Clinical Study Report Synopsis	
Drug Substance	Durvalumab and tremelimumab
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Phase I/II, Open-Label, Multicenter Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of Durvalumab Monotherapy or Durvalumab in Combination with Tremelimumab in Pediatric Patients with Advanced Solid Tumors and Hematological Malignancies

Study dates: First patient enrolled: 07 March 2019
Last patient last visit: 28 February 2023
The analyses presented in this report are based on a clinical data lock date of 20 April 2023.

Phase of development: Clinical pharmacology (I)/Therapeutic exploratory (II)

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

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centers

The study was initiated at 22 sites in 7 countries, and patients were enrolled at 19 sites in 7 countries.

Publications

None at the time of this report.

Objectives and criteria for evaluation

Table S1 Objectives and endpoints

Objectives	Endpoints
Primary (dose-finding phase)	
To determine the adult equivalent exposure/ maximum tolerated dose (MTD) /recommended Phase II (pediatric) dose (RP2D) of durvalumab in combination with tremelimumab and durvalumab as monotherapy following combination therapy.	Pharmacokinetics (PK) parameters (including maximum serum concentration [Cmax], minimum serum concentration [Cmin], area under the curve [AUC], and others). Time of RP2D assessment was to be at the end of the dose-finding phase, when sufficient numbers of evaluable samples had been accrued.
To determine the safety profile of durvalumab in combination with tremelimumab and durvalumab as monotherapy following combination therapy.	Adverse events (AEs), vital signs, physical examinations, electrocardiograms (ECGs), and laboratory evaluations.
Primary (dose-expansion phase)	
To determine the preliminary antitumor activity of durvalumab in combination with tremelimumab and durvalumab as monotherapy following combination therapy, at the recommended dose, using cohort-specific response criteria (eg, Response Evaluation Criteria in Solid Tumours [RECIST] 1.1).	Objective response rate (ORR) as determined by the Investigator assessed RECIST 1.1 or alternative pre-specified tumor specific response rates for different scoring systems. Assessment of antitumor activity was to be specific to tumor cohort. Additional efficacy endpoints that were to be collected included DoR, BOR, DCR, PFS, APF12, and APF18 based on RECIST 1.1 assessed by the Investigator, and OS, OS12, and OS24 as appropriate to each individual cohort.
Secondary (dose-finding and dose-expansion phases)	
To describe the PK of durvalumab and tremelimumab in combination and durvalumab as monotherapy following combination therapy, in children and young adults with solid tumors, or hematological malignancies. [a]	Individual durvalumab and tremelimumab concentrations in serum, and PK parameters including Cmax, Cmin, AUC, and other parameters where appropriate.
To determine the immunogenicity of durvalumab and tremelimumab in combination and durvalumab as monotherapy following combination therapy, in children and young adults with solid tumors.	CCI [redacted]
To determine the immunogenicity of durvalumab in combination with tremelimumab and durvalumab as monotherapy following combination therapy, in children and young adults with hematological malignancies. [a]	

Objectives	Endpoints
To measure effects on immune checkpoint inhibition in response to routine immunizations (dose-expansion phase only).	CCI
To evaluate immune activation and counts of natural killer (NK)-, B-, and T-cells.	
Safety	
To determine the safety profile and tolerability of patients from dose-expansion cohort(s) treated with durvalumab in combination with tremelimumab every 4 weeks (q4w).	Adverse events, vital signs, physical examinations, ECGs, and laboratory evaluations.

[a] Due to feasibility challenges and/or emergence of alternative therapy regimens, and discontinued development by the Sponsor of durvalumab and tremelimumab in adult hematological malignancies, all hematological malignancy cohorts were removed from the study as reflected in Global CSP Versions 5.0 and 6.0. No pediatric patients with hematological malignancies were enrolled and treated in the study. Accordingly, assessments in patients with hematological malignancies were not performed for this study.

Exploratory objectives and endpoints are not included in this CSR synopsis and can be found in the main CSR.

ADA = anti-drug antibody; AE = adverse event; APF12/18 = proportion of patients alive and progression free at 12/18 months from first dose of study treatment; AUC = area under the serum drug concentration-time curve; BOR = best objective response; CD = cluster of differentiation; Cmax = maximum serum concentration; Cmin = minimum serum concentration; CSP = clinical study protocol; CSR = clinical study report; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; MTD = maximum tolerated dose; NK = natural killer; ORR = objective response rate; OS = overall survival; OS12/24 = proportion of patients alive at 12/24 months from first dose of study treatment; PFS = progression-free survival; PK = pharmacokinetics; q4w = every 4 weeks; RECIST = Response Evaluation Criteria in Solid Tumours; RP2D = recommended Phase II dose.

Study design

This was an open-label, non-randomized, international, multicenter study investigating durvalumab in combination with tremelimumab (every 4 weeks for 4 cycles) followed by durvalumab monotherapy (every 4 weeks) in pediatric patients from birth to < 18 years of age with relapsed or refractory malignant solid tumors. The study was conducted in 2 sequential phases: a dose-finding phase (Phase I), followed by a dose-expansion phase (Phase II).

Each treatment cycle was 28 days. During the dose-finding phase, durvalumab was to be given as monotherapy for one cycle followed by the addition of tremelimumab for the next 4 cycles. For the dose-expansion phase, durvalumab was given in combination with tremelimumab for the first 4 cycles, starting on Cycle 1. When durvalumab was given in combination with tremelimumab, a maximum number of four 28-day cycles of tremelimumab was permitted, followed by durvalumab monotherapy administered every 4 weeks. Study treatment was administered until clinical or confirmed disease progression (determined by the

Investigator against tumor-specific objective criteria) or until any of the other discontinuation criteria are met, whichever came first.

Phase I: Dose-finding phase

The dose-finding phase of the study was conducted using a modified 3 + 3 design to determine whether durvalumab and tremelimumab could be administered safely in pediatric patients and if adult exposures could be achieved. Pediatric patients with relapsed or refractory malignant solid tumors including osteosarcoma and Ewing sarcoma (SARC-1 cohort), rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, and other sarcomas (SARC-2 cohort), neuroblastoma (NB cohort), and other solid tumors (STO) were enrolled in 2 arms: Arm A, with patients weighing ≥ 35 kg; Arm B, with patients weighing < 35 kg.

Based on the available clinical and pharmacokinetic (PK) data and simulations, the administration of an adult weight-adjusted dose in children with a body weight of ≥ 35 kg was anticipated to result in PK and target engagement profiles similar to adults; however, patients with a body weight < 35 kg were hypothesized to have exposures lower than those in adults, and thus could require higher doses to achieve exposures similar to adults. Consequently dose-finding was conducted in 2 body weight-based arms (ie, patients ≥ 35 kg and < 35 kg) in parallel. Based on emerging data during the conduct of the study, cohorts could also be backfilled to provide further assessment of safety and PK in specific age groups and to ensure a broad representation of ages/weights at a given dose level.

Three dose levels could be explored in each of the arms. Dose level 1 (DL 1) (durvalumab 20 mg/kg; tremelimumab 1 mg/kg) was 100% of the recommended adult dose of both durvalumab and tremelimumab administered as weight-adjusted doses.

A Data Review Committee (DRC) was established prior to the initiation of the study. The purpose of the DRC was to review all the data from this study, with a primary emphasis on safety and PK, to make decisions on dose escalations and determination of a recommended Phase II dose (RP2D) to be further explored in the dose-expansion phase. Dose escalation decisions and determination of RP2D mainly considered safety assessments from at least 3 patients followed up for 4 cycles, including a single cycle of durvalumab and 3 cycles of the combination of durvalumab and tremelimumab (for a total of 120 days). This included assessment of pre-defined dose-limiting toxicities (DLTs) in the first 2 cycles.

A de-escalation step could occur for durvalumab or tremelimumab, with reduced doses of 15 mg/kg and 0.75 mg/kg, respectively, if DL 1 was considered not tolerated. Furthermore, if exposure of durvalumab or/and tremelimumab proved inadequate, intermediate dose levels could also be tested.

In addition, 3 patients older than 2 years of age had to be treated with durvalumab in combination with tremelimumab and clear the DLT period before children less than 2 years old could be enrolled in the dose-finding phase.

Phase II: Dose-expansion phase

The dose-expansion phase was conducted using a Simon 2-stage optimal design with an additional provision to include one mixed disease cohort (other malignant solid tumors).

Once the RP2D had been established, patients were recruited to each of the following cohorts: SARCOMA (bone sarcomas: osteosarcoma, Ewing sarcoma; soft-tissue sarcomas [≥ 40% of enrollment]: rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, and other sarcomas); STO (other solid tumors).

For the SARCOMA cohort, the initial stage allowed 11 evaluable patients to be dosed. If 2 or more responses were observed in this cohort, additional patients were to be accrued, as part of the second stage, into the expansion cohort; 15 patients were to be accrued into the SARCOMA expansion cohort for a total of 26 evaluable patients. If there was ≤ 1 objective response in the SARCOMA cohort (11 patients) at the time that evaluable patients dosed in the initial stage had been followed/assessed for at least 3 cycles, the cohort was to be discontinued for lack of benefit.

For the STO cohort, 10 evaluable patients were enrolled into this mixed disease cohort; Simon rules were not applicable for this cohort.

The primary completion date of the study for the purpose of the primary analysis occurred approximately 6 months following enrollment of the last patient. End of study was defined as the completion of the 90-day safety follow-up period for the last patient who was no longer receiving study treatment (ie, last patient, last visit). Patients continued to be followed up for survival and subsequent anti-cancer therapies beyond this 90-day period. Patients could be withdrawn from the study if the study itself was stopped. The study was to be stopped if, in the judgment of AstraZeneca, study patients were placed at undue risk because of clinically significant findings.

Target population and sample size

The study was conducted in pediatric patients from birth to < 18 years of age with relapsed or refractory malignant solid tumors (except primary central nervous system malignant tumors) who had histopathologic confirmation of malignancy, had progressed or were refractory to standard therapies, and who had no existing standard of care treatments. Patients had to have evaluable disease, no prior exposure to immune-mediated therapy, adequate organ and marrow function, and a life expectancy of at least 3 months.

A minimum of 12 patients and a maximum of 45 patients (if approximately 20% of patients needed to be replaced due to non-evaluability) were planned to be dosed in the dose-finding phase to enable exploration of a minimum of one dose level or a maximum of 3 dose levels in the dose-finding phase. In total, 29 patients received at least one dose of study treatment and were analyzed in the dose-finding phase.

For the dose-expansion phase, following a Simon 2-stage optimal design, a total of 26 evaluable patients (11 evaluable patients in the initial stage and an additional 15 patients in the second stage) were expected to be enrolled in the SARCOMA cohort. The STO cohort was planned to recruit 10 evaluable patients. Assuming that about 20% of patients may not be evaluable for objective response rate (ORR), the total number of patients dosed in the dose-expansion phase could range from approximately 25 to 43. In total, 21 patients received at least one dose of study treatment and were analyzed in the dose-expansion phase.

Investigational product and comparators: dosage, mode of administration, and batch numbers

Investigational products were administered intravenously every 4 weeks, ie, on 28-day cycles.

In the dose-finding phase, durvalumab monotherapy for the first cycle was followed by durvalumab + tremelimumab combination therapy for 4 cycles, and then further durvalumab monotherapy. Planned dose levels included:

- Dose level 1: Durvalumab 20 mg/kg; tremelimumab 1 mg/kg;
- Dose level 2: Durvalumab 40 mg/kg; tremelimumab 1 mg/kg;
- Dose level 3: Durvalumab 40 mg/kg; tremelimumab 2 mg/kg;
- Dose level -1 (if DL 1 was considered not tolerated): Durvalumab 15 mg/kg; tremelimumab 0.75 mg/kg.

The degree of dose escalation at dose level 2 (DL 2) and dose level 3 (DL 3) was to be determined based on the review of all the safety and emerging PK data. It was anticipated that dose ranges of 24 to 40 mg/kg and 1.2 to 2 mg/kg for durvalumab and tremelimumab, respectively, would be explored in DL 2 and DL 3 (the maximum doses of durvalumab and tremelimumab that were to be explored were 40 mg/kg and 2 mg/kg, respectively).

If at DL 1 durvalumab exposure was adequate and tremelimumab exposure was low, DL 2 could be skipped and tremelimumab alone could be escalated to DL 3 with durvalumab dosing remaining at the initial dose of 20 mg/kg. Furthermore, if exposure of durvalumab or/and tremelimumab proved inadequate based on PK data, intermediate dose levels could also be tested.

In the dose-expansion phase, patients were treated with the combination of durvalumab and tremelimumab (4 cycles followed by durvalumab monotherapy) using the RP2D for each based on data obtained from the dose-finding phase.

Lot numbers of investigational product used in the study were:

- Durvalumab: 24274.23, 24274.24, 24274.27, and 24274.28
- Tremelimumab: 24274.21 and 24274.30

Duration of treatment

Each treatment cycle was 28 days. During the dose-finding phase, durvalumab was to be given as monotherapy for one cycle (administered every 4 weeks) followed by the addition of tremelimumab for the next 4 cycles (administered every 4 weeks). For the dose-expansion phase, durvalumab was given in combination with tremelimumab for the first 4 cycles, starting on Cycle 1. When durvalumab was given in combination with tremelimumab, a maximum number of four 28-day cycles of tremelimumab was permitted, followed by durvalumab monotherapy administered every 4 weeks.

The primary completion date of the study for the purpose of the primary analysis occurred approximately 6 months following enrollment of the last patient. After the final data cutoff (DCO) for this study, AstraZeneca continued to supply durvalumab to patients who were receiving treatment with clinical benefit; treatment was to continue until evidence of disease progression, as judged by the Investigator, or until the patients met any other discontinuation criteria. If, in the opinion of the Investigator, a patient who received clinical benefit from treatment with the combination of durvalumab and tremelimumab subsequently progressed while on durvalumab maintenance monotherapy, the patient could be reconsented to receive another 4 cycles of tremelimumab while continuing durvalumab treatment. Retreatment with an additional combination regimen could only occur once (for a single time).

Statistical methods

There was no formal statistical testing for the dose-finding phase of the study. The dose-expansion phase of the study formally tested the following hypothesis:

- H0: ORR $\leq$ 10%
- H1: ORR > 10%.

The test was intended to be performed at the 1-sided 5% level and was to be performed for the SARCOMA cohort. No formal statistical testing was to be performed for the STO cohort.

Six analysis sets were used for data analysis:

- The full analysis set (FAS) included all patients who were assigned to treatment and received at least one dose of study treatment. The FAS (or subset of the FAS specified below) was used for all efficacy analyses.
- Evaluable for response analysis set was a subset of patients in the FAS who had measurable disease at baseline and had at least one follow-up scan measuring all required target lesions and had been followed for at least 3 cycles (to allow for a confirmatory scan at 4 weeks after the first assessment scan) OR patients in the FAS who had measurable disease at baseline and progressed or died in the absence of a follow-up scan.
- The safety analysis set (SAS) consisted of all patients who received any amount of study treatment. Safety data were summarized using the SAS according to the treatment received.
- The DLT evaluable analysis set was a subset of the SAS for the dose-finding phase of the study. It included all patients enrolled in the dose-finding phase of the study who received the protocol-assigned treatment with durvalumab + tremelimumab and completed the safety follow-up through the DLT evaluation period (Cycle 1 + Cycle 2) or experienced a DLT during the DLT evaluation period.
- The PK analysis set consisted of all patients who received at least one dose of study treatment per the protocol for whom any post-dose data were available and who did not violate or deviate from the protocol in ways that would significantly affect the PK analyses. The population was defined by the Study Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.
- The anti-drug antibody (ADA) analysis set included all patients who received at least one dose of study treatment per the clinical study protocol for whom baseline and any post-dose data were available.

The 2 phases of the study were summarized and analyzed separately. For the dose-finding phase, the arms based on patient weight (Arm A: patients ≥ 35 kg and Arm B: patients < 35 kg) were summarized separately, along with an overall summary by dose level. For the dose-expansion phase, summaries and analyses were presented by cohort. No multiplicity adjustment was applied.

Efficacy analyses were produced for the dose-expansion patients only. All tumor-related endpoints were analyzed using Investigator Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 assessments (Table S2). Objective response rate was the primary endpoint for the dose-expansion phase. The point estimate and 90% confidence interval (CI) (2-sided) of the ORR were presented for each of the analysis cohorts.

Table S2 Planned efficacy analysis to be conducted

Endpoint analyzed	Notes
ORR	Exact 90% 2-sided CI (Mid-P)
DoR	Median estimated from KM curve
DCR	Exact 90% 2-sided CI (Mid-P)
BOR	n (%) of patients in each response category
PFS	Median estimated from KM curve
OS	Median estimated from KM curve
APF12	90% 2-sided CI estimated from KM curve
APF18	90% 2-sided CI estimated from KM curve
OS12	90% 2-sided CI estimated from KM curve
OS24	90% 2-sided CI estimated from KM curve

APF12/18 = proportion of patients alive and progression free at 12/18 months from first dose of study treatment; BoR = best objective response; CI = confidence interval; DCR = disease control rate; DoR = duration of response; KM = Kaplan-Meier; n = number of patients in the analysis; ORR = objective response rate; OS = overall survival; OS12/24 = proportion of patients alive at 12/24 months from first dose of study treatment; PFS = progression-free survival.

Safety and tolerability data were presented using the SAS, with data from all cycles of treatment combined. Data were summarized descriptively for adverse events (AEs) (including serious AEs [SAEs]), deaths, laboratory data, vital signs, electrocardiograms (ECGs), physical examinations, and exposure to durvalumab + tremelimumab combination therapy and durvalumab monotherapy.

Pharmacokinetic parameters were a primary endpoint for the dose-finding phase and were used to facilitate the determination of the recommended Phase II dose. Pharmacokinetic data were listed by patient and summarized and analyzed based on the PK analysis set.

Immunogenicity results were listed by patient, and a summary was provided by the number and percentage of patients who developed detectable anti-durvalumab and anti-tremelimumab antibodies.

Individual vaccine antibody titer data before and after routine immunization and PPD data were to be listed by patient.

Study population

In the text that follows, in general, 'Dxx+T1 group' refers to patients who received xx mg/kg durvalumab in combination with 1 mg/kg tremelimumab; 'A/Dxx+T1 group' and 'B/Dxx+T1 group' refer to patients in Arm A or Arm B, respectively, who received xx mg/kg durvalumab

in combination with 1 mg/kg tremelimumab. For example, A/D20+T1 group refers to patients in Arm A who received 20 mg/kg durvalumab in combination with 1 mg/kg tremelimumab.

The study was initiated at 22 sites in 7 countries. Patients were enrolled at 19 sites in 7 countries, with the first patient enrolled (Informed Consent Form signed) on 07 March 2019 and the last patient's last visit, before the study DCO, completed on 28 February 2023.

The selection of 30 mg/kg durvalumab in combination with 1 mg/kg tremelimumab as DL 2 for the dose-finding phase, and as the RP2D for the dose-expansion phase, was as per the DRC's recommendations based on PK simulations and PK study data available at the time of these decisions.

The study population was representative of the intended target population of pediatric patients with advanced solid tumors. The medical and surgical history data were as expected for this patient population, with histories that were typical of the comorbidities and procedures seen in pediatric patients with advanced solid tumors. Disease characteristics of patients at study entry were representative of the intended population to be treated.

There were no concerns regarding protocol deviations in terms of study conduct or the safety of the patients, and they were not judged to have influenced the study outcome. The coronavirus disease 2019 (COVID-19) pandemic is not judged to have meaningfully impacted the overall quality of the study, including conduct, data, and interpretation of the results.

Dose-finding phase

Overall, 33 patients were enrolled in the dose-finding phase of the study, of whom 29/33 (87.9%) received treatment. In the D20+T1 group, all 10/10 (100%) patients who received durvalumab and all 9/10 (90.0%) patients who received tremelimumab discontinued treatment, the majority due to the development of study-specific discontinuation criteria. In the D30+T1 group, of the 19/19 (100%) patients who received durvalumab and 12/19 (63.2%) patients who received tremelimumab, 18/19 (94.7%) patients and 12/19 (63.2%) patients, respectively, discontinued treatment, with the most common reason being the development of study-specific discontinuation criteria.

At the time of DCO, 2/29 (6.9%) patients in the dose-finding phase were recorded as having been terminated from the study for 'other' reasons: one patient in the D20+T1 group completed the study, and one patient in the D30+T1 group was moved to the post-trial access program. An additional 3 patients in the D30+T1 group were terminated from the study as they were lost to follow-up, had consent withdrawn by a parent/guardian, or developed study-specific discontinuation criteria (1/29 [3.4%] patient each). The remaining 24/29 (82.8%) patients were terminated from the study due to death, in all cases assessed as related to the disease under investigation only (per Investigator assessment), with most events recorded > 90 days after the last dose of study treatment (see Summary of safety results).

Demographic and baseline characteristics were comparable across dose levels for patients in the FAS. As expected, median age, median height, and median body surface area were numerically lower in Arm B (patients < 35 kg), the lower weight group, than in Arm A (patients ≥ 35 kg).

In the D20+T1 group, patients had received a median (range) of 3.0 (1 to 9) prior regimens, and metastatic disease was reported in 9/10 (90.0%) patients. In the D30+T1 group, patients had received a median (range) of 3.0 (1 to 12) prior regimens, and metastatic disease was reported in 15/19 (78.9%) patients, with brain/central nervous system (CNS) metastasis reported in 3/19 (15.8%) patients.

Dose-expansion phase

Overall, 23 patients were enrolled in the dose-expansion phase of the study, of whom 21/23 (91.3%) received treatment. In the SARCOMA cohort, all 11 patients received durvalumab and tremelimumab, and discontinued both treatments, with the most common reason being that the condition under investigation worsened. In the STO cohort, 10 patients received durvalumab and tremelimumab, and discontinued both treatments, with the most common reason being that the condition under investigation worsened.

At the time of DCO, 2/21 (9.5%) patients in the dose-expansion phase were recorded as having been terminated from the study for 'other' reasons, both in the STO cohort: for one patient, this was due to the Sponsor's decision to end the study, and one patient was alive at the time of last reporting. In total, 4/21 (19.0%) patients were terminated from the study as they developed study-specific discontinuation criteria. The remaining 15/21 (71.4%) patients were terminated from the study due to death, in all cases assessed as related to the disease under investigation only (per Investigator assessment), with most events recorded > 90 days after the last dose of study treatment (see Summary of safety results).

In the SARCOMA cohort, patients had received a median (range) of 3.0 (1 to 78) prior regimens (PPD), and metastatic disease was reported in 10/11 (90.9%) patients. In the STO cohort, patients had received a median (range) of 1.5 (1 to 6) prior regimens, and metastatic disease was reported in 8/10 (80.0%) patients, with brain/CNS metastasis reported in 1/10 (10.0%) patient.

Summary of efficacy results

Assessment of preliminary antitumor activity was a primary objective for the dose-expansion phase of this study. Efficacy results were summarized using the FAS, with some analyses also summarized using the evaluable for response analysis set. Efficacy analyses were performed for patients in the dose-expansion phase only.

Dose-finding phase

No formal efficacy analysis was performed for patients in the dose-finding phase; however, based on Investigator assessment of overall RECIST responses, 2 patients in the dose-finding phase, one at each dose level, with osteosarcoma and papillary type renal carcinoma, respectively, had a partial response (PR) for over one year.

Dose-expansion phase

In the dose-expansion phase, an ORR of 5.0% (1/20 patients) was reported in the evaluable for response analysis set, and 4.8% (1/21 patients) in the FAS. No response was observed in the 11 patients initially enrolled in the SARCOMA cohort in the first stage of the Simon 2-stage design; therefore, this cohort was not expanded further in this study. In the STO cohort, an ORR of 11.1% (1/9 patients) was reported in the evaluable for response analysis set, and 10.0% (1/10 patients) in the FAS, as one patient with chordoma had a confirmed response of PR 1.8 months after the first dose of study treatment, with a duration of response of 10.8 months.

In the evaluable for response analysis set, disease control rate was 9.1% (1/11 patients) in the SARCOMA cohort and 11.1% (1/9 patients) in the STO cohort at both Week 16 and Week 24. Similar results were observed for sensitivity analyses performed on the FAS.

The median progression-free survival in the SARCOMA and STO cohorts was 1.7 months (90% CI: 1.58, 1.91) and 1.7 months (90% CI: 0.89, 2.76), respectively, and all patients in the dose-expansion phase of the study had progression events (progressive disease or death). In the SARCOMA cohort, the median overall survival (OS) was 6.6 months (90% CI: 1.87, 15.77), with a survival rate of 25.6% at 12 months. In the STO cohort, the median OS was 6.9 months (90% CI: 1.61, not reached), with a survival rate of 40.0% at 12 months and 30.0% at 24 months.

Summary of pharmacokinetic results

In the dose-finding phase, patients were allocated to a treatment group based on body weight (≥ 35 kg [Arm A] versus < 35 kg [Arm B]); durvalumab area under the serum concentration time curve from 0 to 28 days (AUC(0-28)) was approximately 25% lower for patients < 35 kg compared to patients ≥ 35 kg at both dose levels, while geometric mean tremelimumab AUC(0-28) was nearly the same between these groups (where comparisons could be made, AUC(0-28) was not calculable for B/D20+T1 cohort).

Systemic exposure targets were established for the pediatric population that represented 50% of the adult AUC(0-28). The minimum acceptable AUC(0-28) for this pediatric population was established to be 2105 day*µg/mL durvalumab and 119.5 day*µg/mL tremelimumab. For patients with calculable AUC(0-28), 5 of 6 patients in the A/D20+T1 cohort, and 2 of 3 patients in the B/D20+T1 cohort achieved target durvalumab systemic exposure.

All patients with calculable AUC(0-28) receiving 30 mg/kg durvalumab achieved or exceeded the target durvalumab systemic exposure. Target tremelimumab systemic exposures were achieved for all patients with reportable AUC(0-28), regardless of body weight. On the basis of these results, the RP2D was determined to be 30 mg/kg durvalumab and 1 mg/kg tremelimumab.

Between the 20 mg/kg and 30 mg/kg dosages, durvalumab systemic exposure appeared to increase slightly more than proportionally, as AUC(0-28) and maximum serum concentration (Cmax) increased by 2- to 3-fold and minimum serum concentration (Cmin) increased by 3- to 5-fold.

Geometric mean estimates of the apparent terminal elimination half-life (ie, t½λz) ranged from 14.2 to 25.4 days for durvalumab (where $n \geq 2$, geometric mean not discussed where $n = 1$) and from 15.6 to 31.6 days for tremelimumab; t½λz values were derived from a limited number of samples and should be viewed cautiously. There was no evidence of any notable changes in kinetics following repeat administration; trough and end of infusion sampling demonstrated relatively stable serum levels for both analytes, albeit from a small sampling of patients.

Summary of pharmacodynamic results

No patient received a routine vaccination during the study; therefore, no data were available for reporting the impact of treatment on vaccine antibody titer PPD

The combination of durvalumab and tremelimumab results in enhanced PPD

Summary of immunogenicity results

Assessment of immunogenicity was a secondary objective for the dose-finding and dose-expansion phases of this study. Immunogenicity results were summarized for the ADA analysis set.

PPD

Summary of safety results

Safety analyses were performed on the SAS unless otherwise specified. Assessment of safety was a primary objective for the dose-finding phase of this study.

Overall, the safety profile was as expected for this patient population, and consistent with the known safety profile of durvalumab administered as monotherapy or in combination with tremelimumab, with no new safety concerns identified.

The total treatment duration and actual treatment duration, ie, total duration excluding duration of dose delays, for durvalumab administered as monotherapy or in combination with tremelimumab were comparable within each dose-level group or cohort, indicative of minimal dose delays.

There were no AEs with the outcome of death during the study. For all patients who died due to any cause during the study, death was related to the disease under investigation only (per Investigator assessment), with most events recorded > 90 days after the last dose of study treatment (see Study population for further details).

Dose-finding phase

In the dose-finding phase, 8 DLT-evaluable patients received DL 1 and 12 DLT-evaluable patients received DL 2. No DLTs were reported in any DLT-evaluable patient.

In the D20+T1 group:

- The median (range) total durvalumab treatment duration was 0.92 (0.9 to 25.1) months (10 patients) and durvalumab + tremelimumab total treatment duration was 0.92 (0.9 to 3.7) months (9 patients).
- In total, 9/10 (90.0%) patients experienced a total of 60 AEs, including AEs considered possibly related to study treatment by the Investigator in 50.0% of patients, and Grade 3 or Grade 4 AEs in 40.0% of patients. The most common AE Preferred Terms (PTs) reported were anemia (40.0% of patients), vomiting (30.0% of patients), upper respiratory tract infection, leukopenia, neutropenia, thrombocytopenia, hyperglycemia, pyrexia, and gamma-glutamyl transferase (GGT) increased (20.0% of patients each).
- Overall, 4/10 (40.0%) patients had AEs of special interest (AESIs) or AE of possible interest (AEPIs), and no immune-mediated AEs (imAEs) were reported. One/10 (10.0%) patient had an SAE of anemia, and no patient had an AE that led to the discontinuation of study treatment.
- No clinically important changes or trends were observed in the mean values of clinical laboratory parameters, vital signs, or ECG over time.

In the D30+T1 group:

- The median (range) total durvalumab treatment duration was 0.92 (0.9 to 31.3) months (19 patients) and durvalumab + tremelimumab total treatment duration was 1.38 (0.9 to 3.8) months (12 patients).
- In total, 18/19 (94.7%) patients experienced a total of 198 AEs, including AEs considered possibly related to study treatment by the Investigator in 63.2% of patients, and Grade 3 or Grade 4 AEs in 31.6% of patients. The most common AE PTs reported were nausea (36.8% of patients), headache (31.6% of patients), vomiting, and alanine aminotransferase (ALT) increased (26.3% of patients each).
- Overall, 11/19 (57.9%) patients had AESIs or AEPIs. One patient had a serious Grade 2 imAE of diarrhea, a serious Grade 2 imAE of colitis, and a subsequent non-serious Grade 1 imAE of colitis. Two/19 (10.5%) patients experienced a total of 4 SAEs, including diarrhea, colitis, and dehydration in one patient and transverse sinus thrombosis in one patient; 1/19 (5.3%) patient had an AE of colitis that led to the interruption of durvalumab treatment and the permanent discontinuation of tremelimumab.
- No clinically important changes or trends were observed in the mean values of clinical laboratory parameters, vital signs, or ECG over time. One patient fulfilled potential Hy's law criteria as they had ALT $\geq 3 \times$ upper limit of normal (ULN), aspartate aminotransferase (AST) $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN, with the elevation in transaminases preceding and coinciding with the elevation in total bilirubin. The patient had an alternative explanation for the elevation in liver biochemistry other than durvalumab. This patient had liver metastases at baseline, in addition to elevated AST, $\geq 4 \times$ ULN, coupled with nominal elevations in ALT and total bilirubin at baseline. One other patient had clinically significant ECG abnormalities of cardiac arrythmia (unspecified) and axis deviation (right) at the baseline ECG visit. These abnormalities were reported as pre-treatment Grade 1 AEs of arrythmia and cardiac disorder, with the AE of arrhythmia captured as part of medical history as sinus tachycardia. This patient also experienced a Grade 2 AE of ECG T wave abnormal on Day 1. All 3 events were last reported as unresolved.

Dose-expansion phase

In the SARCOMA cohort:

- The median (range) durvalumab + tremelimumab total treatment duration was 1.84 (0.9 to 3.8) months (11 patients).
- In total, 10/11 (90.9%) patients experienced a total of 91 AEs, including AEs considered possibly related to study treatment by the Investigator in 63.6% of patients, and Grade 3 or Grade 4 AEs in 45.5% of patients. The most common AE PTs reported were pyrexia (63.6% of patients), anemia, abdominal pain (36.4% of patients each), thrombocytopenia, somnolence, ascites, diarrhea, vomiting, back pain, asthenia, and ALT increased (18.2% of patients each).
- Overall, 5/11 (45.5%) patients had AESIs or AEPIs. One patient had a non-serious Grade 2 imAE of myositis. Six/11 (54.5%) patients experienced a total of 10 SAEs,

the most common being pyrexia (3/11 [27.3%] patients), and no patient had an AE that led to the discontinuation of study treatment.

- Overall, no clinically important changes or trends were observed in the mean values of clinical laboratory parameters, vital signs, or ECG over time.

In the STO cohort:

- The median (range) durvalumab + tremelimumab total treatment duration was 1.72 (0.9 to 3.7) months (10 patients).
- In total, 9/10 (90.0%) patients experienced a total of 87 AEs, including AEs considered possibly related to study treatment by the Investigator in 90.0% of patients, and Grade 3 or Grade 4 AEs in 50.0% of patients. The most common AE PTs reported were pyrexia (40.0% of patients), anemia, decreased appetite, cough (30.0% of patients each), headache, constipation, diarrhea, vomiting, rash, asthenia, fatigue, and GGT increased (20.0% of patients each).
- Overall, 6/10 (60.0%) patients had AESIs or AEPIs. One patient each in the STO cohort had a non-serious Grade 2 imAE of hypothyroidism and a non-serious Grade 3 imAE of pneumonitis, respectively. Three/10 (30.0%) patients experienced one SAE each, including pulmonary thrombosis, constipation, and platelet count decreased. An AE of platelet count decreased in 1/10 (10.0%) patient led to the permanent discontinuation of durvalumab, and an AE of pulmonary thrombosis in 1/10 (10.0%) patient led to the permanent discontinuation of durvalumab and tremelimumab.
- Overall, no clinically important changes or trends were observed in the mean values of clinical laboratory parameters, vital signs, or ECG over time.

Conclusions

- The study population was representative of the intended target population of pediatric patients with advanced solid tumors. Durvalumab 20 mg/kg or 30 mg/kg administered intravenously every 4 weeks as monotherapy or in combination with tremelimumab 1 mg/kg was well-tolerated in patients, with the safety profile as expected and no new safety concerns identified. Durvalumab 30 mg/kg in combination with tremelimumab 1 mg/kg was recommended for further investigation in the dose-expansion phase.
- Assessment of preliminary antitumor activity in the dose-expansion phase confirmed an objective response of PR in one patient in the STO cohort; the SARCOMA cohort was closed to further recruitment after the first stage as no objective response was observed in the first 11 evaluable patients. Although no formal efficacy analysis was performed for the dose-finding phase, based on Investigator assessment of overall RECIST responses, 2 patients, one at each dose level, had a PR for over one year.
- The RP2D for pediatric patients was determined to be 30 mg/kg durvalumab in combination with 1 mg/kg tremelimumab based on results from the dose-finding phase. Durvalumab AUC(0-28) was > 2105 day*µg/mL for 5 of 6 patients in the A/D20+T1 cohort, 2 of 3 patients in the B/D20+T1 cohort, and all patients at the 30 mg/kg dose with reportable AUC(0-28) results. Tremelimumab AUC(0-28) was > 119.5 day*µg/mL for all patients at the 1 mg/kg dose with evaluable AUC(0-28), regardless of body weight.

The increase in durvalumab systemic exposure was slightly more than proportional to the 1.5-fold increase in IV dose from 20 to 30 mg/kg, as geometric mean exposure increased by 2- to 3-fold in terms of AUC and Cmax, and by 3- to 5-fold in terms of Cmin. Systemic exposure for patients < 35 kg was generally approximately 70% to 75% of the systemic exposure for patients ≥ 35 kg in terms of geometric mean AUC, Cmax, and Cmin (with one exception where Cmin was reduced by nearly half for patients < 35 kg). Following the first dose, serum concentrations were quantifiable throughout the dosing interval for durvalumab and tremelimumab; trough and end of infusion samples suggest relatively stable PK for both analytes following repeat administration on a 28-day cycle.

- No treatment-emergent ADAs against durvalumab or tremelimumab were reported in patients who were evaluable for ADA in the study.