Clinical Study Report Synopsis	
Drug Substance	Durvalumab, tremelimumab
Study Code	D4190C00022
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NCT Number	NCT02519348

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

Study dates:

Part 1: First/last patient enrolled: 19 October 2015/31 August 2016
Part 2: First/last patient enrolled: 26 January 2017/24 November 2017
Part 3: First/last patient enrolled: 15 January 2018/20 March 2019
Part 4: First/last patient enrolled: 19 April 2019/29 October 2019
China cohort: First/last patient enrolled: 26 October 2017/11 July 2018
The analyses presented in this report are based on a data cut-off date of 06 November 2020 and a database lock date of 21 January 2021.

Phase of development: Therapeutic exploratory (I/II)

International Co-ordinating Investigator:

PPD

Sponsor's Responsible Medical Officer:

PPD

AstraZeneca

PPD

PPD Gaithersburg, MD, 20878, United States

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study sites

The study is being conducted at study sites in Asia, Europe, and North America. In total, 45 study sites in 9 countries enrolled patients and patients were randomized/allocated to treatment at 43 study sites in 9 countries.

Publications

Kelley RK et al. J Clin Oncol. 2021 Jul 22:JCO2003555. doi: 10.1200/JCO.20.03555. Epub ahead of print. PMID: 34292792.

Kudo M et al. Asian Pacific Association for the Study of the Liver 30th Conference 2021.

Kudo M et al. Japan Association of Molecular Targeted Therapy for HCC 23rd Workshop 2021.

Song X et al. J Clin Oncol. 2021;39.3_suppl.313.

Kelley RK et al. J Clin Oncol. 2020;38:15_suppl, 4508.

Kelley RK et al. Ann Oncol. 2020;31(S3):233-4.

Kelley RK et al. Virtual 14th Annual Conference of the International Liver Cancer Association. 2020;O-22.

Kelley RK et al. Ann Oncol. 2020;31(S7):S1439.

Qin S et al. Chinese Society of Clinical Oncology 23rd Annual Meeting 2020.

Objectives and criteria for evaluation

The study objectives and criteria for evaluation are presented in Table 1.

Table 1 Objectives and Outcome Variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To assess the safety and tolerability of durvalumab and tremelimumab administered as monotherapy, and durvalumab in combination with tremelimumab or bevacizumab in patients with advanced HCC	AEs, SAEs, discontinuation of investigational product(s) due to toxicity, and changes from baseline in laboratory parameters (including liver, viral laboratory tests, ECG, and vital signs)
Secondary	Efficacy	To evaluate the efficacy of durvalumab and tremelimumab administered as monotherapy, and durvalumab in combination with tremelimumab or bevacizumab in patients with advanced HCC	OS, ORR, DCR, TTR, TTP, DoR, and PFS based on Investigator assessments and BICR according to RECIST 1.1

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Biomarker	To evaluate the relationship between candidate biomarkers (eg, PD-L1 expression in the tumor microenvironment) and measures of clinical outcome of durvalumab and tremelimumab administered as monotherapy, and durvalumab in combination with tremelimumab or bevacizumab in patients with advanced HCC	PD-L1 expression within the tumor microenvironment [a]
Exploratory	CCI		
Exploratory			
Exploratory			
Exploratory			

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory	CCI		
Exploratory			

[a] This outcome variable should have been described in the CSP as PD-L1 expression in the tumor and association with OS.

CCI

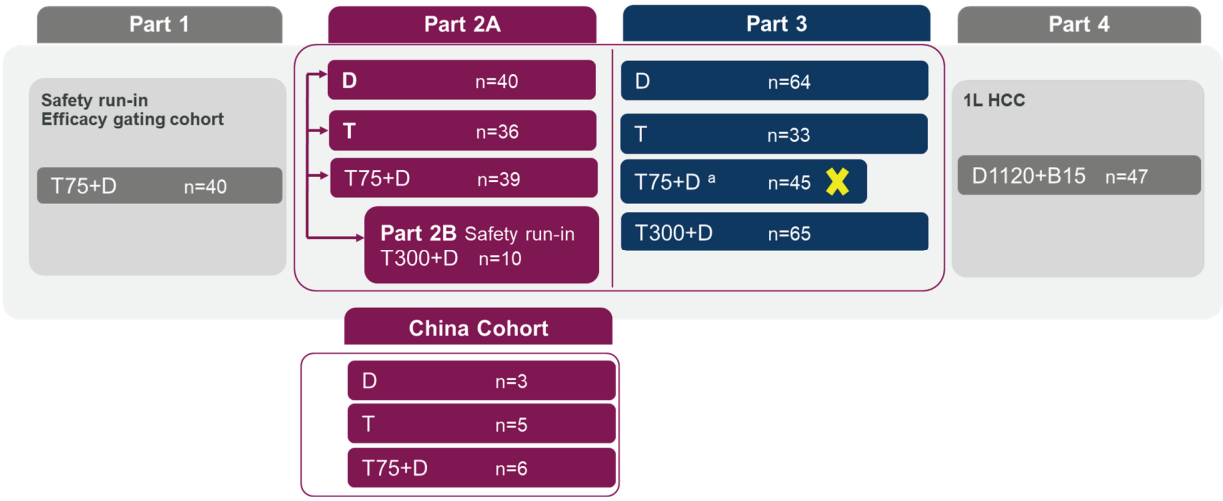
CCI AEs, adverse events; BICR, blinded independent central review; CSP, Clinical Study Protocol; DCR, disease control rate; CCI DoR, duration of response; ECG, electrocardiogram; CCI HCC, hepatocellular carcinoma; CCI ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; CCI RECIST 1.1, Response Evaluation Criteria in Solid Tumours Version 1.1; SAE, serious adverse event; TTP, time to progression; TTR, time to response.

Study design

This is a multi-center, international, open-label, multi-part 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 hepatocellular carcinoma (HCC). The study comprises 6 parts: Parts 1A, 1B, 2A, 2B, 3, and 4. In addition, a separate cohort of patients was enrolled in mainland China once global recruitment in Part 2A closed and is referred to as the China cohort. Patients in the China cohort followed the study design for Part 2A (Figure 1).

This Clinical Study Report Synopsis presents the final analysis of data in all study parts, which was performed 12 months after the first dose of investigational product (IP) was given to the last patient enrolled in the study (data cut-off [DCO]: 06 November 2020). Patients remaining in the study continue to be treated and followed in line with the Clinical Study Protocol (CSP).

Figure 1 Study Design and Flow Diagram



D: durvalumab monotherapy 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 monotherapy 750 mg (10 mg/kg) Q4W × 7 doses followed by Q12W
T75+D: tremelimumab 75 mg (1 mg/kg) × 4 doses + durvalumab 1500 mg (20 mg/kg) Q4W
D1120+B15: durvalumab 1120 mg (15 mg/kg) + bevacizumab 15 mg/kg Q3W

[a] Following protocol amendment 5, enrollment into the T75+D arm in Part 3 was closed. Patients already randomized to T75+D could continue on assigned study treatment (provided the Investigator and patient thought it in the best interests of the patient) until confirmed progressive disease or any other discontinuation criteria were met.

n = the actual number of patients randomized/allocated to treatment in the respective study parts.

Patients were allocated to treatment in Parts 1, 2B, and 4, and randomized to treatment in Parts 2A and 3, and the China cohort.

Weight-based dosing regimens were used in Parts 1, 2A, and 4 (bevacizumab only), and the China cohort; fixed dosing regimens were used in Parts 2B, 3, and 4 (durvalumab only).

1L, first-line; HCC, hepatocellular carcinoma; Q3W, every 3 weeks; Q4W, every 4 weeks; Q12W, every 12 weeks.

In all parts of the study, patients received study treatment until confirmed progressive disease (PD) or until any of the discontinuation criteria were met.

Part 1A

Part 1A was a safety run-in in immunotherapy-naïve patients with advanced HCC who had progressed on, were intolerant to, or had refused sorafenib-based therapy.

- In Stage 1, 9 patients with advanced uninfected or hepatitis C virus (HCV)-infected HCC received durvalumab 20 mg/kg and tremelimumab 1 mg/kg combination therapy every 4 weeks (Q4W) for 4 doses followed by durvalumab 20 mg/kg monotherapy Q4W.

- In Stage 2, 6 additional patients with advanced hepatitis B virus (HBV)-infected HCC were enrolled once the first 3 patients in Stage 1 had been observed on study for at least 4 weeks. Patients received durvalumab 20 mg/kg and tremelimumab 1 mg/kg combination therapy Q4W for 4 doses followed by durvalumab 20 mg/kg monotherapy Q4W.

Part 1B

Part 1B was an efficacy-gating cohort in immunotherapy-naïve patients with advanced HCC who had progressed on, were intolerant to, or had refused sorafenib-based therapy. A total of 25 patients (uninfected, HBV-infected, or HCV-infected) were enrolled to determine if there was sufficient evidence of clinical activity to warrant opening Part 2. All patients received tremelimumab 1 mg/kg × 4 doses + durvalumab 20 mg/kg Q4W followed by durvalumab 20 mg/kg monotherapy Q4W. Enrollment was monitored to achieve at least 12 patients who had refused sorafenib across Parts 1A and 1B and sufficient representation of patients by viral status, ie, uninfected, HBV-infected, or HCV-infected.

Parts 2 and 3

In Part 2A, patients with advanced HCC who had progressed on, were intolerant of, or refused sorafenib-based therapy, were stratified based on viral status (uninfected, HCV-infected, or HBV-infected) and programmed death ligand-1 (PD-L1) expression (positive, negative, or non-evaluable). Eligible patients were randomized in a 1:1:1 ratio within each stratum to 1 of the 3 treatment arms:

- D: durvalumab 20 mg/kg Q4W
- T: tremelimumab 10 mg/kg Q4W × 7 doses followed by every 12 weeks (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 an additional treatment regimen of durvalumab in combination with a higher dose of tremelimumab in immunotherapy-naïve patients with advanced HCC who had progressed on, were intolerant to, or had refused sorafenib-based therapy:

- T300+D: tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.

Part 3 was a dose expansion cohort in immunotherapy-naïve patients with advanced HCC who had progressed on, were intolerant to, or had refused sorafenib-based therapy. Eligible patients were stratified based on viral status (uninfected, HCV infected, or HBV infected) and sorafenib-based therapy (refusers or all others) and were randomized in a 2:2:1:2 ratio to each of the following 4 treatment arms:

- D: durvalumab 1500 mg Q4W
- T300+D: tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W
- T: tremelimumab 750 mg Q4W for 7 doses followed by Q12W
- T75+D: tremelimumab 75 mg Q4W × 4 doses + durvalumab 1500 mg Q4W, followed by durvalumab 1500 mg Q4W.

Following protocol amendment 5, based on the results from the pre-planned interim analysis evaluating tolerability and clinical activity in the current study, enrollment into the T75+D arm in Part 3 was closed and patients were randomized at a ratio of 2:1:2 into each of 3 treatment arms (D, T, and T300+D, respectively). Patients who had been randomized to T75+D before this protocol amendment could continue on assigned study treatment until confirmed PD or any other discontinuation criteria were met. If a patient had not completed or started all 4 doses of tremelimumab, the patient could either continue to complete the full schedule, or continue with durvalumab monotherapy only.

Tumor assessments were performed at Screening as baseline with follow-ups at Week 9 ± 1 week from the date of randomization, at Week 17 ± 1 week, at Week 25 ± 1 week and then every 8 weeks ± 1 week until confirmed PD or any other discontinuation criteria were met.

Part 4

Part 4 was a single arm evaluating the safety and efficacy of durvalumab in combination with bevacizumab, a vascular endothelial growth factor receptor (VEGFR) inhibitor in patients with advanced HCC who had not received any prior systemic therapy. The CSP provided for 100 patients to be recruited in Part 4. However, it was subsequently agreed that approximately 50 patients would provide sufficient data for the evaluation of safety in this cohort. Patients received durvalumab 1120 mg (15 mg/kg) + bevacizumab 15 mg/kg combination therapy every 3 weeks (Q3W).

Target subject population and sample size

Adult patients (aged ≥ 18 years/aged ≥ 20 years in Japan) with a diagnosis of advanced HCC confirmed pathologically or by non-invasive imaging methods and preserved liver function (Child-Pugh Score class A)

Patients must have had World Health Organization / Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and life-expectancy of at least 12 weeks. Patients had to be immunotherapy-naïve and had either progressed on, were intolerant to, or refused treatment with sorafenib or another approved VEGFR tyrosine kinase inhibitor (TKI).

A total of 433 patients were randomized/allocated to treatment:

- 40 patients in Part 1: 15 in Part 1A and 25 in Part 1B
- 332 patients in Parts 2 and 3: 125 in Part 2 (115 in Part 2A and 10 in Part 2B) and 207 in Part 3
- 14 patients in the China cohort
- 47 patients in Part 4.

One patient in China was enrolled in Part 2A before global recruitment in Part 2A was complete. This patient is included within the global cohort for Part 2A only.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Details of the IPs are presented in Table 2.

Table 2 Details of Investigational Products

Investigational product	Dosage form and strength	Manufacturer	Batch number
Durvalumab	50 mg/mL, solution for infusion after dilution, intravenous	AstraZeneca	CCI [redacted]
Tremelimumab	20 mg/mL, solution for infusion after dilution, intravenous	AstraZeneca	
Bevacizumab	25 mg/mL, solution for infusion, intravenous	Roche	

In Parts 1, 2, and 3, the duration of intravenous (IV) infusion was 1 hour (± 15 minutes) for durvalumab and 1 hour (± 15 minutes) for tremelimumab. For durvalumab + tremelimumab combination therapy, tremelimumab was administered first, and the durvalumab infusion started 1 hour (± 15 minutes) after the end of the tremelimumab infusion.

In Part 4, bevacizumab was administered according to the local prescribing information and clinical practice. The duration of the initial IV infusion was 90 minutes. If this was well tolerated, the second infusion was administered over 60 minutes. If well tolerated, subsequent infusions were administered over 30 minutes. The bevacizumab infusion started approximately 1 hour (maximum 2 hours) after the end of the durvalumab infusion.

Duration of treatment

Duration of treatment and retreatment (where permitted) of patients are summarized in Table 3.

Table 3 Duration of Study Treatment

Study part	Duration of treatment
Parts 1A, 1B, 2A, 2B, and 3, and China cohort	**Combination therapy: T300+D and T75+D** Following completion of combination therapy, patients received durvalumab monotherapy until any of the discontinuation criteria were met Patients who progressed on durvalumab monotherapy after completing their first 5 cycles could be retreated with the durvalumab and tremelimumab combination
Parts 2A and 3, and China cohort	**Durvalumab monotherapy** Durvalumab monotherapy continued until any of the discontinuation criteria were met
Part 2A and 3, and China cohort	**Tremelimumab monotherapy** Tremelimumab monotherapy continued until any of the discontinuation criteria were met
Part 4	**Combination therapy: D1120+B15** Combination therapy continued until any of the discontinuation criteria were met. Patients who progressed on combination therapy could continue treatment with durvalumab; bevacizumab was discontinued at initial radiological progression

D1120+B15, durvalumab 1120 mg (15 mg/kg) + bevacizumab 15 mg/kg Q3W; Q3W, every 3 weeks; Q4W, every 4 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.

Patients randomized to the T300+D and T75+D arms who completed their first 5 assigned dosing cycles (with clinical benefit per Investigator judgment), but subsequently had evidence of PD during the durvalumab monotherapy portion of the combination regimen, with or without confirmation according to Investigator assessments using Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1), were allowed to restart treatment with the combination therapy. Patients followed the same treatment guidelines as during the original treatment period and the same schedule of assessments and could only receive retreatment once. Crossover within the study was not permitted except for patients in the T75+D arm of Part 3 who could be retreated with the T300+D regimen with prior approval from the Sponsor's study physician. However, all 4 patients in the T75+D arm in Part 3 who underwent retreatment were retreated with T75+D, ie, no patients in the T75+D arm received retreatment with T300+D.

Treatment through progression was permitted, with the following exceptions:

- Patients with rapid tumor progression (based on Investigator opinion) or with symptomatic progression that required urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) were not eligible for continuing durvalumab and tremelimumab combination therapy.
- In Part 4, patients were permitted to continue durvalumab through progression but bevacizumab was discontinued at initial radiological progression.

For all patients treated through progression, the Investigator had to ensure patients did not have any significant, unacceptable or irreversible toxicities that indicated continuing or restarting treatment would not further benefit the patients.

In Part 4, patients who, in the opinion of the Investigator, had an adverse event (AE) attributed to bevacizumab that met interruption or discontinuation criteria for bevacizumab, could continue the scheduled durvalumab dosing regimen. However, if an AE was attributed to durvalumab and met the interruption or discontinuation criteria for durvalumab, both agents were interrupted or discontinued according to toxicity management guidelines.

Patients who could not continue treatment after PD were followed up for survival. 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.

Statistical methods

Safety data were summarized using the Safety Analysis Set, except dose-limiting toxicity (DLT), which was summarized in Part 1A for the DLT Evaluable Set. Pharmacokinetic data were summarized and analyzed based on the Pharmacokinetic (PK) Analysis Set. Anti-drug antibody (ADA) Evaluable Sets were defined separately for durvalumab, tremelimumab, and bevacizumab, and data summarized for the respective samples. Study population and demography data were summarized based upon the Full Analysis Set (FAS).

Efficacy data were summarized and analyzed based on the FAS. In addition, objective response rate (ORR) was analyzed for the Response Evaluable Population. Objective response rate, including 95% confidence intervals (CIs), was presented; disease control rate (DCR) with exact 95% CIs was estimated. Time-to-event endpoints, including duration of response (DoR), time to response (TTR), progression-free survival (PFS), time to progression (TTP), and overall survival (OS), were analyzed using the Kaplan-Meier method. Only patients with an objective response (best objective response [BOR] of complete response [CR] or partial response [PR]) were included in the analysis of DoR. In addition, efficacy subgroup analyses by treatment arm were defined prior to database lock and conducted for the following subgroups of the FAS: PD-L1 expression level, etiology of liver disease, prior treatment with sorafenib/VEGFR TKI, CCI macrovascular invasion (MVI), and extrahepatic spread (EHS).

In Part 1, data for Parts 1A and 1B were pooled for the analyses of efficacy and safety. In Parts 2 and 3, data were pooled by treatment arm (D, T300+D, T, and T75+D) for analyses of efficacy and safety.

Study population

Across the study, 632 patients were enrolled (consented) at 45 study sites in 9 countries in Asia, Europe and North America. A total of 433 patients were randomized/allocated to treatment at 43 sites in 9 countries.

Part 1

Forty patients were allocated to, and received treatment with, T75+D. At the final DCO, 95.0% of patients had discontinued treatment, primarily due to HCC disease progression (67.5%) or AEs (12.5%). Five (12.5%) patients were ongoing in the study at the final DCO, including 2 (5.0%) patients who were continuing to receive study treatment. Patients had a median age at study entry of 60.5 years (range: 47 to 87 years), 75.0% were male, and most were Asian (47.5%) or White (37.5%). At baseline, 25.0% of patients were HBV-positive, 25.0% were HCV-positive, and 50.0% were uninfected.

Parts 2 and 3

In Parts 2 and 3, 332 patients were randomized/allocated to treatment at 36 study sites across 9 countries in Asia, Europe and North America; 104 patients were randomized to the D arm, 75 patients were randomized/allocated to the T300+D arm, 69 patients were randomized to the T arm, and 84 patients to the T75+D arm.

Of the 332 patients randomized/allocated to treatment, 326 received study treatment: 101 (97.1%) in the D arm, 74 (98.7%) in the T300+D arm, 69 (100.0%) in the T arm, and 82 (97.6%) in the T75+D arm.

Overall, the study population was representative of the intended target population of patients with advanced HCC and demographics and disease characteristics were generally balanced across the 4 treatment arms.

At study entry, the overall median age was 64.0 years (range, 26 to 89 years) with 47.3% of patients aged 65 years and above. The majority of patients were male (85.5%), 35.5% of patients were White, 55.7% were Asian, and 43.7% were included in the Asian region (excluding Japan).

At screening, 71.7% of patients overall had Barcelona Clinic Liver Cancer stage C, 58.7% had EHS and 25.0% had MVI. Liver disease at baseline was rated as Child-Pugh class A/5 or A/6 for the majority of patients (68.7% and 28.9%, respectively); 37.3% of patients were HBV-positive, 28.9% HCV-positive, and the remaining 33.7% of patients were not infected with either virus (determined by the virology laboratory assessments at screening). Overall, 49.1% of patients had tumors that were PD-L1 tumor immune percentage (TIP) ≥ 1% at baseline and 38.6% were TIP < 1%; values were missing for the remaining 12.3% of patients.

Overall, 66.3% of patients had received prior systemic therapy with sorafenib/VEGFR TKI-based therapy. Overall, 15.4% of patients were intolerant to sorafenib (14.4%, 16.0%, 20.3%, and 11.9% in the D, T300+D, T, and T75+D arms, respectively) and 32.8% refused sorafenib (35.6%, 26.7%, 36.2%, and 32.1% in the D, T300+D, T, and T75+D arms, respectively). As expected, patients who received sorafenib or other approved VEGFR TKI-based therapy before study treatment presented with more advanced HCC disease than first-line therapy patients.

A total of 93 (92.1%) patients in the D arm, 67 (90.5%) in the T300+D arm, 66 (95.7%) in the T arm, and 78 (95.1%) in the T75+D arm discontinued study treatment, most frequently due to PD (D: 67.3%, T300+D: 67.6%, T: 59.4%, T75+D: 70.7%) and AE (D: 9.9%, T300+D: 10.8%, T: 14.5%, T75+D: 9.8%).

At the final DCO, 20 (19.2%) patients in the D arm, 23 (30.7%) patients in the T300+D arm, 12 (17.4%) in the T arm, and 15 (17.9%) patients in the T75+D arm remained in the study; 8 (7.9%) patients in the D arm, 7 (9.5%) patients in the T300+D arm, 3 (4.3%) in the T arm, and 4 (4.9%) patients in the T75+D arm remained on study treatment.

China Cohort

Fourteen patients were randomized to treatment in the China cohort and 13 received randomized treatment, 3 with D, 5 with T, and 5 with T75+D. At the final DCO, all patients had discontinued treatment and all had discontinued the study. Patients had a median age at study entry of 49.5 years (range: 26 to 66 years), 92.9% were male, and all were Asian.

Part 4

Forty-seven patients were allocated to, and received treatment with, D1120+B15. At the final DCO, 78.7% of patients had discontinued treatment, primarily due to HCC disease progression (55.3%) and 55.3% were ongoing in the study, including 21.3% who were continuing to receive study treatment. Patients had a median age at study entry of 64.0 years (range: 37 to 84 years), 87.2% were male, and 83.0% were Asian. At baseline, 51.1% of patients were HBV-positive, 12.8% were HCV-positive, and 36.2% were uninfected.

Summary of efficacy results

All efficacy data are presented for the FAS. [redacted]

Part 1

At the final DCO, 12.5% of patients were alive and in survival follow-up. Median duration of follow-up for censored patients was 50.73 months. Median OS was 12.58 months, and the OS

rate was 52.1% at 12 months and 27.4% at 24 months. The confirmed ORR by Investigator assessment according to RECIST 1.1 was 20.0%, and all 8 patients with a confirmed objective response had a BOR of PR. For patients with an objective response, confirmed median DoR from the onset of response by Investigator assessment according to RECIST 1.1 was 16.66 months, with 62.5% of patients remaining in response at 12 months. Median time to onset of response was 2.68 months. At the final DCO, the proportion of patients with PFS events (RECIST 1.1 progression or death) based on Investigator assessment was 90.0%; median PFS was 3.52 months and median TTP was 3.68 months.

Parts 2 and 3

Except where indicated otherwise, data reported in this section are for Parts 2 and 3 combined. The dosing regimens in the D, T, and T75+D arms of Part 2A and the T300+D arm in Part 2B are equivalent to those in the D, T300+D, T, and T75+D arms in Part 3. Data from patients in Parts 2 and 3 who received the same dosing regimen were therefore combined for the purpose of analysis. For example, patients who received durvalumab monotherapy in Part 2A or Part 3 are presented as the D arm in Parts 2 and 3 combined.

Overall Survival

At the final DCO, the percentage of patients alive and in survival follow-up was highest in the T300+D arm (30.7%), followed by the D (19.2%), T75+D arm (17.9%), and T (17.4%) arms (Table 4).

The Kaplan-Meier estimate of median OS was highest for patients receiving regimens with higher doses of tremelimumab, T300+D or T (17.05 months) compared to patients receiving D (12.91 months) and T75+D (11.30 months) (Table 4).

The OS curve for the T300+D arm showed a separation from the D arm starting at approximately 2 months after randomization/treatment allocation. The OS benefit in the T300+D arm was sustained over time, as supported by numerically higher OS rate estimates than the D arm at 12, 18, and 24 months (Table 4 and Figure 2). Overall, data suggest that the T300+D regimen provided clinical benefit in terms of OS compared to D.

The OS curves for the T300+D and T arms overlap for approximately the first 18 months prior to curve separation and a higher OS rate at 24 months in favor of T300+D, suggesting T300+D offers additional clinical benefit when compared with T (Figure 2).

In accordance with the CSP, the safety run-in for the T300+D arm in Part 2B was not initiated in parallel with the other 3 treatment arms but, at the final DCO, the median duration of follow-up in censored patients in all 4 arms in Parts 2 and 3 combined ranged from 23.18 months to 31.03 months. In addition, data from Part 3, where stratification factors,

duration of follow-up, and data maturity were similar and all arms were randomized in parallel are consistent with Parts 2 and 3 combined.

Median OS estimates were similar between the D and T75+D arms (Table 4) and no meaningful separation between these 2 survival curves was observed (Figure 2). Data suggest the T75+D regimen did not provide additional clinical benefit in terms of OS compared to D, thus supporting the decision to close enrollment into the T75+D arm in Part 3 following protocol amendment 5.

Table 4 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.

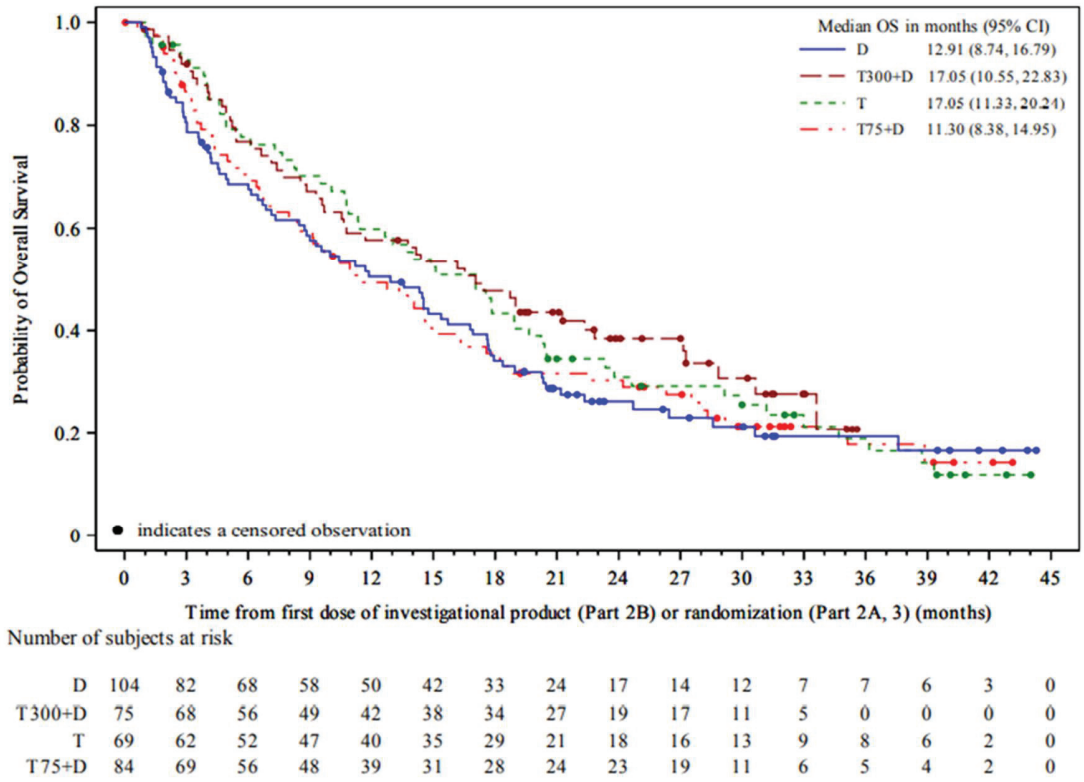
[d] Other reasons (1 patient each): psychiatric issues and study compliance, adverse event, and patient did not receive treatment.

[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 2 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 Q12W; 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.

RECIST 1.1-based Efficacy Variables

PFS: At the final DCO, the proportion of patients with PFS events (RECIST 1.1 progression based on blinded independent central review [BICR] or death) was lowest in the T300+D arm (77.3%) compared to 85.6% in the D arm, 84.1% in the T arm, and 85.7% in the T75+D arm. The Kaplan-Meier estimates of median PFS were numerically similar for the 4 treatment arms: T300+D arm (2.17 months), D arm (2.07 months), T arm (2.69 months), and T75+D arm (1.87 months).

ORR: Patients in the T300+D arm showed the highest confirmed ORR based on BICR per RECIST 1.1 (24.0%), which was more than twice the response rates in the other 3 treatment

arms. Confirmed ORR was numerically similar for the D (11.5%), T (7.2%), and T75+D (9.5%) arms.

In Part 3 only, where all patients were randomized according to the same stratification factors and data follow-up and maturity were similar for the D, T300+D, and T arms, confirmed ORR results based on BICR according to RECIST 1.1 were consistent with those from Parts 2 and 3 combined: patients in the T300+D arm showed the highest confirmed ORR (24.6%), while confirmed ORR was numerically similar for the D, T and T75+D arms (range: 6.1% to 10.9%).

DoR: At the final DCO, median DoR based on BICR confirmed response per RECIST 1.1 exceeded 1 year for all 4 treatment arms and was notably longer for patients in the T arm (23.95 months) than those in the D (14.95 months), T300+D (18.43 months), or T75+D (13.21 months) arms. The percentage of patients remaining in response at 12 months was highest in the T300+D arm (64.6%), followed by the T (60.0%), T75+D (58.3%), and D (56.3%) arms.

TTR: The median TTR (based on BICR confirmed response per RECIST 1.1) was 1.81 months in the T arm, 2.28 months in the T300+D arm, 2.86 months in the T75+D arm and 3.65 months in the D arm.

BOR: 24.0% of patients in the T300+D arm achieved a confirmed BOR of either CR or PR based on BICR, compared to 11.5% in the D arm, 7.2% in the T arm, and 9.5% in the T75+D arm. The majority of patients who responded had a PR (22.7%, 11.5%, 7.2%, and 7.1% of patients in the T300+D, D, T, and T75+D arms, repectively). A CR was achieved by 2 (2.4%) patients in the T75+D arm and 1 (1.3%) patient in the T300+D arm.

DCR: The confirmed DCR, based on BICR per RECIST 1.1, was highest in the T300+D (45.3%) and T (49.3%) arms compared to the D (37.5%) and T75+D (36.9%) arms.

TTP: The median TTP (based on BICR confirmed response per RECIST 1.1) was longest in the T300+D arm (3.71 months) compared to the other 3 treatment arms (2.10 months, 2.76 months, and 1.87 months in the D, T, and T75+D arms, respectively).

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China Cohort

Thirteen patients randomized in the China cohort received study treatment (3 in the D arm, 5 in the T arm, and 5 in the T75+D arm). Clinical activity was observed in the D arm, with 1 (33.3%) patient achieving a confirmed PR to treatment based on Investigator assessment according to RECIST 1.1. No patients in the T or T75+D arms were reported to have a confirmed response (CR or PR) based on Investigator assessment according to RECIST 1.1.

Part 4

At the final DCO, 26 (55.3%) patients were alive and in survival follow-up. Median OS was not reached; the OS rate at 12 months was 71.8%. The confirmed ORR based on BICR according to RECIST 1.1 was 21.3%. One (2.1%) patient had a BOR of CR and 9 (19.1%) patients had a BOR of PR. For patients with an objective response, confirmed median DoR from the onset of response based on Investigator assessment according to RECIST 1.1 was not reached; 56.0% of patients remained in response at 12 months. Median time to onset of response was 2.10 months.

Median PFS based on BICR according to RECIST 1.1 was 4.17 months; median TTP was 4.30 months.

Summary of CCI [redacted] **results**

CCI [redacted]

Part 1

CCI

[redacted]

Parts 2 and 3

CCI

[redacted]

Part 4

CCI

[redacted]

CCI

Summary of CCI **results**

CCI

Summary of CCI **results**

CCI

Summary of safety results

Part 1

Exposure

In Part 1, where all patients received T75+D, the extent of exposure in terms of total treatment-years was 28.4 treatment-years for durvalumab and 9.5 treatment-years for tremelimumab. Median total treatment duration was 4.6 months and 3.6 months for durvalumab and tremelimumab, respectively. The median number of treatment cycles received was 5.0 for durvalumab and 3.5 for tremelimumab.

Adverse Events

Most of the 40 patients in Part 1 experienced at least 1 AE, and 65% of patients experienced at least 1 AE that was considered treatment-related by the Investigator. The majority of the most common treatment-related AEs were Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2; treatment-related CTCAE Grade 3 or 4 AEs were reported for 25% of patients. Three preferred terms (PTs) were reported as CTCAE Grade 3 or 4 in more than 1 patient: alanine aminotransferase increased, aspartate aminotransferase increased, and lipase increased, each reported in 2 (5.0%) patients.

There were no treatment-related AEs leading to death; 2 (5.0%) patients had a fatal AE which was not treatment-related. Treatment-related serious adverse events (SAEs) were reported for 17.5% of patients and 12.5% of patients discontinued study treatment due to a treatment-related AE. Dose-limiting toxicity was assessed in Part 1A only. No DLTs were reported.

Laboratory Parameters

Clinical laboratory data collected throughout the study did not raise any safety concerns. No significant changes in hematology and biochemistry parameters were observed in continuous parameters and grade shifts. Most hematology and biochemistry parameter grade shifts were by only 1 CTCAE grade.

Three (7.5%) patients met biochemical potential Hy's Law (PHL) criteria (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] $\geq 3 \times$ upper limit of normal [ULN] and bilirubin $\geq 2 \times$ ULN). All 3 cases were subject to further investigation by an independent expert in drug-induced liver injury. Following detailed independent review, no cases were confirmed as true Hy's Law cases due to factors indicating the presence of an alternative etiology, complications of HCC progression, and/or a pattern of cholestatic liver injury at the time when PHL criteria were met. However, the role of durvalumab and tremelimumab could not be completely excluded in 1 case.

Although changes in thyroid function were observed during study treatment, there was no evidence to suggest these had a significant clinical impact. Adverse events of hyperthyroidism and hypothyroidism were uncommon, all were maximum CTCAE Grade ≤ 2, and none led to discontinuation of study treatment.

Parts 2 and 3

Exposure

The extent of exposure to durvalumab in terms of total treatment-years was higher in the D arm (58.7 treatment-years) than the other 2 treatment arms (range: 43.0 to

46.8 treatment-years) reflecting the larger number of patients in the D arm. The extent of exposure to tremelimumab in the T arm was 42.6 treatment-years.

The median total treatment duration was similar for the durvalumab component of the T300+D arm and for D monotherapy (3.7 months) but shorter for the durvalumab component of the T75+D arm (2.4 months), likely due to enrollment in this arm closing in Part 3 in November 2018 (protocol amendment 5). Across the treatment arms and for both the durvalumab and tremelimumab components (when given as repeat doses), there was little difference between the median actual treatment duration and the median total treatment duration, ie, the impact of dose delays was small.

The median number of treatment cycles received (4 treatment cycles) was similar for durvalumab in the D and T300+D arms and for tremelimumab in the T arm, but lower for durvalumab in the T75+D arm (2.5 treatment cycles).

Six patients in the T300+D arm were retreated with their assigned T300+D combination treatment and 4 patients in the T75+D arm were retreated with their assigned T75+D combination treatment.

Adverse Events

The observed AE profile of T300+D in Parts 2 and 3 was consistent with the known safety profile of durvalumab monotherapy, durvalumab in combination with tremelimumab (T75+D), and tremelimumab monotherapy in the wider clinical program.

As indicated in Table 5, with the exception of fatal AEs, which were infrequent in all treatment arms, AEs in most categories were more frequent in the T arm than in the other 3 treatment arms.

- AEs considered treatment-related by the Investigator occurred more frequently in the T (84.1%) and T300+D (82.4%) arms than the T75+D (70.7%) and D (61.4%) arms.
- AEs of CTCAE Grade 3 or 4 were more frequent in the T arm (66.7%) compared to the other 3 arms (57.4% to 61.0%). Grade 3 or 4 events considered treatment-related by the Investigator were also most frequent in the T arm (43.5%) compared to the other 3 arms (20.8% to 36.5%).
- The frequency of SAEs was higher in the T arm (52.2%) than in the other 3 arms (43.2% to 45.1%); a similar pattern was observed for treatment-related SAEs (24.6% for the T arm vs. 10.9% to 18.9% for the other 3 treatment arms).
- The frequency of AEs that led to study treatment discontinuation was higher in the T arm (20.3%) than in the other 3 arms (13.5% to 14.6%); a similar pattern was observed for treatment-related AEs that led to study treatment discontinuation (14.5% for the T arm vs. 6.1% to 12.2% for the other 3 treatment arms).

- The incidence of AEs leading to dose delay was higher in patients treated with tremelimumab (43.5% in the T arm, 34.1% in the T75+D arm, and 28.4% in the T300+D arm) than those treated with durvalumab monotherapy (18.8%).

Table 5 Adverse Events in Any Category in Parts 2 and 3 (Safety Analysis Set)

	Number (%) of patients [a]			
Patients with:	**D (N = 101)**	**T300+D (N = 74)**	**T (N = 69)**	**T75+D (N = 82)**
Any AE	95 (94.1)	73 (98.6)	67 (97.1)	80 (97.6)
Any AE causally-related to treatment [b]	62 (61.4)	61 (82.4)	58 (84.1)	58 (70.7)
Any AE of CTCAE Grade 3 or 4	58 (57.4)	44 (59.5)	46 (66.7)	50 (61.0)
Any AE of CTCAE Grade 3 or 4, causally-related to treatment [b]	21 (20.8)	27 (36.5)	30 (43.5)	21 (25.6)
Any AE with outcome of death	4 (4.0)	4 (5.4)	2 (2.9)	2 (2.4)
Any AE with outcome of death, causally-related to treatment [b]	3 (3.0)	2 (2.7)	0	1 (1.2)
Any SAE (including events with outcome of death)	45 (44.6)	32 (43.2)	36 (52.2)	37 (45.1)
Any SAE (including events with outcome of death), causally-related to treatment [b]	11 (10.9)	14 (18.9)	17 (24.6)	13 (15.9)
Any AE leading to discontinuation of study treatment	14 (13.9)	10 (13.5)	14 (20.3)	12 (14.6)
Any AE leading to discontinuation of study treatment, causally-related to treatment [b]	9 (8.9)	9 (12.2)	10 (14.5)	5 (6.1)
Any AE requiring treatment with systemic steroids, causally-related to treatment [b]	10 (9.9)	20 (27.0)	18 (26.1)	20 (24.4)
Any AE leading to dose delay [c]	19 (18.8)	21 (28.4)	30 (43.5)	28 (34.1)
Any infusion reaction AE [b]	1 (1.0)	1 (1.4)	2 (2.9)	1 (1.2)
Immune-mediated AEs				
Any imAE	17 (16.8)	25 (35.8)	17 (24.6)	23 (28.0)
Any imAE causally-related to treatment [b]	16 (15.8)	22 (29.7)	16 (23.2)	23 (28.0)
Any imAE of CTCAE Grade 3 or 4	6 (5.9)	10 (13.5)	11 (15.9)	10 (12.2)
Any imAE of CTCAE Grade 3 or 4, causally-related to treatment [b]	6 (5.9)	9 (12.2)	11 (15.9)	10 (12.2)
Any imAE with outcome of death	2 (2.0)	0	0	0
Any imAE with outcome of death, causally-related to treatment [b]	2 (2.0)	0	0	0
Any immune-mediated SAE (including events with outcome of death)	7 (6.9)	7 (9.5)	10 (14.5)	9 (11.0)

Patients with:	Number (%) of patients [a]			
	D (N = 101)	T300+D (N = 74)	T (N = 69)	T75+D (N = 82)
Any immune-mediated SAE (including events with outcome of death), causally-related to treatment [b]	7 (6.9)	6 (8.1)	10 (14.5)	9 (11.0)
Any imAE leading to discontinuation of study treatment	6 (5.9)	4 (5.4)	3 (4.3)	5 (6.1)
Any imAE requiring treatment with systemic corticosteroids	8 (7.9)	22 (29.7)	16 (23.2)	16 (19.5)
Standardized MedDRA Queries of Hepatic Disorders				
Any SMQ of Hepatic Disorder	56 (55.4)	37 (50.0)	38 (55.1)	39 (47.6)
Any SMQ of Hepatic Disorder causally-related to treatment [b]	20 (19.8)	23 (31.1)	13 (18.8)	18 (22.0)
Any SMQ of Hepatic Disorder of CTCAE Grade 3 or 4	29 (28.7)	24 (32.4)	17 (24.6)	25 (30.5)
Any SMQ of Hepatic Disorder of CTCAE Grade 3 or 4, causally-related to treatment [b]	7 (6.9)	12 (16.2)	7 (10.1)	10 (12.2)

[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 category.

[b] As assessed by the Investigator. Missing responses were counted as treatment-related.

[c] AEs for which the case report form had 'Drug Interrupted' or 'Dose Omitted' under 'Action taken' with study drug.

AEs reported are all AEs with onset or worsening on or after the first dose up to 90 days after the last dose of study medication, or the initiation of subsequent anticancer therapy (date of first subsequent anticancer systemic therapy), whichever occurred first.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events (version 4.03); D, durvalumab monotherapy 1500 mg (20 mg/kg) Q4W; imAE, immune-mediated adverse event; MedDRA, Medical Dictrionary for Regulatory Activities; Q4W, every 4 weeks; SAE, serious adverse event; SMQs, Standardized MedDRA Queries; 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.

All Adverse Events

Across the 4 treatment arms, the majority of AEs reported were in the system organ classes (SOCs) Gastrointestinal Disorders and Skin and Subcutaneous Disorders, plus elevated liver enzymes and elevated pancreatic enzymes. Most cutaneous AEs were mild to moderate in severity.

- The 3 most commonly reported AEs in the D arm were aspartate aminotransferase increased, fatigue, and alanine aminotransferase increased, all of which were reported by a similar proportion of patients in the tremelimumab-containing arms.

- The PTs reported at a higher frequency (≥ 10% difference) in 1 or more tremelimumab-containing arm compared to the D arm were pruritus, diarrhoea, rash, pyrexia, lipase increased, and headache. In addition, amylase increased was reported by a greater proportion of patients in the T300+D arm compared to the D arm, and diarrhoea was more frequent in the T arm compared to all other treatment arms.

Treatment-related Adverse Events

The 4 most commonly reported treatment-related AEs in the D arm were pruritus, hypothyroidism, diarrhoea, and fatigue. Pruritus was also the most common treatment-related AE in 3 of the 4 treatment arms, and was more frequent in the T300+D and T arms than the D arm. All treatment-related AEs of pruritus were mild to moderate in severity, with the exception of 1 Grade 3 event in the T arm.

Diarrhoea was reported by a higher proportion of patients in the T arm than any other arm. Hypothyroidism was less frequent in the T arm than the other treatment arms.

Other treatment-related AEs reported at a higher frequency (≥ 10% difference) in 1 or more tremelimumab-containing arms compared to the D arm were rash, nausea, amylase increased, decreased appetite, and lipase increased. Rash was the most common treatment-related AE in the T300+D arm and the only such event reported at a higher frequency (≥ 10% difference) in the T300+D arm than the other 3 treatment arms. Treatment-related rash was maximum CTCAE Grade 1 or 2 in the majority of patients.

Adverse Events by Severity

The most common AEs of maximum CTCAE Grade 3 or 4 were elevated liver enzymes, elevated pancreatic enzymes, and gastrointestinal events.

Aspartate aminotransferase increased was the most common AE of maximum CTCAE Grade 3 or 4 and the most common treatment-related Grade 3 or 4 AE in all 4 treatment arms but was more frequent in the tremelimumab-containing treatment arms than the D arm.

Lipase increased was the only AE of maximum CTCAE Grade 3 or 4 reported more frequently (≥ 10% difference) in 1 or more of the tremelimumab-containing arms compared to the D arm. Diarrhoea of maximum CTCAE Grade 3 or 4 was more common in the T arm compared to any other treatment arm.

Across the 4 treatment arms, AEs of maximum CTCAE Grade 3 or 4 considered treatment-related were mainly driven by elevated liver and pancreatic enzymes.

Overall, the treatment-related PTs reported and key differences between the tremelimumab-containing arms and the D arm were consistent with the trends observed for all AEs of maximum CTCAE Grade 3 or 4

Fatal Adverse Events

In line with expectations for this patient population, fatal AEs occurred in 2.4% to 5.4% of patients in each of the 4 treatment arms. Overall, 6 (1.8%) patients in the Safety Analysis Set had a fatal AE considered treatment-related by the Investigator, including 5 events with pulmonary or hepatic causes: pneumonitis, hepatic failure, and hepatic function abnormal in the D arm, pneumonia and death in the T300+D arm, and hepatic failure in the T75+D arm. The patient who died of an unknown cause discontinued treatment due to documented rapid disease progression after 1 treatment cycle. Causality was not recorded by the Investigator.

Although the role of durvalumab cannot be excluded in 2 of these fatal events (hepatic failure and hepatic function abnormal), all patients had advanced underlying HCC and these events do not raise any new safety concerns.

Serious Adverse Events

The majority of SAEs reported were in the SOCs Gastrointestinal Disorders (all arms) and Hepatobiliary Disorders (D arm). Serious AEs of elevated liver or pancreatic enzymes were rare and there were no major differences in the type and frequency of SAEs reported between the T300+D arm and the other arms. Hepatic function abnormal was more common in the D arm, and diarrhoea in the T arm. Other than diarrhoea, the type and frequency of SAEs was similar for the 3 tremelimumab-containing treatment arms.

Three treatment-related SAEs were reported by more than 2 patients in any treatment arm (hepatic function abnormal in 4 [4.0%] patients in the D arm, colitis in 3 [4.1%] patients in the T300+D arm, and diarrhoea in 6 [8.7%] patients in the T arm. Other than diarrhoea, there were no major differences in the type and frequency of treatment-related SAEs between the 3 tremelimumab-containing treatment arms, although observations should be viewed with caution due to the small patient numbers.

Adverse Events Leading to Study Treatment Discontinuation

Across treatment arms, most AEs leading to discontinuation of study treatment were CTCAE Grade 3; 3 AEs leading to discontinuation of study treatment had an outcome of death (CTCAE Grade 5) (hepatic function abnormal in the D arm, pneumonia in the T300+D arm, and haemorrhagic stroke in the T75+D arm; hepatic function abnormal and pneumonia were considered treatment-related by the Investigator).

Overall, the number of AEs leading to discontinuation of study treatment was low and consistent with prior experience with durvalumab and/or tremelimumab. The only AE leading to discontinuation of study treatment in more than 2 patients in any treatment arm was hepatic function abnormal (3 patients in the D arm). Three treatment-related AEs led to study treatment discontinuation in more than 1 patient in any treatment arm: hepatic function abnormal, hypophysitis, and diarrhoea.

Immune-mediated Adverse Events

Most categories of immune-mediated adverse event (imAE) (all imAEs, treatment-related imAEs, Grade 3 or 4 imAEs, SAEs and treatment-related SAEs) were reported at a higher frequency in the tremelimumab-containing treatment arms than the D arm. For the other AE categories, patient numbers were too low for reliable comparisons. The frequency of imAEs that led to discontinuation of study treatment was low (≤ 6 patients per arm) and comparable across treatment arms. Two (2.0%) patients in the D arm died due to imAEs (pneumonitis and hepatic function abnormal).

A higher proportion of patients in the tremelimumab-containing treatment arms compared to the D arm received systemic corticosteroids or high-dose corticosteroids. Across treatment arms, the most frequently reported AEs that required systemic corticosteroids were diarrhoea (14 patients), aspartate aminotransferase increased (8), rash (7), hepatic function abnormal (7), and alanine aminotransferase increased (5).

Hepatic Standardized MedDRA Queries

Review of hepatic Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) revealed no evidence that patients in any treatment arm experienced events suggestive of drug-induced liver injury:

- Hepatic SMQ AEs and hepatic SMQ AEs of maximum CTCAE Grade 3 or 4 were reported at a comparable frequency across the 4 treatment arms (47.6% to 55.4% and 24.6% to 32.4%, respectively).
- The most frequently reported hepatic SMQ AEs were aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, and ascites, which were reported at a similar frequency for all 4 treatment arms.
- Hepatic function abnormal was more frequent in the D arm and oesophageal varices haemorrhage was more frequent in the T arm compared to the other treatment arms.
- Hepatitis and hepatic failure were infrequent (≤ 1 to 2 patients per arm). With 1 exception, all were CTCAE Grade ≥ 3.

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Laboratory Parameters

Hematology and clinical chemistry data collected throughout the study did not raise any safety concerns. No significant changes in hematology and biochemistry parameters between treatment arms and over time were observed in continuous parameters and grade shifts. Most hematology and biochemistry parameter grade shifts were by only 1 CTCAE grade.

Thirty-four patients met biochemical PHL criteria (ALT or AST ≥ 3 × ULN and bilirubin ≥ 2 × ULN), with a higher proportion in the D arm (14.9%) than the tremelimumab-containing arms (5.4% to 12.2%). In addition, 1 patient met the biochemical criteria for PHL more than 90 days after their last dose of IP and 2 patients had clinically meaningful elevations in ALT/AST and total bilirubin that occurred sequentially, but not concurrently. All 37 identified cases were subject to further investigation by an independent expert in drug-induced liver injury. Following detailed independent review, no cases were confirmed as true Hy's Law cases due to factors indicating the presence of an alternative etiology, complications of HCC progression, and/or a pattern of cholestatic liver injury at the time when PHL criteria were met. However, the role of durvalumab and/or tremelimumab could not be completely excluded in 4 cases.

Immune-mediated events of hyperthyroidism and hypothyroidism are important known risks of durvalumab monotherapy and of durvalumab in combination with tremelimumab and there was some evidence of effects on thyroid function for all 4 treatment arms in Parts 2 and 3. In the T300+D arm, 33.8% of patients had low on-treatment thyroid-stimulating hormone (TSH) levels suggestive of hyperthyroidism at some point during study treatment compared to between 15.8% to 20.7% in the other arms; across all 4 treatment arms, baseline TSH had been above the lower limit of normal for the majority of these patients. Additionally, free thyroxine changed from normal to high (maximum value) during study treatment more frequently in the T300+D arm (32.3% of patients) than the other arms (8.3% to 22.5%). Similarly, TSH changed from normal to low (minimum value) during study treatment more frequently in the T300+D arm (32.8% of patients) than the other arms (14.6% to 21.9%).

Although changes in thyroid function were observed during study treatment, there was no evidence to suggest these had a significant clinical impact. Grade 3 or 4 treatment-related hyperthyroidism and hypothyroidism were each reported in 1 patient only, and no more than 1 patient per treatment arm discontinued study treatment due to either hyperthyroidism or hypothyroidism.

Other Safety Parameters

No significant changes in vital signs, electrocardiograms, Child-Pugh classification, or ECOG PS were observed between treatment arms or over time.

China Cohort

Exposure

The extent of exposure in terms of total treatment-years was 1.5 treatment-years for the D arm, 1.0 treatment-years for the T arm, and 1.2 treatment-years for durvalumab and 1.1 treatment-years for tremelimumb in the T75+D arm. Median total treatment duration was

1.8 months for the D arm, 1.9 months for the T arm, and 3.7 months for both durvalumab and tremelimumab in the T75+D arm.

Adverse Events

All 13 patients treated in the China cohort experienced at least 1 AE, with 84.6% of patients across the 3 treatment arms experiencing at least 1 AE that was considered treatment-related by the Investigator. Four treatment-related AEs were reported in more than 1 patient in any of the 3 treatment arms: alanine aminotransferase increased, aspartate aminotransferase increased, cough, and pyrexia. There were no fatal AEs. Across the 3 treatment arms, 4 (30.8%) patients had a treatment-related SAE and 1 (7.7%) discontinued study treatment due to a treatment-related AE.

Laboratory Parameters

Clinical laboratory data collected throughout the study in this small cohort did not raise any safety concerns.

One (20.0%) patient in the T75+D arm met biochemical PHL criteria (ALT or AST $\geq 3 \times$ ULN and bilirubin $\geq 2 \times$ ULN) and was subject to further investigation by an independent expert in drug-induced liver injury. Following detailed independent review, this case was not confirmed as a true Hy's Law case due to factors indicating the presence of an alternative etiology, complications of HCC progression, and/or a pattern of cholestatic liver injury at the time when PHL criteria were met.

There was no evidence that changes in thyroid function observed during study treatment had a significant clinical impact.

Part 4

Exposure

The extent of exposure in terms of total treatment-years was 28.0 treatment-years for durvalumab and 25.0 treatment-years for bevacizumab. Median total treatment duration was 6.2 months for durvalumab and 4.1 months for bevacizumab. The median number of treatment cycles received was 9.0 for durvalumab and 6.0 for bevacizumab.

Adverse Events

Most of the 47 patients in Part 4 experienced at least 1 AE, with 70.2% of patients experiencing at least 1 AE that was considered treatment-related by the Investigator. Four (8.5%) patients experienced CTCAE Grade 3 or 4 AEs that were considered treatment-related by the Investigator (all Grade 3), but no Grade 3 AEs were reported by more than 1 patient. There were no fatal AEs. Five (10.6%) patients had a treatment-related SAE and 3 (6.4%) discontinued study treatment due to a treatment-related AE.

Laboratory Parameters

Clinical laboratory data collected throughout the study did not raise any safety concerns.

Three (6.4%) patients met biochemical PHL criteria (ALT or AST ≥ 3 × ULN and bilirubin ≥ 2 × ULN). One additional patient had clinically meaningful elevations in ALT/AST and total bilirubin that occurred sequentially, but not concurrently. All 4 cases were subject to further investigation by an independent expert in drug-induced liver injury. Following detailed independent review, no cases were confirmed as a true Hy's Law case due to factors indicating the presence of an alternative etiology, complications of HCC progression, and/or a pattern of cholestatic liver injury at the time when PHL criteria were met.

Although changes in thyroid function were observed during study treatment, there was no evidence to suggest these had a significant clinical impact. Adverse events of hyperthyroidism and hypothyroidism were uncommon, all were maximum CTCAE Grade ≤ 2, and none led to discontinuation of study treatment.

Conclusions

Study D4190C00022 demonstrated a positive risk-benefit profile for T300+D in patients with advanced HCC compared with both high-dose tremelimumab monotherapy and durvalumab monotherapy:

- The safety and tolerability of durvalumab and tremelimumab administered as monotherapy and in combination were generally consistent with that observed in previous studies with durvalumab and tremelimumab across several indications. No new safety findings were observed in patients with advanced HCC. Similarly, the combination of durvalumab with bevacizumab was found to be tolerable in patients with advanced HCC with no safety signals identified for durvalumab or bevacizumab.
- The priming dose regimen T300+D showed a positive risk-benefit profile. The overall pattern of AEs in patients with advanced HCC was consistent with the known safety profile of durvalumab in combination with tremelimumab and no new safety risks were identified beyond those known for durvalumab in combination with tremelimumab 75 mg × 4 doses. With regard to efficacy, the T300+D combination offered clinically meaningful and durable benefits compared to durvalumab monotherapy.
- At the final analysis, median OS was 17.05 months in both the T300+D and T arms compared with 12.91 months in the D arm and 11.30 months in the T75+D arm. Other secondary efficacy endpoints (TTR, DCR, and TTP) were supportive of an additional clinical benefit in T300+D and T arms compared with the D and T75+D arms. However, the confirmed ORR based on BICR according to RECIST 1.1 was 24.0% for patients in the T300+D arm compared with 11.5%, 7.2%, and 9.5%, in the D, T, and T75+D arms, respectively.