Clinical Study Report Synopsis

Drug Substance	Tremelimumab and MEDI4736 (Durvalumab)
Study Code	D4884C00001
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A Phase II, Multi-Center, Open-Label Study of Tremelimumab Monotherapy in Patients with Advanced Solid Tumors

Study dates: First subject enrolled: 02 November 2015
Data Cut-off: 17 February 2018

Phase of development: Therapeutic exploratory (II)

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

Study centre(s)

The study was performed at 14 sites in 5 countries.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	*Efficacy*	*To assess the efficacy of tremelimumab monotherapy in terms of ORR (according to RECIST 1.1 criteria).*	*ORR=Number (%) of patients with a confirmed overall response of CR or PR with measurable disease at baseline per the site Investigator. Assessed on the FAS.*
Secondary	*Efficacy*	*To further assess the efficacy of tremelimumab monotherapy in terms of DoR, DCR, PFS, BoR, and OS.*	*DoR=the number of days from the date of first documented response until the first date of documented progression or death in the absence of disease progression; DCR=the percentage of patients who had BoR of CR or PR in the first 3 (PDAC patients) or 4 months (UBC/TNBC patients) and 12 months (all patients), respectively, or who had demonstrated SD for a minimum interval of 3 months or 4 months and 12 months, following the start of study treatment; PFS=the number of days from the date of enrollment until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdrew from therapy or received another anticancer therapy prior to progression; BoR=best objective response (from CR, PR, SD, PD, NE) obtained among all tumor assessment visits from baseline until end of treatment or determination of PD; OS=the number of days from the date of first dose of study treatment until death due to any cause. Assessed on the FAS.*
Secondary	*Efficacy*	*To assess the efficacy of durvalumab monotherapy and durvalumab + tremelimumab combination therapy after confirmed PD on tremelimumab monotherapy or during follow-up in terms of ORR, DoR, DCR, PFS, BoR, and OS.*	*Description of variables (ORR, DoR, DCR, PFS, BoR and OS) as above for primary and secondary endpoints. Assessed on the MEDI and COMBO analysis populations.*

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Safety	*Safety*	*To assess the safety and tolerability profile of tremelimumab monotherapy.*	*Adverse events, laboratory assessments, ECG, physical examination and vital signs. Assessed on the Safety analysis population.*
Safety	*Safety*	*To assess the safety and tolerability profile of durvalumab monotherapy and of durvalumab + tremelimumab combination therapy after confirmed PD on tremelimumab monotherapy or during follow-up.*	*Adverse events and laboratory assessments. Assessed on the Safety analysis population.*
Exploratory	CCI	*To assess the* CCI *of tremelimumab monotherapy, durvalumab monotherapy, and durvalumab + tremelimumab combination therapy.*	*Measurement of tremelimumab and durvalumab* CCI *; as data allow, sparse sampling). Assessed on the* CCI *analysis population.*
Exploratory	*Immunogenicity*	*To investigate the immunogenicity of tremelimumab and durvalumab.*	*Number and percentage patients who develop detectable ADAs (positive/negative) for tremelimumab and durvalumab. Assessed on the ADA-evaluable analysis population.*
Exploratory	CCI	*To collect* CCI *to tremelimumab monotherapy, durvalumab monotherapy, and durvalumab + tremelimumab combination therapy and for identifying* CCI *that may correlate with* CCI .	*Measurement of* CCI . *Assessed on the* CCI *population.*

Abbr: ADA Anti-drug antibody; BoR Best objective response; COMBO Durvalumab + tremelimumab combination therapy; CR Complete response; DCR Disease control rate; DoR Duration of response; ECG electrocardiogram; FAS Full analysis set; CCI ; CCI ; MEDI Durvalumab monotherapy; CCI ; CCI ; NE Not evaluable; ORR Objective response rate; OS Overall survival; PD Progressive disease; PDAC Pancreatic ductal adenocarcinoma; CCI ; PFS Progression-free survival; CCI ; PR Partial response; RECIST Response Evaluation Criteria in Solid Tumors; SD Stable disease; TNBC Triple-negative breast cancer; UBC Urothelial bladder cancer.

Study design

This was an open-label, multi-center study to determine the efficacy and safety of tremelimumab monotherapy, with subsequent treatment (if eligible and at the discretion of the treating Investigator) with either durvalumab monotherapy or durvalumab + tremelimumab combination therapy in different patient cohorts with specified advanced solid tumors.

Approximately 38 patients with each selected advanced solid tumor type were to be screened. For each tumor cohort, a minimax Simon 2-Stage design was to be used to stop recruitment early if no response was observed, thus reducing patient exposure to non-active treatment. If 1 or more responses were observed out of the first 20 treated patients with the selected tumor

type, an additional 12 patients were to be enrolled, for a total of 32 evaluable patients. If no responses were observed, the disease control rate (DCR) data were also to be evaluated to make a final decision before discontinuing the tumor cohort. If at least 10 out of the first 20 patients achieved DCR (≥50% DCR) after 2 tumor assessments, then an additional 12 patients were allowed to be enrolled, for a total of 32 evaluable patients. The final decision to continue to enrollment was to be made by the Sponsor after evaluating all of the available clinical data at that time. Patients' tumor response and DCR were to be monitored on an ongoing basis to minimize the time between Stages 1 and 2. CCI [redacted] expression was to be monitored throughout the study so as to plan for further enrollment, and if necessary, a decision to enroll was allowed based on expression status.

Target subject population and sample size

The study enrolled adult patients (age ≥18 years) with advanced and metastatic solid tumors including, but not limited to, histologically or cytologically documented urothelial bladder cancer (UBC), pancreatic ductal adenocarcinoma (PDAC), or triple-negative breast cancer (TNBC) (additional tumor types may be added at the discretion of the Sponsor). Patients were to have had no prior exposure to immune-mediated therapy, including but not limited to, other anti-cytotoxic T lymphocyte-associated antigen 4 (anti-CTLA-4), PD-1, anti-programmed cell death ligand 1 (anti-PD-L1), or anti-programmed cell death ligand 2 (anti-PD-L2) antibodies, including therapeutic anticancer vaccines.

Approximately 38 patients with each selected advanced solid tumor type were to be screened, to ensure that approximately 32 evaluable patients with each tumor type were enrolled into the study. An assessment of response after the first 20 evaluable patients in the tumor types was to be performed based on Investigator/site tumor data Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 assessment. This was to ensure a type I error of no more than 5% (1-sided) and an 83% power for each of the tumor types.

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

The following investigational products were evaluated in the study:

- Tremelimumab monotherapy:
  - Tremelimumab 750 mg was administered via intravenous (IV) infusion every 4 weeks (q4w) for 7 doses (cycles), then every 12 weeks (q12w) for 2 additional doses (cycles), for up to a total of 12 months (9 doses [cycles] total).
- Durvalumab monotherapy:
  - Durvalumab 1.5 g was administered via IV infusion q4w for up to a total of 12 months (13 doses [cycles]).

- Durvalumab + tremelimumab combination therapy:
  - Durvalumab 1.5 g via IV infusion q4w in combination with tremelimumab 75 mg via IV infusion q4w starting on Week 0 for up to 4 cycles each, followed by durvalumab 1.5 g via IV infusion q4w starting on Week 16 for up to a total of 8 months (9 additional cycles).

All investigational products were manufactured and supplied by AstraZeneca.

Investigational product	Batch number
Tremelimumab	CCI [redacted]
Durvalumab	CCI [redacted]

Duration of treatment

Treatment with tremelimumab monotherapy was to continue for a 12-month period until confirmed progressive disease (PD), unacceptable toxicity, withdrawal of consent, initiation of alternative anticancer therapy, or other reasons for discontinuation. After confirmed disease progression during treatment with tremelimumab monotherapy or during follow-up, patients who met the eligibility criteria for sequencing, at the discretion of the Investigator, could be sequenced to durvalumab monotherapy or durvalumab + tremelimumab combination therapy or could be retreated with tremelimumab monotherapy for up to 12 months or until disease progression, whichever came sooner.

Patients who developed PD during the follow-up period could restart their treatment for another 12 months with the same treatment guidelines followed previously.

Statistical methods

The data cut-off for the primary analysis of all study endpoints (including overall survival [OS]) was to take place following database lock after the last evaluable patient had completed approximately 12 months of initial tremelimumab monotherapy, or the last patient has withdrawn from the study, or the study is discontinued by the Sponsor.

The primary objective of this study was to assess the efficacy of tremelimumab monotherapy in terms of objective response rate (ORR). Objective response rate (per RECIST 1.1 as assessed by site Investigator) was defined as the number and percentage of patients with a confirmed overall response of complete response or partial response and was to be based on all treated patients with measurable disease at baseline. The ORR was to be estimated with 2-sided 95% exact confidence intervals. The ORR was calculated based on the Full analysis set (FAS), durvalumab + tremelimumab combination therapy (COMBO) and durvalumab monotherapy (MEDI) analysis sets.

Secondary efficacy variables, including duration of response (DoR), DCR, progression-free survival (PFS), best objective response (BoR), and OS, were to be summarized and analyzed based on the FAS, MEDI analysis set, and COMBO analysis set. CCI data were analyzed using the CCI. Immunogenicity data were analyzed using the ADA-evaluable analysis set. Safety data including exposure data, adverse events (AEs), laboratory measurements, vital signs, electrocardiogram (ECGs), and physical examination were analyzed using the Safety Analysis Set.

Subject population

Overall, 89 patients were enrolled in the study (informed consent obtained). A total of 64 patients were assigned to treatment: 32 patients in the UBC cohort, 12 patients in the TNBC cohort, and 20 patients in the PDAC cohort.

At primary data cut-off (17 February 2018), all patients had discontinued initial tremelimumab monotherapy treatment. The most common reason for initial treatment discontinuation was condition under investigation worsened (70.3%), followed by AEs (15.6%).

A total of 16 patients sequenced to durvalumab + tremelimumab combination therapy phase (7 patients in the UBC cohort, 5 patients in the TNBC cohort, and 4 patients in the PDAC cohort). A total of 5 patients sequenced to durvalumab monotherapy (4 patients in the UBC cohort, 1 patient in the PDAC cohort, and 0 patients in the TNBC cohort). The most common reason for discontinuation from both treatment phases was condition under investigation worsened (75.0% and 80.0% of patients, respectively).

Twelve patients were ongoing in the study at the primary data cut-off: 9 patients in the UBC cohort and 3 patients in the TNBC cohort. Of these, 2 patients with UBC who completed 12 months of tremelimumab monotherapy may be eligible for retreatment (at Investigator and patient's discretion) with tremelimumab or sequencing to the MEDI or COMBO treatment phase if they progress during the follow-up period (PPD). The remaining 52 patients terminated the study and the most common reason for termination was death.

The demographic and baseline disease characteristics were representative of the intended patient population for this study. In the UBC cohort, the majority of patients were white (65.6%) and male (81.3%) with a mean age of 64.8 years. In the TNBC cohort, all patients were female with a mean age of 58.2 years and the majority of patients were Asian (91.7%). In the PDAC cohort, 55.0% of patients were male and the majority of patients were white (40.0%) or Asian (55.0%). The mean age of patients in the PDAC cohort was 59.4 years.

Summary of efficacy results

Primary objective

The primary objective of the study was to assess the efficacy of tremelimumab monotherapy in terms of ORR. In the UBC cohort, the ORR was 18.8% with 6 patients having a confirmed response (2 complete responses [CR] and 4 partial responses [PR]). In the TNBC cohort, the ORR was 8.3% with 1 patient having a confirmed response (of PR). There were no patients with a response in the PDAC cohort.

Secondary objectives

The efficacy of durvalumab + tremelimumab combination therapy and durvalumab monotherapy after confirmed PD on tremelimumab monotherapy or during follow-up were also evaluated in terms of ORR. There were no confirmed responses in the COMBO analysis set. In the MEDI analysis set, 1 patient (25.0%) in the UBC cohort had a confirmed response (of PR). This patient did not respond during tremelimumab monotherapy but responded after resequencing to durvalumab monotherapy.

The DoR from onset of the response for tremelimumab monotherapy patients was not estimable in all cohorts. In the UBC cohort, all responders remained in response at 4 months and 83.3% at 12 months. In the TNBC cohort, 1 responder remained in response at 4 months. No DoR data were available for the COMBO analysis set. In the MEDI analysis set, the DoR for the 1 responder in the UBC cohort was 7.3 months.

For tremelimumab monotherapy patients, the DCR at 4 months was 25.0% (8 patients) in the UBC cohort and 8.3% (1 patient) in the TNBC cohort. The DCR at 12 months was 21.9% (7 patients) in the UBC cohort and 8.3% (1 patient) in the TNBC cohort. In the COMBO analysis set, the DCR at 3 or 4 months was 28.6% (2 patients), 20.0% (1 patient), and 25.0% (1 patient) in the UBC, TNBC, and PDAC cohorts, respectively. In the MEDI analysis set, the DCR at 4 months was 25.0% (1 patient) in the UBC cohort.

For tremelimumab monotherapy patients, the median PFS was 2.63 months, 3.58 months, and 1.77 months in the UBC, TNBC, and PDAC cohorts, respectively.

For tremelimumab monotherapy patients, the median OS was 10.32 months with 19 deaths in the UBC cohort. In the TNBC cohort, the median OS was 12.88 months with 5 deaths. In the PDAC cohort, the median OS was 3.98 months with 17 deaths. The estimated survival rate at 12 months was 36.0% in the UBC cohort, 59.0% in the TNBC cohort, and 6.0% in the PDAC cohort. In the COMBO analysis set, the median OS was 11.86 months (4 deaths) in the UBC cohort and 7.18 months (4 deaths) in the PDAC cohort. The median OS was not estimable in the TNBC cohort. The estimated survival rate at 12 months was 34.0% in the UBC cohort, 67.0% in the TNBC cohort, and 25.0% in the PDAC cohort. In the MEDI analysis set, the

median OS was 4.14 months (1 death) in the PDAC cohort and not estimable in the UBC and TNBC cohorts. The estimated survival rate at 12 months was 50.0% (n=4) in the UBC cohort and 0% in the PDAC cohort (n=1).

Summary of CCI [redacted]

Overall, the CCI [redacted] of tremelimumab and durvalumab across the 3 cohorts were within the expected ranges based on prior knowledge with similar CCI [redacted] achieved across the 3 tumor types evaluated. Moreover, there was no indication of CCI [redacted].

Summary of immunogenicity results

Immunogenicity data were available for 52 patients in the tremelimumab arm and 15 patients in the combination arm who had valid baseline and at least 1 valid post-baseline anti-drug antibody (ADA) result (ADA-evaluable patients). Anti-drug antibody incidence of tremelimumab, (ie, the proportion of evaluable population which was either treatment-induced [post-baseline ADA-positive only] or treatment-boosted ADA-positive) of tremelimumab were 1.9% (1 of 52 ADA-evaluable patients) and 6.7% (1 of 15 ADA-evaluable patients), respectively.

Immunogenicity data were available for 4 ADA-evaluable patients in the durvalumab arm and 10 ADA-evaluable patients in the combination arm. No patients had positive ADA results at any time point. Thus, both ADA prevalence and ADA incidence of durvalumab in both treatment arms were 0%.

Summary of safety results

During tremelimumab monotherapy, the majority of patients across the 3 cohorts had an AE (93.8%, 91.7%, and 100.0% of patients in the UBC, TNBC, and PDAC cohorts, respectively). Grade ≥3 AEs were reported for approximately half of patients in each cohort with a small proportion of those considered possibly related to treatment by the Investigator (9 patients [28.1%] and 6 patients [30.0%] in the UBC and PDAC cohorts, respectively and 0 patients in the TNBC cohort). A small proportion of patients had an AE leading to discontinuation of tremelimumab treatment (10 patients [31.3%], 2 patients [16.7%], and 2 patients [10.0%], in the UBC, TNBC, and PDAC cohorts, respectively). No patients had an AE leading to discontinuation from the study. The most commonly reported preferred term (PTs) across all cohorts were fatigue, pruritus, constipation, diarrhea, and abdominal pain. There were no notable trends in the frequency of individual AEs reported across the 3 cohorts.

During durvalumab + tremelimumab combination therapy, all patients had an AE, with a small proportion of those considered possibly related to tremelimumab or durvalumab by the Investigator (2 patients in the UBC and TNBC cohorts and 1 patient in the PDAC cohort). One patient in the PDAC cohort had a Grade ≥3 AE considered possibly related to treatment

by the Investigator; no patients in the UBC and TNBC cohorts had a Grade ≥3 AE. One patient each in the TNBC and PDAC cohort had a serious adverse event (SAE) considered possibly related to treatment by the Investigator. There were no AEs leading to death. The safety data should be interpreted with caution for this analysis set due to the small number of patients receiving combination therapy.

During durvalumab monotherapy, all patients in the UBC and PDAC cohorts had an AE. One patient in the UBC cohort had an AE considered possibly related to durvalumab by the Investigator. One patient in the UBC cohort had an SAE. The safety data should be interpreted with caution for this analysis set due to the small number of patients receiving durvalumab monotherapy.

Adverse events of special interest which may have required close monitoring included events with potential inflammatory or immune-mediated mechanism and those requiring interventions such as steroids, immunosuppressants or hormone replacement therapy. A high proportion of patients reported an adverse event of special interest (AESI) during tremelimumab monotherapy (19 patients [59.4%], 8 patients [66.7%], and 15 patients [75.0%] in the UBC, TNBC, and PDAC cohorts, respectively). During durvalumab + tremelimumab combination therapy, AESIs were reported for 3 patients (42.9%) in the UBC cohort, 4 patients (80.0%) in the TNBC cohort, and 2 patients (50.0%) in the PDAC cohort. During durvalumab monotherapy, 1 patient in the UBC cohort had a Grade 1 renal event of blood creatinine increased classed as an AESI.

In total, 11 patients (34.4%) in the UBC cohort and 5 patients (25.0%) in the PDAC cohort had an immune-mediated AE (imAE) during tremelimumab monotherapy. No patients in the TNBC cohort had any imAE. A low proportion of patients had Grade 3 or 4 imAEs (5 patients [15.6%] in the UBC cohort and 3 patients [15.0%] in the PDAC cohort) or SAEs (6 patients [18.8%] in the UBC cohort and 4 patients [20.0%] in the PDAC cohort). Five patients (15.6%) and 2 patients (10.0%) in the UBC and PDAC cohorts, respectively, had an imAE leading to treatment discontinuation. There were no imAEs with an outcome death. During durvalumab + tremelimumab combination therapy, 1 patient (14.3%) and 2 patients (50.0%) in the UBC and PDAC cohorts, respectively, had any imAEs. There were no imAEs in the TNBC cohort. The PT reported in the UBC cohort was rash. The imAEs reported in the PDAC cohort were pneumonitis, diarrhea, and hypothyroidism. No imAEs were reported during durvalumab monotherapy.

A total of 13 patients (40.6%) in the UBC cohort, 4 patients (33.3%) in the TNBC cohort, and 12 patients (60.0%) in the PDAC cohort died. The most common reason for death during the study was death related to disease under study. During tremelimumab therapy, 1 patient in the TNBC cohort had an AE (respiratory failure) with an outcome of death which was not considered by the Investigator to be related to tremelimumab. One patient died as a result of

the disease under investigation and also an AE of euthanasia. During durvalumab + tremelimumab combination therapy, 1 patient in the UBC cohort died as a result of the disease under investigation and also an unrelated AE of malignant neoplasm of bladder leading to death. In total, 4 patients died within the first 28 days of study treatment. Of these, disease progression was reported as the primary reason for death for 3 patients. One patient died of respiratory failure 25 days after first dose as described above. In the durvalumab monotherapy phase, 2 patients (50.0%) and 1 patient (100.0%) in the UBC and PDAC cohorts died due to disease under investigation.

During tremelimumab monotherapy, 18 patients (56.3%), 4 patients (33.3%), and 11 patients (55.0%) in the UBC, TNBC, and PDAC cohorts, respectively, had an SAE. The majority of SAEs reported during the study, were reported for a single patient in each cohort, with the exception of hyponatremia, autoimmune colitis, colitis, diarrhea, and acute kidney injury. A small proportion of SAEs were considered by the Investigator to be possibly related to study treatment (9 patients [28.1%] in the UBC cohort, 1 patient [8.3%] in the TNBC cohort, and 5 patients [25.0%] in the PDAC cohort). The majority of SAEs considered possibly related to treatment by the Investigator were reported in a single incidence with the exception of autoimmune colitis, colitis, and diarrhea. During durvalumab + tremelimumab combination therapy, 50.0% of patients had an SAE: 3 patients in the UBC cohort, 2 patients in the TNBC cohort, and 3 patients in the PDAC cohort. All SAEs were reported for a single patient in any cohort. One patient each in the TNBC and PDAC cohorts had an SAE considered possibly related to treatment by the Investigator; the events reported were diarrhea and diarrhea hemorrhagic. During durvalumab monotherapy treatment, 1 patient (25.0%; PPD) in the UBC cohort had an SAE of anemia, which was not considered to be related to study treatment by the Investigator.

No new safety signals were observed with regards to laboratory values, vital signs, or ECG assessments.

Conclusion(s)

- Overall, tremelimumab monotherapy showed antitumor activity in the treatment of patients in the UBC cohort. Due to the small numbers of patients receiving combination therapy, no conclusions regarding efficacy can be drawn.
- Overall, the CCI of durvalumab and tremelimumab across the 3 cohorts were within the expected ranges and there was CCI of CCI between these 2 agents.
- A low ADA incidence was observed for both IPs.
- Tremelimumab and durvalumab as monotherapy and in combination were generally well tolerated and consistent with the known safety profile.

- Adverse events observed in this study were manageable and there were no new safety findings observed for tremelimumab or durvalumab when given as monotherapy or in combination.