A Phase 1/2a Dose Escalation and Cohort Expansion Study for Safety, Tolerability, and Efficacy of BMS-986156 Administered Alone and in Combination with Nivolumab (BMS-936558, anti PD-1 Monoclonal Antibody) in Advanced Solid Tumors

Published: 04-04-2016
Last updated: 31-12-2024

Primary Objective:The primary objective is to determine the safety, tolerability, dose-limiting toxicities (DLTs), and MTD/MAD/alternate dose of BMS-986156 administered alone and in combination with nivolumab in subjects with advanced solid tumors....

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

Summary

ID

NL-OMON47516

Source
ToetsingOnline

Brief title
CA009-002 Phase I/IIa anti-GITR with or without Nivolumab

Condition

- Other condition

Synonym
advanced solid tumors, cancer

Health condition

all solid tumors, except primary CNS tumors, in escalation phase; NSCLC, cervical carcinoma, bladder cancer, squamous cell carcinoma head and neck, ovarian cancer and hepatocellular carcinoma in Expansion phase

Research involving
Human

Sponsors and support

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

Intervention

Keyword: anti-GITR, efficacy, safety, solid tumor

Outcome measures

Primary outcome

Safety Outcome Measures:

Safety assessments will be based on comprehensive medical review of adverse event reports, vital sign measurements, ECGs, physical examinations, and results of laboratory tests. Adverse events will be assessed continuously during the study and for 100 days after the last treatment. The incidence of observed adverse events will be tabulated and reviewed for potential significance and clinical importance.

Efficacy Measures:

Disease assessment with CT and/or MRI, as appropriate, will be performed at baseline and every 8 weeks until disease progression. Once disease progression is noted, no more protocol required tumor assessments are needed unless treatment is continued beyond progression. in this case, tumor assessments will

continue every 8 weeks until confirmed disease progression or study treatment is discontinued.

Secondary outcome

Pharmacokinetic Measures:

Serial serum samples will be collected from all subjects at specified time points to evaluate concentrations of BMS-986156. PK parameters such as Cmax, Ctrough, Tmax, T-HALF, AUC (TAU), CLT, and accumulation index (AI) will be derived, if feasible, from serum concentration versus time data. Sparse serum samples will be collected from subjects in Parts B and D to evaluate concentrations of nivolumab.

Immunogenicity Measures:

Serum samples to evaluate development of anti-drug antibody (ADA) response to BMS-986156 alone, and in combination with nivolumab will be collected at specified time points.

Biomarker Measures:

Biomarker analyses of baseline and on-treatment peripheral blood, serum, and tumor samples will be performed to identify pharmacodynamic markers associated with treatment. Additional analyses will be performed to test hypotheses related to mechanism of action, safety biomarkers and predictive markers of response to BMS-986156 alone and in combination with nivolumab.

Study description

Background summary

Patients with metastatic or refractory tumors have a very poor prognosis. Traditional or conventional treatment options for patients with advanced cancer include surgery, radiation, chemotherapy, hormone therapy and immunotherapy. Despite advances in multimodal therapy, increases in overall survival in this patient population have been limited.
Antibody-based therapy for cancer has become established in recent years and is now one of the most successful and important strategies for treating patients with hematological malignancies and solid tumors. An anti-cancer antigen-specific immune response is the result of a complex dynamic interplay between antigen-presenting cells, T lymphocyte cells and the target cancer cells. The critical balance of T-cell activity is largely understood to be controlled by antigen-specific stimuli sensed by the T-cell receptor and by the combined activity of both positive (co-stimulatory) and negative (co-inhibitory) T-cell surface molecules. In addition to blocking co-inhibitory pathways, activating co-stimulatory pathways to potentiate antitumor immune responses is being considered as a promising approach. Members of the tumor necrosis factor receptor super family (TNFRsf) include several co-stimulatory proteins with key roles in B and T cell development, survival, immune activation, and antitumor immune responses. Preclinical data have provided the basis for the trial of agonist antibodies to, amongst others, glucocorticoid-induced TNFR-related gene (GITR) as potential therapy for patients with cancer.
With recent emerging clinical lines of evidence of significant activity of single agent immunotherapies, it is possible that combination therapies could potentially lead to greater depth of response and overall survival. This raises the possibility that combining strategies involving a broader range of immunotherapies could potentially lead to durable, long term responses and possibly even cures in this high unmet medical need population of patients with metastatic or refractory tumors.

CA009002 is a Phase 1/2a ascending multiple-dose study of BMS-986156, an anti-GITR antibody, in humans with advanced/metastatic solid tumors as monotherapy and in combination with nivolumab. There are no previous data on BMS-986156 in humans. This study will evaluate the safety profile, tolerability, preliminary efficacy, PK, and PD of IV doses of BMS-986156 administered every 2 weeks as monotherapy and in combination with nivolumab in advanced solid tumors and is expected to determine the MTD/MAD or an alternate dose of BMS-986156 to be used in future monotherapy and combination with nivolumab therapy trials. In addition, the study will evaluate BMS-986156 as monotherapy and in combination with nivolumab in 2 disease-restricted populations, NSCLC and cervical cancer.

Study objective

Primary Objective:
The primary objective is to determine the safety, tolerability, dose-limiting toxicities (DLTs), and MTD/MAD/alternate dose of BMS-986156 administered alone and in combination with nivolumab in subjects with advanced solid tumors.

Secondary Objectives:
- To investigate the preliminary anti-tumor activity of BMS-986156 administered alone and in combination with nivolumab in subjects with advanced solid tumors
- To characterize the PK of BMS-986156 administered alone and in combination with nivolumab
- To characterize the immunogenicity of BMS-986156 administered alone and in combination with nivolumab, and the immunogenicity of nivolumab administered with BMS-986156.

Exploratory Objectives:
- To assess the PD effects of BMS-986156 as a function of exposure when administered alone or in combination with nivolumab by evaluation of select biomarkers in the peripheral blood and tumor biopsy specimens
- 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-986156 alone or in combination with nivolumab
- To assess the potential effect of BMS-986156 monotherapy on QTc interval in Part A
- To characterize nivolumab PK in subjects receiving the combination of nivolumab and BMS-986156
- To assess the overall survival in subjects treated with BMS-986156 alone and in combination with nivolumab.
- To characterize DLT profile of BMS-986156 alone or in combination with nivolumab
Per revised protocol nr 5 the overall survival in subjects treated with BMS-986156 alone and in combination with nivolumab will be no longer assessed.

Study design

This is a Phase 1/2a, open-label study of BMS-986156 administered as a single agent and in combination with nivolumab in subjects with advanced solid tumors.

The study will be conducted in 4 parts.
-Parts A and B will consist of dose escalation with BMS-986156 administered as a single agent (Part A) or in combination with nivolumab (Part B) in subjects with advanced solid tumors.
-Cohort expansions will be evaluated with BMS-986156 monotherapy (Part C) and combination therapy (Part D).

Part C consists of cohort expansions with BMS-986156 monotherapy in 2 disease-restricted populations: (i) NSCLC subjects with progressive or recurrent disease during or after anti-PD-L1 therapy, after prior platinum doublet-based chemotherapy , and (ii) persistent, recurrent or metastatic cervical cancer.
Part D consists of cohort expansion with BMS-986156 administered in combination with nivolumab in the two disease-restricted
populations as in Part C. With revised protocol nr 1 there are 4 tumortypes add: bladder cancer, Squamous cell carcinoma head and neck (SCCHN) (oral cavity, pharynx, larynx), Ovarian cancer, Hepatocellular carcinoma (HCC).
Treatment in Parts C and D will be initiated when the MTD/MAD/alternate dose has been determined. The doses selected for Parts C and D will not exceed the MTD or MAD determined in Parts A and B.

Intervention

Dose level BMS-986156 for subjects in Part A and Part B:
Dose level -1: 3 mg
Dose level 1: 10 mg
Dose level 2: 30 mg
Dose level 3: 100 mg
Dose level 4: 240 mg
Dose level 5: 800 mg

Subjects in Part B (and D) will, in addition, receive 240 mg IV q 2 weeks Nivolumab (combination therapy).

Subjects in cohort expansion (Part C and D) will be treated at the MTD, the MAD, or at an alternate BMS-986156 dose, if agreed upon by the investigators and the sponsor. Nivolumab will be administered as flat doses. There will be no dose escalations or reductions of nivolumab allowed once assigned

Study burden and risks

As part of the trial, patients will be expected to attend multiple clinic visits, where they will undergo physical examinations, vital sign measurements (including oxygen saturation levels), blood tests for safety assessment, pregnancy testing (for women of child bearing potential), and monitoring for adverse events. In addition, every 8 weeks, patients will undergo radiographic assessment of their tumours (by CT or MRI) until disease progression or treatment discontinuation whichever occurs later.
Subjects must have a pre-treatment biopsy performed (Part A and B; only when there is no archival material available). Blood will also be collected at certain visits for research purposes (PK, PD, immunogenicity and biomarker studies).
The frequency of visits and number of procedures carried out during this trial

would typically be considered over and above standard of care. These procedures are conducted by medically trained professionals and every effort will be made to minimise any risks or discomfort to the patient. Treatment for cancer often has side effects, including some that are life threatening. Patients will be instructed when to contact their treating physicians if side effects occur and are given a patient card with detailed information.

Contacts

Public
Bristol-Myers Squibb

Orteliuslaan 1000 .
Utrecht 3528 BD
NL
Scientific
Bristol-Myers Squibb

Orteliuslaan 1000 .
Utrecht 3528 BD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

For escalation phase (group A and B):
- Signed Written Informed Consent including consent for (archived or fresh) tumor biopsy samples
- at least 18 years old and have histologic or cytologic confirmation of a malignancy that is

advanced (metastatic and/or unresectable) with measureable disease
- Subjects must have received, and then progressed or been intolerant to, at least one standard treatment regimen in the advanced or metastatic setting or standard therapy is not possible or refused.
- All solid tumor histologies will be permitted except subjects with primary CNS tumors, or with CNS metastases as the only site of active disease
- ECOG performance status of <= 1
- at least one lesion with measurable disease as defined by RECIST v1.1
- Subjects with prior exposure to therapy with any agent specifically targeting checkpoint pathway inhibition or any agent specifically targeting T-cell co-stimulation
pathways except anti-GITR antibody permitted after a washout period of 4 weeks
- Prior palliative radiotherapy must have been completed at least 2 weeks prior to first dose of study drug
- Adequate organ function
- Comply with visit and treatment schedule, sample collection for laboratory tests, and required study follow-up;For expansion phase (group C and D and E):
- Signed Written Informed Consent including consent for (archived and fresh) tumor biopsy samples
- at least 18 years old and have histologic or cytologic confirmation of a malignancy that is advanced (metastatic and/or unresectable) with measureable disease
-The following tumor types will be permitted:
i. Non-Small Cell Lung Cancer (NSCLC): cohort 1 (part C) en cohort 3 (part D) and cohort 10 (part E)
1) All subjects with non-squamous histology must have known EGFR and ALK status
2) Subjects with an activating EGFR mutation must have received an EGFR tyrosine kinase inhibitor
3) Subjects with an ALK translocation must have received an ALK inhibitor
4) Cohort 1 (Part C) and Cohort 3 (Part D): NSCLC subjects with progressive or recurrent disease (per RECIST v1.1) during or after anti-PD-1 or anti-PD-L1 therapy following prior platinum doublet-based chemotherapy
ii. Cervical Cancer: Cohort 2 (Part C) and Cohort 4 (Part D) and cohort 9 (part E)
1) Persistent, recurrent or metastatic cervical cancer with documented disease progression
2) Squamous, adenosquamous or adenocarcinoma histology - confirmation of the original primary tumor is required
3) Must have had at least one prior platinum based regimen
4) Confirmation of tumor HPV status: Prior testing results are acceptable if known. If tumor HPV status is unknown, subjects must consent to allow their submitted archived tumor tissue sample in the form of block or unstained slides to be tested for confirmation of tumor HPV status. Both HPV positive and negative subjects are eligible to enroll
iii. Bladder Cancer: Cohort 5 (part D) and cohort 10 (part E)
1) Histological or cytological evidence of metastatic or surgically unresectable transitional urothelium involving the bladder, urethra, ureter, or renal pelvis
2) Minor histologic variants (< 50% overall) are acceptable
3) Subjects must have metastatic or surgically unresectable disease
4) Subjects must have progression or recurrence after treatment: with at least 1 platinum-containing chemotherapy regimen for metastatic or surgically-unresectable locally advanced urothelial cancer; within 12 months of peri-operative (neo-adjuvant or adjuvant) treatment

with a platinum agent in the setting of cystectomy for localized muscle-invasive urothelial cancer
iv. Squamous cell carcinoma head and neck (SCCHN) (oral cavity, pharynx, larynx): Cohort 6 (part D) and cohort 10 (part E)
1) Must have documented human papillomavirus status p16
2) Patients must have had treatment with a platinum containing regimen and evidence of progression or recurrence within six months of last dose of platinum therapy.
3) Radiation therapy must have been completed at least 4 weeks prior to study drug administration.
4) Histologically confirmed incurable locally advanced, recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).
5) Confirmation of tumor HPV status: Prior testing results are acceptable if known. If tumor HPV status is unknown, subjects must consent to allow their submitted archived tumor tissue sample in the form of block or unstained slides to be tested for confirmation of tumor HPV status.
6) Prior curative radiation therapy must have been completed at least 4 weeks prior to study drug administration. Prior focal palliative radiotherapy must have been completed at least 2 weeks before study drug administration.
v. Ovarian cancer: Cohort 7 (including epithelial OC, primary peritoneal, or fallopian tube carcinoma; part D) and cohort 10 (part E)
1) Histologically- or cytologically-confirmed OC (including epithelial OC, primary peritoneal, or fallopian tube carcinoma) with documented disease progression.
2) Documented germline BRCA mutation status, if known. However, if unknown, subjects must consent to allow their submitted archived tumor tissue sample (block or unstained slides) to be tested. Patients can enroll regardless of BRCA mutation status.
3) Prior therapy requirement: Subjects must have received and then progressed or have been intolerant or refractory to at least 1 standard systemic therapy (eg, platinum-based chemotherapy) for metastatic and/or unresectable disease. Subjects who are sensitive to platinum must have received at least 2 prior platinum-containing lines of treatment.
vi. Hepatocellular carcinoma (HCC): Cohort 8 (part D) and cohort 10 (part E)
1) Subjects must have progressive disease, or been intolerant to, at least one line of therapy or refuse treatment with sorafenib.
2) Child-Pugh score of 6 points or less and must not have encephalopathy and total bilirubin <= 1.5 × ULN (i.e Child Pugh A)
3) Subjects must have testing for hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis B DNA PCR, hepatitis C antibody, or hepatitis C RNA PCR.
4) Subjects with hepatitis B infection must have hepatitis B DNA viral load < 100 IU/mL and must be on anti-viral therapy per institutional guidelines.
5) Subjects with hepatitis B infection must not have co-infection with hepatitis C or hepatitis D (must obtain hepatitis D antibody testing).
6) Subjects must not have clinically significant ascites or clinically significant variceal bleeding.
- ECOG performance status of <= 1
- at least one lesion with measurable disease as defined by RECIST v1.1
- Subjects with prior exposure to therapy with any agent specifically targeting checkpoint pathway inhibition or any agent specifically targeting T-cell co-stimulation

pathways except anti-GITR antibody permitted after a washout period of 4 weeks
- Prior palliative radiotherapy must have been completed at least 2 weeks prior to first dose of study drug
- Adequate organ function
- Comply with visit and treatment schedule, sample collection for laboratory tests, and required study follow-up

Exclusion criteria

- Known or suspected central nervous system (CNS) metastases, untreated
CNS metastases, or with the CNS as the only site of disease are excluded. However, subjects with controlled brain metastases will be allowed to enroll.
- Carcinomatous meningitis
- Participation in any prior clinical study with nivolumab > this criteria is deleted in revised protocol nr 3
- Subjects with prior malignancy, except when a second malignancy is diagnosed more than 2 years ago treated with currative intent
- Any anti-cancer therapy within 4 weeks to start of study drug or prior therapy with anti-GITR antibodies
- Active, known or suspected autoimmune disease
- Interstitial lung disease or chronic Obstructive Pulmonary Disease (including pneumonitis)
- A condition requiring systemic treatment with corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications
- Uncontrolled or significant cardiovascular disease (including history of myocarditis)
- History of any chronic hepatitis (does not apply for hepatocellular cancer) or testing positive for HIV
- Active infection <= 7 days prior to initiation of study drug therapy
- Latent or active TBC
- Major surgeries within 4 weeks of study drug administration
- Allergies and adverse drug reaction

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	01-07-2016
Enrollment:	22
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BMS-986156
Generic name:	BMS-986156
Product type:	Medicine
Brand name:	Nivolumab
Generic name:	Opdivo
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	04-04-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-06-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-07-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-07-2016

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-08-2016
Application type:	Amendment
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:	27-10-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-11-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-03-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-04-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	08-12-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-02-2018
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Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
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Application type:	Amendment
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Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-05-2019
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
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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	EUCTR2015-002505-11-NL
ClinicalTrials.gov	NCT0000
CCMO	NL57057.031.16

Study results

Date completed:	16-12-2019
Results posted:	03-01-2021

First publication
13-11-2020