A Phase 1/2, Open-label Study to Evaluate the Safety and Antitumor Activity of MEDI0680 (AMP-514) in Combination with Durvalumab versus Nivolumab Monotherapy in Subjects with Select Advanced Malignancies

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Primary objectives: Dose-expansion:To evaluate the antitumor activity of MEDI0680 in combination with durvalumab versus nivolumab monotherapy in immunotherapy-naïve subjects with advanced or metastatic ccRCC as based on investigator assessed...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON47649

Source
ToetsingOnline

Brief title
D6020C00001 phase 1/2 study in patients with Select Advanced Malignancies

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
clear-cell renal cell carcinoma (ccRCC), kidney cancer

Research involving

Human

Sponsors and support

Primary sponsor: MedImmune, LLC, a wholly-owned subsidiary of AstraZeneca PLC
Source(s) of monetary or material Support: MedImmune;LLC

Intervention

Keyword: D6020C00001, MEDI0680, Phase 1/2, Select Advanced Malignancies

Outcome measures

Primary outcome

Primary objectives endpoints:

Dose-expansion:

The primary endpoint is objective response (OR) of MEDI0680 in combination with durvalumab versus nivolumab monotherapy. Secondary endpoints include best overall response (BOR), disease control (DC), time to response (TTR), duration of response (DR), progression free survival (PFS), change from baseline in tumor size and overall survival (OS). Efficacy endpoints except OS are based on an application of RECIST v1.1 to investigator-assessed tumor measurements.

Secondary outcome

Secondary objectives endpoints:

Dose-expansion:

The endpoints for assessment of safety include the presence of AEs and SAEs, as well as changes from baseline in laboratory parameters, vital signs, physical examination, and ECG results.

The endpoints for assessment of antitumor activity include BOR, OR, DC, TTR, DR, PFS, and change from baseline in tumor size as based on BICR-assessed response using RECIST v1.1.

Dose-escalation and Dose-expansion:

- The endpoints for assessment of PK include individual MEDI0680 and durvalumab concentrations in serum. PK parameters include peak concentration (Cmax) and trough concentration (Cmin)
- The endpoints for assessment of immunogenicity of MEDI0680 and durvalumab include the presence of detectable anti-drug antibodies (ADAs).
- PD-L1 expression / localization on tumor membrane and tumor-infiltrating immune cells within the tumor microenvironment

Exploratory endpoints:

1. The endpoints related to candidate predictive and/or prognostic biomarkers in dose-expansion will focus on tissue-based, protein or gene expression measures and peripheral gene

signatures including, but not limited
to immunohistochemistry (IHC) measures of markers associated with infiltrating
immune cells (eg, cluster
of differentiation 80)
2. Gene expression signatures associated with response to therapy will include
expression of messengerribonucleic acid in blood and tumor samples before and
after treatment to examine gene expression
patterns at baseline and changes in response to treatment. Analysis may also
include but is not limited to:
evaluation of key oncogenic mutations and/or mutations in immune-related
molecules.
3. Levels of circulating free DNA and/or circulating soluble factors which may
include cytokines,
chemokines, growth factors, soluble receptors, and antibodies against tumor and
self-antigens, may be
evaluated before and after treatment to evaluate response to treatment with
MEDI0680 and durvalumab
compared with nivolumab monotherapy
4. Pharmacodynamic assessments of MEDI0680 and durvalumab combination in the
periphery include:
a. Flow cytometric assessment of cell populations such as T cells and B cells
before and after treatment
to evaluate their association with drug exposure and response to treatment;
analysis may include

characterization of phenotype, expression of activation markers, proliferation, and production of
cytokines and effector molecules
b. Dose escalation only: Serum soluble PD-L1 levels before and after treatment may be measured to
evaluate their association with drug exposure and response to treatment with MEDI0680 and
durvalumab
c. Dose escalation only: MEDI0680 receptor occupancy on peripheral blood T cells before and after
treatment may be measured to evaluate associations with drug exposure and response to treatment with
MEDI0680 and durvalumab
5. Expression and localization of key molecules such as PD-L1, PD-L2, and PD-1 within the tumor
microenvironment, as well as the frequency, localization, and phenotype of tumor-infiltrating lymphocytes,
may be examined in biopsy specimens by IHC, immunofluorescence, and/or flow cytometry and correlated
with response to treatment
6. Antitumor activity, including OR, DR, DC, and PFS, may be assessed by irRECIST

Study description

Background summary

There continues to be a high unmet need for new treatment options in advanced solid malignancies. An estimated 338,000 new cases of RCC are diagnosed worldwide, approximately 30% of patients present with metastatic disease at the time of diagnosis (Ferlay et al, 2015; Fisher et al, 2013; Motzer 2015).
Recent approval of a check-point inhibitor monotherapy has afforded RCC patients an increased number of treatment options. However, there is an unmet need for additional treatment strategies for patients that do not respond or have limited clinical response to current therapeutic options.

Based upon the available nonclinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, and the strength of the scientific hypotheses under evaluation, combination therapy with MEDI0680 and MEDI4736 proposed for evaluation in this study may provide meaningful clinical benefit with a manageable safety and tolerability profile by generating durable and improved rate of clinical responses, as compared with monotherapy.

Study objective

Primary objectives:
Dose-expansion:
To evaluate the antitumor activity of MEDI0680 in combination with durvalumab versus nivolumab monotherapy in immunotherapy-naïve subjects with advanced or metastatic ccRCC as based on investigator assessed response using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Secondary objectives:
Dose-expansion:
To describe the safety and tolerability of MEDI0680 in combination with durvalumab versus nivolumab monotherapy in immunotherapy-naïve subjects with advanced or metastatic ccRCC

To evaluate the antitumor activity of MEDI0680 in combination with durvalumab or nivolumab monotherapy in immunotherapy-naïve subjects with advanced or metastatic ccRCC as based on blinded independent central review (BICR) assessed response using RECIST v1.1

Dose-escalation and Dose-expansion:
1. To describe the pharmacokinetics (PK) of MEDI0680 in combination with durvalumab
2. To describe the PK of durvalumab in combination with MEDI0680

3. To determine the immunogenicity of MEDI0680 in combination with durvalumab
4. To determine the immunogenicity of durvalumab in combination with MEDI0680
5. To determine whether PD-L1 is a predictive biomarker for response to therapy with MEDI0680 in combination with durvalumab.

Exploratory objectives:
1. To identify biomarkers that are predictive of antitumor response to MEDI0680 monotherapy or in combination with MEDI4736
2. To profile gene expression changes that may correlate with antitumor response to MEDI0680 monotherapy or in combination with MEDI4736
3. To evaluate additional biomarkers that may correlate with antitumor activity of MEDI0680 monotherapy or in combination with MEDI4736
4. To evaluate the pharmacodynamic activity of MEDI0680 monotherapy and in combination with MEDI4736 in the periphery.
5. To compare the pharmacodynamic changes resulting from complete PD-1/PD-L1 pathway blockade versus treatment with MEDI0680 monotherapy
6. To evaluate the antitumor activity of MEDI0680 monotherapy or in combination with MEDI4736 in subjects with advanced or metastatic ccRCC as assessed by immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)

Study design

This is a multicenter, open-label, Phase 1/2 study to evaluate the safety, tolerability, PK, immunogenicity, and antitumor activity of MEDI0680 in combination with durvalumab or nivolumab monotherapy in adult immunotherapy-naïve subjects with selected advanced malignancies. The study will be conducted at approximately 50 study centers globally.
The study includes 2 phases, dose-escalation and dose-expansion. In the dose-escalation phase, subjects with selected solid tumors will receive MEDI0680/MEDI4736 combination therapy. In the dose-expansion phase, subjects with ccRCC will receive MEDI0680/MEDI4736 combination therapy or nivolumab monotherapy.

In the dose-escalation phase, subjects may receive treatment for up to 12 months; in the dose expansion phase, subjects may remain on treatment until unacceptable toxicity, confirmed progressive disease (PD), or development of other reason for treatment discontinuation. Subjects in dose expansion may receive study drug(s) for a maximum of 2 years. At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive study drug(s). Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of the sponsor. The sponsor reserves the right to terminate access to study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic

alternatives become available in the local market. All subjects will be evaluated regularly. Clinical status will be classified according to modified RECIST v1.1 for subjects in the dose-escalation phase and by RECIST v1.1 for subjects in the dose expansion phase, and other disease-specific assessments. All subjects will be followed for survival until the end of study. Adverse events and SAEs will be followed.

As of Protocol Amendment 3, the dose-escalation phase completed enrollment. Subjects were treated through the highest planned dose-level cohort of 20 mg/kg MEDI0680 Q2W in combination with durvalumab Q2W and the MTD was not reached. The dose-expansion phase will begin after the dose-escalation phase. As of Amendment 5, immunotherapynaïve subjects with ccRCC will be randomized in a 2:1 ratio to 1 of 2 treatment arms: (1) MEDI0680/durvalumab combination therapy or (2) nivolumab monotherapy. Stratification factors will include the Memorial Sloan Kettering Cancer Center (MSKCC) risk group (0 = favorable risk; 1 or 2 = intermediate risk; 3 = poor risk) and PD-L1 expression status (* 1% and > 1%). Up to 40 subjects may be randomized in to the MEDI0680/durvalumab combination therapy arm and up to 20 subjects in the nivolumab monotherapy arm based on evaluation of emerging safety and efficacy parameters in the current study as well as other ongoing studies. An interim futility analyses will be performed for the MEDI0680/durvalumab combination therapy arm in the dose-expansion phase after 20 subjects have been randomized and have reached their second post-baseline disease assessment or have completed study.
An evaluation of a possible correlation between clinical activity of MEDI0680 in combination with durvalumab or nivolumab and potential biomarkers (eg, PD-L1 expression on tumor) will be ongoing throughout the study.
Randomization into the dose expansion phase may be discontinued at the discretion of the sponsor should
emerging clinical or pre-clinical data suggest that continued treatment may not be beneficial

Intervention

In the dose-expansion phase, subjects will receive either 20 mg/kg MEDI0680 in combination with 750 mg (fixed dose) durvalumab Q2W or nivolumab Q2W monotherapy. Subjects in the dose-expansion phase will remain on treatment until unacceptable toxicity, confirmed PD, or development of other reason for treatment discontinuation.

Prior to the removal of a MEDI0680 monotherapy arm in this protocol amendment, some subjects were
randomized and began receiving MEDI0680 monotherapy. These subjects are to continue receiving 20 mg/kg
MEDI0680 Q2W monotherapy until unacceptable toxicity, confirmed progressive disease (PD), or development
of other reason for treatment discontinuation and will follow the schedule of study procedures for

MEDI0680/durvalumab combination therapy.

In the event of an initial assessment of PD (based on RECIST v1.1) in either the dose-escalation or
dose-expansion phases, a subject may continue to receive the assigned study treatment until confirmation of PD
if the subject fulfills the criteria for treatment in the setting of PD and does not meet any of the investigational
product discontinuation criteria. If the lesions included in the tumor burden subsequently regress to the extent
that the criteria for PD are no longer met, then treatment may continue according to the treatment schedule.
Initial observation of PD must be confirmed by a subsequent scan no earlier than 4 weeks from the initial scan.
Subjects with confirmed PD must discontinue treatment.

Study burden and risks

The study involves a screening period, treatment period, and a follow-up period. The screening period will take up to 28 days, the treatment phase will take approximately 12 months depending on how the patient responds to the treatment. After the last treatment the patient will return 30, 60 and 90 days after last treatment for safety follow-up visits. In addition, there will be a long-term follow-up in person or by phone every 3 months for the first 12 months, then every 6 months for the remainder of the study.
In total, the patient will visit the hospital approximately 33 times over a period of approximately 24 months.

The following tests and procedures will take place during the different visits during estimated 12 cycles of treatment and 2 yrs follow-up:

1x check Medical history, 2x complete physical examination, 27x shortened physical examination, 29x vital signs, 12x ECG, 25x ECOG performance status, 14x Disease assessments (CT or MRI scans), 29x blood collection, 16x pregnancy test (if applicable), 19x urine sample, 0-4 x providing fresh tumor biopsy, 33x Assessment of Adverse Events and Serious Adverse Events and any medications being taken, 24x IMP administration.

Please refer to the IB and patient information regarding side effects that are expected and for other risks and discomforts.

Contacts

Public

MedImmune, LLC, a wholly-owned subsidiary of AstraZeneca PLC

One MedImmune Way 0
Gaithersburg 20878
US
Scientific
MedImmune, LLC, a wholly-owned subsidiary of AstraZeneca PLC

One MedImmune Way 0
Gaithersburg 20878
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age * 18 years at the time of screening.
2. ECOG performance status of 0 - 1.
3. N/A for NLD as only dose expansion
4. For dose-expansion:
a. Histological confirmation of advanced or metastatic RCC with a clear-cell component
b. Must have received at least 1 and no more than 2 prior anti-angiogenic therapy regimens (including, but not limited to, sunitinib, sorafenib, pazopanib, axitinib, tivozanib, and bevacizumab), in the advanced or metastatic setting.
c.Must have received no more than 3 total prior systemic treatment regimens in the advanced or metastatic setting, and must have evidence of radiographic progression on or after the last treatment regimen received and within 6 months prior to study enrollment.
d. No prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
e. No prior treatment with an mammalian target of rapamycin (mTOR) inhibitor (including,

but not limited to everolimus, temsirolimus, sirolimus, and ridaforolimus)
f. Prior cytokine therapy (eg, IL-2, IFN-*) or treatment with cytotoxics is allowed.
g. Subjects must have at least 1 measurable lesion according to RECIST v1.1. A previously irradiated lesion cannot be considered a target lesion. Radiographic disease assessment can be performed up to 28 days prior to the first dose.;5.Biopsy requirements:
a. N/A for NLD as only dose-expansion
b. Able and willing to give valid written consent for fresh tumor samples if required.
Fresh tumor biopsies should be preferentially obtained from tumor tissues that are safely accessible as determined by the investigator and achieved via non-significant risk procedures (refer to Section 4.3.2.1).
c.. For dose-expansion:
i. Tumor tissue (formalin fixed paraffin embedded [FFPE] archival or fresh tumor tissue) must be received by the central vendor (block or unstained slides) and evaluable for PD-L1 expression status in order to randomize a subject to study treatment.
ii. All subjects are encouraged to consent to and provide both pre-treatment and on-treatment fresh tumor biopsies;however, on-treatment biopsies are optional.;6. For dose-escalation and dose-expansion: (If evaluations performed as part of standard of care for other purposes prior to obtaining informed consent are suitable for screening and occurred within 7 days prior to starting treatment, those evaluations do not need to be repeated if the subject consents to their use):
a. Adequate organ and marrow function, as defined below:
i. Hemoglobin * 9 g/dL
ii. Absolute neutrophil count * 1,500/mm3
iii. Platelet count * 100,000/mm3
iv. Total bilirubin * 1.5 × ULN except subjects with documented Gilbert*s syndrome (> 3 × ULN) or liver metastasis, who must have a baseline total bilirubin * 3.0 mg/dL
v. Alanine aminotransferase (ALT) and AST * 2.5 × ULN; for subjects with hepatic metastases, ALT and AST * 5 × ULN
vi. Calculated creatine clearance or 24-hour urine creatine clearance * 40mL/min determined by the Cockroft-Gault formula (using actual body weight);7. Written informed consent and any locally required authorization obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations.;8. Female subjects of childbearing potential who are sexually active with a nonsterilized male partner must use at least one highly effective method of contraception from screening and must agree to continue using such precautions for 120 days after the subject*s last dose of MEDI0680 or durvalumab or 150 days after the subject's last dose of nivolumab. It is strongly recommended for the male partner of a female subject to use male condom plus spermicide throughout this period. Effective methods of contraception are described in table 4.1.2-1 in the protocol. Female subjects should refrain from egg cell donation and breastfeeding throughout this period.
a. Females of childbearing potential are defined as those who are not surgically sterile or who are not post-menopausal.
i. Females < 50 years of age will be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments, and if they have luteinizing hormone and follicle-stimulating hormone levels in the postmenopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

ii. Females * 50 years of age will be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses > 1 year ago, had chemotherapy-induced menopause with last menses > 1 year ago, or underwent surgical sterilization.
b. A highly effective method of contraception is defined as one that results in a low failure rate (i.e, less than 1% per year) when used consistently and correctly. Note that some contraception methods are not considered highly effective.;9. Nonsterilized males who are sexually active with a female partner of childbearing potential must use male condom plus spermicide from Day 1 through 120 days after the subject*s last dose of MEDI0680 or durvalumab or 150 days after the subject's last dose of nivolumab. In addition, male subjects must refrain from fathering a child or donating sperm while on study and for 120 days after the subject*s last dose of MEDI0680 or durvalumab or 150 days after the subject's last dose of nivolumab.

Exclusion criteria

1. Concurrent enrollment in another clinical study, unless in a follow-up period or it is an observational study
2. Central Nervous system (CNS) metastatic disease and leptomeningeal disease are exclused. (NOTE: spinal cord compression which has been stabilized is allowed).
3. Any concurrent chemotherapy, immunotherapy, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable
(NOTE: Local treatment of isolated lesions for palliative intent is acceptable [eg, by local surgery or radiotherapy])
4. Any investigational anticancer therapy received within 28 days prior to the first dose of durvalumab and MEDI0680 or nivolumab.
5. Major surgical procedure (as defined by the investigator) within 28 days prior to the first dose of durvalumab and MEDI0680 or nivolumab or still recovering from prior surgery.
6. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to NCI CTCAE v4.03 Grade 0 or 1 with the exception of alopecia and laboratory values listed per the inclusion criteria. Subjects with prior endocrine toxicities (eg, hypothyroidism) who are stable on replacement therapy are not excluded. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by durvalumab and MEDI0680 or nivolumab may be included (eg, hearing loss).
7. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab and MEDI0680 or nivolumab with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent
8. Active or prior documented autoimmune or inflammatory disease (including inflammatory bowel disease, diverticulitis with the exception of diverticulosis, celiac disease, irritable bowel disease; Wegener*s granulomatosis; Hashimoto syndrome) within the past 3 years. Subjects with vitiligo, alopecia, Grave*s disease, or psoriasis not requiring systemic treatment (within the past 3 years) are not excluded.

9. History of primary immunodeficiency or tuberculosis
10. Test results indicating active infection with human immunodeficiency virus (HIV), or hepatitis A, B, or C
11. Receipt of live, attenuated vaccine within 28 days prior to the first dose of durvlumab and MEDI0680 or nivolumab. NOTE: Subjects, if enrolled, should not receive live vaccine during the study and 90 days after the last dose of durvalumab and MEDI0680 or nivolumab.
12. Females who are pregnant, lactating, or intend to become pregnant during the participation to the study
13. Uncontrolled inter-current illness including, but not limited to, ongoing or active infection, current pneumonitis, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, or psychiatric illness/social situations that would limit compliance with study requirement substantially increase risk of incurring AEs from durvalumab or MEDI0680 or nivolumab, or compromise the ability of the subject to give written informed consent
14. Diagnosis of a second malignancy within the last 2 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death, treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)
15. Known allergy or hypersensitivity to study drug formulations
16. Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results
17.Subjects with advanced NSCLC with tumors harboring anaplastic lymphoma kinase gene rearrangements or epidermal growth-factor receptor-sensitizing mutations who have not received appropriate TKI therapy. These subjects can be enrolled after documented progression or intolerance to appropriate TKIs

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	06-03-2018
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Durvalumab
Generic name:	Durvalumab
Product type:	Medicine
Brand name:	MEDI0680 (AMP-514)
Generic name:	MEDI0680 (AMP-514)
Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-06-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-10-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-01-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-01-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	20-02-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-03-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-04-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-06-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-10-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-04-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-000323-43-NL
ClinicalTrials.gov	NCT02118337
CCMO	NL58684.042.17