12 October 2023
EMA/146357/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imfinzi

International non-proprietary name: Durvalumab

Procedure No. EMEA/H/C/004771/II/0057

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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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
BCLC	Barcelona Clinic Liver Cancer
BICR	Blinded Independent Central Review
BOR	Best objective response
BRAF	B-Raf
CD	Cluster of differentiation
CI	Confidence interval
C_{max}	Maximum serum concentration
C_{min}	Minimum serum concentration
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
eCTD	electronic Common Technical Document
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	Non-inferiority
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
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
SD	Stable disease
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
VEGF	Vascular endothelial growth factor
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 29 November 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 as 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 (HIMALAYA). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 9, Succession 1 of the RMP has also been submitted. In addition, the PI is brought in line with the latest QRD template version 10.3.

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/0366/2022 (9 September 2022) on the agreement of a modified paediatric investigation plan (PIP).

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 (EMA/CHMP/SAWP/286452/2017). The Scientific Advice pertained to 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

Timetable	Actual dates
Submission date	29 November 2022
Start of procedure:	31 December 2022
CHMP Rapporteur Assessment Report	24 February 2023
PRAC Rapporteur Assessment Report	1 March 2023
PRAC members comments	8 March 2023
Updated PRAC Rapporteur Assessment Report	9 March 2023
PRAC Outcome	16 March 2023
CHMP members comments	20 March 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 March 2023
Request for supplementary information (RSI)	30 March 2023
CHMP Rapporteur Assessment Report	26 June 2023
CHMP members comments	10 July 2023
Updated CHMP Rapporteur Assessment Report	13 July 2023
Request for Supplementary Information	20 July 2023
CHMP Rapporteur Assessment Report	18 Sep 2023
CHMP members comments	02 Oct 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	05 Oct 2023
Opinion	12 Oct 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Advanced hepatocellular carcinoma (HCC) regardless of tumoral PD-L1 expression.

State the claimed the therapeutic indication

IMFINZI as monotherapy 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 based on non-inferior survival as compared 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 [i.e., 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, tremelimumab in combination with durvalumab were approved by the EC in February 2023 upon results from the HIMALAYA trial, which showed superior survival from the combination in comparison to sorafenib (Abou-Alfa et al, JCO 2022).

Unmet medical need

Despite recent advances in treatment options, patients with advanced HCC 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 advanced HCC, who are at higher risk of bleeding events, so there exist an unmet medical need for better and tolerable treatment options for these patients.

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), in combination with gemcitabine and cisplatin for 1L treatment of unresectable or metastatic biliary tract cancer (BTC) (EMEA/H/C/004771/II/0046), in combination with tremelimumab for advanced HCC (EMEA/H/C/004771/II/0045) and in combination with tremelimumab and platinum-based chemotherapy for metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations (EMEA/H/C/004771/II/0041).

The indication, as initially proposed and adopted by CHMP, is:

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

The recommended dose is 1500 mg every 4 weeks. Treatment should be continued until disease progression or unacceptable toxicity.

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 1. Listing of Clinical Trials

Study	Data cut-off	Objectives of study	Study design and type of control	Dosage regimen [a]
Pivotal study				
D419CC00002 (HIMALAYA) Randomized, open-label, multicenter Phase III study of durvalumab and tremelimumab as first-line treatment in patients with advanced hepatocellular carcinoma (HIMALAYA)	27Aug2021	Efficacy and safety of durvalumab and tremelimumab in combination versus durvalumab alone and sorafenib as SoC	Randomized, open-label study	**Monotherapy:** Durvalumab 1500 mg Q4W **Combination therapy:** Tremelimumab 300 mg single dose + Durvalumab 1500 mg Q4W OR Tremelimumab 75 mg Q4W for 4 doses + Durvalumab 1500 mg Q4W **SoC:** Sorafenib 400 mg BID
Supporting studies				
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 uHCC	06Nov2020	Safety, tolerability, efficacy, PK, and immunogenicity	Open-label, multiple-arm, randomized study	***Part 1*** **Combination therapy:** Tremelimumab 75 mg (1 mg/kg) Q4W × 4 doses + Durvalumab 1500 mg (20 mg/kg) Q4W ***Part 2A and China cohort*** **Monotherapy**: Durvalumab 1500 mg (20 mg/kg) Q4W OR Tremelimumab 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W **Combination therapy**: Tremelimumab 75 mg (1 mg/kg) Q4W × 4 doses + Durvalumab 1500 mg (20 mg/kg) Q4W ***Part 2B***

Study	Data cut-off	Objectives of study	Study design and type of control	Dosage regimen [a]
				Combination therapy: Tremelimumab 300 mg (4 mg/kg) single dose + Durvalumab 1500 mg (20 mg/kg) Q4W ***Part 3*** **Monotherapy:** Durvalumab 1500 mg (20 mg/kg) Q4W OR Tremelimumab 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W **Combination therapy:** Tremelimumab 75 mg (1 mg/kg) Q4W × 4 doses + Durvalumab 1500 mg (20 mg/kg) Q4W OR Tremelimumab 300 mg (4 mg/kg) single dose + Durvalumab 1500 mg (20 mg/kg) Q4W ***Part 4*** **Combination therapy**: Durvalumab 1120 mg (15 mg/kg) + Bevacizumab 15 mg/kg Q3W
D4190C00011 (Study 11) A Phase I multicenter, open-label, dose-exploration, and dose-expansion study of durvalumab in combination with tremelimumab in subjects with recurrent or metastatic SCCHN	08Nov2017	Safety, tolerability, efficacy, PK, pharmacodynamics, and immunogenicity	Non-randomized, open-label study	***Dose-expansion*** **Combination therapy:** Cohort 1: Tremelimumab 3 mg/kg Q4W + Durvalumab 15 mg/kg Q4W Cohort 2: Tremelimumab 1 mg/kg Q4W + Durvalumab 10 mg/kg Q2W Cohort 3: Tremelimumab 1 mg/kg Q4W + Durvalumab 20 mg/kg Q4W Cohort 4: Tremelimumab 3 mg/kg Q4W + Durvalumab 20 mg/kg Q2W
				Dose-exploration **Cohort A - PD-L1 high**

Study	Data cut-off	Objectives of study	Study design and type of control	Dosage regimen [a]
				Monotherapy: Durvalumab 10 mg/kg Q2W **Combination therapy**: Tremelimumab 1 mg/kg Q4W + Durvalumab 10 mg/kg Q2W **Cohort B - PD-L1 low or negative** **Monotherapy:** Durvalumab 10 mg/kg Q2W **Combination therapy:** Tremelimumab 1 mg/kg Q4W + Durvalumab 10 mg/kg Q2W **Cohort C (prior IMT treatment)** **Combination therapy:** Tremelimumab 1 mg/kg Q4W + Durvalumab 20 mg/kg Q4W then Durvalumab 10 mg/kg Q2W
CD-ON-MEDI4736-1108 (Study 1108) A Phase I/II study to evaluate the safety, tolerability, and pharmacokinetics of MEDI4736 in subjects with advanced solid tumors	16Oct2017	Safety, tolerability, efficacy, PK, and immunogenicity	Open-label, multiple-arm, non-randomized study	***Dose-escalation phase*** **Monotherapy:** 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*** **Monotherapy**: Durvalumab20 mg/kg Q4W for up to 12 months ***Dose-expansion phase*** **Monotherapy:** Durvalumab10 mg/kg Q2W for up to 12 months
D4190C00006 (Study 06) A Phase Ib open-label study to evaluate the safety and tolerability of durvalumab (MEDI4736) in combination with tremelimumab in subjects with advanced NSCLC	28Feb2017 [b] 19Nov2019	Safety, tolerability, and efficacy of durvalumab in combination with tremelimumab	Open-label study	***Dose-escalation phase*** **Combination therapy:** Tremelimumab 1-10 mg/kg Q4W × 6 doses, then Q12W × 3 doses + Durvalumab 3-20 mg/kg Q4W or 10 mg/kg Q2W ***Dose-expansion phase*** **Combination therapy:** Tremelimumab1 mg/kg Q4W × 4 doses + Durvalumab 20 mg/kg Q4W × 4 doses then 20 mg/kg Q4W × 9 doses

Study	Data cut-off	Objectives of study	Study design and type of control	Dosage regimen [a]
D4190C00002 (Japan Study 02) A Phase I, open-label, multicenter study to evaluate the safety, tolerability, and pharmacokinetics of MEDI4736 in patients with advanced solid tumors	31Mar2018	Safety and tolerability of durvalumab monotherapy or in combination with tremelimumab	Open-label, non-randomized study	***Dose-escalation phase*** **Monotherapy:** Durvalumab 1, 3, 10 mg/kg Q2W; 15 mg/kg Q3W; 20 mg/kg Q4W ***Dose-expansion phase*** **Monotherapy:** Durvalumab 10 mg/kg Q2W **Combination therapy:** Tremelimumab 1 mg/kg Q4W × 4 doses + Durvalumab 20 mg/kg Q4W × 4 doses then 20 mg/kg Q4W
D4190C00010 (Study 10) A Phase I study of MEDI4736 (anti-PD-L1 antibody) in combination with tremelimumab (anti-CTLA-4 antibody) in subjects with advanced solid tumors	11Apr2018	Safety, tolerability, and efficacy of the combination of durvalumab and tremelimumab	Open-label study	***Dose-exploration phase*** **Combination therapy:** Tremelimumab 1 mg/kg Q4W × 7 doses then Q12W × 2 doses + Durvalumab at 20 mg/kg Q4W for 12 months OR Tremelimumab 3 mg/kg Q4W × 7 doses then Q12W × 2 doses + Durvalumab 10 mg/kg Q2W for 12 months ***Dose-expansion phase*** **Combination therapy:** Tremelimumab 1 mg/kg Q4W × 4 doses + Durvalumab 20 mg/kg Q4W × 4 doses then 10 mg/kg Q2W
D419MC00004 (POSEIDON) A Phase III, randomized, multicenter, open-label, comparative 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	12Mar2021	Efficacy, PK, immunogenicity, safety, and tolerability versus SoC	Randomized, multicenter, open-label, comparative active comparator study	***Treatment Arm*** **Monotherapy:** Durvalumab 1500 mg Q3W × 4 doses + SoC, then Durvalumab 1500 mg Q4W until PD ***Treatment Arm:*** **Combination therapy:** Tremelimumab 75 mg Q3W × 4 doses + 1 dose at Week 16 + Durvalumab 1500 mg Q3W × 4 doses then durvalumab 1500 mg Q4W until PD ***Treatment Arm:*** **SoC:** Abraxane + carboplatin, pemetrexed + cisplatin or carboplatin, or gemcitabine + cisplatin or carboplatin
D419LC00001 (KESTREL) A Phase III randomized, open-label, multicenter, global study of MEDI4736 alone or in	06Jul2020	Efficacy and safety of durvalumab monotherapy and in combination with tremelimumab versus SoC	Randomized, open-label, multicenter, global study	**Monotherapy:** Durvalumab 1500 mg Q4W **Combination therapy:** Tremelimumab 75 mg Q4W × 4 doses + Durvalumab 1500 mg Q4W

Study	Data cut-off	Objectives of study	Study design and type of control	Dosage regimen [a]
combination with tremelimumab versus SoC in the treatment of first-line recurrent or metastatic SCCHN				**SoC alone:** Cisplatin or carboplatin + 5-FU + cetuximab up to 6 cycles
D419BC00001 (DANUBE) A Phase III, randomized, open-label, controlled, multicenter, global study of first-line MEDI4736 (durvalumab) monotherapy and MEDI4736 (durvalumab) in combination with tremelimumab versus SoC in patients with unresectable Stage IV urothelial cancer	27Jan2020	Efficacy and safety of durvalumab monotherapy and in combination with tremelimumab versus SoC	Randomized, open-label, controlled (SoC), multicenter study	**Monotherapy:** Durvalumab 1500 mg Q4W **Combination therapy:** Tremelimumab 75 mg Q4W × 4 doses + Durvalumab 1500 mg Q4W **SoC:** Cisplatin + gemcitabine, carboplatin + gemcitabine
D4190C00021 (Study 21) A Phase Ib/II study of MEDI4736 in combination with tremelimumab, MEDI4736 monotherapy, and tremelimumab monotherapy in subjects with metastatic or recurrent gastric or gastroesophageal junction adenocarcinoma	18Oct2019	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 Ib*** **Combination therapy:** Tremelimumab 1 mg/kg Q2W + Durvalumab 20 mg/kg Q4W then 10 mg/kg Q2W ***Phase II*** **Arm A** **Combination therapy:** Tremelimumab 1 mg/kg Q2W + Durvalumab 20 mg/kg Q4W then 10 mg/kg Q2W **Arm B** **Monotherapy:** Durvalumab 10 mg/kg Q2W **Arm C** **Monotherapy:** Tremelimumab 10 mg/kg Q4W **Arm D** **Combination therapy:** Tremelimumab 1 mg/kg Q2W + Durvalumab 20 mg/kg Q4W then 10 mg/kg Q2W **Arm E** **Combination therapy:** Tremelimumab 1 mg/kg Q2W + Durvalumab 20 mg/kg Q4W then 10 mg/kg Q2W
D4193C00001 (HAWK) A Phase II, multicenter, single-arm, global study of MEDI4736 monotherapy in patients with recurrent or metastatic SCCHN	05Oct2018	Efficacy of durvalumab monotherapy and health-related quality of life	Open-label, single-arm study	**Monotherapy:** Durvalumab 10 mg/kg Q2W for 12 months or until PD

Study	Data cut-off	Objectives of study	Study design and type of control	Dosage regimen [a]
D4191C00003 (ATLANTIC) A Phase II, non-comparative, open-label, multicenter, international study of MEDI4736, in patients with locally advanced or metastatic non-small-cell lung cancer (Stage IIIB-IV) who have received at least 2 prior systemic treatment regimens including one platinum-based chemotherapy regimen	03Jun2016	Efficacy, safety, tolerability, PK, and immunogenicity	Open-label, single-arm, non-randomized study	**Monotherapy:** Durvalumab 10 mg/kg Q2W for up to 12 months
D4191C00001 (PACIFIC) A Phase III, randomized, double-blind, placebo-controlled, multicenter, international study of MEDI4736 as sequential therapy in patients with locally advanced, unresectable non-small-cell lung cancer (Stage III) who have not progressed following definitive, platinum-based, concurrent chemoradiation therapy	22Mar2018	Efficacy, safety, tolerability, PK, immunogenicity, and health-related quality of life of durvalumab versus placebo	Randomized, double-blind, placebo-controlled study	**Monotherapy:** Durvalumab 10 mg/kg Q2W for up to 12 months OR Placebo Q2W for up to 12 months
D419AC00001 (MYSTIC) A Phase III randomized, open-label, multicenter, global study of MEDI4736 in combination with tremelimumab therapy or MEDI4736 monotherapy versus standard of care platinum-based chemotherapy in first-line treatment of patients with advanced or metastatic NSCLC	04Oct2018	Efficacy versus SoC	Open-label, randomized, active comparator study	**Monotherapy:** Durvalumab 20 mg/kg Q4W **Combination therapy:** Tremelimumab 1 mg/kg Q4W × 4 doses + Durvalumab 20 mg/kg Q4W × 4 doses then 20 mg/kg Q4W until PD **SoC**: Paclitaxel + carboplatin, gemcitabine + cisplatin, pemetrexed + cisplatin, or pemetrexed + carboplatin 4 to 6 cycles
D419AC00003 (NEPTUNE) A Phase III randomized, open-label, multicenter, global study of	24Jun2019	Efficacy, PK, immunogenicity, safety, and tolerability versus SoC	Open-label, randomized, active comparator study	**Combination therapy:** Tremelimumab 1 mg/kg Q4W × 4 doses + Durvalumab 20 mg/kg Q4W × 4 doses then 20 mg/kg Q4W

Study	Data cut-off	Objectives of study	Study design and type of control	Dosage regimen [a]
MEDI4736 in combination with tremelimumab therapy versus standard of care platinum-based chemotherapy in first-line treatment of patients with advanced or metastatic NSCLC				**SoC:** Paclitaxel + carboplatin, gemcitabine + cisplatin, gemcitabine + carboplatin, pemetrexed + cisplatin, pemetrexed + carboplatin
D4191C00004 (ARCTIC) A Phase III, open-label, randomized, multicenter, international study of MEDI4736, given as monotherapy or in combination with tremelimumab, determined by PD L1 expression, versus standard of care in patients with locally advanced or metastatic non-small-cell lung cancer (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	09Feb2018	Efficacy, safety, tolerability, PK, and immunogenicity versus SoC	Open-label, randomized, active comparator study	**Monotherapy:** Durvalumab 10 mg/kg Q2W for up to 12 months OR Tremelimumab 10 mg/kg Q4W for 24 weeks followed by 10 mg/kg Q12W for 24 weeks **Combination therapy**: Tremelimumab 1 mg/kg Q4W for 12 weeks (maximum of 22 doses of durvalumab + 4 doses of tremelimumab) + Durvalumab 20 mg/kg Q4W for 12 weeks then 10 mg/kg Q2W for 34 weeks **SoC:** Vinorelbine, gemcitabine, or erlotinib
D419QC00001 (CASPIAN) A 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	27Jan2020	Efficacy, PK, immunogenicity, safety, and tolerability versus SoC	Open-label, randomized, active comparator study	**Combination therapy:** Durvalumab 1500 mg Q3W × 4 doses then 1500 mg Q4W until PD + EP for 4 cycles OR Tremelimumab 75 mg Q3W × 4 doses + EP for 4 cycles + Durvalumab 1500 mg Q3W × 4 doses then 1500 mg Q4W until PD **SoC:** EP for up to 6 cycles[c]

Study	Data cut-off	Objectives of study	Study design and type of control	Dosage regimen [a]
D4193C00003 (CONDOR) A Phase II, randomized, open-label, multicenter, global study of MEDI4736 monotherapy, tremelimumab monotherapy, and MEDI4736 in combination with tremelimumab in patients with recurrent or metastatic SCCHN	31Mar2017	Efficacy of durvalumab in combination with tremelimumab and health-related quality of life	Open-label, randomized study	**Monotherapy:** Durvalumab 10 mg/kg Q2W for up to 12 months OR Tremelimumab 10 mg/kg Q4W × 7 doses then Q12W for 2 doses for up to 12 months **Combination therapy:** Tremelimumab 1 mg/kg Q4W × 4 doses + Durvalumab 20 mg/kg Q4W × 4 doses then 10 mg/kg Q2W to complete 12 months of treatment
D4193C00002 (EAGLE) A Phase III randomized, open-label, multicenter, global study of MEDI4736 monotherapy and MEDI4736 in combination with tremelimumab versus standard of care therapy in patients with recurrent or metastatic SCCHN	10Sep2018	Efficacy of durvalumab monotherapy and durvalumab in combination with tremelimumab versus SoC	Open-label, randomized study	**Monotherapy:** Durvalumab 10 mg/kg Q2W **Combination therapy:** Tremelimumab 1 mg/kg Q4W × 4 doses + Durvalumab 20 mg/kg Q4W × 4 doses then 10 mg/kg Q2W for 12 months or until PD **SoC:** Cetuximab; docetaxel or paclitaxel; methotrexate; or 5-FU, TS-1, or capecitabine
D4884C00001 A Phase II multicenter, open-label study of tremelimumab monotherapy in patients with advanced solid tumors	17Feb2018	Efficacy and safety	Open-label study	**Monotherapy:** Durvalumab 1500 mg Q4W for up to 12 months OR Tremelimumab 750 mg Q4W × 7 doses then Q12W × 2 doses
				Combination therapy: Tremelimumab 75 mg/kg Q4W × 4 doses + Durvalumab 1500 mg Q4W × 4 doses then Durvalumab 1500 mg Q4W for up to 8 months

2.3.2. Pharmacokinetics

Durvalumab is an established product that has received global marketing approvals for use in locally advanced or metastatic UC and Stage III locally advanced unresectable NSCLC. The present application concerns the intended indication of durvalumab (IMFINZI™, MEDI4736) monotherapy for treatment of patients with uHCC, who have not received prior systemic therapy. Treatment is by IV administration of 1500 mg of durvalumab at an administration frequency of once every 4 weeks.

The clinical pharmacology data supporting the intended indication contains updated PK, pharmacodynamics (PD), and immunogenicity data, as well as PopPK and E-R analyses for durvalumab to support this application. However, the present application is based on data from the phase 3 HIMALAYA trial in which SoC was tested against durvalumab monotherapy or durvalumab + a single dose of tremelimumab. The use of durvalumab + a single dose of tremelimumab for uHCC was authorised in the EU on 30 January 2023 (EMEA/H/C/004771/II/0045). No new studies have been conducted for the present application. The HIMALAYA study is the pivotal study for this application. The

other 21 studies provide supportive data. All studies enrolled male and female patients aged 18 years or older with advanced solid tumours.

Durvalumab was administered IV in all studies either as monotherapy or in combination with another therapy.

The PK of durvalumab has been characterised and evaluated in previous procedures and is therefore known. Durvalumab administration is IV and therefore absorption and bioavailability are 100%.

Evaluation and Qualification of Models (report MS-2022-02)

Data assembly for the population PK dataset has been described and assessed in the previous report. The most recent population PK model of durvalumab was updated by including all studies in previous PopPK models (1108, ATLANTIC, PACIFIC, CASPIAN and POSEIDON) and data from HIMALAYA and Study 22 (MS-2021-02). The results from this PopPK analysis are consistent with previous models, and all identified covariates changed durvalumab population parameter estimates by less than or about 20% and can thus be regarded of minor clinical relevance. The Cox proportional-hazards model analysis identified aspartate aminotransferase (AST) and neutrophil-lymphocyte ratio (NLR) as the significant ($p<0.001$) prognostic factors for the OS hazard in durvalumab 1500 mg Q4W + tremelimumab 300 mg single dose arm (T300+D) of HIMALAYA study. No covariate was identified as significant factor ($p<0.001$) for the PFS hazard. No clinically relevant exposure-response relationship was observed for durvalumab or tremelimumab PK exposure and the safety endpoints of adverse events of Grade 3 and above treatment-related AE, Grade 3 and above treatment-related AESI, or AE leading to treatment discontinuation in T300+D patients of HIMALAYA study (MS-2021-02). The current analysis is considered as an addition of previous analysis (MS-2021-02) and explored potential relationships between exposure metrics of durvalumab with clinical efficacy and safety using data collected in the durvalumab 1500 mg Q4W monotherapy arm of HIMALAYA study.

The final durvalumab population PK model (MS-2021-02) was used to obtain empirical Bayes estimates (EBEs) of individual PK parameters of all treated patients from the durvalumab monotherapy arm of HIMALAYA study. Exposure metrics (AUC,dose 1, Cmax,dose 1, Cmin,dose 1, AUCss, Cmax,ss, Cmin,ss) were derived using simulated durvalumab time-course PK profiles based on individual post-hoc PK parameters following administration of 1500 mg durvalumab Q4W IV.

Overall survival (OS) and progression free survival (PFS) in durvalumab monotherapy arm were examined with Kaplan-Meier plots stratified by quartiles of exposure of durvalumab. The sorafenib treatment was included in the KM plots as control. Cox proportional hazard regression of the OS and PFS were evaluated using durvalumab exposure metrics. Demographic characteristics, baseline covariates and exposure metrics were tested using a forward-addition and backward-elimination method and with significant levels of $P < 0.01$ and $P < 0.001$, respectively.

The relationship between durvalumab exposure and safety endpoints (Grade 3+ drug-related AE, Grade 3+ drug-related AESI, AE leading to treatment discontinuation) were evaluated using boxplots stratified by response values. The probability of response was plotted versus exposure, after binning patients according to durvalumab exposure quartiles. Binary logistic regression was used to characterize the exposure / response relationship. All predefined exposure metrics were evaluated on all safety variables. The base model to which the different exposure metrics were added to include all covariates that had statistically significance level of 0.001 when tested univariately.

All relevant covariates were included/tested in the exposure-response analyses.

R, version 4.0.2 and above (R-project, www.r-project.org) were used for exploratory analysis, and for the exposure-response analysis.

2.3.3. PK/PD modelling

Exposure-response relationship

These analyses evaluated the potential relationships between exposure metrics of durvalumab with clinical efficacy and safety using data collected in the durvalumab 1500 mg Q4W monotherapy arm of the HIMALAYA study. Treatment with durvalumab was via intravenous administration. The objectives of these analyses included:

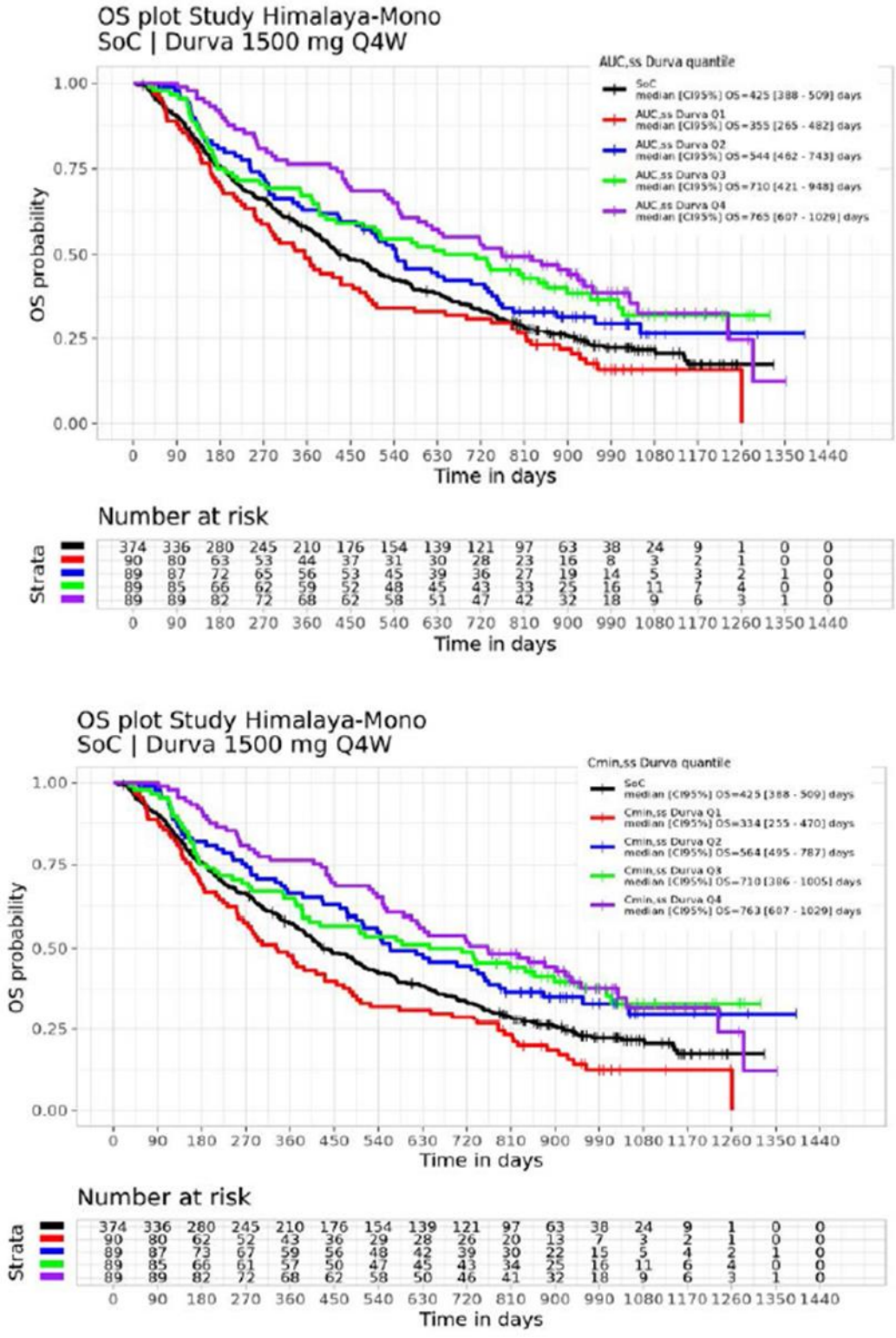
- Derivation of predicted exposure metrics of durvalumab for patients treated with durvalumab monotherapy.
- To assess the durvalumab E-R for 2 efficacy endpoints, OS and PFS, using data from the durvalumab monotherapy treatment arm of HIMALAYA.
- To assess durvalumab E-R for safety endpoints, including Grade 3+ drug-related AEs, Grade 3+ drug-related AESIs, and AEs leading to treatment discontinuation.

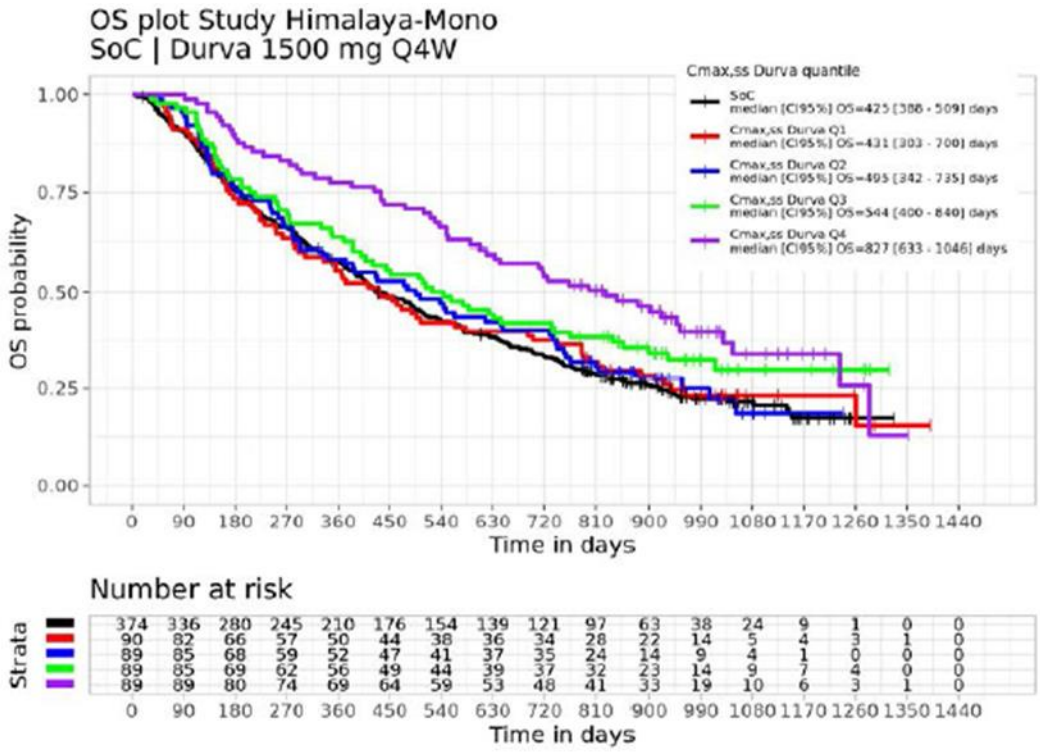
Of the 388 patients in this cohort, 31 were considered as PK non-evaluable, and therefore, 357 patients were included in the E-R analysis for durvalumab.

Exposure-efficacy relationship for OS

The data presented are the durvalumab monotherapy cohort. The data are stratified by model-predicted exposure metrics and overlaid with data from patients in the SoC arm. There were 6 exposure metrics used for durvalumab (AUCdose 1, Cmin,dose 1, Cmax,dose 1, AUCss, Cmin,ss, and Cmax,ss). Figure 1 shows the Kaplan-Meier plots for OS with steady state exposure metrics of durvalumab. The number of patients at risk is indicated below each plot. Additional explorative analyses of the covariates, body weight and ADA status, found in Figure 2 and Figure 3, indicate that there is no clear association between OS and body weight or ADA status. However, due to the relatively small number (n = 8, 2.24%) of ADA-positive patients after durvalumab treatment, the results for ADA status should be interpreted with caution.

Figure 1. OS Kaplan-Meier Plots for Durvalumab Exposure Metrics by Quartiles at Steady State

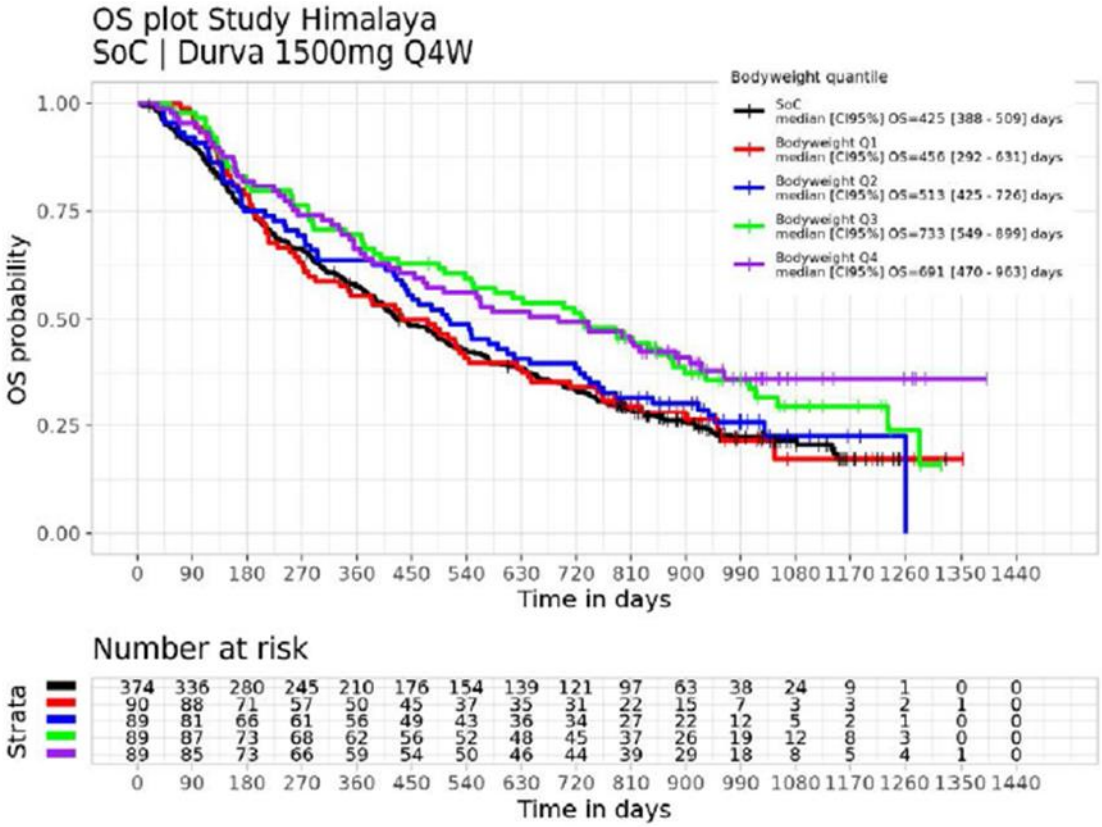




Abbreviations: AUC_{ss}, area under the serum concentration-time curve at steady state; CI, confidence interval; $C_{max,ss}$, maximum serum concentration at steady state; $C_{min,ss}$, minimum serum concentration at steady state; Durva, durvalumab; Mono, monotherapy; OS, overall survival; Q, quartile; Q4W, every 4 weeks; SoC, standard of care.

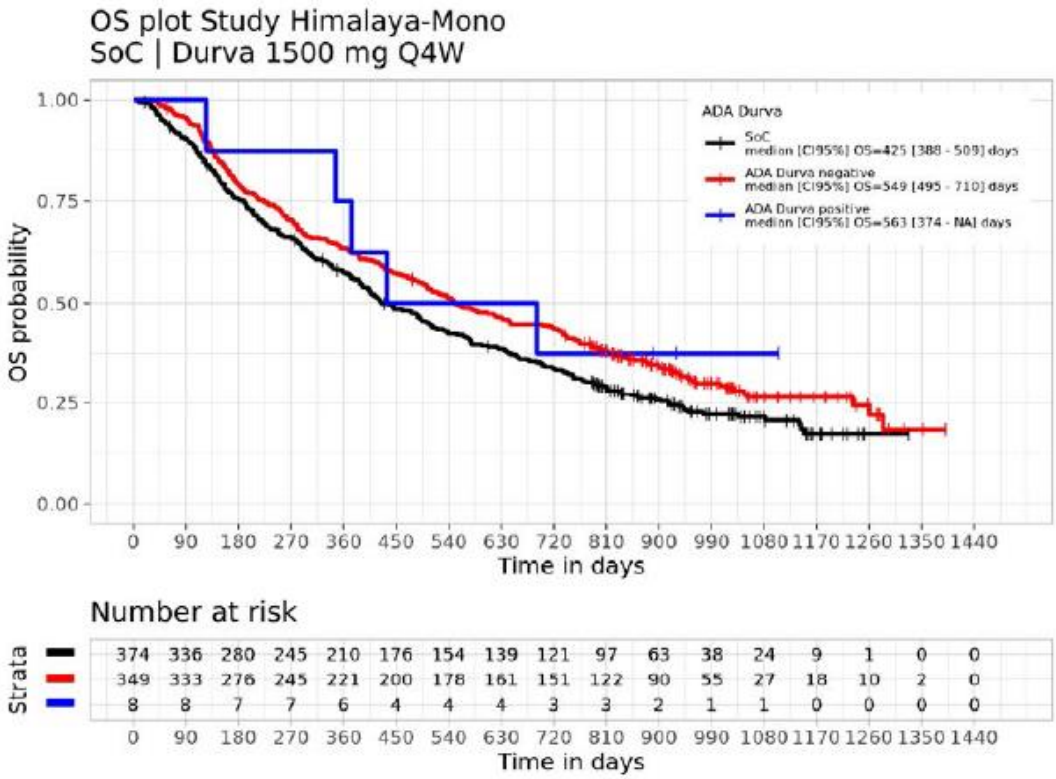
Source: See Figure 2 in Exposure-Response Report (MS-2022-02), Module 5.3.4.2.

Figure 2. OS Kaplan-Meier Plots for Body Weight by Quartiles



Abbreviations: CI, confidence interval; Durva, durvalumab; OS, overall survival; Q, quartile; Q4W, every 4 weeks; SoC, standard of care.
Source: See Figure 3 in Exposure-Response Report (MS-2022-02), Module 5.3.4.2.

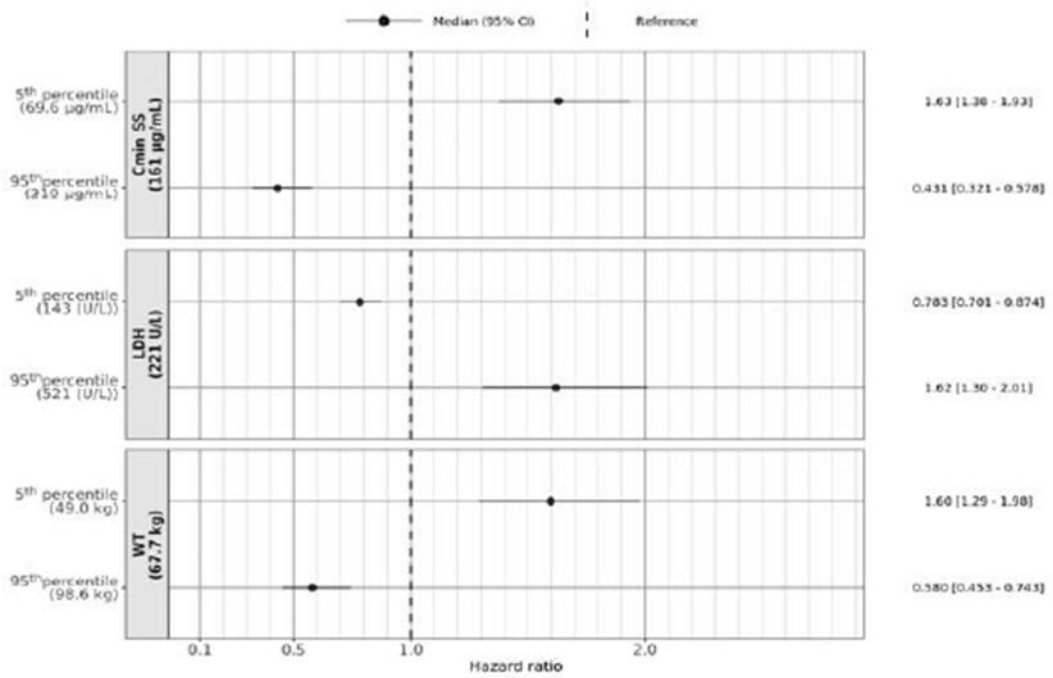
Figure 3. OS Kaplan-Meier Plots by ADA Status Due to Durvalumab



Abbreviations: ADA, anti-drug antibody; CI, confidence interval; Durva, durvalumab; Mono, monotherapy; OS, overall survival; Q, quartile; Q4W, every 4 weeks; SoC, standard of care.
Source: See Figure 4 in Exposure-Response Report (MS-2022-02), Module 5.3.4.2.

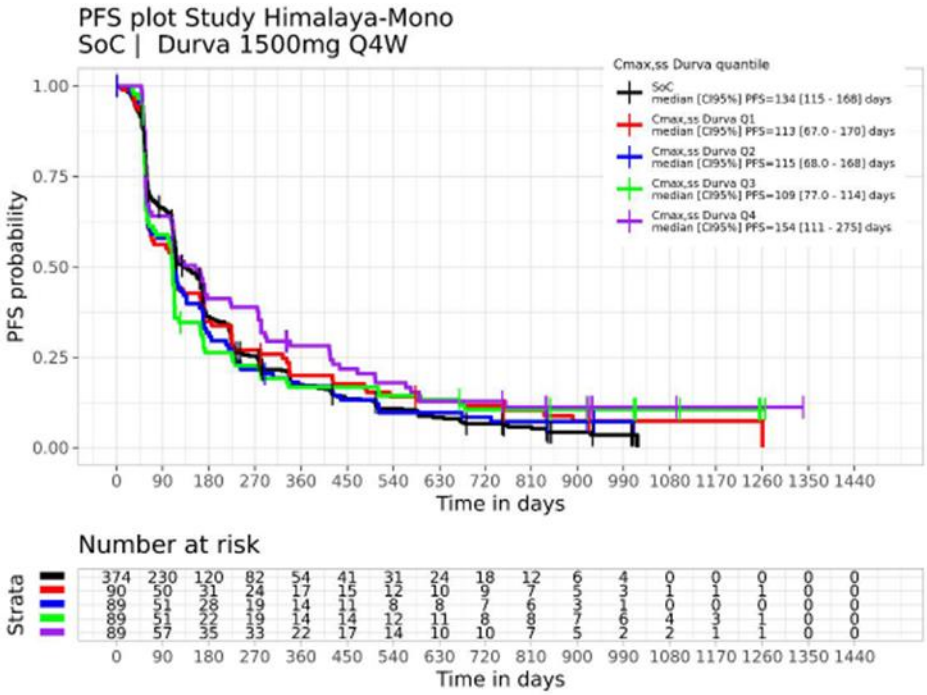
The E-R CPH model for OS was developed based on durvalumab-treated patients in HIMALAYA. Demographic characteristics, baseline covariates, and exposure metrics were tested using a forward-addition and backward-elimination method and with significant levels of $p < 0.01$ and $p < 0.001$, respectively (likelihood ratio test). Following the likelihood ratio test, LDH, weight, and $C_{min,ss}$ were identified as significant covariates in the model. A forest plot of the final CPH model for OS is shown in Figure 4.

Figure 4. Forest Plot if the Final CPH Model for OS



Note: Numbers at the right of the graph are the predicted HR and associated 95% CI.
Abbreviations: CI, confidence interval; $C_{min\,SS}$, minimum serum concentration at steady state; CPH, Cox proportional hazard; LDH, lactate dehydrogenase; OS, overall survival; WT, body weight.
Source: See Figure 5 in Exposure-Response Report (MS-2022-02), Module 5.3.4.2.

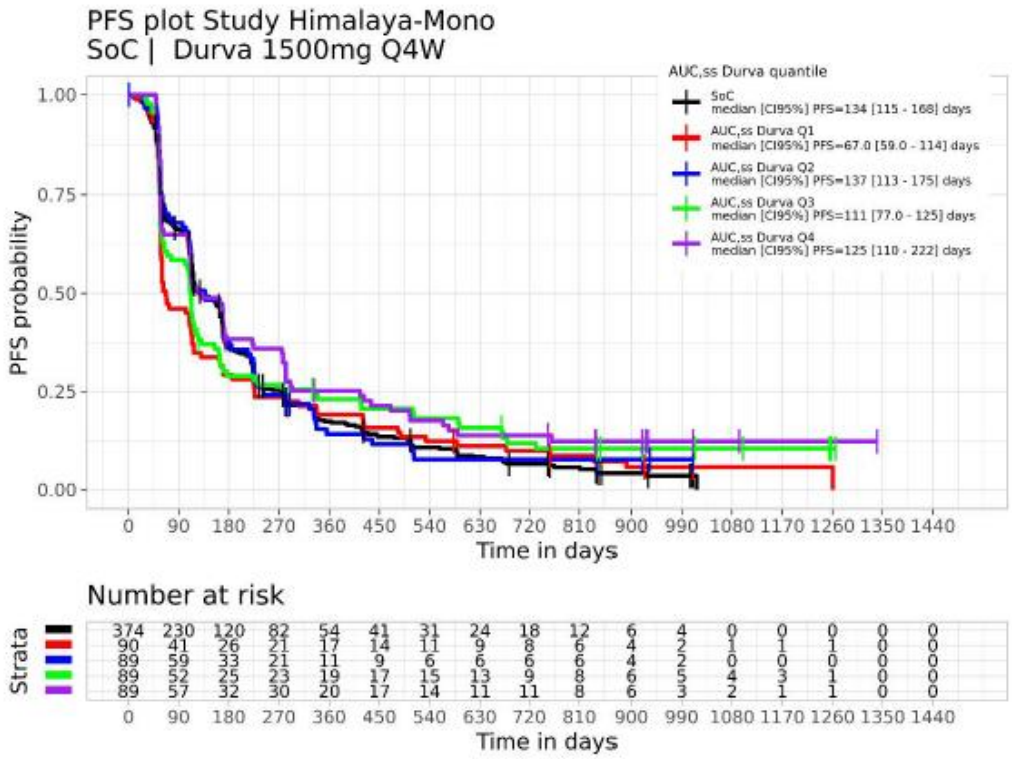
Exposure-efficacy relationship for progression-free survival (PFS)

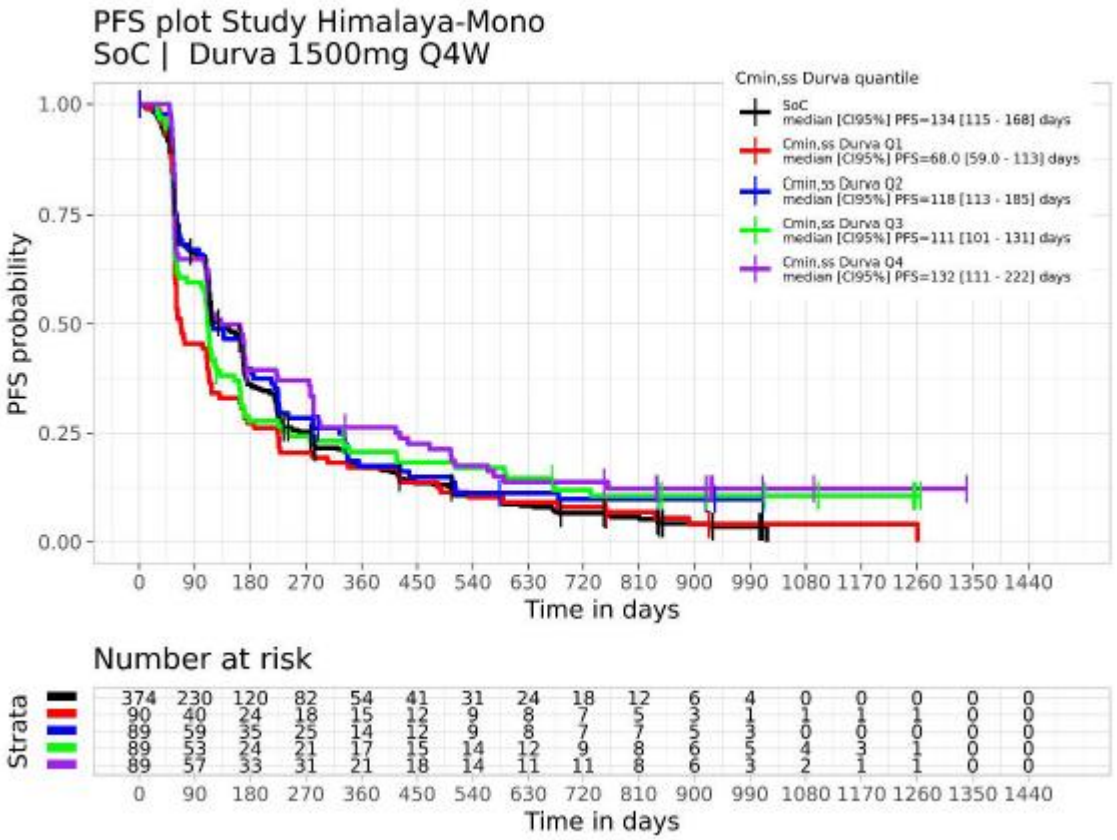


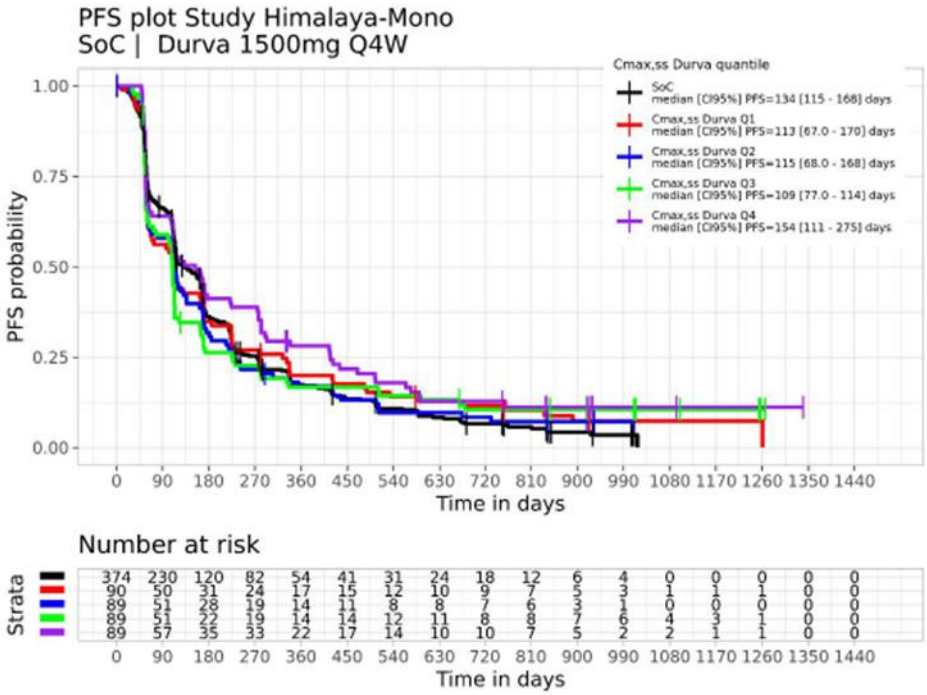
Abbreviations: AUC_{ss}, area under the serum concentration-time curve at steady state; CI, confidence interval; $C_{max,ss}$, maximum serum concentration at steady state; $C_{min,ss}$, minimum serum concentration at steady state; Durva, durvalumab; Mono, monotherapy; PFS, progression-free survival; Q, quartile; Q4W, every 4 weeks; SoC, standard of care.

shows PFS Kaplan-Meier curves for patients receiving **steady state** durvalumab monotherapy, stratified by model-predicted exposure metrics and overlaid with data from patients in the SoC arm. The number of patients at risk is indicated below each plot. Additional explorative analyses of the covariates, body weight, and ADA status for durvalumab can be found in Figure 6 and Figure 7. These analyses indicated no clear trend between PFS and body weight or ADA status. However, due to the relatively small number (n = 8, 2.24%) of ADA-positive patients after durvalumab treatment, the Kaplan-Meier plots for ADA status should be interpreted with caution.

Figure 5. PFS Kaplan-Meier Plots for Durvalumab Exposure Metrics by Quartiles at Steady State

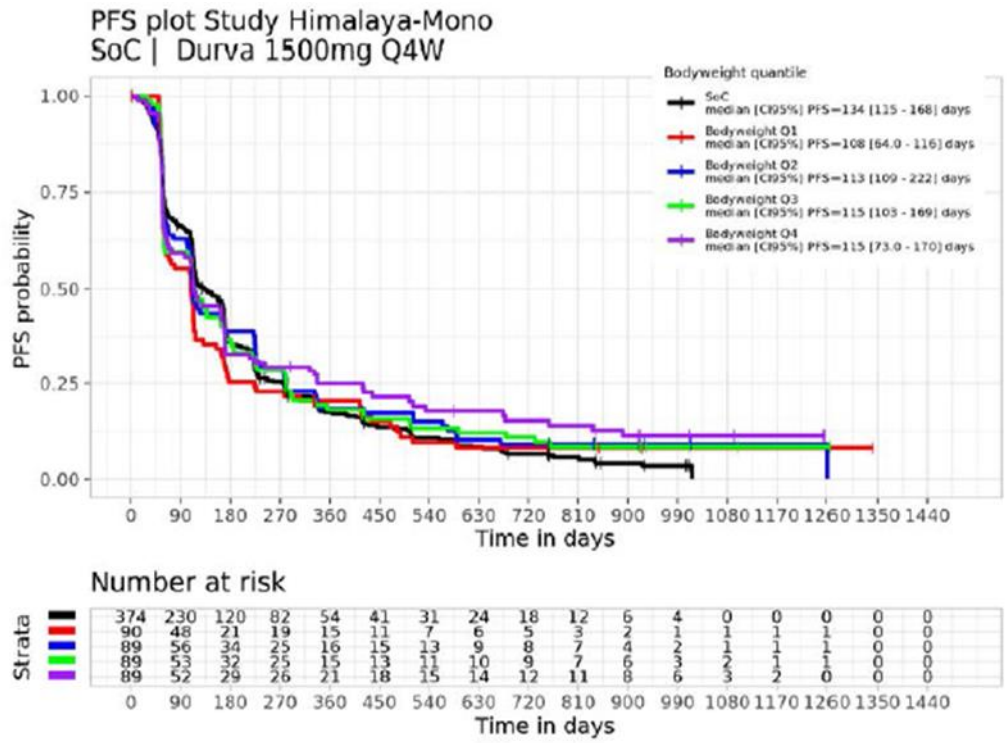

PFS plot Study Himalaya-Mono
SoC | Durva 1500mg Q4W
AUC,ss Durva quantile
SoC
median [CI95%] PFS=134 [115 - 168] days
AUC,ss Durva Q1
median [CI95%] PFS=67.0 [59.0 - 114] days
AUC,ss Durva Q2
median [CI95%] PFS=137 [113 - 175] days
AUC,ss Durva Q3
median [CI95%] PFS=111 [77.0 - 125] days
AUC,ss Durva Q4
median [CI95%] PFS=125 [110 - 222] days
PFS probability
1.00
0.75
0.50
0.25
0.00
0 90 180 270 360 450 540 630 720 810 900 990 1080 1170 1260 1350 1440
Time in days
Number at risk
Strata
374 230 120 82 54 41 31 24 18 12 6 4 0 0 0 0 0
90 41 26 21 17 14 11 9 8 6 4 2 1 1 1 0 0
89 59 33 21 11 9 6 6 6 6 4 2 0 0 0 0 0
89 52 25 23 19 17 15 13 9 8 6 5 4 3 1 0 0
89 57 32 30 20 17 14 11 11 8 6 3 2 1 1 0 0
0 90 180 270 360 450 540 630 720 810 900 990 1080 1170 1260 1350 1440
Time in days


PFS plot Study Himalaya-Mono
SoC | Durva 1500mg Q4W
Cmin,ss Durva quantile
SoC
median [CI95%] PFS=134 [115 - 168] days
Cmin,ss Durva Q1
median [CI95%] PFS=68.0 [59.0 - 113] days
Cmin,ss Durva Q2
median [CI95%] PFS=118 [113 - 185] days
Cmin,ss Durva Q3
median [CI95%] PFS=111 [101 - 131] days
Cmin,ss Durva Q4
median [CI95%] PFS=132 [111 - 222] days
PFS probability
1.00
0.75
0.50
0.25
0.00
0 90 180 270 360 450 540 630 720 810 900 990 1080 1170 1260 1350 1440
Time in days
Number at risk
Strata
374 230 120 82 54 41 31 24 18 12 6 4 0 0 0 0 0
90 40 24 18 15 12 9 8 7 5 3 1 1 1 1 0 0
89 59 35 25 14 12 9 8 7 7 5 3 0 0 0 0 0
89 53 24 21 17 15 14 12 9 8 6 5 4 3 1 0 0
89 57 33 31 21 18 14 11 11 8 6 3 2 1 1 0 0
0 90 180 270 360 450 540 630 720 810 900 990 1080 1170 1260 1350 1440
Time in days



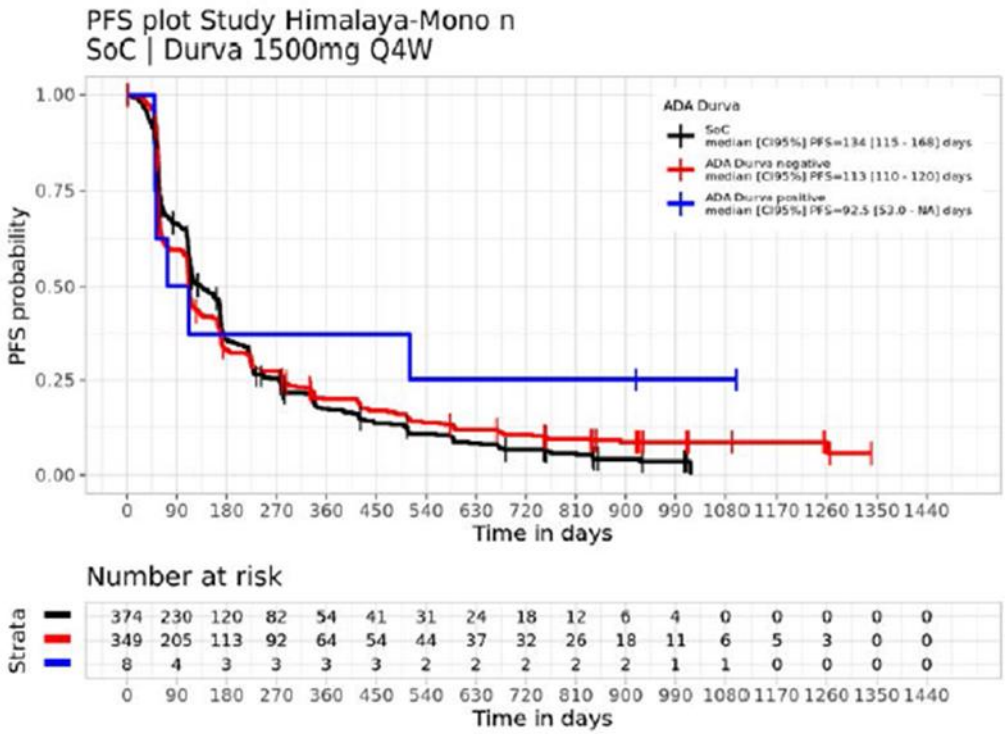
Abbreviations: AUC_{ss}, area under the serum concentration-time curve at steady state; CI, confidence interval; $C_{max,ss}$, maximum serum concentration at steady state; $C_{min,ss}$, minimum serum concentration at steady state; Durva, durvalumab; Mono, monotherapy; PFS, progression-free survival; Q, quartile; Q4W, every 4 weeks; SoC, standard of care.

Figure 6. PFS Kaplan-Meier Plots for Body Weight by Quartiles



Abbreviations: CI, confidence interval; Durva, durvalumab; Mono, monotherapy; PFS, progression-free survival; Q, quartile; Q4W, every 4 weeks; SoC, standard of care.

Figure 7. PFS Kaplan-Meier Plots by ADA Status Due to Durvalumab



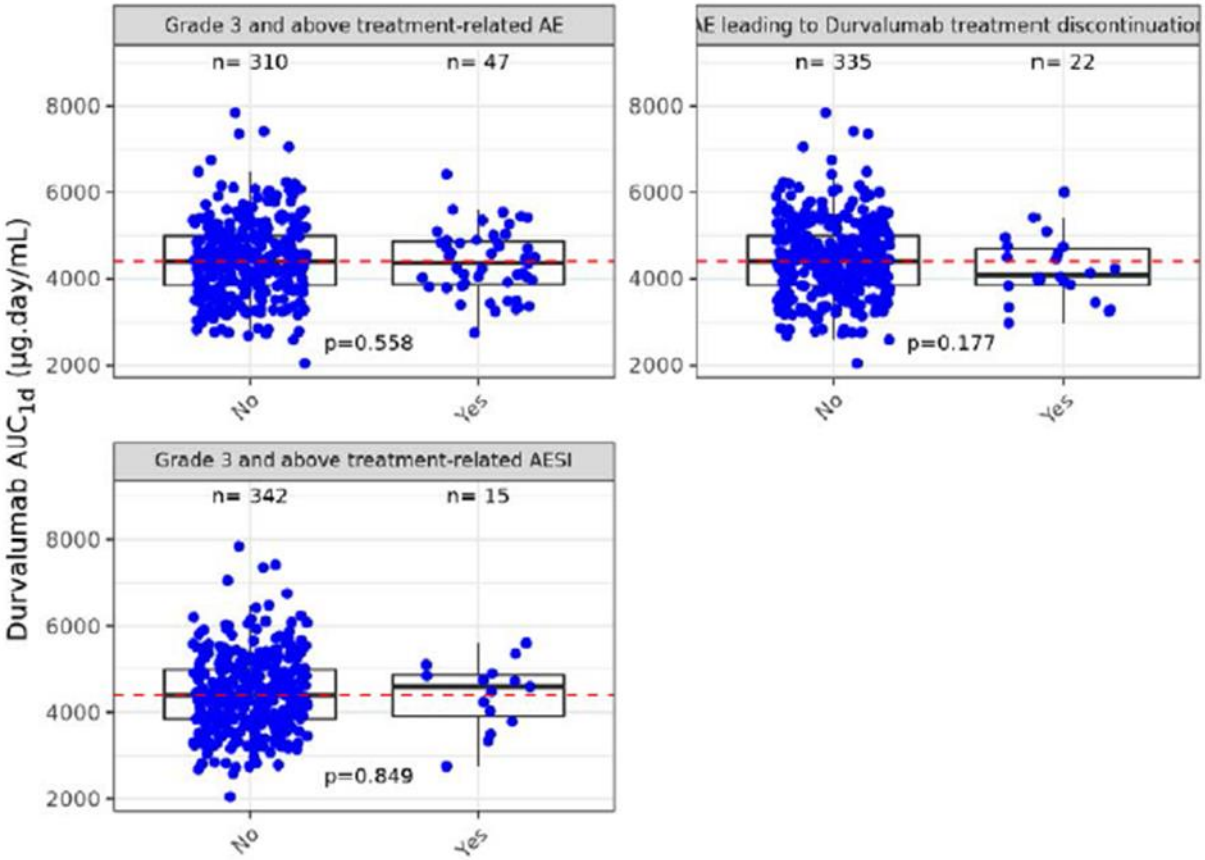
Abbreviations: ADA, anti-drug antibody; CI, confidence interval; Durva, durvalumab; Mono, monotherapy; NA, not applicable (right censored); PFS, progression-free survival; Q4W, every 4 weeks; SoC, standard of care.
Source: See Figure 13 in Exposure-Response Report (MS-2022-02), Module 5.3.4.2.

Exposure-safety relationship

The following pre-planned analyses were conducted:

The relationship between durvalumab exposure and the safety endpoints, Grade 3 and above treatment-related AEs, Grade 3 and above treatment-related AESIs, and AEs leading to durvalumab treatment discontinuation, focusing on the durvalumab 1500 mg Q4W monotherapy arm only. Distribution of AUC after the first dose of durvalumab in patients with and without the specified AE are shown in Figure 8. None of the distribution plots suggested any clear relationship between exposure and any AE. Cmin and Cmax exposure metrics were also evaluated, and similar results were obtained.

Figure 8. Distribution of AUC After the First Dose of Durvalumab in Patients With and Without the Specified AE



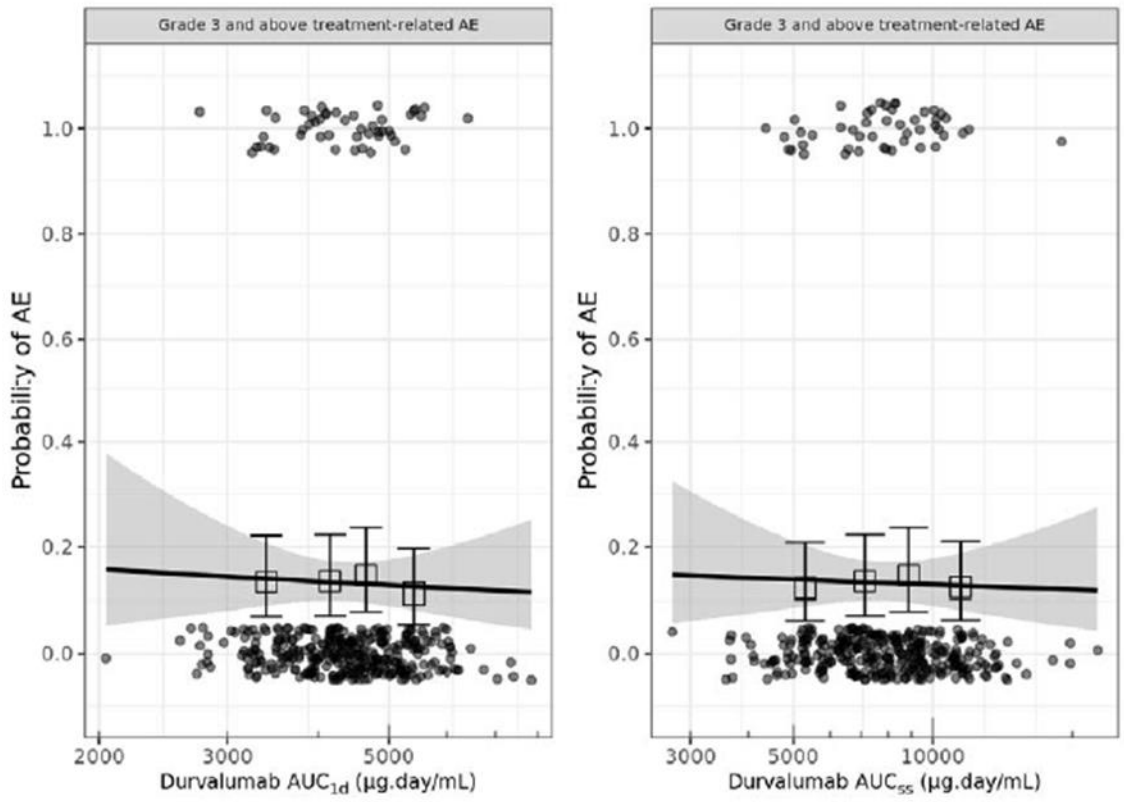
Notes: The blue dots represent the values observed in patient; the dark line is the median; the lower and upper parts of the box are the 25% and 75% percentiles of the distribution, respectively; and the lower and upper whiskers are the median -1.5 IQR and median +1.5 IQR, respectively.
Note: "Yes" represents patients with the specified AE; "No" represents patients without the specified AE.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; AUC, area under the serum concentration-time curve; AUC_{1d}, AUC after first dose of durvalumab; IQR, interquartile range.
Source: See Figure 14 in Exposure-Response Report (MS-2022-02), Module 5.3.4.2.

Grade 3 and Above Treatment-Related AEs

The probability of AEs calculated in quartiles of the AUCdose 1 and steady state for durvalumab exposure metrics is shown in

.

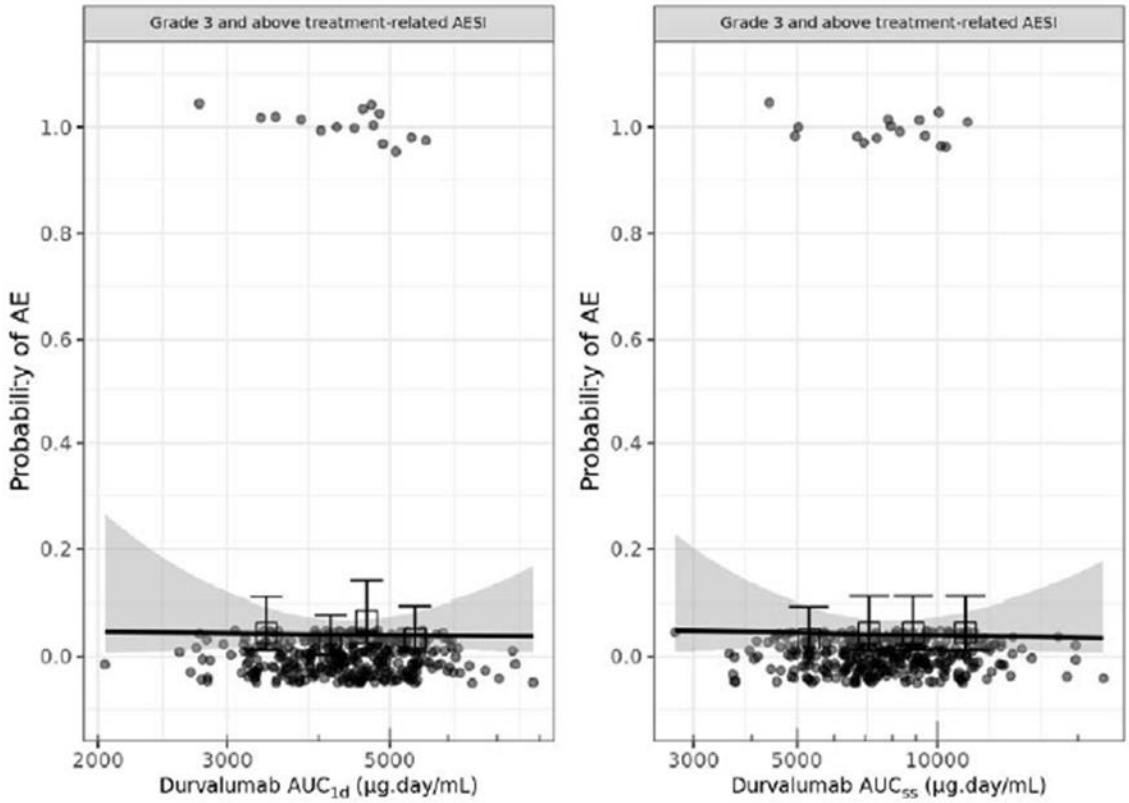
Figure 9. Relationship Between the Probability of Having Grade 3 and Above Treatment-related AEs and AUC_{dose1} and AUC_{ss} for Durvalumab



Notes: 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 2 variables, and the gray area represents the associated confidence interval.
Abbreviations: AE, adverse event; AUC, area under the serum concentration-time curve; $AUC_{dose\ 1}/AUC_{1d}$, area under the serum concentration-time curve during one dosing interval following the first dose; AUCss, area under the serum concentration-time curve at steady state.
Source: See Figure 15 in Exposure-Response Report (MS-2022-02), Module 5.3.4.2.

The probability of grade 3 and above AESIs calculated in quartiles of the $AUC_{dose\ 1}$ and steady state for durvalumab exposure metrics is shown in Figure 10.

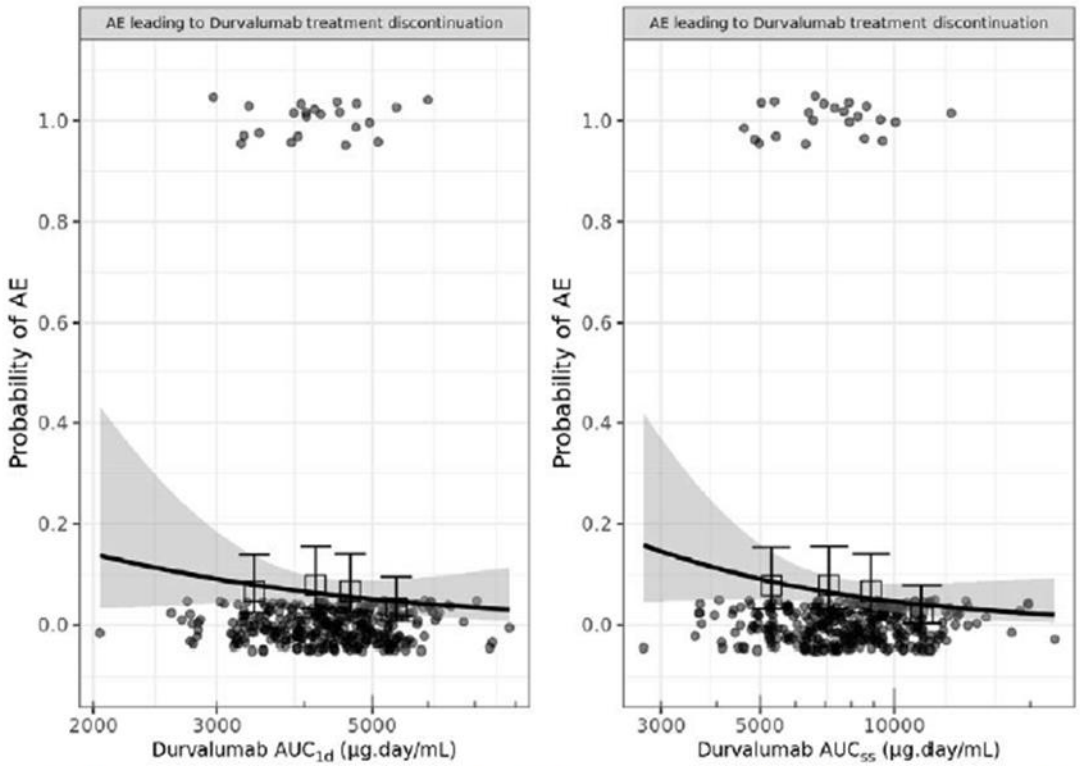
Figure 10. Relationship Between the Probability of Having Grade 3 and Above Treatment-related AESIs and AUC_{dose1} and AUC_{ss} for Durvalumab



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 2 variables, and the gray area represents the associated confidence interval.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; AUC, area under the serum concentration-time curve; $AUC_{dose\ 1}/AUC_{1d}$, area under the serum concentration-time curve during one dosing interval following the first dose; AUC_{ss}, area under the serum concentration-time curve at steady state.
Source: See Figure 16 in Exposure-Response Report (MS-2022-02), Module 5.3.4.2.

The probability of having AEs leading to treatment discontinuation calculated in quartiles of the $AUC_{dose\ 1}$ and steady state for durvalumab exposure metrics is shown in Figure 11.

Figure 11. Relationship Between the Probability of Having AEs Leading to Durvalumab Treatment Discontinuation and AUC_{dose1} and AUC_{ss} for Durvalumab



Notes: 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 2 variables, and the gray area represents the associated confidence interval.
Abbreviations: AE, adverse event; AUC, area under the serum concentration-time curve; $AUC_{dose\ 1}/AUC_{1d}$, area under the serum concentration-time curve during one dosing interval following the first dose; AUC_{ss}, area under the serum concentration-time curve at steady state.
Source: See Figure 17 in Exposure-Response Report (MS-2022-02), Module 5.3.4.2.

2.3.4. Discussion on clinical pharmacology

The application is based on data from the phase 3 HIMALAYA trial in which SoC was tested against durvalumab monotherapy or durvalumab + a single dose of tremelimumab. The use of durvalumab + a single dose of tremelimumab for uHCC was approved by CHMP in December 2022. No new studies have been conducted for the present application. The PK of durvalumab has been characterised and evaluated in previous procedures and is therefore considered known. For this application new E-R analyses have been provided. Also, the paragraph on Immunogenicity was updated in the SmPC, section 4.8, now reporting data from 3069 patients. With updated data, 84 patients (2.7%) tested positive for treatment emergent ADAs (decrease from 3.0%), while neutralising antibodies (nAb) against durvalumab were detected in 0.5% (16/3 069) of patients (data not shown).

Evaluation of population PK, exposure-response and QTc-modelling methodology was assessed in a previous procedure (EMEA/H/C/004771/Imfinzi II/0045-45). No new data or modelling methodology was included in this extension of indication variation. Individual durvalumab exposure metrics were derived from the individual EBEs of the final durvalumab population PK model (MS-2021-02) and used in the subsequent ER analyses. The final durvalumab population PK model (MS-2021-02) has been evaluated in a previous procedure and was considered suitable to derive individual EBEs. All relevant covariates were included/tested in the exposure-response analyses.

No amendments have been proposed in section 5.2 of the SmPC since no new data was added to the population PK model.

E-R analyses were conducted using durvalumab monotherapy data from HIMALAYA. All OS and PFS Kaplan-Meier plots have overlapping quartiles, indicating that there is no clear relationship between OS/PFS and the durvalumab steady state exposure metrics. Data from ADA positive patients are very sparse but there is no indication of an effect of ADA against durvalumab on OS. There is no indication of any impact of body weight on PFS. The apparent positive effect of ADAs on PFS is considered a chance finding based on a very small number (n = 8, 2.24%). LDH, weight, and $C_{min,ss}$ were identified as significant covariates of OS in the Cox proportional hazard model.

E-R analyses for safety did not show any relationship between steady state AUC of durvalumab 1500 mg Q4W monotherapy and the selected AEs. Similar results were observed for Cmin and Cmax (data not shown).

The Applicant has provided graphical diagnostics of the Proportional hazard assumptions for Cox PH final models of OS. The χ^2 statistical tests indicated a $p>0.1$ for all the significant covariates. Exact p-values for each covariate were not provided. The global test for the model as a whole was not provided but this issue is not pursued. From the graphical inspection, there is no significant pattern with time. The assumption of proportional hazards appears to be supported.

2.3.5. Conclusions on clinical pharmacology

The PK of IV durvalumab 1500 mg Q4W monotherapy has been adequately characterised and evaluated in previous procedures and is therefore considered known. Data on immunogenicity was updated in the SmPC and no clinically relevant changes are observed, so this is acceptable. No new studies have been conducted for the present application, but new E-R analyses have been provided, not evidencing clear relationship between OS/PFS and the durvalumab steady state exposure metrics.

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 advanced or 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 2. Overview of Studies in the Clinical Development Program for Durvalumab Monotherapy in Patients With uHCC

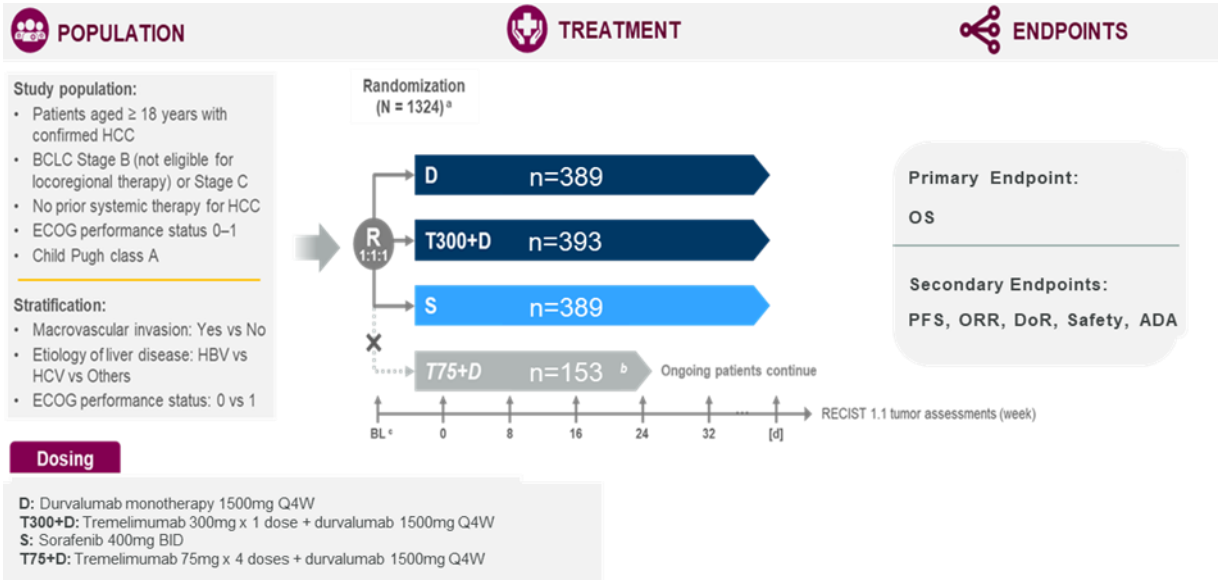
Study number and acronym	Study title	Study design	Objective	DCO date(s)	Location in Module 5
Pivotal Study					
D419CC00002 **HIMALAYA**	A Randomized, Open-label, Multicenter Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients With Advanced Hepatocellular Carcinoma (HIMALAYA)	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

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

Figure 12. HIMALAYA: Study Design



Patient numbers shown correspond to the actual enrolment. Enrolment into the T75+D arm was closed following protocol edition 4.0 (29 November 2018), because T75+D did not meaningfully differentiate from D in terms of efficacy in IA3 of Phase 2 Study 22. 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 fulfil 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 tumour 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 (i.e., not eligible for locoregional therapy) or stage C.

8. Child-Pugh score class A.

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

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 enrolment. 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 enrolment. 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 enrolment.

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. Haemoglobin ≥ 9 g/dL

b. Absolute neutrophil count ≥ 1000/μL

c. Platelet count ≥ 75000/μL

d. TBL ≤ 2.0 × ULN

e. AST and ALT ≤ 5 × ULN

f. Albumin ≥ 2.8 g/dL

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

h. Calculated creatinine clearance ≥ 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 enrolment 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 ≥ 2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria:

- Patients with Grade ≥ 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 (e.g., 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 (e.g., liver transplant).

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

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

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

14. Active or prior documented GI bleeding (e.g., oesophageal 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 oesophageal 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 diarrhoea, or other contraindication to oral therapy.

17. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., 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 (e.g., 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 diarrhoea, 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 (e.g., intra-articular injection)

- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent
- Steroids as premedication for hypersensitivity reactions (e.g., 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.

Patients were recruited from 181 sites across 16 countries.

Treatments

Table 3. 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 (D, arm A) is new in the proposed setting of advanced HCC and encompasses 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 other treatment arm with T300+D (tremelimumab 300 mg as a single dose and durvalumab 1500 mg Q4W, arm C) is also relevant for this procedure since this regimen was recently approved by the CHMP. However, the T75+D regimen (tremelimumab 75 mg Q4W × 4 doses + durvalumab 1500 mg Q4W, followed by durvalumab 1500 mg Q4W, arm B) is not considered relevant for this procedure.

Objectives

Table 4. 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 4 above regarding the objectives and endpoints for the pivotal study Himalaya.

The primary objective of the pivotal Himalaya study was to assess the superiority of efficacy of T300+D (arm C) vs standard of care (sorafenib, arm D) regarding OS for the ITT population. The two key secondary objectives of the trial were related to 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, which is the scope of this procedure.

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 enrolment 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). According to the Applicant, 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.

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), aetiology 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 occurred 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 5. 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 aetiology 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 was >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 was 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 chi-square 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, aetiology 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 chi-square test was to be used to compare the difference in KM estimators at 36 months.

It was 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.

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 (aetiology of liver disease, ECOG, and macrovascular invasion) were 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, aetiology 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 6. 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 enrolment with Amendment 4) were planned to be summarized descriptively, however were not to be formally analysed.

Multiplicity

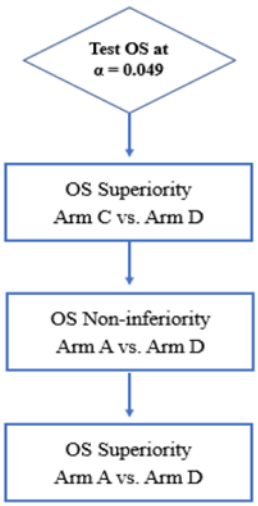
To strongly control the familywise error rate (FWER) at the 5% level (2-sided), an alpha level of 0.1% was planned to be spent on the interim ORR analysis (IA1) while the remaining 4.9% alpha level were

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



Two interim and 1 final analyses were planned. 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. A hierarchical approach was implemented 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.

Changes to Planned Analyses

Changes to the statistical analyses planned are shown below. The AstraZeneca study team was responsible for all changes to the planned statistical analyses. Several changes occurred before first interim analysis (DCO: 02 September 2019), however following changes to the analysis plan was either clarifying or pertaining to exploratory endpoints. These changes were made prior to the DBL for the final analysis (DCO: 27 August 2021) (data not shown). Additional 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 7. Changes to Planned Analyses

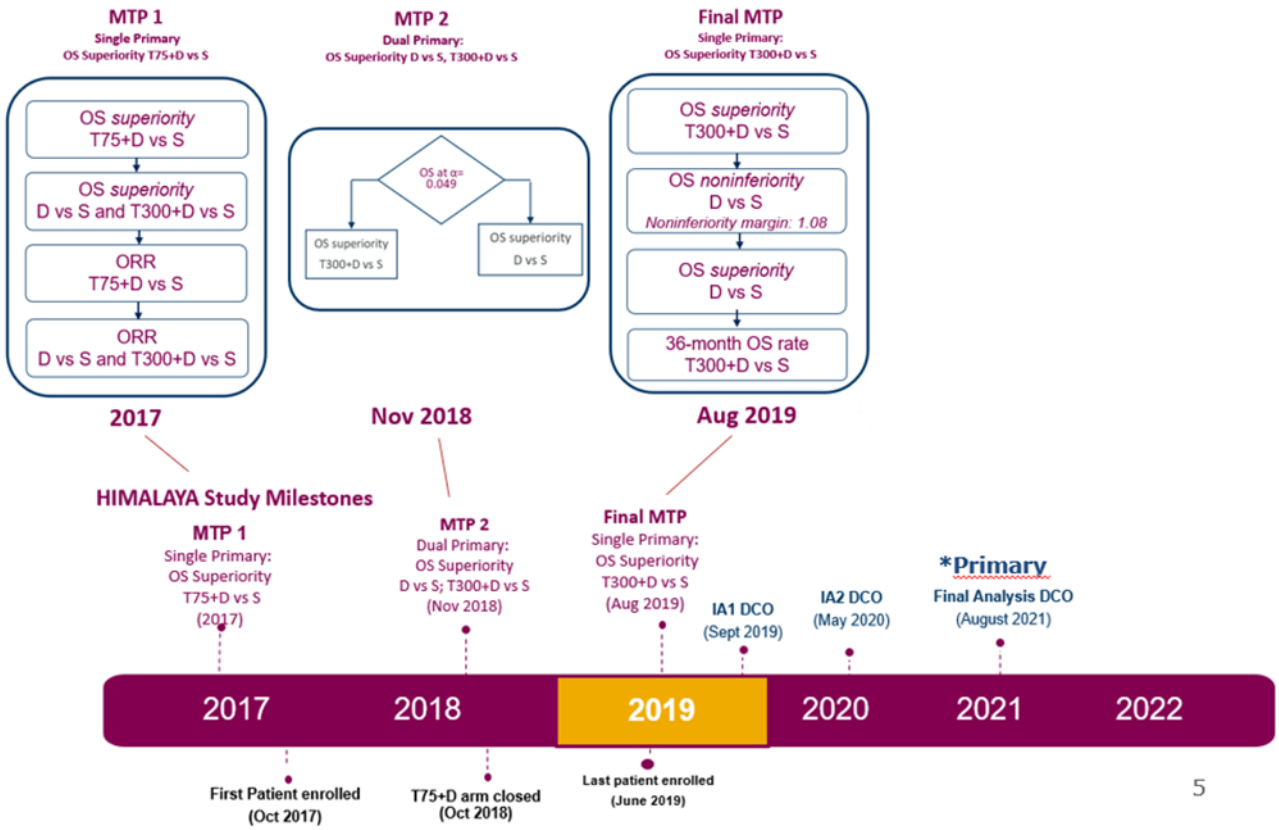
Key Details of Change (Section of Report Affected)	Reason for Change
Two additional efficacy endpoints that were not detailed in the CSP were calculated: time to response and time from randomization to first subsequent therapy or death. Neither endpoint is reported in the CSR	To support the payer analysis
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.

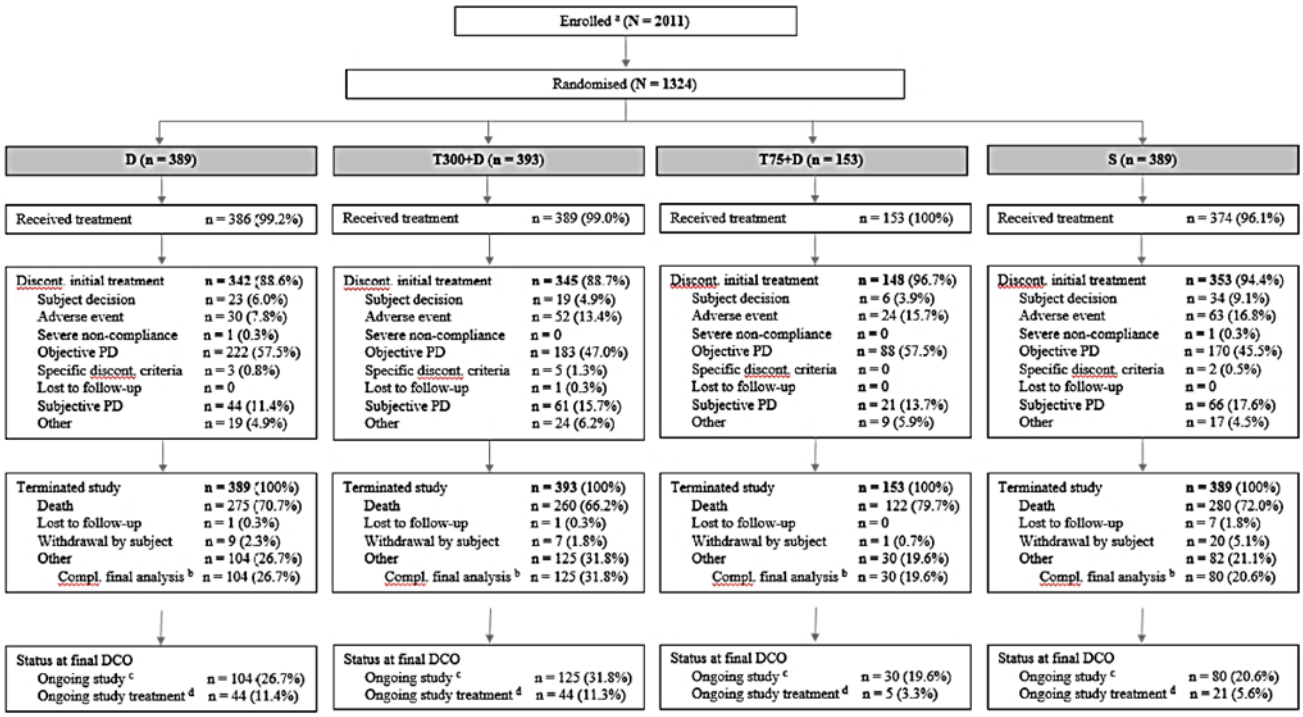
Figure 14. Changes to multiple testing procedure in function of study milestones



Results

Participant flow

Figure 15. 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

No study sites were terminated or paused due to the COVID-19 pandemic. Patient enrolment 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 8).

Table 8. 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 9. 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:	1
Exceeded screening time (new screening number)	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. 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 (Table 9): 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.

Recruitment

The first patient was enrolled on 11 October 2017 and the last patient on 19 June 2019.

Conduct of the study

Table 10. 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)	
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.

Baseline data

Table 11. Demographic and Baseline Patient Characteristics in HIMALAYA (Pivotal Study) and Study 22 (Supportive Study)

Study	**HIMALAYA**			**Study 22 (Parts 2 and 3)**	
Analysis set (DCO)	**FAS (Final Analysis)**			**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)

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)
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)
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 12. 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)

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)**
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)
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 13. Post- Discontinuation Anticancer Systemic Therapy

Anticancer therapy [a]	Number (%) of patients				
	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 14. 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 15. Overall Survival in HIMALAYA (Pivotal Study) (FAS) DCO 27 August 2021

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, aetiology 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.

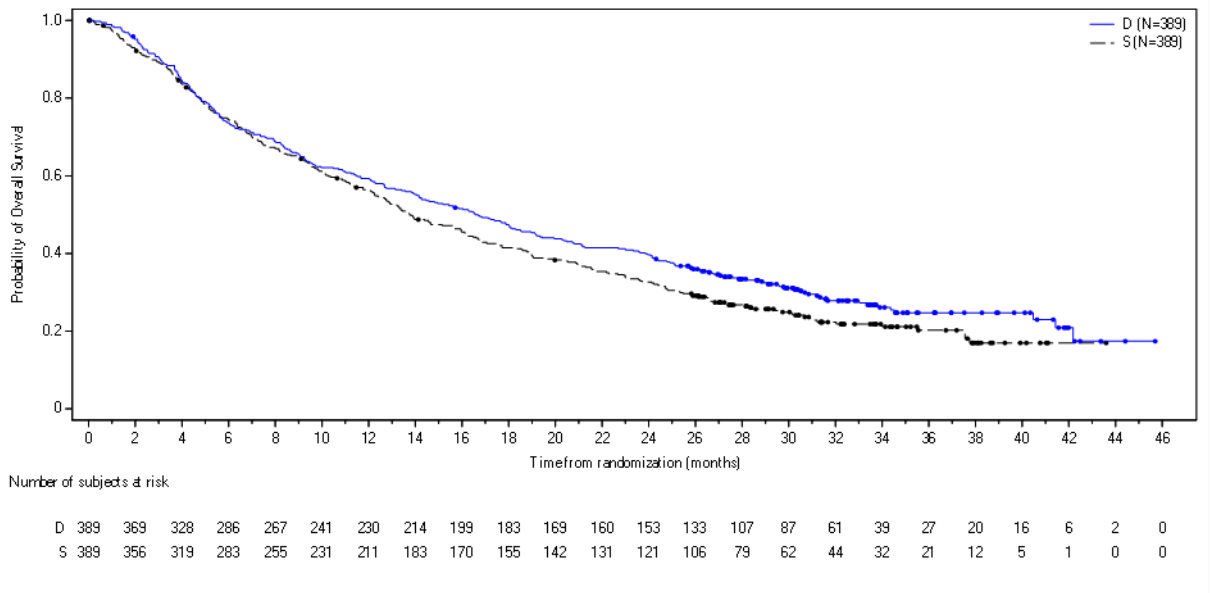
[i] Calculated using the reverse Kaplan-Meier technique (with censor indicator reversed).

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.

Table 16. Overall Survival in HIMALAYA (Pivotal Study) (FAS) 4 years follow up DCO: 23 January 2023

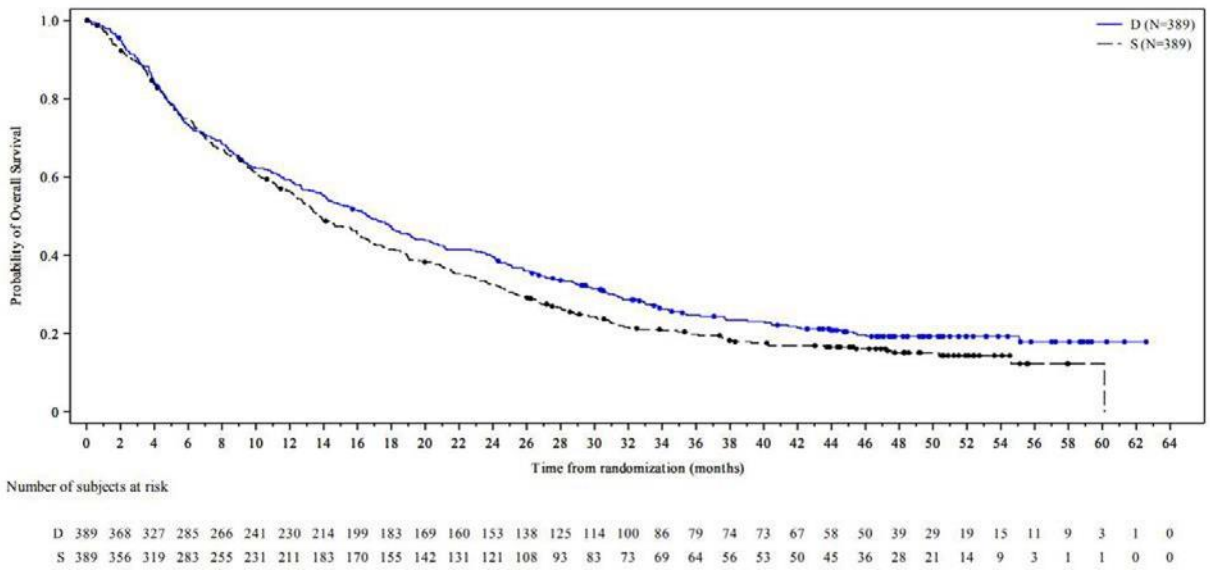
Study **Analysis set (DCO)**	**HIMALAYA** **FAS (44 years follow up)**		
	D **(N = 389)**	**T300+D** **(N = 393)**	**S** **(N = 389)**
HR (compared to sorafenib) [a]	**0.86**	**0.78**	-
95% CI [a]	0.744 - 1.011	0.66 - 0.92	-
96.02% CI for HR (T300+D vs S) [a, b]	-	0.65 - 0.93	**-**
2-sided p-value (T300+D vs S)	**-**	**0.0035**	-
2-sided p-value (D vs S) [d]	**0.06667667**	-	-
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	1919.8
OS rate at 48 months, %	19.3		15.1
Deaths, n (%)	305305 (78.44)	262 (66.7)	316316 (81.22)
Median (95% CI) duration of follow-up in all patients (months) [i]	48.46 (46.82-49.81)	49.12 (46.95–50.1717	47.31 (45.08–49.15)

Figure 16. Kaplan-Meier Plot of Overall Survival in the D and S Arms in HIMALAYA, FAS (Final Analysis) DCO 27 August 2021



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

Figure 17: Kaplan-Meier Plot of Overall Survival in the D and S Arms in HIMALAYA at the 4-Year Follow Up (Full Analysis Set)



D, durvalumab 1500 mg (20 mg/kg) Q4W; Q4W, every 4 weeks; S, sorafenib 400 mg twice daily.

Secondary endpoints:

Progression-free survival (PFS)

Table 17. 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 18. Kaplan-Meier Plot for Progression-free Survival by Investigator Assessment According to RECIST 1.1 (FAS)

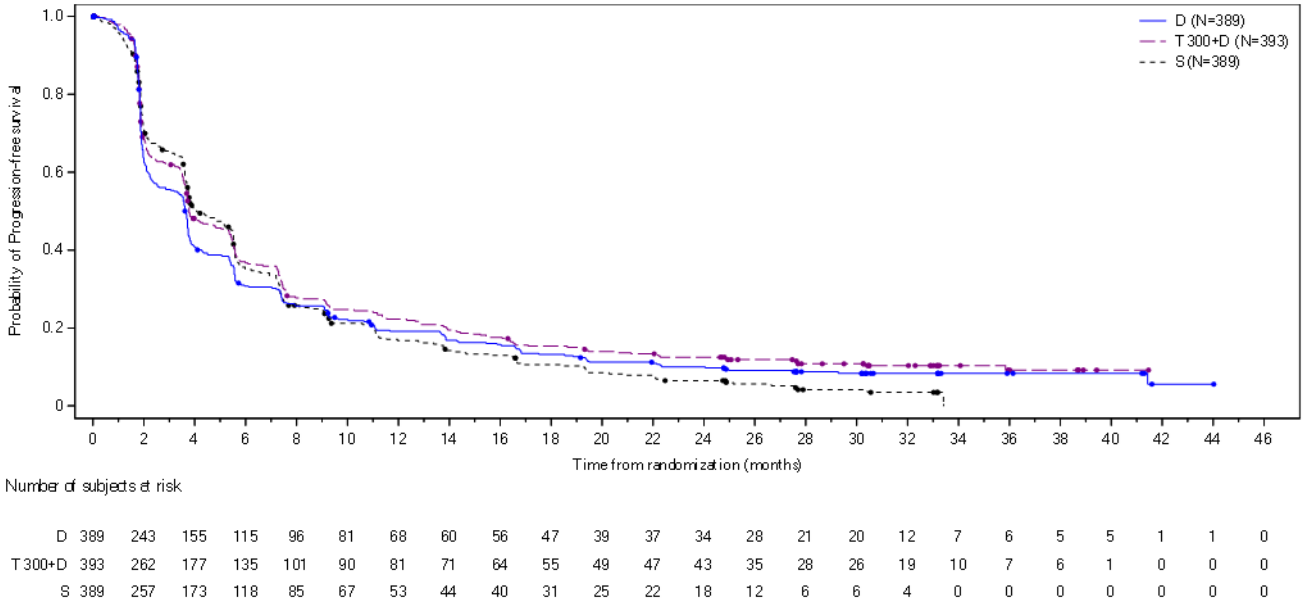


Table 18. Progression-free survival (FAS 32w FUP) based on BICR assessments per RECIST 1.1 (DCO 27-AUG-2021)

	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.
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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 relevant arms (D vs T300+D vs S).

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 3.65 months in the D arm versus 4.07 months in the S arm; HR 1.02 (95%CI: 0.88; 1.19) for D vs S comparison. The PFS analyses are mature with 88.7% and 84.1% events in the D and S arms, respectively. The KM curves for PFS is shown in Figure 18 and do not clearly separate at any time. Moreover, the shape of the curves indicates a large number of events at each evaluation time point.

PFS by BIRC was 3.48 months in the D arm (n=236 patients) and 3.78 months in the S arm (n=236 patients); but this is not directly comparable with PFS by Investigator, since the evaluation was only done in subsets of patients.

Overall response rate (ORR) and best objective response

Table 19. 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 20. 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 21. 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 22. 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 23. Duration of Response and Time to Onset of Objective Response in HIMALAYA 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.

The DOR by IRC in a subset and the disease control rate (DCR) is not shown or assessed, as these are exploratory analyses and not considered relevant for the target disease of advanced HCC.

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 24 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 25 Summary of Change from Baseline in EORTC QLQ-HCC18 Symptoms (FAS)

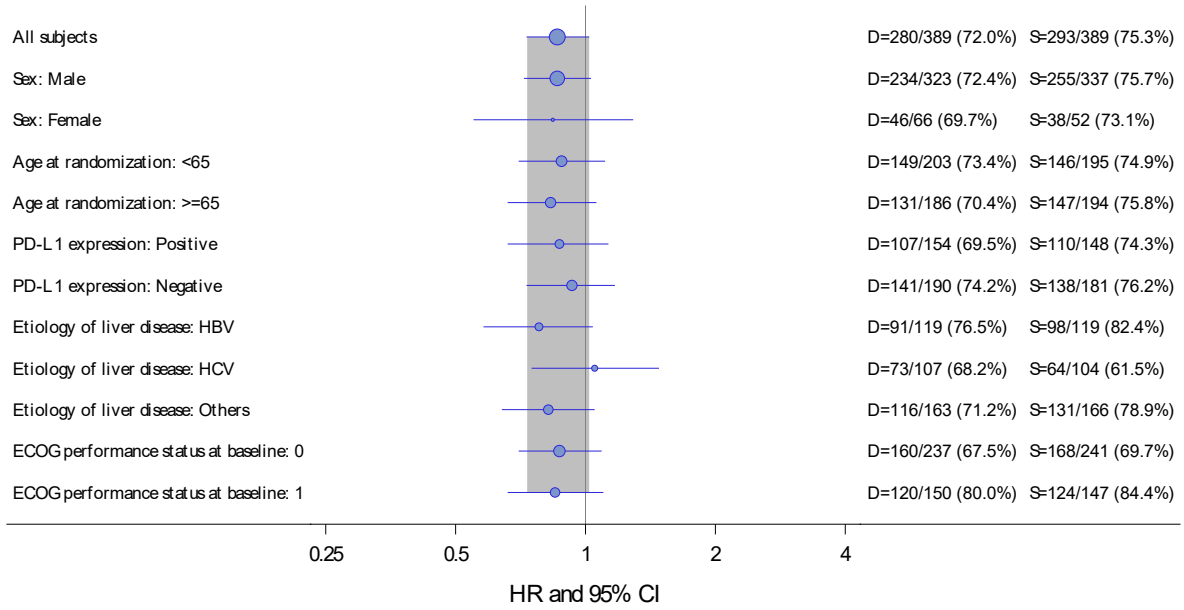
Symptom Scale Item	Statistic	Number (%) of patients			
		D (N= 389)	T300+D (N= 393)	T75+D (N = 153)	S (N= 389)
Abdominal swelling	n	280	238	112	253
	Adjusted mean (SE)	1.0 (1.32)	-0.1 (1.37)	-0.7 (2.15)	NE
	95% CI	-1.64, 3.56	-2.84, 2.55	-4.93, 3.52	NE
	Estimated difference	NE	NE	-	-
	95% CI for difference	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	-	-

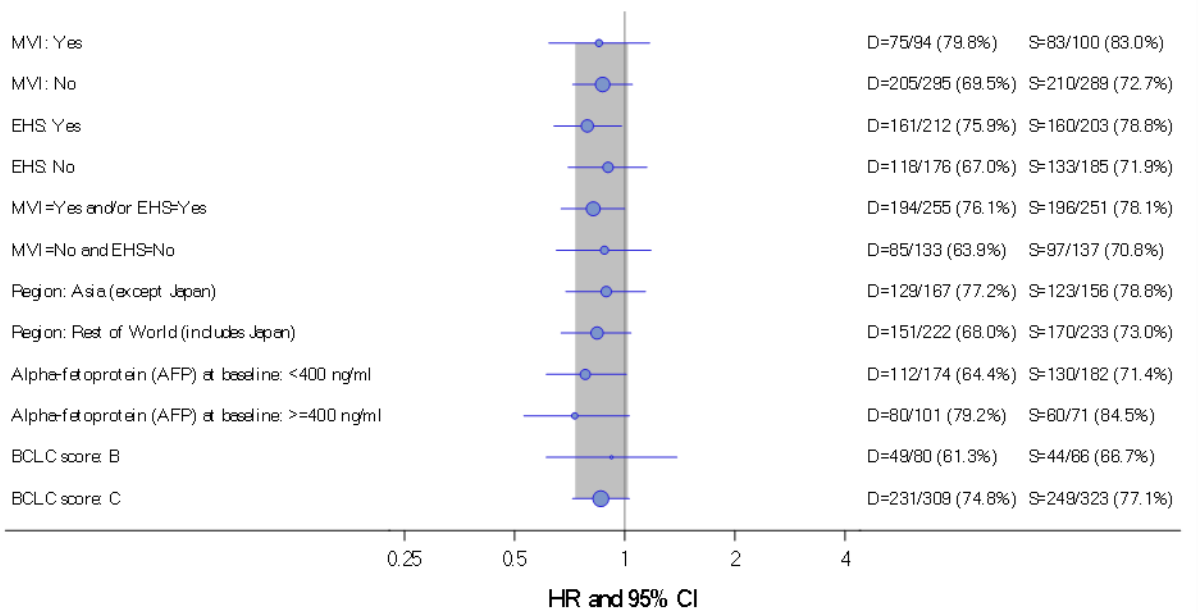
EORTC Score Interpretation: All scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. A high score for functional scales (physical, role, emotional, cognitive, social) and global health status/QoL represents a high functioning/QoL, but a 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 19. Forest Plots of Overall Survival by Subgroup for D vs Sorafenib in HIMALAYA (FAS)





A hazard ratio < 1 implies a lower risk of death for D.

Size of circle is proportional to the number of events. Grey band represents the 95% confidence interval for the overall (all subjects) hazard ratio.

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; MVI = macrovascular invasion; PD-L1 = programmed cell death ligand-1; TIP = tumor immune percentage.

Source: Figure 14.2.1.2, HIMALAYA CSR, Module 5.3.5.1.

Figure 20. Summary of stepwise regression analysis of overall survival

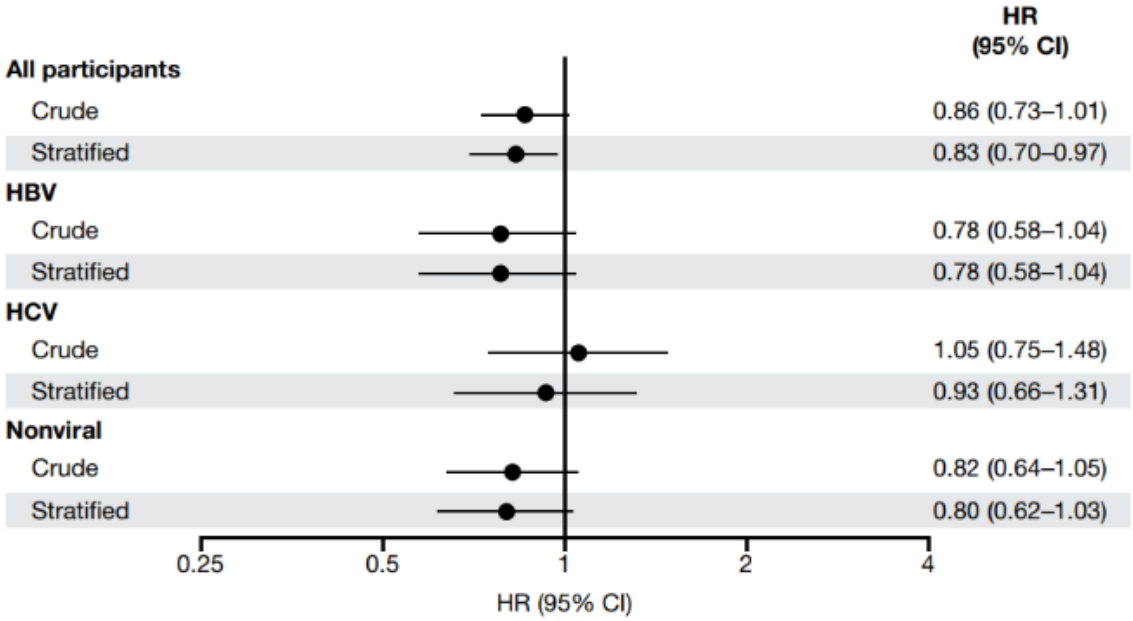


Table 26. Subgroup Analysis of Overall Survival by PD-L1 Expression Level, HIMALAYA (FAS)

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.

Table 27. 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.

Table 27 shows a supplementary analysis of PD-L1 status on all PD-L1 evaluable patients, regardless of the tissue sample age, and presents OS results according to PD-L1 status (PD-L1 Positive (TIP ≥ 1%) vs PD-L1 Negative (TIP < 1%)).

Summary of main study

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

Table 28. 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 and non-inferiority of D vs S in terms of OS	
Treatments groups	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
	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 endpoint	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 (months)	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 29. 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 (e.g., 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.

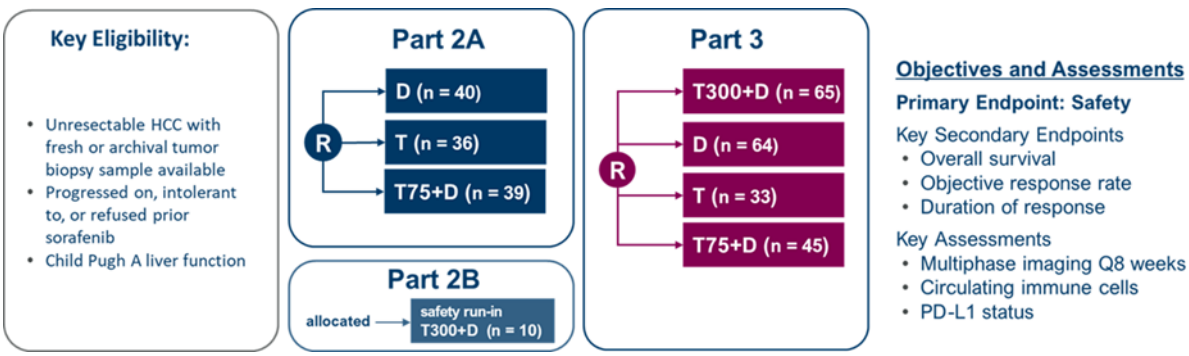
- MANDATORY: Provision of a tumour biopsy, formalin fixed and embedded in paraffin, for the purpose of PD-L1 expression analyses (and for enabling exploratory analyses as described in the proceeding section). A newly acquired tumor biopsy (<3 months) was strongly preferred; however, if not feasible with 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 (i.e., 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 (e.g., 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 SP263 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.

Supportive study

Figure 21. Study 22: Study Design



Following protocol amendment 5, enrolment 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).

Baseline data for the most relevant D arm showed a median age of 64.5 years, and half of the patients were less than 65 years of age. The vast majority of the patients were male (88.5%) and many were of white (33.7%) or Asian (52.9%) race. Information on alcohol use was not collected.

Disease characteristics show that the half of the patients were ECOG PS 0 (50%) and disease of advanced BCLC stage C (76.9%) plus macrovascular invasion and/or extrahepatic spread (69.2%). The poor prognostic factor of AFP >400 ng/ml was observed in a third of patients (37.5%). Approximately half of the included patients had tumours that were PD-L1 positive (TIP≥1%) and 13.5% of the patients had missing data on PD-L1 status.

Table 30. 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 11 and Table 12 in the Results section above.

Table 31. 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.

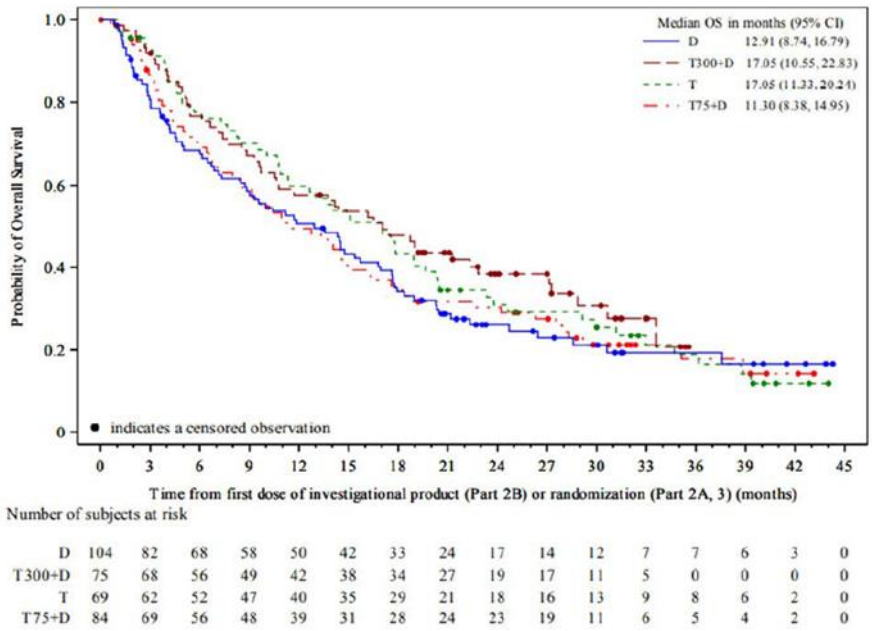
[d] 'Other' reasons (1 patient each): psychiatric issues and study compliance, adverse event, and patient did not receive treatment.

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



Number of subjects at risk

D	104	82	68	58	50	42	33	24	17	14	12	7	7	6	3	0
T300+D	75	68	56	49	42	38	34	27	19	17	11	5	0	0	0	0
T	69	62	52	47	40	35	29	21	18	16	13	9	8	6	2	0
T75+D	84	69	56	48	39	31	28	24	23	19	11	6	5	4	2	0

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 32. 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 33. 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).

The final analysis performed 12 months after the first dose of investigational product (DCO: 06 November 2020) showed a median OS of 12.91 months (75% events) for patients who received the proposed dosing regimen of durvalumab monotherapy (n=104), while the ORR was 11.5% and the duration of response (DoR) was ~15 months. The median OS in the T300+D arm was 17 months and the ORR and DoR were also better (24% and 18.43 months), which may be attributed to the added tremelimumab.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of the PD-L1 inhibitor durvalumab (D)as monotherapy for the treatment of advanced hepatocellular carcinoma (HCC) is primarily based on the pivotal Himalaya study. This was a randomised, open-label, multicentre Phase III study in patients with advanced HCC 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 (Barcelona Clinic Liver Cancer Stage C or B not eligible for locoregional therapy and Child-Pugh Score Class A), which is not necessarily considered reflective of the general patient population with advanced HCC. However, the inclusion and exclusion criteria are reflected in the SmPC section 5.1 to inform treating physicians.

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). The screen failure reasons are in line with what could be expected for a clinical trial with the targeted patient population. Randomization was stratified according to macrovascular invasion (yes versus no), aetiology 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 advanced HCC. 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.

Himalaya was initiated in October 2017 and was fully recruited in less than 2 years, which is acceptable. The median duration of follow-up for OS is acceptable although the study population encompasses patients from the most favourable prognostic group. The overall design of this pivotal study is endorsed as it allows to assess the efficacy of the proposed dosing of durvalumab monotherapy 1500 mg Q4W versus standard of care (Sorafenib - S) in the proposed first-line setting. Of note, the treatment regimen of a single dose of tremelimumab + durvalumab (T300+D) was approved based on the positive outcome of the primary endpoint of this trial (OS superiority T300+D vs S) by the European Commission for the 1L treatment of advanced HCC in February 2023.

Of note, enrolment into the T75+D arm was closed in both Himalaya and Study 22 following a benefit-risk decision based on results from a preplanned interim analysis of Study 22 (Parts 2+3 DCO: 31-Aug-2018), which showed that although the T75+D regimen was tolerable, efficacy data were not meaningfully better compared to the sorafenib arm, which no longer justified continued enrolment into the T75+D arm (Protocol Amendment 3 in HIMALAYA [29 November 2018], and Protocol Amendment 5 in Study 22 [26 November 2018]). This led to changes in sample size calculations. The multiple testing plan in protocol v4.0 was changed to split the alpha of 0.049 between the dual primary comparisons of D vs S and T300+D vs S. According to the MAH, those changes were driven by results from interim analysis of the ongoing Study 22 (DCO May 7, 2018). Protocol amendment 5 (protocol v6.0, August 2019) was introduced almost 2 years after the study was initiated and also pertained to important changes, dual primary objective was again changed, now to a single primary objective T300+D vs S for superiority (at alpha-level of 0.049) and 2 key secondary objectives to be tested subsequently: D vs S for OS non-inferiority (which was new objective with NI margin of 1.08) and D vs S for OS superiority.

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. After an oral explanation, the CHMP agreed that the decision to make these crucial changes was based on external data from the mentioned sources. Especially, the post-hoc analysis presented by the Applicant, which showed that the Himalaya trial data would not have been informative, as the data just before the changes made in September 2019 indicated that at ~30% maturity, the OS curve for durvalumab monotherapy was above the curve for T300+D, which contradicts the decision made, which was to add T300+D on the top of the hierarchy and add NI for D. In protocol version 6, the median OS and 18-month OS rate for sorafenib was increased. The required number of events at the second interim analysis and at the final analysis were also changed.

Updates to sample size during trial conduct are understood as driven by observed overall response rates, and that these were different from the assumptions at trial start. Hence there would be insignificant impact on control of type 1 error.

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, which is not the scope of this application. The two key secondary objectives of the trial were to assess non-inferiority of the efficacy of durvalumab monotherapy versus SoC (sorafenib) in terms of OS and superiority of the efficacy of durvalumab monotherapy versus SoC (sorafenib) also in terms of OS, which are relevant objectives for the applied indication of durvalumab monotherapy for 1L treatment of advanced HCC. Hence, the current extension of indication for durvalumab monotherapy for 1L advanced HCC is based on efficacy results from the secondary objectives of the pivotal study.

Other important secondary endpoints are PFS and overall response rate plus duration of response. The recent CHMP approval of T300+D 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.

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.

The baseline characteristics in the pivotal Himalaya study are well balanced between the arms, but only approximately 40% 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 overall 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 more favourable prognostic factors. However, the mentioned characteristics were fairly well distributed between the treatment arms. It is noted that only a third of the included patients had tumours that were PD-L1 positive (TIP≥1%) and that there were ~10% of the patients in the D arm of the pivotal study Himalaya, who had missing data on PD-L1 status. Overall, disease characteristics are well distributed between the treatment arms and they are adequately reflected in the SmPC. 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.

Efficacy data and additional analyses

The focus for this procedure is the durvalumab monotherapy arm (D), the T300+D and the S arms, and the sample sizes of these arms are considered appropriate for the comparisons.

The median follow-up for OS at DCO (27 August 2021) was ~32 months in the D arm and the S arm.

The primary objective was met as treatment with T300+D showed a statistically significant and clinically relevant improvement in **OS** compared to the standard of care arm with sorafenib. Median OS was improved 2.66 months 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. The KM curves begin to separate after 4 months of therapy and stay separated.

It should be considered that the primary endpoint for Himalaya was to demonstrate superiority of T300+D vs S in terms of OS and the pivotal study protocol was amended to demonstrate non-inferiority of D vs S for OS as the next analysis in the hierarchical testing, which is the main scope of this procedure. When comparing **OS in the D vs S arm**, there was a 2.79 months difference, i.e. from 13.77 months to 16.56 months, HR 0.86 (95%CI: 0.73; 1.02), which meets the key secondary objective of Non-inferiority as demonstrated by the upper bound of the 95.67% CI (0.73, 1.03) falling below the pre-specified clinical NI margin of 1.08. This numerical OS difference of 2.79 months is considered clinically meaningful in this clinical context. Moreover, a similar OS benefit to the T300+D regimen is observed (median OS for T300+D was 16.43 months), without the added toxicity of the tremelimumab. Hence, treatment with durvalumab monotherapy is considered clinically significantly improved compared to sorafenib and non-inferior and clinically similar to the T300+D regimen.

Of note, the median OS with sorafenib was 13.77 months, which is line with the efficacy of sorafenib in other studies of sorafenib in a similar setting (REFLECT, median OS from sorafenib was 12.3 months vs. 13.6 from lenvatinib; IMbrave150, median OS from sorafenib was 13.4 months vs. 19.2 from atezolizumab + bevacizumab), so the performance of the control arm is reassuring and considered acceptable in this context.

The MAH has informed that the non-inferiority (NI) margin for D vs S in the HIMALAYA study was based on relevant historical studies of sorafenib. It was concluded that a clinical NI margin of 1.08 was adequate for the comparison of D vs S and the MAH claims that the determination of the NI margin was consistent with guidance (EMA 2005; FDA 2016).

Of note, the Protocol amendment 5 changed the efficacy comparison of D vs T300+D according to PD-L1 expression from a secondary to an exploratory objective. The main argument for this was that aging of the tissue samples of more than 3 years may affect and diminish the PD-L1 expression measured. This change is not endorsed, considering that durvalumab's approved indication for locally advanced unresectable NSCLC is PD-L1 restricted and there is a strong scientific rationale that the efficacy of durvalumab could be driven by effect only in tumours with positive PD-L1 expression. Hence, this change weakens the credibility of the efficacy analyses according to PD-L1 status and hampers interpretability of the results. The supplementary analysis of PD-L1 status showed a trend towards improved efficacy in the PD-L1 positive subgroup who had durvalumab monotherapy (n=190/344, 55%); i.e. the median OS was 15.06 months in the PD-L1 negative vs 17.22 months in the PD-L1 positive (HR 0.93 vs HR 0.87, respectively). However, these exploratory data also support a clinically meaningful OS benefit compared to sorafenib and the HRs for OS in both the PD-L1 negative and positive subgroups are acceptable, considering that more than half of the patients in the D arm was PD-L1 negative. Therefore, efficacy benefit from durvalumab seems to occur regardless of PD-L1 expression in advanced HCC.

The secondary endpoint of **ORR** by investigator was 17% for the D arm compared to 5.1% in the sorafenib arm, while 1.5% had a BOR of CR and 15.4% of PR in the D arm compared to 0 and 5.1% with sorafenib. The overall response rate is considered borderline clinically meaningful in its magnitude. Moreover, the disagreement between the Investigator and BIRC is considered large, even for an open-label study, and it is noted that especially late the discrepancy rate is high.

The responders in the D arm (n=66) had durable responses with a median **DoR** of 16.82 months. The time to response for this subgroup was median 2.09 months and this is lower than for the S arm; however, due to small number of responders in the S arm, there are too many uncertainties for any firm conclusions. The ORR and DoR of T300+D vs D was slightly better (ORR 20.1% and DoR 22.34 months), which is interpreted as there is still clinically significant and comparable efficacy of durvalumab monotherapy and the improvement of ORR and DOR are considered clinically significantly improved compared to sorafenib.

The **PFS** analyses were not in the testing hierarchy, so they are not controlled for multiplicity. PFS by investigator was not clinically significantly improved and numerically shorter for the D arm, since the median PFS was 3.65 months in the D arm versus 4.07 months in the S arm, HR 1.02 (95%CI: 0.88, 1.19). The PFS analyses are mature with 88.7% and 84.1% events in the D and S arms, respectively and the KM curves do not clearly separate at any time. Moreover, the shape of the curves indicates a large number of events at each evaluation time point. This finding is considered consistent with the pattern of efficacy previously observed for immunotherapy, where a PFS benefit is often lacking or of a small magnitude, while OS is often clinically significantly improved. Hence, this is an acceptable result because the primary endpoint was OS, and an OS benefit has been shown for the proposed treatment regimen of durvalumab monotherapy vs sorafenib. It should be noted that the final analysis of ORR and PFS was done by investigators and this is not considered optimal since the pivotal Himalaya study was open-label.

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 to be reflected in the SmPC.

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

Supportive Study 22:

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 D and the T300+D arm are considered of most relevance for the proposed indication (n=104 and n=75, respectively), 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.

Baseline data for the most relevant D arm showed that the median age was 64.5 years and the vast majority of the patients were male (88.5%) and of white (33.7%) or Asian (52.9%) race. Although patients should have had prior treatment with sorafenib or a VEGFR TKI, this was only true for 63.5%. The baseline characteristics are acceptable for the 2L+ setting; however, only approximately a third of the study population are considered EU like according to region and race characteristics. Disease characteristics show that the half of patients were ECOC PS 0 and disease of advanced BCLC stage C (76.9%) plus macrovascular invasion and/or extrahepatic spread (69.2%). Overall, the baseline and disease characteristics are acceptable for the supportive study.

The final analysis showed a median OS of almost 13 months (75% events) for patients who received the proposed dosing regimen of durvalumab monotherapy, while the ORR was 11.5% and the duration of response (DoR) was ~15 months. Although the results from the T300+D arm were better, the results from the durvalumab monotherapy arm can be considered supportive and acceptable.

2.4.3. Conclusions on the clinical efficacy

The results from the pivotal Himalaya study showed that survival in the durvalumab monotherapy arm was non-inferior to that of the control sorafenib arm in the targeted population, with a non-inferiority margin which is considered acceptable. Although fundamental changes had been made in the protocol and SAP during the pivotal study, the CHMP has agreed that the decision to make the changes was based on external data only.

2.5. Clinical safety

Introduction

Table 34. 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)
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 monotherapy in the proposed indication was derived from pooled data from HIMALAYA and Study 22 and the Pan-tumor D pool as described below:

- **HCC D pool (N=492):** 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.
- **Pan-tumor D Pool (N=4045):** The Pan-tumor D pool consists of all patients who have received at least 1 dose of durvalumab monotherapy given at a dose of either 10 mg/kg Q2W IV (or equivalent) or 20 mg/kg Q4W IV (or equivalent) for any line of therapy (across tumor types, including HCC).

The overall safety population, who received durvalumab monotherapy (D) consists in the pivotal Himalaya study and the supportive study 22, in total 492 patients. Moreover, the MAH also provides supportive safety data from the Pan-tumor D pool from patients, who have received at least 1 dose of durvalumab monotherapy given at a dose of either 10 mg/kg Q2W IV (or equivalent) or 20 mg/kg Q4W IV (or equivalent) for any line of therapy (across tumor types, including HCC).

Since the applied indication is best reflected by the study population from the Himalaya study, it is the 492 patients from the HCC D pool compared to the safety profiles of sorafenib (SOC) and T300+D, which will be of main focus for the safety assessment.

Patient exposure

Table 35. Summary of Study Treatment Exposure (Safety Analysis Set)

	HCC D pool (N = 492)	**Pan-tumor D pool (N = 4045)**
Total treatment duration (weeks) [a]		
n	492	4045
Mean (SD)	38.0 (41.49)	28.9 (32.18)
Median (min, max)	19.9 (1, 193)	16.1 (0, 220)
Total treatment years	358.6	2240.4
Total treatment duration (weeks); n (%)		
≥ 24	225 (45.7)	1671 (41.3)
≥ 52	120 (24.4)	793 (19.6)
≥ 76	82 (16.7)	246 (6.1)
≥ 104	53 (10.8)	179 (4.4)

a. Total treatment duration = (last dose date + X days or death date or DCO whichever occurs earlier - first dose date +1) / 7. X is defined as the planned frequency in dosing (in days) - 1. For Q4W, X = 27. For Q2W, X = 13.

D, durvalumab 1500 mg (or equivalent); DCO, data cut-off; max, maximum; min, minimum; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation.

Source: Table 2.7.4.1.3, Pooled Safety Outputs, Module 5.3.5.3.

The median treatment duration of durvalumab in the HCC D pool (n=492) were 19.9 weeks (range: 1-193), while the median treatment duration was 16.1 weeks in the Pan-tumor D pool.

For context, the median treatment duration was 4.1 months (range: 0.1-38.6 months) in the S arm (n=374).

In the HCC D pool (1500 mg Q4W), about 50% of patients received at least 6 cycles (≥24 weeks of exposure) of treatment at DCO (See Table 35 above).

Adverse events

Table 36. Overview of Adverse Events (Safety Analysis Set)

	Number (%) of patients [a]			
	HIMALAYA		HCC D pool (N = 492)	Pan-tumor D pool (N = 4045)
AE category	D (N = 388)	S (N = 374)		
Any AE	345 (88.9)	357 (95.5)	443 (90.0)	3825 (94.6)
Any AE possibly related to any study treatment [b]	202 (52.1)	317 (84.8)	267 (54.3)	2339 (57.8)
Any AE of CTCAE Grade 3 or 4 [c]	144 (37.1)	196 (52.4)	204 (41.5)	1754 (43.4)
Any AE with outcome of death	26 (6.7)	27 (7.2)	30 (6.1)	231 (5.7)
Any SAE (including events with outcome of death) [d]	115 (29.6)	111 (29.7)	161 (32.7)	1446 (35.7)
Any AE leading to discontinuation of any study treatment	32 (8.2)	63 (16.8)	47 (9.6)	397 (9.8)
Any AE leading to discontinuation of any study treatment, possibly related to any study treatment [b]	16 (4.1)	41 (11.0)	26 (5.3)	183 (4.5)
Any AE leading to dose delay or interruption of any study treatment	95 (24.5) [e]	178 (47.6) [e]	112 (22.8) [f]	1120 (27.7) [f]

b. 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.

c. As assessed by the investigator. Missing responses are counted as related.

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

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

f. AEs on the AE CRF with action taken = drug interrupted.

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

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 are not included in this summary.
AE, adverse event; CRF, case report form; 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; S, sorafenib 400 mg twice daily; SAE, serious adverse event. Source: Table 2.7.4.2.1, Pooled Safety Outputs, Module 5.3.5.3 and Table 14.3.2.1, HIMALAYA CSR, Module 5.3.5.1.

For comparison, most of the patients, who received **T300+D**, experienced at least one AE (88.9%), and 37.1% experienced a grade 3 or 4 AE. SAEs were observed in 29.6% of the patients, of which 6.7% had an SAE leading to death. The overall discontinuation rate due to AEs was 13.7%.

Table 37. Adverse Events and Event Rate Occurring in ≥10% of Patients in Any Treatment Group by Preferred Term (Safety Analysis Set)

MedDRA preferred term	HCC D pool (N = 492)		Pan-tumor D pool (N = 4045)	
	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	443 (90.0)	123.5	3825 (94.6)	170.7
Aspartate aminotransferase increased	85 (17.3)	23.7	277 (6.8)	12.4
Diarrhoea	78 (15.9)	21.7	650 (16.1)	29.0
Pruritus	76 (15.4)	21.2	463 (11.4)	20.7
Alanine aminotransferase increased	70 (14.2)	19.5	256 (6.3)	11.4
Decreased appetite	68 (13.8)	19.0	769 (19.0)	34.3
Fatigue	62 (12.6)	17.3	997 (24.6)	44.5
Abdominal pain	54 (11.0)	15.1	318 (7.9)	14.2
Constipation	54 (11.0)	15.1	652 (16.1)	29.1
Rash	53 (10.8)	14.8	395 (9.8)	17.6
Asthenia	52 (10.6)	14.5	463 (11.4)	20.7
Back pain	50 (10.2)	13.9	448 (11.1)	20.0
Nausea	49 (10.0)	13.7	678 (16.8)	30.3
Arthralgia	45 (9.1)	12.5	559 (13.8)	25.0
Pyrexia	44 (8.9)	12.3	525 (13.0)	23.4
Cough	43 (8.7)	12.0	643 (15.9)	28.7
Anaemia	36 (7.3)	10.0	509 (12.6)	22.7
Dyspnoea	26 (5.3)	7.2	598 (14.8)	26.7
Vomiting	23 (4.7)	6.4	423 (10.5)	18.9

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

[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 are not included in this summary.
MedDRA version 23.1.
AE, adverse event; D, durvalumab 1500 mg (or equivalent); HCC, hepatocellular carcinoma; MedDRA, Medical Dictionary for Regulatory Activities; pt, patient.
Source: Table 2.7.4.2.5, Pooled Safety Outputs, Module 5.3.5.3.

Table 38. Adverse Events by Maximum Reported CTCAE Grade (Safety Analysis Set)

Category of AE	Number (%) of patients	
	HCC D pool (N = 492)	Pan-tumor D pool (N = 4045)
Patients with any AE	443 (90.0)	3825 (94.6)
Grade 1	91 (18.5)	564 (13.9)
Grade 2	134 (27.2)	1432 (35.4)
Grade 3	168 (34.1)	1412 (34.9)
Grade 4	20 (4.1)	188 (4.6)
Grade 5	30 (6.1)	229 (5.7)
Unknown	0	0
Grade 3 or higher	218 (44.3)	1829 (45.2)
Grade 3 or 4	188 (38.2)	1600 (39.6)

Patients with multiple AEs are counted once at 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 occurs first). Disease progression AEs reported in Study 1108 are not included in this summary. AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events (version 4.03); D, durvalumab 1500 mg (or equivalent); HCC, hepatocellular carcinoma. Source Table 2.7.4.2.3, Pooled Safety Outputs, Module 5.3.5.3.

Table 39. Adverse Events of Maximum CTCAE Grade 3 or 4 by Preferred Term ≥ 2% of Patients in Any Treatment Group; Safety Analysis Set)

MedDRA preferred term	Number (%) of patients [a]	
	HCC D pool (N = 492)	Pan-tumor D pool (N = 4045)
Patients with any AE of maximum CTCAE Grade 3 or 4	188 (38.2)	1600 (39.6)
Aspartate aminotransferase increased	36 (7.3)	83 (2.1)
Lipase increased	17 (3.5)	51 (1.3)
Anaemia	11 (2.2)	177 (4.4)
Dyspnoea	4 (0.8)	126 (3.1)

a. Number (%) of patients with AEs, sorted in decreasing frequency of preferred term (HCC D pool 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 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; MedDRA, Medical Dictionary for Regulatory Activities. Source: Table 2.7.4.2.6, Pooled Safety Outputs, Module 5.3.5.3.

Common AEs in the HCC D pool (n=492) were pruritus (15.4%), diarrhoea (15.9%), and AST increased (17.3%).

In comparison, common AEs in the S arm of the pivotal Himalaya study (n=374) were PPE (46.5%), diarrhoea (44.7%), fatigue (19%), and hypertension (18.2%), while pruritus (6.4%) and rash (13.6%) were less commonly observed. Hence, the toxicity profile of the TKI sorafenib differs from the proposed regimen, which is to be expected due to the different mechanisms of action.

Common AEs in the CHMP-approved T300+D regimen (n=388) were diarrhoea (26.5%), pruritus (22.9%) and rash (22.4%), decreased appetite (17%) and fatigue (17%). As expected with an immune checkpoint inhibitor combined with an anti-CTLA4 antibody, endocrine disorders were also common, such as hypothyroidism (12.1%).

Common grade 3 or 4 adverse events in HCC D pool were AST increased (2.3%) and lipase increased (2.1%), while they were palmar-plantar erythrodysaesthesia syndrome (PPE) (8.8%), hypertension (5.3%), and diarrhoea (4.0%) in the sorafenib treated patients. Common grade 3 or 4 adverse events in the T300+D arm were increased lipase (6.2%), ASAT increased (5.2%), and skin and subcutaneous disorders (3.9%).

Adverse drug reactions

Pooling strategy is described in introduction of section 2.5 of this report. ADR frequencies in the product information are updated with revised data from the Pan-tumour pool (increased from 3006 to 4045 patients) and new specific paragraph on the HCC indication are based on the HCC D pool (492 patients).

Table 40. Adverse Drug Reactions by CIOMS III Category in the HCC D Pool and the Pan-tumour D Pool (Safety Analysis Set)

MedDRA system organ class preferred term	Number (%) of patients					
	HCC D pool (N = 492)			Pan-tumor D pool (N = 4045)		
	CIOMS III [a] Any CTCAE grade		Maximum CTCAE Grade 3-4	CIOMS III [a] Any CTCAE grade		Maximum CTCAE Grade 3-4
Blood and lymphatic system disorders						
Immune thrombocytopenia	Not known	0	0	Rare	2 (< 0.1)	1 (< 0.1)
Cardiac disorders						
Myocarditis [b]	Uncommon	2 (0.4)	2 (0.4)	Uncommon	5 (0.1)	5 (0.1)
Endocrine disorders						
Hypothyroidism [b]	Common	41 (8.3)	0	Very common	439 (10.9)	5 (0.1)
Hyperthyroidism [b]	Common	14 (2.8)	0	Common	199 (4.9)	0
Thyroiditis [b]	Uncommon	4 (0.8)	0	Uncommon	30 (0.7)	2 (< 0.1)
Adrenal insufficiency	Common	6 (1.2)	3 (0.6)	Uncommon	25 (0.6)	6 (0.1)
Hypophysitis/ hypopituitarism	Not known	0	0	Rare	3 (< 0.1)	3 (< 0.1)
Type 1 diabetes mellitus	Uncommon	1 (0.2)	1 (0.2)	Rare	2 (< 0.1)	2 (< 0.1)
Diabetes insipidus	Not known	0	0	Rare	1 (< 0.1)	1 (< 0.1)
Gastrointestinal disorders						
Diarrhoea	Very common	78 (15.9)	8 (1.6)	Very common	650 (16.1)	34 (0.8)
Abdominal pain [b]	Very common	88 (17.9)	11 (2.2)	Very common	525 (13.0)	73 (1.8)

Table 40. Adverse Drug Reactions by CIOMS III Category in the HCC D Pool and the Pan-tumour D Pool (Safety Analysis Set)

MedDRA system organ class preferred term	Number (%) of patients					
	HCC D pool (N = 492)			Pan-tumor D pool (N = 4045)		
	CIOMS III [a] Any CTCAE grade		Maximum CTCAE Grade 3-4	CIOMS III [a] Any CTCAE grade		Maximum CTCAE Grade 3-4
Colitis [b]	Uncommon	4 (0.8)	1 (0.2)	Uncommon	38 (0.9)	13 (0.3)
Pancreatitis [b]	Uncommon	1 (0.2)	0	Uncommon	8 (0.2)	5 (0.1)
General disorders and administration site conditions						
Pyrexia	Common	44 (8.9)	8 (1.6)	Very common	525 (13.0)	21 (0.5)
Oedema peripheral [b]	Common	40 (8.1)	1 (0.2)	Common	379 (9.4)	12 (0.3)
Hepatobiliary disorders						
AST or ALT increased [b]	Very common	100 (20.3)	40 (8.1)	Common	376 (9.3)	116 (2.9)
Hepatitis [b]	Common	10 (2.0)	3 (0.6)	Common	44 (1.1)	19 (0.5)
Infections and infestations						
Upper respiratory tract infections [b]	Common	28 (5.7)	0	Very common	490 (12.1)	6 (0.1)
Pneumonia [b]	Common	19 (3.9)	6 (1.2)	Common	322 (8.0)	129 (3.2)
Oral candidiasis	Uncommon	1 (0.2)	0	Common	76 (1.9)	0
Dental and oral soft tissue infections [b]	Uncommon	4 (0.8)	0	Common	57 (1.4)	2 (< 0.1)
Influenza	Common	7 (1.4)	1 (0.2)	Common	58 (1.4)	3 (< 0.1)
Injury, poisoning and procedural complications						
Infusion related reaction [b]	Uncommon	4 (0.8)	0	Common	55 (1.4)	5 (0.1)
Musculoskeletal and connective tissue disorders						
Arthralgia	Common	45 (9.1)	0	Very common	559 (13.8)	23 (0.6)
Myalgia	Common	10 (2.0)	0	Common	200 (4.9)	2 (< 0.1)
Myositis [b]	Uncommon	1 (0.2)	1 (0.2)	Uncommon	9 (0.2)	3 (< 0.1)
Polymyositis	Not known	0	0	Not known	0	0
Nervous system disorders						

Table 40. Adverse Drug Reactions by CIOMS III Category in the HCC D Pool and the Pan-tumour D Pool (Safety Analysis Set)

MedDRA system organ class preferred term	Number (%) of patients					
	HCC D pool (N = 492)			Pan-tumor D pool (N = 4045)		
	CIOMS III [a] Any CTCAE grade		Maximum CTCAE Grade 3-4	CIOMS III [a] Any CTCAE grade		Maximum CTCAE Grade 3-4
Myasthenia gravis [b]	Uncommon	2 (0.4)	1 (0.2)	Rare	3 (< 0.1)	2 (< 0.1)
Meningitis	Not known	0	0	Rare	1 (< 0.1)	1 (< 0.1)
Guillain-Barre syndrome	Not known	0	0	Not known	0	0
Encephalitis [b]	Not known	0	0	Not known	0	0
Renal and urinary disorders						
Blood creatinine increased	Common	10 (2.0)	0	Common	146 (3.6)	4 (< 0.1)
Dysuria	Uncommon	4 (0.8)	0	Common	59 (1.5)	0
Nephritis [b]	Not known	0	0	Uncommon	12 (0.3)	5 (0.1)
Cystitis noninfective	Not known	0	0	Rare	4 (< 0.1)	1 (< 0.1)
Respiratory, thoracic and mediastinal disorders						
Cough or productive cough	Common	48 (9.8)	0	Very common	755 (18.7)	11 (0.3)
Pneumonitis [b]	Common	6 (1.2)	0	Common	133 (3.3)	28 (0.7)
Dysphonia	Common	5 (1.0)	0	Common	103 (2.5)	2 (< 0.1)
Interstitial lung disease	Uncommon	1 (0.2)	1 (0.2)	Uncommon	20 (0.5)	5 (0.1)
Skin and subcutaneous tissue disorders						
Rash [b]	Very common	75 (15.2)	1 (0.2)	Very common	626 (15.5)	23 (0.6)
Pruritus	Very common	76 (15.4)	0	Very common	463 (11.4)	2 (< 0.1)
Night sweats	Uncommon	3 (0.6)	0	Common	59 (1.5)	1 (< 0.1)
Dermatitis [b]	Uncommon	4 (0.8)	0	Uncommon	29 (0.7)	2 (< 0.1)
Pemphigoid [b]	Uncommon	1 (0.2)	0	Uncommon	6 (0.1)	0

Table 40. Adverse Drug Reactions by CIOMS III Category in the HCC D Pool and the Pan-tumour D Pool (Safety Analysis Set)

MedDRA system organ class preferred term	Number (%) of patients					
	HCC D pool (N = 492)			Pan-tumor D pool (N = 4045)		
	CIOMS III [a] Any CTCAE grade		Maximum CTCAE Grade 3-4	CIOMS III [a] Any CTCAE grade		Maximum CTCAE Grade 3-4
Psoriasis	Uncommon	1 (0.2)	0	Uncommon	29 (0.7)	2 (< 0.1)

Table 41. Adverse Drug Reactions by CIOMS III Category in the HIMALAYA Study (Safety Analysis Set)

MedDRA system organ class/ preferred term	D (N = 388)			S (N = 374)		
	CIOMS III [a] Any CTCAE grade		Maximum CTCAE Grade 3-4	CIOMS III [a] Any CTCAE grade		Maximum CTCAE Grade 3-4
Cardiac disorders						
Myocarditis [b]	Uncommon	1 (0.3)	1 (0.3)	Not known	0	0
Endocrine disorders						
Adrenal insufficiency	Common	6 (1.5)	3 (0.8)	Not known	0	0
Hyperthyroidism [b]	Common	10 (2.6)	0	Uncommon	2 (0.5)	0
Hypopituitarism/hypophysitis	Not known	0	0	Not known	0	0
Hypothyroidism [b]	Common	27 (7.0)	0	Common	21 (5.6)	0
Thyroiditis [b]	Common	4 (1.0)	0	Uncommon	2 (0.5)	0
Type 1 diabetes mellitus	Uncommon	1 (0.3)	1 (0.3)	Not known	0	0
Gastrointestinal disorders						
Abdominal pain [b]	Very common	62 (16.0)	8 (2.1)	Very common	87 (23.3)	15 (4.0)
Colitis [b]	Uncommon	3 (0.8)	0	Uncommon	2 (0.5)	0
Diarrhoea	Very common	58 (14.9)	6 (1.5)	Very common	167 (44.7)	16 (4.3)
Pancreatitis [b]	Uncommon	1 (0.3)	0	Uncommon	2 (0.5)	1 (0.3)
General disorders						
Oedema peripheral [b]	Common	24 (6.2)	1 (0.3)	Common	24 (6.4)	0
Pyrexia	Common	36 (9.3)	7 (1.8)	Common	33 (8.8)	0
Hepatobiliary disorders						
AST or ALT increased [b]	Very common	67 (17.3)	30 (7.7)	Common	35 (9.4)	15 (4.0)
Hepatitis [b]	Common	9 (2.3)	2 (0.5)	Uncommon	1 (0.3)	0
Infections and infestations						
Dental and oral soft tissue infections [b]	Uncommon	3 (0.8)	0	Uncommon	2 (0.5)	0
Influenza	Common	7 (1.8)	1 (0.3)	Common	4 (1.1)	1 (0.3)
Oral candidiasis	Not known	0	0	Not known	0	0
Pneumonia [b]	Common	15 (3.9)	3 (0.8)	Common	13 (3.5)	6 (1.6)
Upper respiratory tract infections [b]	Common	21 (5.4)	0	Common	15 (4.0)	0
Injury, poisoning and procedural complications						
Infusion related reaction [b]	Common	4 (1.0)	0	Uncommon	2 (0.5)	0
Musculoskeletal disorders						
Myalgia	Common	8 (2.1)	0	Common	10 (2.7)	0
Myositis [b]	Not known	0	0	Not known	0	0
Polymyositis	Not known	0	0	Not known	0	0
Nervous Systems Disorders						
Myasthenia gravis [b]	Uncommon	1 (0.3)	1 (0.3)	Not known	0	0
Renal and urinary disorders						

MedDRA system organ class/ preferred term	D (N = 388)			S (N = 374)		
	CIOMS III [a] Any CTCAE grade		Maximum CTCAE Grade 3-4	CIOMS III [a] Any CTCAE grade		Maximum CTCAE Grade 3-4
Blood creatinine increased	Common	8 (2.1)	0	Common	5 (1.3)	1 (0.3)
Dysuria	Uncommon	3 (0.8)	0	Uncommon	3 (0.8)	0
Nephritis [b]	Not known	0	0	Uncommon	1 (0.3)	1 (0.3)
Respiratory thoracic and mediastinal disorders						
Cough or productive cough	Common	35 (9.0)	0	Common	26 (7.0)	1 (0.3)
Dysphonia	Common	4 (1.0)	0	Common	26 (7.0)	0
Interstitial lung disease	Uncommon	1 (0.3)	1 (0.3)	Not known	0	0
Pneumonitis [b]	Common	5 (1.3)	0	Uncommon	2 (0.5)	0
Skin and subcutaneous tissue disorders						
Dermatitis [b]	Common	4 (1.0)	0	Common	6 (1.6)	1 (0.3)
Night sweats	Uncommon	3 (0.8)	0	Uncommon	2 (0.5)	0
Pemphigoid [b]	Uncommon	1 (0.3)	0	Uncommon	1 (0.3)	1 (0.3)
Pruritus	Very common	56 (14.4)	0	Common	24 (6.4)	1 (0.3)
Rash [b]	Very common	55 (14.2)	1 (0.3)	Very common	80 (21.4)	8 (2.1)

a. The corresponding frequency category for each ADR is based on the CIOMS III convention and is defined as: (1) very common (≥ 1/10); (2) common (≥ 1/100 to < 1/10); (3) uncommon (≥ 1/1000 to < 1/100); (4) rare (≥ 1/10000 to < 1/1000); (5) very rare (< 1/10000); and (6) not known (cannot be estimated from available data).

b. Grouped term included multiple Preferred Terms reported as indicated (see Table 2.7.4.7.16.1 Pooled Safety Outputs, Module 5.3.5.3).

A patient can have one or more ADR term reported under a given system organ class.

Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increased 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). ADR Terms are grouped preferred terms. Includes infusion-related reaction and urticaria with onset on the day of dosing or 1 day after dosing. MedDRA version 23.1. ADR, adverse drug reaction; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CIOMS, Council for International Organizations of Medical Sciences; CTCAE, Common Terminology Criteria for Adverse Events (version 4.03); D, durvalumab 1500 mg (or equivalent); MedDRA, Medical Dictionary for Regulatory Activities. Source: Table 2.7.4.7.16.2 and Table 2.7.4.16.3, Pooled Safety Outputs, Module 5.3.5.3.

Adverse events of special interest - Immune-mediated adverse events

Table 42. Immune-Mediated Adverse Events in Any Category (Safety Analysis Set)

AE category	Number (%) of patients [a]			
	HIMALAYA	HCC D pool (N = 492)	Pan-tumor D pool (N = 4045)	
	D (N = 388)	S (N = 374)		
Any AE	64 (16.5)	30 (8.0)	84 (17.1)	703 (17.4)
Any AE of CTCAE Grade 3 or 4	25 (6.4)	9 (2.4)	31 (6.3)	177 (4.4)
Any SAE (including AEs with outcome of death) [b]	20 (5.2)	4 (1.1)	27 (5.5)	155 (3.8)
Any AE with outcome of death	0	0	2 (0.4)	14 (0.3)
Received systemic corticosteroids	42 (10.8)	16 (4.3)	52 (10.6)	417 (10.3)
Received high dose corticosteroids	37 (9.5)	7 (1.9)	45 (9.1)	274 (6.8)
Received endocrine therapy	26 (6.7)	13 (3.5)	38 (7.7)	358 (8.9)
Received other immunosuppressants	3 (0.8)	1 (0.3)	4 (0.8)	15 (0.4)
Any AE leading to discontinuation of study treatment	10 (2.6)	6 (1.6)	16 (3.3)	111 (2.7)

c. 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 of each of those categories.

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

MedDRA version 23.1. Percentages are calculated from number of patients in the treatment group (N).

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 medication 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 (or equivalent); HCC, hepatocellular carcinoma; MedDRA, Medical Dictionary for Regulatory Activities; S, sorafenib 400 mg twice daily; SAE, serious adverse event. Source: Table 2.7.4.7.1, Pooled Safety Outputs, Module 5.3.5.3 and Table 14.3.2.30, HIMALAYA CSR, Module 5.3.5.1.

Adverse events of special interest are immune-mediated AEs. The incidence of imAEs is much more common in the HCC D pool vs the S arm (17.1% vs 8%), and these were of grade 3 or 4 in 6.3% vs 2.4% of the patients, respectively.

SAEs were not common in either group (5.5% vs 1.1%) and only 2 patients in the HCC D pool (0.4%) died from these. Approximately 10% of the patients need systemic corticosteroids in the HCC D pool vs 4.3% in the S arm. Some of the patients needed endocrine therapy (7.7% vs 3.5%). Very few patients had to discontinue treatment due to imAEs (3.3% vs 1.6%).

Serious adverse event/deaths/other significant events

Table 43. Serious Adverse Events by System Organ Class and Preferred Term (≥ 2% Patients in Any Treatment Group; Safety Analysis Set)

	Number (%) of patients [a]	
MedDRA preferred term	**HCC D pool (N = 492)**	**Pan-tumor D pool (N = 4045)**
Patients with any SAE [b]	161 (32.7)	1446 (35.7)
Infections and infestations	28 (5.7)	387 (9.6)
Pneumonia	4 (0.8)	152 (3.8)
Respiratory, thoracic and mediastinal disorders	16 (3.3)	330 (8.2)
Dyspnoea	3 (0.6)	82 (2.0)
Hepatobiliary disorders	31 (6.3)	80 (2.0)
Hepatic function abnormal	14 (2.8)	21 (0.5)

e. Number (%) of patients with SAEs, sorted by international order for system organ class and alphabetically for preferred term.

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

Patients with multiple SAEs 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 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; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event. Source: Table 2.7.4.4.1, Pooled Safety Outputs, Module 5.3.5.3.

Table 44. Serious Adverse Events by System Organ Class and Preferred Term in the HIMALAYA Study (≥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.

Source: Table 14.3.4.1.1.

Serious adverse events (SAEs) were observed in approximately a third of the patients in both D pools (32.7% and 35.7%), most commonly Hepatobiliary disorders and Infections and infestations.

In comparison, SAEs were very common with the T300+D regimen and observed in a similar frequency in the S arm (40.5% vs 29.7%). 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%).

Table 45. Adverse Events with Outcome of Death, by Preferred Term (Safety Analysis Set)

MedDRA preferred term	Number (%) of patients [a]	
	HCC D pool (N = 492)	**Pan-tumor D pool (N = 4045)**
Patients with any AE with outcome of death	30 (6.1)	231 (5.7)
Death	8 (1.6)	21 (0.5)
Cardiac arrest	1 (0.2)	7 (0.2)

MedDRA preferred term	Number (%) of patients [a]	
	HCC D pool (N = 492)	**Pan-tumor D pool (N = 4045)**
Hepatic failure	3 (0.6)	5 (0.1)
Pneumonia	0	15 (0.4)
Pneumonitis	1 (0.2)	7 (0.2)
Acute kidney injury	0	3 (<0.1)
Gastrointestinal haemorrhage	3 (0.6)	5 (0.1)
Myocardial infarction	1 (0.2)	8 (0.2)
Oesophageal varices haemorrhage	1 (0.2)	1 (< 0.1)
Pulmonary embolism	0	6 (0.1)
Sepsis	0	13 (0.3)
Septic shock	1 (0.2)	6 (0.1)
Asthenia	1 (0.2)	1 (< 0.1)
Bleeding varicose vein	2 (0.4)	2 (< 0.1)
Cardio-respiratory arrest	1 (0.2)	6 (0.1)
Cerebrovascular accident	1 (0.2)	4 (< 0.1)
Completed suicide	1 (0.2)	3 (< 0.1)
Hepatic cirrhosis	1 (0.2)	1 (< 0.1)
Hepatic function abnormal	1 (0.2)	2 (< 0.1)
Hepatorenal syndrome	1 (0.2)	1 (< 0.1)
Peripheral ischaemia	1 (0.2)	1 (< 0.1)
Restlessness	1 (0.2)	1 (< 0.1)

g. Number (%) of patients with AEs, sorted by decreasing frequency of preferred term (HCC D pool column) and alphabetically for 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 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; MedDRA, Medical Dictionary for Regulatory Activities. Source: Table 2.7.4.3.1, Pooled Safety Outputs, Module 5.3.5.3.

Table 46. Adverse Events with Outcome of Death by Preferred Term in the HIMALAYA Study (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.

In the HCC D pool, 6.1% of the patients died from an adverse event, while it was 5.7% in the Pan-tumor D pool. In the HCC D pool, deaths from AEs most commonly pertained to hepatic failure, GI haemorrhage and Bleeding varicose vein.

Table 46 above summarises the adverse events with death as outcome in the pivotal Himalaya study. No patients died from AEs in the D arm vs 15 of 388 patients died from AEs in the T300+D arm (3.8%), while 11/374 patients died from AEs in the S arm (2.9%).

Laboratory findings

Table 47. Clinically Important Changes in Haematology Parameters (Safety Analysis Set)

Parameter	n/N (%) of patients			
	HCC D pool (N = 492)		Pan-tumor D pool (N = 4045)	
	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
Hemoglobin	31/476 (6.5)	23/476 (4.8)	209/3868 (5.4)	193/3868 (5.0)
Leukocytes	15/473 (3.2)	6/473 (1.3)	75/3868 (1.9)	22/3868 (0.6)
Lymphocytes - Low	81/450 (18.0)	38/450 (8.7)	738/3828 (19.3)	506/3828 (13.2)
Neutrophils	24/451 (5.3)	6/451 (1.3)	119/3833 (3.1)	37/3833 (1.0)
Platelets	16/475 (3.4)	14/475 (2.9)	64/3865 (1.7)	44/3865 (1.1)

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.

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

Table 48. Clinically Important Changes in Clinical Chemistry Parameters (Safety Analysis Set)

Parameter	n/N (%) of patients			
	HCC D pool (N = 492)		Pan-tumor D pool (N = 4045)	
	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4	≥ 2 CTCAE grade changes	CTCAE grade changes to 3 or 4
AST	87/476 (18.3)	112/476 (23.5)	259/3850 (6.7)	235/3850 (6.1)
Alkaline phosphatase	30/474 (6.3)	44/474 (9.3)	192/3840 (5.0)	168/3840 (4.4)
ALT	62/477 (13.0)	56/477 (11.7)	224/3860 (5.8)	145/3860 (3.8)
Albumin	74/473 (15.6)	7/473 (1.5)	475/3821 (12.4)	60/3821 (1.6)
Total bilirubin	81/477 (17.0)	40/477 (8.4)	202/3853 (5.2)	103/3853 (2.7)
Creatinine	19/475 (4.0)	3/475 (0.6)	154/3796 (4.1)	33/3796 (0.9)
GGT	8/116 (6.9)	20/116 (17.2)	187/1765 (10.6)	170/1765 (9.6)
Lipase	75/460 (16.3)	54/460 (11.7)	130/1225 (10.6)	103/1225 (8.4)
Amylase	37/459 (8.1)	32/459 (7.0)	83/1225 (6.8)	66/1225 (5.4)
Glucose (high)	75/471 (15.9)	39/471 (8.3)	500/3826 (13.1)	209/3826 (5.5)
Potassium (high)	38/471 (8.1)	21/471 (4.5)	222/3853 (5.8)	80/3853 (2.1)
Sodium (low)	35/474 (7.4)	37/474 (7.8)	313/3861 (8.1)	319/3861 (8.3)
Corrected Calcium (low)	1/367 (0.3)	1/367 (0.3)	54/3696 (1.5)	20/3696 (0.5)

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.

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.

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

The changes in haematological parameters in both pools were mostly of low grade and the highest frequency observed pertained to a decrease in lymphocytes ≥grade 2 for 18% and 19.3% of the patients in the HCC D pool and the Pan-tumor pool, respectively. High grade events were rare in both pools and overall acceptable and considered manageable. Especially, the low incidence of low platelets is considered positive, since the underlying disease may also cause low platelets and increase the overall risk of bleeding.

Laboratory shifts for clinical chemistry in both pools most often pertained to changes of low grade in liver parameters. Otherwise, most shifts were rare and mostly to low grade events.

It is noted that increased glucose was quite common in the HCC D pool (15.9%) and that grade 3 or 4 were observed in 8.3% of the patients.

It was clarified that the liver plays a key role in glucose metabolism and HCC has risk factors in patients with baseline metabolic dysfunction, so it would not be unexpected to observe small differences in glucose abnormalities between patients with HCC in the HCC D pool and patients with varied tumor types in the Pan-tumor pool. Moreover, hyperglycaemia/New Onset diabetes mellitus was identified in 30 (6.1%) of 492 participants in the D monotherapy HCC pool who reported hyperglycaemia events. There were 6 (1.2%) SAEs reported and 14 (2.8%) Grade 3 or Grade 4 events reported, while no Grade 5 events were reported. The majority of the patients (28/30 [93.3%]) did not receive intervention/treatment (i.e., endocrine therapy, adjustment to existing treatment, or any other antidiabetic therapy) for the reported hyperglycaemic event.

Table 49. Liver Function Abnormalities (Safety Analysis Set)

	Number (%) of patients	
	HCC D pool (N = 492)	Pan-tumor D pool (N = 4045)
ALT or AST		
≥ 3 × to ≤ 5 × ULN	84 (17.1)	242 (6.0)
> 5 × to ≤ 8 × ULN	56 (11.4)	127 (3.1)
> 8 × to ≤ 10 × ULN	31 (6.3)	57 (1.4)
> 10 × to ≤ 20 × ULN	33 (6.7)	67 (1.7)
> 20 × ULN	11 (2.2)	29 (0.7)
TBL		
≥ 2 × to ≤ 3 × ULN	41 (8.3)	67 (1.7)
> 3 × to ≤ 5 × ULN	18 (3.7)	48 (1.2)
> 5 × ULN	22 (4.5)	56 (1.4)
Potential Hy's law [a]	65 (13.2)	131 (3.2)

[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; TBL, total bilirubin; ULN, upper limit of normal. Source: Table 2.7.4.10.3, Pooled Safety Outputs, Module 5.3.5.3.

Hepatic toxicity was often observed in the HCC D pool regarding elevated hepatic laboratory parameters, and also more often than for the Pan-tumour pool. This may be due to the underlying disease.

In the HCC D pool, the majority of elevations in ALT or AST were ≥3 x to ≤5 x ULN (17%) and > 5 × to ≤ 8 × ULN (11.4%).

Potential Hy's law cases were reported for 65 patients (13.2%) in the HCC D pool, which is slightly higher than reported for the in the HCC T300+D pool (57 patients (12.3%)).

Table 50. Abnormal On-Treatment Thyroid Tests (Safety Analysis Set)

	Number (%) of patients	
Category	HCC-tumor pool (N = 492)	Pan-tumor D pool (N = 4045)
On-treatment elevated TSH > ULN	180 (36.6)	1269 (31.4)
On-treatment elevated TSH > ULN with TSH ≤ ULN at baseline *	116	780
with at least one T3 free/T4 free < LLN [a]	68 (58.6)	456 (58.5)
with all other T3 free/T4 free ≥ LLN [a]	38 (32.8)	270 (34.6)
with T3 free/T4 free missing [a]	10 (8.6)	54 (6.9)
On-treatment low TSH < LLN	82 (16.7)	880 (21.8)
On-treatment low TSH < LLN with TSH ≥ LLN at baseline *	74	709

Category	Number (%) of patients	
	HCC-tumor pool (N = 492)	Pan-tumor D pool (N = 4045)
with at least one T3 free/T4 free > ULN [a]	28 (37.8)	310 (43.7)
with all other T3 free/T4 free ≤ ULN [a]	36 (48.6)	348 (49.1)
with T3 free/T4 free missing [a]	10 (13.5)	51 (7.2)
Number of patients with at least one baseline and post-baseline TSH result *	464	3679
On-treatment elevated TSH > ULN and above baseline [a]	162 (34.9)	1108 (30.1)
On-treatment decreased TSH < LLN and below baseline [a]	80 (17.2)	816 (22.2)

[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; LLN, lower limit of normal; T3, free triiodothyronine; T4, free thyroxine; TSH, thyroid-stimulating hormone; ULN, upper limit of normal. Source: Table 2.7.4.10.8, Pooled Safety Outputs, Module 5.3.5.3.

In both pools, elevated and low TSH was observed frequently, as 36.6% of the patients in the HCC D pool had TSH>ULN, while 16.7% of the patients had TSH <ULN while on treatment. In the pan-tumor pool, this pattern was similar, so this effect is considered related to durvalumab treatment and does not seem to be worse in the HCC patient population.

Safety in special populations

Table 51. Adverse Events in any Category – Patient Level by Age Group (Safety Analysis Set)

AE category	Number (%) of patients [a]	
	HCC D pool (N1 = 254) (N2 = 163) (N3 = 75)	Pan-tumor pool (N1 = 2250) (N2 = 1356) (N3 = 439)
Any AE possibly related to any study treatment [b]		
< 65 years	132 (52.0)	1287 (57.2)
≥ 65 to < 75 years	93 (57.1)	804 (59.3)
≥ 75 years	42 (56.0)	248 (56.5)
Any AE possibly related to durvalumab [b]		
< 65 years	132 (52.0)	1283 (57.0)
≥ 65 to < 75 years	93 (57.1)	801 (59.1)
≥ 75 years	42 (56.0)	248 (56.5)
Any AE with outcome of death		
< 65 years	11 (4.3)	112 (5.0)
≥ 65 to < 75 years	13 (8.0)	90 (6.6)
≥ 75 years	6 (8.0)	29 (6.6)
Any AE leading to discontinuation of any study treatment		
< 65 years	19 (7.5)	188 (8.4)
≥ 65 to < 75 years	19 (11.7)	156 (11.5)
≥ 75 years	9 (12.0)	53 (12.1)
Any AE leading to discontinuation of durvalumab		
< 65 years	19 (7.5)	183 (8.1)
≥ 65 to < 75 years	19 (11.7)	151 (11.1)
≥ 75 years	9 (12.0)	53 (12.1)

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.

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 are not included in this summary.

AE, adverse event; D, durvalumab 1500 mg (or equivalent); HCC, hepatocellular carcinoma; N1, total number of < 65 years patients, N2, total number of ≥ 65 to < 75 years patients, N3, total number of ≥ 75 years patients. Source: Table 2.7.4.2.1.1, Pooled Safety Outputs, Module 5.3.5.3.

Effect of 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.

Effect of ECOG Performance Status

In the HCC D pool, patients with a baseline ECOG status of 1 experienced a higher incidence of Grade 3 to 4 AEs (49.8% vs 35.6%), SAEs (38.4% vs 28.7%), and AEs leading to death (7.9% vs 4.8%).

Effect of Baseline HCC Disease Characteristics

In the HCC D pool, more patients with BCLC stage B at study entry than stage C reported AEs related to study treatment (62.6% vs 51.7%). Similar differences between patients with BCLC stage B and C were observed in the Pan tumor D pool (62.6% vs 51.7%). In the HCC D pool, no notable differences in the nature and incidence of other AEs were observed in the D pool with respect to BCLC stage at study entry.

A higher proportion of patients with confirmed HCV at Screening reported CTCAE Grade 3 to 4 AEs compared with those who had confirmed HBV at Screening in the HCC D pool (50.8% vs 34.3%).

This difference between confirmed HCV and HBV at screening was also observed for the proportion of patients with SAEs in the HCC D pool (36.9% vs 25.0%) and was consistent with the Pan-tumor D pool (36.9% vs 25.0%). In the HCC D pool and the Pan-tumor D pool, increased AST of Grade 3 or 4 was similar in patients with confirmed HCV and HBV (9.2% vs 8.1% in each pool).

No other notable differences in the nature and incidence of other AEs were observed in the HCC D pool with respect to virology status at Screening. Also, no clinically meaningful differences were observed in the safety profile with respect to macrovascular invasion and extrahepatic spread.

Geographical Region

In the HCC D pool, there were no clinically meaningful differences in the safety profile with respect to geographical region. Differences in the number of patients with Grade 3 or 4 AEs and AEs leading to discontinuation of any treatment were observed in the HCC D pool between geographic regions. These differences did not affect the comparative safety profiles of the HCC D pool and were generally consistent with differences between geographic regions observed in the Pan tumor D pool.

Increased toxicity with increasing age was observed in the HCC D pool, as the incidence of treatment-related AEs were 52% in the patients of <65 years of age vs 57.1% in patients of 65-75 years of age and 56% in those of ≥85 years of age. A trend towards more discontinuations with increasing age was also observed. The incidences are in line with the findings from the Pan-tumor pool.

In comparison, for the T300+D regimen, there was the same trend and the incidences were significantly higher for all age groups: as the incidence of treatment-related AEs were 72.1% in the patients of <65 years of age vs 79% in patients of 65-75 years of age and 85.7% in those of ≥85 years of age.

Hence, the incidence of treatment-related AEs according to increasing age was clinically significantly worse for T300+D compared to durvalumab monotherapy.

Toxicity according to body weight, ECOG PS status, Baseline HCC Disease Characteristics and geographical region was also reported. It is noted that increased toxicity regarding grade 3-4 AEs was

observed in the high-weight group ≥ 90 kg (N = 55), compared to patients < 70 kg (54.5% vs 36.2%), and similarly for SAEs (49.1% vs 29.4%). ECOG PS status of 1 was also predictive of increased toxicity regarding grade 3-4 AEs (49.8% vs 35.6%), SAEs (38.4% vs 28.7%), and AEs leading to death (7.9% vs 4.8%).

Baseline HCC Disease Characteristics was mainly connected to increased toxicity regarding that if patients had a confirmed HCV at Screening, they reported more grade 3-4 AEs compared with those who had confirmed HBV at Screening in the HCC D pool (50.8% vs 34.3%). This was also observed for SAEs: 36.9% vs 25.0%. There were no clinically meaningful differences in the safety profile with respect to the remaining HCC Disease Characteristics reported or geographical region.

Overall, the findings summarized above are considered related to the underlying disease of HCC and probably hepatic cirrhosis.

Safety related to drug-drug interactions and other interactions

As durvalumab is a mAb, no formal PK drug-drug interaction studies have been conducted.

Discontinuation due to adverse events

Table 52. 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)

h. 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). Source: Table 2.7.4.5.1.1, Pooled Safety Outputs, Module 5.3.5.3.

Table 53. Adverse Events Leading to Dose Delay/Interruption by System Organ Class and Preferred Term (≥ 1% Patients in Any Treatment Group) (Safety Analysis Set)

MedDRA preferred term	Number (%) of patients [a]				
	HCC-tumor pool		Pan-tumor pool		
	T300+D (N = 462)	D (N = 492)	D (N = 4045)	T75+D (N = 3319)	T750 (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

i. 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). Source: Table 2.7.4.5.4, Pooled Safety Outputs, Module 5.3.5.3.

In the HCC D pool, 9.6% of the patients discontinued treatment due to adverse events while 13.7% of the- patients discontinued treatment due to adverse events with T300+D in the pivotal Himalaya study. The discontinuations were in line with the Pan-tumor pool, which is considered reassuring.

Most commonly the patients discontinued treatment due to AST increased (0.6%) and diarrhoea (0.4%), which reflects the safety profile of durvalumab monotherapy, which was considered tolerable and manageable in the HCC setting.

Dose delays were common in patients in the HCC D pool (22.8% but was even further increased in the patients who had T300+D in the HCC pool (32.3%). The most common AEs leading to dose delay was increased liver enzymes for the HCC D pool, and the level is considered acceptable in the context of the underlying disease.

Post marketing experience

The cumulative global post-marketing patient exposure to durvalumab (10 mg/kg) since launch to 30 June 2021 has been estimated to be 52006 patient-years. No new safety concern was identified based on the post-marketing safety reports.

2.5.1. Discussion on clinical safety

The safety populations of interest are patients with advanced HCC, who have received durvalumab monotherapy (N=492) and patients from the pan-tumour pool, who have received durvalumab monotherapy for any tumour (N=4045). The safety profiles of the CHMP-approved dosing regimen of a single dose of Tremelimumab 300 mg + durvalumab in combination followed by durvalumab monotherapy (T300+D), and the patients from the sorafenib arm of the pivotal Himalaya study are also used for contextualisation.

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 D pool (N=492), the median duration of exposure was 19.9 weeks and about 50% of patients received at least 6 cycles (≥24 weeks of exposure) of treatment at DCO , so the exposure to durvalumab monotherapy for advanced HCC is considered sufficient for a safety assessment.

Almost all of the patients in the HCC D pool experienced at least one **adverse event** (AE), and 41.5% experienced a grade 3 or 4 AEs. SAEs were observed in 32.7% of the patients, of which 6.1% had an SAE leading to death. The overall discontinuation rate due to AEs was 9.6%. In comparison, 95.5% of the patients in the Sorafenib arm of the Himalaya study 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%. For comparison, most of the patients, who received T300+D, experienced at least one AE (88.9%), and 37.1% experienced a grade 3 or 4 AE. SAEs were observed in 29.6% of the patients, of which 6.7% had an SAE leading to death. The overall discontinuation rate due to AEs was 13.7%. Overall, grade 3-4 AEs are more common with both sorafenib and the T300+D regimen in comparison to durvalumab monotherapy.

Treatment-related AEs were reported in 54.3% of patients in the HCC D pool and 57.8% of patients in the Pan tumor D pool, most commonly (any grade) were AST or ALT increased (17.2%), rash (14.2%) and pruritus (14.4%) and diarrhoea (14.9%). Grade 3-4 treatment-related AEs were rare, mostly pertaining to AST or ALT increased (7.7%), pyrexia (1.8%) and diarrhoea (1.5%). In comparison, common treatment-related AEs in the S arm of the pivotal Himalaya study (n=374) were diarrhoea (38.8%), PPE (43.9%), hypertension (15%), and fatigue (14.7%), while common grade 3 or

4 events were PPE (8.8%), hypertension (5.3%), and diarrhoea (4%), so in comparison there are more high-grade toxicity with sorafenib in favour of durvalumab monotherapy. For further contextualisation, the most common treatment-related AEs in the T300+D arm of the pivotal Himalaya study were rash (19.6%), pruritus (17%), diarrhoea (16.5%), and hypothyroidism (12.1%), while the most common grade 3 or 4 events were increased lipase (4.4%), diarrhoea (3.4%), and ASAT increased (2.3%).

Overall, the safety profile regarding treatment-related adverse events is in favour of durvalumab monotherapy both regarding any grade events and high-grade events, and the differences observed between treatment with D vs S and T300+D are considered of clinically significant magnitude for the targeted patient population.

Serious adverse events (SAEs) were observed in approximately a third of the patients in both D pools (32.7% and 35.7%), most commonly Hepatobiliary disorders and Infections and infestations. In comparison, SAEs were very common with the T300+D regimen and observed in a similar frequency in the S arm (40.5% vs 29.7%), clearly indicating that the addition of the single dose of 300 mg tremelimumab adds significantly more severe toxicity. Hence, 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 level of SAEs with durvalumab monotherapy is considered acceptable and in favour of this treatment compared to the T300+D regimen. Moreover, the level of SAEs with D is considered comparable to treatment with sorafenib.

In the HCC D pool, 6.1% of the patients **died from an adverse event**, while it was 5.7% in the pan-tumor pool. In the HCC D pool, deaths from AEs most commonly pertained to hepatic failure, GI haemorrhage and Bleeding varicose vein, which is considered to be due to the underlying disease, especially hepatic cirrhosis. No patients died from AEs in the D arm versus 3.8% in the T300+D arm and 2.9% in the S arm (2.9%). Overall, these data confirm that durvalumab monotherapy carries less severe toxicity and no treatment-related deaths in the HCC setting compared to both sorafenib and T300+D.

Laboratory findings showed that the changes in haematological parameters in both pools were mostly of low grade and the highest frequency pertained to a decrease in lymphocytes ≥grade 2 for 18% of the patients and 19.3% of the patients in the HCC D pool and the Pan-tumor pool, respectively. High grade events were rare in both pools and overall acceptable and considered manageable. Especially, the low incidence of low platelets is considered positive, since the underlying disease may also cause low platelets and increase the overall risk of bleeding. It is noted that increased glucose was quite common in the HCC D pool (15.9%) and that grade 3 or 4 were observed in 8.3% of the patients. The SmPC already has adequate information on immune-mediated diabetes mellitus, and the Applicant has not updated the SmPC, which is acceptable.

Potential Hy's law cases were reported for 65 patients (13.2%) with liver function abnormalities in the HCC D pool, which is slightly higher than reported for the in the HCC T300+D pool (57 patients (12.3%)). Narratives from 2 patients from Study 22 and 2 from the Himalaya study were provided. From these narratives, it can be concluded that the Hy's law cases observed in Study 22 and the HIMALAYA study were consistent with that observed in other populations treated with durvalumab. The text on immune-mediated hepatitis is updated in the SmPC regarding frequencies, which is acceptable.

Adverse events of special interest are immune-mediated AEs (imAEs). The incidence of imAEs is much higher in the HCC D pool vs the S arm (17.1% vs 8%), and these were of grade 3 or 4 in 6.3% vs 2.4% of the patients, respectively. It is noted that very few patients had to discontinue treatment due to imAEs (3.3% vs 1.6%), which is reassuring. Overall, the incidence of imAEs was more common with durvalumab monotherapy compared to sorafenib; however, the level is considered acceptable and

manageable. Moreover, the incidence of imAEs, SAEs and deaths are in line with the already well-known safety profile of durvalumab monotherapy as reflected by the pan-tumour pool.

Increased toxicity with increasing age was observed in the HCC D pool. A trend towards more discontinuations with increasing age was also observed. The incidences are in line with the findings from the Pan-tumour pool, which is reassuring. In comparison, for the T300+D regimen, there was the same trend and the incidences were significantly higher for all age groups.

The overall **discontinuation rate** due to AEs in the HCC D pool was 9.6%, while in the pivotal Himalaya study 13.7% and 16.8% vs of the patients discontinued treatment due to adverse events with T300+D and sorafenib, respectively. This difference is considered clinically significant and in favour of the D arm. Most commonly the patients discontinued treatment due to AST increased (0.6%) and diarrhoea (0.4%), which reflects the safety profile of durvalumab monotherapy, which was considered tolerable and manageable in the HCC setting. Dose delays were common in patients in the HCC D pool (22.8%), but was even further increased in the patients who had T300+D in the HCC pool (32.3%). Overall, the rate of discontinuations and dose delays are considered acceptable for the proposed indication and targeted patient population, i.e. durvalumab monotherapy in the first-line treatment of advanced HCC.

2.5.2. Conclusions on clinical safety

The overall toxicity of durvalumab monotherapy in the proposed setting of 1L advanced HCC is considered clinically manageable and when compared with sorafenib or T300+D, the safety profile of durvalumab monotherapy is considered favourable, mainly due to the lower discontinuation rate and no treatment-related deaths.

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 to reflect the new indication of durvalumab as monotherapy for the first-line treatment of adults with advanced or unresectable hepatocellular carcinoma.

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

The PRAC considered that the risk management plan version 9.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 9.1 with the following content:

Safety concerns

There are no safety concerns.

Pharmacovigilance plan

Not applicable.

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, section 4.1 of the SmPC has been updated to include the new indication of IMFINZI as monotherapy for the treatment of adults with unresectable hepatocellular carcinoma (uHCC), section 4.2 has been updated to include the recommended dose in this indication, section 4.8 has been updated with specific summary of safety profile of durvalumab as monotherapy in HCC, and ADR frequencies were revised throughout the section based on updated safety pool for durvalumab pan tumour, and 5.1 has been updated 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 (HIMALAYA). 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:

This variation for an extension of the indication for durvalumab (IMFINZI) concerns the same route of administration (intravenous use) and age group (adults). The Type II variation only affects the Package Leaflet Section 1 (What IMFINZI is and what it is used for) and Section 4 (Possible side effects). Overall, the wording in the PL is very similar to the text previously tested at the time of the IMFINZI MAA.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The extension of indication applied for and approved is:

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

The aim of the applied regimen of durvalumab monotherapy (D) in comparison to Sorafenib (SOC) in the targeted population is to demonstrate non-inferior overall survival (OS).

3.1.2. Available therapies and unmet medical need

The first-line treatment of advanced HCC includes sorafenib (a tyrosine-kinase inhibitor - TKI), based on OS benefit when compared to placebo (10.7 vs 7.9 months) (Llovet et al 2008) and lenvatinib,

another TKI, which is non-inferior when compared to sorafenib (median OS 13.6 vs 12.3 months) (Kudo et al 2018). 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 (Finn et al 2020b, Finn et al 2021). In addition, the combination of tremelimumab (an anti-CTL4 antibody) in combination with durvalumab (an anti-PD-L1 antibody) was approved by the EC in February 2023 upon results from the HIMALAYA trial, which showed superior survival from the combination in comparison to sorafenib (Abou-Alfa et al, JCO 2022).

Despite recent advances in treatment options, patients with advanced HCC 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 (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 advanced HCC, 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 advanced HCC.

Despite all these choices of first-line treatment, there is still an unmet need for effective and more tolerable treatment options for patients with advanced HCC.

3.1.3. Main clinical studies

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

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. However, this is not the scope of this procedure.

For the applied indication the following results are relevant:

- The key secondary objective (statistical non-inferiority of durvalumab vs. sorafenib), the scope of this procedure, was also met. At data cutoff 27 August 2021 and after ~33 months of follow up, 72% OS events had occurred in the D arm versus 75.3% OS events in the Sorafenib arm, treatment with D showed **non-inferior OS** as compared with S: median OS was 13.77 months

in the sorafenib arm and 16.56 months in the durvalumab, HR 0.86 (95%CI: 0.73; 1.02). The upper bound of the confidence interval fell under the prespecified non-inferiority margin of 1.08.

- The secondary endpoint of **ORR** by investigator was 17% for the D arm compared to 5.1% in the sorafenib arm, and the median duration of response was 16.82 months in the D arm vs 18.43 months in the sorafenib arm.
- Relevant **subgroup analyses** of the primary endpoint of OS show that the benefit of D vs S is maintained across important subgroups of age, HBV or other reasons for liver disease, ECOG performance status, macrovascular invasion (MVI), PD-L1 status, AFP at baseline and BCLB score C.

3.3. Uncertainties and limitations about favourable effects

- Although PFS analyses were not controlled for multiplicity, PFS by investigator was not significantly improved compared to sorafenib: median PFS was 3.65 months in the D arm versus 4.07 months in the S arm; HR 1.02 (95%CI: 0.88; 1.19) for D vs S comparison. The event rates were 88.7% and 84.1% events in the D and S arms, respectively.

3.4. Unfavourable effects

The safety populations of interest are patients with advanced HCC, who have received durvalumab monotherapy (N=492) and patients from the pan-tumour pool, who have received durvalumab monotherapy for any tumour (N=4045). The safety profiles of the CHMP-approved dosing regimen of a single dose of Tremelimumab 300 mg + durvalumab in combination followed by durvalumab monotherapy (T300+D), and the patients from the sorafenib arm of the pivotal Himalaya study are also used for contextualisation.

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 D pool (N=492), the median duration of exposure was 19.9 weeks. Almost all of the patients in the HCC D pool experienced at least one adverse event (AE), and 41.5% experienced a grade 3 or 4 AEs. SAEs were observed in 29.6% of the patients in the D arm of the Himalaya study, of which 6.7% had an SAE leading to death. The overall discontinuation rate due to AEs was 8.2%. In comparison, 95.5% of the patients in the Sorafenib arm of the Himalaya study 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%.

For comparison, most of the patients, who received T300+D, experienced at least one AE (88.9%), and 37.1% experienced a grade 3 or 4 AE. SAEs were observed in 29.6% of the patients, of which 6.7% had an SAE leading to death. The overall discontinuation rate due to AEs was 13.7%.

The most common (> 10%) adverse reactions in the HCC D pool were AST increased/ALT increased, abdominal pain, diarrhoea, pruritus and rash. The most common (> 2%) Grade ≥ 3 adverse reactions were AST increased/ALT increased and abdominal pain.

Serious adverse events (SAEs) were observed in approximately a third of the patients in HCC and pan-tumour D pools (32.7% and 35.7%), most commonly hepatobiliary disorders and infections and infestations.

In the HCC D pool, 6.1% of the patients died from an adverse event, while it was 5.7% in the pan-tumour pool. In the HCC D pool, deaths from AEs most commonly pertained to hepatic failure, gastrointestinal haemorrhage and bleeding varicose vein.

Adverse events of special interest are immune-mediated AEs (imAEs). The incidence of imAEs is much higher in the HCC D pool vs the S arm (17.1% vs 8%), and these were of grade 3 or 4 in 6.3% vs 2.4% of the patients, respectively.

IMFINZI was discontinued due to adverse reactions in 3.7% of patients in the HCC D pool. The most common adverse reactions leading to treatment discontinuation were AST increased/ALT increased and hepatitis.

Laboratory findings showed that the changes in haematological parameters in both pools were mostly of low grade and the highest frequency pertained to a decrease in lymphocytes ≥grade 2 for 18% of the patients and 19.3% of the patients in the HCC D pool and the Pan-tumour pool, respectively.

3.5. Uncertainties and limitations about unfavourable effects

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

3.6. Effects Table

Table 54. Effects Table for durvalumab monotherapy in the treatment of advanced HCC for the Himalaya Study (data cut-off: 27 August 2021)

Effect	Short Description	Unit	Control T300+D	Control Sorafenib	Durvalumab mono	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 72% events, HR for D vs S: 0.86 (95%CI: 0.73; 1.03)	
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		
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 (n=492)	
Grade 3 or 4 AEs	High-grade AEs	%	50.5	52.4	41.5		
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		

Effect	Short Description	Unit	Control T300+D	Control Sorafenib	Durvalumab mono	Uncertainties/ Strength of evidence	Ref
ImAEs	Immune-mediated AEs	%	36.1	8	17.1	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

Efficacy of durvalumab monotherapy was the secondary endpoint of the pivotal Himalaya study. Non-inferiority of the durvalumab monotherapy vs. the sorafenib arm in terms of OS was met, although the subsequent test for superiority was not successful. Albeit the two experimental arms (T300+D and durvalumab monotherapy) were not formally compared, treatment with durvalumab monotherapy showed a similar and clinically meaningful survival benefit as that from T300+D in the 1L treatment of advanced hepatocellular carcinoma. PFS was not substantially different between the durvalumab monotherapy and sorafenib arms, but this pattern of survival benefit without pronounced increments of PFS from anti-PD-1 treatment has also been seen in other aggressive cancers, e.g. small cell lung cancer.

The non-inferiority margin used in statistical setting was appropriately justified and is thus considered acceptable. Although fundamental changes had been made in the protocol and multiple testing procedure during the ongoing study, the CHMP has agreed that the decision to make the changes was based on external data.

The ORR was also significantly improved in comparison with sorafenib and although the magnitude of response is borderline clinically significant in magnitude, the responses were durable. Hence, the non-inferiority of OS is supported by the improvement in ORR. Overall, the ORR and DoR are considered slightly lower/shorter but comparable to the ORR and DoR achieved with T300+D.

The safety profile of durvalumab monotherapy was overall in line with the well-known toxicity profile of durvalumab. While the safety profile of tremelimumab in combination with durvalumab (T300+D) was substantial, the safety profile of durvalumab monotherapy compares favourably to both the safety profiles of T300+D and sorafenib. The lower risk of immune-mediated AEs, the lower discontinuation rate due to adverse events and no treatment-related deaths with durvalumab monotherapy are considered of particular clinical importance.

3.7.2. Balance of benefits and risks

Durvalumab monotherapy has demonstrated non-inferiority of efficacy in terms of OS and a favourable safety profile in comparison with standard of care, sorafenib, the benefit-risk balance is therefore considered positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of durvalumab monotherapy is positive for the first line treatment of first-line advanced HCC.

4. Recommendations

Outcome

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

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

Extension of indication to include IMFINZI as monotherapy 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 (HIMALAYA). As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 9.1 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.