Clinical Study Report Synopsis	
Drug Substance	MEDI0457+Durvalumab
Study Code	D8860C00005
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A Phase 1b/2a, Multi-Center Open-Label Study to Evaluate the Safety and Efficacy of Combination Treatment with MEDI0457 (INO-3112) and Durvalumab (MEDI4736) in Patients with Recurrent / Metastatic Human Papilloma Virus Associated Head and Neck Squamous Cancer

Study dates: First subject enrolled: 26 June 2017
Last subject last visit: 16 July 2019
The analyses presented in this report are based on a data cut-off date of 19 March 2021
Database lock date: 28 June 2021

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

International Co-ordinating Investigator: PPD
PPD
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Sponsor's Responsible Medical Officer: PPD
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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

This was a multi-center study conducted at 14 study centers within the United States.

Publications

Aggarwal C, Halmos B, Porosnicu M, et al. Phase 1b/2a, multicenter, open-label study to evaluate the safety and efficacy of combination treatment with MEDI0457 (INO-3112) and durvalumab (MEDI4736) in patients with recurrent/ metastatic HPV-related head and neck squamous cell cancer. Poster presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; June 1–5, 2018; Chicago, IL, USA.

Aggarwal C, Saba NF, Algazi AP, et al. 916MO Safety and efficacy of MEDI0457 plus durvalumab in patients (pts) with human papillomavirus-associated recurrent/metastatic head and neck squamous cell carcinoma (HPV+ R/M HNSCC). Ann Oncol 2020; 31(S4):S661-S662.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Outcome Measure
Primary	
To determine the safety profile of MEDI0457 in combination with durvalumab in patients with recurrent/metastatic head and neck cancer.	Adverse events/SAEs Collection of hematology, serum chemistry, urinalysis, CPK, thyroid function testing, and pregnancy test Electrocardiograms (ECGs): The following parameters were recorded for each ECG: date and time of electrocardiogram, heart rate (HR) (beats/min), PR interval (ms), QRS interval (ms), RR interval (ms), QT interval (ms), QTcB interval (ms), QTcF interval (ms), sinus rhythm (yes/no), and overall evaluation (normal/abnormal) Vital signs Physical examinations Concomitant medications World Health Organization (WHO)/ECOG performance status
To evaluate the anti-tumor activity of MEDI0457 in combination with durvalumab in patients with confirmed HPV-16 or HPV-18 associated recurrent/metastatic head and neck cancer	Objective response rate by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (response-evaluable population)
Secondary	
To evaluate the pharmacokinetics and anti-drug antibodies (ADAs) for durvalumab	Serum concentrations of durvalumab Anti-drug antibodies for durvalumab

Objectives	Outcome Measure
To evaluate the anti-tumor activity of MEDI0457 in combination with durvalumab	Objective response rate by RECIST version 1.1 (as-treated population) and immune-related RECIST (irRECIST) Disease control rate at 16 weeks by RECIST version 1.1 Overall survival Progression-free survival as assessed by RECIST version 1.1
Exploratory	
CCI	CCI
CCI	CCI
CCI	

CPK= creatine phosphokinase; CSR= Clinical Study Report; ECOG= Eastern Cooperative Oncology Group; ELISPOT=enzyme-linked immunospot; HPV= human papilloma virus; IgG=immunoglobulin G; CCI ; PD-L1= programmed death ligand 1; QTcB=QT interval corrected for heart rate based on the Bazett formula ; QTcF= QT interval corrected for heart rate based on the Fridericia formula; SAE=serious adverse event.

Study Design

The study was a Phase 1b/2a, open-label, multi-center study to evaluate the safety and tolerability, anti-tumor activity, and immunogenicity of MEDI0457 (also known as INO-3112) in combination with durvalumab (also known as MEDI4736) in patients with

recurrent or metastatic human papilloma virus (HPV)-associated head and neck squamous cancer. Adult, male or female, patients with a histologically or cytologically confirmed diagnosis of squamous cell carcinoma of the head and neck (SCCHN) associated with HPV, with recurrent or metastatic disease and who met the eligibility criteria were enrolled.

Enrollment started with an initial 3 patients (Safety Analysis Run-in patients), who received up to 4 doses of MEDI0457 (Limited Schedule) in combination with durvalumab. CCI [redacted] None of the initial 3 patients experienced a dose-limiting toxicity (DLT) during the DLT evaluation period. Safety during the run-in period was deemed acceptable by the SDMC; therefore, all subsequent patients were enrolled directly to the Indefinite (Planned) Schedule. Patients in the Indefinite Schedule received MEDI0457 and durvalumab until disease progression, unacceptable toxicity, or withdrawal of consent.

A further 32 patients were enrolled for the Indefinite Schedule. Patients were administered CCI [redacted] MEDI0457 intramuscularly followed by electroporation (EP) on Day 1 (Week 1), Week 3, Week 7, Week 12, and every 8 weeks thereafter, until disease progression, unacceptable toxicity, or withdrawal of consent. Durvalumab 1500 mg was administered intravenously on Week 4 and then every 4 weeks until disease progression, unacceptable toxicity, or withdrawal of consent.

Target Population and Sample Size

It was planned to enroll approximately 50 patients with HPV-associated recurrent/metastatic SCCHN in this study. However, a total of 35 patients were enrolled in the study.

Eligible patients were males or females aged 18 years or older, with a histologically or cytologically confirmed diagnosis of SCCHN associated with HPV by a p16 immunohistochemistry assay or HPV-16 or HPV-18 positive by nucleic acid testing. Patients with recurrent or metastatic disease who had been treated with at least one platinum-containing regimen and lacking a curative treatment option were enrolled. Platinum-ineligible patients were included only if they had received and failed an approved treatment, and lacked a treatment option with curative potential.

Patients were enrolled if they had at least 2 SCCHN CCI [redacted] – one for biopsy and one for Response Evaluation Criteria in Solid Tumors (RECIST) tracking; and with measurable disease defined as having at least one lesion that could be accurately measured in at least one dimension. The longest diameter of the lesion as recorded by computed tomography (CT) scan had to be at least 10 mm, except for lymph nodes which were to have a minimum short axis size of 15 mm (CT scan slice thickness no greater than 5 mm in both cases).

Investigational Product and Comparator(s): Dosage, Mode of Administration and Batch Numbers

CCI [redacted]

Dosage, route of administration and frequency: CCI [redacted]

The following lot numbers were used: CCI [redacted] (expiry date: CCI [redacted]), CCI [redacted] (expiry date: CCI [redacted]), and CCI [redacted] (expiry date: CCI [redacted]).

Durvalumab (also known as MEDI4736), a human Immunoglobulin G1 kappa monoclonal antibody directed against human PD-L1, was supplied by MedImmune as a 500-mg vial solution for infusion after dilution. The solution contained 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; with a pH of 6.0. The nominal fill volume was 10 mL.

Dosage, route of administration and frequency: Durvalumab was administered as 1500 mg intravenous infusion at Week 4, Week 8, Week 12, and every 4 weeks thereafter, until disease progression, unacceptable toxicity, or withdrawal of consent.

The following lot numbers were used: CCI [redacted] (expiry date: CCI [redacted]), CCI [redacted] (expiry date: CCI [redacted]), CCI [redacted] (expiry date: CCI [redacted]), and CCI [redacted] (expiry date: CCI [redacted]).

Duration of Treatment

CCI [redacted]

In the Planned Schedule, patients received MEDI0457 and durvalumab until disease progression, unacceptable toxicity, or withdrawal of consent.

Statistical Methods

Statistical analyses were performed using Statistical Analysis Software version 9.4 or higher. Categorical variables were summarized using counts and percentages. Continuous variables were summarized using the number of observations (n), mean, standard deviation, median, minimum, and maximum. Confidence intervals (CIs) were 2-sided and used the exact binomial method at a 95% confidence level.

Safety

Safety was assessed by incidence, severity and type of adverse events (AEs), changes from baseline in laboratory parameters (chemistry, hematology, urinalysis, and thyroid function testing), vital signs, electrocardiogram (ECG), physical examination findings, and Eastern Cooperative Oncology Group (ECOG) performance status.

Adverse events were summarized by the count and percentage of patients with AEs and listed individually by-patient. Adverse events were categorized by relationship to study drug (MEDI0457-related, durvalumab-related), study-procedure related, and device-related, or treatment-related (any relation or missing relation). Summaries of AEs leading to discontinuation from either study drug or modifications (delay, interruption, reduction, or omission) of either study drug were provided, grouped by system organ class (SOC) and preferred term (PT). The number and percentage of patients reporting each AE, categorized by SOC and PT coded according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary v24.0, was presented.

The number and percentage of patients reporting at least one AE of special interest (AESI) were tabulated; AESIs were further tabulated by severity, treatment relation, and seriousness. The number and percentage of patients experiencing SAEs was presented by SAE criteria and total. Serious AE and treatment-related SAE were tabulated by SOC and PT. All deaths were listed.

The following were considered AESI for this study: diarrhea, colitis, pneumonitis, alanine aminotransferase /aspartate aminotransferase (AST) increases/hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis/rash/pruritus, nephritis, pancreatitis, myocarditis/pericarditis, uveitis, infusion-related reactions/hypersensitivity/ anaphylactic reactions, and administration site reactions. Administration site reactions were graded using Common Terminology Criteria for Adverse Events (CTCAE) and the Administration Site Reaction Grading Scale (Mild: Grade 1, Moderate: Grade 2, Severe: Grade 3, Potentially life threatening: Grade 4).

Descriptive statistics were provided for the clinical laboratory results (chemistry, hematology, urinalysis and thyroid function testing) and vital signs and changes from baseline by visit for visits with more than 5 patients. Standard shift tables were prepared for hematology and serum chemistry parameters presenting worst postbaseline CTCAE toxicity grade vs baseline. Laboratory and safety data were listed by-patient. A table and listing was provided for laboratory results for patients with potential Hy's law.

Change from baseline for minimum, maximum, and last record on treatment were tabulated for ECGs. The number and percentage of patients meeting criteria for notable QT-intervals

were presented. A shift summary of ECOG performance status presenting worst postbaseline status vs baseline was provided.

A listing of AEs for anti-drug antibody (ADA) positive patients was provided. Bleeding and pneumonitis questionnaire data were presented in listings. Blood gases, serum interstitial lung disease (ILD) markers, and pulmonary function tests were not tabulated or listed.

Efficacy

The primary efficacy variable was objective response rate (ORR) defined as the number (%) of patients with confirmed complete response (CR) or partial response (PR) via RECIST 1.1 in patients within the response-evaluable population. The response-evaluable population included all patients with confirmed HPV-16 or HPV-18 associated disease who received one dose of both study drugs, had a baseline scan with measurable disease at baseline and at least one follow-up scan (including discontinuations due to disease progression or death without follow-up scan) with the opportunity to be followed for ≥16 weeks.

The ORR estimate was accompanied by a 2-sided exact binomial 95% CI.

The secondary efficacy variables included ORR by RECIST v1.1 in the as-treated population and ORR by immune-related RECIST (irRECIST) in both response-evaluable and as-treated population. Other secondary efficacy variables included disease control at 16 weeks (DCR-16w), overall survival (OS), and progression-free survival (PFS). DCR-16w was classified as the number (%) of patients with CR, PR, and stable disease (SD) for ≥16 weeks according to RECIST v1.1, and was summarized in the response-evaluable and as-treated population. The estimate was accompanied by a 2-sided exact binomial 95% CI.

Overall survival was defined as the time from the start date of investigational product (IP) treatment until death (+1 day) due to any cause. Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive. Progression-free survival was defined as the time from the start date of IP treatment until the documentation of disease progression according to RECIST version 1.1 or death due to any cause, whichever occurred first (+1 day). Progression-free survival and OS were summarized descriptively in the response-evaluable and as-treated populations using the Kaplan-Meier method.

Pharmacokinetics and immunogenicity data (secondary objectives) were summarized and tabulated.

Study Population

The study was conducted at 14 centers in the United States. A total of 43 patients were screened; 35 patients with HPV-associated recurrent/metastatic head and neck squamous cell cancer from 12 centers were enrolled in this study. Eight patients were screen failures.

Of the 35 patients enrolled, the majority were male (34 [97.1%]) and white (33 [94.3%]). The median age was 59 years (range 41 to 81 years). At baseline, 19 (54.3%) patients had an ECOG performance status of 0 and 16 (45.7%) patients had an ECOG performance status of 1. Twenty-three (65.7%) patients were former smokers, 10 (28.6%) were non-smokers, and 2 (5.7%) were current smokers. The disease stage at initial diagnosis was Stage IV for most patients (26 [74.3%] patients).

Of the 35 patients enrolled in the study (15 patients in the first-line recurrent/metastatic [1L R/M] platinum non-refractory cohort, 9 patients in the 1L R/M platinum-refractory cohort, and 11 patients in the second-line+[2L+] R/M cohort):

- Nine (25.7%) patients were ongoing: 6/15 (40.0%) patients in the 1L R/M platinum non-refractory cohort, 2/9 (22.2%) patients in the 1L R/M platinum-refractory cohort, and 1/11 (9.1%) patient in the 2L+R/M cohort.
- Twenty-six (74.3%) patients discontinued the study: 9/15 (60.0%) patients in the 1L R/M platinum non-refractory cohort, 7/9 (77.8%) patients in the 1L R/M platinum-refractory cohort, and 10/11 (90.9%) patients in the 2L+R/M cohort.
  - Six (17.1%) patients completed the study (completed study indicates that the patient completed all protocol specified scheduled study assessments): 4/15 (26.7%) in the 1L R/M platinum non-refractory cohort, 1/9 (11.1%) in the 1L R/M platinum-refractory cohort, and 1/11 (9.1%) in the 2L+R/M cohort.
  - Seventeen (48.6%) patients died during the study: 4/15 (26.7%) in the 1L R/M platinum non-refractory cohort, 5/9 (55.6%) in the 1L R/M platinum-refractory cohort, and 8/11 (72.7%) in the 2L+R/M cohort; Of these 17 patients, 16 (45.7%) died due to disease under investigation, and 1 (2.9%) patient died due to an adverse event (respiratory failure) not related to study drug.
  - Two (5.7%) patients withdrew from the study, and
  - One (2.9%) patient was lost to follow-up.

In general, patient demographics and baseline disease characteristics were in line with what was expected of the target population.

Summary of Efficacy Results

The primary efficacy endpoint was ORR via RECIST 1.1 in the response-evaluable population. Analysis was performed by grouping patients on the basis of line of therapy and platinum sensitivity status.

A total of 29 (82.9%) patients were included in the response-evaluable population. Within the response-evaluable population, ORR was 27.6% (8 patients; 95%CI: 12.73, 47.24) with CR in 13.8% (4 patients). Eight patients (27.6%) had a best response of SD, and 13 (44.8%) patients had PD.

Secondary efficacy endpoints:

- Objective response by RECIST version 1.1 in the as-treated population: Objective response rate was 25.7% (9 patients; 95% CI: 12.49, 43.26) with 4 (11.4%) CRs and 5 (14.3%) PRs; 11 (31.4%) patients had a best response of SD, and 14 (40.0%) patients had PD.
- Objective Response by irRECIST in the response-evaluable population and as-treated population:
  - In the response-evaluable population, a total of 5 (17.2%) patients achieved irCR; 4 (13.8%) patients had irPR. Stable disease (irSD) was observed in 10 (34.5%) patients; unconfirmed progressive disease was observed in 9 (31.0%) patients. The status of disease was not evaluable (irNE) for 1 (3.4%) patient.
  - In the as-treated population, 5 (14.3%) patients achieved complete response (irCR); partial response (irPR) was observed for 5 (14.3%) patients. Stable disease (irSD) was observed in 13 (37.1%) patients; confirmed PD was observed in 1 (2.9%) patient; unconfirmed PD was observed in 9 (25.7%) patients. The status of disease was irNE for 2 (5.7%) patients.
- Disease control at 16 weeks (DCR-16w) was observed for 13 (44.8%) patients (95%CI: 26.45, 64.31) in the response-evaluable population.
- Overall survival: In the as-treated population18 (51.4%) patients were alive at DCO. The median OS was 29.2 months (95%CI: 15.2, NC);The OS rate at 6 months was 0.9% (95%CI: 0.72, 0.96); OS rate at 12 months was 0.8% (95%CI: 0.59, 0.88); and OS rate at 24 months was 0.6% (95%CI: 0.38, 0.72). In the response-evaluable population, 16 (55.2%) patients were alive at DCO. The median OS was 29.2 months (95%CI:15.2, NC). The OS rate at 6 months was 0.9% (95%CI: 0.71, 0.96); OS rate at 12 months was 0.8% (95%CI: 0.59, 0.90); and OS rate at 24 months was 0.6% (95%CI: 0.37, 0.75).

Summary of Pharmacokinetic Results

CCI [redacted]

Summary of Immunogenicity Results

CCI [redacted]

Summary of Safety Results

All 35 patients enrolled received at least one dose of study drug and were included in the as-treated population and evaluated for safety.

The mean (standard deviation [sd]) total number of MEDI0457 doses administered during the study was 7.9 (6.20). The mean (sd) duration of exposure to MEDI0457 was 51.4 (50.27) weeks.

The median number of MEDI0457 doses administered across all cohorts was 4.0 doses. This was similar across cohorts, except for the 1L R/M platinum non-refractory cohort, which had a median of 9.0 doses. The median duration of exposure to MEDI0457 (19 weeks) was similar across cohorts except for the 1L R/M platinum non-refractory cohort for which mean duration of exposure was 59.1 weeks.

MEDI0457 administration with successful delivery of EP was achieved for most doses (mean [sd]: 98.28% [5.035] doses).

The mean (sd) total number of durvalumab doses administered during the study was 11.6 (12.11). The mean (sd) duration of exposure to durvalumab was 47.6 (49.59) weeks.

The median number of durvalumab doses administered across all cohorts was 4.0 doses. This was similar across cohorts except for 1L R/M platinum non-refractory cohort, which had a median of 14.0 doses. The median duration of exposure to durvalumab across all the cohorts was 20.0 weeks (56.1 weeks in the 1L R/M platinum non-refractory cohort, 16 weeks in the 1L R/M platinum-refractory cohort, and 17 weeks in the 2L+R/M cohort).

No DLTs were observed in the DLT-evaluable population.

The most frequently reported AEs by preferred term (PT) (reported in ≥15% patients) in the as-treated population were fatigue (19 [54.3%]), cough (16 [45.7%]), anemia (12 [34.3%]), dyspnea (11 [31.4%]), hypertension (10 [28.6%]), nausea (10 [28.6%]), injection site pain (9 [25.7%]), back pain (8 [22.9%]), constipation (8 [22.9%]), weight decreased (8 [22.9%]), headache (7 [20.0%]), hypothyroidism (7 [20.0%]), pyrexia (7 [20.0%]), rash (7 [20.0%]), arthralgia (6 [17.1%]), decreased appetite (6 [17.1%]), diarrhea (6 [17.1%]), dysphagia (6 [17.1%]), hyponatremia (6 [17.1%]), lymphocyte count decreased (6 [17.1%]), and vomiting (6 [17.1%]).

MEDI0457-related treatment-emergent AEs (TEAEs) were reported in 25 (71.4%) patients; The most frequently reported MEDI0457-related TEAEs (in ≥10% patients), were: fatigue (9 [25.7%]), injection site pain (7 [20.0%]), and arthralgia (4 [11.4%] patients).

Treatment-emergent AEs of CTCAE Grade 3 or 4 were reported for 17 (48.6%) patients; Treatment-related TEAEs of CTCAE Grade 3 were reported in 5 (14.3%) patients.; These included: AST increased (2 [5.7%] patients), and lipase increased (1 [2.9%] patient), myocarditis (1 [2.9%] patient), ophthalmic herpes zoster (1 [2.9%] patient), and wheezing (1 [2.9%] patient). No treatment-related TEAEs of Grade 4 or 5 were reported. AEs of any

grade considered related to study treatment by the Investigator were reported for 28 (80.0%) patients.

Treatment-emergent AESI were reported in 19 (54.3%) patients.

A treatment-emergent AE with the outcome of death (respiratory failure not related to study drug) was reported in 1 (2.9%) patient. Treatment-emergent SAEs were reported in 14 (40.0%) patients. Treatment-emergent AEs leading to discontinuation of either study medication were reported in 4 (11.4%) patients.

Findings related to laboratory investigations were transient and did not appear to impact the safety profile of the study medication. There were no clinically meaningful findings related to vital signs, ECG, or physical examination.

Conclusion(s)

- In patients with recurrent/metastatic head and neck cancer associated with HPV-16 and/or HPV-18, treatment with MEDI0457 in combination with durvalumab demonstrated an overall objective response of 27.6% (95% CI: 12.73, 47.24). Based on the interim analysis of 35 patients, the predictive probability of success/futility defined via P(ORR≥0.30) did not reach the corresponding threshold for success or futility prespecified in the CSP, therefore, further enrollment was halted.
- PPD
- Treatment with CCI MEDI0457 intramuscular injection followed by electroporation (EP) in combination with durvalumab 1500 mg intravenous infusion was well tolerated.