Clinical Study Report Synopsis	
Drug Substances	Durvalumab, tremelimumab
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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 dates:
First patient enrolled: 11 October 2017
Last patient enrolled: 19 June 2019
Data cut-off: 27 August 2021

Phase of development:
Therapeutic confirmatory (III)

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.
This submission document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study Centers

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 (USA; 21) and Vietnam (3).

Publications

There were no publications or pending publications at the time of writing this report.

Objectives and Criteria for Evaluation

The study objectives and criteria for evaluation are presented in Table S1.

Table S1 Objectives and Outcome Variables

Objective	Outcome measure
Primary objective:	**Primary endpoint/variables:**
To assess the efficacy of T-high+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 T-high+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 T-high+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 T-high+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 T-high+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)

Table S1 Objectives and Outcome Variables

Objective	Outcome measure
To investigate the immunogenicity of D and T-high+D	• Presence of ADA for durvalumab and tremelimumab
To evaluate the population PK and pharmacodynamics in D and T-high+D	• Durvalumab and tremelimumab concentrations and PK parameters in individual groups
Safety objectives:	**Safety endpoint/variables:**
To assess the safety and tolerability profile across all treatment groups	• AEs and laboratory findings [a]

[a] Safety endpoint/variables included categories of AEs, most frequently reported AEs, serious adverse events, fatal AEs, AEs leading to discontinuation of study treatment, other AEs, adverse events of special interest, laboratory findings, immune-mediated AEs, vital signs, and electrocardiograms.

ADA, anti-drug antibody; AE, adverse event; BICR, Blinded Independent Central Review; BOR, best objective response; D, durvalumab monotherapy CCI DCR, disease control rate; DCR-16w, disease control rate at 16 weeks; DCR-24w, disease control rate at 24 weeks; DoR, duration of response; EORTC, European Organization for Research and Treatment of Cancer; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; OS18, OS at 18 months; OS24, OS at 24 months; OS36, OS at 36 months; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PK, pharmacokinetics; QLQ-C30, 30-item core quality of life questionnaire; QLQ-HCC18, hepatocellular cancer health-related quality of life questionnaire; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; S, sorafenib CCI T-low+D, tremelimumab CCI + durvalumab CCI T-high+D, tremelimumab CCI + durvalumab CCI TTP, time to progression.

Study Design

This is a randomized, open-label, sponsor-blind, multicenter, global, Phase III study to assess the efficacy and safety of durvalumab monotherapy and of durvalumab in combination with tremelimumab vs sorafenib in the treatment of patients with unresectable hepatocellular carcinoma (HCC) who are not eligible for locoregional therapy and have not received prior systemic therapy for HCC (first-line setting).

Patients were randomly assigned to treatment using an interactive web response system (IWRS) system in a 1:1:1:1 ratio to each of the following 4 treatment arms:

- D: Durvalumab CCI
- T-high+D: Tremelimumab CCI + durvalumab CCI
- T-low+D: Tremelimumab CCI + durvalumab CCI
- S: Sorafenib CCI

Patients were stratified according to macrovascular invasion (MVI; yes vs no), etiology of liver disease (confirmed hepatitis B virus [HBV] vs confirmed hepatitis C virus [HCV] vs others), and Eastern Cooperative Oncology Group performance status (ECOG PS; 0 vs 1).

Following a benefit-risk assessment based on the results of a pre-planned analysis of Phase II Study 22, recruitment in the T-low+D treatment arm was closed due to non-meaningful differentiation in terms of efficacy from D, and the planned sample size was increased from 1200 to 1310 patients. At the time of closure, approximately 155 patients were estimated to be randomized to the T-low+D arm. Thereafter, patients were randomized in a 1:1:1 ratio to each of the remaining 3 treatment arms: D, T-high+D, and S, 1155 patients in total with the target of 385 patients per arm. Stratification was unchanged and patients previously randomized to T-low+D prior to protocol amendment 3 were allowed to continue on the assigned study treatment, provided the Investigator and patient agreed this was in the best interest of the patient. Patients randomized to T-low+D who had not completed or started all CCI of tremelimumab could either complete the full schedule or continue with durvalumab monotherapy only.

Target Subject Population and Sample Size

The study population included adult patients (aged ≥ 18 years) with confirmed HCC, based on histopathological findings, and with preserved liver function (Child-Pugh score class A). Patients must have been Barcelona Clinic Liver Cancer (BCLC) Stage B (not eligible for locoregional therapy) or C, ECOG PS score of 0 or 1, and a life expectancy of more than 12 weeks. Patients must not have received any prior systemic therapy for HCC.

A total of 1324 patients were randomized in this study based on a planned randomization of 1310 (385 per arm for the D, T-high+D and S treatment arms and 155 for the T-low+D arm prior to closure):

- D: 389 patients
- T-high+D: 393 patients
- T-low+D: 153 patients
- S: 389 patients

Investigational Product and Comparators: Dosage, Mode of Administration and Batch Numbers

Durvalumab was supplied by AstraZeneca as a CCI vial solution for infusion after dilution. Tremelimumab was supplied by AstraZeneca as a CCI vial solution for infusion after dilution. Sorafenib (co-developed and co-marketed by Bayer and Onyx Pharmaceuticals) was either locally sourced or centrally supplied by AstraZeneca and administered according to prescribing information or treatment guidance in general use by the investigating site. The batch numbers used can be found in Table S2.

Table S2 Identity of Study Treatments

Investigational product	Dosage form and strength	Manufacturer	Batch numbers
Durvalumab	CCI solution for infusion after dilution	Cook Pharmica LLC [a]	CCI
Tremelimumab	CCI solution for infusion after dilution	Boehringer Ingelheim Pharma GMBH & Co [a]	
Sorafenib [a]	CCI tablets) orally CCI	Bayer/Onyx [b]	

[a] Manufacturers of AstraZeneca IPs: Durvalumab: Cook Pharmica LLC, CCI and Tremelimumab: Boehringer Ingelheim Pharma GMBH & Co. KG, CCI

[b] Sorafenib is co-developed and co-marketed by Bayer and Onyx Pharmaceuticals. Under certain circumstances when local sourcing was not feasible, sorafenib could be supplied centrally through AstraZeneca.

Infliximab CCI vials (Batch numbers: CCI and mycophenolate CCI capsules (Batch numbers: CCI were also supplied by AstraZeneca (when not sourced locally) for the treatment of suspected immune-mediated AEs.
CCI

Sorafenib was administered CCI in accordance with the locally-approved product label.

Duration of Treatment

Patients received their assigned randomized treatment regimen until confirmed progressive disease (PD), unacceptable toxicity, or any discontinuation criteria were met. Patients who discontinued treatment due to toxicity or symptomatic deterioration, or who commenced subsequent anticancer therapy, were followed-up until confirmed PD and for survival. All patients were followed-up for survival until the end of the study unless they withdrew consent to survival follow-up.

Crossover within the study was not permitted, except for patients in the T-low+D arm who could be rechallenged with T-high+D as outlined below.

Treatment Through Disease Progression

At the Investigator's discretion, patients could continue to receive their original assigned treatment after the first assessment of PD by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 until PD was confirmed on a follow-up scan evaluated by Confirmation of Radiological Progression criteria. A follow-up scan was collected after the initial RECIST 1.1-defined PD, preferably at the next visit, and no earlier than 4 weeks after the prior assessment of PD.

Patients with confirmed PD who, in the Investigator's opinion, continued to receive benefit from their assigned treatment and met the criteria for treatment in the setting of PD could continue to receive their assigned treatment. However, patients who developed progression in target lesions after a clear response (per RECIST 1.1) were not permitted to continue therapy.

Rechallenge Option for Combination Therapy Arms

Patients in the durvalumab and tremelimumab combination arms (T-high+D and T-low+D) who completed their first CCI assigned dosing cycles and, in the Investigator's opinion, were benefiting from IP, but had evidence of PD with or without confirmation according to RECIST 1.1 during subsequent durvalumab monotherapy, could be rechallenged if they met the eligibility criteria for rechallenge. Patients were only eligible for rechallenge once and rechallenge could not begin earlier than Cycle 6.

Statistical Methods

The following general principles were followed:

- Descriptive statistics were used for all variables, as appropriate, and presented by treatment arm. Continuous variables are summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables are summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages are calculated out of the total for the corresponding treatment arm.
- In general, for efficacy, the last observed measurement prior to randomization is considered the baseline measurement. For safety and patient-reported outcome (PRO) endpoints, the last observation prior to the first dose of study treatment is considered the baseline measurement, unless otherwise specified.

Two interim analyses (IA1 and IA2) and a Final Analysis were planned for this study:

The first interim analysis (IA1) was performed after 100 subjects per treatment arm had the opportunity for at least 32 weeks of follow-up (ie, randomized ≥ 32 weeks prior to IA1 data cut-off [DCO]) and after all patients had been enrolled in the study (DCO: 02 September 2019). The objective was to evaluate the efficacy of the T-high+D and D arms in terms of objective response rate (ORR) and duration of response (DoR).

The second interim analysis (IA2) was performed when 415 overall survival (OS) events had occurred in the T-high+D and sorafenib arms combined (~52% maturity) (DCO: 22 May 2020). The objective was to assess the primary objective of OS superiority for T-high+D vs S in the Full Analysis Set (FAS) population. The threshold for data reporting was not met at IA2 (i.e., the OS comparison for T-high+D vs S was not statistically significant at a 2-sided alpha level of 0.0244) and the Independent Data Monitoring Committee (IDMC) recommended that the study continue to final analysis.

The final analysis was performed once 555 OS events occurred in the T-high+D and S arms combined (71% maturity), 46 months after the first patient was randomized.

The formal statistical analysis of OS (primary endpoint) was performed for the following efficacy test hypotheses (alternative hypotheses):

- H1 (primary): Difference between T-high+D and S arms (for superiority).
- H2 (key secondary): D is not inferior to S with non-inferiority margin of 1.08.
- H3 (key secondary): Difference between D and S (for superiority).

No formal statistical analysis was conducted for the T-low+D arm since it was closed for enrollment with protocol amendment 3.

Subject Population

Disposition

Of the total of 1324 patients randomized, 1302 patients (98.3%) received study treatment.

At the final DCO (27 August 2021), most patients (91.2%) had discontinued study treatment. Overall, the most frequently reported reason for discontinuing study treatment was objective PD: 222 patients (57.5%) in the D arm, 183 (47.0%) in the T-high+D arm and 170 (45.5%) in the S arm. A further 14.7% of patients discontinued due to subjective PD; 44 patients (11.4 %) in the D arm, 61 (15.7 %) in the T-high+D arm and 66 (17.6 %) in the S arm. Discontinuations due to adverse events (AEs) were reported for 13.0% of patients, with a lower proportion in the D arm (7.8%) compared with the T-high+D arm (13.4%) and the S arm (16.8%). Other reasons for discontinuation were similar across treatment arms.

At the final DCO, 339 patients (25.6%) were still on study: 26.7% in the D arm, 31.8% in the T-high+D arm and 20.6% in the S arm.

Demographic and Baseline Characteristics

Overall, the patient population was representative of the target population of patients with unresectable HCC and treatment arms were balanced in terms of demographic and baseline characteristics. The median age at study entry was 64.0 years (range: PPD 83.7% of patients were male and 40.7% were from the Asian region (excluding Japan). Programmed cell death ligand-1 status was balanced across treatment arms, with 38.9% of patients having positive programmed cell death ligand-1 (PD-L1) expression (Tumor and Immune Cell Positivity [TIP] ≥ 1%). The majority of patients had an ECOG PS score of 0 or 1 (62.6% and 37.2%, respectively).

Disease Characteristics

Patients' disease characteristics at screening were generally balanced across the treatment arms, and representative of the intended target population with unresectable HCC. At screening, 30.6% of patients were HBV positive, 27.2% were HCV positive, and 42.2% were uninfected. A total of 99.5% of patients were Child-Pugh Class A. At study entry, 19.2% of patients were BCLC Stage B and 80.8% were BCLC Stage C. Importantly, stratification factors comprising etiology of liver disease (determined by virology laboratory assessments at screening), MVI and ECOG PS were balanced across treatment arms.

Summary of Efficacy Results

Overall Survival

At the final OS DCO, 555 deaths had occurred across the T-high+D and S arms (71% maturity), and 573 deaths had occurred across the D and S arms (74% maturity). A total of 109 patients (28.0%) in the D arm, 131 (33.3%) in the T-high+D arm, and 96 (24.7%) in the S arm were alive and in survival follow-up.

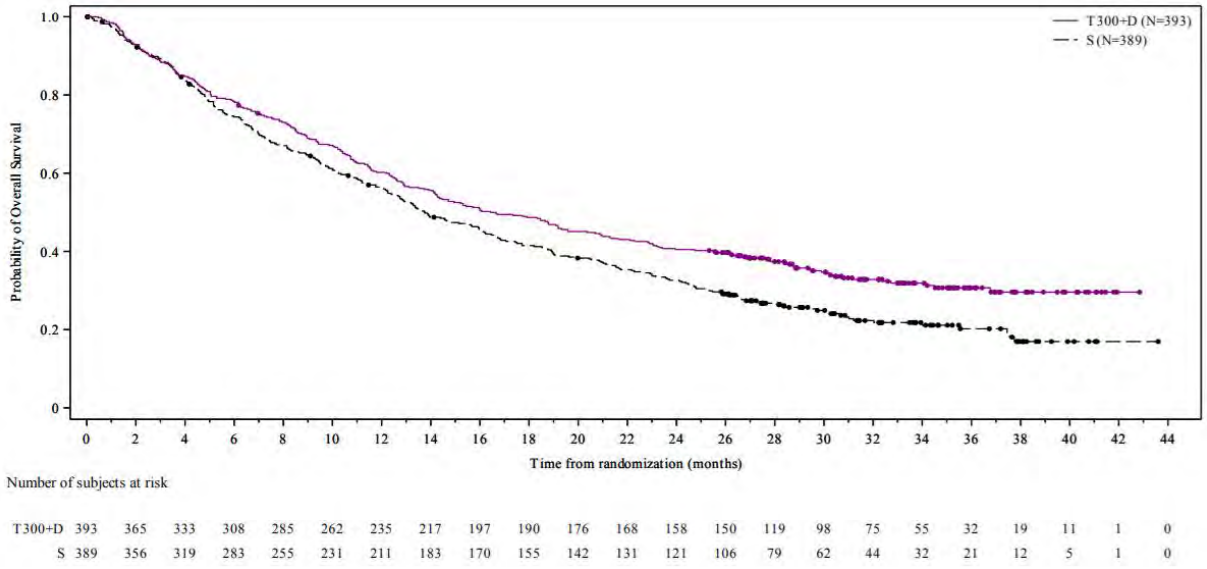
T-high+D vs S

Treatment with T-high+D demonstrated a statistically significant, clinically meaningful and sustained improvement in OS compared with S; the hazard ratio (HR), adjusted for stratification factors (per IWRS), was 0.78 (96.02% CI: 0.65, 0.93; stratified log-rank 2-sided p = 0.0035). The Kaplan-Meier (KM) estimates for median OS were 16.43 months in T-high+D and 13.77 in the S arm, an estimated 2.7-month difference in median values. The OS curves separate approximately 4 months after randomization through the remainder of patient follow-up (Figure S1). The landmark estimate of the proportion of patients alive at 24 months was 40.5% in the T-high+D arm compared with 32.6% in the S arm. At 36 months, the KM estimates were 30.7% in the T-high+D arm and 20.2% in the S arm.

The 36-month OS rate was not formally compared in an alpha-controlled fashion, but a post-hoc analysis comparing the KM estimates of T-high+D vs S was statistically significant at a 5% level ($p < 0.0029$).

In a post-hoc analysis calculating piecewise constant treatment effects for the comparison of T-high+D vs S before the observed separation at 4 months, no initial detriment was evident for T-high+D prior to the separation observed at 4 months. Subsequently, the observed treatment effect of T-high+D vs S led to a statistically significant OS benefit when accounting for the totality of the data.

Figure S1 KM Plot of Overall Survival, T-high +D vs S Comparison (FAS)



FAS, Full Analysis Set; KM, Kaplan-Meier; CCI S, sorafenib CCI T-high+D, tremelimumab CCI + durvalumab CCI

The OS benefit favoring T-high+D treatment vs S was consistent across most prespecified subgroups, as demonstrated by the fact that the HR point estimate for each subgroup was contained within the 95% CI of the HR for the overall population. Some variability was observed, in particular sex and etiology of liver disease (females and HCV). The CIs for females in the T-high+D vs S subgroup analysis are wide likely due to the small sample size (< 100 patients). For HCV, a post-hoc analysis of baseline covariates within the HCV subgroup identified potential imbalances in prognostic factors between the groups. The study was not sized for any of the individual subgroup evaluations and no adjustments were made for multiple testing subgroup analyses.

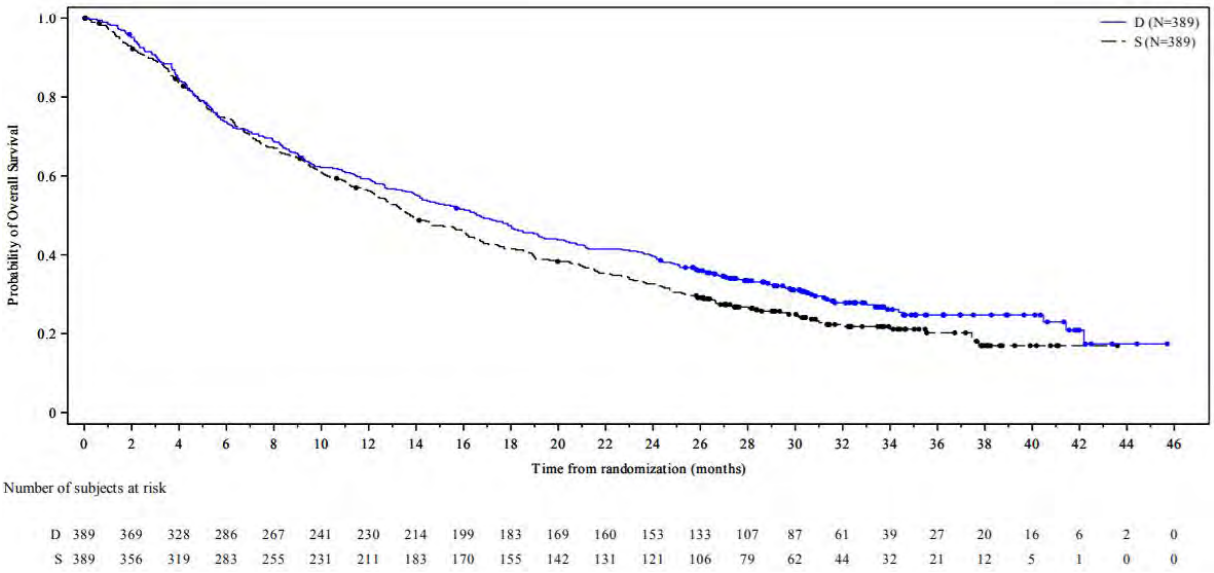
D vs S Comparison

The comparison of D monotherapy vs S met the key secondary objective of non-inferiority (NI) as demonstrated by the upper bound of the 95.67% CI (0.73, 1.03) which fell below the prespecified clinical NI margin of 1.08. However, the study did not meet the key secondary objective of superiority for the D vs S comparison (p = 0.0674). The HR, adjusted for stratification factors (per IWRS), was 0.86 and the KM estimates for median OS were 16.6 months in the D arm and 13.8 months in the S arm. The landmark estimate of the proportion of patients alive at 24 months was 39.6% in the D arm compared with 32.6% in the S arm. At 36 months, the estimates were 24.7% in the D arm and 20.2% in the S arm.

The OS curves for D and S overlapped for approximately the first 9 months from randomization (Figure S2), but separation in favor of D was maintained from 9 months

onward. As there was evidence of non-proportionality a post-hoc analysis applying a time-varying covariate to the treatment effect between the observed separation at 9 months found a HR of 0.98 prior to the separation (0 to 9 months) and a subsequent HR of 0.77 from 9 months onwards. Given the nearly complete length of follow-up for the first 26 months in the D and S arms, the survival estimates shown in the D vs S curve can be considered as stable estimates.

Figure S2 KM Plot of Overall Survival, D vs S Comparison for Noninferiority (FAS)



D, durvalumab monotherapy [redacted] FAS, Full Analysis Set; KM, Kaplan Meier; [redacted]
S, sorafenib [redacted]

The OS non-inferiority of D treatment vs S was consistent across all prespecified subgroups, except for etiology of liver disease (HCV), as demonstrated by the fact that the HR point estimate for each subgroup was contained within the 95% CI of the HR for the overall population. For HCV, a post-hoc analysis of baseline covariates within the HCV subgroup identified potential imbalances in prognostic factors between the groups. The study was not sized for any of the individual subgroup evaluations and no adjustments were made for multiple testing subgroup analyses.

Objective Response Rate

At the final DCO, the ORR based on Investigator assessment according to RECIST 1.1 for confirmed responses was 17.0% for the D arm, 20.1% for the [redacted]+D arm, and 5.1% for the S arm.

Treatment with T-high+D or D had a higher likelihood of response when compared with S. The odds ratio for the comparison of T-high+D vs S was 4.69 (95% CI: 2.85, 8.04; nominal $p < 0.0001$) in favor of the T-high+D arm. In the comparison of D vs S, the odds ratio was 3.80 (95% CI: 2.29, 6.57; nominal $p < 0.0001$) in favor of the D arm (Table S3). Of note, the study was not sized for this comparison and no multiplicity adjustments were made.

Table S3 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	95% CI	2-sided p-value
D	389	66 (17.0)	17.0	3.80	2.29, 6.57	< 0.0001
T-high+D	393	79 (20.1)	20.1	4.69	2.85, 8.04	< 0.0001
T-low+D	153	26 (17.0)	17.0	-	-	-
S [b]	389	20 (5.1)	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 > 1 favors IO treatment arms.

CI, confidence interval; D, durvalumab monotherapy CCI ECOG, Eastern Cooperative Oncology Group; FAS, Full Analysis Set; IO, immuno-oncology; MVI, macrovascular invasion; PS, performance status; CCI RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; S, sorafenib CCI T-low+D, tremelimumab CCI + durvalumab CCI T-high+D, tremelimumab CCI + durvalumab CCI

Best Objective Response

In the FAS, 23.9% of patients in the T-high+D arm, 18.5% in the D arm and 6.7% in the S arm achieved a best objective response (BOR) of either complete response (CR) or partial response (PR) based on Investigator assessment (including unconfirmed responses). Complete responses were only observed in the D-containing arms: 7 patients (1.8%) in the D arm and 13 patients (3.3%) in the T-high+D arm. Among patients who had a response, the rate of PR was numerically higher in patients in the T-high+D and D arms when compared with that in the S arm, namely 81 patients in the T-high+D arm (20.6%) and 65 patients in the D arm (16.7%) compared with 26 patients in the S arm (6.7%).

A subgroup analysis of OS by BOR (unconfirmed response by Investigator assessment by RECIST 1.1) was conducted for the T-high+D vs S comparison. The results show that response status correlated with OS outcome, with the longest survival benefit observed in the CR/PR, followed by stable disease (SD), and then PD. Importantly, patients with BOR of PD in the T-high+D arm experienced a better OS outcome when compared with the same group of

patients in the S arm. A subgroup analysis of OS by BOR for D vs S was consistent with that observed with T-high+D vs S.

Duration of Response and Time to Onset of Response

Median DoR from onset of response based on Investigator assessment according to RECIST 1.1 for patients in the FAS with an objective response was greater for patients in the T-high+D arm (22.3 months) than in the D (16.8 months) and S arms (18.4 months). The estimates of the 75th percentiles for DoR also show the benefit of T-high+D and D over S, as estimates for T-high+D and D were not reached vs S.

Median time to onset of response from randomization for patients with confirmed objective response based on Investigator assessment according to RECIST 1.1 was approximately 1 month shorter for patients in the T-high+D (2.2 months) and D (2.1 months) arms compared with the S arm (3.8 months).

Progression-free Survival

Progression-free survival was not included in the multiple testing procedure (MTP) and thus, not controlled for multiplicity; statistical testing was performed at a nominal 5% significance level. At the final DCO, a higher proportion of patients in the T-high+D arm (12.5%) were progression-free than in the D (8.2%) and S (4.9%) arms. At that time, the KM estimate for median progression-free survival (PFS) in the FAS was 3.7 months in the D arm, 3.8 months in the T-high+D arm and 4.1 months in the S arm; the HR was 0.90 (95% CI: 0.77, 1.05), p = 0.1625 for the T-high+D vs S comparison and 1.02 (95% CI: 0.88, 1.19), p = 0.7736 for the D vs S comparison.

Disease Control Rate

The proportion of patients in the FAS who achieved overall controlled disease based on RECIST 1.1 Investigator assessment (ie, patients achieving either CR, PR, or SD) was similar in all treatment arms (disease control rate [DCR] was 54.8% in the D arm, 60.1% in the T-high+D arm and 60.7% in the S arm). At Weeks 16 and 24, DCR was numerically higher in the T-high+D arm than in the D and S arms (D: 39.6% and 32.9%, respectively; T-high+D: 46.1% and 37.9%, respectively; S: 44.5% and 31.4%, respectively).

Patient-reported Outcomes

Time to Deterioration

- Treatment with T-high+D resulted in a longer median time to deterioration (TTD) of all scores compared with S with nominally significant differences reported for the following:
    - European Organization for Research and Treatment of Cancer (EORTC) 30-item core quality of life questionnaire (QLQ-C30) global health status (GHS)/quality of life (QoL), physical functioning, fatigue, nausea and appetite loss

  - EORTC 18-item hepatocellular cancer health-related quality of life questionnaire (QLQ-HCC18) abdominal pain and abdominal swelling

- Treatment with D resulted in a longer median TTD of all scores compared with S. Nominally significant differences were reported in all scores apart from EORTC QLQ-C30 nausea, and EORTC QLQ-HCC18 shoulder pain and abdominal swelling.

Improvement Rate

- Treatment with T-high+D resulted in increased odds ratios of clinically meaningful improvement compared with S in disease-related symptoms, physical functioning, and GHS/QoL, with nominally significant differences vs S for EORTC QLQ-C30 cognitive/social functioning, insomnia, fatigue, and diarrhoea, and EORTC QLQ-HCC18 fatigue, pain, abdominal swelling, nutrition, weight loss, and muscle loss.
- Treatment with D resulted in increased odds ratios of clinically meaningful improvement compared with S in disease-related symptoms, physical functioning, and GHS/QoL, with nominally significant differences vs S for EORTC QLQ-C30 cognitive/social functioning, insomnia, fatigue, and diarrhoea, and EORTC QLQ-HCC18 pain, abdominal swelling, nutrition, and muscle loss.

Summary of Pharmacokinetic Results

No formal non-compartmental analysis for durvalumab or tremelimumab was conducted due to the sparse pharmacokinetic (PK) sampling scheme in this study. Durvalumab and tremelimumab PK concentrations were within the expected exposures at their respective dosing regimens.

Overall, PK profiles of durvalumab were similar for patients treated in the D arm and those in the T-high+D and T-low+D arms, suggesting tremelimumab does not have an impact on the PK of durvalumab when administered as combination therapy.

Summary of Immunogenicity Results

The overall immunogenicity results of durvalumab, ie, low percentage of treatment-emergent ADA-positive patients, ADA-positive at a single time point with low ADA titer and few neutralizing antibody (nAb) positive patients, are consistent with the known immunogenicity profile of durvalumab.

The overall immunogenicity profile of tremelimumab, ie, the majority of ADA-positive patients were classified as treatment-emergent ADA-positive with low ADA titer, is consistent with the known immunogenicity profile of tremelimumab.

The development of treatment-emergent ADA to either durvalumab or tremelimumab did not have an apparent effect on serum concentrations of the respective investigational product (IP).

Summary of Safety Results

Extent of Exposure

The extent of exposure to durvalumab in terms of total treatment-years (118.0 treatment-years) and median total treatment duration (4.6 months) was lowest in the T-low+D arm reflecting the impact of protocol amendment 3 (closure of enrollment to T-low+D arm). The extent of exposure to durvalumab in terms of total treatment-years was similar for the durvalumab component of the D (312.7 treatment-years) and T-high+D (341.7 treatment-years) arms. The extent of exposure to sorafenib in the S arm was 234.9 treatment-years. The median total treatment duration was the same for the durvalumab component of the D (5.5 months) and T-high+D (5.5 months) arms. In the S arm, the median total treatment duration was 4.1 months.

Thirty patients in the T-high+D arm were retreated with CCI in combination with durvalumab. Twelve patients in the T-low+D arm were rechallenged with tremelimumab in combination with durvalumab. Of these, 5 patients in the T-low+D arm were rechallenged with 1 dose of tremelimumab CCI in combination with durvalumab in accordance with protocol amendment 3.

No dose reductions of durvalumab or tremelimumab were allowed per protocol except for patients with a body weight falling to ≤ 30 kg. There were no durvalumab or tremelimumab dose reductions reported for weight-based dosing. Durvalumab and tremelimumab infusion interruptions were infrequent and the overall frequency of durvalumab dose/cycle delays were generally similar in the tremelimumab-containing arms. Sorafenib dose reductions occurred in approximately half of patients (183 patients [48.9%]) and most dose reductions were due to AEs (162 patients [43.3%]).

Adverse Events

All data presented in this section is for patients in the Safety Analysis Set.

Overall, the nature of AEs and frequency of events within AE categories were generally consistent with the known safety profiles of each regimen.

- Most patients in the study experienced at least 1 AE during the study, with a similar incidence across the 4 treatment arms ranging from 88.9% in the D arm to 97.4% in the T-high+D arm.
- Treatment-related Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 AEs were lower for immune-oncology (IO)-containing regimens (D, 12.9%; T-high+D, 25.8%; T-low+D, 21.1% patients), compared with those in arm S (36.9% patients).

- Treatment-related AE leading to discontinuation to IP were lower for IO containing regimens, (D, 4.1%; T-high+D, 8.2%; T-low+D, 8.6% patients), compared with those in arm S (11.0% patients).
- The frequency of fatal AEs was similar across arms and occurred in 6.7% to 7.9% of patients across the 4 treatment arms.
- The frequency of treatment-related fatal AEs, in decreasing order of frequency, were as follows: T-high+D, 9 patients (2.3%); T-low+D, 2 patients (1.3%); S, 3 patients (0.8%); D, no patients (0%).

All Adverse Events

At the system organ class (SOC) level, AEs were most commonly reported (≥ 30% in any treatment arm) in the SOCs of Gastrointestinal disorders, Skin and subcutaneous tissue disorders, General disorders and administration site conditions, Investigations, and Metabolism and nutrition disorders.

The 6 most frequent AEs for patients in the D arm were diarrhoea (14.9%), pruritus (14.4%), aspartate aminotransferase increased (14.4%), decreased appetite (13.7%), asthenia (12.6%), and alanine aminotransferase increased (11.2%). Of these AEs, diarrhoea, pruritus, aspartate aminotransferase increased, and alanine aminotransferase increased are known adverse drug reactions (ADRs) for durvalumab. Asthenia occurred at a similar frequency in the D, T-high+D, and S arms.

The 6 most frequent AEs for patients in the T-high+D arm were diarrhoea (26.5%), pruritus (22.9%), rash (22.4%), decreased appetite (17.0%), fatigue (17.0%), and pyrexia (12.9%). Of these AEs, diarrhoea, pruritus, and rash are known ADRs for either durvalumab or tremelimumab.

The majority of the events that were reported at a ≥ 5% greater frequency in the T-high+D arm compared with those reported in the D arm are known ADRs for either durvalumab or tremelimumab (diarrhoea, pruritus, rash, and hypothyroidism).

Diarrhoea, palmar-plantar erythrodysaesthesia syndrome, alopecia, and hypertension were all reported at a higher frequency (≥ 5% greater frequency) in the S arm than the T-high+D arm. All of these AEs are known ADRs for sorafenib.

Treatment-related Adverse Events

The frequency of patients with treatment-related AEs was lower in the IO containing regimens: D (52.1%), T-low+D (69.7%) and T-high+D (75.8%) patients compared with that in arm S (84.8%). Of note, the incidence of palmar-plantar erythrodysaesthesia syndrome, diarrhoea, and hypertension were markedly higher in the S arm than the

durvalumab-containing treatment arms. Treatment-related AEs were reflective of the known safety profiles of each study treatment.

Adverse Events by Severity

The 2 most frequent AEs of maximum CTCAE Grade 3 or 4 (≥ 5% patients) in the D arm and T-high+D arm were aspartate aminotransferase increased and lipase increased; these events occurred at a similar frequency in these arms.

The 2 most frequent AEs of maximum CTCAE Grade 3 or 4 (≥ 5% patients) for the S arm were palmar-plantar erythrodysaesthesia syndrome (9.1%) and hypertension (6.1%).

There were more treatment-related AEs of maximum CTCAE Grade 3 or 4 in the S arm compared with those in the IO-containing arms, with the 3 most frequent AEs by preferred term (PT) in the S arm being palmar-plantar erythrodysaesthesia syndrome (8.8% patients), hypertension (5.3% patients), and diarrhoea (4.0% patients). There were more treatment-related AEs in the tremelimumab-containing arms than in the D arm, but frequencies of treatment-related AEs were low overall.

Deaths

The majority of deaths in each treatment arm were attributed to progression of HCC disease by the Investigator. The frequency of fatal AEs was consistent across treatment arms (26 patients [6.7%] in arm D, 30 patients [7.7%] in arm T-high+D, 12 patients [7.9%] in arm T-low+D, and 27 patients [7.2%] in arm S). The frequency of fatal AEs considered treatment-related by the Investigator was: no patients (0%) in arm D, 9 patients (2.3%) in arm T-high+D (fatal AE PTs: 1 patient with each of myasthenia gravis, nervous system disorder, myocarditis, acute respiratory distress syndrome, pneumonitis, hepatic failure, hepatitis, and 2 events of immune-mediated hepatitis), 2 patients (1.3%) in arm T-low+D (fatal AE PTs: 1 patient with septic shock and 1 patient with hepatic failure and multiple organ dysfunction syndrome), and 3 patients (0.8%) in arm S (fatal AE PTs: 1 patient with each of cerebral haematoma, hepatic failure, and haematuria).

Serious Adverse Events

Serious adverse events were reported for more patients in the tremelimumab-containing arms than in the D and S arms. The reported serious adverse events (SAEs) by PT were low in frequency with no trends by treatment arm contributing to the overall SAE data profile.

Treatment-related SAEs were reported for more patients in the tremelimumab-containing arms than in the D and S arms (D, 8.2%; T-high+D, 17.5%; T-low+D, 18.4%; S, 9.4% patients). There were no treatment-related SAEs by PT reported by ≥ 5% patients. Few treatment-related SAEs resulted in death.

Adverse Events Leading to Study Treatment Discontinuation

Frequencies of AEs resulting in treatment discontinuation were similar across the T-high+D and T-low+D arms. Fifty-three patients (13.7%) in arm T-high+D, 23 patients (15.1%) in arm T-low+D, and 63 patients (16.8%) in arm S reported AEs leading to discontinuation of study treatment. The frequency of AEs resulting in treatment discontinuation was lowest in the D arm; 32 patients (8.2%).

Immune-mediated Adverse Events

For immune-mediated adverse events (imAEs) in all categories, imAEs were reported at a higher frequency in the tremelimumab-containing treatment arms (T-high+D, 35.8%; T-low+D, 34.9% patients) compared with those reported in the D arm (16.5% patients). The frequency of imAEs that led to discontinuation of study treatment was low (≤ 5.7% patients per arm). Six patients (1.5%) in the T-high+D arm died due to imAEs (pneumonitis, 3 hepatic events, myocarditis, and myasthenia gravis); there were no fatal imAEs in the other treatment arms.

The overall frequency of hepatic AEs per Hepatic Disorder Standardized MedDRA Queries (SMQs) was similar across all treatment arms and there was no observed increase in the tremelimumab-containing arms compared with the D arm. Reported events were consistent with the disease under study.

The overall frequency of AEs captured under Hemorrhage SMQs was comparable across all treatment arms and there was no observed increase in the tremelimumab-containing arms compared with the D arm. The frequencies of fatal hemorrhages were similar across treatment arms (D, 1.5%, T-high+D, 2.1%; T-low+D, 0.7%; S, 1.3%). Treatment-related fatal hemorrhages were reported in the S arm 2 (0.5%). None of the IO-containing treatment arms had treatment-related fatal hemorrhage PTs reported during the study.

Across the AE profile, there was no marked difference in categorical AE data for patients positive for either durvalumab or tremelimumab ADA compared with ADA-negative patients.

Conclusions

HIMALAYA demonstrated a positive benefit/risk profile for T-high+D and D compared with S for the treatment of patients with unresectable HCC who are not eligible for locoregional therapy and have not received prior systemic therapy:

- The study met its primary objective, demonstrating a clinically meaningful and statistically significant improvement in OS in T-high+D-treated patients compared with S-treated patients (HR: 0.78; 96.02% CI: 0.65, 0.93; p = 0.0035). Median OS was 16.4 months in the T-high+D arm and 13.8 months in the S arm, which corresponded to a clinically meaningful improvement of 2.7 months.

- The OS benefit in the T-high+D arm was sustained over time, as supported by the greater proportion of patients treated with T-high+D who were alive at 36 months (30.7%) compared with patients treated with S (20.2%).
- Patients in the T-high+D arm showed the highest confirmed ORR based on Investigator per RECIST 1.1 (20.1%), compared with 17.0% for D and 5.1% for S.
- The median DoR based on Investigator assessment was numerically longer in the T-high+D arm (22.3 months) than in the S arm (18.4 months), and the D arm (16.8 months) with a numerically shorter median time to onset of response (2.2 months for T-high+D vs 3.8 months for S and 2.1 months for D).
- A BOR (either CR or PR) by Investigator assessment, was achieved by 23.9% of patients in the T-high+D arm, 6.7% of patients in the S arm and 18.5% in the D arm. Of the patients who had a response, 13 patients (3.3%) in the T-high+D arm, 7 (1.8%) in the D arm, and no patients in the S arm had CR; 81 patients (20.6%) in the T-high+D arm, 65 (16.7%) in the D arm, and 26 (6.7%) in the S arm had PR.
- Treatment with D was noninferior to S in terms of OS (HR: 0.86; 95.67% CI: 0.73, 1.03; p = 0.0674), as the upper limit of the 95.67% CI for the HR was lower than the 1.08 NI margin. The KM estimate of median OS was 16.6 months in the D arm and 13.8 months in the S arm, which corresponded to a clinically meaningful difference of 2.8 months.
- Progression-free survival was comparable in the 3 treatment arms: with median of 3.8 months in the T-high+D arm, 3.7 months in the D arm and 4.1 months in the S arm.
- Treatment with T-high+D and D regimens resulted in longer TTD, clinically meaningful improvement rate in disease-related symptoms, Physical Functioning, and GHS/QoL, and was well-tolerated from the patient perspective with no meaningful impact on health-related quality of life (HRQoL) compared with S.
- Durvalumab and tremelimumab PK concentrations were within the expected exposures at their respective dosing regimens. In addition, PK profiles of durvalumab were similar across the T-high+D, T-low+D and D arms, suggesting tremelimumab does not have an impact on the PK of durvalumab when administered as combination therapy.
- Treatment-emergent ADA positive rates were similar to previous studies for both durvalumab and tremelimumab, and nAb rate was low.
- No new safety risks for D or T-high+D were identified beyond those known for durvalumab monotherapy or durvalumab in combination with tremelimumab and no new ADRs were identified for T-high+D.

The T-high+D regimen demonstrated a significant improvement in OS versus S, with a single priming dose of tremelimumab contributing to over 30% of patients surviving at least 3 years, and a favorable benefit-risk profile. Additionally, D monotherapy was noninferior to S for OS, with a more tolerable safety profile. The T-high+D regimen offers a novel combination therapy option for the first-line treatment of unresectable HCC. HIMALAYA data provide two new options for treatment of patients with first-line unresectable HCC, including a novel combination regimen.