A Phase Ib Open-Label, Dose-Finding Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Avelumab in Combination with M9241 (NHS-IL12) in Subjects with Locally Advanced, Unresectable, or Metastatic Solid Tumors

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The purpose of this study is to evaluate the safety and preliminary efficacy of avelumab in combination with M9241in subjects with metastatic or locally advanced unresectable solid tumors. This dose escalation study will establish a safe dose of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON48631

Source
ToetsingOnline

Brief title
MS201781-0031

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Cancer, solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Merck KGaA
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Avelumab, M9241 (NHS-IL12), Phase Ib, Solid Tumors

Outcome measures

Primary outcome

Primary endpoints:

* Confirmed best overall response (BOR) by Investigator assessment according to

RECIST v1.1 by selected tumor type

* Occurrence, severity, and duration of TEAEs and TRAEs, graded according to

the NCI CTCAE v4.03.

Secondary outcome

Secondary endpoints:

* Progression-free survival (PFS) time

* Overall survival (OS) time

* Duration of response (DOR)

* PK profiles of avelumab and M9241

* Immunogenicity of avelumab and immunogenicity of M9241 in combination

therapy, as measured by ADA assays.

Exploratory endpoints:

* irBOR using the irRECIST

* immune-related PFS (irPFS) using the irRECIST

* Change from baseline of PRO disease-related symptoms and physical functioning

concepts from the European Organisation for Research and Treatment of Cancer

(EORTC) item bank.

Study description

Background summary

Based on the complementary and potentially synergistic mechanisms of M9241 and avelumab, the combination was explored preclinical models. When IL-12 was combined with avelumab, there was a significant increase in antibody-dependent cell-mediated cytotoxicity (ADCC) lysis in most cell lines, including lung and colorectal carcinoma. It was concluded that the increased lysis in these cases was due to increased NK-cell activity, not to increased avelumab-mediated ADCC. Preclinical data from an in vivo study showed that the combination of NHS-muIL12 and avelumab elevated the percentage of TBET+ NK cells and CD8+ T cells, synergistically stimulated the differentiation of central memory T cells and effector memory T cells, significantly increased IFN * generation (but not IDO activation), and dramatically enhanced the necrotic fraction and CD8+ T-cell infiltration in EMT6 tumors.
In the EMT6 breast cancer model, combination treatment with avelumab and NHS-muIL12 generated an additive antitumor effect and significantly improved survival. Furthermore, cured mice were protected from tumor rechallenge.
In other experiments, NHS-muIL12 (2.0 *g) showed combination activity in the MC38 colon tumor model by decreasing tumor volume over time and significantly improved survival. Avelumab (200 *g) and NHS-muIL12 (2.0 *g) combination treatment generated an additive antitumor effect in MB49 bladder cancer.
These data provide evidence that an IL-12-based therapeutic agent such as M9241 can be combined with avelumab to enhance antitumor responses via T cell and NK cell-mediated killing, including ADCC.

Study objective

The purpose of this study is to evaluate the safety and preliminary efficacy of avelumab in combination with M9241in subjects with metastatic or locally advanced unresectable solid tumors. This dose escalation study will establish a safe dose of M9241 to be given in combination with avelumab. After determination of the RP2D, enrollment in 4 expansion cohorts will be opened to assess the safety and preliminary estimate of clinical activity for the combination regimen in selected tumor types (Urothelial carcinoma, Non-small cell lung cancer (not in the Netherlands), Renal cell carcinoma, Colorectal cancer). This Phase I clinical study is being proposed as part of a regular

development program to design rational combination therapy with avelumab, in order to achieve clinical benefit with immunotherapy in a greater proportion of subjects. Objectives for this expansion part:

Primary
* To evaluate the confirmed best overall response (BOR) as assessed by the Investigator according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) of avelumab in combination with M9241 at the recommended Phase II dose (RP2D) in selected tumor types
* To evaluate the safety and tolerability of combination therapy with avelumab and NHS IL12 at the RP2D.

Secondary:
* To characterize PK profiles of avelumab and M9241 when given in combination at the M9241 RP2D
* To evaluate the immunogenicity of combination therapy with avelumab and NHS IL12
* To evaluate antitumor activity of combination therapy with avelumab and NHS IL12 in selected solid tumor types.

Exploratory objectives:
* To describe immunologic effects of combination therapy with avelumab and M9241
* To evaluate association of immune endpoints and other biomarkers with clinical outcomes
* To evaluate the relationship of cytokine changes to treatment related adverse events (TRAE) and clinical outcomes.
* To assess symptom severity via patient-reported outcome (PRO) measures.

Study design

This is a Phase Ib open label, dose finding study with a planned consecutive expansion in selected solid tumor types (Urothelial carcinoma, Non-small cell lung cancer, Renal cell carcinoma, Colorectal cancer).

Intervention

-M9241 as a subcutaneous injection (16.8ug/kg), once every 4 weeks.
-Intravenous infusion of avelumab at a dose of 800mg, once every week for first 12 weeks (3 cycles), then once every two weeks.

Study burden and risks

Subjects have to attend visits in which the drugs are administered (subcutanious and intravenous) and a variety of tests will be done to check their health. These include vital signs, height, weight, ECGs, blood and urine

samples, imaging by CT or MRI, patient questionnaires and ECOG performance status. A tumor biposy will be done for the kidney cancer and colon cohort and possibly for the NSCLC and bladder cancer cohort (if not available / optional during treatment). Subjects must use a birth control method.

Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions have been identified as important risks for avelumab (in addition to general side effects). Subjects are at risk of developing drug hypersensitivity reactions due to M9241, mainly mild to moderate, but which may also be life-threatening.
Cytokine release has been observed with NHS IL12, which needs further investigation and evaluation.
Adverse effects reported from clinical studies with IL 12-based therapies include: flu like symptoms, fever, injection site reactions, myalgia and arthralgia, fatigue, stomatitis, anorexia, hepatic toxicity with increased transaminases, neutropenia, lymphocytopenia, thrombocytopenia, anemia, dyspnea, vascular leak syndrome, gastrointestinal hemorrhage, and sepsis-like syndrome.
Combination therapy with M9241 may enhance the effectiveness of avelumab in sensitive tumors, may rescue anti-PD-L1 refractory tumors, or may make primary anti-PD-L1 unresponsive tumor types susceptible to checkpoint inhibition by inducing local inflammation and immunogenicity (ie, M9241 may be used as an immune sensitizer/primer).
In general there are risks associated with the study procedures (Blood draws, Tumor biopsy, CT scans, bone scans, and MRI scans, 12-lead ECG) in addition to potential harm to the unborn child.

The risk-benefit relationship has been carefully considered in the planning of the study. Based on the pre-clinical and clinical data available to date, the conduct of the study is considered justifiable using the dose and dosage regimen of avelumab as specified in this clinical study protocol. An SMC is planned for the ongoing assessment of the risk-benefit ratio. The study shall be discontinued in the event of any new findings that indicate a relevant deterioration of the risk benefit relationship and would render continuation of the study unjustifiable.

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

UrothelialSigned written informed consent
2. Male or female subjects age * 18 years
3. Subjects must have one of the following tumor specific indications:
-a. Locally advanced or metastatic urothelial carcinoma (UC) post-that has progressed during or after at least one platinum:-based chemotherapy and not previously been treated with anti-PD-1/PD-L1 agents (PD-x naïve):
Histologically or cytologically confirmeddocumented locally advanced or metastatic transitional cell carcinoma of the urothelium (including renal pelvis, ureters, urinary bladder, and urethra). Subjects must have progressed during or after treatment with at least 1 platinum -containing regimen (eg, platinum plus another agent such as gemcitabine, methotrexate, vinblastine, doxorubicin, etc) for inoperable locally advanced or metastatic UC or disease recurrence. Availability of either tumor archival material or fresh biopsiesSubjects who received prior adjuvant/neoadjuvant chemotherapy and progressed within 28 days is acceptable12 months of treatment with one of these being mandatory. For FFPE samples, either block or sections (> 15) maya platinum-containing regimen will be provided. Tumor biopsies and tumor archival material must be suitable for biomarker assessment.considered as second line.
Subjects with mixed histologies are required to
have a dominant transitional cell pattern
b. Non-small cell lung cancer, first-line metastatic: Histologically proven Stage IV (per seventh International Association for the Study of Lung Cancer

classification) NSCLC.
Subjects must not have received treatment for their metastatic disease.
Subjects could have received adjuvant chemotherapy or loco-regional treatment that included chemotherapy for locally advanced disease, as long as disease recurrence occurred at least 6 months after the completion of the last administration of chemotherapy. Only epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) wild-type are allowed (ie, EGFR mutation and ALK translocation / rearrangement excluded). Non squamous cell histologies and never / former light smoker (< 15 pack years) squamous cell carcinoma subjects (per local standard of care) require testing if status is unknown.
Subjects must have low tumor PD-L1 expression defined as < 50% tumor proportion score determined using PD-L1 IHC 22C3 pharmDx test or an equivalent FDA-approved PD-L1 test. This cohort will not be opened for enrollment in Belgium, Czech Republic, France, Germany,
Hungary, Italy,
Netherlands, Spain, and United Kingdom
c. Colorectal cancer, second line or later: Histologically or cytologically confirmed recurrent or refractory metastatic CRC (according to American Joint Committee on Cancer / International Union Against Cancer Tumor Node Metastasis [TNM] Staging System seventh edition) after failure of prior therapy containing oxaliplatin / fluoropyrimidine and / or irinotecan / fluoropyrimidine and, if eligible, cetuximab (Erbitux®) and bevacizumab (Avastin®). Only subjects with MSI-low or MSS metastatic CRC are eligible.
Subjects without existing MSI test results will have MSI status
- performed locally by a CLIA-certified IHC or PCR-based test (PCRbasedPCR-based MSI test is preferred). Subjects must be willing to undergo an ontreatment biopsy procedure. For Belgium, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Spain, and United Kingdom, subjects in the second -line setting should have exhausted or be considered ineligible or intolerant (in the opinion of the Investigator) of available second -line chemotherapy options.

Exclusion criteria

1. Concurrent treatment with a non-permitted drug/intervention (listed below)
a. Anticancer treatment (eg, cytoreductive therapy, radiotherapy, immune therapy, cytokine therapy, monoclonal antibody, targeted small molecule therapy) or any investigational drug within 4 weeks or 5 half-lives, whichever is shorter, prior to start of study treatment, or not recovered from adverse events (AE) related to such therapies, with the following exceptions:
i. Palliative radiotherapy delivered in a normal organ-sparing technique is permitted (concurrently or within pretreatment period).
ii. Erythropoietin, darbepoetin-*, and granulocyte colony-stimulating factor are permitted.
iii. Hormonal therapies acting on the hypothalamic pituitary gonadal axis are

permitted (ie, luteinizing hormone releasing hormone agonist/antagonists). No other hormonal anticancer therapy is permitted.
b. Major surgery (as deemed by Investigator) for any reason (except diagnostic biopsy) within 4 weeks prior to start of study treatment, or not fully recovered from surgery within 4 weeks prior to start of study treatment
c. Subjects receiving immunosuppressive agents (such as steroids) for any reason should be tapered off these drugs before start of study treatment, with the following exceptions:
i. Subjects with adrenal insufficiency, may continue corticosteroids at physiologic replacement dose, equivalent to * 10 mg prednisone daily.
ii. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intra-ocular, or inhalation) is permitted.
iii. Previous or ongoing administration of systemic steroids for the management of an acute allergic phenomenon is acceptable as long as it is anticipated that the administration of steroids will be completed in 14 days, or that the dose after 14 days will be equivalent to * 10 mg prednisone daily.
2. Any prior treatment with any form of IL-12
3. For the NSCLC, CRC, and UC expansion cohorts, prior therapy with any antibody / drug targeting T cell co regulatory proteins (immune checkpoints) such as anti-PD-1, anti PD L1, or anticytotoxic T lymphocyte antigen-4 (CTLA 4) antibody is prohibited
4. Intolerance to checkpoint inhibitor therapy, as defined by the occurrence of an AE requiring drug discontinuation.
5. Active or history of primary or metastatic central nervous system tumors
6. Prior organ transplantation, including allogeneic stem cell transplantation
7. Previous malignant disease (other than the indication for this study) within the last 5 years (except adequately treated nonmelanoma skin cancers, carcinoma in situ of skin, bladder, cervix, colon/rectum, breast, or prostate) unless a complete remission without further recurrence was achieved at least 2 years prior to study entry and the subject was deemed to have been cured with no additional therapy required or anticipated to be required.
8. Significant acute or chronic infections requiring systemic therapy including, among others:
a. History of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome
b. Hepatitis B or C infection (HBV surface antigen positive and HBV core antibody positive with reflex to positive HBV DNA or HBV core antibody positive alone with reflex to positive HBV DNA or positive hepatitis C virus [HCV] antibody with reflex to positive HCV RNA). Subjects with history of infection must have PCR documentation that infection is cleared
9. Active or history of autoimmune disease that might deteriorate when receiving an immuno stimulatory agent. Subjects with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible if they are stable on other medical treatment and do not fulfill exclusion criterion 15
10. Known severe hypersensitivity reactions to monoclonal antibodies (Grade * 3

NCI CTCAE v4.03), or uncontrolled asthma (ie, 3 or more features of partially controlled asthma)
11. History of allergic reaction to methotrexate (trace methotrexate may be present in NHS IL12 as a part of the manufacturing process) or history of severe hypersensitivity reaction to any other ingredient of the study drug(s) and / or their excipients. Since NHS IL12 contains sucrose as an excipient, subjects suffering from hereditary fructose intolerance are also excluded
12. Persisting toxicity related to prior therapy of Grade > 1 NCI-CTCAE v4.03 with the following exceptions:
a. Neuropathy Grade * 2 is acceptable.
b. All grades of alopecia are acceptable.
c. Endocrine dysfunction on replacement therapy is acceptable.
13. Pregnancy or lactation
14. Known alcohol or drug abuse as deemed by the Investigator
15. Uncontrolled intercurrent illness including, but not limited to:
a. Hypertension uncontrolled by standard therapies (not stabilized to 150/90 mmHg or lower)
b. Uncontrolled active infection
c. Uncontrolled diabetes (eg, glycosylated hemoglobin * 8%)
16. Clinically significant (or active) cardiovascular disease: cerebral vascular accident / stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (New York Heart Association Classification Class * II), or serious cardiac arrhythmia requiring medication
17. All other significant diseases (eg, inflammatory bowel disease, current severe acute or chronic colitis) or chronic medical conditions (including laboratory abnormalities) that in the opinion of the Investigator might impair the subject*s tolerance of study treatment or interpretation of study results.
18. Any psychiatric condition that would prohibit the understanding or rendering of informed consent or that would limit compliance with study requirements
19. Legal incapacity or limited legal capacity
20. Administration of a live vaccine within 30 days prior to study entry
21. Any subject with possible area of ongoing necrosis (non-disease related), such as active ulcer, non-healing wound, or intercurrent bone fracture that may be at risk of delayed healing due to protocol therapy
22. Oxygen saturation < 90% at rest, known pulmonary fibrosis, or active interstitial lung disease
23. History of congenital or active immunodeficiency, with the exception of acquired treatment-related hypogammaglobulinemia requiring periodic IV immunoglobulin infusion.

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):	11-10-2018
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bavencio
Generic name:	Avelumab
Product type:	Medicine
Brand name:	NHS-IL12
Generic name:	NHS-IL12

Ethics review

Approved WMO Date:	24-01-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-10-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-03-2019

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-04-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-04-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-07-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	22-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2017-002212-13-NL
ClinicalTrials.gov	NCT02994953
CCMO	NL63448.056.18

Study results

Results posted: 27-01-2022

Summary results
Trial ended prematurely

First publication
30-04-2021