Clinical Study Report	
Drug Substance	Durvalumab (MEDI4736) and Tremelimumab
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A Phase III Randomized, Open-label, Multi-center, Global Study of Durvalumab Alone or in Combination with Tremelimumab versus Standard of Care in the Treatment of First-line Recurrent or Metastatic Squamous Cell Head and Neck Cancer Patients – (KESTREL)

Study dates: First subject enrolled: 15 October 2015
Last subject enrolled: 02 March 2017
Data cut-off date: 06 July 2020

Phase of development: Therapeutic confirmatory (III)

International Co-ordinating Investigators: PPD

Sponsor's Responsible Medical Officer:

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

2. SYNOPSIS

Study Centers

Patients were randomized into 183 centers overall in Japan (19 centers), United States (16 centers), Spain (13 centers), Russia (12 centers), Brazil (12 centers), Ukraine (11 centers), France (10 centers), South Korea (10 centers), Germany (10 centers), Poland (9 centers), Canada (8 centers), United Kingdom (7 centers), Italy (7 centers), Taiwan (6 centers), Greece (6 centers), India (6 centers), Belgium (5 centers), Austria (4 centers), Thailand (4 centers), Vietnam (3 centers), Slovakia (2 centers), the Philippines (2 centers), and Romania (1 center).

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

The primary objective of the study was to assess the efficacy of durvalumab monotherapy versus standard of care (SoC; EXTREME) in the programmed cell death ligand 1 (PD-L1) tumor cell (TC)/immune cell (IC) high subgroup in terms of overall survival (OS).

Table S1 Objectives and Outcome Variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To assess the efficacy of durvalumab monotherapy compared to SoC (EXTREME) in terms of OS	OS in the PD-L1 TC/IC high subgroup.
Secondary	Efficacy	To assess the efficacy of durvalumab monotherapy compared to SoC (EXTREME) in terms of OS, PFS, ORR, DoR, BOR, TTR, TFST, TSST, APF6, APF12, PFS2, OS12, OS18, and OS24	OS in the low risk of EM subgroup, ctDNA TMB (≥ 16 mut/Mb) high subgroup, and FAS. OS12, OS18, OS24 in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high (≥ 16 mut/Mb) subgroup, and FAS. PFS, ORR, APF6, and APF12 using site Investigator assessments according to RECIST 1.1 in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high (≥ 16 mut/Mb) subgroup, and FAS. DoR, BOR, and TTR using site Investigator assessments according to RECIST 1.1 in the PD-L1 TC/IC high subgroup, and FAS. PFS2 using local standard clinical practice in the PD-L1 TC/IC high subgroup, and FAS. TFST and TSST in the PD-L1 TC/IC high subgroup, and FAS.

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Efficacy	To assess the efficacy of durvalumab + tremelimumab combination therapy compared to SoC (EXTREME) in terms of OS, PFS, ORR, DoR, BOR, TTR, TFST, TSST, APF6, APF12, PFS2, OS12, OS18, and OS24	OS, OS12, OS18, OS24 in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high (≥ 16 mut/Mb) subgroup, and FAS. PFS, ORR, APF6, and APF12 using site Investigator assessments according to RECIST 1.1 in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high (≥ 16 mut/Mb) subgroup, and FAS. DoR, BOR, and TTR using site Investigator assessments according to RECIST 1.1 in the PD-L1 TC/IC high subgroup, and FAS. PFS2 using local standard clinical practice in PD-L1 TC/IC high subgroup, and FAS. TFST and TSST in the PD-L1 TC/IC high subgroup, and FAS.
Secondary	Efficacy	To assess the efficacy of durvalumab + tremelimumab combination therapy compared to durvalumab monotherapy in terms of PFS, ORR, and OS	PFS and ORR using site Investigator assessments according to RECIST 1.1 in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high (≥ 16 mut/Mb) subgroup, and FAS. OS in the PD-L1 TC/IC high subgroup, low risk of EM subgroup, ctDNA TMB high (≥ 16 mut/Mb) subgroup, and FAS.
Secondary	PRO	To assess disease-related symptoms and HRQoL in patients treated with durvalumab + tremelimumab combination therapy and durvalumab monotherapy compared to SoC (EXTREME) using the EORTC QLQ C30 v3 and the QLQ-H&N35 module	EORTC QLQ-C30: global health QoL, functioning (physical) and symptoms (fatigue) in the PD-L1 TC/IC high subgroup and FAS. EORTC QLQ-H&N35: symptoms (pain, swallowing) in the PD-L1 TC/IC high subgroup and FAS. Changes in WHO/ECOG performance status in the PD-L1 TC/IC high subgroup and FAS.
Secondary	PK	To assess the PK of durvalumab + tremelimumab combination therapy and durvalumab monotherapy	Concentration of durvalumab and tremelimumab in blood and PK parameters, such as peak concentration and trough (as data allow; sparse sampling)
Secondary	Immunogenicity	To investigate the immunogenicity of durvalumab and tremelimumab	Presence of ADAs for durvalumab and tremelimumab

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Safety	To assess the safety and tolerability profile of durvalumab + tremelimumab combination therapy and durvalumab monotherapy compared to SoC (EXTREME) in the first-line setting for treatment of HNSCC	AEs, physical examinations, laboratory findings (including clinical chemistry, hematology, and urinalysis), vital signs (including BP and pulse), and ECGs in the PD-L1 TC/IC high subgroup, low risk EM subgroup, and safety analysis set
Exploratory	CCI		
Exploratory			
Exploratory			
Exploratory[a]			
Exploratory[a]			

[a] Reported separately from this CSR.

ADA Anti-drug antibody; AE Adverse event; APF6 Proportion of patients alive and progression free at 6 months; APF12 Proportion of patients alive and progression free at 12 months; BOR Best objective response; BP Blood pressure; CSR Clinical study report; CCI ctDNA Circulating tumor DNA; DoR Duration of response; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EM Early mortality; EORTC European Organisation for Research and Treatment of Cancer; CCI FAS Full analysis set; HNSCC Head and neck squamous cell carcinoma; HRQoL Health-related quality of life; IC Immune cell; IHC Immunohistochemistry; NCI National Cancer Institute; CCI ORR Objective response rate; OS Overall survival; OS12 Proportion of patients alive at 12 months after randomization; OS18 Proportion of patients alive at 18 months after randomization; OS24 Proportion of patients alive at 24 months after randomization; PD-L1 Programmed cell death ligand 1; PFS Progression-free survival; PFS2 Time from randomization to second progression or death; PK Pharmacokinetics; CCI QLQ-C30 v3 30-item core quality of life questionnaire; QLQ-H&N35 35-item head and neck quality of life questionnaire; QoL Quality of life; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; SoC Standard of care (EXTREME); TC Tumor cell; TTR Time to response; TFST Time from randomization to first subsequent therapy or death; TMB Tumor mutational burden; TSST Time from randomization to second subsequent therapy or death; WHO World Health Organization.

Study Design

This was a randomized, open-label, multi-center, 3-arm, global Phase III study to determine the efficacy and safety of durvalumab monotherapy and durvalumab + tremelimumab combination therapy compared to SoC (EXTREME regimen) in the treatment of patients with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) who were not amenable to local curative therapy with surgery or radiation and who had not received prior systemic therapy for R/M disease, unless it was given as part of multimodality treatment for locally advanced or locally recurrent disease.

Patients were randomized in a 2:1:1 manner to either the durvalumab + tremelimumab combination arm, the durvalumab monotherapy arm, or the SoC (EXTREME) arm, respectively, in a stratified manner according to PD-L1 tumor expression status (using a TC25% cut-off), tumor location (oropharyngeal cancer [OPC] or non-OPC), and smoking history (> 10 or ≤ 10 pack-years). Patients with OPC were further stratified by their human papilloma virus (HPV) status (positive or negative).

Patients in all arms continued therapy until disease progression.

Following clinical study protocol (CSP) amendment 11 (CSP version 12), the primary objective was changed to characterize the OS benefit of durvalumab monotherapy versus SoC in the primary analysis population (PD-L1 TC/IC high subgroup) that consisted of the subset of patients in the full analysis set (FAS) with PD-L1 evaluable samples and available results. PD-L1 high was defined as either ≥ 50% of the TC or ≥ 25% of the IC staining for PD-L1 at any intensity if > 1% of the tumor area contained IC, or ≥ 50% of TC or 100% of IC staining for PD-L1 at any intensity if 1% of the tumor area contained IC.

Target Subject Population and Sample Size

Males and females aged 18 and over with histologically or cytologically confirmed, PD-L1-positive or -negative R/M HNSCC (oral cavity, oropharynx, hypopharynx, or larynx). Patients who were not amenable to local curative therapy with surgery or radiation and who had not received prior systemic therapy for R/M disease unless it was given as part of multimodality treatment for locally advanced or locally recurrent disease.

This study planned to enroll approximately 1016 patients globally to randomize 760 patients across the 3 treatment arms. The study was initially sized to characterize the OS benefit of durvalumab + tremelimumab combination therapy versus SoC in the FAS. Following CSP amendment 11 (CSP version 12), the primary analysis of OS was to be performed when approximately 147 death events had occurred in approximately 172 patients (85% maturity) across the durvalumab monotherapy and SoC treatment arms in the PD-L1 TC/IC high subgroup.

If OS at 24 months in the PD-L1 TC/IC high subgroup was 30% with durvalumab monotherapy and 12% with SoC (with a 10.1-month median OS), and assuming the true average OS hazard ratio (HR) was 0.59, the study would have approximately 90% power to demonstrate statistical significance at the 5% level (using a 2-sided test) for the comparison of durvalumab monotherapy versus SoC, with the smallest treatment difference that could be statistically significant being an average HR of 0.72.

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

Durvalumab monotherapy: Durvalumab (1500 mg) was administered via intravenous (IV) infusion every 4 weeks (q4w) until PD.

Durvalumab + tremelimumab combination therapy: tremelimumab (75 mg) was administered via IV infusion q4w for a maximum of 4 doses, and durvalumab (1500 mg) was administered via IV infusion q4w until PD.

SoC (EXTREME): either cisplatin (at a dose of 100 mg/m^2 of body surface area as an IV infusion) or carboplatin (at an area under the concentration curve of 5 mg/mL/min as an IV infusion) on Day 1 of up to six 3-week cycles, and an infusion of 5-fluorouracil (5FU) (at a dose of 1000 mg/m^2/day on Days 1 through 4) every 3 weeks, along with 400 mg/m^2 of cetuximab on Cycle 1 Day 1 and 250 mg/m^2 weekly for up to 6 cycles and maintenance cetuximab at 250 mg/m^2 administered via IV infusion weekly thereafter in patients who achieved stable disease (SD) or better upon completion of chemotherapy until PD, toxicity, or withdrawal of consent.

Durvalumab, supplied by AstraZeneca, was provided as a 500 mg/vial solution for IV infusion after dilution to 50 mg/mL. Batch numbers used in this study were CCI [redacted]

Tremelimumab, supplied by AstraZeneca, was provided as a 400 mg/vial solution for IV infusion after dilution to 20 mg/mL. Batch numbers used in this study were CCI [redacted]

Each SoC agent was sourced as commercially available material/locally sourced, prescribed according to local regulations, and was administered according to prescribing information or treatment guidance in general use by the investigating site.

Duration of Treatment

Treatment with durvalumab + tremelimumab combination therapy, durvalumab monotherapy, or SoC commenced within 5 working days of randomization and continued until confirmed progression, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met at the Investigator's discretion. Patients

in the SoC arm were treated with SoC for a maximum of six 3-week cycles of cetuximab, a platinum, and 5FU, with continuation of maintenance cetuximab in patients who achieved SD or better until confirmed PD, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

Statistical Methods

Statistical analyses were performed in accordance with the comprehensive SAP, which detailed all analyses to be performed and summaries to be produced, and the analysis sets upon which they were to be based.

Analysis sets

- The full analysis set (FAS [all-comers]) included all randomized patients (all-comers) (ie, the Intent-to-Treat population) and was used for all efficacy analyses (including patient-reported outcomes [PROs]). Treatment arms were compared based on randomized study treatment, regardless of the treatment actually received.
- The PD-L1 TC/IC analysis set (primary analysis set) consisted of subgroups defined as PD-L1 TC/IC high, low, and unknown. The PD-L1 TC/IC high subgroup included the subset of patients in the FAS whose tumors had high PD-L1 expression as determined by the analytically validated VENTANA PD-L1 (SP263) assay. PD-L1 TC/IC high was defined as either:
  - PD-L1 staining at any intensity in ≥ 50% of the TC or ≥ 25% of the IC if > 1% of the tumor area contained IC
  - PD-L1 staining at any intensity in ≥ 50% of TC or 100% of IC if 1% of the tumor area contained IC

  PD-L1 low was defined as not meeting any of the criteria for PD-L1 high.
- Low risk of early mortality (EM) analysis set consisted of patients identified as having low risk of EM based on laboratory values according to a specific prognostic model CCI [redacted]
- The circulating tumor DNA (ctDNA) tumor mutational burden (TMB) analysis set included the subset of patients in the FAS with ctDNA TMB evaluable samples and available results. Subgroups were defined as ctDNA TMB high (≥ 16 mut/Mb), low (< 16 mut/Mb), and unknown.
- The safety analysis set included all patients who received at least one dose of study treatment; patients were classified on the basis of the treatment actually received.
- The pharmacokinetic (PK) analysis set included all patients who received at least one dose of study treatment per the protocol for whom any post-dose PK data were available.

- The anti-drug antibody (ADA) evaluable analysis set included patients in the safety analysis set with a non-missing baseline ADA result and at least one post-baseline ADA result.

The primary objective of this study was to assess the efficacy of durvalumab monotherapy treatment compared with SoC (EXTREME) in the PD-L1 TC/IC high subgroup in terms of OS, defined as the time from the date of randomization until death due to any cause. Overall survival was analyzed using a stratified log-rank test (stratified for PD-L1 expression tumor status [PD-L1 TC ≥ 25% versus TC < 25%], tumor location [OPC vs non-OPC, with a subsequent adjustment for HPV status in patients with OPC], and smoking history [> 10 vs ≤ 10 pack-years] as entered in the Interactive Voice Response System). The effect of treatment was estimated by the HR together with its corresponding 95% confidence interval (CI) and p-value. The primary analysis of OS tested durvalumab monotherapy versus SoC in the PD-L1 TC/IC high subgroup at the 2-sided 5% level; if superiority over SoC was found, a hierarchical multiple testing procedure was employed to strongly control for the overall type I error at the 5% level (2-sided). Subsequent hypotheses in the hierarchy were to test durvalumab monotherapy versus SoC in the low risk of EM subgroup and ctDNA TMB high subgroup, followed by durvalumab + tremelimumab combination therapy versus SoC in the ctDNA TMB high subgroup, durvalumab monotherapy versus SoC in the FAS, and finally durvalumab + tremelimumab combination therapy versus SoC in the FAS. All tests were at the 2-sided 5% alpha level and the procedure stopped at the first failure to find statistically significant evidence of superiority or if tests of all hypotheses showed superiority over SoC.

Safety, PK, and immunogenicity data were summarized descriptively.

Subject Population

In total, 1084 patients were enrolled in 183 study centers across 23 countries in Asia, Europe, North America, and South America. Of these, 823 were randomized to receive treatment with durvalumab monotherapy (204 patients), durvalumab + tremelimumab combination therapy (413 patients), or SoC therapy (206 patients).

In the FAS, the demographics and disease characteristics were representative of the intended patient population and were generally balanced across the treatment arms. Overall, patients had a median age of 61.0 years (range: 22 to 89 years); 83.7% were male; 73.4% were white and 24.9% were Asian, with a lower proportion of Asian participants in the SoC arm (20.4%) compared with the durvalumab monotherapy (26.5%) and durvalumab + tremelimumab (26.5%) arms. The majority of patients were former (57.8%) or current (23.5%) smokers; and the majority were former (37.9%) or current (28.4%) alcohol users. The PD-L1 prevalence at TC25% was 31.1% PD-L1 positive patients and 68.9% PD-L1 negative patients. Overall, 15.1% of patients with OPC were HPV positive.

Summary of Efficacy Results

Primary Endpoint

In the primary analysis, patients in the durvalumab monotherapy arm did not have a statistically significant improvement in OS compared with patients in the SoC arm in the PD-L1 TC/IC high subgroup (HR: 0.96; 95% CI: 0.69, 1.32; p = 0.787).

The Kaplan-Meier estimates of median duration of OS were 10.9 months in the durvalumab monotherapy arm (95% CI: 9.0, 14.3) and 10.9 months (95% CI: 8.3, 13.4) in the SoC arm.

Secondary Endpoints

Given the study did not meet the primary endpoint, all efficacy analyses following the primary analysis were considered exploratory. Statistics, including p-values, associated with all other efficacy analyses are descriptive only.

In the FAS, a total of 176 patients (86.3%) in the durvalumab monotherapy arm and 171 patients (83.0%) in the SoC arm had OS events (HR: 1.03; 95% CI: 0.83, 1.27; p = 0.811). The Kaplan-Meier estimates of median duration of OS were 9.9 months in the durvalumab monotherapy arm (95% CI: 8.9, 11.9) and 10.3 months (95% CI: 9.0, 12.1) in the SoC arm.

In the PD-L1 TC/IC high subgroup, a total of 85 patients (85.9%) and 72 patients (76.6%) in the durvalumab monotherapy and SoC arms, respectively, had reported progression-free survival (PFS) events (Resoponse Evaluation Criteria in Solid Tumors [RECIST] version 1.1 progression or death) (HR: 1.30; 95% CI: 0.94, 1.80; p = 0.287). The Kaplan-Meier estimate of median duration of PFS was 2.8 months in the durvalumab monotherapy arm (95% CI: 1.7, 4.2) and 5.3 months (95% CI: 4.3, 5.8) in the SoC arm.

In the FAS, a total of 178 patients (87.3%) and 171 patients (83.0%) in the durvalumab monotherapy and SoC arms, respectively, had reported PFS events (RECIST 1.1 progression or death) (HR: 1.36; 95% CI: 1.10, 1.68; p = 0.006). The Kaplan-Meier estimate of median duration of PFS was 2.8 months in the durvalumab monotherapy arm (95% CI: 2.0, 2.8) and 5.4 months (95% CI: 4.4, 5.7) in the SoC arm.

In the PD-L1 TC/IC high subgroup, a total of 16 patients (16.2%) and 47 patients (50.0%) in the durvalumab monotherapy and SoC arms, respectively, had an objective response, ie, had a complete response (CR) or a partial response (PR; odds ratio: 0.19; 95% CI: 0.10, 0.37; p = < 0.001). In the durvalumab monotherapy arm, the best objective response (BOR) in 99 patients was PR for 16 patients (16.2%), SD for 38 patients (38.4%), and PD for 40 patients (40.4%). Of those patients with a BOR of PD, 32 (32.3%) had RECIST 1.1-assessed progression and 8 (8.1%) died. No patients had a BOR of CR. The BOR in 94 patients in the SoC arm was CR for 3 patients (3.2%), PR for 44 patients (46.8%), SD for 27 patients

(28.7%), and PD for 9 patients (9.6%). Of those patients with a BOR of PD, 4 (4.3%) had RECIST 1.1-assessed progression and 5 (5.3%) died.

In the FAS, a total of 35 patients (17.2%) and 101 patients (49.0%) in the durvalumab monotherapy and SoC arms, respectively, had an objective response (odds ratio: 0.21; 95% CI: 0.13, 0.33; p = < 0.001). In the durvalumab monotherapy arm, the BOR in 204 patients was CR for 3 patients (1.5%), PR for 32 patients (15.7%), SD for 73 patients (35.8%), and PD for 88 patients (43.1%). Of those patients with a BOR of PD, 67 (32.8%) had RECIST 1.1-assessed progression and 21 (10.3%) died. The BOR in 206 patients in the SoC arm was CR for 4 patients (1.9%), PR for 97 patients (47.1%), SD for 59 patients (28.6%), and PD for 28 patients (13.6%). Of those patients with a BOR of PD, 12 (5.8%) had RECIST 1.1-assessed progression and 16 (7.8%) died. In the durvalumab + tremelimumab arm, the BOR in 413 patients was CR for 16 patients (3.9%), PR for 74 patients (17.9%), SD for 148 patients (35.8%), and PD for 161 patients (39.0%). Of those patients with a BOR of PD, 126 (30.5%) had RECIST 1.1-assessed progression and 35 (8.5%) died.

In the PD-L1 TC/IC high subgroup, treatment with durvalumab monotherapy resulted in a longer duration of response (DoR) compared to SoC. The median DoR was 12.3 months in the durvalumab monotherapy arm and 4.2 months in the SoC arm. Similarly, in the FAS, treatment with durvalumab monotherapy resulted in a longer DoR compared to SoC. The median DoR was 11.9 months in the durvalumab monotherapy arm and 4.2 months in the SoC arm.

Similar trends were observed for durvalumab + tremelimumab compared to SoC and for the low risk of EM subgroup and ctDNA TMB high subgroups. In the ctDNA TMB high subgroup, the ORR was 31.0% in the durvalumab + tremelimumab arm (8.6% with CR) compared to 43.5% in the SoC arm (4.3% with CR).

Summary of Pharmacokinetic and Immunogenicity Results

Serum concentrations data for durvalumab and tremelimumab were as expected.

In the FAS, the incidence of ADA to durvalumab was 0% for durvalumab monotherapy, and 1.5% (4/274 patients) for durvalumab + tremelimumab. The incidence of ADA to tremelimumab was 10.2% (25/245 patients) for durvalumab + tremelimumab. The development of ADA did not appear to have a clinically significant effect on the PK or safety, although this was not formally tested.

Summary of Safety Results

During the study, 185 patients (91.6%), 381 patients (93.4%), and 195 patients (99.5%) in the durvalumab monotherapy, durvalumab + tremelimumab, and SoC arms, respectively, reported adverse events (AEs) in the safety analysis set. In the durvalumab monotherapy arm, the most

frequently reported AEs by preferred term were: fatigue (18.3%); constipation (12.4%); anaemia (10.9%); hypothyroidism (10.4%); decreased appetite, and pneumonia (each 9.9%). In the durvalumab + tremelimumab arm, the most frequently reported AEs by preferred term were: diarrhoea (18.9%); fatigue (16.9%); hypothyroidism (16.7%); anaemia (15.2%); constipation (14.5%); and nausea (13.5%). In the SoC arm, the most frequently reported AEs by preferred term were: rash (41.3%); nausea (38.3%); anaemia (34.2%); neutropenia (33.7%); diarrhoea (32.1%); and fatigue (29.1%). The majority of AEs reported in the study were Grade 2 or Grade 3. A lower proportion of patients in the durvalumab monotherapy (39.6%) and durvalumab + tremelimumab (46.6%) arms reported Grade 3 and Grade 4 AEs compared with SoC (68.9%). A total of 92 patients (45.5%), 246 patients (60.3%), and 184 patients (93.9%) in the durvalumab monotherapy, durvalumab + tremelimumab, and SoC arms, respectively, reported AEs considered possibly related to treatment by the Investigator.

Adverse events of special interest were reported in 35.1%, 45.8%, and 64.3% of patients treated with durvalumab monotherapy, durvalumab + tremelimumab, and SoC, respectively. Adverse events of possible interest were reported in 22.8%, 31.1%, and 39.8% of patients treated with durvalumab monotherapy, durvalumab + tremelimumab, and SoC, respectively. Consistent with the immune-mediated mechanism of action for durvalumab and tremelimumab, 8.9%, 20.8%, and 5.1% of patients treated with durvalumab monotherapy, durvalumab + tremelimumab, and SoC, respectively, reported AESIs and/or AEPIs that were considered to be imAEs. The AESIs, AEPIs and/or imAEs were generally manageable and/or reversible with appropriate medical management, which included the use of steroids, withholding durvalumab and/or tremelimumab, or permanent discontinuation of durvalumab and/or tremelimumab.

Similar proportions of patients in each group reported hemorrhage standardized Medical Dictionary for Regulatory Activities query (SMQ) AEs (17.3%, 16.2%, and 14.8% of patients in the durvalumab monotherapy, durvalumab + tremelimumab, and SoC arms, respectively); however, a lower event rate was observed in the durvalumab + tremelimumab arm (21.91 per 100 patient-years) compared to the durvalumab monotherapy (27.01 per 100 patient-years) and SoC (27.20 per 100 patient-years) arms. There was no difference in severity or seriousness of hemorrhage SMQ AEs across the groups.

Adverse events with an outcome of death occurred in 10.4%, 9.3%, and 10.7% of patients treated with durvalumab monotherapy, durvalumab + tremelimumab, and SoC, respectively. Serious AEs were reported in 38.6%, 41.2%, and 48.0% of patients treated with durvalumab monotherapy, durvalumab + tremelimumab, and SoC, respectively. The SAEs most frequently reported were pneumonia and tumour haemorrhage. Serious AEs considered possibly related to treatment by the Investigator were reported for 7.4%, 14.5%, and 23.5% of patients treated with durvalumab monotherapy, durvalumab +tremelimumab, and SoC, respectively. Adverse events leading to discontinuation of study treatment were reported in 13.4%, 15.0%, and

33.2% of patients treated with durvalumab monotherapy, durvalumab + tremelimumab, and SoC, respectively.

There were no clinically meaningful changes in hematology or chemistry laboratory parameters, vital signs, or electrocardiogram data in patients treated with durvalumab monotherapy, durvalumab + tremelimumab, or SoC.

Conclusions

- The primary endpoint was not met. In the PD-L1 TC/IC high subgroup, patients in the durvalumab monotherapy arm did not have a statistically significant improvement in OS compared with patients in the SoC arm.
- Both durvalumab monotherapy and durvalumab + tremelimumab combination therapy demonstrated well-tolerated and manageable safety profiles. In general, the safety profiles observed in this study were consistent with the established safety profiles of durvalumab and tremelimumab to date.