First-in-human study of intratumoral MEDI1191 (mRNA encoding IL-12) plus durvalumab in patients with advanced solid tumors

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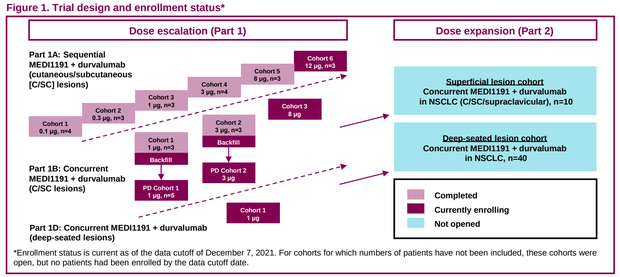
Background

- MEDI1191 is a lipid nanoparticle-formulated mRNA encoding IL-12, developed for intratumoral (IT) injection. It is designed to increase local IL-12 production and enhance T cell response with improved tolerability compared with systemic administration.[1]
  - In syngeneic mouse models, IT mouse IL-12 mRNA (a surrogate for MEDI1191) induced IFNγ production and CD8+ T cell-dependent tumor regression, which was enhanced by anti-programmed cell death ligand-1 (PD-L1) therapy,[1] providing the rationale to evaluate the combination of MEDI1191 with anti-programmed cell death 1 (PD-1)/PD-L1 therapy to augment antitumor immunity.
  - This phase 1, first-in-human, multicenter, open-label study is evaluating the safety and antitumor activity of IT MEDI1191 with either sequential or concurrent intravenous (IV) durvalumab (anti-PD-L1) in patients with advanced or metastatic solid tumors (NCT03946800).
- Early data in patients receiving MEDI1191 with sequential durvalumab have been reported previously.[2] Here we present updated results on sequential dosing and the first report of concurrent dosing from the dose-escalation phase.

Methods

- The trial comprises an initial dose-escalation phase (Part 1, with three sub-parts A, B, and D) followed by a dose-expansion phase (Part 2) upon identification of the recommended phase 2 dose (**Figure 1**). Parts 1A and 1B are reported here (data cutoff: December 7, 2021).
- Eligibility criteria include:
  - Age ≥18 years
  - Histologic or cytologic confirmation of advanced solid tumors
  - At least 1 lesion measurable by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, other than the planned injected lesion
  - Progression on or refractoriness to ≥1 line of standard systemic therapy for recurrent/metastatic disease.
- Treatment schedule
  - In Part 1A (sequential treatment), patients receive IT MEDI1191 on Days 1 and 22 only followed by IV durvalumab 1500 mg on Day 43 and then every 4 weeks (Q4W).
  - In Part 1B (concurrent treatment), patients receive IT MEDI1191 on Days 1, 29, 57, and then every 8 weeks (Q8W), with IV durvalumab 1500 mg on Day 1 and then Q4W.
  - Treatment continues for up to 2 years or until progression or unacceptable toxicity.

Figure 1. Trial design and enrollment status*



*Enrollment status is current as of the data cutoff of December 7, 2021. For cohorts for which numbers of patients have not been included, these cohorts were open, but no patients had been enrolled by the data cutoff date.

- Primary objectives:
  - Safety and tolerability of sequential and concurrent MEDI1191 with durvalumab as measured by adverse events (AEs), serious AEs (SAEs), abnormal laboratory parameters, vital signs, and ECG results, dose-limiting toxicities (DLTs), and discontinuations due to toxicities
  - Determination of the maximum tolerated dose (MTD) or highest protocol-specified dose.
- Secondary objectives:
  - Preliminary antitumor activity as measured by objective response rate (ORR), disease control rate (DCR, defined as complete responses [CRs], partial responses [PRs], and stable disease [SD] ≥12 weeks), time to response, duration of response, and progression-free survival per RECIST v1.1, and overall survival
  - Clinical activity in terms of qualitative evaluation of non-target and injected lesions per RECIST v1.1, including abscopal effects (defined as reduction in tumor size in any non-injected lesion)
  - Systemic pharmacokinetics of MEDI1191 and durvalumab
  - Immunogenicity measured as antidrug antibodies to MEDI1191, MEDI1191-derived protein, and durvalumab.

Results

Patients and exposure

- As of December 7, 2021, 31 patients had received sequential MEDI1191 and durvalumab (Part 1A dose-escalation cohorts, MEDI1191 0.1–12 µg; n=20) or concurrent MEDI1191 and durvalumab (Part 1B cohorts MEDI1191 1.0 or 3.0 µg; n=11).
  - Patient demographics and baseline characteristics are shown in **Table 1**.
- In Part 1A, 15/20 (75.0%) patients completed the planned MEDI1191 treatment (2 doses); in Part 1B, the number of MEDI1191 doses was not limited to 2. Across Parts 1A and 1B, 14/31 (45.2%) patients discontinued MEDI1191 treatment, most commonly (9/31; 29.0%) because of progressive disease.
- Across Parts 1A and 1B, 27/31 patients received durvalumab treatment; 23/27 (85.2%) patients discontinued durvalumab, most commonly (20/27; 74.1%) because of progressive disease.
- Study drug exposure is shown in **Table 2**.

Safety

- As of December 7, 2021, no DLTs had occurred and the MTD was not reached.
- The safety profiles for MEDI1191 and durvalumab are summarized in **Table 3**.
  - Overall, 30 (96.8%) patients had ≥1 treatment-emergent AE (TEAE), including 12 (38.7%) patients with ≥1 grade 3/4 TEAE. There were no grade 5 TEAEs.
  - The most common TEAEs were fatigue (19.4%), dyspnea (16.1%), pruritus (16.1%), pyrexia (12.9%), diarrhea (12.9%), and nausea (12.9%) (**Table 4**).
  - Apart from ascites (n=2, 6.5%), no individual grade 3/4 TEAE occurred in more than 1 patient.

Table 1. Baseline demographics and disease characteristics

Characteristic	Part 1A: sequential MEDI1191 + durvalumab (N=20)	Part 1B: concurrent MEDI1191 + durvalumab (N=11)
Median age (range), years	59.5 (18–74)	59.0 (34–80)
Male/female, n (%)	11 (55.0) / 9 (45.0)	7 (63.6) / 4 (36.4)
Race, n (%)	n=19	
White	15 (78.9)	7 (63.6)
Asian	1 (5.3)	1 (9.1)
African American	0	1 (9.1)
Other	2 (10.5)	2 (18.2)
Multiple categories checked	1 (5.3)	0
Tumor type, n (%)		
Melanoma	3 (15.0)	5 (45.5)
Breast cancer	3 (15.0)	1 (9.1)
Head and neck cancer	3 (15.0)	1 (9.1)
Non-small-cell lung cancer	2 (10.0)	0
Colorectal cancer	1 (5.0)	0
Gastric cancer	1 (5.0)	0
Bladder cancer	0	1 (9.1)
Other	7 (35.0)	3 (27.3)
Previous lines of systemic therapy, n (%)		
1	1 (5.0)	5 (45.5)
2	7 (35.0)	1 (9.1)
≥3	12 (60.0)	5 (45.5)
Median number of prior regimens (range)	5.5 (2–12)	3.0 (1–8)
Prior radiation, n (%)	11 (55.0)	9 (81.8)
Prior surgery, n (%)	15 (75.0)	7 (63.6)
Previous immunotherapy, n (%)		
Previous PD-1 inhibitor therapy	13 (65.0)	7 (63.6)
Previous PD-L1 inhibitor therapy	1 (5.0)	3 (27.3)
Previous CTLA-4 inhibitor therapy	3 (15.0)	8 (72.7)

CTLA-4, cytotoxic T lymphocyte-associated antigen 4.

Table 2. Study drug exposure

	Part 1A: sequential MEDI1191 + durvalumab (N=20)	Part 1B: concurrent MEDI1191 + durvalumab (N=11)
MEDI1191 exposure		
Median number of doses (range)	2.0 (1–2)	2.0 (1–6)
Received all planned doses,* n (%)	15 (75.0)	Not applicable
Median duration of exposure (range), weeks	6.0 (3.0–6.3)	8.0 (4.0–40.3)
Durvalumab exposure	n=16	
Median number of doses (range)	2.0 (1–16)	2.0 (1–10)
Median duration of exposure (range), weeks	8.0 (2.1–63.9)	8.0 (4.0–40.3)

*In Part 1A, two doses of MEDI1191 were planned; in Part 1B, there was no planned total number of MEDI1191 doses.

- 13 (41.9%) patients had ≥1 MEDI1191-related AE, but only 1 (3.2%) of them had a grade 3 event (pyrexia). There were no grade 4 MEDI1191-related AEs.
  - 1 (3.2%) patient had a MEDI1191-related SAE (grade 2 confusion).
- 7 (22.6%) patients had ≥1 durvalumab-related AE, of whom 2 (6.5%) had grade 3 events (pyrexia also related to MEDI1191, and pruritus). There were no durvalumab-related grade 4 AEs or SAEs.

Table 3. Safety summary

Event, n (%)	Part 1A: sequential MEDI1191 + durvalumab (N=20)	Part 1B: concurrent MEDI1191 + durvalumab (N=11)	Total (N=31)
Any TEAE	19 (95.0)	11 (100)	30 (96.8)
Grade 3/4 TEAE	9 (45.0)	3 (27.3)	12 (38.7)
Treatment-emergent SAE	8 (40.0)	1 (9.1)	9 (29.0)
AE leading to death	0	0	0
MEDI1191-related AE	10 (50.0)	3 (27.3)	13 (41.9)
MEDI1191-related grade 3/4 AE	0	1 (9.1)	1 (3.2)*
MEDI1191-related SAE	1 (5.0)	0	1 (3.2)
AE leading to discontinuation of MEDI1191	0	0	0
Durvalumab-related AE	2 (10.0)	5 (45.5)	7 (22.6)
Durvalumab-related grade 3/4 AE	1 (5.0)	1 (9.1)	2 (6.5)†
Durvalumab-related SAE	0	0	0
AE leading to discontinuation of durvalumab	0	0	0

*One patient had MEDI1191-related grade 3 pyrexia.
†Two patients had durvalumab-related grade 3 AEs of pyrexia (n=1, also considered MEDI1191-related) and pruritus (n=1).

Table 4. TEAEs occurring in ≥3 patients overall

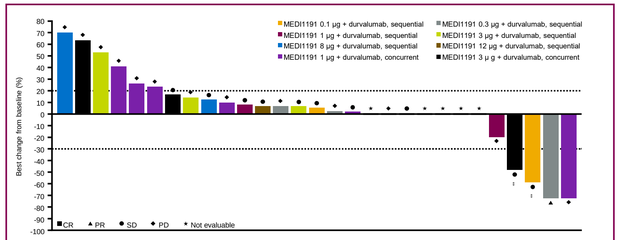
Event, n (%)	Part 1A: sequential MEDI1191 + durvalumab (N=20)		Part 1B: concurrent MEDI1191 + durvalumab (N=11)		Total (N=31)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4*
Any TEAE	19 (95.0)	9 (45.0)	11 (100)	3 (27.3)	30 (96.8)	12 (38.7)
Fatigue	2 (10.0)	1 (5.0)	4 (36.4)	0	6 (19.4)	1 (3.2)
Dyspnea	2 (10.0)	1 (5.0)	3 (27.3)	0	5 (16.1)	1 (3.2)
Pruritus	3 (15.0)	1 (5.0)	2 (18.2)	0	5 (16.1)	1 (3.2)
Pyrexia	3 (15.0)	0	1 (9.1)	1 (9.1)	4 (12.9)	1 (3.2)
Diarrhea	3 (15.0)	0	1 (9.1)	0	4 (12.9)	0
Nausea	4 (20.0)	0	0	0	4 (12.9)	0
Anemia	1 (5.0)	0	2 (18.2)	1 (9.1)	3 (9.7)	1 (3.2)
Dysphagia	3 (15.0)	1 (5.0)	0	0	3 (9.7)	1 (3.2)
Erythema	1 (5.0)	0	2 (18.2)	0	3 (9.7)	0
Hyponatremia	3 (15.0)	1 (5.0)	0	0	3 (9.7)	1 (3.2)
Injection site pain	3 (15.0)	0	0	0	3 (9.7)	0
Rash	2 (10.0)	0	1 (9.1)	0	3 (9.7)	0
Insomnia	3 (15.0)	0	0	0	3 (9.7)	0

*In Parts 1A and 1B combined, additional grade 3/4 TEAEs included ascites (n=2), abdominal pain, cancer pain, esophagitis, gastric stenosis, lower gastrointestinal hemorrhage, lymphedema, pneumonia, and sepsis (each n=1)

Efficacy

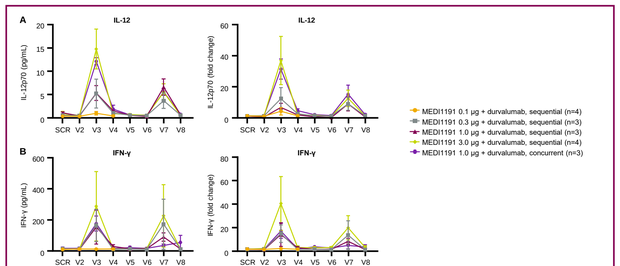
- Best change in target lesion size is shown in **Figure 2**.
- Overall, 3 patients had confirmed or unconfirmed PRs, including:
  - 1 patient with head and neck cancer (unconfirmed PR) who received sequential MEDI1191 0.1 µg with durvalumab
  - 2 patients with anti-PD-1-resistant melanoma: one received sequential MEDI1191 0.3 µg with durvalumab and had a confirmed PR lasting 9+ months, and the other received concurrent MEDI1191 3 µg with durvalumab and had an unconfirmed PR. At data cutoff, treatment was ongoing in both patients.
- 10 (32.3%) patients had stable disease (including the 2 with unconfirmed PRs), 13 (41.9%) patients had progressive disease, and 5 (16.1%) patients were not evaluable for tumor response.
- Three out of 4 patients with >30% target lesion regression had 1 confirmed PR and 2 unconfirmed PRs, and the DCR was 29.0%.

Figure 2. Best change in target lesion size per RECIST 1.1



†The 2 patients with a >30% reduction in target lesion size had unconfirmed PRs (1 received 0.1 µg and 1 received 3 µg)

Figure 3. MEDI1191 induces serum IL-12 and IFNγ release in the periphery



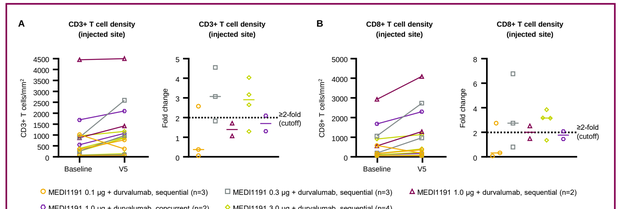
(A) Serum IL-12 and **(B)** IFNγ levels (pg/mL) and fold change across the 5 dose cohorts. Serum IL-12 and serum IFNγ levels were measured by Erenna immunoassay system Singulex and Meso Scale Discovery, respectively. The 0.1 µg dose resulted in the lowest increases in IL-12 and IFNγ levels in the periphery. No clear dose dependence was observed above 0.1 µg. The highest IL-12 and IFNγ serum levels were observed in the 3 µg Part 1A dose cohort, followed by the 1 µg Part 1B dose cohort. Points and error bars show mean ± standard deviation.

SCR, screening visit; Vx, visit number x.

Pharmacodynamic changes

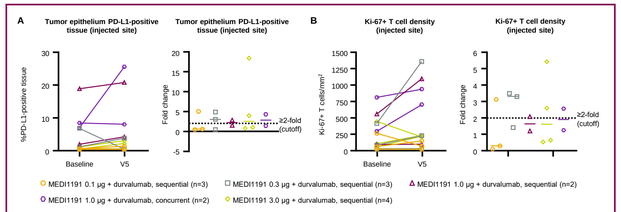
- Overall, 17 patients were evaluable for pharmacodynamic studies (up to MEDI1191 3 µg in Part 1A and 1 µg in Part 1B).
- MEDI1191 increased IL-12 production in 15/17 (88.2%) patients as determined by ≥2-fold increases in serum IL-12 levels 24 hr after injection, compared with baseline (**Figure 3A**).
  - MEDI1191 0.1 µg resulted in the lowest increase in IL-12 levels in the periphery.
  - No clear dose dependence was observed above the transition from MEDI1191 0.1 µg to 0.3 µg (**Figure 3A**). Serum IL-12 levels were highest at 3 µg in Part 1A and 1 µg in Part 1B.
- Increased IL-12 was associated with ≥2-fold parallel increases in serum IFNγ in 10/17 (58.8%) patients (**Figure 3B**).
- Consistent with its expected mechanism of action, IT MEDI1191 was also associated with increases in tumor-infiltrating T cells compared with baseline (**Figure 4**), as well as IT increases in other biomarkers indicating increased T cell activation.
  - 7/14 patients had a ≥2-fold increase from baseline in CD3+ T cells.
  - 8/14 patients had a ≥2-fold increase from baseline in CD8+ T cells.
  - 6/14 patients had a ≥2-fold increase from baseline in proliferating T cells.
- IT MEDI1191 led to a ≥2-fold increase in PD-L1 expression on tumor epithelium (injected site) in 7/14 patients (**Figure 5**).

Figure 4. MEDI1191 increases intratumoral T cell density



(A) CD3+ T cell and **(B)** CD8+ T cell densities (cells/mm²) were assessed with immunohistochemistry in patient tumor biopsies and quantified with HALO AI digital image analysis by the study pathologist. (Left) Plots show cells/mm² at baseline and visit 5 (V5). Each line represents a patient. (Right) Plots show the fold change at day 15 (visit 5) for each dose cohort; horizontal lines represent medians, and dotted lines represent the cutoff set at ≥2-fold increase.

Figure 5. MEDI1191 induces PD-L1 expression in tumor epithelium and T cell proliferation



(A) The percentage of PD-L1-positive tissue in tumor epithelium and **(B)** the density of Ki-67-positive cells were assessed with immunohistochemistry in patient tumor biopsies and quantified with HALO AI digital image analysis by the study pathologist. (Left) Plots shows percentage positive tissue for PD-L1 or cells/mm² for Ki-67, at baseline and visit 5 (V5). Each line represents a patient. (Right) Plots shows the fold change at day 15 (visit 5) for each dose cohort; horizontal lines represent medians, and dotted lines represent the cutoff set at ≥2-fold increase.

Conclusion

- IT MEDI1191 combined with either sequential or concurrent IV durvalumab was safe and feasible in patients with previously treated advanced solid tumors and cutaneous or subcutaneous lesions.
- No AEs led to discontinuation of MEDI1191 or durvalumab.
- The combination showed preliminary evidence of clinical benefit, with 29.0% of patients exhibiting PRs or SD ≥12 weeks as best overall response.
- Pharmacodynamic effects, including increases in peripheral IL-12 and IFNγ, as well as tumoral CD8+ T cell recruitment, were consistent with the expected mechanism of action of MEDI1191.
- Patients with injectable, deep-seated visceral lesions, as well as superficial lesions, are now being recruited.

References:

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2. Hamid O, et al. Presented at ESMO TAT 2021, abstract 19O.

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