE of CTCAE grade 3 or 4, possibly related to treatment [e]	0	0	2 (10.0)	32 (12.2)	2 (22.2)	1 (20.0)	5 (20.8)	66 (24.4)	0	0	0	19 (19.0)
Any AE with outcome of death	0	0	1 (5.0)	9 (3.4)	0	0	2 (8.3)	8 (3.0)	1 (20.0)	0	1 (12.5)	5 (5.0)
Any AE with outcome of death, possibly related to treatment [e]	0	0	0	0	0	0	0	2 (0.7)	0	0	0	1 (1.0)
Any SAE (including events with outcome of death)	0	0	5 (25.0)	65 (24.8)	3 (33.3)	2 (40.0)	8 (33.3)	103 (38.1)	3 (60.0)	0	3 (37.5)	30 (30.0)
Any SAE (including events with outcome of death), possibly related to treatment [e]	0	0	0	17 (6.5)	0	0	1 (4.2)	43 (15.9)	1 (20.0)	0	1 (12.5)	16 (16.0)
Any AE leading to discontinuation of study treatment [f]	0	0	1 (5.0)	13 (5.0)	1 (11.1)	1 (20.0)	2 (8.3)	26 (9.6)	0	0	0	15 (15.0)
Any AE leading to discontinuation of study treatment, possibly related to treatment [e,f]	0	0	0	6 (2.3)	1 (11.1)	1 (20.0)	1 (4.2)	16 (5.9)	0	0	0	8 (8.0)
Any AE leading to dose delay/interruption [g]	0	0	4 (20.0)	73 (27.9)	4 (44.4)	0	11 (45.8)	99 (36.7)	1 (20.0)	0	2 (25.0)	39 (39.0)
Any AESI	1 (12.5)	0	4 (20.0)	113 (43.1)	4 (44.4)	2 (40.0)	12 (50.0)	193 (71.5)	5 (100)	0	6 (75.0)	62 (62.0)
Any AESI, possibly related to treatment [e]	1 (12.5)	0	1 (5.0)	81 (30.9)	4 (44.4)	1 (20.0)	10 (41.7)	162 (60.0)	4 (80.0)	0	5 (62.5)	53 (53.0)
Any infusion reaction AEs [h]	0	0	0	5 (1.9)	0	0	0	16 (5.9)	0	0	0	3 (3.0)

[a] Positive and negative results are with respect to durvalumab. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

[b] Treatment-emergent ADA positive is defined as either treatment-induced or treatment-boosted.

[c] ADA positive, ie, positive ADA result at any time, baseline or post-baseline.

[d] ADA negative, ie, without any ADA positive results (at baseline or post-baseline).

[e] Possibly related to any of the study treatments, as assessed by the Investigator. Missing responses are counted as related.

[f] AEs on the AE eCRF with action taken of 'drug permanently discontinued' for at least one treatment.

[g] AEs on the AE eCRF with action taken of 'drug interrupted' for either molecule.

[h] As assessed by the Investigator.

MedDRA version 23.1. CTCAE version 4.03.

Denominator is the number of ADA evaluable patients (patients in the Safety Analysis Set who have a non-missing baseline ADA and at least one non-missing post-baseline result) in the ADA category.

Includes TEAEs.

ADA, anti-drug antibody; AE, adverse event; AESI, adverse event of special interest; eCRF, electronic case report form; CTCAE, Common Terminology Criteria for Adverse Events; D, durvalumab monotherapy 1500 mg Q4W; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients; nAb, neutralizing antibody; Q4W, every 4 weeks; SAE, serious adverse event; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TE, treatment-emergent.

Source: Table 14.3.9.3.

Table 72. Adverse Events in any Category, by ADA Category to Tremelimumab (Safety Analysis Set)

AE category [a]	Number (%) of patients							
	T300+D (N = 388)				T75+D (N = 152)			
	TE-ADA+ [b]	nAb+	ADA+ [c]	ADA- [d]	TE-ADA+ [b]	nAb+	ADA+ [c]	ADA- [d]
Number of tremelimumab ADA-evaluable patients in the category	20	8	29	153	23	16	30	72
Any AE	19 (95.0)	8 (100)	28 (96.6)	150 (98.0)	23 (100)	16 (100)	30 (100)	70 (97.2)
Any AE possibly related to treatment [e]	15 (75.0)	8 (100)	23 (79.3)	120 (78.4)	18 (78.3)	13 (81.3)	23 (76.7)	54 (75.0)
Any AE of CTCAE Grade 3 or 4	9 (45.0)	6 (75.0)	13 (44.8)	77 (50.3)	10 (43.5)	8 (50.0)	12 (40.0)	27 (37.5)
Any AE of CTCAE Grade 3 or 4, possibly related to treatment [e]	4 (20.0)	3 (37.5)	7 (24.1)	37 (24.2)	1 (4.3)	1 (6.3)	1 (3.3)	15 (20.8)
Any AE with outcome of death	0	0	0	5 (3.3)	2 (8.7)	1 (6.3)	4 (13.3)	2 (2.8)
Any AE with outcome of death, possibly related to treatment [e]	0	0	0	2 (1.3)	0	0	1 (3.3)	0
Any SAE (including events with outcome of death)	9 (45.0)	5 (62.5)	12 (41.4)	58 (37.9)	5 (21.7)	3 (18.8)	8 (26.7)	24 (33.3)
Any SAE (including events with outcome of death), possibly related to treatment [e]	6 (30.0)	3 (37.5)	7 (24.1)	25 (16.3)	1 (4.3)	1 (6.3)	3 (10.0)	13 (18.1)
Any AE leading to discontinuation of study treatment [f]	3 (15.0)	2 (25.0)	4 (13.8)	14 (9.2)	3 (13.0)	3 (18.8)	4 (13.3)	10 (13.9)
Any AE leading to discontinuation of study treatment, possibly related to treatment [e,f]	2 (10.0)	2 (25.0)	3 (10.3)	11 (7.2)	0	0	1 (3.3)	7 (9.7)
Any AE leading to dose delay/interruption [g]	8 (40.0)	2 (25.0)	10 (34.5)	57 (37.3)	9 (39.1)	8 (50.0)	10 (33.3)	28 (38.9)
Any AESI	16 (80.0)	6 (75.0)	20 (69.0)	104 (68.0)	15 (65.2)	9 (56.3)	19 (63.3)	46 (63.9)
Any AESI, possibly related to treatment [e]	14 (70.0)	6 (75.0)	17 (58.6)	89 (58.2)	12 (52.2)	9 (56.3)	16 (53.3)	40 (55.6)
Any infusion reaction AEs [h]	2 (10.0)	1 (12.5)	2 (6.9)	10 (6.5)	0	0	0	3 (4.2)

[a] Positive and negative results are with respect to tremelimumab. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] Treatment-emergent ADA positive is defined as either treatment-induced or treatment-boosted.

[c] ADA positive, ie, positive ADA result at any time, baseline or post-baseline.

[d] ADA negative, ie, without any ADA positive results (at baseline or post-baseline).

[e] Possibly related to any of the study treatments, as assessed by the Investigator. Missing responses are counted as related.

[f] AEs on the AE eCRF with action taken of 'drug permanently discontinued' for at least one treatment.

[g] AEs on the AE eCRF with action taken of 'drug interrupted' for either molecule.

[h] As assessed by Investigator.

MedDRA version 23.1. CTCAE version 4.03.

Denominator is the number of ADA evaluable patients (patients in the Safety Analysis Set who have a non-missing baseline ADA and at least one non-missing post-baseline result) in the ADA category.

Includes TEAEs.

ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; eCRF, electronic case report form; CTCAE, Common Terminology Criteria for Adverse Events; D, durvalumab monotherapy 1500 mg Q4W; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients; nAb, neutralizing antibody; Q4W, every 4 weeks; SAE, serious adverse event; T75+D, tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TE, treatment-emergent.

Safety related to drug-drug interactions and other interactions

Durvalumab and tremelimumab are immunoglobulins, therefore, no formal pharmacokinetic drug-drug interaction studies have been conducted.

Discontinuation due to adverse events

Table 73. Adverse Events leading to discontinuation of study medication by system organ class, preferred term and maximum reported CCAE grade (Safety Analysis Set) – DCO: 27 AUG 2021

System organ class / MedDRA Preferred term	Maximum reported CTCAE grade	Number (%) of subjects[a]			
		Durva 1500 mg (N=388)	Treme 300 mg x1 dose + Durva 1500 mg (N=388)	Treme 75 mg x4 doses + Durva 1500 mg (N=152)	Sora 400 mg BID (N=374)
Subjects with any AE	Total	32 (8.2)	53 (13.7)	23 (15.1)	63 (16.8)
	Grade 1	0	2 (0.5)	0	2 (0.5)
	Grade 2	6 (1.5)	7 (1.8)	5 (3.3)	16 (4.3)
	Grade 3	13 (3.4)	21 (5.4)	6 (3.9)	27 (7.2)
	Grade 4	2 (0.5)	4 (1.0)	5 (3.3)	1 (0.3)
	Grade 5	11 (2.8)	19 (4.9)	7 (4.6)	17 (4.5)
	Grade >=3	26 (6.7)	44 (11.3)	18 (11.8)	45 (12.0)
	Grade 3-4	15 (3.9)	25 (6.4)	11 (7.2)	28 (7.5)

Table 74. Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term (≥ 1% Patients in Any Treatment Group) (Safety Analysis Set)

	Number (%) of patients [a]				
	HCC-tumor pool		Pan-tumor pool		
	T300+D	D	D	T75+D	T750
MedDRA preferred term	(N = 462)	(N = 492)	(N = 4045)	(N = 3319)	(N = 643)
Patients with any AE leading to discontinuation of any study treatment	63 (13.6)	47 (9.6)	397 (9.8)	550 (16.6)	155 (24.1)
Respiratory, thoracic and mediastinal disorders	4 (0.9)	2 (0.4)	84 (2.1)	113 (3.4)	9 (1.4)
Pneumonitis	2 (0.4)	1 (0.2)	36 (0.9)	49 (1.5)	2 (0.3)
Gastrointestinal disorders	14 (3.0)	9 (1.8)	41 (1.0)	125 (3.8)	98 (15.2)
Colitis	2 (0.4)	1 (0.2)	6 (0.1)	32 (1.0)	26 (4.0)
Diarrhoea	3 (0.6)	2 (0.4)	8 (0.2)	37 (1.1)	63 (9.8)
Investigations	8 (1.7)	6 (1.2)	25 (0.6)	42 (1.3)	11 (1.7)
Aspartate aminotransferase increased	5 (1.1)	3 (0.6)	6 (0.1)	8 (0.2)	1 (0.2)

[k] Number (%) of patients with AEs leading to discontinuation, sorted by international order for system organ class and alphabetically for preferred term.

Patients with multiple AEs are counted once for each system organ class/preferred term.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication, or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Disease progression AEs reported in Study 1108, Study 6, Study 10, and Study 11 are not included in this summary.

Percentages are based on the total numbers of patients in the treatment group (N).

MedDRA version 23.1.

AE, adverse event; D, durvalumab 1500 mg (or equivalent); HCC, hepatocellular carcinoma; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg Q4W; T75+D, durvalumab given at a dose of 20 mg/kg Q4W (or equivalent) IV in combination with tremelimumab 1 mg/kg Q4W (or equivalent), for any line of therapy (across tumor types); T750, tremelimumab monotherapy 10 mg/kg Q4W (or equivalent) for any line of therapy (across tumor types).

Table 75: Adverse Events Leading to Dose Delay/Interruption by System Organ Class and Preferred Term (≥ 1% Patients in Any Treatment Group) (Safety Analysis Set)

	Number (%) of patients [a]				
	HCC-tumor pool		Pan-tumor pool		
	T300+D	D	D	T75+D	T750
MedDRA preferred term	(N = 462)	(N = 492)	(N = 4045)	(N = 3319)	(N = 643)
Patients with any AE leading to dose delay/interruption of any study treatment	149 (32.3)	112 (22.8)	1120 (27.7)	945 (28.5)	144 (22.4)
Infections and infestations	22 (4.8)	12 (2.4)	255 (6.3)	183 (5.5)	18 (2.8)
Pneumonia	6 (1.3)	1 (0.2)	88 (2.2)	63 (1.9)	7 (1.1)
Blood and lymphatic system disorders	12 (2.6)	11 (2.2)	64 (1.6)	53 (1.6)	9 (1.4)
Anaemia	6 (1.3)	4 (0.8)	39 (1.0)	28 (0.8)	7 (1.1)
Endocrine disorders	9 (1.9)	6 (1.2)	75 (1.9)	88 (2.7)	7 (1.1)
Hyperthyroidism	5 (1.1)	0	28 (0.7)	34 (1.0)	0
Respiratory, thoracic and mediastinal disorders	7 (1.5)	5 (1.0)	171 (4.2)	116 (3.5)	12 (1.9)
Pneumonitis	3 (0.6)	1 (0.2)	48 (1.2)	39 (1.2)	3 (0.5)
Gastrointestinal disorders	23 (5.0)	12 (2.4)	140 (3.5)	186 (5.6)	54 (8.4)
Colitis	5 (1.1)	0	4 (< 0.1)	25 (0.8)	1 (0.2)
Diarrhoea	16 (3.5)	4 (0.8)	48 (1.2)	82 (2.5)	43 (6.7)
Hepatobiliary disorders	18 (3.9)	15 (3.0)	44 (1.1)	38 (1.1)	1 (0.2)
Hepatic function abnormal	3 (0.6)	5 (1.0)	8 (0.2)	7 (0.2)	1 (0.2)
Hepatitis	6 (1.3)	1 (0.2)	6 (0.1)	9 (0.3)	0
Skin and subcutaneous tissue disorders	21 (4.5)	12 (2.4)	64 (1.6)	91 (2.7)	19 (3.0)
Rash	10 (2.2)	3 (0.6)	14 (0.3)	34 (1.0)	7 (1.1)
General disorders and administration site conditions	13 (2.8)	3 (0.6)	147 (3.6)	112 (3.4)	19 (3.0)
Pyrexia	9 (1.9)	1 (0.2)	43 (1.1)	25 (0.8)	5 (0.8)
Investigations	47 (10.2)	45 (9.1)	214 (5.3)	203 (6.1)	19 (3.0)
Alanine aminotransferase increased	13 (2.8)	15 (3.0)	47 (1.2)	52 (1.6)	2 (0.3)
Amylase increased	14 (3.0)	1 (0.2)	22 (0.5)	34 (1.0)	2 (0.3)
Aspartate aminotransferase increased	12 (2.6)	23 (4.7)	64 (1.6)	53 (1.6)	4 (0.6)
Lipase increased	11 (2.4)	7 (1.4)	27 (0.7)	58 (1.7)	6 (0.9)
Injury, poisoning and procedural complications	5 (1.1)	0	73 (1.8)	40 (1.2)	4 (0.6)
Radiation pneumonitis	0	0	41 (1.0)	1 (< 0.1)	0

Number (%) of patients with AE leading to dose delay or interruption, sorted by international order for system organ class and alphabetically for preferred term.

Patients with multiple AEs are counted once for each system organ class/preferred term.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to and including 90 days following the date of last dose of study medication or up to and including the date of initiation of the first subsequent therapy (whichever occurs first).

Disease progression AEs reported in Study 1108, Study 6, Study 10, and Study 11 are not included in this summary.

MedDRA version 23.1.

AE, adverse event; D, durvalumab 1500 mg (or equivalent); HCC, hepatocellular carcinoma; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg for a single dose in combination with durvalumab 1500 mg Q4W; T75+D, durvalumab given at a dose of 20 mg/kg Q4W (or equivalent) IV in combination with tremelimumab 1 mg/kg Q4W (or equivalent), for any line of therapy (across tumor types); T750, tremelimumab monotherapy 10 mg/kg Q4W (or equivalent) for any line of therapy (across tumor types).

Post marketing experience

Durvalumab was first approved for marketing in the US on 01 May 2017. The total post-marketing exposure of durvalumab since launch and until 30 June 2021 is estimated to be 52006 patient-years. No new safety concerns have been identified based on post-marketing safety reports

2.5.1. Discussion on clinical safety

The safety population of interest are patients with unresectable HCC (uHCC), who have received the proposed dosing regimen of a single dose of tremelimumab 300 mg + durvalumab in combination followed by durvalumab monotherapy (T300+D), which consists of 388 patients from the pivotal Himalaya study and 74 patients from the supportive study 22, in total 462 patients.

The median treatment duration in the Himalaya study were 5.5 months, while the median treatment duration was 4.1 months in the Sorafenib arm (n=374). In the HCC pool, the median duration of exposure was 20 weeks and approximately 50% of patients received at least 24 weeks of treatment at DCO, while ~28% had 52 weeks of treatment. Hence, the exposure to the proposed regimen and the size of the safety database are considered sufficient for a safety assessment.

Almost all patients in the HCC pool, who received T300+D, experienced at least one **adverse event** (AE) (97.6%), and 51.9% experienced a grade 3 or 4 AEs. For the Himalaya study, a similar pattern was observed in T300+D arm: 97.4% experienced at least one AE, 50.5% experienced a grade 3 or 4 AE, and SAEs were observed in 40.5% of the patients, noting 7.7% had an SAE leading to death. The discontinuation rate due to AEs was 13.7%. In comparison, 95.5% of the patients in the Sorafenib arm also experienced at least one AE, and 52.4% experienced a grade 3 or 4 AE. SAEs were observed in 29.7% of the patients, of which 7.2% had an SAE leading to death, while the discontinuation rate due to AEs was 16.8%.

Treatment-related AEs in the T300+D arm of the pivotal Himalaya study were rash (19.6%), pruritus (17%), diarrhoea (16.5%), and hypothyroidism (10.8%). In comparison, common treatment-related AEs in the Sorafenib arm were diarrhoea (38.8%), palmar-plantar erythrodysaesthesia (PPE) (43.9%), hypertension (15%), and fatigue (14.7%). The most common grade 3 or 4 treatment-related AEs in the T300+D arm were increased lipase (4.4%), diarrhoea (3.4%), amylase increased (2.6%) and ASAT increased (2.3%). Common grade 3 or 4 treatment-related AEs in the S arm were PPE (8.8%), hypertension (5.3%), and diarrhoea (4%), so in comparison there are more high-grade toxicity with sorafenib in favour of T300+D (data not shown).

Adverse events of special interest for T300+D include immune-mediated AEs (imAEs) and as expected, the occurrence of imAEs are much more common in the HCC pool vs the Sorafenib arm (36.1% vs 7.5%), and these were of grade 3 or 4 in 13.4% vs 2.4% of the patients, respectively. Serious imAEs are considered common (10.2% vs 1.1%) and 6 patients (1.3%) died from these, while a quarter of the patients need systemic corticosteroids in the HCC pool versus only 4% in the Sorafenib arm. Moreover, many patients needed endocrine therapy, when treated with T300+D vs Sorafenib (14.9% vs 3.5%). It is noted that very few patients had to discontinue treatment due to imAEs (5.6% vs 1.6%), which is reassuring. Other common imAEs with T300+D were hepatic events (7.4%) and diarrhoea/colitis (6.5%). Grade 3 or 4 hepatic events (5%) and diarrhoea/colitis (3.7%) were the most frequent high-grade events, and these are difficult to manage in the clinic, so it is important that this is clear from the SmPC section 4.4, which is the case. Overall, imAEs were frequently reported and the number of AESIs and imAEs significantly differ for dermatitis/rash, pancreatic events, hepatic events, diarrhoea/colitis, hypothyroid and hyperthyroid events, pneumonitis. Some imAEs such as endocrinopathies, hepatotoxicity, dermatitis/rash are expected to be more manageable than others, such as

diarrhoea/colitis, pancreatic events and pneumonitis. The latter are more difficult to manage, often require hospitalisation, and might not be assumed as immune-mediated events by clinicians.

Events of Stevens-Johnson Syndrome or toxic epidermal necrolysis have been reported in patients treated with PD-1 inhibitors and CTLA-4 inhibitors. Patients should be monitored for signs and symptoms of rash or dermatitis and managed through dose interruption, treatment discontinuation and/or corticoisteroid treatment (see sections 4.2 and 4.4 of the SmPC).

Patients should be monitored for alanine aminotransferase, aspartate aminotransferase, total bilirubin, and alkaline phosphatase levels prior to initiation of treatment and prior to each subsequent infusion. Additional monitoring is to be considered based on clinical evaluation. Patients should be monitored for abnormal renal function tests prior to and periodically during treatment. Patients should also be monitored for signs and symptoms of immune-mediated pancreatitis and myocarditis. Immune mediated hepatitis, nephritis, pancreatitis and myocarditis should be managed through dose interruption, treatment discontinuation and/or corticoisteroid treatment (see sections 4.2 and 4.4 of the SmPC).

Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed through dose interruption, treatment discontinuation and corticosteroid treatment (see sections 4.2 and 4.4 of the SmPC).

Patients should be monitored for signs and symptoms of colitis/diarrhoea and intestinal perforation and managed through dose interruption, treatment discontinuation and/or corticoisteroid treatment (see sections 4.2 and 4.4 of the SmPC).

Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and as indicated based on clinical evaluation. Immune-mediated hypothyroidism, hyperthyroidism, and thyroiditis should be managed through dose interruption, symptomatic treatment or thyroid hormone replacement as clinically indicated (see sections 4.2 and 4.4 of the SmPC).

Immune mediated adrenal insufficiency occurred in patients receiving tremelimumab in combination with durvalumab. Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For symptomatic adrenal insufficiency, patients should be managed through dose interruption, corticoisteroid treatment and hormone replacement (see sections 4.2 and 4.4 of the SmPC).

Immune mediated type 1 diabetes mellitus, which can first present as diabetic ketoacidosis that can be fatal if not detected early, occurred in patients receiving tremelimumab in combination with durvalumab. Patients should be monitored for clinical signs and symptoms of type 1 diabetes mellitus. For symptomatic type 1 diabetes mellitus, patients should be managed via treatment with insulin as clinically indicated (see sections 4.2, 4.4 and 4.8 of the SmPC).

Patients should be monitored for clinical signs and symptoms of hypophysitis or hypopituitarism. For symptomatic hypophysitis or hypopituitarism, patients should be managed as recommended through dose interruption and corticoisteroid treatment (see sections 4.2 and 4.4 of the SmPC).

Given the mechanism of action of tremelimumab in combination with durvalumab, other potential immune mediated adverse reactions may occur. The following immune-related adverse reactions have been observed in patients treated with tremelimumab in combination with durvalumab: myasthenia gravis, myositis, myelitis transverse, polymyositis, meningitis, encephalitis, Guillain-Barré syndrome, immune thrombocytopenia and cystitis noninfective. Patients should be monitored for signs and symptoms and managed through dose interruption, treatment discontinuation and/or corticoisteroid treatment (see sections 4.2 and 4.4 of the SmPC).

Although the rate of imAEs with the T300+D is considered high, these are considered generally clinically manageable.

Patients should also be monitored for signs and symptoms of IRRs. IRRs should be managed through dose interruption, treatment discontinuation, prophylaxis and appropriate treatment (see sections 4.2 and 4.4 of the SmPC).

Serious adverse events (SAEs) were very common in the T300+D arm vs the S arm in Himalaya study (40.5% vs 29.7%) and it is noted that 10% less SAEs were observed with durvalumab monotherapy, suggesting that the addition of the single dose of 300 mg tremelimumab significantly adds toxicity. The most frequent SAEs in the T300+D arm vs the S arm were diarrhoea (2.3% vs 1.6%), sepsis (2.1% vs 0), and pneumonia (1.8% vs 2.1%). Overall, the high level of SAEs with T300+D is worrisome although the targeted patient population is previously untreated patients and this may influence the tolerability in the general patient population in the first-line setting. Of note, diarrhoea and colitis are important identified risks of the anti-CTLA-4 agent ipilimumab, which has a similar mechanism of action as tremelimumab. Moreover, the targeted patient population from the 2L+ setting is expected to have even more serious toxicity.

AEs leading to death occurred in 34 patients (7.4%) in the HCC T300+D pool and 30 patients (7.7%) in the T300+D arm of the Himalaya study.

The overall **discontinuation rate** due to AEs in the HCC pool was 13.6%, while it was 13.7% of the patients in the pivotal Himalaya study. Most commonly the patients discontinued treatment due to AST increased and diarrhoea, which reflects the safety profile of T300+D. Dose delays were very common in the patients who had T300+D in the HCC pool (32.3%) and mostly due to diarrhoea and increased liver enzymes.

Laboratory findings showed that the changes in haematological parameters were mostly of low grade and pertaining to a decrease in lymphocytes ≥grade 2 for 20% of the patients and grade 3 or 4 in 11.8%. This is in line with the findings in the pivotal Himalaya study. Laboratory shifts for clinical chemistry parameters were rare and mostly to low grade events. It is noted that increased glucose was common in the HCC pool (19.4%) and that grade 3 or 4 were observed in 14.6% of the patients. New onset diabetes mellitus was identified in 39 (8.4%) of 462 patients in the T300+D HCC pool and 30 (6.1%) of 492 patients in the D monotherapy HCC pool. Eight (1.7%) SAE reports of hyperglycaemia occurred in the T300+D HCC pool and most patients did not receive therapy for the hyperglycaemic event and the reported events were resolved in 21 (4.5%) of the patients in the T300+D HCC pool. One patient with hyperglycaemia and one patient with T2DM discontinued treatment. Liver toxicity was very often observed regarding elevated hepatic laboratory parameters in the HCC pool. Potential Hy's law cases were reported for 57 patients (12.3%) in the HCC pool and the narratives for the 4 patients, who met the Hy's law criteria in the T300+D arm of the pivotal Himalaya study are all agreed.

Increased toxicity with increasing age was observed in the HCC pool, as the incidence of ADRs were 72.1% in the patients of <65 years of age vs 79.8% in patients of 65-75 years of age and 85.7% in those of ≥75 years of age. A trend towards more discontinuations with increasing age was also observed.

Safety and tolerability profiles were similar in patients with ADAs and in those without ADAs. According to the Applicant, there were no new types of events or events clearly suggestive or indicative of infusion reactions or immune complex disease.

Overall, the toxicity observed in the first-line study Himalaya was significantly less than what was observed for the entire HCC pool, which is to be expected for the included study population, who was previously systemically untreated patients, who are usually more fit and able to tolerate toxicities. The toxicity observed with Sorafenib is similar to the toxicity level observed in the HCC pool and in some

cases worse than what was observed for the T300+D arm of the Himalaya study. However, the toxicity profiles of T300+D and Sorafenib differs due to different mechanisms of action mainly between immune checkpoint inhibition and a tyrosine kinase inhibitor (TKI).

2.5.2. Conclusions on clinical safety

The toxicity of the proposed dosing regimen of T300+D is considerable, since approximately half of the patients experience grade 3 or 4 adverse events and 40% of the patients have serious adverse events, mostly pertaining to diarrhoea and immune-mediated adverse events. The discontinuation rate is however relatively low (~13%) and most of the toxicity observed is clinically manageable and the toxicity profile of T300+D is not considered significantly worse than that of Sorafenib, the current standard of care.

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 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 8 succession 1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 8 succession 1 with the following content:

Safety concerns

There are no safety concerns.

Pharmacovigilance plan

Not applicable as there are no safety concerns.

Risk minimisation measures

Not applicable as there are no safety concerns.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

A readability test was performed for the original dossier and provided during the assessment of the initial dossier. This variation aims at extending the indication for durvalumab to be used in combination with tremelimumab for the treatment of adults with unresectable hepatocellular carcinoma. The same route of administration (intravenous use) and age group (adults) is applicable to this variation. The package leaflet is being updated in section 1-4 and are otherwise similar to the text previously tested at the time of the MAA. The changes are not considered too significant and an additional user consultation is not considered necessary for this new indication.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Imfinzi (durvalumab) is included in the additional monitoring list as it contains a new active substance and it is a biological product that is not covered by the previous category and authorised after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The approved therapeutic indication is:

IMFINZI in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).

The aim of the applied dosing regimen of tremelimumab plus durvalumab (T300+D) in comparison to Sorafenib (SOC) in the targeted population is to prolong overall survival (OS).

3.1.2. Available therapies and unmet medical need

The first-line treatment of uHCC includes sorafenib (a tyrosine-kinase inhibitor - TKI) based on OS benefit when compared to placebo (10.7 vs 7.9 months) and lenvatinib, another TKI, which is non-inferior when compared to sorafenib (median OS 13.6 vs 12.3 months). Atezolizumab (a PD-L1 inhibitor) in combination with bevacizumab (a vascular endothelial growth factor receptor inhibitor) has also been approved in the first-line setting, based on the Phase III IMbrave150 study showing improvements of OS and PFS compared to sorafenib i.e. the median OS was 19.2 months with atezolizumab + bevacizumab vs 13.4 months with Sorafenib (HR, 0.66 [95%CI: 0.52, 0.85]), while the PFS by blinded review was 6.9 vs. 4.3 months (HR 0.65 [95%CI: 0.53, 0.81]).

Despite recent advances in treatment options, patients with uHCC continue to have a short life expectancy and the underlying liver disease and portal vein hypertension increase the risk of gastrointestinal bleeding, which can be potentially life-threatening. Currently available therapies provide only a modest improvement in survival with safety profiles that require management due to adverse events such as diarrhoea, hypertension, and palmar-plantar erythrodysaesthesia (PPE). Treatment with atezolizumab plus bevacizumab also carries a higher incidence of bleeding, including fatal bleeding,

despite attempts to exclude patients at risk for gastrointestinal bleeding from the pivotal study. Moreover, the underlying liver cirrhosis may result in moderate liver dysfunction, which may exacerbate the toxicity of systemic therapies such as TKIs. Hence, additional therapeutic options are needed, including options for patients with uHCC, who are at higher risk of bleeding events, so there exist an unmet medical need for better and more tolerable treatment options for patients with uHCC.

3.1.3. Main clinical studies

The pivotal study Himalaya is a randomised, open-label, multicentre Phase III study in patients with unresectable HCC not eligible for locoregional therapy, which compared tremelimumab + durvalumab (T300+D) to standard of care, sorafenib, in the first-line setting. The primary endpoint was OS in the ITT population.

Additional supportive evidence of clinical efficacy was provided from Study 22, a randomised, phase I/II, open-label study conducted in the 2L+ setting, comparing the efficacy of T300+D and durvalumab monotherapy.

3.2. Favourable effects

The primary endpoint for the Himalaya study was met as treatment with T300+D showed a statistically significant improvement in **overall survival (OS)** compared to standard of care, Sorafenib.

- At data cutoff 27 August 2021 and after ~33 months of follow up, 66.7% OS events had occurred in the T300+D arm versus 75.3% OS events in the Sorafenib arm, treatment with T300+D showed a statistically significant survival benefit as compared with SoC: Median OS was improved from 13.77 months to 16.43 months, HR 0.78 (96.02% CI: 0.65, 0.93).
- The secondary endpoint of **ORR** by investigator was 20.1% for the T300+D arm compared to 5.1% in the sorafenib arm, and the median duration of response was 22.34 months in the T300+D arm vs 18.43 months in the sorafenib arm.
- The **PFS** analyses were not controlled for multiplicity. PFS by investigator was not significantly improved, since the median PFS was 3.78 months in the T300+D arm versus 4.07 months in the S arm; HR 0.90 (95%CI: 0.77, 1.05). The event rates were 85.2% and 84.1% in the T300+D and S arms, respectively.
- Relevant **subgroup analyses** of the primary endpoint of OS show that the benefit of T300+D vs S is maintained across important subgroups of age of less than or ≥ 65 years, HBV or other reasons for liver disease, ECOG performance status, macrovascular invasion (MVI), AFP at baseline and BCLB score C.

3.3. Uncertainties and limitations about favourable effects

None.

3.4. Unfavourable effects

The safety populations of interest are the 388 patients from the pivotal Himalaya study and the patients included in the HCC pool (n=462), which also contains patients from the supportive study 22. The median

treatment duration in the Himalaya study were 5.5 months, while the median treatment duration was 4.1 months in the Sorafenib arm (n=374).

Almost all of the patients in the HCC pool, who received T300+D, experienced at least one **adverse event** (AE) (97.6%), and 51.9% experienced a grade 3 or 4 AE. For the Himalaya study, a similar pattern was observed.

Adverse drug reactions (ADRs) in the T300+D arm of the pivotal Himalaya study were rash, pruritus, diarrhoea, and abdominal pain. The most common grade 3 or 4 ADRs in the T300+D arm were increased aspartate aminotransferase/ alanine aminotransferase, increased lipase, increased amylase and diarrhoea.

Adverse events of special interest for T300+D include immune-mediated AEs (imAEs) and as expected, the occurrence of imAEs are much more common in the HCC pool vs the Sorafenib arm (36.1% vs 7.5%), and these were of grade 3 or 4 in 13.4% vs 2.4% of the patients, respectively. Serious imAEs were observed in 10.2% vs 1.1% and 6 patients (1.3%) died from these.

The most common **serious adverse reactions** in the T300+D HCC pool are colitis (2.6%), diarrhoea (2.4%), pneumonia (2.2%), and hepatitis (1.7%).

In the pivotal Himalaya study, 6.1% of the patients in the T300+D arm **died from an adverse event**, while it was 7.4% in the HCC pool.

The overall **discontinuation rate** due to ADRs was 6.5%. Most commonly the patients discontinued treatment due to ADRs of hepatitis (1.5%) and aspartate aminotransferase increased/alanine aminotransferase increased (1.3%).

Laboratory findings showed that the changes in haematological parameters and clinical chemistry were mostly to low grade events. It is noted that increased glucose was common in the HCC pool (19.4%) and that grade 3 or 4 were observed in 14.6% of the patients. Liver toxicity was often observed regarding elevated hepatic laboratory parameters in the HCC pool and potential Hy's law cases were reported for 57 patients (12.3%) in the HCC pool.

3.5. Uncertainties and limitations about unfavourable effects

There are very limited safety data on elderly aged 75 years and older (see section 4.8 of the SmPC).

3.6. Effects Table

Table 76. Effects Table for T300+D in the treatment of uHCC for the Himalaya Study (data cut-off: 27 August 2021)

Effect	Short Description	Unit	Treatment T300+D	Control Sorafenib	Control Durvalumab	Uncertainties/ Strength of evidence	Ref
Favourable Effects			**N=393**	**N=389**	**N=389**		
OS	Median overall survival	Months 95%CI	**16.43** 14.16; 19.58	**13.77** 12.25; 16.13	16.56 14.06; 19.12	At 71% events, HR for T300+D vs S **0.78** (96.02%CI: 0.65; 0.93) P=0.0035	
PFS by INV	Progression-free survival	Months 95%CI	3.78 3.68; 5.32	4.07 3.75; 5.49	3.65 3.19, 3.75	Comparison was not formally tested; no BICR assessment	
ORR	Overall response rate	%	20.1	5.1	17.0		

Effect	Short Description	Unit	Treatment T300+D	Control Sorafenib	Control Durvalumab	Uncertainties/ Strength of evidence	Ref
DoR	Duration of response	Months	22.34	18.43	16.82		
Unfavourable Effects							
Any AE	Any adverse event	%	97.4	95.5	90.0	Incidences from the Himalaya study, except for the Durvalumab monotherapy arm; which are from the HCC D pool	
Grade 3 or 4 AEs	High-grade AEs	%	50.5	52.4	38.2		
Grade 5 AEs	AEs leading to death	%	7.7	7.2	6.1		
SAEs	Serious AEs	%	40.5	29.7	32.7		
AEs disc.	AEs leading to dis-continuation	%	13.7	16.8	9.6		
ImAEs	Immune-mediated AEs	%	36.1	7.5	16.5	Incidences from the HCC pool for T300+D group	
	Hepatic events	%	7.4	NA	1.6		
	Diarrhoea/ colitis	%	6.5	NA	1.4		

Abbreviations: OS: Overall survival; PFS: Progression free survival; INV: Investigator; ORR: Objective response rate; DoR: Duration of response; AE: Adverse event; SAE: Serious adverse event; ImAEs: Immune-mediated adverse events; HCC: hepatocellular carcinoma; BICR: Blinded independent central review.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The proposed dosing regimen of tremelimumab + durvalumab provides a statistically significant and clinically meaningful survival benefit compared to the current standard of care, sorafenib, in a head-to-head comparison from the pivotal Himalaya study, in a population of patients with unresectable hepatocellular carcinoma, who had not received prior systemic treatment. The ORR was also significantly improved; however, the magnitude of patients who had an objective response with T300+D is still low (~20%). The few objective responses were durable (~22 months), which is considered clinically significant. Hence, the efficacy of T300+D in the first-line setting could be considered shown. Supportive evidence for the application comes from Study 22, which compared T300+D to durvalumab monotherapy in the 2L+ setting.

The safety profiles of T300+D versus sorafenib are distinct as they have different mechanisms of action (immune checkpoint inhibition vs TKI) and the toxicity does not seem worse than sorafenib regarding grade 3 or 4 AEs (50.5% vs 52.4%), AEs leading to discontinuation (13.7% vs 16.8%), and AEs leading to death (7.7% vs 7.2%) as reported in the pivotal Himalaya study. The safety profile of tremelimumab in combination with durvalumab in the HCC setting is serious and has to be weighed against the seriousness of palliative setting and individual patient (ECOG status, age, comorbidities). This is of particular importance since a significant proportion of the immune-mediated adverse events observed with the T300+D regimen were serious (e.g. diarrhoea/colitis, pancreatitis and pneumonitis), expected

to be less manageable and often require hospitalisation. Immune-mediated AEs have therefore been included as important identified risks in the list of safety concerns for durvalumab.

3.7.2. Balance of benefits and risks

The shown overall survival benefit and the safety profile of T300+D not worse than that of standard of care, sorafenib, support a positive benefit-risk balance in the first-line treatment setting of advanced, unresectable HCC.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall benefit /risk balance of durvalumab + tremelimumab in the first line treatment of uHCC is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of indication to include IMFINZI in combination with tremelimumab for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (uHCC), based on final results from Study D419CC00002 (HIMALAYA); This was a randomized, open-label, multi-center phase III study of durvalumab and tremelimumab as first-line treatment in patients with unresectable hepatocellular carcinoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and Package Leaflet. Version 8.1 of the RMP has also been submitted.

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

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

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 'Imfinzi-II-45'.