Clinical Study Report	
Drug Substance	Durvalumab (MEDI4736) and tremelimumab
Study Code	D419MC00004
Edition Number	1.0
Date	06 September 2021
EudraCT Number	2017-000920-81
NCT Number	NCT03164616

A Phase III, Randomized, Multi-Center, Open-Label, Comparative Global Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination With Platinum-Based Chemotherapy for First-Line Treatment in Patients With Metastatic Non-Small-Cell Lung Cancer (NSCLC) (POSEIDON)

Study dates:
First patient randomized: 27 June 2017
Last patient randomized: 19 September 2018
The analyses presented in this report are based on data cut-off dates of 24 July 2019 and 12 March 2021.

Phase of development:
Therapeutic confirmatory (III)

International Coordinating Investigator:
PPD
Sarah Cannon Research Institute
Nashville, TN 37203
Oncology
Research Site Support
PPD
Tel: PPD

Sponsor's Responsible Medical Officer:
PPD
PPD
AstraZeneca, Global Medicines Development
PPD Gaithersburg
MD, 20878, USA

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Study center(s)

The study was conducted at study centers in North and Latin America, Europe, Asia Pacific, and Africa. Patients were recruited from 142 centers overall in Brazil (13 centers), Bulgaria (6 centers), Germany (10 centers), Hong Kong (1 center), Hungary (5 centers), Japan (18 centers), South Korea (9 centers), Mexico (9 centers), Peru (5 centers), Poland (4 centers), Russia (9 centers), South Africa (7 centers), Taiwan (10 centers), Thailand (6 centers), Ukraine (10 centers), United Kingdom (5 centers), United States (12 centers) and Vietnam (3 centers).

Publications

No publications were published or pending publication 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 endpoints

Objective	Endpoints/variables
Primary	
• To assess the efficacy of durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS and OS in all patients	• PFS in all patients using BICR assessments according to RECIST 1.1 • OS in all patients
Secondary	
• To assess the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS and OS	• PFS in all patients using BICR assessments according to RECIST 1.1 (key secondary objective) • OS in all patients (key secondary objective)

Table S1 Objectives and endpoints

Objective	Endpoints/variables
• To further assess the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS, OS, ORR, BOR, DoR, APF12 and PFS2	• PFS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25% and patients with PD-L1 TC <1% using BICR assessments according to RECIST 1.1 • OS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25% and patients with PD-L1 TC <1% • ORR, DoR, BOR and APF12 in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using BICR assessments according to RECIST 1.1 • PFS2 in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using local standard clinical practice
• To further assess the efficacy of durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS, OS, ORR, DoR, BOR, APF12 and PFS2	• PFS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25% and patients with PD-L1 TC <1% using BICR assessments according to RECIST 1.1 • OS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25% and patients with PD-L1 TC <1% • ORR, DoR, BOR and APF12 in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using BICR assessments according to RECIST 1.1 • PFS2 in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using local standard clinical practice
• To assess the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with durvalumab monotherapy + SoC chemotherapy in terms of PFS, OS and ORR	• PFS and ORR in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using BICR assessments according to RECIST 1.1 • OS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients
• To assess the association of TMB with the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS, OS, ORR, BOR, DoR, APF12 and PFS2	• PFS, ORR, BOR, DoR, APF12 in patients with TMB high using BICR assessments according to RECIST 1.1 • PFS2 in patients with TMB high using local standard clinical practice • OS in patients with TMB high

Table S1 Objectives and endpoints

Objective	Endpoints/variables
• To assess the association of TMB with the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with durvalumab monotherapy + SoC chemotherapy in terms of PFS, OS, ORR, BOR, DoR, APF12 and PFS2	• PFS, ORR, BOR, DoR, APF12 in patients with TMB high using BICR assessments according to RECIST 1.1 • PFS2 in patients with TMB high using local standard clinical practice • OS in patients with TMB high
• To assess the association of TMB with the efficacy of durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy in terms of PFS, OS, ORR, BOR, DoR, APF12 and PFS2	• PFS, ORR, BOR, DoR, APF12 in patients with TMB high using BICR assessments according to RECIST 1.1 • PFS2 in patients with TMB high using local standard clinical practice • OS in patients with TMB high
• To assess the PK of durvalumab + tremelimumab combination therapy and durvalumab monotherapy	• Concentrations of durvalumab and tremelimumab
• To investigate the immunogenicity of durvalumab and tremelimumab	• Presence of ADAs for durvalumab and tremelimumab
• To assess disease-related symptoms and HRQoL in patients treated with durvalumab + tremelimumab combination therapy + SoC chemotherapy and durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone using the EORTC QLQ-C30 v3, the QLQ-LC13 module, and WHO/ECOG performance status assessments	• EORTC QLQ-C30 • EORTC QLQ-LC13 • Changes in WHO/ECOG performance status
Safety	
• To assess the safety and tolerability profile of durvalumab + tremelimumab combination therapy + SoC chemotherapy and durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone	• AEs, physical examinations, laboratory findings, and vital signs

CCI [redacted]

AE=Adverse event; APF12=percentage of patients alive and progression free at 12 months from randomization; BICR=blinded independent central review; CSR=clinical study report; CTCAE=Common Terminology Criteria for Adverse Events; CCI [redacted] ORR=objective response rate; OS=overall survival; PD-L1=programmed cell death ligand 1; PFS=progression-free survival; CCI [redacted] PK=pharmacokinetics; CCI [redacted] SoC=standard of care; TMB=tumor mutational burden.

Study design

POSEIDON was a Phase III, randomized, open-label, multi-center, global, study to determine the efficacy and safety of durvalumab + tremelimumab + standard of care (SoC) chemotherapy or durvalumab + SoC chemotherapy versus SoC chemotherapy alone as 1L treatment in patients with metastatic non-small cell lung cancer (NSCLC) with tumors that lack activating epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) fusions. This was an open-label study; however, the AstraZeneca study team were blinded to aggregate treatment information. During the programming and preparation of statistical outputs, data were dummy blinded prior to database lock and study unblinding.

Patients who fulfilled all of the inclusion criteria and none of the exclusion criteria were randomized in a stratified manner according to programmed cell death ligand 1 (PD-L1) status (PD-L1 expression on ≥50% vs <50% of tumor cells [TCs]), disease stage (IVA vs IVB), and histology (non-squamous vs squamous) in a 1:1:1 ratio to receive treatment with T + D + SoC chemotherapy (Arm 1), D + SoC chemotherapy (Arm 2), or SoC chemotherapy (Arm 3). SoC chemotherapy was the investigator's choice of one of the following regimens: Abraxane + carboplatin (squamous and non-squamous patients), pemetrexed + cisplatin or carboplatin (non-squamous patients only), or gemcitabine + cisplatin or carboplatin (squamous patients only).

Durvalumab, with or without tremelimumab, was administered for 4 cycles with SoC chemotherapy in the experimental arms (Arm 1 and Arm 2) (combination stage) and continued to be administered post-chemotherapy (maintenance stage) until clinical or radiological disease progression. The control arm (Arm 3) received 4 to 6 cycles of SoC chemotherapy if clinically indicated, at the Investigators' discretion.

Crossover was not permitted as part of the study. Tumor evaluation scans were performed at screening (as baseline) with follow-ups at Week 6 ±1 week from the date of randomization, at Week 12 ±1 week from the date of randomization, and then every 8 weeks ±1 week until radiological disease progression.

The analyses presented in this report are based on the data cut-off (DCO) dates of 24 July 2019 (all RECIST-related endpoints) and 12 March 2021 (all other data).

Target population and sample size

Adult patients (aged ≥18 years) with histologically or cytologically documented Stage IV NSCLC not amenable to curative surgery or radiation (according to Version 8 of the IASLC Staging Manual in Thoracic Oncology 2016). Patients had to have tumors that lacked activating EGFR mutations and ALK fusions. Patients with suspected brain metastases required IV contrast-enhanced magnetic resonance imaging /computed tomography of the

brain prior to study entry and were eligible provided they were stable 4 weeks after the imaging, had returned neurologically to baseline, and were off steroids at least 5 days prior to randomization.

Approximately 1000 eligible patients were planned to be randomized at sites worldwide across the 3 study arms. Once global enrollment was complete, enrollment continued in mainland China only. This clinical study report (CSR) provides data from the global cohort (excluding China) only. No data from patients in China were analyzed in this CSR.

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

Details of the investigational products are presented in Table S2.

Table S2 Details of study treatments

Investigational product	Dosage form and strength	Manufacturer	Batch number
Durvalumab	50 mg/mL, solution for IV infusion after dilution	MedImmune	Refer to Appendix 16.1.6
Tremelimumab	20 mg/mL, solution for IV infusion after dilution	MedImmune	Refer to Appendix 16.1.6
Standard of care[a]			
Abraxane	IV (as sourced locally)	Sourced locally	NA
Carboplatin	IV (as sourced locally)	Sourced locally	NA
Cisplatin	IV (as sourced locally)	Sourced locally	NA
Gemcitabine	IV (as sourced locally)	Sourced locally	NA
Pemetrexed	IV (as sourced locally)	Sourced locally	NA

[a] Under certain circumstances when local sourcing was not feasible, standard of care treatment was supplied centrally through AstraZeneca. The choice of SoC was as the discretion of the investigator.

IV=intravenous; NA=not applicable.

Patients were randomized in a 1:1:1 ratio to receive treatment with T + D + SoC chemotherapy, D + SoC chemotherapy, or SoC chemotherapy alone as follows:

Treatment arm 1: durvalumab + tremelimumab + SoC chemotherapy

During chemotherapy (combination) stage

NSCLC type	Agent and dose	Route	Duration	Schedule
Squamous and non-squamous patients	Durvalumab (1500 mg)	IV	60 min	4 doses Q3W Weeks 0, 3, 6, and 9
Squamous and non-squamous patients	Tremelimumab (75 mg)	IV	60 min	4 doses Q3W Weeks 0, 3, 6, and 9
Squamous and non-squamous patients	SoC (Abraxane [100 mg/m^2] with carboplatin [AUC 5 or 6])	IV	-	Days 1, 8, and 15 of each 21-day cycle (Abraxane) and on Day 1 of each 21-day cycle (carboplatin) for 4 cycles
Squamous patients only	SoC (gemcitabine [1000 mg/m^2 or 1250 mg/m^2] with cisplatin [75 mg/m^2])	IV	-	Days 1 and 8 of each 21-day cycle (gemcitabine) and on Day 1 of each 21-day cycle (cisplatin) for 4 cycles
Squamous patients only	SoC (gemcitabine [1000 mg/m^2 or 1250 mg/m^2] with carboplatin [AUC 5 or 6])	IV	-	Days 1 and 8 of each 21-day cycle (gemcitabine) and on Day 1 of each 21-day cycle (carboplatin) for 4 cycles
Non-squamous patients only	SoC (pemetrexed [500 mg/m^2] with carboplatin [AUC 5 or 6])	IV	-	Day 1 of each 21-day cycle for 4 cycles
Non-squamous patients only	SoC (pemetrexed [500 mg/m^2] and cisplatin [75 mg/m^2])	IV	-	Day 1 of each 21-day cycle for 4 cycles

Patients whose weight fell to 30 kg or below received weight-based dosing, equivalent to 20 mg/kg of durvalumab and 1 mg/kg of tremelimumab Q3W until the weight improved to >30 kg, at which point the patient started receiving the fixed dosing of durvalumab at 1500 mg and tremelimumab at 75 mg. If there was a dosing delay during chemotherapy while on the Q3W schedule, all future dosing days were delayed to ensure that the intervals between dosing study treatment were always at least 21 days.
AUC=area under the plasma drug concentration time curve; IV=intravenous; NSCLC=non-small cell lung cancer; Q3W=every 3 weeks; SoC=standard of care.

Post-chemotherapy (maintenance) stage

Agent	Dose	Route	Duration	Schedule
Durvalumab	1500 mg	IV	60 min	Q4W Week 12 to PD[a]
Tremelimumab	75 mg	IV	60 min	1 dose at Week 16[b]
Pemetrexed[c]	500 mg/m^2	IV	-	Q4W Week 12 to PD[d]

[a] Patients were treated until clinical progression or radiological progression unless there was unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met. For criteria for treatment through progression and for retreatment with the combination, see Section 7.2.2.2 of the CSP (CSR Appendix 16.1.1).

[b] For patients in Treatment Arm 1, an additional dose of durvalumab + tremelimumab was given at Week 16 post-chemotherapy. In the case of dose delay(s), more than 1 tremelimumab + durvalumab combination dose could be given at and after Week 16 post-chemotherapy to ensure that up to 5 combination doses were administered in Treatment Arm 1. If patients received fewer than 4 cycles of platinum doublet chemotherapy, the remaining cycles of combined durvalumab/tremelimumab (up to a total of 5) were to be given after combination of platinum doublet chemotherapy (with maintenance pemetrexed, if applicable).

[c] Non-squamous patients who received carboplatin/cisplatin + pemetrexed and who had not progressed after 4 cycles of carboplatin/cisplatin + pemetrexed could receive pemetrexed maintenance therapy, unless contraindicated per the investigator.

[d] Patients were treated until clinical progression or RECIST1.1 defined radiological progression unless there was unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

Patients whose weight fell to 30 kg or below received weight-based dosing, equivalent to 20 mg/kg of durvalumab and 1 mg/kg of tremelimumab Q4W until the weight improved to >30 kg, at which point the patient started receiving the fixed dosing of durvalumab at 1500 mg and tremelimumab at 75 mg.
IV=intravenous; PD=progressive disease; Q4W=every 4 weeks.

Note: Dose reductions of durvalumab and tremelimumab were not permitted.

Treatment arm 2: durvalumab + SoC chemotherapy

During chemotherapy (combination) stage

NSCLC type	Agent and dose	Route	Duration	Schedule
Squamous and non-squamous patients	Durvalumab (1500 mg)	IV	60 min	4 doses Q3W Weeks 0, 3, 6, and 9
Squamous and non-squamous patients	SoC (Abraxane [100 mg/m^2] with carboplatin [AUC 5 or 6])	IV	-	Days 1, 8, and 15 of each 21-day cycle (Abraxane) and on Day 1 of each 21-day cycle (carboplatin) for 4 cycles
Squamous patients only	SoC (gemcitabine [1000 mg/m^2 or 1250 mg/m^2] with cisplatin [75 mg/m^2])	IV	-	Days 1 and 8 of each 21-day cycle (gemcitabine) and on Day 1 of each 21-day cycle (cisplatin) for 4 cycles
Squamous patients only	SoC (gemcitabine [1000 mg/m^2 or 1250 mg/m^2] with carboplatin [AUC 5 or 6])	IV	-	Days 1 and 8 of each 21-day cycle (gemcitabine) and on Day 1 of each 21-day cycle (carboplatin) for 4 cycles
Non-squamous patients only	SoC (pemetrexed [500 mg/m^2] with carboplatin [AUC 5 or 6])	IV	-	Day 1 of each 21-day cycle for 4 cycles
Non-squamous patients only	SoC (pemetrexed [500 mg/m^2] and cisplatin [75 mg/m^2])	IV	-	Day 1 of each 21-day cycle for 4 cycles

Patients whose weight fell to 30 kg or below received weight-based dosing, equivalent to 20 mg/kg of durvalumab Q3W until the weight improved to >30 kg, at which point the patient started receiving the fixed dosing of durvalumab at 1500 mg.
If there was a dosing delay during chemotherapy while on the Q3W schedule, all future dosing days were delayed to ensure that the intervals between dosing study treatment were always at least 21 days.
IV=intravenous; NSCLC=non-small cell lung cancer; Q3W=every 3 weeks; SoC=standard of care.

Post-chemotherapy (maintenance) stage

Agent	Dose	Route	Duration	Schedule
Durvalumab	1500 mg	IV	60 min	Q4W Week 12 to PD[a]
Pemetrexed[b]	500 mg/m^2	IV	-	Q4W Week 12 to PD[c]

[a] Patients were treated until clinical progression or radiological progression unless there was unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met. For criteria for treatment through progression, see Section 7.2.2.2 of the CSP (Appendix 16.1.1).
[b] Non-squamous patients who received carboplatin/cisplatin + pemetrexed and who had not progressed after 4 cycles of carboplatin/cisplatin + pemetrexed could receive pemetrexed maintenance therapy, unless contraindicated per the investigator.
[c] Patients were treated until clinical progression or RECIST1.1 defined radiological progression unless there was unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.
Patients whose weight fell to 30 kg or below received weight-based dosing, equivalent to 20 mg/kg of durvalumab Q4W until the weight improved to >30 kg, at which point the patient started receiving the fixed dosing of durvalumab at 1500 mg.
IV=intravenous; PD=progressive disease; Q4W=every 4 weeks.

Note: Dose reductions of durvalumab were not permitted.

Treatment arm 3: SoC chemotherapy alone

NSCLC type	Agent and dose	Route	Duration	Schedule
Squamous and non-squamous patients	SoC (Abraxane [100 mg/m^2] with carboplatin [AUC 5 or 6])	IV	-	Days 1, 8, and 15 of each 21-day cycle (Abraxane) and on Day 1 of each 21-day cycle (carboplatin) for 4 cycles[a]
Squamous patients only	SoC (gemcitabine [1000 mg/m^2 or 1250 mg/m^2] with cisplatin [75 mg/m^2])	IV	-	Days 1 and 8 of each 21-day cycle (gemcitabine) and on Day 1 of each 21-day cycle (cisplatin) for 4 cycles[a]
Squamous patients only	SoC (gemcitabine [1000 mg/m^2 or 1250 mg/m^2] with carboplatin [AUC 5 or 6])	IV	-	Days 1 and 8 of each 21-day cycle (gemcitabine) and on Day 1 of each 21-day cycle (carboplatin) for 4 cycles[a]
Non-squamous patients only	SoC (pemetrexed [500 mg/m^2] with carboplatin [AUC 5 or 6])[b]	IV	-	Day 1 of each 21-day cycle for 4 cycles[a]
Non-squamous patients only	SoC (pemetrexed [500 mg/m^2] and cisplatin [75 mg/m^2])[b]	IV	-	Day 1 of each 21-day cycle for 4 cycles[a]

[a] An additional 2 doses of SoC (Weeks 12 and 15) could have been given at the investigator's discretion, if clinically indicated.

[b] Non-squamous patients who received carboplatin/cisplatin + pemetrexed and who had not progressed after 4 to 6 cycles of carboplatin/cisplatin + pemetrexed could receive pemetrexed maintenance therapy given Q3W or Q4W, dependent on investigator decision and local standards, unless contraindicated per the investigator. **Note:** RECIST 1.1 assessment was performed at Week 12 ±1 week from the date of randomization, and then Q8W±1 week thereafter until radiological progression (regardless of whether Q3W or Q4W was chosen).

Patients who received extra cycles of SoC were still expected to follow the planned scan schedule visits. If there was a dosing delay during chemotherapy while on the Q3W schedule, all future dosing days were delayed ensuring that the intervals between dosing study treatment were always at least 21 days.

AUC=area under the plasma drug concentration time curve; IV=intravenous; NSCLC=non-small cell lung cancer; SoC=standard of care.

The full dosing scheme is provided below in Table S3.

Table S3 Dosing scheme

Treatment arms	During chemotherapy (combination) stage 1 cycle=3 weeks (21 days)				Post-chemotherapy (maintenance) stage 1 cycle=4 weeks (28 days)		
	Cycle 1 Week 0	Cycle 2 Week 3	Cycle 3 Week 6	Cycle 4 Week 9	Week 12	Week 16	Week 20 to PD
T + D + SoC chemotherapy (Treatment Arm 1)	T + D + SoC	T + D + SoC	T + D + SoC	T + D + SoC	D + pemetrexed[a]	T + D[b] + pemetrexed[a]	D + pemetrexed[a]
D + SoC chemotherapy (Treatment Arm 2)	D + SoC	D + SoC	D + SoC	D + SoC	D + pemetrexed[a]	D + pemetrexed[a]	D + pemetrexed[a]
SoC chemotherapy alone (Treatment Arm 3)	SoC	SoC	SoC	SoC[c]	pemetrexed[a]	pemetrexed[a]	pemetrexed[a]

[a] Pemetrexed maintenance therapy was for non-squamous NSCLC patients who received treatment with pemetrexed and carboplatin/cisplatin during chemotherapy and did not progress after 4 to 6 cycles, unless contraindicated per the investigator. Pemetrexed maintenance therapy could have been given Q3W or Q4W (ie, Q4W for Treatment Arms 1 and 2. For Treatment Arm 3, pemetrexed maintenance therapy could have been given either Q3W or Q4W dependent on investigator decision and local standards). **Note:** RECIST 1.1 assessment was performed at Week 12 ±1 week from the date of randomization, and then Q8W±1 week thereafter until radiological progression (regardless of whether Q3W or Q4W was chosen).

[b] For patients in Treatment Arm 1, an additional dose of durvalumab + tremelimumab was given at Week 16 post-chemotherapy. In the case of dose delay(s), more than 1 durvalumab + tremelimumab combination dose could have been given at and after Week 16 post-chemotherapy to ensure that up to 5 combination doses were administered in Treatment Arm 1. If patients received fewer than 4 cycles of platinum doublet chemotherapy, the remaining cycles of combined durvalumab/tremelimumab (up to a total of 5) were to be given after combination of platinum doublet chemotherapy (with maintenance pemetrexed, if applicable).

[c] In Treatment Arm 3, SoC chemotherapy could have been given for an additional 2 cycles Q3W on Weeks 12 and 15 (ie, total of 6 cycles post-randomization) if clinically indicated, at the investigator's discretion before patients entered follow-up. This did not alter the planned scan schedule Q8W starting at Week 12 for patients in Treatment Arm 3.

Note: Patients whose weight fell to 30 kg or below received weight-based dosing, equivalent to 20 mg/kg of durvalumab and 1 mg/kg of tremelimumab until the weight improved to >30 kg, at which point the patient started receiving the fixed dosing of durvalumab at 1500 mg and tremelimumab at 75 mg. Durvalumab dose was 1500 mg during chemotherapy and 1500 mg post-chemotherapy; tremelimumab dose was 75 mg.

D=durvalumab; NSCLC=non-small cell lung cancer; PD=progressive disease; Q3W=every 3 weeks; Q4W=every 4 weeks; SoC=standard of care; T=tremelimumab.

Duration of treatment

Treatment with SoC chemotherapy in Treatment Arms 1 and 2 was limited to 4 cycles on a Q3W schedule subsequent to randomization. Patients in Treatment Arm 3 (SoC chemotherapy alone) could receive an additional 2 doses of SoC chemotherapy at Weeks 12 and 15 (a total of 6 doses post-randomization), as clinically indicated, at the investigator's discretion.

Treatment with immunotherapy + SoC chemotherapy in Treatment Arms 1 and 2, as well as treatment with SoC chemotherapy alone in Treatment Arm 3, was administered beginning on Cycle 1 Day 1.

For patients randomized to Treatment Arms 1 and 2, immunotherapy treatment with durvalumab monotherapy continued until clinical progression or radiological progression unless there was unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met. For patients in Treatment Arm 1, an additional dose of durvalumab + tremelimumab was given at Week 16 post chemotherapy. In the case of dose delay(s), more than 1 durvalumab + tremelimumab combination dose could be given at and after Week 16 post chemotherapy to ensure that up to 5 combination doses are administered in Treatment Arm 1. If patients received fewer than 4 cycles of platinum doublet chemotherapy, the remaining cycles of combined durvalumab/tremelimumab (up to a total of 5) was to be given after combination of platinum doublet chemotherapy (with maintenance pemetrexed if applicable). All nonsquamous patients who received a pemetrexed doublet in the initial part of the study were to receive pemetrexed maintenance in the 'post-chemotherapy' phase of the study, unless contraindicated per the investigator.

For patients randomized to Treatment Arms 1 and 2, when SoC chemotherapy was discontinued due to treatment-related toxicity, durvalumab monotherapy or durvalumab + tremelimumab could continue at the investigator's discretion when toxicity resolved to at least Grade 2 or less.

Treatment Through Progression (Treatment Arms 1 and 2)

Patients in Treatment Arms 1 and 2 (immunotherapy + SoC chemotherapy) with objective radiological progression who, in the investigator's opinion, continued to receive benefit from their assigned treatment and who met the criteria for treatment in the setting of (PD) could continue to receive durvalumab monotherapy for as long as they were gaining clinical benefit.

Patients with rapid tumor progression or with symptomatic progression that required urgent medical intervention (eg, central nervous system metastasis [CNS], respiratory failure due to tumor compression, or spinal cord compression) were not be eligible for continuing any study treatment.

For all patients in Treatment Arms 1 and 2 who were treated through progression, the investigator ensured the patients did not have any significant, unacceptable, or irreversible toxicities that indicated continuing treatment would not further benefit the patient.

Patients in Treatment Arms 1 and 2 could continue receiving their assigned therapy in the setting of unconfirmed PD, at the investigator's discretion, until PD was confirmed with a subsequent scan.

Retreatment (Treatment Arm 1)

Patients in Treatment Arm 1 (T + D + SoC chemotherapy) with radiological progression who, in the investigator's opinion, continued to receive benefit from their assigned treatment and who met the criteria for retreatment in the setting of PD, could have retreatment with durvalumab + tremelimumab combination therapy.

Patients with rapid tumor progression or with symptomatic progression that required urgent medical intervention (eg, CNS metastasis, respiratory failure due to tumor compression, or spinal cord compression) were not eligible for starting retreatment with durvalumab + tremelimumab combination therapy.

For all patients in Treatment Arm 1 who began retreatment, the investigator ensured the patients did not have any significant, unacceptable, or irreversible toxicities that indicated restarting treatment would not further benefit the patient.

Patients in Treatment Arm 1 who met the retreatment criteria below followed the same treatment guidelines followed during the original post-chemotherapy maintenance Q4W treatment period.

Patients who met the criteria for retreatment could receive retreatment only once.

For patients randomized to Treatment Arm 3, treatment through progression and retreatment was not permitted.

Statistical methods

Descriptive statistics were used for all variables, as appropriate, and are 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 were calculated out of the population total for the corresponding treatment arm.

Baseline was the last assessment of the variable under consideration prior to the intake of the first dose of investigational product, except for efficacy variables. In general, for efficacy and patient-reported outcome (PRO) endpoints the last observed measurement prior to

randomization was considered the baseline measurement. However, if an evaluable assessment was only available after randomization but before the first dose of randomized treatment then this assessment was used as baseline.

Efficacy data were summarized and analyzed by treatment arm based on the full analysis set (FAS), the PD-L1 TC <50% analysis set, the PD-L1 TC <25% analysis set, the PD-L1 TC <1% analysis set, blood tumor mutational burden (bTMB)20 high analysis set, bTMB16 high analysis set and bTMB12 high analysis set. PRO data were summarized and analyzed by treatment arm based on the FAS. Pharmacokinetics (PK) data were summarized and analyzed based on the PK analysis set. Safety and treatment exposure data were summarized using the safety analysis set. Study population and demography data were summarized based upon the FAS (unless otherwise stated).

Results of all statistical analysis are presented using appropriately sized confidence intervals (CIs) and 2-sided p values, unless otherwise stated.

Table S4 details which endpoints were subjected to formal statistical analysis, together with prespecified sensitivity analyses, making it clear which analyses are regarded as primary and key secondary for that endpoint. In order to strongly control the type I error at 5% (2 sided), a multiple testing procedure (MTP) with gatekeeping strategy was used across the dual primary endpoints of overall survival (OS) and progression free disease (PFS) (Arm 2 vs 3), the key secondary endpoints of OS and PFS (Arm 1 vs Arm 3), and the secondary endpoints of OS in the bTMB high (bTMB20, bTMB16, and bTMB12) populations (Arm 1 vs Arm 3) included in the MTP.

Table S4 Pre-planned statistical and sensitivity analyses to be conducted

Endpoints analyzed	Notes
Overall survival	Stratified log-rank tests for: • Dual primary analysis: - Durvalumab monotherapy + SoC chemotherapy and SoC chemotherapy alone for the ITT population • Key secondary analysis: - Durvalumab + tremelimumab combination therapy + SoC chemotherapy and SoC chemotherapy alone for the ITT population • Other secondary analyses: - Durvalumab + tremelimumab combination therapy + SoC chemotherapy and SoC chemotherapy alone for PD-L1 TC <50% population (stratified only for disease stage and histology), PD-L1 TC <25% population (stratified only for disease stage and histology), PD-L1 TC <1% population (stratified only for disease stage and histology) and bTMB high (bTMB ≥20, ≥16 and ≥12) populations

Endpoints analyzed	Notes
	- Durvalumab monotherapy + SoC chemotherapy and SoC chemotherapy alone for PD-L1 TC <50% population (stratified only for disease stage and histology), PD-L1 TC <25% population (stratified only for disease stage and histology), PD-L1 TC <1% population (stratified only for disease stage and histology) and bTMB high (≥20, ≥16 and ≥12) populations
PFS	Stratified log-rank tests for: • Dual primary analysis using BICR RECIST 1.1 assessments: - Durvalumab monotherapy + SoC chemotherapy and SoC chemotherapy alone for the ITT population • Key secondary analysis using BICR RECIST 1.1 assessments: - Durvalumab + tremelimumab combination therapy + SoC chemotherapy and SoC chemotherapy alone for the ITT population • Other secondary analyses using BICR RECIST 1.1 assessments: - Durvalumab + tremelimumab combination therapy + SoC chemotherapy and SoC chemotherapy alone for PD-L1 TC <50% population (stratified only for disease stage and histology), PD-L1 TC <25% population (stratified only for disease stage and histology), PD-L1 TC <1% population (stratified only for disease stage and histology) and bTMB high population (≥20, ≥16 and ≥12) populations - Durvalumab monotherapy + SoC chemotherapy and SoC chemotherapy alone for PD-L1 TC <50% population (stratified only for disease stage and histology), PD-L1 TC <25% population (stratified only for disease stage and histology), PD-L1 TC <1% population (stratified only for disease stage and histology) and bTMB high (≥20, ≥16 and ≥12) populations • Sensitivity analyses using investigator assessments (RECIST 1.1) • CCI
APF12	• Kaplan-Meier estimates of PFS at 12 months
Objective response rate	Logistic regression for: • Secondary analysis for the ITT, PD-L1 TC <50%, PD-L1 TC <25%, PD-L1 TC <1% and TMB high (bTMB ≥20, ≥16 and ≥12) populations using BICR RECIST 1.1 assessments • Sensitivity analysis for the ITT, PD-L1<50%, PD-L1 <25%, PD-L1 <1% and TMB high (≥20, ≥16 and ≥12) populations using investigator RECIST 1.1 assessments • CCI
Duration of response	Kaplan-Meier estimates for: • Secondary analysis using BICR assessments (RECIST 1.1)
Time from randomization to second progression	Stratified log-rank test

Endpoints analyzed	Notes
Time to deterioration (EORTC QLQ-C30 and QLQ-LC13 endpoints)	Stratified log-rank test
Symptom improvement rates (EORTC QLQ-C30 and QLQ-LC13 endpoints)	Logistic regression

BICR=blinded independent central review; bTMB=blood tumor mutational burden; DoR=duration of response; EORTC=European Organisation for Research and Treatment of Cancer; CCI [redacted] ITT=intent-to-treat; PD-L1=programmed cell death ligand 1; PFS=progression-free survival; QLQ-C30=30-item Core Quality of Life Questionnaire; QLQ-LC13=13-item Lung Cancer Quality of Life Questionnaire; RECIST 1.1=Response Evaluation Criteria in Solid Tumors, version 1.1; SoC=standard of care; TC=tumor cell; TMB=tumor mutational burden.

Note: In the results section below, Arm 1 is referred to as the T + D + SoC arm (tremelimumab + durvalumab + standard of care chemotherapy), Arm 2 as the D + SoC arm (durvalumab + standard of care chemotherapy) and Arm 3 as the SoC alone arm (standard of care chemotherapy alone).

- The final analyses of PFS (DCO: 24 July 2019) were conducted after 511 PFS events were reported across the combined D + SoC and SoC alone arms (75.7% maturity). The PFS hazard ratio (HR) favored the D + SoC treatment and was statistically significant at the 1% alpha level. Therefore, per MTP, the 1% alpha was recycled to test PFS for the T + D + SoC versus SoC alone comparison (key secondary endpoint). The PFS HR favored the T + D + SoC treatment and was statistically significant at the 1% alpha level.

- The final analyses of OS (DCO: 12 March 2021) were conducted after 549 OS events were reported across the combined D + SoC and SoC alone arms (81.3% maturity). While the OS HR numerically favored the D + SoC treatment, it did not cross the prespecified statistical threshold at the 4% alpha level.

- Therefore, per the MTP, the 1% alpha level from the PFS for T + D + SoC versus SoC alone was recycled to test OS for the T + D + SoC versus SoC alone comparison. The OS HR favored the T + D + SoC treatment and was statistically significant at the 1% alpha level.

- Finally, the OS in the bTMB20 population for the T + D + SoC versus SoC alone comparison was tested at the 1% alpha recycled from Level 2 of the MTP. The OS HR favored the T + D + SoC treatment compared with SoC alone; however, it did not cross the prespecified threshold of statistical significance. Therefore, the bTMB16 and bTMB12 populations were not tested for significance.

Study population

A total of 1013 patients were randomized in a 1:1:1 ratio into one of the study arms (T + D + SoC, D + SoC or SoC alone arms) at 142 study centers across 18 countries in North and Latin America, Europe, Asia Pacific, and Africa.

Of the 1013 randomized patients, 338 were randomized to the T + D + SoC and D + SoC arms each, and 337 to the SoC alone arm. A total of 331 (97.9%) patients randomized to the T + D + SoC arm, 335 (99.1%) randomized to the D + SoC arm, and 331 (98.2%) randomized to the SoC alone arm received study treatment. In the T + D + SoC arm, 7 (2.1%) patients did not receive any study treatment (3 due to medical reason, 2 due to incorrect randomization, 1 due to withdrawal of consent by patient, and 1 due to patient decision not to receive treatment). In the D + SoC arm, 3 (0.9%) patients did not receive any study treatment (1 due to incorrect randomization, 1 due to patient decision not to receive treatment, and 1 due to patient died). In the SoC alone arm, 6 (1.8%) patients did not receive any study treatment (1 due to medical reason and 5 due to withdrawal of consent by patient).

In the T + D + SoC arm, a total of 213 (64.4%) completed treatment with tremelimumab and 117 (35.3%) patients discontinued tremelimumab; the most common reasons for discontinuation of tremelimumab included condition under investigation worsened (20.8%) and adverse events (AEs) (10.6%). A total of 294 (88.8%) patients discontinued durvalumab; the most common reasons for discontinuation of durvalumab included condition under investigation worsened (65.3%) and AEs (18.4%). A total of 311 (94.0%) patients discontinued SoC chemotherapy; the most common reasons for discontinuation of SoC chemotherapy (corresponding to last SoC chemotherapy agent received) included condition under investigation worsened (41.7%), and AEs (18.7%). Ninety-five (28.7%) patients discontinued SoC chemotherapy due to maximum cycles of chemotherapy reached. One patient was randomized to the T + D + SoC treatment arm but did not receive SoC.

In the D + SoC arm, 303 (90.4%) patients discontinued durvalumab; the most common reasons for discontinuation of durvalumab included condition under investigation worsened (67.5%) and AEs (16.7%). A total of 314 (93.7%) patients discontinued SoC chemotherapy; the most common reasons for discontinuation of chemotherapy (corresponding to last SoC chemotherapy agent received) included condition under investigation worsened (39.4%) and AEs (18.8%). Ninety-five (28.4%) patients discontinued SoC chemotherapy due to maximum cycles of chemotherapy reached.

In the SoC alone arm, a total of 326 (98.5%) patients discontinued SoC chemotherapy; the most common reasons for discontinuation of SoC chemotherapy (corresponding to last SoC chemotherapy agent received) included condition under investigation worsened (55.3%) and AEs (13.3%). Seventy-three (22.1%) patients discontinued SoC chemotherapy due to maximum cycles of chemotherapy reached.

At the time of final DCO, 80 (23.7%) patients in the T + D + SoC arm, 65 (19.2%) in the D + SoC arm, and 40 (11.9%) in the SoC alone arm had completed the study (ie, were receiving ongoing study treatment and/or were in survival follow up); 37 (11.2%) in the T + D + SoC arm, 31 (9.3%) in the D + SoC arm, and 5 (1.5%) in the SoC alone arm were receiving ongoing study treatment.

Demographics and baseline disease characteristics were generally representative of treatment-naïve patients with metastatic NSCLC who are eligible to receive 1L treatment. Demographics and baseline disease characteristics and were generally balanced across the 3 treatment arms.

The median age was 64 years (range: PPD approximately 47% of patients were of age 65 years and above. The majority of patients were Male (76.0%). Across the 3 treatment arms, a lower percentage of Female patients was noted in the T + D + SoC arm, compared with the D + SoC and SoC alone arms (20.4% vs 25.1% and 26.4%, respectively). The majority of patients were White (55.9%), followed by Asian (34.6%); a lower percentage of patients were Asian in the T + D + SoC arm compared with the D + SoC and SoC alone arms (29.3% vs 36.4% and 38.0%).

Most patients (78%) were either current or former smokers, with 21.9% of patients who reported being never-smokers. Across the 3 treatment arms, a lower percentage of never smokers was noted in the T + D + SoC arm, compared with the D + SoC and SoC alone arms (17.5% vs 24.9% and 23.4%, respectively). As per the study eligibility criteria, at study entry, patients had either normal (Eastern Cooperative Oncology Group [ECOG] Performance Status [PS] 0: 33.4%) or restricted activity (ECOG PS 1: 66.5%).

The majority of patients had metastatic lesions (99.6%) with Stage IVA (50.0%) or IVB disease (49.6%). The predominant reported histology was non-squamous (62.9%) and 36.9% of patients had squamous histology; the histologic distribution was balanced across the 3 treatment arms. Baseline brain/CNS metastases were reported in 10.5% of patients.

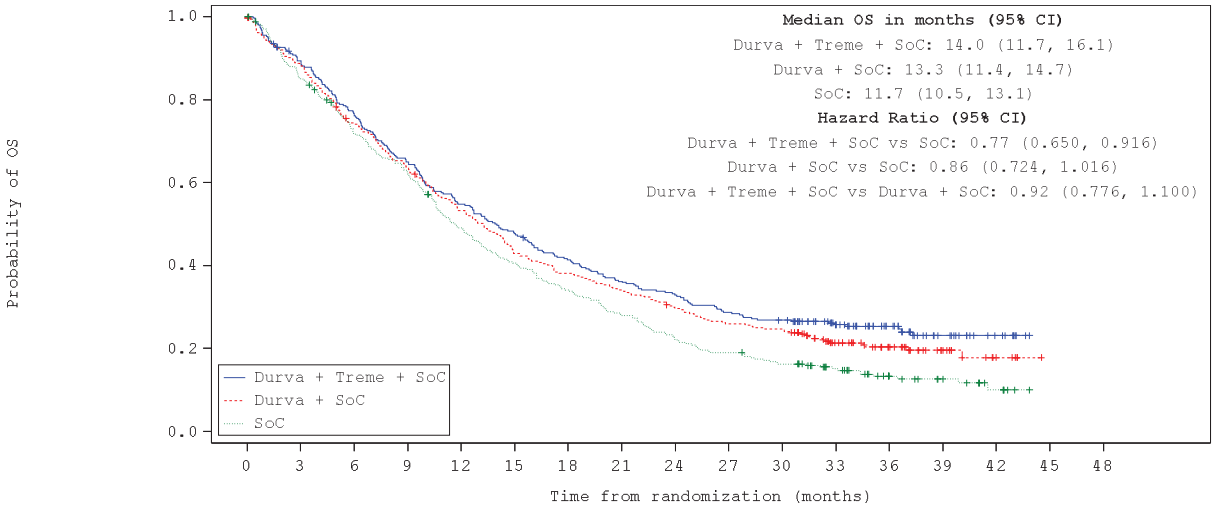
Summary of efficacy results

T + D + SoC versus SoC alone

Overall survival: OS for the comparison of T + D + SoC versus SoC in the FAS was a key secondary endpoint. At the time of the OS final analysis, 536 death events had occurred (79.4% maturity for OS overall). The final analysis of OS met the prespecified boundary for declaring statistical significance between the T + D + SoC versus SoC alone arms (2-sided p-value boundary of 0.00797 for a 1% overall alpha recycled from the significant PFS test of T + D + SoC versus SoC alone in the FAS). T + D + SoC provided a statistically significant improvement in OS compared with SoC alone; the OS HR was 0.77 (95% CI: 0.650, 0.916; p=0.00304) in favor of T + D + SoC, representing a 23% reduction in the risk of death. The

median OS was 14.0 months (95% CI: 11.7, 16.1) in the T + D + SoC arm and 11.7 months (95% CI: 10.5, 13.1) in the SoC alone arm.

Figure S1 Kaplan-Meier plot of overall survival (full analysis set) All treatments



Number of patients at risk — Number of events/Number of randomized patients

Durva + Treme + SoC	338	298	256	217	183	159	137	120	109	95	88	64	41	20	9	0	0 251/338
Durva + SoC	338	296	247	212	176	142	126	112	97	85	81	51	33	15	5	0	0 264/338
SoC	337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0	0 285/337

The separation of the Kaplan-Meier OS curves in favor of T + D + SoC versus SoC alone appeared approximately 3 months after randomization, with a pronounced separation visible around 10 months (Figure S1). The delay in separation of the curves indicated existence of non-proportional hazards (p=0.039). The OS HR, therefore, is to be interpreted as an average estimate of the observed benefit alongside the survival curves, with survival landmarks and durable response rates helping to further characterize the totality of the clinical benefit. After 10 months, the OS separation was sustained over the treatment period and was supported by numerically higher OS rates for T + D + SoC compared with SoC alone at 12 months (54.8% vs 49.1%, respectively); at 18 months (41.3% vs 34.1%, respectively); at 24 months (32.9% vs 22.1%, respectively); and at 36 months (25.3% vs 13.3%, respectively). Sensitivity analyses, including a stratified max-combo test and RMST, were performed to evaluate the robustness of the treatment effect. The results of all sensitivity analyses were generally consistent with the primary analysis of OS treatment benefit of T + D + SoC vs SoC.

In general, survival benefit of T + D + SoC versus SoC alone was observed across the prespecified subgroups (based on demographics, baseline disease characteristics, PD-L1 expression status, bTMB status, histology, and planned chemotherapy administered) except for patients who reported being never smokers. However, the subgroup analyses should be

interpreted with caution due to a low number of patients and events across the individual subgroups, which leads to greater uncertainty in their point estimates and wide CIs.

OS in the bTMB high analysis sets for the comparison of T + D + SoC versus SoC was included in the MTP hierarchy. The final analysis of OS in the bTMB20 high analysis set did not meet the prespecified boundary for declaring statistical significance between the T + D + SoC versus SoC alone arms (2-sided p-value boundary of 0.00334 for a 1% overall alpha recycled from the significant PFS and OS tests of T + D + SoC vs SoC alone in the FAS). Consequently, the bTMB16 and bTMB12 populations were not tested for significance. OS favored T + D + SoC compared with SoC alone (HR <1) across all tumor mutational burden high analysis sets. In the bTMB20 high analysis set, the OS HR was 0.68 (95% CI: 0.460, 0.989; p=0.04332) in favor of T + D + SoC compared with SoC alone. The median OS was 13.5 months (95% CI: 9.7, 19.6) in the T + D + SoC arm and 10.3 months (95% CI: 7.4, 13.1) in the SoC alone arm. The OS rates were higher for T + D + SoC compared with SoC alone at 12 months (54.1% vs 44.8%, respectively); at 18 months (41.9% vs 27.1%, respectively); at 24 months (33.8% vs 14.9%, respectively); and at 36 months (29.3% vs 10.3%, respectively). The separation of the OS Kaplan-Meier curves in favor of T + D + SoC versus SoC alone appeared approximately 2 months after randomization across the bTMB high analysis sets and was sustained over the treatment period and was sustained over the treatment period. OS favored T + D + SoC compared with SoC alone (HR <1) across the PD-L1 analysis sets.

Progression-free survival: PFS for the comparison of T + D + SoC versus SoC in the FAS was a key secondary endpoint. At the PFS final analysis, 496 PFS events had occurred across the T + D + SoC and SoC alone arms (73.5% maturity for PFS overall). The final analysis of PFS met the prespecified boundary for declaring statistical significance between the T + D + SoC versus SoC alone arms (2-sided p-value boundary of 0.00735 for a 1% overall alpha recycled from the significant PFS test of D + SoC vs SoC in the FAS). T + D + SoC provided a statistically significant improvement in PFS (key secondary endpoint) compared with SoC alone; the PFS HR assessed by blinded independent central review (BICR) was 0.72 (95% CI: 0.600, 0.860; p=0.00031) in favor of T + D + SoC, representing a 28% reduction in the risk of progression or death. The median PFS was 6.2 months (95% CI: 5.0, 6.5) in the T + D + SoC arm and 4.8 months (95% CI: 4.6, 5.8) in the SoC alone arm. The separation of the Kaplan-Meier PFS curves in favor of T + D + SoC versus SoC alone appeared approximately 2 months after randomization. The separation was sustained over the treatment period and was supported by the estimates of the 12-month PFS rate, with the T + D + SoC treatment demonstrating >10% higher PFS rate compared with SoC alone (26.6% vs 13.1%, respectively). The complementary PFS log-log plot showed evidence of non-proportionality of hazards (p=0.049). Sensitivity analyses (possibility of evaluation-time bias, attrition bias and ascertainment bias, and using eCRF-derived stratification variables) supported the results from the primary analysis. The PFS benefit of T + D + SoC versus SoC alone was observed across

all prespecified subgroups (prespecified stratification factors, demographics, planned chemotherapy administered, and baseline disease characteristics). PFS favored T + D + SoC compared with SoC alone (HR <1) across the bTMB high and PD-L1 analysis sets.

Objective response rate and duration of response: The pre-specified objective response rate (ORR) using unconfirmed responses based on BICR was higher in the T + D + SoC arm (46.3%) compared with the SoC alone arm (33.4%), with an odds ratio of 1.72 in favor of T + D + SoC (95% CI: 1.260, 2.367; nominal p<0.001). Responses were more durable in the T + D + SoC arm compared with the SoC alone arm with a median duration of response (DoR) of 7.4 months in the T + D + SoC arm compared with 4.2 months in the SoC alone arm. The percentage of responders with an estimated DoR of 12 months or longer was 42.5% in the T + D + SoC arm compared with 16.4% in the SoC alone arm. ORR favored T + D + SoC compared with SoC alone (odds ratio >1) across the bTMB high and PD-L1 analysis sets. Durability of response in the T + D + SoC arm compared with the SoC alone arm was shown across the bTMB high and PD-L1 analysis sets.

A post-hoc analysis was conducted to determine the confirmed ORR, defined as the number (%) of patients with at least one visit, response of CR or PR and a confirmatory scan no sooner than 4 weeks after the initial CR/PR. The confirmed ORR also demonstrated 14.4% incremental improvement favoring T + D + SoC over SoC (38.8% vs 24.4%, respectively, odds ratio: 2.00; 95% CI: 1.428, 2.807; nominal p<0.001). A post-hoc analysis, based on patients with a confirmed ORR, also demonstrated durable responses in the T + D + SoC arm compared to SoC alone arm (median DoR: 9.5 months vs 5.1 months respectively). For patients who had a confirmed ORR, 49.7% in the T + D + SoC arm remained in response at 12 months compared with 21.4% in the SoC alone arm.

T + D + SoC provided an improvement in PFS2 compared with SoC alone. The PFS2 HR was 0.75 (95% CI: 0.632, 0.883; nominal p<0.001) in favor of T + D + SoC. A delay in PFS2 favored T + D + SoC compared with SoC alone (HR <1) in the bTMB20 high analysis set and across the PD-L1 analysis sets.

T + D + SoC demonstrated a statistically significant improvement in OS while delaying the deterioration in health-related quality of life (HRQoL). Longer time to deterioration (TTD) was observed for patient-reported global health status/QoL, and all functioning and symptom scales in favor of T + D + SoC compared to SoC alone. Greater improvement rates in the T + D + SoC versus SoC alone were observed for patient-reported global health status/QoL, and all functioning and symptom scales.

D + SoC versus SoC alone

Overall survival: OS for the comparison of D + SoC versus SoC in the FAS was a dual primary endpoint. At the time of the OS final analysis, 549 death events had occurred across

the D + SoC and SoC alone treatment arms (81.3% maturity for OS overall). The final analysis of OS did not meet the prespecified boundary for declaring statistical significance between the D + SoC versus SoC alone arms (2-sided p-value boundary of 0.02879 for a 4% overall alpha in the FAS). The OS favored D + SoC over SoC alone, with an HR of 0.86 (95% CI: 0.724, 1.016; p=0.07581) in the FAS. The median OS was 13.3 months (95% CI: 11.4, 14.7) in the D + SoC arm and 11.7 months (95% CI: 10.5, 13.1) in the SoC alone arm. The separation of the Kaplan-Meier OS curves in favor of D + SoC versus SoC alone appeared around 11 months and remained separated from SoC throughout the treatment period (Figure S1). The OS rates for D + SoC compared with SoC alone at 12 months were 53.2% versus 49.1%, respectively; at 18 months were 38.1% versus 34.1%, respectively; at 24 months were 29.6% versus 22.1%, respectively; and at 36 months were 20.3% versus 13.3%, respectively. Sensitivity analyses supported the results from the primary analysis. In general, the survival benefit of D + SoC versus SoC alone was observed across the prespecified subgroups. OS favored D + SoC compared with SoC alone (HR <1) across the bTMB high analysis sets. OS in the D + SoC and SoC alone arms favored D + SoC in the PD-L1 <50% and PD-L1 <25% analysis sets (HR <1) and were similar (HR of approximately 1) in the PD-L1 <1% analysis set.

Progression-free survival: PFS for the comparison of D + SoC versus SoC in the FAS was a dual primary endpoint. At the time of the PFS final analysis, 511 PFS events had occurred across the D + SoC and SoC alone arms (75.7% maturity for PFS overall). The final analysis of PFS met the prespecified boundary for declaring statistical significance between the D + SoC versus SoC alone arms (2-sided p-value boundary of 0.00819 for a 1% overall alpha in the FAS). D + SoC provided a statistically significant improvement in the PFS compared with SoC alone; the PFS HR assessed by BICR was 0.74 (95% CI: 0.620, 0.885; p=0.00093) in favor of D + SoC, representing a 26% reduction in the risk of progression or death. The median PFS was 5.5 months (95% CI: 4.7, 6.5) in the D + SoC arm and 4.8 months (95% CI: 4.6, 5.8) in the SoC alone arm. The Kaplan-Meier curves for PFS in the D + SoC and SoC alone arms separated at approximately 2 months after randomization. The separation was sustained over the treatment period and was supported by the estimates of the 12-month PFS rates: 24.4% (95% CI: 19.7, 29.5) and 13.1% (95% CI: 9.3, 17.6), in the D + SoC and SoC alone arms, respectively. The complementary PFS log-log plot showed evidence of non-proportionality of hazards (p=0.030). Sensitivity analyses (possibility of evaluation-time bias, attrition bias and ascertainment bias, and using eCRF-derived stratification variables) supported the results from the primary analysis. The PFS benefit of D + SoC versus SoC alone was observed across all prespecified subgroups (prespecified stratification factors, demographics, planned chemotherapy administered, and baseline disease characteristics). PFS favored D + SoC compared with SoC alone (HR <1) across the bTMB high and PD-L1 analysis sets.

Objective response rate and duration of response: The pre-specified ORR using unconfirmed responses based on BICR was higher in the D + SoC arm (48.5%) compared with the SoC alone arm (33.4%), with an odds ratio of 1.90 in favor of D + SoC (95% CI: 1.382, 2.619; nominal p<0.001). Responses were more durable in the D + SoC arm compared with the SoC alone arm with a median DoR of 6.0 months in the D + SoC arm compared with 4.2 months in the SoC alone arm. The percentage of responders with an estimated DoR of 12 months or longer was 34.1% in the D + SoC arm compared with 16.4% in the SoC alone arm.

A post-hoc analysis was conducted to determine the confirmed ORR. The confirmed ORR also demonstrated 17.1% incremental improvement favoring D + SoC over SoC (41.5% vs 24.4%, respectively, odds ratio: 2.26; 95% CI: 1.611, 3.185; nominal p<0.001). A post-hoc analysis, based on patients with a confirmed ORR, also demonstrated durable responses in the D + SoC arm compared with the SoC alone arm (median DoR 7.0 vs 5.1 months, respectively). For patients who had a confirmed ORR, 38.9% in the D + SoC arm remained in response at 12 months compared with 21.4% in the SoC alone arm.

D + SoC provided an improvement in PFS2 compared with SoC alone. The PFS2 HR was 0.79 (95% CI: 0.666, 0.928; nominal p=0.004) in favor of D + SoC. A delay in PFS2 favored D + SoC compared with SoC alone (HR <1) in the bTMB20 high analysis set and across the PD-L1 analysis sets.

D + SoC demonstrated a numerical improvement in OS while delaying the deterioration in HRQoL. Longer TTD was observed for patient-reported global health status/QoL, and all functioning and symptom scales in favor of D + SoC compared to SoC alone, except for appetite loss. Greater improvement rates in the D + SoC versus SoC alone were observed for patient reported global health status/QoL, and all functioning and symptom scales.

T + D + SoC versus D + SoC

At the time of the OS final analysis, 515 death events had occurred (76.2% maturity for OS overall). As the prespecified MTP did not include an alpha-controlled comparison between the T + D + SoC and D + SoC arms, the 2 treatment arms were compared based on descriptive statistics. There was an incremental improvement in OS in the T + D + SoC arm compared with the D + SoC arm (HR: 0.92; 95% CI: 0.776, 1.100; nominal p=0.373) in the FAS. The median OS was 14.0 months (95% CI: 11.7, 16.1) in the T + D + SoC arm and 13.3 months (95% CI: 11.4, 14.7) in the D + SoC arm. The improvement in OS in the T + D + SoC arm compared with the D + SoC arm was observed throughout the OS Kaplan-Meier curve and this separation was particularly pronounced in the long term (Figure S1). Due to delayed separation of the Kaplan-Meier curves, the totality of the clinical benefit of the T + D + SoC treatment regimen is most appropriately described based on the OS HR in combination with the clinical benefits observed at long-term survival landmarks and durable responses. The OS

rates for T + D + SoC compared with D + SoC at 12 months were 54.8% versus 53.2%, respectively; at 24 months were 32.9% versus 29.6%, respectively; and at 36 months were 25.3% versus 20.3%, respectively.

At the time of the PFS final analysis, 491 PFS events had occurred across the T + D + SoC and D + SoC arms (72.6% maturity for PFS overall). PFS was similar in the T + D + SoC arm compared to the D + SoC arm, with an HR of 0.97 (95% CI: 0.815, 1.166; nominal p=0.796). The median PFS was 6.2 months (95% CI: 5.0, 6.5) in the T + D + SoC arm and 5.5 months (95% CI: 4.7, 6.5) in the D + SoC arm. The PFS rates at 12 months were 26.6% (95% CI: 21.7, 31.7) in the T + D + SoC arm and 24.4% (95% CI: 19.7, 29.5) in the D + SoC arm.

The pre-specified ORR using unconfirmed responses based on BICR was similar in the T + D + SoC arm (46.3%) compared with the D + SoC arm (48.5%), with an odds ratio in favor of D + SoC of 0.91 (95% CI: 0.668, 1.244; nominal p=0.561). The post-hoc analysis based on patients with a confirmed ORR was similar in the T + D + SoC arm (38.8%) compared with the D + SoC arm (41.5%), with an odds ratio in favor of D + SoC of 0.89 (95% CI: 0.646, 1.218; nominal p=0.461).

In terms of the pre-specified analysis using unconfirmed responses based on BICR, the median time to response was the same in the T + D + SoC and D + SoC arms (1.5 months in both arms). Responses were more durable in the T + D + SoC arm compared with the D + SoC arm with a median DoR of 7.4 months in the T + D + SoC arm compared with 6.0 months in the D + SoC arm. The percentage of responders in the T + D + SoC and D + SoC arms with an estimated DoR of 12 months or longer was 42.5% vs 34.1%, respectively; and with an estimated DoR of 18 months or longer was 34.7% vs 25.9%, respectively. In terms of the post-hoc analysis based on patients with a confirmed ORR, the median time to response was the same in the T + D + SoC and D + SoC arms (1.5 months in both arms). The median DoR was 9.5 months in the T + D + SoC arm compared with 7.0 months in the D + SoC arm. The percentage of responders in the T + D + SoC and D + SoC arms with an estimated DoR of 12 months or longer was 49.7% vs 38.9%, respectively; and with an estimated DoR of 18 months or longer was 40.7% vs 29.6%, respectively.

The median PFS2 was 10.4 months (95% CI: 9.4, 12.2) in the T + D + SoC arm and 10.2 months (95% CI: 9.0, 11.5) in the D + SoC arm.

Summary of pharmacokinetic results

No formal non-compartmental analysis for durvalumab or tremelimumab was conducted due to the sparse 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 between T + D + SoC and D + SoC arms,

suggesting tremelimumab or SoC do not have an impact on PK of durvalumab when administered as combination therapy. Overall, PK results of gemcitabine and Abraxane were similar between T + D + SoC, D + SoC, and SoC alone arms, suggesting durvalumab or tremelimumab do not have an impact on PK of SoC chemotherapy (gemcitabine or Abraxane) when administered as combination therapy.

Summary of immunogenicity results

The anti-drug antibody (ADA) results in this study were consistent with those reported previously. Transient ADA responses with low ADA titer and few neutralizing antibody (nAb)-positive patients are consistent with the known immunogenicity profile of durvalumab. The mean serum trough durvalumab concentrations of the patients with treatment-emergent ADA detected against durvalumab were lower than those in ADA negative patients. ADA prevalence and incidence of tremelimumab were within the range of those reported in other studies. Consistent with the known immunogenicity profile of tremelimumab, the majority of ADA-positive patients were classified as treatment-emergent ADA positive and tested positive for nAb. The mean serum trough tremelimumab concentrations of the patients with treatment-emergent tremelimumab ADA were similar to those in ADA-negative patients.

Summary of safety results

Extent of exposure

At the DCO of 12 March 2021, the total duration of treatment across all patients in the T + D + SoC arm was 313.8 years, in the D + SoC arm was 289.9 years and in the SoC alone arm was 164.9 years.

Tremelimumab: The median exposure to tremelimumab was 20.00 weeks (range: 1.1 to 38.3). Patients received a median of 5.0 cycles (range: 1 to 9) of tremelimumab. The planned 5 cycles of tremelimumab were completed by 66.1% of patients, and 3.3% of patients received tremelimumab retreatment (≥6 cycles).

Durvalumab: The median exposure to durvalumab was generally similar between the T + D + SoC and D + SoC arms. The median duration of exposure was 29.79 weeks in the T + D + SoC arm and 28.71 weeks in the D + SoC arm. The median number of durvalumab cycles was 8.0 in both treatment arms. Overall, 28.5% of patients in the T + D + SoC arm and 26.6% of patients in the D + SoC arm received ≥14 cycles of durvalumab (approximately 12 months of treatment).

SoC chemotherapy: Patients received histology specific doublet chemotherapies per local treatment guidelines. In the combination stage, across the 3 treatment arms, 60.2% of patients received pemetrexed doublet therapy, 32.7% received gemcitabine doublet therapy, and 7.0% received Abraxane doublet chemotherapy.

The chemotherapies administered were generally balanced across the 3 treatment arms. In the combination stage, the planned 4 cycles of chemotherapy were completed by 78.5% of patients in the T + D + SoC arm, 81.7% of patients in the D + SoC arm, and 74.2% of patients in the SoC alone arm. Per study criteria, patients in the SoC arm were eligible to receive an additional 2 cycles of chemotherapy (total 6 cycles) as clinically indicated and per Investigator's discretion; 27.3% of patients received ≥5 cycles, and 23.1% of patients received ≥6 cycles of chemotherapy. The addition of tremelimumab did not compromise the ability to administer durvalumab + doublet chemotherapies.

The majority of patients who received pemetrexed during the combination stage received pemetrexed maintenance chemotherapy: 75.3% in the T + D + SoC, 80.3% in the D + SoC, and 64.2% in the SoC alone arms. The addition of tremelimumab + durvalumab or durvalumab did not compromise the ability to administer doublet chemotherapies, or where appropriate, pemetrexed maintenance therapy.

Adverse events, deaths, serious adverse events, discontinuations of investigational product, immune-mediated adverse events

Overall, the majority of patients experienced at least 1 AE (97.3%, 96.1%, and 96.1% in the T + D + SoC, D + SoC, and SoC alone arms, respectively).

T + D + SoC versus SoC alone

In the T + D + SoC arm compared with the SoC alone arm, the most commonly reported (≥20% of patients in either arm, respectively) AEs by preferred term (PT) were anemia (49.7% vs 48.9%), nausea (41.5% vs 36.6%), neutropenia (30.0% vs 23.4%), decreased appetite (28.2% vs 24.6%), fatigue (24.5% vs 22.2%), diarrhea (21.5% vs 15.3%), and constipation (19.1% vs 23.7%). AEs that were reported in a higher percentage of patients (≥5% difference between arms) in the T + D + SoC arm compared with the SoC alone arm, respectively were neutropenia (30.0% vs 23.4%), diarrhea (21.5% vs 15.3%), rash (19.4% vs 6.6%), pyrexia (16.1% vs 6.9%), arthralgia (12.4% vs 6.3%), hypothyroidism (11.8% vs 1.2%), pruritis (10.9% vs 4.5%), and hyperthyroidism (5.8% vs 0.6%). The only AE reported in a lower percentage of patients (≥5% difference) in the T + D + SoC arm compared with the SoC alone arm, respectively was neutrophil count decreased (11.8% vs 17.7%). As noted previously the event of neutropenia was reported at a numerically higher incidence in the T + D +SoC arm (30.0% vs 23.4%). As such an event of neutropenia or neutrophil count decreased was reported for approximately 41% of patients in each treatment arm. After adjusting for exposure, these events occurred with a similar incidence in both arms, except for a higher incidence in the T + D + SoC arm of hypothyroidism and rash, and a lower incidence of diarrhea, neutropenia, and neutrophil count decreased compared with the SoC alone arm. In the T + D + SoC arm compared with the SoC alone arm, the incidence of AEs that were

considered to be causally-related to 1 or more of the agents within the treatment regimen by the investigator were similar in both arms (92.7% vs 89.5%, respectively).

In the T + D + SoC arm compared to the SoC alone arm, there was a ≥3% difference between the total Grade 3 or 4 AEs reported in the System Organ Class of Infections and infestations (13.0% vs 8.4%). The most common Grade 3 or 4 AEs by PT were generally similar between the treatment arms except for a higher percentage of patients (≥3% difference) in the T + D + SoC arm compared to the SoC alone arm reporting neutropenia (17.0% vs 12.3%) and pneumonia (7.0% vs 3.0%).

AEs leading to death were reported in a higher percentage of patients in the T + D + SoC arm compared with the SoC alone arm (12.4% vs 9.0%).

Serious adverse events (SAEs) were reported in a higher percentage of patients in the T + D + SoC arm (44.2%) compared with the SoC alone arm (35.1%). In the T + D + SoC arm compared to the SoC alone arm, there was a ≥2% difference between total SAEs reported in the System Organ Classes of Infections and infestations (17.9% vs 10.2%, respectively), Gastrointestinal disorders (7.6% vs 2.7%), Nervous system disorders (5.8% vs 3.0%), Respiratory, thoracic and mediastinal disorders (5.5% vs 8.1%), General disorders and administration site conditions (3.9% vs 1.5%), and Renal and urinary disorders (3.3% vs 0.9%). The frequency of SAEs by PT was generally similar in the T + D + SoC arm compared to the SoC alone arm, except for a ≥2% difference between arms in the incidence of pneumonia (10.9 vs 4.8%, respectively) and pyrexia (2.4% vs 0.3%).

AEs leading to discontinuation of any study treatment were reported in a higher percentage of patients in the T + D + SoC arm compared with the SoC alone arm (22.1% vs 15.3%). AEs leading to permanent discontinuation of 1 or more agents within each treatment arm by PT were dispersed across the 3 treatment arms with no obvious trends. In the T + D + SoC arm compared to the SoC alone arm, there was a ≥2% difference between total AEs leading to discontinuation of study treatment reported in the System Organ Classes of Infections and infestations (4.5% vs 2.4%, respectively) and Gastrointestinal disorders (3% vs 0.9%).

A total of 111 (33.6%) patients in the T + D + SoC arm and 17 (5.1%) patients in the SoC alone arm met the criteria for immune-mediated adverse events (imAEs). In the majority of patients, imAEs were of Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2. CTCAE Grade 3 or 4 imAEs were reported in 33 (10.0%) and 5 (1.5%) patients in the T + D+ SoC and SoC alone arms, respectively. imAEs that were considered by the investigator to be possibly related to treatment were reported in 105 (31.8%) and 12 (3.6%) patients in the T + D + SoC and SoC alone arms, respectively. imAEs with an outcome of death were reported in 2 (0.6%) patients in the T + D + SoC arm and no patients in the SoC alone arm. imAEs led to study treatment discontinuation in 19 (5.8%) and 2 (0.6%) patients in the T + D + SoC and SoC alone arms, respectively.

D + SoC versus SoC alone

In the D + SoC arm compared with the SoC alone arm, the most commonly reported (≥20% of patients in either arm, respectively) AEs by PT were anemia (45.2% vs 48.9%), nausea (36.2% vs 36.6%), fatigue (24.3% vs 22.2%), neutropenia (23.7% vs 23.4%), decreased appetite (21.6% vs 24.6%), and constipation (21.6% vs 23.7%).

AEs that were reported in a higher percentage of patients (≥5% difference between arms) in the D + SoC arm compared with the SoC alone arm, respectively were rash (14.1% vs 6.6%), hypothyroidism (6.3% vs 1.2%), and hyperthyroidism (6.0% vs 0.6%). After adjusting for exposure, these events occurred with a similar incidence in both arms, except for a higher incidence in the D + SoC arm of hyperthyroidism compared with the SoC alone arm. In the D + SoC arm compared with the SoC alone arm, the incidence of AEs that were considered to be causally-related by the investigator were similar in both arms (88.6% vs 89.5%, respectively).

The frequency of total Grade 3 or 4 AEs reported by System Organ Class were similar in the D + SoC and SoC alone arms (<3% difference between arms). The most common Grade 3 or 4 AEs by PT were generally similar between the treatment arms except for a lower percentage of patients (≥3% difference) in the D + SoC arm compared to the SoC alone arm, respectively reporting anemia (17.7% vs 22.5%).

AEs leading to death were reported in a similar percentage of patients in the D + SoC and SoC alone arms (10.2% vs 9.0%).

SAEs were reported in a higher percentage of patients in the D + SoC arm compared with the SoC alone arm (40.1% vs 35.1%). In the D + SoC arm compared to the SoC alone arm, there was a ≥2% difference between total SAEs reported in the System Organ Classes of Infections and infestations (12.3% vs 10.2%, respectively), Blood and lymphatic system disorders (10.8% vs 8.7%), General disorders and administration site conditions (4.8% vs 1.5%), and Gastrointestinal disorders (5.7% vs 2.7%).

AEs leading to discontinuation of any study treatment were reported in a higher percentage of patients in the D + SoC arm compared with the SoC alone arm (20.4% vs 15.3%). AEs leading to permanent discontinuation of 1 or more agents within each treatment arm by PT were dispersed across the 3 treatment arms with no obvious trends.

A total of 64 (19.2%) patients in the D + SoC arm and 17 (5.1%) patients in the SoC alone arm met the criteria for imAEs. In the majority of patients, imAEs were of CTCAE Grade 1 or 2. CTCAE Grade 3 or 4 imAEs were reported in 23 (6.9%) and 5 (1.5%) patients in the D + SoC and SoC alone arms, respectively. imAEs that were considered by the investigator to be possibly related to treatment were reported in 55 (16.5%) and 12 (3.6%) patients in the

D + SoC and SoC alone arms, respectively. imAEs with an outcome of death were reported in 1 (0.3%) patient in the D + SoC arm and no patients in the SoC alone arm. imAEs led to study treatment discontinuation in 14 (4.2%) and 2 (0.6%) patients in the D + SoC and SoC alone arms, respectively.

T + D + SoC versus D + SoC

AEs by PT that were reported in a higher percentage of patients (≥5% difference between arms) in the T + D + SoC arm compared with the D + SoC arm, respectively were nausea (41.5% vs 36.2%), neutropenia (30.0% vs 23.7%), decreased appetite (28.2% vs 21.6%), rash (19.4% vs 14.1%), thrombocytopenia (18.2% vs 12.9%), asthenia (17.0% vs 9.9%), pyrexia (16.1% vs 9.3%), and hypothyroidism (11.8% vs 6.3%). After adjusting for exposure, these events occurred with a similar incidence in both arms, except for a higher incidence in the T + D + SoC arm of asthenia, pyrexia, and hypothyroidism compared with the D + SoC arm. In the T + D + SoC arm compared with the D + SoC arm, the incidence of AEs that were considered to be causally-related by the investigator were similar (92.7% vs 88.6%, respectively).

In the T + D + SoC arm compared to the D + SoC arm, respectively there was a ≥3% difference between total Grade 3 or 4 AEs reported in the System Organ Class of Blood and lymphatic system disorders (33.3% vs 29.6%). The most common Grade 3 or 4 AEs by PT were generally similar between treatment arms except for a higher percentage of patients (≥3% difference) in the T + D + SoC arm compared to the D + SoC arm, respectively reporting neutropenia (17.0% vs 13.8%).

AEs leading to death were reported in a higher percentage of patients in the T + D + SoC arm compared with the D + SoC arm (12.4% vs 10.2%).

SAEs were reported in a higher percentage of patients in the T + D + SoC arm compared with the D + SoC arm (44.2% vs 40.1%). In the T + D + SoC arm compared to the D + SoC arm, there was a ≥2% difference between total SAEs reported in the System Organ Class of Infections and infestations(17.9% vs 12.3% respectively) and Nervous system disorders (5.8% vs 1.8%). The frequency of SAEs by PT was generally similar in the T + D + SoC arm compared to the D + SoC arm, except for a ≥2% difference between arms in the incidence of pneumonia (10.9% vs 6.3%, respectively) and pyrexia (2.4% vs 0.3%).

AEs leading to discontinuation of any study treatment were reported in a similar percentage of patients in both treatment arms (22.1% vs 20.4%). In the T + D + SoC arm compared to the D + SoC arm, there was a ≥2% difference between total AEs leading to discontinuation of study treatment reported in the System Organ Class of Infections and infestations (4.5% vs 2.4%, respectively).

A total of 111 (33.6%) patients in the T + D + SoC arm and 64 (19.2%) patients in the D + SoC arm met the criteria for imAEs. In the majority of patients, imAEs were of CTCAE Grade 1 or 2. CTCAE Grade 3 or 4 imAEs were reported in 33 (10.0%) and 23 (6.9%) patients in the T + D + SoC and D + SoC arms, respectively. imAEs that were considered by the investigator to be possibly related to treatment were reported in 105 (31.8%) and 55 (16.5%) patients in the T + D + SoC and D + SoC arms, respectively. imAEs with an outcome of death were reported in 2 (0.6%) patients in the T + D + SoC and 1 (0.3%) patient in the D + SoC arms. imAEs led to study treatment discontinuation in 19 (5.8%) patients in the T + D + SoC and 14 (4.2%) patients in the D + SoC arms.

Conclusions

- T + D + SoC demonstrated a statistically significant and clinically meaningful improvement in both OS and PFS compared to SoC alone.
    - The OS HR of T + D + SoC compared with SoC alone was 0.77 (95% CI: 0.650, 0.916; p=00304). Consistent with the mechanistic understanding of CTLA-4 and PD-L1 inhibition, a delayed separation of survival curves was observed between T + D + SoC and SoC alone and the proportional-hazards assumption was not met (p=0.039). The OS HR, therefore, provides an average estimate of benefit and is most appropriately interpreted in the context of the shape of the curves, which is characterized by transient initial survival benefit with chemotherapy, followed by long-term benefit with tremelimumab and durvalumab.
    - The survival benefits with T + D + SoC were sustained long term with a higher proportion of patients alive at the 24-month (32.9% vs 22.1%, respectively) and 36-month (25.3% vs 13.3%, respectively) landmarks.
    - OS analyses based on the prespecified stratification factors were consistent with those of the primary analysis. Similarly, the OS benefit was observed across all prespecified subgroups except for the never-smoker subgroup, but the results should be interpreted with caution due to the low number of patients and wide CI that included 1.
    - In addition, the overall risk of progression or death was reduced by an average of 28% (PFS HR: 0.72; 95% CI: 0.600, 0.860; p=0.00031), and a 14.4% incremental increase in the confirmed ORR was noted over SoC. Patients in the T + D + SoC arm experienced durable responses compared to those in the SoC alone arm (median DoR: 9.5 months vs 5.1 months respectively). For patients who had a confirmed ORR, 49.7% in the T + D + SoC arm remained in response at 12 months compared with 21.4% in the SoC alone arm.
    - T + D + SoC demonstrated a delay in the deterioration in HRQoL analyses.
- While D + SoC numerically improved the OS compared with SoC chemotherapy alone, the comparison did not cross the prespecified threshold of statistical significance (HR of 0.86; 95% CI: 0.724, 1.016; p=0.07581; threshold p=0.02879). It is however clear that a

higher percentage of patients derive long-term survival benefit in the D + SoC arm compared to the SoC alone arm with OS landmarks at 24 months (29.6% vs 22.1%, respectively) and 36 months (20.3% vs 13.3%, respectively). D + SoC demonstrated a statistically significant and clinically meaningful improvement in PFS compared with SoC chemotherapy alone (HR of 0.74; 95% CI: 0.620, 0.885; p=0.00093).

- The individual components of T + D + SoC provided distinct contributions to the efficacy of the T + D + SoC combination regimen and together drive significant survival benefits. The individual components of the treatment complement one another, with chemotherapy providing an early disease control and immunotherapies providing durable and sustained survival benefits.
- The overall safety findings in all arms remained consistent with the known safety profiles of tremelimumab plus durvalumab, durvalumab and individual chemotherapies. No new safety concern was identified.
- In conclusion, the totality of evidence demonstrates that the combination of tremelimumab, durvalumab, and SoC chemotherapy has a favorable benefit: risk profile as 1L treatment in patients with metastatic NSCLC.