| Clinical Study Report | |
|---|---|
| Drug Substance | Durvalumab (MEDI4736), Olaparib |
| Study Code | D933IC00003 |
| Edition Number | 1.0 |
| Date | 20 April 2021 |
| EudraCT Number | 2017-004556-27 |
| NCT Number | NCT03459846 |

# A Phase II, Randomized, Multicenter, Double-Blind, Comparative Global Study to Determine the Efficacy and Safety of Durvalumab in Combination With Olaparib for First-Line Treatment in Platinum-Ineligible Patients With Unresectable Stage IV Urothelial Cancer

**Study dates:** First patient enrolled: 16 March 2018

The analyses presented in this report are based on a data cut-off date of 15 October 2020

**Phase of development:** Therapeutic exploratory (II)

**International Co-ordinating Investigator:**
PPD
PPD
PPD
New York, NY 10065 USA
PPD

**Sponsor's Responsible Medical Officer:**
PPD
PPD
PPD
AstraZeneca R&D Oncology
PPD
New York, NY 10016 USA
PPD

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

# 2. SYNOPSIS

## Study center(s)

This study was performed at 38 centers in 7 countries.

## Publications

None at the time of writing this report.

## Objectives and criteria for evaluation

**Table S1 Objectives and outcome variables**

| Objective | | | Outcome Variable |
|---|---|---|---|
| **Priority** | **Type** | **Description** | **Description** |
| Primary | Efficacy | To assess the efficacy of durvalumab + olaparib combination therapy compared with durvalumab + placebo in terms of PFS | PFS as determined by Investigator assessment according to RECIST 1.1 |
| Key Secondary | Efficacy | To assess the efficacy of durvalumab + olaparib combination therapy compared with durvalumab + placebo | OS |
| Secondary | Efficacy | To assess the efficacy of durvalumab + olaparib combination therapy compared with durvalumab + placebo | DoR, ORR, and PFS6 according to RECIST 1.1 using Investigator assessment<br>OS12, OS18 |
| Secondary | Efficacy | To assess the efficacy of durvalumab + olaparib combination therapy compared with durvalumab + placebo in the subset of patients with HRRm | PFS, DoR, ORR, and PFS6 according to RECIST 1.1 using Investigator assessment |
| Secondary | PK | To assess the PK of durvalumab and olaparib in both treatment arms | Concentration of durvalumab and olaparib |
| Secondary | Immunogenicity | To investigate the immunogenicity of durvalumab in both treatment arms | Presence of ADAs for durvalumab |
| Secondary | PRO | To assess disease-related symptoms and HRQoL in patients with UC treated with durvalumab + olaparib combination therapy compared with durvalumab + placebo | EORTC QLQ-C30: Global health status/QoL, functioning (physical), and multi-term symptoms (fatigue and pain) |

| Objective | | | Outcome Variable |
|---|---|---|---|
| **Priority** | **Type** | **Description** | **Description** |
| Safety | Safety | To assess the safety and tolerability profile of durvalumab + olaparib combination therapy compared with durvalumab + placebo | AEs/SAEs, physical examinations, laboratory findings (including clinical chemistry, hematology and urinalysis), WHO/ECOG performance status, and vital signs |
| Exploratory | PRO | To assess overall change in health status since the start of study treatment in UC patients treated with durvalumab + olaparib combination therapy compared with durvalumab + placebo | PGIC |
| Exploratory | PRO | To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L during assigned treatment | EQ-5D-5L index used to derive health state utility based on patient-reported data |
| Exploratory | Pharmacogenetic | To collect blood, urine, and tissue samples for defining biological responses to durvalumab + olaparib and for identifying candidate markers that may correlate with likelihood of clinical benefit [a] | Biomarkers (eg, DNA or ctDNA alterations, protein expression detected by IHC, change in ctDNA levels, and mRNA expression) correlating with clinical response |

[a] Will be reported separately from the CSR.

ADA Anti-drug antibody; AE Adverse event; CSR Clinical study report; ctDNA Circulating tumor deoxyribonucleic acid; DNA Deoxyribonucleic acid; DoR Duration of response; ECOG Eastern Cooperative Oncology Group; EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire; EQ-5D-5L EuroQoL 5 dimension, 5-level health state utility index; HRQoL Health-related quality of life; HRRm Homologous recombination repair mutated; IHC Immunohistochemistry; mRNA Messenger ribonucleic acid; ORR Objective response rate; OS Overall survival; OS18 Patients alive at 18 months; PD-L1 Programmed death ligand 1; PFS Progression-free survival; PFS6 Progression-free at 6 months; PGIC Patient Global Impression of Change; PK Pharmacokinetic(s); RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; SAE Serious adverse event; UC Urothelial cancer; WHO World Health Organization.

## Study design

This was a Phase II, randomized, double-blind, placebo-controlled, multicenter, comparative global study to determine the efficacy and safety of durvalumab + olaparib combination therapy versus durvalumab + placebo (durvalumab monotherapy) as first-line treatment in

patients ineligible for platinum-based therapy with unresectable Stage IV urothelial cancer (UC).

Patients were randomized in a 1:1 ratio to either durvalumab + olaparib or durvalumab + placebo, and stratified based on the patient's homologous recombination repair (HRR) status (mutant versus wild-type) and Bajorin risk index (a composite stratification for visceral metastases [lymph node only metastasis versus metastasis to any other organ system] and Eastern Cooperative Oncology Group [ECOG] performance status [0, 1, versus 2]).

A number of mechanistically relevant biomarkers were assessed within the study population. The first of these was presence of mutations in genes associated with homologous recombination repair, which has been previously associated with clinical benefit from olaparib in prostate and ovarian cancer. In this study, homologous recombination repair mutated (HRRm) status was determined prospectively using the validated FMI FoundationOne assay. Patients were considered HRRm positive if their tumors demonstrated presence of a qualifying deleterious, or suspected deleterious, alteration in at least 1 of the 15 prespecified genes selected for their direct or indirect role in homologous recombination repair: *BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D*, and *RAD54L*.

The second of these was PD-L1 expression, assessed by immunohistochemistry (IHC), which has been associated with clinical benefit following treatment with anti-PD-L1 agents in a number of settings, including bladder cancer.

Additional biomarkers assessed were genomic loss of heterozygosity (LOH), which has previously been associated with clinical benefit following treatment with PARP inhibitors, tumor mutational burden (TMB) and microsatellite instability (MSI), which have been associated with clinical benefit following treatment with anti-PD-L1/PD-1 antibodies. Details of baseline biomarker status are discussed in Section **Error! Reference source not found.**.

**Target patient population and sample size**

The study was sized to characterize the progression-free survival (PFS) benefit of durvalumab in combination with olaparib versus durvalumab monotherapy in first-line platinum-ineligible patients with unresectable Stage IV UC. Approximately 150 patients globally were planned to be randomized, and 154 patients were ultimately randomized and 152 patients received study treatment (76 patients in each group). The original study design (as found in Version 1 of the Clinical Study Protocol [CSP] in Appendix 16.1.1) featured an HRR-enrichment strategy that targeted randomization in a 1:1 balance of HRRm and HRR wild-type (HRRwt) patients into the study; due to the lower than anticipated prevalence of HRRm subjects, this HRR-enrichment strategy was removed in CSP Amendment 1 (see Section **Error! Reference source not found.** for details).

The PFS and OS analysis data cut-off date would occur when approximately 118 PFS events (79% maturity) and approximately 100 OS events had occurred across both treatment groups. If the true PFS hazard ratio (HR) was 0.55 (likely to correspond to an 82% prolongation of PFS), the study would provide at least 90% power to demonstrate a statistically significant difference for PFS (with a 2-sided significance level of 5%). The smallest treatment difference that could be statistically significant at the primary analysis of PFS was an HR of 0.69 (assuming a 2-sided p-value of 0.05).

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

Durvalumab (MEDI4736), manufactured by AstraZeneca, was provided at a concentration of 500 mg/vial for intravenous infusion after dilution to 50 mg/mL. Batch numbers used in this study are presented in Appendix 16.1.6.

Olaparib, manufactured by AstraZeneca, was available as a film-coated tablet containing 100 or 150 mg of olaparib. Placebo, manufactured by AstraZeneca, was provided as a matching tablet. Batch numbers used in this study are presented in Appendix 16.1.6.

**Duration of treatment**

Durvalumab and olaparib/placebo were administered beginning on Day 1 of the study until confirmed PD as per RECIST 1.1 as assessed by the Investigator unless there was unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

For all patients who were treated through progression, the Investigator was to ensure that patients did not have any significant, unacceptable, or irreversible toxicities which may indicate that continuing treatment would not further benefit the patient.

Patients who continued to receive benefit from their assigned treatment at the final data cut-off and database closure could continue to receive their assigned treatment for as long as they and their physician believed that they were gaining clinical benefit.

**Statistical methods**

This CSR provides data from the data cut-off of 15 October 2020. The PFS and OS analyses were conducted when 117 PFS events of the target 118 events and 98 OS events of the target 100 events were observed.

Statistical analyses were performed in accordance with the comprehensive Statistical Analysis Plan (SAP), which details all analyses to be performed and summaries to be produced, and the analysis sets upon which they were based.

Full analysis set

The statistical analysis of the efficacy of durvalumab + olaparib versus durvalumab + placebo included all randomized patients and compared the treatment groups on the basis of randomized treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study drug were included in the Full analysis set (FAS, also called Intent-to-treat) population.

Safety analysis set

The Safety analysis set consisted of all patients who received at least 1 dose of any study treatment. Patients were classified based on the treatment actually received, eg, patients randomized to durvalumab + placebo who receive 1 or more doses of olaparib in error, were to be reported in the durvalumab + olaparib group.

Pharmacokinetics analysis set

Two pharmacokinetics (PK) analysis sets were identified.

The olaparib PK analysis set included all patients who receive at least 1 dose of olaparib for whom an evaluable olaparib PK profile for at least 1 treatment period was available. The durvalumab PK analysis included all patients who received at least 1 dose of durvalumab for whom an evaluable durvalumab PK profile for at least 1 treatment period was available.

Any subject who violated or deviated from the protocol in ways that would significantly affect the PK analyses were excluded from the PK analysis sets.

Populations analyzed

Efficacy and PRO data were summarized and analyzed based on the FAS. Safety data were summarized and analyzed based on the Safety analysis set. PK data were summarized and analyzed based on the PK analysis set. Study population and demography summaries were summarized by FAS.

**Patient population**

- The demographics were representative of the intended patient population and were well balanced between randomized treatment groups.
- The disease characteristics were also representative of the intended patient population and were generally well balanced between the treatment groups.
- Among patients with a PD-L1 high result recorded at baseline, the overall prevalence of PD-L1 high expression was evenly balanced between treatment groups (durvalumab + olaparib: 56%; durvalumab + placebo: 59%), despite the marker being tested retrospectively and not used for stratification, which was consistent with other first-line urothelial carcinoma studies.

- Similar numbers of patients in each group were assessed as having HRRm (durvalumab + olaparib: 21.8%; durvalumab + placebo: 18.4%) and HRRwt (durvalumab + olaparib: 78.2%; durvalumab + placebo: 81.6%) status at baseline.
- Among patients with a LOH result recorded at baseline, 13% of patients in the durvalumab + olaparib group and 32% of patients in the durvalumab + placebo group were LOH high (LOH ≥16), and 87% in the durvalumab + olaparib group and 68% in the durvalumab + placebo group were LOH low (LOH <16).
- However some imbalance was noted in other baseline characteristics: more patients in the durvalumab + olaparib group (43.6% versus 36.8% in the durvalumab + placebo group) had an ECOG performance score of 2 at baseline (indicating "in bed ≤50% of the time"); no patients had ECOG of ≥3 at baseline.
- More patients in the durvalumab + olaparib group (53.8% versus 40.8%) had a VES-13 score of ≥3 (where higher scores indicate worse prognoses), suggesting a frailer patient population in that group at baseline.
- The medical and surgical history as well as the types of concomitant medication used is typical for this population.
- The incidence of important protocol deviations was low (durvalumab + olaparib: 5 patients; durvalumab + placebo: 1 patient) and those observed do not raise major concerns regarding the overall conduct or quality of the study.
- There were no important protocol deviations that were attributed to changes in study conduct arising from the COVID-19 pandemic and no COVID-19 related issues thought to impact efficacy and safety endpoints. One AE was reported due to COVID-19 and there were no deaths reported due to COVID-19.

**Summary of efficacy results**

- Median PFS (95% confidence interval [CI]) was 4.2 months (3.6, 5.6) in the durvalumab + olaparib group and 3.5 months (1.9, 5.1) in the durvalumab + placebo group. Overall, durvalumab + olaparib did not demonstrate a statistically significant benefit in PFS over durvalumab + placebo treatment in platinum-ineligible patients with unresectable Stage IV UC (HR: 0.94; 95% confidence interval [CI]: 0.641, 1.387; p=0.789).
  - A PFS benefit was observed for the durvalumab + olaparib group in the HRRm subgroup (durvalumab + olaparib: 5.6 months; durvalumab + placebo: 1.8 months; HR=0.18; 95% CI [0.064, 0.474]; p<0.001), however the number of patients in this subgroup was small (n=31) and this was not an alpha-controlled endpoint.
  - A PFS benefit was also observed in the subgroup of patients with a baseline Bajorin Risk Index=0: (durvalumab + olaparib: 10.1 months; durvalumab + placebo: 3.8 months; HR=0.42; 95% CI [0.181, 0.915]), however the number of patients in this subgroup was small (n=34) and this was not an alpha-controlled endpoint.
  - An ad hoc analysis was performed in order to include the 13 patients (durvalumab + olaparib: 1 patient; durvalumab + placebo: 12 patients) with clinical progression that were not confirmed by RECIST and were thus not defined as having a PD event in the primary PFS analysis. The inclusion of these events did not change the inability to demonstrate a statistical significant benefit of durvalumab and olaparib on PFS, however, the median PFS for durvalumab + placebo in the FAS group decreased

from 3.5 months to 2.0 months which is more closely aligned to the median PFS for durvalumab + placebo in the HRRm subgroup; the significance of durvalumab + olaparib in the HRRm subgroup remains unchanged ($p<0.001$).

- Overall, durvalumab + olaparib did not demonstrate a statistically significant benefit in OS over durvalumab + placebo treatment in platinum-ineligible patients; median OS was 10.2 months in the durvalumab + olaparib group (95% CI: 7.0, 13.9), compared to 10.7 months (95% CI: 7.2, 17.3) in the durvalumab + placebo group; the difference in median OS was not statistically significant between groups ($p=0.728$).
  - Within the HRRm subgroup, observed OS was numerically longer in the durvalumab + olaparib group (8.6 months) than in the durvalumab + placebo group (5.8 months) (HR=0.56; 95% CI: 0.252, 1.226); the overall number was low (31 patients), and the 95% CIs of the HR contain 1.
- A total of 22 patients (28.2%) in the durvalumab + olaparib group and 14 patients (18.4%) in the durvalumab + placebo group experienced response (unconfirmed CR or PR) during the study (odds ratio of 1.76; 95% CI: 0.821, 3.778; $p=0.142$).
  - Of the patients with response in the durvalumab + olaparib group, 3 patients (3.8%) had CR and 19 patients (24.4%) had PR; in the durvalumab + placebo group, 4 patients (5.3%) had CR and 10 patients (13.2%) had PR.
  - Within the HRRm subgroup, a total of 6 patients (35.3%) in the durvalumab + olaparib group showed response while in the study, all of which were PR; no patients in the durvalumab + placebo group showed response.
- The median duration of response was shorter in the durvalumab + olaparib group (8.9 months) than in the durvalumab + placebo group (14.8 months), notwithstanding the higher response rate in the durvalumab + olaparib group.
- No meaningful differences were noted between treatment arms across PRO scales analyzed (MMRM analyses), indicating that the combination of olaparib with durvalumab did not contribute to additional symptom burden or QoL deterioration
- Olaparib pre-dose geometric mean concentration on Cycle 4 were lower than that on Cycle 2 but both were within the range observed in olaparib monotherapy studies (further information regarding the pharmacological properties can be found in the Olaparib Investigator's Brochure 2021).
- There were 67 ADA-evaluable patients (88.2%) in each treatment group in the Safety analysis set. The ADA prevalence of the durvalumab + olaparib group and the durvalumab + placebo group were 1 patient (1.5%) and 8 patients (11.9%), respectively. Of the 9 ADA positive patients, 3 patients (4.5%) in the durvalumab + placebo group and no patients in the durvalumab + olaparib group were persistently positive for the presence of ADA.

**Summary of safety results**

- The number of patients exposed and the total exposure and follow up in the study were adequate to characterize the safety profile of durvalumab + olaparib versus durvalumab monotherapy (durvalumab + placebo).
- Overall, durvalumab + olaparib was well-tolerated and had a manageable safety profile relative to durvalumab monotherapy (durvalumab + placebo) for the population under

study. Generally, the type, incidence, and severity of AEs were comparable between the treatment groups. Where not comparable, the type, incidence, and severity of events were consistent with the established durvalumab and olaparib safety profiles to date.

- There was a higher incidence of AEs possibly related to olaparib/placebo in the durvalumab + olaparib group, which was driven by the known hematological toxicities associated with olaparib administration.
- The most common AEs included anemia (durvalumab + olaparib: 48.7%; durvalumab + placebo: 28.9%), fatigue (durvalumab + olaparib: 31.6%; durvalumab + placebo: 18.4%), decreased appetite (25.0% and 13.2%), nausea (durvalumab + olaparib: 26.3%; durvalumab + placebo: 7.9%), and urinary tract infection (durvalumab + olaparib: 18.4%; durvalumab + placebo: 11.8%).
- There was a higher incidence of CTCAE Grade 3 or 4 AEs in the durvalumab + olaparib group (durvalumab + olaparib: 43.4%, durvalumab + placebo: 31.6%), which was primarily driven by anemia (durvalumab + olaparib: 15.8%; durvalumab + placebo: 2.6%); an expected AE with olaparib.
- A similar number of patients in each group had an AE with the outcome of death (durvalumab + olaparib: 6 patients, 7.9%; durvalumab + placebo: 5 patients, 6.6%); there was 1 AE with the outcome of death that was considered to be possibly related to study treatment (anemia, possibly related to both study treatments in the durvalumab + placebo group).
- SAEs were reported in 48.7% and 34.2% of patients receiving durvalumab + olaparib and durvalumab + placebo, respectively. The difference was primarily due to the higher incidence of anemia (durvalumab + olaparib: 6.6%; durvalumab + placebo: 1.3%) and renal failure (durvalumab + olaparib: 5.3%; durvalumab + placebo: 0%); baseline renal impairment was expected to be high for the target patient population, and a slight imbalance in baseline disease characteristics may have driven the imbalance in renal failure cases.
- There was a higher incidence of AEs leading to discontinuation of both study treatments (durvalumab + olaparib: 6.6%, durvalumab + placebo: 10.5%), discontinuation of durvalumab (durvalumab + olaparib: 7.9%, durvalumab + placebo: 10.5%), and discontinuation of olaparib/placebo (durvalumab + olaparib: 11.8%, durvalumab + placebo: 15.8%), in the durvalumab + placebo group, although the actual numbers of patients discontinued for a given AE was low in both groups.
- The AESIs/imAEs for durvalumab and AESIs for olaparib were as expected based on the known safety profile of these treatments, and were generally manageable and/or reversible with appropriate medical management, which included the use of steroids or endocrine therapy, withholding durvalumab until the event resolved, or permanent discontinuation of durvalumab. No patient had an AESI with an outcome of death across treatment groups; 1 patient had a serious olaparib AESI for durvalumab + olaparib and 5 patients had serious durvalumab AESIs for durvalumab + placebo; 1 patient on durvalumab + placebo had a durvalumab AESI leading to discontinuation of treatment of durvalumab and 2 patients on durvalumab + olaparib had an AESI leading to discontinuation of both durvalumab and placebo. Three patients (3.9%) in the durvalumab + olaparib group experienced olaparib AESIs: 1 patient had a new primary

malignancy (basal cell carcinoma) and 2 patients had pneumonitis AEs (immune-mediated pneumonitis; pulmonary toxicity).

- The incidence of imAEs was as expected and consistent with the immune-mediated mechanism of action for the study treatments.
- No clinically important changes from baseline or trends in hematology or clinical chemistry values over time were observed in either treatment group.
- One patient in the durvalumab + olaparib group met the biochemical criteria for a potential Hy's Law case (non-serious AE).
- No notable changes from baseline in vital signs were observed in either treatment group.
- Overall, the safety findings were in line with the known safety profile of the individual investigational products (IPs).

**Conclusion(s)**

- The coadministration of durvalumab and olaparib did not demonstrate a significant therapeutic advantage over durvalumab alone in platinum-ineligible patients with unresectable Stage IV urothelial cancer.
  - There was, however, a notable treatment effect favoring durvalumab + olaparib in PFS in the HRRm subgroup, suggesting that there may be a potential role for PARP inhibitors in the treatment of bladder cancer.
- There was no notable difference between durvalumab + olaparib and durvalumab + placebo in patient-reported quality of life.
- No new safety signals were detected that could be associated with the combination treatment of durvalumab and olaparib versus durvalumab alone.