Abbreviated Clinical Study Report Synopsis	
Drug Substance	MEDI5395, durvalumab
Study Code	D6450C00001
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An Open-label Phase 1 Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Preliminary Efficacy of MEDI5395 in Combination with Durvalumab in Subjects with Select Advanced Solid Tumors

Study dates:
First subject enrolled: 24 October 2019
Last subject enrolled: 29 June 2021
Date of early termination: 27 July 2021
The analyses presented in this report are based on a data cutoff date of 19 November 2021

Phase of development:
Clinical pharmacology (I)

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

Study Sites

The study was conducted at 10 study sites in the United Kingdom (2) and the United States (8). Thirty-nine participants were assigned to treatment at these sites.

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

The study objectives and criteria for the evaluation of primary and secondary endpoints are presented in Table S1.

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability, describe the DLTs, and determine the dose and schedule of administration of MEDI5395 in combination with durvalumab	• Incidence of AEs, SAEs, DLTs, discontinuation of IP(s) due to toxicity, and clinically significant alterations in vital signs, laboratory parameters, ECGs, ECHOs, and ECOG score
Secondary	
Efficacy	
• To evaluate the preliminary efficacy of MEDI5395 administered at different dose levels in combination with durvalumab	• ORR, DC, DoR, TTR, PFS according to RECIST 1.1 and OS
MEDI5395 PK (eg, viremia, transgene expression)	
• To determine the presence and duration of viremia from MEDI5395	• Viral genome copies in blood collected over time
• To determine the levels of GM-CSF in blood	• GM-CSF plasma concentrations collected over time
Immunogenicity	
• To determine the immunogenicity of MEDI5395	• Markers of antiviral immune response (anti-MEDI5395 nAbs)
Pharmacodynamics	
• Evaluate if MEDI5395 alters the tumor microenvironment as it relates to tumor immunity	• CD8 T-cell infiltration and PD-L1 expression in tumors pre- and post-dosing by IHC

AE, adverse event; CD8, cluster of differentiation 8; DC, disease control; DLT, dose-limiting toxicity; DoR, duration of response; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; GM-CSF, granulocyte macrophage-colony-stimulating factor; IHC, immunohistochemistry; IP, investigational product; nAb, neutralizing antibody; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PK, pharmacokinetics; RECIST 1.1, Response Evaluation Criteria in Solid Tumours Version 1.1; SAE, serious adverse event; TTR, time to response.

Study Design

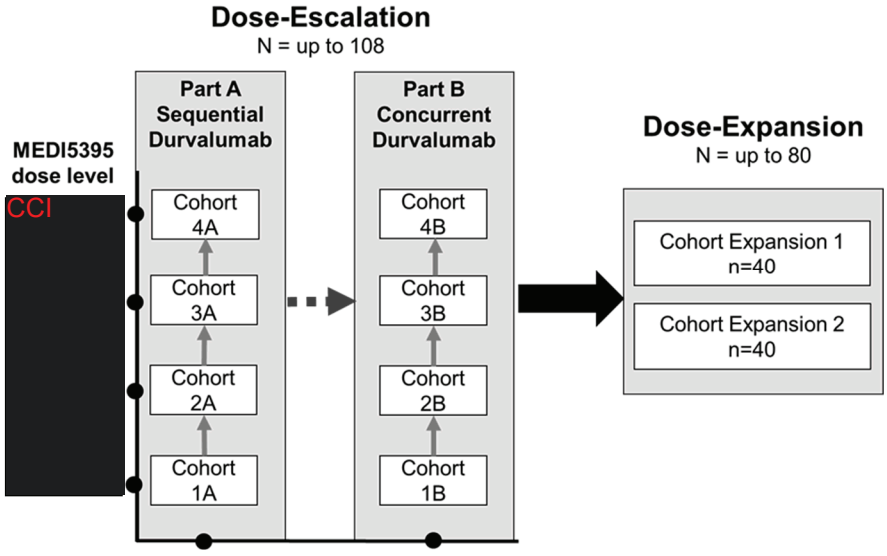
This was a Phase I, first-in-human, open-label, dose escalation and dose expansion study to assess the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy of MEDI5395 administered in combination with durvalumab in participants with selected advanced solid tumors.

As shown in Figure S1, the dose-escalation phase evaluated up to 4 planned, sequentially ascending dose levels of MEDI5395 in participants with select advanced solid tumors who had relapsed, or were refractory or intolerant to available standard of care treatment options. Each MEDI5395 dose level was first assessed when administered in combination with durvalumab given sequentially and then in combination with durvalumab given concurrently. Escalations in the concurrent cohorts occurred once the Dose Escalation Committee (DEC) had cleared both the same dose level cohort in the sequential regimen and the prior dose level cohort in the concurrent regimen (where applicable). In addition, any dose cohort that was cleared by the DEC and confirmed as not exceeding the maximum tolerated dose (MTD), could subsequently be backfilled with a maximum of 18 participants in order to provide additional PK, safety, and efficacy data.

Following completion of the dose-escalation phase, the DEC was to select the MEDI5395 dose level and dosing schedule to be utilized during the dose-expansion phase. However, following completion and clearance of Cohort 4A, the Sponsor decided to prioritize another Newcastle Disease Virus formulation and to stop further development of MEDI5395. As a result, the dose expansion phase of the study was not initiated. In view of this decision, the results of the dose escalation phase (primary and secondary endpoints) are presented as an abbreviated Clinical Study Report. CCI [redacted]

This Synopsis presents the analysis of data as of the data cut-off (DCO), 19 November 2021. Participants remaining in the study at the DCO continued to be followed in line with the Clinical Study Protocol (CSP).

Figure S1 Flowchart of Study Design



Dosing in the concurrent regimen began with Cohort 1B once Cohort 2A had been cleared. Initiation of dosing in subsequent concurrent dosing cohorts was contingent on both DEC clearance of the prior concurrent dose cohort and clearance of the same dose level cohort in the sequential regimen, eg, Cohort 3B could only be initiated after Cohorts 2B (concurrent) and 3A (sequential) had been cleared by the DEC.

Following protocol amendment 3 (21 August 2020), Cohort 2B and subsequent concurrent cohorts could be opened once the same dose level had been cleared in the sequential regimen.

3 – 12 participants/cohort could be enrolled to make a dose-escalation decision per mTPI-2; on-treatment biopsy was required.

Additional participants (up to a total of 18 per cohort and with a maximum of 108 total in dose escalation) could be enrolled (backfill); pre-treatment and on-treatment biopsy were required.

DEC, Dose-escalation Committee; CCI mTPI-2, modified toxicity probability interval.

Target Population and Sample Size

Adult participants (aged ≥ 18 years) with select advanced solid tumors (triple negative breast cancer, colorectal cancer, hepatocellular carcinoma, renal cell carcinoma, non-small cell lung cancer [NSCLC], head and neck squamous cell carcinoma [HNSCC], or melanoma) who had relapsed, or were refractory or intolerant to available standard of care treatment options were enrolled in the study.

Participants must have met the CSP-mandated disease stage, biomarker testing, and prior treatment requirements for their tumor type and have had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and a life-expectancy of at least 12 weeks.

A total of 39 participants were assigned to treatment as follows:

- Cohort 1A: 4 participants
- Cohort 2A: 3 participants
- Cohort 3A: 4 participants
- Cohort 3A backfill: 13 participants
- Cohort 4A: 4 participants
- Cohort 1B: 5 participants
- Cohort 2B: 3 participants
- Cohort 3B: 3 participants

Investigational Products: Dosage, Mode of Administration and Lot Numbers

Details of the investigational products (IPs) are presented in Table S2.

Table S2 Details of Investigational Products

Investigational product	Dosage form and strength	Manufacturer	Lot numbers
MEDI5395	CCI after dilution	MedImmune	CCI, CCI, CCI, CCI
Durvalumab	CCI after dilution	AstraZeneca	CCI, CCI

CCI

MEDI5395

- For the first 2 dose levels CCI and the first 4 participants at the CCI dose level (Cohort 3A), CCI was administered over a minimum of 120 minutes and CCI were administered over a minimum of 60 minutes.
- 1-step desensitization: Following the DEC meeting on 13 October 2020, a 1-step desensitization regimen was implemented for future participants at the CCI dose level, such that CCI was administered at CCI over a minimum of 120 minutes and CCI were administered at CCI over a minimum of 60 minutes. On 15 March 2021, the DEC determined that the desensitizing dose was tolerable CCI CCI. Thereafter, for all subsequent cohorts at CCI (including the Cohort 3A backfill), CCI was administered at CCI.
- CCI CCI was administered over a minimum of 120 minutes. CCI was administered at CCI over a minimum of 180 minutes, and CCI were administered at CCI over a minimum of 65 minutes.

Two-step desensitization was permitted for the CCI dose level, with CCI administered at CCI over a minimum of 120 minutes, CCI administered at CCI over a minimum of 60 minutes, CCI administered at CCI over a minimum of 180 minutes, and CCI administered at CCI over a minimum of 65 minutes. However, this option was not used.

Durvalumab

- Durvalumab was administered over 1 hour (± 15 minutes). Where MEDI5395 and durvalumab were administered on the same day (concurrent dosing regimen), durvalumab was administered at least 1 hour after the end of administration of MEDI5395.

Duration of Treatment

CCI

Durvalumab 1500 mg every 4 weeks (Q4W) was administered either sequentially or concurrently with MEDI5395 for a maximum of 2 years or until radiologically confirmed disease progression, clinical deterioration, withdrawal of consent, or unacceptable toxicity:

- Sequential durvalumab regimen: the first dose of durvalumab was administered CCI after the last dose of MEDI5395
- Concurrent durvalumab regimen: the first dose of durvalumab was administered on the same day as the third dose of MEDI5395 CCI

Participants benefitting from durvalumab at the time of the DCO were permitted to enter the Continued Treatment Period in order to continue receiving durvalumab after the DCO. During

the Continued Treatment Period, assessments reverted to local standard of care and no data were entered into the clinical study database.

Statistical Methods

Sample Size

Dose Escalation: Assuming 4 dose levels for both the sequential and the concurrent dosing regimens, and 3 to 12 participants per dose cohort, between 24 to 96 participants were to be treated in the dose-escalation phase. In addition, up to a maximum of 18 participants could be treated in selected dose level cohorts and the selected expanded dose level could treat up to a maximum of 24 participants

Statistical Analyses

Safety: Safety data, including adverse events (AEs), serious adverse events (SAEs), laboratory evaluations, vital signs, ECOG PS, echocardiogram, and electrocardiogram (ECGs) results were summarized for the As-treated Population, which included all participants who received at least 1 dose of any IP. Summary statistics are provided for AEs, SAEs, clinical laboratory parameters, vital signs, ECOG PS, and ECGs. Adverse events are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0) and described by System Organ Class and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). Laboratory abnormalities with toxicity grades according to the NCI-CTCAE v5.0 were derived and summarized.

As the number of dose-limiting toxicities (DLTs) was low and every cohort passed DEC review and was considered tolerated, there was no indication that the MTD had been reached. Thus, the planned analysis of MTD and DLT rates was not performed.

Efficacy: Efficacy analyses are based on the As-treated Population. The efficacy endpoints include: objective response rate (ORR), disease control (DC), progression-free survival (PFS), time to response (TTR), and duration of response (DoR) based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1), and overall survival (OS). Objective response rate was estimated by the proportion of objective responses (ORs) with a 95% confidence interval (CI) using the exact probability method. Disease control rate (DCR) was estimated by the proportion of DC with 95% CI using the exact probability method. The Kaplan-Meier method was used to estimate PFS and OS curves and the PFS and OS rates at time points of interest. Time to response and DoR were evaluated, using the Kaplan-Meier method, for those participants with an OR.

Pharmacokinetics: Genome copies of MEDI5395 in whole blood and granulocyte macrophage-colony-stimulating factor (GM-CSF) protein concentrations in plasma were summarized by dose cohort along with descriptive statistics. CCI

CCI [redacted]

Immunogenicity: The immunogenic response to MEDI5395 was assessed by summarizing the number and percentage of participants who developed detectable anti-MEDI5395 neutralizing antibodies (nAbs). The immunogenic response to the viral transgene product, human GM-CSF, was assessed by summarizing the number and percentage of participants who developed detectable anti-human GM-CSF antibodies.

Pharmacodynamics: Immune activation in the tumor microenvironment was assessed by measuring changes in cluster of differentiation 8 (CD8) T-cell infiltration and programmed cell death ligand-1 (PD-L1) expression in the tumor pre- and post-dosing with MEDI5395 using matched pairs of tumor specimens obtained at screening and on-treatment. CD8-positive cells (CD8+) within the designated tumor area were reported as cell density (number of positive cells per mm^2). PD-L1 expression was evaluated as an estimated percentage of positivity in tumor cells (TC score) and an estimated total percentage of positivity for the whole biopsy, without differentiation between tumor or stromal/immune compartments (total tissue positive score, [TIP]).

CCI [redacted]

Study Population

A total of 39 participants were assigned to study treatment and all 39 received study treatment with MEDI5395. Thirty-four (87.2%) participants completed treatment with MEDI5395 CCI and all completed treatment prior to the DCO on 19 November 2021. Five (12.8%) participants discontinued MEDI5395, 3 (7.7%) due to the participant's decision, 1 (2.6%) due to an AE, and 1 (2.6%) due to the investigator's decision.

Thirty-six participants, including 2 participants who discontinued treatment with MEDI5395, received treatment with durvalumab. All participants discontinued study treatment with durvalumab, most frequently due to progressive disease (27 participants, 75.0%). Other reasons for discontinuing durvalumab included participant choice (2 [5.6%] participants) and death (1 [2.8%] participant). For 6 (16.7%) participants, the reason for discontinuing durvalumab was 'Other', where 'Other' was defined as discontinuing durvalumab in the main study and entering the Continued Treatment Period, in which participants continued to receive durvalumab after the DCO. No participants discontinued durvalumab due to an AE.

At the time of the DCO, all 39 (100%) participants had discontinued the study according to the CSP definition. Overall, 14 (35.9%) participants discontinued due to death, 3 (7.7%) participants discontinued due to the participant's decision, and 2 (5.1%) participants were lost to follow-up. For 20 (51.3%) participants, the reason for discontinuing the study was recorded as 'Other'. This included 14 participants who were in survival follow-up and who, per the CSP, completed the End-of study Visit prior to the DCO and 6 (16.7%) participants who entered the Continued Treatment Period and who, per the CSP, were considered to have discontinued the study.

Between 3 and 5 participants were treated in each of Cohorts 1A, 2A, 3A, 4A, 1B, 2B, and 3B and an additional 13 participants were assigned to, and treated in, Cohort 3A backfill. Given the small number of participants, no evaluation of whether cohorts were balanced in terms of demographic and other baseline characteristics was made.

Summary of Efficacy Results: Tumor Assessment

All data are presented for the As-treated Population.

Best Overall Response

As shown in Table S3, 4 (10.3%) participants had a best overall response (BOR) of partial response (PR) according to RECIST 1.1, including 1 (25.0%) participant (with NSCLC) in Cohort 1A, 2 (15.4%) participants in Cohort 3A backfill (1 with NSCLC and 1 with HNSCC), and 1 (33.3%) participant in Cohort 3B (with HNSCC). There was no evidence of a MEDI5395 dose response.

Table S3 Disease Response According to RECIST 1.1 (As-treated Population)

BOR, n (%)	Dose escalation cohorts								
	Sequential dosing regimen					Concurrent dosing regimen			Total (N = 39)
	Cohort 1A (N = 4)	Cohort 2A (N = 3)	Cohort 3A (N = 4)	Cohort 3A backfill (N = 13)	Cohort 4A (N = 4)	Cohort 1B (N = 5)	Cohort 2B (N = 3)	Cohort 3B (N = 3)	
CR	0	0	0	0	0	0	0	0	0
PR	1 (25.0)	0	0	2 (15.4)	0	0	0	1 (33.3)	4 (10.3)
SD	2 (50.0)	0	0	3 (23.1)	1 (25.0)	2 (40.0)	0	0	8 (20.5)
PD	0	2 (66.7)	2 (50.0)	7 (53.8)	3 (75.0)	2 (40.0)	3 (100)	2 (66.7)	21 (53.8)
NE	1 (25.0)	1 (33.3)	2 (50.0)	1 (7.7)	0	1 (20.0)	0	0	6 (15.4)

BOR, best overall response; CR, complete response, NE, not evaluable, PR, partial response, RECIST 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1; SD, stable disease.

Objective Response, Time to Response, and Duration of Response

Overall, the ORR (95% CI) according to RECIST 1.1 was 10.3% (2.9%, 24.2%). For the 4 participants with an OR to treatment (ie, complete response [CR] or PR) according to

RECIST 1.1, median TTR (95% CI) was 1.7 months (1.1, not calculated). Median DoR was not reported.

Disease Control

As shown in Table S4, overall, 30.8% of participants achieved DC (an OR to treatment of CR, PR, or stable disease [SD] according to RECIST 1.1). There was no evidence of a MEDI5395 dose response.

Table S4 Disease Control According to RECIST 1.1 (As-treated Population)

	Dose escalation cohorts								
	Sequential dosing regimen					Concurrent dosing regimen			Total (N = 39)
Disease control	Cohort 1A (N = 4)	Cohort 2A (N = 3)	Cohort 3A (N = 4)	Cohort 3A backfill (N = 13)	Cohort 4A (N = 4)	Cohort 1B (N = 5)	Cohort 2B (N = 3)	Cohort 3B (N = 3)	
CR+PR+SD n (%)	3 (75.0)	0	0	5 (38.5)	1 (25.0)	2 (40.0)	0	1 (33.3)	12 (30.8)
95% CI	19.4, 99.4	0.0, 70.8	0.0, 60.2	13.9, 68.4	0.6, 80.6	5.3, 85.3	0.0, 70.8	0.8, 90.6	17.0, 47.6

CI, confidence interval; CR, complete response, PR, partial response, RECIST 1.1, Response Evaluation Criteria In Solid Tumours Version 1.1; SD, stable disease.

Progression-free Survival and Overall Survival

Due to the early termination of the study, the limited duration of follow-up for a number of cohorts, and the censoring rules applied at DCO, evaluation of PFS and OS data was not possible.

Target Lesion Size

Although based on low participant numbers, changes in target lesion (TL) size suggest that for the 5 participants with demonstrable tumor shrinkage, reduction in TL size was a function of time and was sustained over time.

Summary of Pharmacokinetic Results

Interpretation of MEDI5395 PK was limited by the small number of samples. Subject to this limitation, a tendency towards dose-dependent PK of MEDI5395 viral genome was observed in whole blood. Low levels of viral genome were detected in approximately 67% of participants treated with MEDI5395 CCI, while all participants had detectable viral genome with increased levels of genome copies in whole blood along with increasing dose levels at MEDI5395 CCI and above. Following repeat administration of MEDI5395, t_{max} was observed CCI. Whole blood viral genome levels were generally detected from the end of the first infusion and lasted approximately 13 to 51 days. Cumulative peak exposure and extent of exposure increased with increasing dose level over

the tested range and was comparable for participants in the sequential and concurrent dose cohorts.

None of the tested whole blood samples collected at certain time points contained infectious virus titer above the lower limit of quantification (LLOQ) of 4.28 log FFU/mL.

Detectable plasma GM-CSF values (above the LLOQ, 2.15 pg/mL) were reported for 7 samples from 5 participants [redacted]. It was therefore not possible to evaluate GM-CSF as planned.

Summary of Pharmacodynamic Results

Evaluable pre- and on-treatment samples were identified for 20 participants from all dose cohorts except Cohort 1A.

PD-L1 Expression

No clear trend for an overall change in PD-L1 expression based on either TIP or TC scores was observed in on-treatment biopsies compared to pre-treatment. However, tumors from participants who had a tumor response of SD or PR were all PD-L1 positive at baseline and tended to have higher PD-L1 expression than those whose disease had progressed.

CD8

No clear trend for an overall change in tumoral CD8+ cell density was observed in on-treatment biopsies compared to pre-treatment. However, participants with a tumor response of SD or PR had higher tumoral CD8+ T cells at baseline than those whose disease progressed.

Tumoral CD8+ T cells showed an increase of > 50% post-treatment in 7 of the 20 evaluable participants. In these 7 participants, an increase of ≥ 50% in PD-L1 TIP and PD-L1 TC score was also observed in 5 and 2 participants, respectively.

Summary of Immunogenicity Results

At baseline, 7 (17.8%) of the 39 participants were positive for anti-MEDI5395 nAbs and all 38 evaluable participants were nAb-positive post-baseline. For the 31 participants who became nAb-positive post-baseline, the median of maximum titer (25th, 75th percentile) was 10.0 (9.0, 11.0). No participants were transiently positive (as nAb-negative at the last post-baseline assessment and positive at only 1 post-baseline assessment or at ≥ 2 post-baseline assessments with ≥ 16 weeks between the first and last positive assessment). Of the 4 participants with a BOR to treatment of PR, 1 had been nAb-positive at baseline and the other 3 participants became nAb-positive post-treatment.

CCI [redacted]

CCI [redacted]

CCI [redacted]

Summary of Safety Results

Unless indicated otherwise, all data are presented for the As-treated Population.

Exposure

MEDI5395

Overall, the mean (± standard deviation [StD]) duration of exposure to MEDI5395 was 17.67 (± 4.29) days. Mean duration of exposure was shortest in Cohorts 3A and 1B (15.75 [± 8.50] days and 15.80 [± 7.26] days, respectively), the 2 dose cohorts in which 1 participant received only 1 dose of MEDI5395. Across all dose cohorts, most participants (89.7% overall) were exposed to MEDI5395 for ≥ 15 days.

Overall, the mean (± standard deviation) number of MEDI5395 injections was 5.38 (± 1.29), with 27 (69.2%) participants receiving all [redacted] planned doses of MEDI5395. The mean (± StD) number of doses of MEDI5395 was lowest in Cohorts 3A and 1B (4.75 [± 2.50] and 5.00 [± 2.24], respectively).

Mean dose intensity (DI) (actual dose of IP given per dose) was as planned for all participants in Cohorts 1A, 2A, 3A, 1B, and 2B and slightly reduced from the planned dose for the remaining dose cohorts reflecting the fact that dosing CCI [redacted] in Cohorts 3A backfill, 4A, and 3B followed a desensitization regimen. Relative dose intensity (RDI) for MEDI5395 was between 95% to 100% for all 39 participants.

Two (5.1%) participants had a single MEDI5395 infusion interruption, which, in both cases, was due to a Grade 2 AE of Infusion related reaction. The MEDI5395 infusion was subsequently completed in both cases. MEDI5395 dose omissions were reported for 9 (23.1%)

participants and occurred more frequently in the higher dose cohorts. For 8 participants, dose omission was due to 1 or more AEs.

Durvalumab

Overall, 21 (58.3%) participants received ≥ 2 months of durvalumab and 3 (8.3%) participants received ≥ 6 months of durvalumab.

Overall, the median number of durvalumab cycles was 3.0, with 28 (77.8%) participants receiving ≥ 2 cycles and 15 (41.7%) receiving ≥ 4 cycles.

Median DI for durvalumab was as planned for all participants. Median RDI was 100%, and RDI for was 100% for all 36 participants who received durvalumab.

There were no durvalumab dose interruptions and no doses of durvalumab were omitted. Ten (25.6%) participants had 1 or more durvalumab dosing delays and, overall, the median delay was 6.5 days and the maximum delay was 19 days. Dosing delays were reported for both sequential and concurrent dosing regimens.

Adverse Events

As shown in Table S5, there was no evidence of MEDI5395 dose-dependent toxicity within any of the AE categories.

- Across all dose cohorts, most participants (89.7% overall) experienced at least 1 treatment-emergent adverse event (TEAE) considered related to MEDI5395
- Grade 3 or 4 TEAEs were reported for 27 (69.2%) participants across all dose cohorts
- There were no TEAEs with a fatal outcome
- The frequency of MEDI5395-related SAEs was low, reported for 3 (7.7%) participants in 3 different dose cohorts
- 1 (2.6%) participant (Cohort 1B) discontinued treatment with MEDI5395 due to a TEAE (Fatigue)
- MEDI5395-related adverse events of special interest (AESI) occurred in 13 (33.3%) participants across the dose cohorts.

Table S5 Overall Summary of TEAEs in Any Category (As-treated Population)

Participants [a], n (%) with:	Dose escalation cohorts								
	Sequential dosing regimen					Concurrent dosing regimen			Total (N = 39)
	Cohort 1A (N = 4)	Cohort 2A (N = 3)	Cohort 3A (N = 4)	Cohort 3A backfill (N = 13)	Cohort 4A (N = 4)	Cohort 1B (N = 5)	Cohort 2B (N = 3)	Cohort 3B (N = 3)	
At least 1 AE	4 (100)	3 (100)	4 (100)	13 (100)	4 (100)	5 (100)	3 (100)	3 (100)	39 (100)
At least 1 MEDI5395-related AE	4 (100)	3 (100)	4 (100)	11 (84.6)	4 (100)	4 (80.0)	2 (66.7)	3 (100)	35 (89.7)
At least 1 durvalumab-related AE	1 (25.0)	1 (33.3)	0	4 (30.8)	0	0	1 (33.3)	1 (33.3)	8 (20.5)
At least 1 CTCAE Grade 3-4 AE [b]	2 (50.0)	2 (66.7)	4 (100)	10 (76.9)	3 (75.0)	2 (40.0)	2 (66.7)	2 (66.7)	27 (69.2)
Fatal AE (CTCAE Grade 5) [b]	0	0	0	0	0	0	0	0	0
At least 1 SAE	2 (50.0)	1 (33.3)	4 (100)	3 (23.1)	2 (50.0)	1 (20.0)	1 (33.3)	2 (66.7)	16 (41.0)
At least 1 SAE and/or CTCAE Grade 3-4 AE	2 (50.0)	2 (66.7)	4 (100)	10 (76.9)	3 (75.0)	2 (40.0)	2 (66.7)	2 (66.7)	27 (69.2)
At least 1 MEDI5395-related SAE	0	1 (33.3)	1 (25.0)	0	0	0	0	1 (33.3)	3 (7.7)
At least 1 durvalumab-related SAE	0	0	0	0	0	0	0	0	0
At least 1 AE leading to discontinuation of MEDI5395	0	0	0	0	0	1 (20.0)	0	0	1 (2.6)
At least 1 AE leading to discontinuation of durvalumab	0	0	0	0	0	0	0	0	0
At least 1 AESI [c]	0	1 (33.3)	4 (100)	2 (15.4)	3 (75.0)	3 (60.0)	0	1 (33.3)	14 (35.9)
At least 1 MEDI5395 AESI related to MEDI5395	0	1 (33.3)	4 (100)	1 (7.7)	3 (75.0)	3 (60.0)	0	1 (33.3)	13 (33.3)
At least 1 durvalumab AESI [d]	3 (75.0)	2 (66.7)	4 (100)	7 (53.8)	3 (75.0)	2 (40.0)	1 (33.3)	1 (33.3)	23 (59.0)
At least 1 durvalumab AESI related to durvalumab	0	0	0	1 (7.7)	0	0	1 (33.3)	0	2 (5.1)

[a] Participants are counted once for each category regardless of the number of events.

[b] Grade 3, severe; Grade 4, life-threatening; Grade 5, fatal.

[c] AEs identified as AESI as determined by the investigator and recorded in the case report form.

[d] AEs identified as AESI programmatically according to the pre-defined list of AESI for durvalumab.

AEs are TEAEs, defined as events present at baseline that worsen in intensity after administration of any IP or events absent at baseline that emerge after administration of any IP.

AE, adverse event; AESI, adverse event of special interest; CTCAE, Common Terminology Criteria for Adverse Events Version 5; IP, investigational product; SAE, serious adverse event; TEAE, treatment-emergent adverse event

All Adverse Events

Overall, the most frequently reported TEAEs (MedDRA PT) (reported in ≥ 35% of participants) were Fatigue, Nausea, Chills, Headache, Pyrexia, Vomiting, and Diarrhoea.

Treatment-related Adverse Events

Overall, the most frequently reported TEAEs (MedDRA PT) (reported in ≥ 20% of participants) considered related to MEDI5395 by the investigator were Chills, Pyrexia, Fatigue, Headache, Nausea, Influenza like illness, Vomiting, Diarrhoea, Infusion related reaction, and Myalgia.

All 4 participants in Cohort 3A (CCI [redacted] MEDI5395) had 1 or more TEAE of Infusion related reaction, all of which were assessed by the investigator as being related to MEDI5395. Following implementation of 1-step desensitization for subsequent participants dosed at CCI [redacted] MEDI5395, there was a reduction in the frequency of MEDI5395-related Infusion related reaction in the later cohorts (Cohorts 3A backfill, 4A, and 3B) compared to Cohort 3A, underlining the value and effectiveness of the desensitization approach.

Adverse Events by Severity

Overall, the most frequently reported Grade 3 or 4 TEAEs (MedDRA PT) (in ≥ 3 participants overall) were Fatigue, Hypertension, Anaemia, Neutropenia, Neutrophil count decreased, and White blood cell count decreased, and there was no evidence of a MEDI5395 dose response.

No Grade 5 TEAEs were reported; Grade 4 TEAEs reported for 5 (12.8%) participants. Three Grade 3 or 4 TEAEs (MedDRA PTs) were reported in 2 participants in the same dose cohort (Cohort 3A backfill): Seizure, Hypertension, and Neutropenia.

Overall, the only MEDI5395-related Grade 3 or 4 TEAEs (MedDRA PT) reported in > 1 participant were Neutropenia, Neutrophil count decreased, White blood cell count decreased, and Lymphocyte count decreased.

Neutropenia was the only MEDI5395-related Grade 3 or 4 TEAE (MedDRA PTs) reported in 2 participants in the same dose cohort (Cohort 3A backfill).

Dose-limiting Toxicity

Two (5.1%) participants in the DLT Evaluation Population experienced a DLT during the 28-day DLT evaluation period: 1 participant in Cohort 1B who had Grade 3 Fatigue and 1 participant in Cohort 3A backfill who had a Grade 2 or higher MEDI5395-related toxicity (Neutropenia) that prevented administration of > 1 dose of MEDI5395 within the 18-day dosing period.

Adverse Events of Special Interest

Treatment-emergent AESI were reported for 14 (35.9%) participants, and, with 2 exceptions, each AESI (MedDRA PT) was reported in 1 (2.6%) participant only:

- Infusion related reaction was reported in 8 (20.5%) participants
- Chills was reported in 2 (5.1%) participants.

Most treatment-emergent AESI were CTCAE Grade 1 or 2.

Fatal Adverse Events

No TEAEs with a fatal outcome were reported.

Serious Adverse Events

Overall, the only SAEs (MedDRA PT) reported in > 1 participant were Pneumonia, Seizure, and Acute kidney injury, each reported in 2 (5.1%) participants.

Three SAEs were considered related to MEDI5395 by the investigator (Atrial fibrillation, Infusion related reaction, and Chronic obstructive pulmonary disease), and each was reported for a single participant in a different dose cohort.

Adverse Events Leading to Discontinuation of Investigational Product

One (2.6%) participant in Cohort 1B had a TEAE (Grade 3 Fatigue) that led to permanent discontinuation of treatment with MEDI5395. The event, which was also an AESI, was considered by the investigator to be related to MEDI5395 and also met the criteria for a DLT.

Other Significant Adverse Events

In addition to DLT, overall, other significant AEs were reported as follows with no MEDI5395 dose dependent relationship:

- 3 (7.7%) participants experienced left ventricular ejection fraction (LVEF) < 50% at any post-baseline time point with a 10% decrease from baseline
- 2 (5.1%) participants experienced QTcF > 500 msec at any post-baseline time point
- 17 (43.6%) participants experienced a Grade ≥ 3 shift in a laboratory parameter from baseline.

Laboratory Parameters

Hematology and clinical chemistry data collected throughout the study did not raise any safety concerns. No significant changes in hematology or clinical chemistry parameters between dose cohorts or over time were observed and most laboratory parameter grade shifts were by only 1 CTCAE grade. Excursions in serum sodium levels were reviewed by the DEC and

attributed by the investigator to either an underlying concurrent condition or to the disease under study.

Two (5.1%) participants met biochemical criteria for potential Hy's Law (PHL) (alanine aminotransferase or aspartate aminotransferase ≥ 3 × upper limit of normal [ULN] and bilirubin ≥ 2 × ULN). Following detailed review by the investigator, neither case was confirmed as a true Hy's Law case due to the presence of disease progression at the time PHL criteria were met.

Other Safety Parameters

No significant changes over time in vital signs, ECG variables, LVEF, or ECOG PS were observed, either overall or between dose cohorts.

Conclusions

Overall, Study D6450C00001 demonstrated that the combination of MEDI5935 at doses CCI CCI in combination with durvalumab 1500 mg Q4W administered as either a sequential or concurrent regimen had a manageable safety profile in this small population of participants with select advanced solid tumors who had relapsed, or were refractory to or intolerant of available standard of care options:

- There was no evidence of dose-dependent toxicity with MEDI5395, with the exception of Infusion related reaction reported for Cohort 3A, which was addressed at higher dose levels through the introduction of a simple 1-step desensitization regimen.
- The incidence of DLT was low, reported in 2 (5.1%) participants, and did not impact the planned dose-escalation schedule.
- No safety signals were identified for MEDI5395.
- Although based on a small number of samples, levels of infectious virus shed from saliva and urine samples were low and transient and are not expected to raise environmental safety concerns.
- No safety signals were identified for durvalumab beyond the established safety profile for durvalumab.