A Phase 1 Multicenter, Open-label Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, Immunogenicity, and Antitumor Activity of MEDI0562 in Combination with Immune Therapeutic Agents in Adult Subjects with Advanced Solid Tumors

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Primary ObjectiveThe primary objective is to assess safety and tolerability, describe the dose limiting toxicities (DLTs), and determine the maximum tolerated dose (MTD) or the maximum administered dose (MAD; in the absence of exceeding the MTD) for...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON45907

Source
ToetsingOnline

Brief title
D6060C00002

Condition

- Metastases

Synonym
cancer, tumour

Research involving
Human

Sponsors and support

Primary sponsor: Medimmune
Source(s) of monetary or material Support: Medimmune

Intervention

Keyword: cancer, tumour

Outcome measures

Primary outcome

The primary endpoint is safety as assessed by presence of adverse event (AE), serious adverse event (SAE), DLT, abnormal laboratory parameter, vital sign, and electrocardiogram results.

Secondary outcome

Secondary Endpoints

1. The endpoints for assessment of antitumor activity include best overall response, objective response (OR), disease control (DC), duration of response (DoR), progression-free survival (PFS), and overall survival (OS), and the percent change from baseline in target lesion sum of diameters. RECIST Version 1.1 will be used for assessment of tumor response.

2. The endpoints for assessment of PK of MEDI0562, durvalumab, and tremelimumab include individual MEDI0562, durvalumab, and tremelimumab concentrations at different time points after administration. PK parameters that may be modeled on these data include, but are not limited to, maximum observed concentration, area under the concentration-time curve, clearance, and terminal half-life.

3. The endpoints for assessment of immunogenicity of MEDI0562, durvalumab, and

tremelimumab include the number and percentage of subjects who develop detectable antidrug antibodies.

4. The endpoints for assessment of pharmacodynamic activity include induction of Ki67 on peripheral cluster of differentiation (CD)4+ and CD8+ memory T-cell populations and assessment of tumor-infiltrating lymphocytes (TILs) in tumor biopsy specimens.

Study description

Background summary

The importance of the immune system in cancer development and progression has been recognized during the past decade (Hanahan and Weinberg, 2000). Failure of immune surveillance of pre-neoplastic lesions and micro-metastases is a key step in cancer development. Chronically immunosuppressed individuals show higher rates of cancer. This observation led to the hypothesis that sporadic cancers among immunocompetent individuals are likely to be minimally immunogenic, allowing for passive escape from immune surveillance. Recent data suggests that this may be an oversimplification. Some sporadic tumors are highly immunogenic, but actively suppress the local immune environment through production of immunosuppressive cytokines (Shields et al, 2010). As such, the local tumor environment is likely a highly dynamic environment where most tumors grow and metastasize through adaptive responses that modulate antitumor immunity.
Tumor-infiltrating lymphocytes (TILs) have the capacity to control the growth of many types of cancer (Gooden et al, 2011). Most tumors show infiltration by TILs, but tumors modulate the local microenvironment through expression of inhibitory molecules. Engagement of TIL cell-surface receptors with these inhibitory ligands leads to a dysfunctional immune response, causes T cell exhaustion, and facilitates tumor progression (Baitsch et al, 2012; Crespo et al, 2013). Novel monoclonal antibodies (mAbs) that block these inhibitory receptors have shown significant clinical activity across a number of tumor types (Wolchok et al, 2009; Hodi et al, 2010; Robert et al, 2011; Brahmer et al, 2010; Topalian et al, 2012). Specifically, blockade of immune-checkpoint inhibitors cytotoxic T lymphocyte-associated antigen 4 (CTLA 4), programmed death 1 (PD 1), and programmed death ligand 1 (PD L1) have shown clinical activity not only in conventionally immune-responsive tumors such as melanoma (MEL) and renal cell carcinoma (RCC) but also in non small cell lung cancer (NSCLC); (Brahmer et al, 2010; Brahmer et al, 2012; Topalian et al, 2012;

Gordon et al, 2013); hepatocellular (Sangro et al, 2013), prostate (Harzstark and Small, 2010; Slovin et al, 2013), and pancreatic (Royal et al, 2010) cancers; mesothelioma, (Calabro et al, 2013); and other solid tumors (Brahmer et al, 2010; Brahmer et al, 2012; Gordon et al, 2013).

Study objective

Primary Objective
The primary objective is to assess safety and tolerability, describe the dose limiting toxicities (DLTs), and determine the maximum tolerated dose (MTD) or the maximum administered dose (MAD; in the absence of exceeding the MTD) for the combination of MEDI0562 and durvalumab or tremelimumab in subjects with advanced solid tumors.

Study design

This is a Phase 1, multicenter, open-label study of MEDI0562 in combination with immune therapeutic agents to evaluate the safety, tolerability, PK, pharmacodynamics, immunogenicity, and antitumor activity in adult subjects with advanced solid tumors.

The study includes 2 phases, dose escalation and dose expansion, with 2 treatment arms in each phase: MEDI0562/durvalumab combination therapy (Arm A) and MEDI0562/tremelimumab combination therapy (Arm B). Subjects will remain on treatment until unacceptable toxicity, progressive disease (PD), or development of other reason for treatment discontinuation.

Intervention

Up to 6 dose levels of MEDI0562 (2.25, 7.5, 22.5, 75, 225, or 750 mg) via IV infusion Q2W in combination with either durvalumab (1500 mg) via IV infusion Q4W (Arm A) or tremelimumab (75, 225, or 750 mg) via IV infusion Q4W for 4 doses only followed by MEDI0562 monotherapy Q2W (Arm B) may be explored.

Study burden and risks

The proposed combination of MEDI0562 with other immune therapeutic agents, such as durvalumab or tremelimumab, may increase the frequency or severity of toxicities of the respective individual agents and thus, a Phase 1 dose-exploration study is the appropriate setting to explore the combination of MEDI0562 with durvalumab or tremelimumab. This study is intended to establish the MTD or highest protocol defined dose in the absence of an MTD and the safety profile of MEDI0562 in combination with immune therapeutic agents. Other data to be evaluated include the PK, pharmacodynamics, immunogenicity, and antitumor activity of MEDI0562 combinations. The results from this study will

form the basis for designing future studies.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Written and signed informed consent and any locally required authorization obtained from the subject/legal representative (where permissible) prior to performing any protocol-related procedures, including screening evaluations.;2. Age * 18 years at the time of study entry.;3.Subjects must have received and have progressed, are refractory, or are intolerant to standard therapy appropriate for the specific tumor type. Subjects should not have received more than 3 prior lines of systemic therapy for recurrent or metastatic disease (including both standard of care and investigational therapies).;4. Subjects in the dose-escalation phase must have histologic documentation of advanced solid tumors, excluding primary CNS tumors and hematologic malignancies.;5. Subjects in the dose-expansion phase

must have recurrent or metastatic disease for the
following tumor types based on treatment arm (see protocol);6. During dose escalation, subjects who have received prior therapy with regimens containing CTLA 4, PD L1, or PD 1 antagonists are permitted to enroll if all of the criteria listed in the protocol are met;7. Subjects must have at least 1 lesion that is measurable using RECIST Version 1.1 guidelines ;8. All subjects are encouraged to consent to and provide both pretreatment and on treatment tumor biopsies. If during dose escalation any dose-level cohort is expanded beyond the initial 3 to 6 subjects, the additional subjects enrolled under pharmacodynamic expansion must consent to and undergo both a pre-treatment and an on treatment tumor biopsy. ;9. ECOG Performance score of 0 or 1, with the exception of the UC cohort where an ECOG
performance score of 2 may be permitted

Exclusion criteria

1. Prior treatment with TNFRSF agonists ;2. History of severe allergic reactions to any unknown allergens or any components of the study drug formulations ;3. Active or prior documented autoimmune disease within the past 2 years. ;4. Concurrent enrollment in another clinical study.;5. Receipt of any conventional or investigational anticancer therapy not otherwise specified above within 28 days prior to the first dose of MEDI0562 and durvalumab or tremelimumab combination treatment; in the case of mAbs, 28 days or 5 half lives, whichever is shorter, prior to the first dose of MEDI0562 and durvalumab or tremelimumab combination treatment;6. Any concurrent chemotherapy, IMT, or biologic or hormonal therapy for cancer treatment.;7. Unresolved toxicities from prior anticancer therapy.;8. Systemic therapeutic anticoagulation or daily aspirin dose exceeding 325 mg/per day. ;9. Current or prior use of immunosuppressive medication within 14 days prior to the first dose of MEDI0562. ;10. History of primary immunodeficiency, solid organ transplantation, or tuberculosis;11. Test results indicating active infection with human immunodeficiency virus (HIV) or hepatitis B or C defined by positive serologic testing and confirmatory viral nucleic acid testing .;12. Receipt of live, attenuated vaccine within 28 days prior to the first dose of investigational products ;13. Major surgery (as defined by the investigator) within 4 weeks prior to first dose of MEDI0562 ;14. Other invasive malignancy within 2 years (exception per protocol);15. Uncontrolled intercurrent illness

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-10-2016
Enrollment:	33
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MEDI0562 750mg
Generic name:	MEDI0562
Product type:	Medicine
Brand name:	MEDI1123 750mg
Generic name:	Tremelimumab
Product type:	Medicine
Brand name:	MEDI4736 1500mg
Generic name:	Durvalumab

Ethics review

Approved WMO

Date:	31-05-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	26-08-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	28-09-2016
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-09-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-01-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-06-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-06-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-06-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-01-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	25-01-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-04-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-08-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2016-000177-20-NL
ClinicalTrials.gov	NCT02705482
CCMO	NL57430.031.16