A Phase 1/2a Study of BMS-986178 Administered Alone or in Combination with Nivolumab and/or Ipilimumab in Subjects with Advanced Solid Tumors

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The primary objective is to determine the safety, tolerability, dose-limiting toxicities (DLTs), and maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab in...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON47099

Source
ToetsingOnline

Brief title
CA012-004 phase 1/2a of BMS-986178alone and with Nivolumab and Ipilimumab

Condition

- Other condition

Synonym
advanced solid tumors, cancer

Health condition

During the Dose Escalation phase the following tumor histologies permitted except primary CNS tumors; Melanoma, NSCLC, Head and neck, Transitional cell carcinoma of the

genitourinary tract, Renal cell carcinoma, Pancreatic adenocarcinoma, Colorectal cancer, Cervical cancer, Triple negative breast cancer, Adenocarcinoma of the endometrium, Ovarian cancer, Prostate adenocarcinoma, Hepatocellular cancer-Child Pugh A only, Small cell lung cancer, Gastric and gastric esophageal junction cancer. Dose Expansion, Safety cohort and schedule and dose exploration:Melanoma, NSCLC, Head and neck cancer, Transitional cell carcinoma of the genitourinary tract, Renal cell carcinoma, Pancreatic adenocarcinoma, CRC, Cervical cancer, Triple negative breast cancer, Adenocarcinoma of the endometrium, Ovarian cancer, Prostate adenocarcinoma, Hepatocellular cancer, Small cell lung cancer, Gastric and gastric esophageal junction cancer, Bladder cancer and Thyroid cancer.

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: pharmaceutical industry

Intervention

Keyword: BMS-986178, Ipilimumab, Nivolumab, Solid Tumour

Outcome measures

Primary outcome

Safety:

The primary endpoint of this Phase I / IIa study's safety as measured using extensive medical assessment of adverse events (AEs), vital signs (blood pressure etc), ECGs, physical examination, and clinical significant laboratory abnormalities. Side effects are continuously monitored during the investigation and 100 days after the last treatment. Reported side effects will be further analysed significance and clinical importance.

Secondary outcome

Efficacy:

Anti-tumour activity is monitored by means of CT / MRI during screening and every 8 weeks until disease progression. When disease progression occurs, there

is no need more scans to be performed unless there are by treated (by treatment after disease progression). In this case, every 12 weeks, scans are carried out to there again stops until disease progression or the treatment. Consideration will be given to overall survival, duration of response and progression-free survival at 24 weeks.

pharmacokinetics:

Selected PK parameters such as Cmax, Tmax, AUC () - t), AUC (TAU) will be determined in two cycles depending on the scheduling of mono- or combination therapy. Parameters such as Ctau, CLT, Css-avg, accumulation index (AI), and effective elimination half-life (THALFeff) will be assessed in the second cycle when intensive PK are collected. A separate listing, summary, and plot will be generated for Ctrough.

immunogenicity:

This consists of collection of serum samples to the development of specific antibodies (ADA's) in response to research tool (s) to evaluate BMS-986 178 and nivolumab or ipilimumab. Blood samples will be collected at several intervals.

Exploratory biomarkers:

Overall survival rate will be determined at a fixed time and the number of patients who are still alive at that time.

Overall survival is defined as the time between the first dose and date of death from any cause.

Analyses of biomarkers of samples obtained at baseline and during treatment from peripheral blood, serum and tumour biopsy to study markers of pharmacodynamics. Additional research is to investigate the hypothesis related to mechanisms, biomarkers for safety and biomarkers that predict what the response will be to treatment with BMS-986 178 as monotherapy or in combination with nivolumab and/ or ipilimumab.

Study description

Background summary

Immunotherapy for cancer has become established in recent years and is now one of the most successful and important strategies for treating patients with haematological malignancies and solid tumours.

The most extensively studied immunotherapies in cancer are the negative regulatory receptors, CTLA-4, and PD-1. Following the success of CTLA-4 and anti-PD-1 pathway-targeted agents in several cancers, the field of tumour immunotherapy is rapidly expanding. In addition to blocking co-inhibitory pathways, activating co-stimulatory pathways to potentiate anti-tumour immune responses is being considered as a promising approach. Members of the tumour necrosis factor receptor super family (TNFRsf) include several co-stimulatory proteins with key roles in B- and T-cell development, survival, immune activation, and anti-tumour immune responses. Preclinical data have provided the basis for the trial of agonist antibodies to TNFRsf co-stimulatory receptors as potential therapies for patients with cancer. Overall, enhancement of the magnitude and potency of tumour antigen-specific adaptive cellular responses by CD8 and CD4 T-cells is now considered a major goal in cancer immunotherapy.

With these recent emerging clinical lines of evidence of significant activity of single-agent immunotherapies, combination therapies could potentially lead to greater depth of response and OS, as has been noted with the combination of anti-PD-1 and anti-CTLA-4 in advanced melanoma patients.

BMS-986178 is an anti-OX40 agonist mAb under exploration as a treatment for advanced malignancies. Nivolumab is an anti-programmed cell death-1 (PD-1) monoclonal antibody (mAb) approved for the treatment of metastatic melanoma, non-small cell lung cancer (NSCLC), and advanced renal cell carcinoma (RCC) in

multiple countries, and Ipilimumab is an anti-cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) mAb approved for the treatment of metastatic melanoma in multiple countries.

The proposed clinical study, CA012004, is a Phase 1/2a dose escalation and dose expansion study of BMS-986178 in monotherapy and in combination with nivolumab or/and ipilimumab in patients with advanced solid tumours. It is the first study of BMS-986178 in humans. This study will evaluate the safety profile, tolerability, preliminary efficacy, PK, and PD of intravenous (IV) doses of BMS-986178 administered as monotherapy and in combination with nivolumab or/and ipilimumab in patients with advanced solid tumours. This study will also determine the maximum tolerated dose (MTD) and RP2D of BMS-986178 to be used in future monotherapy and in combination with nivolumab or/and ipilimumab.

Study objective

The primary objective is to determine the safety, tolerability, dose-limiting toxicities (DLTs), and maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab in patients with advanced solid tumours.

The secondary objectives are;
• To investigate the preliminary anti-tumour activity of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab in patients with advanced solid tumours
• To characterise the pharmacokinetics (PK) of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab
• To characterise the immunogenicity of BMS-986178 administered alone or in combination with nivolumab and/or ipilimumab and the immunogenicity of nivolumab or ipilimumab administered with BMS-986178

The exploratory objectives are:
• To explore potential associations between anti-tumor activity and select biomarker measures in tumor biopsy specimens and peripheral blood prior to treatment and following administration of BMS-986178 alone or in combination with nivolumab and/or ipilimumab
• To assess the potential effect of BMS-986178 monotherapy and combination therapy on QTc interval
• To characterize nivolumab PK in subjects receiving the combination of nivolumab and BMS-986178 or the combination of nivolumab, ipilimumab, and BMS-986178
• To characterize ipilimumab PK in subjects receiving the combination of ipilimumab and BMS-986178 or the combination of nivolumab, ipilimumab, and BMS-986178
• To assess the overall survival (OS) in subjects treated with BMS-986178 alone andor in combination with nivolumab and/or ipilimumab

Study design

This is a Phase I / IIa, open-label study of BMS-986 178 administered as monotherapy or in combination with ipilimumab or/and nivolumab in patients with advanced solid tumours.

The research is conducted in 4 parts. Part 1 (dose escalation) has 3 groups, Part 2 (dose expansion) has 4 groups, Part 3 (schedule and dose exploration) has 2 groups and Part 4 (safety cohort) has 2 groups.

Part 1 is the escalation phase and represents the phase I of this study. It has 3 treatment groups (Group A, B and C).

In group A, patients have received increasingly higher doses treated with monotherapy BMS-986 178. The clinical data that come from the first 3 dosage levels, have formed the basis for the dose of BMS-986178 which was administered in combination with nivolumab and was given in increasingly higher doses in patients in Group B. Subsequently, the clinical data composed of both group A and group B formed the basis for the pre-dose of BMS-986178 which was administered in combination with ipilimumab also in increasingly higher doses in patients in group C. Phase 1 is now complete.

The expansion dose (Part 2), the schedule and dose exploration cohort (Part 3) and the safety cohort (Part 4) represent the phase IIa of this study.

After Part 1 established the maximum tolerated dose and recommended dose for Part 2, this dose will be launched in a select group of tumours. This selected group of tumour types consists of cervix, colorectal, bladder, ovarian, renal cell, non small cell lung cancer, and other signal seeking cancers. Patients with colorectal, bladder, cervical or other signal seeking tumours will be treated with BMS-986 178 + nivolumab. Patients with ovarian cancer or other signal seeking tumours will be treated with BMS-986 178 + ipilimumab. Patients with renal cell cancer or with non-small cell lung cancer will be treated with BMS-986178 in combination with Nivolumab and Ipilimumab.

In the schedule and dose exploration (Part 3), patients with cervix, colorectal, bladder, cancer or other signal seeking tumours, will receive Nivolumab in combination BMS-986178. Patients with ovarian cancer or other signal seeking tumours will be treated with ipilimumab in combination BMS-986178. The tested doses of Nivolumab and ipilimumab will be higher than the ones tested in the dose escalation and the dose expansion parts. The tested dose of BMS-986178 will be a dose that has been found to safe in Part 1.

In the safety cohort (Part 4), patients with renal cell cancer or non-small cell lung cancer will be treated with BMS986-178 in combination with Ipilimumab and Nivolumab.

Intervention

Group A, every two weeks, 24 weeks
Dose Level 1: 20 mg
Dose Level 2: 40 mg
Dose Level 3: 80 mg
Dose Level 4: 160 mg
Dose Level 5: 320 mg

Group B, every 2 weeks, 24 weeks. 3 dosage level BMS-986178 is based on the results of the first three dose level BMS-986178 from group A.
Test patients in this group will also, every two weeks, are treated with 240 mg (intravenously) Nivolumab.

Group C, every 3 weeks, 24 weeks. 3 dosage level BMS-986178 is based on the results of the first three dose level BMS-986178 of group A and group B.
Test patients in this group will also, every three weeks, are treated with 1 mg / kg (intravenously) ipilimumab. A maximum of 4x ipilimumab is given, then is BMS-986178 administered as monotherapy to 24 weeks.

Patients in the expansion phase will be treated with the MTD, MAD, or an alternative dose of BMS-986178 in combination with nivolumab (groups 2B, 2C. 2D or 2E), with ipilimumab (groups 3B or 3C) or nivolumab with ipilimumab (groups 6B and 7B), as agreed with the sponsor and investigators. For Groups 2B-2E, Nivolumab will be administered in a fixed dose of 240 mg. For Groups 3B-3C, ipilimumab will be administered at a dose of 1 mg / kg.

Patients in Group 6B will receive 40 mg of BMS986-178 with 240 mg of nivolumab and ipilimumab at 1 mg/kg every 3 weeks for 4 cycles. They will then receive BMS-986178 (40 mg) and nivolumab (480 mg) every 4 weeks for 3 cycles, as a maintenance therapy. Patients in Group 7B will receive 40 mg of BMS-986178 will be administered at a flat dose of 40 mg and a flat dose of 240 mg of nivolumab every 2 weeks and ipilimumab , at 1 mg/kg; every 6 weeks for 4 cycles.

Patients in the safety cohort will receive the same treatment as patients in Groups 6B and 7B.

Patients in the schedule and dose exploration (Groups 4 and 5) will receive a dose BMS986-178 that has been shown to be safe in Group B in combination with 480 mg of nivolumab every 4 weeks.

Patients in the safety cohort (Groups 6A and 7A) will receive the same treatment as patents in Groups 6B and 7B.

The doses of ipilimumab and nivolumab cannot be adjusted. Courses and duration of treatment is the same in all groups so two-weekly for BMS-986 178 as

monotherapy or in combination with nivolumab, 3-week BMS-986 178 when combined with ipilimumab alone, or 4 weekly for Group 6B and 6-weekly for Group 7B.

Study burden and risks

Patients are expected in the research to repeatedly visit the hospital for physical examination, measurement of vital signs, routine blood test for assessing safety, pregnancy test (for women of childbearing potential) and control side effects. In addition, the tumours of the patients will be assessed every 8 weeks radiographically (with CT or MRI scan) until progression of the disease or if patients stop the treatments. Patients will have to undergo mandatory biopsies before and during treatment. On some visits blood will be drawn for scientific purposes (pharmacokinetics, pharmacodynamics, immunogenicity and biomarkers). The frequency of the visits, and the number of procedures that is run during this study, is generally more than with the standard treatment. Patients will be instructed to contact directly with the research / physician if they experience side effects. They also get a patient emergency card along with all the necessary study information (emergency number, etc.)

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Patients must have at least 1 standard treatment regimen in the advanced, recurrent or metastatic setting;• ECOG (Eastern Cooperative Oncology Group) 0-1;• Men and women 18 years old or older;• At least one measurable lesion at baseline by CT (computed tomography) or MRI (magnetic resonance imaging) as per RECIST (Response Evaluation Criteria In Solid Tumors) v1.1

Exclusion criteria

• Known central nervous system metastases or central nervous system as the only source of disease;• Concomitant malignancies;• Active known or suspected autoimmune disease;• Uncontrolled or significant cardiovascular disease;• Major surgery less than 4 weeks before the start of the study

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	06-06-2016
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	BMS-986178
Generic name:	BMS-986178
Product type:	Medicine
Brand name:	Ipilimumab
Generic name:	Yervoy
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Nivolumab
Generic name:	Opdivo
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tetanus
Generic name:	Tetanus
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	28-07-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-08-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	31-08-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	22-12-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	04-01-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	08-02-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-02-2017
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:	13-07-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-02-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-03-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van

	Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-06-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-06-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-10-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-10-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-07-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-07-2019
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	EUCTR2015-004816-39-NL
ClinicalTrials.gov	NCT02737475
CCMO	NL57826.031.16

Study results

Date completed: 01-01-2022

Results posted: 11-01-2022

First publication
01-01-1900