| **Clinical Study Report Synopsis** | |
|---|---|
| Drug Substance | MEDI1191-Durvalumab |
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# A Phase 1, Open-label, Dose-escalation and Expansion Study of MEDI1191 Administered Intratumorally as Monotherapy and in Combination with Durvalumab in Subjects with Advanced Solid Tumors

**Study dates:** First subject enrolled: 08 May 2019

Last subject last visit: 24 August 2023

The analyses presented in this report are based on a clinical data lock date of 07 November 2023

**Phase of development:** Phase I

**International Co-ordinating Investigator:** [redacted]

**Sponsor's Responsible Medical Officer:** Analia Azaro, MD PhD

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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 centre(s)

A total of 11 centers in 2 countries (USA and Spain).

## Publications

1 Castañón E, et al. Intratumoral (IT) MEDI1191 + durvalumab (D): Update on the first-in-human study in advanced solid tumors [abstract]. Cancer Res. 2023;83(8_Supplement): CT004. https://doi.org/10.1158/1538-7445.AM2023-CT004.

2 Abadier M, et al. MEDI1191 (IL-12 mRNA) induces peripheral and intratumoral immunostimulatory effect in patients with cutaneous or subcutaneous (C/SC) lesions [abstract]. J Immunother Cancer. 2022;10: 708. doi: 10.1136/jitc-2022-SITC2022.0708.

3 Carneiro BA, et al. First-in-human study of intratumoral MEDI1191 (mRNA encoding IL-12) plus durvalumab in patients with advanced solid tumors [abstract]. Cancer Res. 2022;82(12_Supplement): CT183. https://doi.org/10.1158/1538-7445.AM2022-CT183.

4 Hamid O, et al. 190 - Preliminary safety, antitumor activity and pharmacodynamics results of the human intratumoral immunotherapy (HIT-IT) trial of MEDI1191 (mRNA IL-12) in patients with advanced solid tumours and superficial lesions. ESMO Targeted Anticancer Therapies (TAT) Virtual Congress (1-2 March 2021).

## Objectives and criteria for evaluation

**Table S1 Objectives and Endpoints**

| | Objectives | Endpoints |
|---|---|---|
| **Primary** | | |
| **Part 1** | | |
| Safety | • To investigate the safety and tolerability of sequential and concurrent IT administration of MEDI1191 with durvalumab combinations.<br>• To determine the MTD or the highest protocol-specified dose (in the absence of establishing the MTD) for sequential and concurrent IT MEDI1191 with durvalumab combinations. | • Presence of AEs, SAEs, and abnormal laboratory parameters, vital signs, and ECG results.<br>• Occurrence of DLTs and discontinuations due to toxicities. |
| **Part 2** | | |
| Efficacy | • To investigate the antitumor activity of concurrent IT MEDI1191 with durvalumab combination in subjects with immunotherapy pre-treated NSCLC. | • ORR per RECIST v1.1. |

| | Objectives | Endpoints |
|---|---|---|
| **Secondary** | | |
| **Part 1 and/or Part 2 (as indicated below)** | | |
| Safety (Part 2) | • To evaluate the safety and tolerability of concurrent IT MEDI1191 with durvalumab combination in subjects with immunotherapy pre-treated NSCLC. | • Presence of AEs, SAEs, and abnormal laboratory parameters, vital signs, and ECG results.<br>• Occurrence of discontinuations due to toxicities. |
| Efficacy | • To evaluate preliminary antitumor activity of sequential and concurrent IT MEDI1191 with durvalumab combination (Part 1).<br>• To further assess clinical activity (including abscopal effect) of sequential and concurrent IT MEDI1191 with durvalumab combinations (Parts 1 and 2). | • ORR per RECIST v1.1 (Part 1).<br>• DCR, TTR, DoR, and PFS per RECIST v1.1 and OS (Parts 1 and 2).<br>• Qualitative assessment of efficacy in the non-target and injected lesions (present, absent, or in rare cases unequivocal progression) per RECIST v 1.1 (Parts 1 and 2).<br>• Abscopal effect defined as tumor shrinkage in any non-injected lesion (Parts 1 and 2). |
| Pharmacokinetic | • To characterize the systemic PK of IT MEDI1191 when administered sequentially or concurrently with durvalumab (Parts 1 and 2).<br>• To characterize the systemic PK of durvalumab when administered sequentially or concurrently with MEDI1191 (Parts 1 and 2). | • Systemic PK of MEDI1191 ($C_{max}$, $T_{max}$, AUC, clearance, volume of distribution, and $t_{1/2}$ as data allows) and durvalumab ($C_{max}$, and $C_{trough}$ as data allows) (Parts 1 and 2). |
| Immunogenicity | • To characterize the immunogenicity of IT MEDI1191 and MEDI1191 derived protein when administered sequentially or concurrently with durvalumab (Parts 1 and 2).<br>• To characterize the immunogenicity of durvalumab when administered sequentially or concurrently with MEDI1191 (Parts 1 and 2). | • Development of ADA and titer (if confirmed ADA-positive) against MEDI1191, MEDI1191 derived protein, and durvalumab during treatment and follow-up (Parts 1 and 2). |
| **Exploratory** | | |
| **Parts 1 and 2** | | |
| Biomarkers | • To evaluate baseline and on-treatment blood-based analyses (mRNA signatures, circulating immune cells, cytokines, chemokines, and ctDNA) for correlation with MEDI1191 PK, and correlation with changes in tumor gene expression signatures linked to IL-12 biology, and clinical activity. | • Changes in gene expression profiles, circulating immune cells (including T-cell receptor repertoire), changes in transgene derived RNA in circulating blood (rt-qPCR), changes in cytokines, (eg, IFNγ, IL-12, TNF-α, IL-6), chemokines (eg, CXCL10), and ctDNA levels between baseline and post-treatment time points. |

| | Objectives | Endpoints |
|---|---|---|
| | • To compare the relationship between ctDNA mutations and clinical activity for sequential and concurrent IT MEDI1191 with durvalumab combinations. | • Clinical activity by individual ctDNA gene mutations at baseline. |
| | • To evaluate baseline and on-treatment biopsy of tumor-related parameters (mRNA signatures, composition of IT immune cells, expression of proteins by IHC, TMB) for correlation with MEDI1191 PK, changes in peripheral concentrations of IFNγ, CXCL10 or other cytokines/chemokines linked to IL-12 biology, changes in peripheral gene expression signatures linked to IL-12 biology, and clinical activity. | • Clinical activity by baseline TMB and expression of proteins (eg, PD-L1) and changes in gene expression profiles (eg, Th1) and cell number and phenotype of IT immune cells (eg, CD8, NKp46, and TILs). |
| | • To evaluate baseline and on-treatment gut microbiome characteristics for correlation with clinical activity. | • Clinical activity by baseline and on-treatment changes in gut microbiome. |
| Efficacy | • To evaluate the clinical activity (including abscopal effect) of sequential and concurrent IT MEDI1191 with durvalumab per iRECIST. | • ORR, DCR, TTR, DoR and PFS per iRECIST. |
| | • To evaluate changes in the injected lesion size after IT administration with MEDI1191. | • Change from baseline in the tumor diameter of individual injected lesion. |
| Digital health | • To assess the effect of sequential and concurrent MEDI1191 durvalumab combinations on a biometric profile associated with cytokine production and release into systemic circulation using a biosensor. | • Biophysical parameters, including but not limited to serial measurements of skin temperature, heart rate, respiratory rate, blood oxygenation and physical activity, from a biosensor. |

AE = adverse event; ADA = antidrug antibody; AUC = area under the concentration-time curve; CD = cluster of differentiation; $C_{max}$ = maximum plasma concentration; ctDNA = circulating tumor DNA; $C_{trough}$ = trough plasma concentration; CXCL = CXC chemokine ligand; DCR = disease control rate; DLT = dose-limiting; DoR = duration of response; ECG = electrocardiogram; IFNγ = interferon gamma; IHC = immunohistochemistry; IL = interleukin; iRECIST = immune Response Evaluation Criteria In Solid Tumors; IT = intratumoral; mRNA = messenger ribonucleic acid; MTD = maximum tolerated dose; NK = natural killer; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival; PK = pharmacokinetics; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors version 1.1; RNA = ribonucleic acid; rt-qPCR = quantitative reverse transcription polymerase chain reaction; SAE = serious adverse event; $t_{1/2}$ = terminal half-life; Th1 = T helper cell type 1; TIL = tumor infiltrating lymphocyte; $T_{max}$ = time to maximum plasma concentration; TMB = tumor mutational burden; TNF = tumor necrosis factor; TTR = time to response.

Note: Exploratory endpoint results are not described in this abbreviated CSR.

## Study design

This was a Phase 1, first-time-in-human, multicenter, open-label, dose-escalation (Parts 1A, 1B, and 1D) and dose expansion (Part 2) study of MEDI1191 delivered by intratumoral injection administered sequentially with durvalumab after a 21-day washout period (Part 1A), and in concurrent combination with IV durvalumab (Parts 1B and 1D, and 2) to evaluate the safety, tolerability, PK, pharmacodynamic, immunogenicity, and antitumor activity in subjects with advanced or metastatic solid tumors. Part 1C was designed to evaluate MEDI1191 sequentially with durvalumab in deep lesions and was removed from the study in the clinical study protocol (CSP) Amendment 3.

Following an internal review of study data, the Sponsor decided to terminate the study, for reasons unrelated to the safety of MEDI1191 and durvalumab treatment. The CSP was subsequently amended and on approval of CSP Amendment 4, the dose escalation component of the study was terminated, and Part 2 of the study was not conducted.

Subjects in Parts 1 and 2 were to be followed for safety throughout the study. A study-specific Dose Escalation Committee provided ongoing safety surveillance of the study, with regularly scheduled reviews of safety, pharmacokinetics (PK), and other relevant data. This committee could also have met to review data at other time points (eg, in response to adverse events [AEs] assessed as medically relevant by the Medical Monitor). This committee was responsible for making recommendations for dose-escalation or dose de-escalation decisions, cohort expansion decisions, opening of pharmacodynamic (backfill) expansion cohorts, starting dose/schedule for Parts 1B and 1D, and making recommendations regarding further conduct of the study. The maximum tolerated dose (MTD) was defined as the highest dose with a DLT rate closest to 30% in Part 1 dose escalation.

Subjects were treated in either the dose-escalation or the dose-expansion phase of the study for up to 2 years, or until disease progression, withdrawal of consent, unacceptable toxicity, or development of other reasons for treatment discontinuation. All subjects were to be followed for survival, disease progression, and subsequent anticancer treatment for a maximum of 18 months post-treatment discontinuation or until the end of the study, whichever occurred first. The end of the study (“study completion”) was defined as the last subject last visit. The end of the study occurred after the last subject had discontinued study treatment and completed any applicable follow-up visit per the schedule of study procedures, or the date the study was closed by the Sponsor, whichever occurred first.

Part 1 (Dose Escalation) was divided into 4 parts:

- Part 1A: intratumoral (IT) administration of sequential MEDI1191 with systemic durvalumab in subjects with cutaneous or subcutaneous lesions.
- Part 1B: IT administration of concurrent MEDI1191 with systemic durvalumab in subjects with cutaneous or subcutaneous lesions.

- Part 1C: IT administration of sequential MEDI1191 with durvalumab in deep lesions. This part was removed per CSP Amendment 3, dated 12 May 2020 (Appendix 16.1.1).
- Part 1D: IT administration of concurrent MEDI1191 with systemic durvalumab in subjects with deep-seated lesions.

Part 1 utilized the modified toxicity probability interval (mTPI-2) algorithm with a target DLT rate of 30% for MTD. See CSP for details (Appendix 16.1.1).

Cutaneous or subcutaneous tumor lesions were defined as visible or palpable non-visceral lesions. This definition included lesions involving superficial muscle tissue and lesions involving the fascia overlying these muscles (eg, breast mass, supraclavicular lymph nodes etc). MEDI1191 was administered by a physician, or a delegate, trained, and experienced in administering IT medications.

Deep-seated tumor lesions were defined as visceral lesions not visible or palpable, and which require image guidance for injection (eg, hepatic, pulmonary lesions). These lesions were selected based on imaging and the advice of the Investigator and consultant staff and injected by an interventional radiologist, trained, and experienced in administering IT medications.

For Parts 1A and 1B (superficial lesion dose escalation), a mandatory baseline lesion biopsy during screening (by Day −3) and on-treatment (Day 15) was required of the lesion selected for MEDI1191 injection and if clinically feasible, also, of a lesion not selected for injection. The timing of the on-treatment biopsy may have been changed based on emerging data. Additional on-treatment biopsies were optional for Parts 1A and 1B. In Part 1D (deep-seated lesion dose escalation) and Part 2 (dose expansion), a baseline biopsy (by Day −3) of the lesion selected for injection was preferred; however, any archival tumor tissue obtained within 6 months of enrollment was acceptable. On-treatment biopsies of the lesion selected for injection were optional for, Part 1D and 2. For any pharmacodynamic expansion cohort during dose escalation, a baseline (by Day −3) and on-treatment biopsy (on Day 15) of the injected (mandatory) and a non-injected lesion (if clinically feasible) was required for Parts 1A and 1B. Injection of a deep-seated lesion and biopsy of the same lesion were to occur on different days due to the inherent risk of deep-seated procedures.

The Sponsor continued to supply MEDI1191 and durvalumab up to the expiry date of the current clinical batch of MEDI1191. Any subject who was deriving benefit from durvalumab at the time of termination of the main portion of this study regardless of the part in which the subject was enrolled and dosed, was to be able to maintain continued access to durvalumab monotherapy until access under an alternative study became available. As a result, 2 subjects continued to receive study drug after consenting to a roll-over study.

This continued treatment period was to last until the last subject (who was participating in the continued treatment period) had completed treatment and a safety follow-up within 30 days of end of treatment (EoT). The EoT was performed to evaluate for safety, and long-term

follow-up for a maximum of 18 months post-EoT or until study was terminated by the Sponsor. Under CSP Amendment 4, subjects in long-term follow-up were discontinued from the study and were initiated into standard-of-care treatment per local requirements as deemed necessary by their healthcare professional.

After the main study closed and during the continued treatment period, the only data collected were study drug dosing data and serious adverse event (SAE) data.

**Target subject population and sample size**

Subjects with histologically or cytologically confirmed advanced solid tumors were enrolled in this study. Part 1A, 1B, and 1D consisted of subjects ≥18 years of age with advanced solid tumors who received and progressed on or were refractory to at least 1 line of standard systemic therapy in the recurrent/metastatic setting. The target sample size for Parts 1A, 1B, and 1D was up to 156 subjects.

Part 2 (Dose Expansion) was planned with up to 40 subjects ≥18 years of age with confirmed diagnosis of locally advanced or metastatic non-small cell lung cancer (NSCLC) that progressed or was refractory to no more than 2 lines of standard of care therapy for recurrent or metastatic setting, including PD-(L)1-based immunotherapy.

Following an internal review of study data, the Sponsor decided to terminate the study, for reasons unrelated to the safety of MEDI1191 and durvalumab treatment. The CSP was subsequently amended and on approval of CSP Amendment 4, dated 18 November 2022, the dose escalation component of the study was terminated after 61 subjects were enrolled in Parts 1A, 1B, and 1D, and Part 2 of the study was not conducted.

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

MEDI1191 was administered by injection directly into a tumor lesion. Doses administered during Part 1 (dose escalation) were 0.1 μg, 0.3 μg, 1 μg, 3 μg, 8 μg, and 12 μg. Batch numbers of MEDI1191 used in the study are listed patient-wise, in Appendix 16.2.4.6.

Durvalumab was administered systemically at a fixed dose of 1500 mg Q4W by IV infusion. Batch numbers of durvalumab used in the study are listed patient-wise, in Appendix 16.2.4.6.

**Duration of treatment**

Subjects were to be treated in either the dose-escalation or the dose-expansion phase of the study for up to 2 years, or until disease progression, withdrawal of consent, unacceptable toxicity, or development of other reasons for treatment discontinuation.

## Statistical methods

Upon approval of CSP Amendment 4, the dose escalation component of the study was terminated for reasons unrelated to the safety of MEDI1191 and durvalumab treatment. The analyses pertinent to the dose escalation component (Part 1) of the study were completed as outlined in the Statistical Analysis Plan (SAP) Version 2.0, dated 31 August 2023.

Efficacy analyses were based on the As-treated Population defined as all subjects who received at least 1 dose of any study drug. The primary efficacy endpoint was objective response (OR) based on RECIST v1.1. ORR was defined as the proportion of subjects with confirmed complete response (CR) or confirmed partial response (PR). The objective response rate (ORR) was estimated with a 95% CI using the exact probability method. Secondary efficacy endpoints included the following:

- Disease control (DC) was defined as a best overall response of CR, PR or stable disease (SD) if SD was maintained for ≥ 12 weeks (± 3 days) according to RECIST v1.1.
- Disease control rate (DCR) was estimated by the proportion of DC, and its 95% CI was estimated using the exact probability method.
- Time to response (TTR) was defined as the time from the start date of treatment with study drugs until the first documentation of a subsequently confirmed OR.
- Duration of response (DoR) was defined as the duration from the date of first documentation of OR to the first documented disease progression or death due to any cause, whichever occurred first. The TTR and DoR were evaluated using the Kaplan-Meier method, only for the subgroup of subjects with an OR.
- Progression-free survival (PFS) was measured from the start date of treatment with study drugs until the first documentation of disease progression or death due to any cause, whichever occurred first. The Kaplan-Meier method was used to estimate the PFS curve and the PFS rate at time points of interest.
- Overall survival (OS) was determined as the time from the start date of treatment with study drugs until death due to any cause. The Kaplan-Meier method was used to estimate the OS curve and the OS rate at time points of interest.
- Change from baseline in tumor diameter for target lesions, injected (non-target), and other non-target lesions were assessed by disease assessment time, where measurable. In addition, qualitative assessment of efficacy in the non-target and injected lesions (present, absent, or in rare cases unequivocal progression) per RECIST v 1.1 were performed.
- Change in tumor size (kinetics) was assessed over time and was defined as percent change from baseline in the sum of tumor burden. Change in size in target tumors, and non-target injected tumors were analyzed separately.

Safety evaluation was based on the As-treated Population, and the MTD evaluation was based on the DLT evaluable Population (defined as all subjects enrolled in the dose-escalation phase who received study drugs as per protocol and completed the safety follow-up through the DLT evaluation period or experienced any DLT during the DLT evaluation period). The number of DLTs were summarized descriptively for each dose level. The MTD was determined by

isotonic regression analysis applied to DLT rates observed at each dose level. Summary statistics were provided for treatment-emergent AEs (TEAEs), AEs that led to treatment discontinuation, SAEs, AE grade, relationship to study drugs, clinical laboratory parameters, vital signs, and ECGs. The use of a biosensor device for serial measurements of changes in skin temperature, heart rate, respiratory rate, blood oxygenation, and physical activity, was evaluated in this study.

Only subjects who received at least 1 dose of MEDI1191 or durvalumab and provided at least 1 post-treatment sample were included in the PK data analysis. Individual MEDI1191 and durvalumab concentrations were tabulated by dose cohort along with descriptive statistics. If the data allowed, noncompartmental PK data analysis was to be performed for each MEDI1191 dose cohort with descriptive statistics of PK parameters of MEDI1191 (maximum plasma concentration [$C_{max}$], time to maximum plasma concentration [$T_{max}$], area under the concentration-time curve [AUC], apparent clearance, apparent volume of distribution, apparent terminal elimination half-life).

The antidrug antibody (ADA) incidence rate and titer of anti-IL-12 derived protein and anti-MEDI1191 antibodies were tabulated for each study drug to monitor immunogenicity of MEDI1191 and durvalumab. Tiered analyses were performed to include screening, confirmatory and titer assay components; samples confirmed positive for ADA were tested and analyzed for antibody titer and reported and could have been utilized for further characterization of the ADA response.

Descriptive statistics were used to describe the exploratory laboratory (biomarker) analyses when possible. Depending on the nature of the data, geometric mean and other appropriate statistical summaries could have been used as well.

Interim analyses and continuous interim monitoring were to be performed for data from subjects who had the opportunity to be followed up for at least 16 weeks and was to be performed after the first 20 subjects, then after every 5 additional subjects. However, planned interim analysis was no longer relevant due to study termination during escalation phase (See Section 4.0 of the SAP; Appendix 16.1.9).

**Study population**

A total of 61 subjects were enrolled in the study and received MEDI1191, including 25 subjects in Part 1A, 27 subjects in Part 1B, and 9 subjects in Part 1D. The most common reason for discontinuation of MEDI1191 overall, was disease progression due to symptomatic/clinical deterioration (17/61, 27.9% subjects), followed by progressive disease (PD; 10/61, 16.4% subjects).

A total of 57 subjects received durvalumab overall, including 21 subjects in Part 1A, 27 subjects in Part1B, and 9 subjects in Part 1D. The most common reason for discontinuation

of durvalumab overall, was disease progression due to symptomatic/clinical deterioration (27/57, 47.4% subjects), followed by PD (18/57, 31.6% subjects).

At the end of the study, a total of 10/61 (16.4%) subjects completed the study (7 subjects in Part 1A, 3 subjects in Part1B, and none in Part 1D), while 28/61 (45.9%) subjects died due to disease under investigation (13 subjects in Part 1A, 9 subjects in Part1B, and 6 subjects in Part 1D). None of the subjects were ongoing in the study at the time of data cutoff. The mean (standard deviation) values for potential and theoretical duration of follow-up overall, were 18.5 months (12.5 months) and 25.3 months (9.1 months), respectively.

**Summary of safety results**

Overall, the median duration of MEDI1191 therapy was 6 weeks (2 cycles) in Part 1A, 8 weeks (2 cycles) in Part 1B, and 4 weeks (1 cycle) in Part 1D. The majority of subjects had relative dose intensity in the range of 90% to 110%.

No DLTs were reported in this study. The incidence of TEAEs was similar across the dose levels studied in each part. The only exception was fewer durvalumab-related TEAEs in Part 1A (2 [8.0%] subjects). No dose-related trend was noted. The most commonly reported TEAEs overall were fatigue (16 [26.2%] subjects) and pyrexia (14 [23.0%] subjects). Grade ≥ 3 TEAEs reported at preferred term level in >1 subject were anaemia (4 [6.6%] subjects, with 2 each in Parts 1B and 1D), ascites (3 [4.9%] subjects, with 2 subjects in Part 1A and 1 subject in Part 1D), pyrexia (2 [3.3%] subjects, both from Part 1B), and lymphocyte count decreased (2 [3.3%] subjects, with 1 subject each, in Parts 1A and 1D). The most commonly reported MEDI1191-related TEAEs were pyrexia (13 [21.3%] subjects) and fatigue (9 [14.8%] subjects), similar to the most commonly reported durvalumab-related TEAEs of fatigue (6 [9.8%] subjects), pyrexia (4 [6.6%] subjects).

One subject overall, (1/27 [3.7%] subjects in Part 1B, who received 12 µg MEDI1191 concurrent with durvalumab) died due to TEAE of Grade 5 hepatic function abnormal, which was assessed by the Investigator as not related to MEDI1191 or durvalumab.

Overall, SAE PTs were reported by 1 subject each, across all dose levels and parts, except for ascites, which was reported for 3 (4.9%) subjects overall (2 subjects in Part 1A [0.1 and 1 µg MEDI1191 dose levels] and 1 in Part 1D [1 µg MEDI1191]). MEDI1191-related SAEs were reported for 2 subjects overall: pyrexia (1 [1.6%] subject in Part 1B [3 µg MEDI1191]) and confusional state (1 [1.6%] subject in Part 1A [12 µg MEDI1191]). Durvalumab-related SAE was reported for 1 subject overall: pyrexia (1 [1.6%] subject in Part 1B [3 µg MEDI1191]).

TEAE leading to discontinuation of MEDI1191 or durvalumab was reported for a single subject in Part 1B (3 µg MEDI1191): Grade 2 urinary tract infection.

The most commonly reported adverse events of special interest were diarrhoea (8 [13.1%] subjects, with 4 subjects from Part 1A, 3 subjects from Part 1B, and 1 subject in Part 1D), dyspnoea (6 [9.8%] subjects, with 2 subjects from Part 1A and 4 subjects from Part 1B), and pruritus (6 [9.8%] subjects, with 4 subjects from Part 1A and 2 subjects from Part 1B).

Grade 3 or 4 TEAEs related to laboratory results were reported across all study parts: platelet count decreased (1/9 subjects in Part 1D; 3 µg MEDI1191), blood alkaline phosphatase increased (1/25 subjects in Part 1A; 12 µg MEDI1191), alanine aminotransferase increased (1/27 subjects in Part 1B; 12 µg MEDI1191), aspartate aminotransferase increased (1/27 subjects in Part 1B; 12 µg MEDI1191; 12 µg MEDI1191), amylase increased (1/27 subjects in Part 1B; 1 µg MEDI1191), blood bilirubin increased (1/9 subjects in Part 1D; 3 µg MEDI1191), gamma-glutamyltransferase increased (1/25 subjects in Part 1A; 12 µg MEDI1191), lymphocyte count decreased (1/25 subjects in Part 1A; 12 µg MEDI1191 and 1/9 subjects in Part 1D; 3 µg MEDI1191), hypernatraemia (1/9 subjects in Part 1D; 3 µg MEDI1191), and hyponatraemia (1/25 subjects in Part 1A; 0.1 µg MEDI1191).

**Summary of efficacy results**

An ORR of 9.8% (n=6, 95% CI=3.7% to 20.2%) was achieved, with best overall response of CR in 1 subject (1 µg MEDI1191 in Part 1B), confirmed PR in 5 subjects (1 subject given 0.3 µg MEDI1191 in Part 1A and 1 subject at each dose level in Part 1B), unconfirmed PR in 2 subjects (1 subject given 0.1 µg MEDI1191 in Part 1A and another given 3 µg MEDI1191 in Part 1B). No response was observed in Part 1D.

Disease control rate (≥ 12 weeks) overall, was 31.1% (n=19, 95% CI=19.9% to 44.3%), median TTR was 1.8 months (95% CI=1.5, NA), DoR across all parts was 6 months (95% CI=3.7, NA). Overall, median PFS was 1.8 months (number of PFS events=45, 95% CI=1.6 to 3.4) and median OS was 13.7 months (number of OS events=28, 95% CI=7.6 to NE). Qualitative status of non-target, injected lesions was reported as “absent” for 5 subjects overall, while mean (±standard deviation, min, max) values observed for best percent change from baseline describing abscopal effect was 1.01% (±52.29%, min = -100.0%, max = 140.0%).

**Conclusions**

MEDI1191 delivered by IT injection into cutaneous/subcutaneous or deep-seated lesions at 0.1, 0.3, 1, 3, 8, and 12 µg dose levels, administered sequentially or concurrently with IV durvalumab was safe and well tolerated in subjects with advanced solid tumors in this study. No dose related trend was noted for incidence or severity of TEAEs.

An ORR of 9.8% was achieved in this study. Efficacy parameters showed comparatively larger reductions in tumor size for both, target and non-target lesions when MEDI1191 was

administered concurrently with durvalumab rather than sequentially, and in cutaneous or subcutaneous lesions rather than deep-seated lesions. The responses observed in this study were not correlated with dose or disease setting.