A Phase 1, Open-label, Dose-escalation and Dose-expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Immunogenicity, and Antitumor Activity of MEDI5752 in Subjects with Advanced Solid Tumors

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This study has been transitioned to CTIS with ID 2023-509605-77-00 check the CTIS register for the current data. Primary objectives (Dose-escalation Phase):• To evaluate the safety and tolerability, describe the dose-limiting toxicities (DLTs), to...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON54211

Source
ToetsingOnline

Brief title
0597/0102 (MedImmune D7980C00001)

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Advanced solid tumors: subjects with, clear-cell renal cell carcinoma (referred to as RCC expansion cohort) and subjects with first-line, Stage IIIB or IV nonsquamous non-small cell lung cancer (NSCLC; referred to as NSCLC expansion cohort). = renal cell carcinoma and

nonsquamous non-small cell lung 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: The study sponsor as listed in question B6/B7

Intervention

Keyword: Advanced Solid Tumors, MEDI5752, Open-label, Phase 1

Outcome measures

Primary outcome

Primary Endpoints (Dose-escalation Phase):

• Safety will be assessed by the presence of adverse events (AEs), serious adverse events (SAEs), DLTs, and abnormal laboratory parameters, vital signs, and electrocardiogram (ECG) results.

• The MTD will be determined by DLTs during the dose-escalation phase. The OBD will be determined from the safety, efficacy, PK, pharmacodynamic, and biomarker data.

Primary Endpoints (Dose-expansion Phase Parts 1 and 2):

• Assessment of antitumor activity based on OR using RECIST v1.1 .

Primary Endpoints (Dose-expansion Phase Part 3):

• Safety will be assessed by the presence of AEs, SAEs, abnormal laboratory parameters, vital signs, and ECG results.

Please refer to protocol for exploratory end points

Secondary outcome

• Assessment of antitumor activity to include DoR, DC, and PFS as assessed by RECIST v1.1, and OS

Secondary Endpoints (Dose-expansion Phase Parts 1 and 2):

• Assessment of antitumor activity to include OR, DoR, DC, and PFS, as assessed by RECIST v1.1, and OS

• Safety will be assessed by the presence of AEs, SAEs, abnormal laboratory parameters, vital signs, and ECG results.

Secondary Endpoints (Dose-expansion Phase Part 3):

• Assessment of antitumor activity to include OR, DoR, DC, and PFS, as assessed by RECIST v1.1 and OS

Secondary Endpoints (Dose-escalation Phase and Dose-expansion Phase Parts 1, 2, and 3):

• PK parameters to be evaluated to include maximum observed serum concentration (Cmax), area under the concentration-time curve (AUC), clearance (CL), and terminal elimination half-life (t1/2).

• Immunogenicity will be assessed by the number and percentage of subjects who develop detectable antidrug antibodies (ADAs) to MEDI5752.

• To determine PD-L1 baseline expression in tumor by immunohistochemistry (IHC) in subjects with advanced solid tumors.

Please refer to protocol for exploratory end points

Study description

Background summary

Cancer and Immune Function
Cancer continues to be a major global health burden and is the second leading cause of death globally (1 in 6 deaths) totaling 8.8 million deaths in 2015 (World Health Organization, 2015). In the past decade, a reduction in cancer mortality rates has been observed in some countries.

Unfortunately, despite this progress, there continues to be an unmet medical need for more effective and less toxic therapies, especially for patients with advanced refractory disease. Recent advances in immunotherapy offer promise for improving clinical outcomes in patients with advanced solid tumors.

Immunotherapy
The importance of the immune system in cancer development and progression is well recognized (Dunn et al, 2006). Failure of immune surveillance of pre-neoplastic lesions and micro-metastases is a key step in cancer development. It is increasingly understood that cancers are recognized by the immune system and, under some circumstances, the immune system may control or even eliminate tumors (Dunn et al, 2004; Peggs et al, 2009).

PD-1/CTLA-4 Combined Checkpoint Blockade
[Programmed cell-death-1 (PD-1)/ Cytotoxic T-lymphocyte-associated Antigen-4]

Preclinical and clinical studies with cancer immunotherapy agents show that antibodies that block immune checkpoints such as PD-1 and CTLA-4 can potentiate immune responses to cancer cells in a wide range of tumor types (Hodi et al 2010, Oh et al 2017). PD-1 and CTLA-4 modulate effector T cell activation, proliferation, and function through distinct, complementary mechanisms (Okazaki et al 2013). The expression of PD-1 and CTLA-4 on tumor-infiltrating T cell populations contributes to suppression and immunological escape. In preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity versus blockade of either pathway alone. Therefore, a combined blockade of CTLA-4 and PD-1 is predicted to produce greater antitumor activity than either agent alone and has led to investigating the combination of anti-PD-1 and anti-CTLA 4 antibodies in various malignancies in patients. The anti-PD-1 agents nivolumab and pembrolizumab have demonstrated clinical activity as single agents with a manageable safety profile in several tumor types, most notably in melanoma. Both anti-PD-1 agents were first approved by the US FDA and Japan Pharmaceuticals and Medical Devices Agency (nivolumab

only) for this indication in 2014, and in 2015 by other regulatory agencies including the European Medicines Agency (EMA) and Australia*s Therapeutic Goods Association.(Ribas et al 2015, Weber et al 2015). Nivolumab and pembrolizumab were associated with objective responses (ORs) in 30% to 40% of metastatic melanoma patients, with the majority of responses being durable.(Robert et al 2015a, Robert et al 2015b). Nivolumab, pembrolizumab, and the anti-PD-L1 antibodies atezolizumab and durvalumab have been granted approvals by the US FDA and/or the EMA for the treatment of various malignancies including melanoma, cell non small cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck (SCCHN), urothelial bladder cancer (UBC), renal cell carcinoma (RCC), classical Hodgkin lymphoma, and microsatellite instability (MSI)-high or mismatch repair deficient metastatic colorectal cancer (CRC) (refer to the current prescribing information for these agents).
The anti-CTLA 4 antibodies ipilimumab and tremelimumab block the interaction of CTLA 4 to the B7 ligands, thus enhancing T cell activation, proliferation, and antitumor activity. (Ribas 2008, Weber 2008). Ipilimumab has demonstrated an overall survival (OS) benefit in two Phase 3 studies (Hodi et al 2010, Robert et al 2011) and was granted approval by the US FDA and EMA for the treatment of unresectable or metastatic melanoma and as adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection.(Eggermont et al 2015). Tremelimumab is in development in combination with the anti-PD L1 antibody durvalumab in NSCLC and SCCHN (Antonia et al 2016), AstraZeneca.com).
An improvement in PFS of nivolumab combined with ipilimumab in metastatic melanoma as compared to either agent alone (Larkin et al 2015) resulted in the first US FDA approval of this combination in 2015. This combination is also now approved by the FDA for front-line treatment of intermediate- and poor-risk RCC (Motzer et al 2018, Motzer et al 2019b), NSCLC (Hellmann et al 2019, Paz-Ares et al 2021), and malignant pleural mesothelioma (Baas et al 2021); accelerated approvals are in place for refractory hepatocellular carcinoma (Yau et al 2020) and microsatellite instability-high/mismatch repair deficient colorectal carcinoma (Lenz et al 2019). However, the toxicity of this combination precludes it from broad use especially in the community setting.
MEDI5752 as a monotherapy has been engineered to mitigate the toxicity associated with the PD-L1 and CTLA-4 inhibitor combinations (see below) and therefore once an appropriate dose level has been established, warrants testing in tumors driven by CTLA 4 and/or PD 1 biology. Given the previous recognition of anti-PD-1 and anti-CTLA-4 antitumor activity in RCC and NSCLC, these tumor types have been selected for further evaluation in the dose expansion phase of the study.

Study objective

This study has been transitioned to CTIS with ID 2023-509605-77-00 check the CTIS register for the current data.

Primary objectives (Dose-escalation Phase):

• To evaluate the safety and tolerability, describe the dose-limiting toxicities (DLTs), to determine the maximum tolerated dose (MTD), optimal biological dose (OBD), or highest protocol-defined dose (HPDD) of MEDI5752 in subjects with advanced tumors, when administered as a single agent.

Primary Objectives (Dose-expansion Phase Parts 1 and 2):
• To describe the preliminary antitumor activity of MEDI5752 (versus pembrolizumab, where applicable) using objective response (OR) based on Response Evaluation Criteria in Solid Tumors (RECIST) Version (v)1.1 in subjects with advanced solid tumors, when administered as a single agent or combined with chemotherapy.

Primary Objectives (Dose-expansion Phase Part 3):
• To evaluate the safety and tolerability of MEDI5752 in subjects with advanced solid tumors when combined with chemotherapy.

Secondary Objectives (Dose-escalation Phase):
• To describe the preliminary antitumor activity of MEDI5752 (versus pembrolizumab, where applicable) using duration of response (DoR), disease control (DC), and progression-free survival (PFS) based on RECIST v1.1, and overall survival (OS) in subjects with advanced solid tumors, when administered as a single agent (Dose-expansion phase).
• To describe the preliminary antitumor activity of MEDI5752 using OR, DoR, DC, and PFS based on RECIST v1.1, and OS in subjects with advanced solid tumors, when administered as a single agent or combined with chemotherapy.
• To describe the pharmacokinetics (PK) of MEDI5752 in subjects with advanced solid tumors, when
administered as a single agent or combined with chemotherapy.

Secondary Objectives (Dose-expansion Phase Part 3):
• To describe the preliminary antitumor activity of MEDI5752 using OR, DoR, DC, and PFS based on RECIST v1.1 and OS, in subjects with advanced solid tumors, when combined with chemotherapy.

Secondary Objectives (Dose-escalation Phase and Dose-expansion Phase Parts 1, 2, and 3):
• To determine the immunogenicity of MEDI5752 in subjects with advanced solid tumors when
administered as a single agent or combined with chemotherapy.
• To determine programmed cell-death ligand-1 (PD-L1) baseline expression in subjects with advanced
solid tumors.

For the Exploratory objectives refer to protocol

Study design

This is a Phase 1, first-time-in-human, multicenter, open-label, dose-escalation and dose-expansion study to evaluate the safety and tolerability, and efficacy, pharmacokinetics and immunogenicity of MEDI5752 in adult subjects with advanced solid tumors, when administered as a single agent or combined with chemotherapy. Dose escalation initially utilizes an accelerated titration design (ATD) for up to 2 dose levels followed by a modified toxicity probability interval (mTPI) algorithm for the subsequent dose levels. With the potential exception of the initial 2 cohorts, which will follow specific rules associated with ATD, the mTPI algorithm will be used throughout dose escalation to guide dose escalation and de-escalation decisions. Dose escalation is followed by dose-expansion. The dose-expansion phase consists of 3 Parts described below.

Expansion Part 1:
During Expansion Part 1, 2 cohorts of immunotherapy-naïve subjects with advanced clear-cell renal cell carcinoma (RCC; RCC Cohort 1 [RCC-C1]) and subjects with first-line, Stage IIIB or IV nonsquamous non-small cell lung cancer (NSCLC; NSCLC Cohort 1 [NSCLC C1]) will be evaluated as detailed below.
RCC-C1: Up to 50 subjects will receive MEDI5752 monotherapy.

NSCLC-C1: Up to as 104 subjects will be randomized 1:1 (NSCLC Cohort 1 Randomized [NSCLC C1R]) to MEDI5752 in combination with chemotherapy (NSCLC C1R Arm A; n = 52) or pembrolizumab in combination with chemotherapy (NSCLC C1R Arm B; n = 52). Before initiating randomization of the NSCLC expansion , safety and tolerability of MEDI5752 combined with chemotherapy in a minimum of 7 subjects will be assessed in a Safety Run-in (NSCLC Cohort 1 Safety Run-in [NSCLC C1S]). The starting dose of this cohort will be determined based upon the safety, PK, pharmacodynamic, and antitumor activity data obtained during the escalation phase of MEDI5752 as monotherapy.

In Expansion Part 1, RCC-C1 was closed after enrollment of 27 subjects and will not be reopened (22 subjects were included in the interim analysis). NSCLC-C1R was closed after randomization of 41 subjects randomized for the interim analysis and will not be reopened. The interim analysis for these cohorts is described in Statistical Methods below.

Expansion Parts 2 and 3:
Expansion Part 2 and 3 will evaluate subjects as detailed below. Enrollment in a cohort or a treatment arm of a cohort may be closed at any time at the discretion of the Sponsor.

Expansion Part 2:
RCC Cohort 2 (RCC C2): Up to approximately 60 subjects with first-line advanced clear-cell RCC may be randomized 1:1 to MEDI5752 750 mg (RCC C2 Arm A; n =30) or MEDI5752 500 mg (RCC-C2 Arm B; n = 30).
NSCLC Cohort 2 (NSCLC-C2): Up to approximately 150 subjects with first-line Stage IIIB to IV nonsquamous NSCLC may receive MEDI5752 750 mg or MEDI5752 500

mg in combination with chemotherapy.

*Expansion Part 3:
• NSCLC Cohort 3 (NSCLC-C3): Up to approximately 20 subjects with first-line Stage IIIB to IV squamous NSCLC may receive MEDI5752 750 mg in combination with chemotherapy.

All subjects in the study will remain on treatment until confirmed progressive disease (PD), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur. All subjects in the study will be followed for survival until the end of the study defined as 2 years after the final subject has been entered into the study or when the Sponsor stops the study, whichever occurs first.

Intervention

Dose-escalation phase:
Following a screening period of up to 28 days, the subjects will be dosed with MEDI5752 via intravenous (IV) infusion in an every 3 weeks (Q3W) dosing schedule. The dose-limiting toxicities (DLTs) will be evaluated during the dose-escalation phase. The DLT-evaluation period during dose escalation will be 21 days from the first dose of MEDI5752. Dose escalation will initially commence with an accelerated titration design (ATD) at 2.25 and 7.5 mg dose levels (Cohorts 1 and 2, respectively). A minimum of 1 and a maximum of 3 subjects will be enrolled at each dose level in ATD. If predefined safety criteria are met at any point during accelerated titration, dose escalation will switch to the mTPI algorithm. Dose escalation will be conducted using the mTPI algorithm with subjects receiving one of 7 planned sequential dose levels of MEDI5752 (dose levels, 22.5, 75, 225, 750, 1500, 2000, and 2500 mg: Cohorts 3 to 9, respectively). A minimum of 3 and a maximum of 12 subjects will be enrolled at each dose level using the mTPI algorithm.

With the potential exception of the initial 2 cohorts, which will follow specific rules associated with ATD, the
mTPI algorithm will be used throughout the dose-escalation phase to guide to dose-escalation and
de-escalation decisions. De-escalation may be triggered at any dose level of MEDI5752, including at the first
dose level (2.25 mg in Cohort 1). At least 1 dose level below the starting cohort dose may be evaluated at the
discretion of the Sponsor. In addition, intermediate dose levels may be explored if warranted by emerging
safety, PK, pharmacodynamic data, and preliminary antitumor activity from this study as well as from other studies with MEDI5752.

Based on emerging safety, PK, and pharmacodynamic data, and at the discretion of the Sponsor, any

previously cleared dose level during dose escalation may be expanded up to a total of 12 subjects with
mandatory pre- and on-treatment tumor biopsies obtained from these additional enrolled subjects, referred to
as the pharmacodynamic cohorts. Subjects with specific tumor types may be enrolled in these
pharmacodynamic cohorts based on the emerging data. Once the optimal biological dose (OBD), the maximum tolerated dose (MTD), or Highest protocol-defined dose (HPDD) has been determined,
a specific cohort of up to 25 subjects with specific tumor types may be enrolled based on emerging data,
referred to as the MTD/OBD cohort.

Dose-expansion phase:
All subjects will be enrolled and treated regardless of the PD-L1 IHC status (positive, negative, or not available). MEDI5752 will be administered via IV infusion over 60 minutes (± 10 minutes) The treatment regimens are detailed below for Expansion Part 1,2 and 3.
Expansion Part 1:
Subjects in RCC-C1 will receive MEDI5752 1500 mg Q3W.
. • Subjects in NSCLC C1S receive : * Arm A: MEDI5752 2000mg Q3W combined with carboplatin area under the concentration-time curve (AUC) 5 mg/mL*min and pemetrexed 500 mg/m2 Q3W delivered for 4 doses followed by indefinite MEDI5752 and pemetrexed maintenance therapy Q3W MEDI5752 and pemetrexed maintenance therapy Q3W (n = 52). * Arm B: Pembrolizumab 200 mg Q3W combined with carboplatin AUC 5 mg/mL*min and pemetrexed 500 mg/m2 Q3W delivered for 4 doses followed by pembrolizumab for 21 months (a total of 24 months) and indefinite pemetrexed maintenance therapy Q3W C1R will be stratified based on the presence of liver metastases (Yes/No). Expansion Part 2
Subjects in RCC-C2 will be randomized in a 1:1 ratio to receive one of the following treatments:
RCC-C2 Arm A: MEDI5752 750 mg Q3W (n = 30) or
RCC-C2 Arm B: MEDI5752 1500 mg Q3W (n = 30)
Subjects in NSCLC-C2 will receive MEDI5752 750 mg Q3W combined with carboplatin AUC 5 mg/mL*min and pemetrexed 500 mg/m2 Q3W delivered for 4 doses followed by indefinite MEDI5752 and pemetrexed maintenance therapy Q3W (n = 50)). If emerging safety data suggest that the 750 mg dose of MEDI5752 is intolerable, additional subjects in this cohort will be dosed at a MEDI5752 dose of 500 mg in combination with chemotherapy.
Please refer to Protocol for details of Expansion Part 2 and 3:

Study burden and risks

The study design aims to minimize potential risks to subjects participating in this study based on the protocol inclusion and exclusion criteria (Protocol Section 4.1.2 and Section 4.1.3), safety monitoring (including review of all safety, PK, and pharmacodynamics data by the dose escalation committee (DEC),

Toxicity Management Guidelines (TMGs; Protocol Section 3.1.7), starting dose selection (Protocol section 3.2.1), dose-escalation scheme (Protocol Section 3.1.2), and stopping criteria (Protocol Section 4.1.8). Specific intensive safety monitoring is in place (Protocol Section 4.2.2) for those risks deemed to be most likely based on MEDI5752 toxicology studies (imAEs, ICD, CRS, infusion reactions, and pneumonitis).

There remains a significant unmet need for additional treatment options for patients with recurrent or metastatic solid tumors.

Based upon the available nonclinical data, the clinical safety data from checkpoint inhibitors durvalumab and tremelimumab, and the strength of the scientific hypothesis under evaluation, MEDI5752 is proposed for evaluation in patient populations with limited life expectancy due to metastatic malignant disease and limited survival benefit provided by currently available treatment options.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

General criteria applicable to the entire population enrolled in the study: 1 Age >= 18 years at the time of screening 2 World Health Organization/Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at enrollment 3 Life expectancy >= 12 weeks 4 Histologically- or cytologically-confirmed advanced solid tumors 5 Body weight (WT) > 35 kg 6 Subjects who have received prior anti-PD-1, anti-PD-L1, or anti-CTLA-4 therapy or any prior chemotherapy, investigational, biologic, or hormonal therapy for cancer treatment may be eligible to enter the study (see inclusion criterion #20 [RCC-C1] and #28 [RCC-C2] for requirements for RCC expansion cohorts and #25 for requirements for NSCLC expansion cohorts) [NSCLC-C1 and NSCLC-C2]) following a washout period of these treatments of at least 21 days before the first dose; 7 day washout period is required for palliative radiotherapy (exception: 14-day washout period for central nervous system [CNS] metastases) and washout period of 5 half-lives is required for TKIs before the first dose; 7 Females of childbearing potential who are sexually active with a nonsterilized male partner must use at least one highly effective method of contraception (See Table 27 in the protocol for recommended methods of contraception) from screening and must agree to continue using such precautions for the specified number of days after the final dose of investigational product: (a) MEDI5752: 90 days (b) Carboplatin: 90 days (c) Pemetrexed: 180 days (d) Pembrolizumab: 120 days (e) Paclitaxel: 6 months (ie, 180 days) (f) Nab-paclitaxel: 6 months (ie, 180 days) See protocol for definition of Females of childbearing potential definition. 8 Nonsterilized males who are sexually active with a female partner of childbearing potential must use a male condom with spermicide where locally available from Day 1 and for 90 days after the final dose of investigational product. Males receiving pemetrexed, carboplatin, paclitaxel, or nab-paclitaxel treatment must use contraception during study treatment and up to 6 months thereafter. Male subjects should refrain from sperm donation throughout this period. It is strongly recommended that the female partner of childbearing potential to use at least one highly effective method of contraception (see protocol). Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. 9 Subjects must have at least one measurable lesion according to RECIST v1.1. A previously irradiated lesion can be considered a target lesion if the lesion is progressing and well defined, accurately measured at baseline as being >= 10 mm in the longest diameter (except lymph nodes, which must have a short axis >= 15 mm) with CT or magnetic resonance imaging (MRI), and that is suitable for accurate repeated measurements as per RECIST v1.1 guidelines. Subjects must consent to providing the prior CT scan or MRI before enrolling in the study. Radiographic disease assessment at baseline can be performed up to 28 days prior to the first dose

of investigational product. For subjects who undergo biopsies on study, the biopsied lesion must be distinct from any lesion used in the RECIST evaluation. 10 Adequate organ and marrow function (subjects must not have received transfusions or growth factor support within 28 days prior to first dose of investigational product) as defined below: (a) Hemoglobin >= 9.0 g/dL (b) Absolute neutrophil count (ANC) >= 1,500 mm3 (c) Platelet count >= 100,000/mm3 (d) TBL <= 1.5 × ULN; for subjects with documented/suspected Gilbert's disease, bilirubin <= 3 × ULN (e) AST and ALT <= 2.5 × ULN (AST/ALT can be up to 5 × ULN in the presence of liver metastasis or HCC, but cannot be associated with elevated bilirubin) (f) GFR calculated creatinine clearance >= 45 mL/min (g) Left ventricular ejection fraction >= 50% as assessed by echocardiography (not required for randomized subjects in the NSCLC expansion cohort) (h) Troponin I or T <= ULN (per institutional guidelines) 11 Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the US and EU Data Privacy Directive) obtained from the subject/legal representative prior to performing any protocol-related procedures including screening evaluations. NOTE: If evaluations performed for other purposes prior to obtaining informed consent are considered standard of care, are suitable for screening, eg scans obtained within 28 days prior to starting treatment, those evaluations do not need to be repeated if the subject consents to their use. See protocol section 4.1.2. for more Inclusion Criteria applicable for the subjects enrolled in: • the dose-escalation part only; • the pharmacodynamic cohorts and the maximum tolerated dose (MTD)/ the optimal biological dose (OBD)-cohort in the dose-escalation part only; • the RCC expansion part (renal cell cancer) only; • the nonsquamous NSCLC expansion part (non-small cell lung cancer) only.

Exclusion criteria

1 Involvement in the planning and/or conduct of the study (applies to both MedImmune staff and/or staff at the study site) 2 Concurrent enrollment in another clinical study, unless it is an observational (noninterventional) clinical study or the follow-up period of an interventional study 3 Any prior Grade >= 3 imAE while receiving immunotherapy or any unresolved imAE > Grade 1 4 For subjects who have received prior anti-PD-1, anti-PD-L1, or anti-CTLA-4: (a) Subjects must not have received anti-PD-1, anti-PD-L1, anti-CTLA-4 or any other immunotherapy or IO agent within 21 days of commencing treatment with investigational product. (b) Subject must not have experienced a toxicity that led to permanent discontinuation of prior immunotherapy. (c) All AEs while receiving prior immunotherapy must have completely resolved or resolved to Grade 1 prior to screening for this study. NOTE: Subjects with an endocrine AE of <= Grade 2 are permitted to enroll if they are stably maintained on appropriate endocrine replacement therapy and are asymptomatic. (d) Subject must not have experienced a >= Grade 3 imAE or an immune-related neurologic or ocular AE of any grade while receiving prior immunotherapy. NOTE: Subjects with

endocrine AE of <= Grade 2 are permitted to enroll if they are stable on appropriate replacement therapy and are asymptomatic. (e) Subject must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE, must not have experienced recurrence of an AE if rechallenged, and must not currently require maintenance doses of > 12 mg prednisone or equivalent per day. 5 Any concurrent chemotherapy, radiotherapy, investigational, biologic, or hormonal therapy for cancer treatment (see Inclusion Criterion 6 for washout periods [Section 4.1.2]). Concurrent use of hormonal therapy for noncancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable. NOTE: Local treatment of isolated lesions for palliative intent is acceptable (eg, metastasis treated by local surgery or radiotherapy) 6 Current or prior use of immunosuppressive medication within 14 days before the first dose of investigational product is excluded. The following are exceptions to this criterion: (a) Intranasal, inhaled, topical steroids, or local steroid injections (eg, intraarticular injection) (b) Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication) or a single dose for palliative purpose (eg, pain control) 7 Receipt of live attenuated vaccine within 30 days prior to the first dose of investigational product. Note: Subjects, if enrolled, should not receive live vaccine while receiving investigational product and up to 30 days after the last dose of investigational product. 8 Active or prior documented autoimmune or inflammatory disorders including inflammatory bowel disease (eg, colitis or Crohn's disease), diverticulitis (with the exception of diverticulosis), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, pneumonitis (past medical history of ILD, drug induced ILD. Radiation pneumotitis requiring steroid treatment or any evidence of clinically active ILD),etc). The following are exceptions to this criterion: (a) Subjects with vitiligo or alopecia (b) Subjects with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement (c) Any chronic skin condition that does not require systemic therapy (d) Subjects without active disease in the last 5 years may be included but only after consultation with the Medical Monitor (e) Subjects with celiac disease controlled by diet alone 9 Evidence of the following infections: (a) Active infection including tuberculosis (TB) (clinical evaluation that includes clinical history, physical examination, and radiographic findings and TB testing in line with local practice), (b) or human immunodeficiency virus (HIV) (positive for HIV-1 or HIV-2 antibodies), (c) or chronic or active hepatitis B (subjects with positive hepatitis B surface antigen [HBsAg] or isolated positive hepatitis B core antibody [anti-HBc] with detectable hepatitis B virus (HBV) DNA; refer to Section 4.3.5 and Figure 5 for screening tests), chronic or active hepatitis C, (refer to Section 4.3.5 for screening tests) (d) or active hepatitis A (refer to Section 4.3.5 for screening tests). 10 History of organ transplant 11 Known allergy allergy or hypersensitivity to investigational product(s), or any excipients of the investigational product(s).or reaction to any component of the MEDI5752, or pembrolizumab, carboplatin, and pemetrexed (in the case of inclusion in the NSCLC expansion cohort). 12 Untreated or progressive CNS

metastatic disease, any leptomeningeal disease, or cord compression. Note: Subjects previously treated for CNS metastases who are asymptomatic, clinically stable, and who do not require corticosteroids (at doses > 12 mg of prednisone or equivalent) for at least 14 days prior to the first dose of investigational product are not excluded. 13 History of another primary malignancy except for (a) Malignancy treated with curative intent and with no known active disease >= 2 years before the first dose of investigational product and of low potential risk for recurrence (b) Adequately treated nonmelanoma skin cancer or lentigo maligna without evidence of disease (c) Adequately treated carcinoma in situ without evidence of disease (d) Cancer subjects with incidental histologic findings of prostate cancer that, in the opinion of the investigator, is not deemed to require active therapy (eg, incidental prostate cancer identified following cystoprostatectomy that is tumor/node/metastasis stage <= pT2N0) may be enrolled, pending discussion and approval by the Medical Monitor. 14 Unresolved toxicities from prior anticancer therapy, defined as having not resolved to NCI CTCAE v4.03 Grade 0 or 1, or to levels dictated in the inclusion/exclusion criteria with the exception of alopecia. Subjects with irreversible toxicity not reasonably expected to be exacerbated by MEDI5752, pembrolizumab, carboplatin, or pemetrexed may be included (eg, hearing loss) after consultation with the Medical Monitor. 15 Major surgical procedure (as defined by the investigator) within 28 days prior to the first dose of investigational product or still recovering from prior surgery. Note: Local surgery of isolated lesions for palliative intent is acceptable. 16 Female subjects who are pregnant or breastfeeding, as well as male or female subjects of reproductive potential who are not willing to employ one highly effective method of birth control as defined in the protocol. 17 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, cardiomyopathy of any etiology, symptomatic congestive heart failure (as defined by New York Heart Association class > 2), uncontrolled hypertension, unstable angina pectoris, history of myocardial infarction within the past 12 months, cardiac arrhythmia, (ILD), serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the subject to give written informed consent. 18 Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of the subject*s safety or study results 19 Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug. 20 Judgment by the investigator that the subject is unsuitable to participate in the study and the subject is unlikely to comply with study pr

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-03-2022
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Armisarte (Alimta)
Generic name:	pemetrexed
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	KEYTRUDA
Generic name:	pembrolizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	MEDI5752
Generic name:	MEDI5752

Ethics review

Approved WMO Date:	10-02-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	08-07-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	24-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-09-2021

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-11-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-04-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	27-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-11-2023

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-11-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-03-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-04-2024
Application type:	Amendment
Review commission:	METC NedMec

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
EU-CTR	CTIS2023-509605-77-00
EudraCT	EUCTR2018-003075-35-NL
ClinicalTrials.gov	NCT03530397
CCMO	NL72486.031.20