2. SYNOPSIS

This Clinical Study Report (CSR) presents data from 4 Initial Stage Cohorts of the study (small cell lung cancer [SCLC] cohort, germline breast cancer susceptibility gene mutated [*gBRCAm*] breast cancer cohort, *gBRCAm* ovarian cancer cohort, and gastric cancer cohort). Results from other cohorts will be presented in subsequent addenda, as will further survival data from the *gBRCAm* ovarian cancer cohort.

Study center(s)

The 4 Initial Stage Cohorts reported in this CSR were assessed at CCI across 7 countries: France CCI, the United Kingdom (UK) and the Republic of Korea CCI, the United States of America (USA) and the Netherlands CCI, Israel CCI, and Switzerland CCI.

Publications

- Angell HK, et al. J Immuno Cancer. 2017;5 (Supplement 2):87. P257.
- Bang Y-J, et al. J Clin Oncol. 2019;37 (Supplement 4):140.
- Domchek SM, et al. Annals of Oncology. 2019;30 (Supplement 5): v475-v532.
- Domchek SM, et al. Cancer Res. 2019;79 (Supplement 4):PD5-04.
- Domchek SM, et al. Cancer Res. 2018;78 (Supplement 4):PD6-11.
- Drew Y, et al. Ann Oncol. 2019;30 (Supplement 5): v475-v532.
- Drew Y, et al. Gynecol Oncol 2018;149:246-7.
- Krebs M, et al. J Thorac Oncol 2017;12 (Supplement 2):S2044-5.
- Tang M, et al. PharmSci360, Washington, DC, Nov. 4-7, 2018. Poster M1430-05-034.

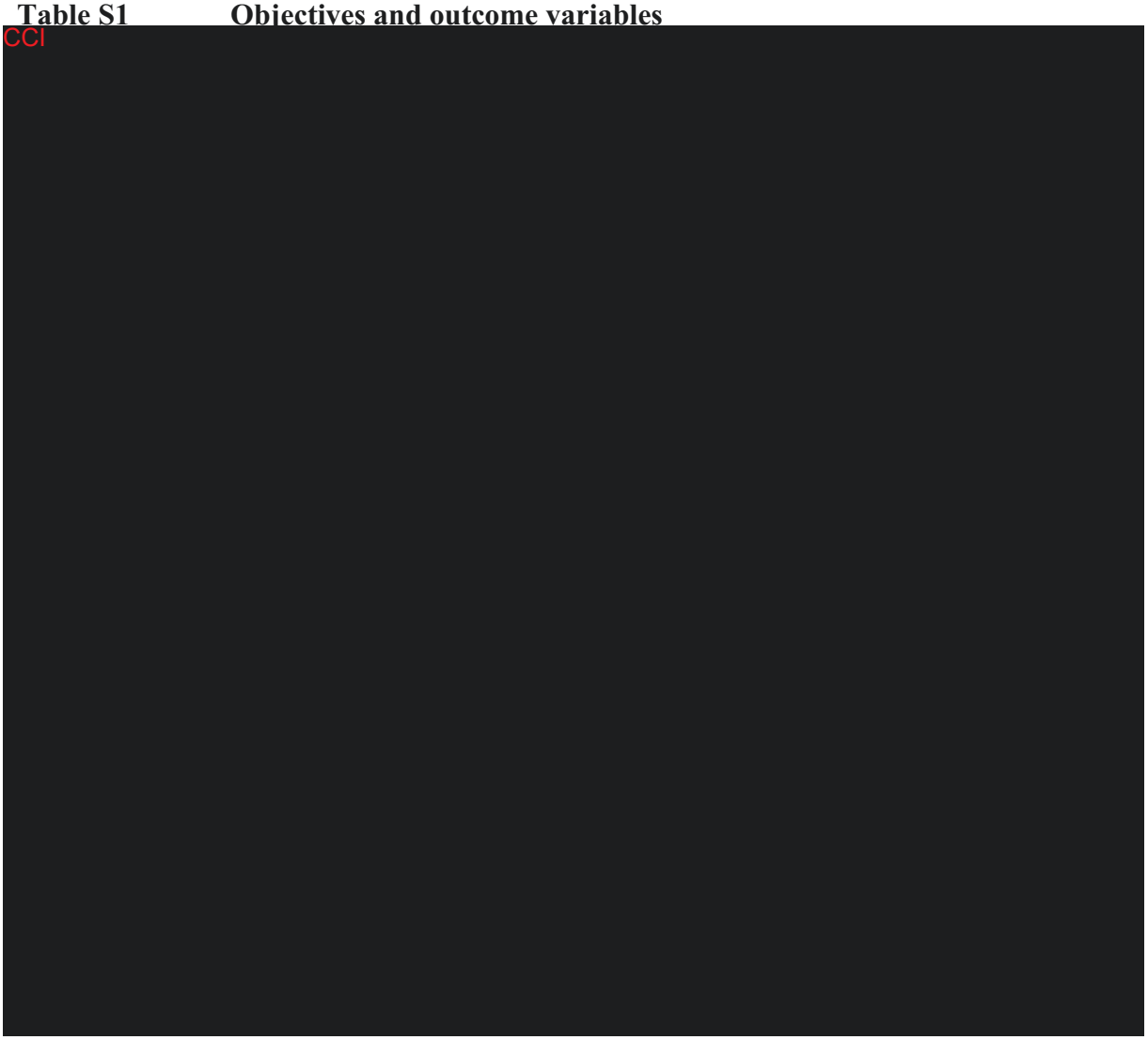
Objectives and criteria for evaluation

Objectives and endpoints for the 4 Initial Stage Cohorts described in this CSR are presented below.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To assess the effect of MEDI4736 in combination with olaparib in patients with selected advanced solid tumors	DCR (CR + PR + SD) based on RECIST 1.1 at 12 weeks
Primary	Safety	To assess the safety and tolerability of MEDI4736 in combination with olaparib in patients with selected advanced solid tumors	• Adverse events, vital signs including blood pressure, pulse, ECG, and laboratory findings including clinical chemistry and hematology • irAEs - given the intended mechanisms of action of MEDI4736, particular attention will be given to AEs that may follow enhanced T-cell activation, or other irAE • Dose interruptions, dose reductions • Causes of olaparib and MEDI4736 discontinuation
Secondary	Efficacy	To investigate the preliminary antitumor activity of MEDI4736 in combination with olaparib in patients with selected advanced solid tumors	• DCR at 28 weeks[a] • ORR (CR + PR) based on RECIST 1.1[a] • DoR based on RECIST 1.1[a] • PFS based on RECIST 1.1[a] • Percentage change from baseline in tumor size at 12 weeks and 28 weeks. • Best percentage change from baseline in tumor size. • TDT. • Overall survival.
Secondary	PK	• To determine plasma concentrations of olaparib after single and multiple dosing when given orally to patients alone and in combination with MEDI4736 • To characterize the PK, immunogenicity, and pharmacodynamics of MEDI4736 after single dosing and multiple dosing when given intravenously to patients in combination with olaparib	• Serum concentrations of MEDI4736, MEDI4736 ADA. • Plasma concentrations of olaparib. • Presence of ADAs for MEDI4736. • CCI
Secondary	Pd	CCI	

Table S1 Objectives and outcome variables



[a] Also by blinded independent central review in the *gBRCAm* breast cancer and *gBRCAm* ovarian cancer cohorts. Blinded independent central review assessments are not presented in this report (see Section 9.9.2).

ADA anti-drug antibody; AE adverse event; CCI ; *BRCA(m)* breast cancer susceptibility gene (mutated); CR complete response; DCR disease control rate; DNA deoxyribonucleic acid; DoR duration of response; ECG electrocardiogram; *gBRCAm* germline breast cancer susceptibility gene mutated; HLA-DR human leukocyte antigen – antigen D related; irAE immune-related adverse event; ORR objective response rate; OS overall survival; Pd pharmacodynamic; PD-1 programmed cell death 1; CCI ; PFS progression-free survival; PK pharmacokinetic; PR partial response; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; RNA ribonucleic acid; SD stable disease; CCI ; TDT time to study treatment discontinuation.

Study design

This was a Phase I/II open-label, multicenter study to evaluate the safety, tolerability, pharmacokinetic (PK), and antitumor activity of 28 days of olaparib monotherapy, followed by MEDI4736 in combination with olaparib, in patients with advanced solid tumors, selected based on a rationale for response to olaparib. The doses of MEDI4736 and olaparib in combination were previously determined in a dose-escalation Phase I study.

Target subject population and sample size

Patients had advanced solid tumors and were polyadenosine 5'diphosphoribose (poly [ADP ribose]) polymerization (PARP)-inhibitor and immunotherapy (IMT)-naïve (defined as no prior exposure to PARP inhibitors or IMT, including, but not limited to, other anti-cytotoxic T-lymphocyte-associated protein 4, programmed cell death 1 (PD-1), CCI [redacted] monoclonal antibodies (mAbs), or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

The primary efficacy endpoint of the study in the Initial Stage Cohorts was Disease Control Rate (DCR), assessed at 12 weeks. Disease control rate as an endpoint was used to define the sample size in these cohorts using olaparib monotherapy or standard of care as a historical comparator, as described below for each of the Initial Stage Cohorts:

- **Small cell lung cancer cohort**: the target DCR was 60%, with a value of 40% or less considered undesirable. Given these figures, the maximum sample size for this cohort was 38 patients.
- ***gBRCAm* breast cancer cohort**: the target DCR was 75%, with a value of 55% or less considered undesirable. Given these figures, the maximum sample size for this cohort was 30 patients.
- ***gBRCAm* ovarian cancer cohort**: the target DCR was 90%, with a value of 70% or less considered undesirable. Given these figures, the maximum sample size for this cohort was 31 patients.
- **Gastric cancer cohort**: the target DCR was 70%, with a value of 50% or less considered undesirable. Given these figures, the maximum sample size for this cohort was 34 patients.

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

The Investigational Products (IPs) in this study were olaparib (AZD2281, KU-0059436, LYNPARZA®[1]) and MEDI4736 (durvalumab, IMFINZI®[2]).

In the cohorts being reported in this CSR, patients received olaparib monotherapy for 4 weeks before starting MEDI4736 + olaparib combination treatment; olaparib treatment was taken orally, 300 mg twice daily (bid; 2 × 150 mg tablets) and MEDI4736 treatment was by intravenous (IV) infusion, 1.5 g every 4 weeks (±3 days). The initial safety and tolerability of the combination of 300 mg bid olaparib and 1.5 g every 4 weeks (q4w) MEDI4736 was established in a Phase I study (MEDI-O study).

[1] LYNPARZA is a trademark of the AstraZeneca group of companies.
[2] IMFINZI is a trademark of the AstraZeneca group of companies.

CCI [redacted] individual batch numbers and further information are included in the CSR.

Duration of treatment

Patients were to continue to receive combination treatment until objective radiological disease progression per Response Evaluation Criteria in Solid Tumors (RECIST 1.1), as assessed by the Investigator, or as long as, in the Investigator's opinion, they were benefiting from treatment and they did not meet any other discontinuation criteria.

Statistical methods

All data collected were listed. Efficacy data were summarized and analyzed by cohort on the full analysis set. Safety data were summarized by cohort based on the safety analysis set.

Efficacy

For all the Initial Stage Cohorts presented in this CSR the primary efficacy endpoint was DCR at 12 weeks using Investigator assessments per RECIST 1.1. Each cohort was sized to characterize the DCR of MEDI4736 + olaparib. All formal statistical analyses were performed on a per cohort basis, to test the main hypotheses that the DCR was above the threshold of interest defined for each cohort.

The primary efficacy variable (DCR at 12 weeks) was summarized (ie, number of patients, %) in each cohort. Patients who did not complete the DCR assessment at Week 12 (eg, due to drop out prior to the assessment) were considered as a treatment failure. The mean and median of the posterior distribution along with the standard deviation (StDev) and a 90% credible interval around the mean (based on the highest posterior density) was presented. An exact 90% confidence interval (CI) and 1-sided p-value was also presented.

For secondary efficacy endpoints, descriptive statistics were used for all variables, as appropriate, and were presented by cohort. Kaplan-Meier (KM) plots were presented for progression-free survival (PFS), overall survival (OS), time to study treatment discontinuation (TDT), and duration of response (DoR).

Continuous variables were summarized by the number of observations, mean, StDev, minimum, first quartile (Q1), median, third quartile (Q3), and maximum. For log transformed data it was more appropriate to present geometric mean, geometric StDev, coefficient of variation (CV), median, minimum, and maximum. Categorical variables were summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages were calculated out of the population total and for each cohort.

Baseline was the last assessment of the variable under consideration prior to or on the day of the intake of the first dose of olaparib.

Safety

All safety and tolerability data were presented for each cohort.

Summaries for safety data were provided for the entire study (not broken down by monotherapy treatment period and combination treatment period). Listings of adverse event (AE) data included indication of the study treatment period of onset (monotherapy, combination treatment, follow-up, or post follow-up [more than 90 days post last-dose of study treatment]).

All AEs, both in terms of current Medical Dictionary for Regulatory Activities (MedDRA) preferred term and Common Terminology Criteria for Adverse Events (CTCAE; version 4.03) grade, were summarized descriptively by count (n) and percentage (%). The current MedDRA (version 22.0) was used for coding.

Pharmacokinetic

All plasma olaparib concentration and serum MEDI4736 concentration data were presented in data listings, and summaries were presented for patients in the respective PK analysis set specific to each study drug.

Summaries of plasma concentration of olaparib and serum concentration of MEDI4736 were by study drug and by cohort.

A summary of immunogenicity results was provided showing the number and percentage of patients who developed detectable anti-drug antibodies (ADAs) to MEDI4736 based on the patients in the safety analysis set who had non-missing baseline ADA and at least 1 non-missing post-baseline ADA result.

Serum concentration of CCI [redacted] data were reported in data listings, and summaries for patients in the Safety analysis set who received at least 1 MEDI4736 dose and had non-missing baseline CCI [redacted] and at least 1 non-missing post-baseline CCI [redacted]. Serum concentration was summarized using descriptive statistics.

Subject population

The data cut-off for this report on the 4 Initial Stage Cohorts was 14 June 2019. Patient contact was allowed until shortly after to collect OS data, but all other data collected after 14 June 2019 are not included in the analyses presented in this CSR.

In the SCLC cohort 40 patients received olaparib treatment and were included in the safety analysis set, and 37 (92.5%) received MEDI4736 treatment. Thirty-eight patients from 18 study centers were included in the full analysis set. At the time of data cut-off, no patients were receiving either study treatment and no patients were still being followed in the study.

The most common reason for olaparib and MEDI4736 treatment discontinuation was objective disease progression (26 patients for both drugs, representing 68.4% of patients who received olaparib and 74.3% of patients who received MEDI4736). The most common reason for terminating the study was death (36 patients; 90.0%). The majority of patients in the full analysis set were White, male, and ≥ 50 to <65 years old. All patients in the full analysis set had received chemotherapy prior to study entry; 71.1% had received 1 prior line of chemotherapy, 28.9% had received 2 prior lines. The cohort population was representative of the overall target population of patients with platinum-sensitive relapsed SCLC.

In the *gBRCAm* breast cancer cohort, 34 patients received olaparib and MEDI4736 treatment and were included in the safety analysis set. Thirty patients from 12 study centers were included in the full analysis set. At the time of data cut-off, 3 patients (10.0%) were still receiving both olaparib and MEDI4736. Eight patients (23.5%) were still being followed in the study at the time of data cut-off. The most common reason for olaparib and MEDI4736 treatment discontinuation was objective disease progression (23 patients [76.7%] for olaparib; 21 patients [70.0%] for MEDI4736). The most common reason for terminating the study was death (24 patients; 70.6%). The majority of patients in the full analysis set were White, all but 1 were female, and the majority were < 50 years old. All patients in the full analysis set had received chemotherapy (including in the neoadjuvant/adjuvant setting) prior to study entry; 36.7% had received 1 prior line of chemotherapy in the metastatic setting and 33.3% had received 2 prior lines in the metastatic setting. The cohort population was representative of the overall target population of patients with *gBRCAm* human epidermal growth factor receptor 2-negative metastatic or locally advanced breast cancer

In the *gBRCAm* ovarian cancer cohort, 34 patients received olaparib treatment and were included in the safety analysis set, and 32 (94.1%) received MEDI4736 treatment. Thirty-two patients from 20 study centers were included in the full analysis set. At the time of data cut-off, 8 patients (25.0%) were still receiving olaparib and 7 (23.3%) were still receiving MEDI4736. Twenty-two patients (64.7%) were still being followed in the study at the time of data cut-off. The most common reason for olaparib and MEDI4736 treatment discontinuation was objective disease progression (17 patients [53.1%] for olaparib; 16 patients [53.3%] for MEDI4736). The most common reason for terminating the study was death (11 patients; 32.4%). All patients were female. The majority of patients in the full analysis set were White and ≥ 50 to < 65 years old. All patients in the full analysis set had received chemotherapy prior to study entry; 40.6% had received 1 prior line of chemotherapy: 28.1% had received 2 prior lines, 21.9% had received 3 prior lines, and 9.4% had received ≥ 4 prior lines. The cohort population was representative of the overall target population of patients with platinum-sensitive *gBRCAm* relapsed ovarian cancer.

In the gastric cancer cohort, 40 patients received olaparib treatment and were included in the safety analysis set, and 37 (92.5%) received MEDI4736 treatment. Thirty-nine patients from

16 study centers were included in the full analysis set. At the time of data cut-off, 1 patient (2.6%) was still receiving olaparib, and 1 (2.8%) was still receiving MEDI4736. Four patients (10.0%) were still being followed in the study at the time of data cut-off. The most common reason for olaparib and MEDI4736 treatment discontinuation was objective disease progression (29 patients [74.4%] for olaparib; 30 patients [83.3%] for MEDI4736). The most common reason for terminating the study was death (35 patients; 87.5%). The majority of patients in the full analysis set were White and male. No predefined age group represented a majority of patients; 46.2% of patients were ≥ 50 to < 65 years old. All patients in the full analysis set had received chemotherapy prior to study entry; all but 1 patient had received 1 prior line of chemotherapy, 1 patient (2.6%) had received 2 lines. The cohort population was representative of the overall target population of patients with platinum-sensitive metastatic or relapsed gastric cancer.

Summary of efficacy results

SCLC cohort

- The 12-week DCR as assessed by Investigators was 28.9%. The pre-specified target for 12-week DCR in the SCLC cohort was 60%.
- The median PFS as assessed by Investigators was 2.4 months (95% CI: 0.9, 3.0 months).
- The objective response rate (ORR) as assessed by Investigators was 10.5% (95% CI: 2.94%, 24.80%). One patient (2.6%) had a best objective response (BoR) of complete response (CR) and 3 patients (7.9%) had a BoR of partial response (PR).
- The median DoR as assessed by Investigators was 3.6 months for 4 patients with objective responses.
- The median TDT, calculated by KM technique, was 2.8 months (95% CI: 2.0, 3.8 months).
- The median OS in the SCLC cohort was 7.6 months (95% CI: 5.6, 8.8 months).
- The mean percentage change from Baseline in target tumor size at 12 weeks was 17.23% (StDev: 54.752%) and at 28 weeks was -2.05% (StDev: 15.671%) .
- The mean best percentage change from Baseline in target tumor size was 6.27% (StDev: 32.398%).

gBRCAm breast cancer cohort

- The 12-week DCR as assessed by Investigators was 80.0%. The pre-specified target for 12-week DCR in the *gBRCAm* breast cancer cohort was 75%.
- The median PFS as assessed by Investigators was 8.2 months (95% CI: 4.6, 11.8 months).
- The ORR for the *gBRCAm* breast cancer cohort as assessed by Investigators was 63.3% (95% CI: 43.86%, 80.07%). One patient (3.3%) had a BoR of CR and 18 patients (60.0%) had a BoR of PR.

- The median DoR in the *gBRCAm* breast cancer cohort as assessed by Investigators was 9.2 months for 19 patients with objective responses.
- The median TDT, calculated by KM technique, was 7.8 months (95% CI: 6.2, 12.1 months).
- The median OS in the *gBRCAm* breast cancer cohort was 20.5 months (95% CI: 16.2, 25.5 months).
- The mean percentage change from Baseline in target tumor size at 12 weeks was -26.13% (StDev: 43.033%) and at 28 weeks was -40.85% (StDev: 39.541%).
- The mean best percentage change from Baseline in target tumor size was -47.60% (StDev: 36.823%).

<u>*gBRCAm* ovarian cancer cohort</u>

- The 12-week DCR as assessed by Investigators was 81.3%. The pre-specified target for 12-week DCR in the *gBRCAm* ovarian cancer cohort was 90%.
- The median PFS as assessed by Investigators was 12.0 months (95% CI: 8.2, 15.9 months).
- The ORR for the *gBRCAm* ovarian cancer cohort as assessed by Investigators was 71.9% (95% CI: 53.25, 86.25%). Eight patients (25.0%) had a BoR of CR and 15 patients (46.9%) had a BoR of PR.
- The median DoR in the *gBRCAm* ovarian cancer cohort as assessed by Investigators was 10.2 months for 23 patients with objective responses.
- The median TDT, calculated by KM technique, was 13.1 months (95% CI: 8.2, 15.9 months).
- The median OS in the *gBRCAm* ovarian cancer cohort had not been reached at the data cut-off; the median follow-up at the point of data cut-off was 26.3 months.
- The mean percentage change from Baseline in target tumor size at 12 weeks was -35.86% (StDev: 29.791%) and at 28 weeks was -53.74% (StDev: 31.147%).
- The mean best percentage change from Baseline in target tumor size was -55.55% (StDev: 35.789%).

<u>Gastric cancer cohort</u>

- The 12-week DCR as assessed by Investigators was 25.6%. The pre-specified target for 12-week DCR in the gastric cancer cohort was 70%.
- The median PFS was 2.6 months (95% CI: 1.4, 2.8 months).
- The ORR for the gastric cancer cohort as assessed by Investigators was 10.3% (95% CI: 2.87%, 24.22%). Three patients (7.7%) had a BoR of CR and 1 patient (2.6%) had a BoR of PR.
- The median DoR in the gastric cancer cohort as assessed by Investigators was 14.8 months for 4 patients with objective responses.

- The median TDT, calculated by KM technique, was 2.8 months (95% CI: 2.1, 3.2 months).
- The median OS in the gastric cancer cohort was 6.4 months (95% CI: 4.3, 9.1 months).
- The mean percentage change from Baseline in target tumor size at 12 weeks was 20.81% (StDev: 75.944%) and at 28 weeks was -41.00% (StDev: 43.625%).
- The mean best percentage change from Baseline in target tumor size was 1.64% (StDev: 42.338%).

Summary of pharmacokinetic results

- Overall, the olaparib PK data were consistent across the Initial Stage Cohorts, in terms of overall trend and between-patient variability.
- Comparison of olaparib PK data between the monotherapy and the combined therapy periods suggested no apparent impact of MEDI4736 on olaparib exposure.
- MEDI4736 exposure was consistent across all 4 Initial Stage Cohorts and reached steady state at approximately Week 16.
- MEDI4736 exposure in patients from all 4 Initial Stage Cohorts in this study was within the exposure range observed in Study 1108, the MEDI4736 exposure in combination therapy with olaparib was consistent with that observed in MEDI4736 monotherapy.
- CCI [redacted]
- Only 1 patient (in the *gBRCAm* breast cancer cohort) was found to be positive for ADA on Cycle 1 Day 1 and this patient was not positive for ADA at any other point in the treatment period.

Summary of pharmacodynamic results

CCI [redacted]

CCI

Summary of pharmacogenetic results

- Breast cancer susceptibility gene (*BRCA*) mutation in tumor tissue status, positive homologous recombination deficiency status, and homologous recombination repair mutations were associated with improved clinical outcomes in a small population of patients in the gastric cancer cohort.
- Higher tumor mutational burden was associated with better clinical outcomes in all Initial Stage Cohorts with the exception of the gastric cancer cohort.

Summary of safety results

SCLC cohort

- No new safety findings were observed for olaparib in combination with MEDI4736 in patients with SCLC. Safety findings were consistent with the known profiles of olaparib and MEDI4736.
- All patients experienced at least 1 AE. The 3 most commonly reported AEs were anaemia (75.0% of patients), nausea (47.5% of patients), and fatigue (40.0% of patients).
- A total of 80.0% of patients had at least 1 CTCAE Grade ≥ 3 AE.

- A total of 80.0% of patients had AEs related to olaparib treatment. The most common CTCAE Grade ≥ 3 AE related to olaparib was anaemia (32.5% of patients); all other Grade ≥ 3 AEs related to olaparib occurred in 1 patient.
- A total of 27.5% of patients had AEs related to MEDI4736 treatment. The most common CTCAE Grade ≥ 3 AEs related to MEDI4736 was hepatocellular injury (5.0% of patients); all other Grade ≥ 3 AEs related to MEDI4736 occurred in 1 patient.
- A total of 89.5% of patients died; the majority of deaths (30 of 34) were related to the disease under investigation. Three patients died as a result of AEs (pancytopenia, gastric haemorrhage, and acute respiratory distress syndrome).
- A total of 57.5% of patients had 1 or more serious adverse events (SAEs) during the study. The only SAEs reported in more than 1 patient were chronic obstructive pulmonary disease (3 patients; 7.5%) and pneumonia and atrial fibrillation (each 2 patients; 5.0%). 10.0% of patients had an SAE related to olaparib and 7.5% had an SAE related to MEDI4736.
- The olaparib and MEDI4736 adverse event of special interest (AESI) of pneumonitis occurred in 1 patient. The most commonly reported MEDI4736 AESIs were diarrhoea (17.5% of patients), lipase increased (12.5% of patients), and blood creatinine increased and amylase increased (each 10.0% of patients).
- There were no clinically significant changes in vital signs in the SCLC cohort. There were no clinically significant trends observed in laboratory parameters during the study in the SCLC cohort with the exception of expected reductions in haemoglobin and increases in creatinine during treatment.

gBRCAm breast cancer cohort

- No new safety findings were observed for olaparib in combination with MEDI4736 in patients with breast cancer. Safety findings were consistent with the known profiles of olaparib and MEDI4736.
- All patients experienced at least 1 AE. The 3 most commonly reported AEs were fatigue (64.7% of patients), nausea (58.8% of patients), and anaemia (41.2% of patients).
- A total of 35.3% of patients had at least 1 CTCAE Grade ≥ 3 AE.
- A total of 91.2% of patients had AEs related to olaparib treatment. The most common CTCAE Grade ≥ 3 AEs related to olaparib were anaemia (8.8% of patients) and neutropenia (5.9% of patients).
- A total of 52.9% of patients had AEs related to MEDI4736 treatment. Other than pancreatitis (5.9% of patients), other Grade ≥ 3 AEs related to MEDI4736 occurred in 1 patient only.
- A total of 70.0% of patients died; the majority of deaths (20 of 21) were related to the disease under investigation.
- A total of 11.8% of patients had 1 or more SAEs during the study, no SAEs occurred in more than 1 patient. 2.9% of patients had an SAE related to olaparib and 2.9% had an SAE related to MEDI4736.

- No olaparib AESIs were reported. The most commonly reported MEDI4736 AESIs were diarrhoea (26.5% of patients) and hypothyroidism (14.7% of patients).
- There were no clinically significant changes in vital signs in the *gBRCAm* breast cancer cohort. There were no clinically significant trends observed in laboratory parameters during the study in the breast cancer cohort with the exception of expected increases in creatinine during treatment.

gBRCAm ovarian cancer cohort

- No new safety findings were observed for olaparib in combination with MEDI4736 in patients with *gBRCAm* ovarian cancer. Safety findings were consistent with the known profiles of olaparib and MEDI4736.
- A total of 97.1% of patients experienced at least 1 AE. The 3 most commonly reported AEs were nausea (76.5% of patients), fatigue (58.8% of patients), and anaemia (55.9% of patients).
- A total of 58.8% of patients had at least 1 CTCAE Grade ≥ 3 AE.
- A total of 88.2% of patients had AEs related to olaparib treatment. The most common CTCAE Grade ≥ 3 AEs related to olaparib were anaemia (17.6% of patients) and neutropenia, fatigue, and lymphocyte count decreased (all 5.9% of patients).
- A total of 58.8% of patients had AEs related to MEDI4736 treatment. The most common CTCAE Grade ≥ 3 AEs related to MEDI4736 were lipase increased (8.8% of patients) and amylase increased (5.9% of patients).
- A total of 31.3% of patients died; the majority of deaths (9 of 10) were related to the disease under investigation.
- A total of 29.4% of patients had 1 or more SAEs during the study. The only SAE reported in more than 1 patient was pneumonia (2 patients; 5.9%). All other SAEs occurred in 1 patient only. 2.9% of patients had an SAE related to olaparib and 8.8% had an SAE related to MEDI4736.
- The olaparib AESI of pneumonitis occurred in 1 patient. The most commonly reported MEDI4736 AESIs were diarrhoea (23.5% of patients), rash (20.6% of patients), and hypothyroidism (17.6% of patients).
- There were no clinically significant changes in vital signs in the *gBRCAm* ovarian cancer cohort. There were no clinically significant trends observed in laboratory parameters during the study in the *gBRCAm* ovarian cancer cohort with the exception of expected increases in creatinine during treatment.

Gastric cancer cohort

- No new safety findings were observed for olaparib in combination with MEDI4736 in patients with gastric cancer. Safety findings were consistent with the known profiles of olaparib and MEDI4736.
- All patients experienced at least 1 AE. The 3 most commonly reported AEs were nausea (50.0% of patients), vomiting (42.5% of patients), and constipation (40.0% of patients).

- A total of 57.5% of patients had at least 1 CTCAE Grade ≥ 3 AE.
- A total of 70.0% of patients had AEs related to olaparib treatment. The most common CTCAE Grade ≥ 3 AE related to olaparib was anaemia (7.5% of patients); all other Grade ≥ 3 AEs related to olaparib occurred in 1 patient.
- A total of 22.5% of patients had AEs related to MEDI4736 treatment. No events occurred in more than 1 patient.
- A total of 87.2% of patients died in the gastric cancer cohort, all deaths were related to the disease under investigation.
- A total of 25.0% of patients had 1 or more SAEs during the study. The only SAE that occurred in more than 1 patient was dysphagia (2 patients; 5.0%). All other SAEs occurred in 1 patient only. No patients had an SAE related to olaparib and 2.5% had an SAE related to MEDI4736.
- No olaparib AESIs were reported. The most commonly reported MEDI4736 AESIs were diarrhoea (17.5% of patients), rash (15.0% of patients), and lipase increased (7.5% of patients).
- There were no clinically significant changes in vital signs in the gastric cancer cohort. There were no clinically significant trends observed in laboratory parameters during the study in the gastric cancer cohort with the exception of expected increases in creatinine during treatment.

Conclusions

The combination of olaparib and MEDI4736 has been shown to be well-tolerated in 4 cohorts of patients with advanced solid tumors. The safety profile of the combination is consistent with the known safety profiles of olaparib and MEDI4736 as monotherapies, as well as the combination of the 2 drugs previously observed in the Phase I/II MEDI-O study. No new safety concerns have been identified. The efficacy data from the *gBRCAm* breast and *gBRCAm* ovarian cancer cohorts show an antitumor effect of the combination of olaparib and MEDI4736 and suggest that there may be a benefit to the treatment combination beyond that previously observed for olaparib monotherapy. Further investigation of the combination in breast and ovarian cancer patients is merited, particularly to identify patients who may gain the greatest benefit.