A randomized phase 2 single blind study of Temozolomide plus Radiation Therapy combined with Nivolumab or Placebo in newly diagnosed adult subjects with MGMT-Methylated (tumour 06-methylguanine DNA methyltransferase) Glioblastoma.

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To compare PFS of subjects with newly-diagnosed MGMT methylated or indeterminate GBM subtypes treated with RT plus TMZ combined with nivolumab or placebo. PFS will be determined by BICR based on RANO criteria.To compare OS of subjects with newly-...

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

Summary

ID

NL-OMON53134

Source
ToetsingOnline

Brief title
CA209-548

Condition

- Other condition

Synonym
brain tumour, Glioblastoma, grade IV astrocytoma

Health condition

Glioblastoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Glioblastoma, Nivolumab, Radiation, Temozolomide

Outcome measures

Primary outcome

Primary Objective:

To compare PFS of subjects with newly-diagnosed MGMT methylated or

indeterminate GBM subtypes

treated with RT plus TMZ combined with nivolumab or placebo. PFS will be

determined by BICR based

on RANO criteria.

To compare OS of subjects with newly-diagnosed MGMT methylated or indeterminate

GBM subtypes

without baseline corticosteroids and regardless of baseline corticosteroids

(ie, all-comers) treated with RT

plus TMZ combined with nivolumab or placebo.

Secondary outcome

Secondary Objective:

• To compare OS of subjects with newly-diagnosed MGMT methylated or indeterminate GBM subtypes without baseline corticosteroids and regardless of baseline corticosteroids (ie, all comers) treated with RT plus TMZ combined with nivolumab or placebo at 12 and 24 months.

•* To compare PFS based on investigator assessment by RANO criteria of subjects with newly-diagnosed MGMT methylated or indeterminate GBM subtypes treated with RT plus TMZ combined with nivolumab or placebo.To compare progression-free survival (PFS) of subjects with newly-diagnosed MGMT-methylated, partially methylated, or indeterminate GBM treated with RT plus TMZ with nivolumab or placebo

Exploratory Objectives:

•* To evaluate the relation of OS and PFS of subjects with newly-diagnosed MGMT-methylated or indeterminate GBM subtypes treated with RT + TMZ combined with nivolumab or placebo with tumor mutational burden (TMB).

•* To evaluate the safety and tolerability of RT+TMZ combined with nivolumab or placebo.

•* To assess immune-related tumor effects during nivolumab treatment using histopathology and advanced imaging in conjunction with assessment by RANO and iRANO criteria.

•* To assess neurocognitive function of RT+TMZ with nivolumab or placebo using

the Neurologic Assessment in Neuro-Oncology (NANO) Scale and the Cogstate tool.

•* To evaluate health-related quality of life using the EQ-5D3L and the

European Organization for Research and Treatment of Care General Cancer Module

(QLQ-C30) and brain cancer module (QLQ-BN20).

Study description

Background summary

Glioblastoma is a particularly invasive and aggressive brain tumour with high mortality and morbidity despite the
current treatments. The adverse events associated with 2nd-line treatment such as repeated brain tissue resection,
radiation therapy and other chemotherapy agents in these subjects can be highly toxic to the patient and can involve
long term complications.
There is an urgent need for novel treatment interventions to improve clinical outcomes and quality of life for subjects
suffering from GBM. Nivolumab monotherapy has shown clinical activity across several tumour types, including
advanced melanoma, Non-Small Cell Lung Cancer and Renal Cell Cancer. Nivolumab has demonstated a manageable
safety profile in greater than 700 patients in clinical trials.
Given the recent benefits in overall survival achieved with immunotherapeutics in melanoma and prostate cancer,
researchers believe that treatment with immunotherapy agents (medications that use the body's immune system to
attack cancer cells) may offer promise in other difficult to treat cancers such as GBM.
This study will include subjects with newly diagnosed glioblastoma whose tumour has a certain biomarker profile that is referred to as methylated O6-methylguanine-DNA methyltransferase (MGMT). This MGMT gene type has been shown to be important in predicting the response of GBM tumours to chemotherapy treatment.

Patients with MGMT-unmethylated GBM are being studied in CA209-498, but patients with MGMT-methylated GBM may also benefit from addition of

immunotherapy to chemoradiation. In this companion phase 2 trial we will estimate the added benefit of nivolumab in subjects receiving RT+TMZ. Depending on test conditions, MGMT status is anticipated to be reported as partially-methylated or indeterminate in approx. 5-10% of the overall population.

Study objective

To compare PFS of subjects with newly-diagnosed MGMT methylated or indeterminate GBM subtypes treated with RT plus TMZ combined with nivolumab or placebo. PFS will be determined by BICR based on RANO criteria.
To compare OS of subjects with newly-diagnosed MGMT methylated or indeterminate GBM subtypes without baseline corticosteroids and regardless of baseline corticosteroids (ie, all-comers) treated with RT plus TMZ combined with nivolumab or placebo.

Study design

STUDY DESIGN
This is a randomised (an automatic system allocates the treatment the patient will be given depending on their date of birth, date of consent and gender) single blind phase 2 study in adults (>=18 years old) male and female subjects with a newly diagnosed histologically confirmed supratentorial glioblastoma (Grade 4 malignant glioma by World Health Organization including gliosarcoma).

Following surgical resection subjects will be randomized 1:1 to receive radiotherapy, temozolomide plus nivolumab or radiotherapy, temozolomide plus placebo. Stratification will be based on complete or partial resection. Patients in both arms will start therapy upon recovery from the surgical procedure.

Subjects will undergo a screening period to determine eligibility within 42 days prior to start of radiation therapy. Subjects will be assigned to one of the two treatment arms.
WHAT WILL HAPPEN TO THE PARTICIPANTS
Subjects randomized to the radiation + nivolumab arm will receive nivolumab therapy for 16 weeks. Nivolumab will be administered at the dose of 240 mg every two weeks. Patients that remain on nivolumab therapy for 16 weeks will transition at Week 17 to nivolumab 480 mg administered every 4 weeks beginning at Week 17.
Nivolumab will be administered as an IV infusion over 30 minutes on Treatment Day 1. A Treatment will continue until documented disease progression, discontinuation due to toxicity, withdrawal of consent, or the study ends.
All subjects will receive Radiation Therapy and temozolomide over a 6 weeks period. A total dose of 60 Gy will be administered in daily doses of 2 Gy, typically on a 5 days on and 2 days off schedule as appropriate for scheduling,

over 6 weeks. The therapy will be combined with temozolomide treatment. Patients will receive temozolomide (TMZ, Temodar®) daily for 6 weeks. Temozolomide will be dosed at 75 mg/m2 once per day continuously throughout Radiation Therapy. After completion of RT, there will be a 4 week break. Subjects will then receive 6 cycles of temozolomide daily x 5 days every 28 days.
10-20% Patients treated with Radiation Therapy have been shown to experience pseudo-progression. Pseudoprogression is well-recognized in neuro-oncology, namely the radiographic enlargement of tumor lesions that would be interpreted as disease progression by conventional response criteria, but upon histologic examination reveal necrosis and/or inflammation, not disease progression. Treatment is permitted with RT-related pseudo-progression based on RANO guidelines. Immuno-oncology subjects have been shown to have treatment-related changes, and subjects can continue on treatment if changes are observed, but must be confirmed within 12 weeks of the scan.

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug. Study drug will be supplied via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS.

A total of 320 patients will be randomised to treatment. Enrolment and randomization of the targeted number of patients is expected to require approx. 12 months.
STUDY PROCEDURES
Patients will be asked to sign an informed consent form before any study related procedures are performed.

There are three periods to the study: screening, treatment and follow-up.

SCREENING PERIOD: (may take up to 42 days to complete)
The screening tests/procedures include:
• Review of medical history
• Review of medications a patient is currently taking and has taken in the past including herbal supplements, over the counter medications, and steroid medications
• A physical examination including measurement of height, weight and vital signs (temperature, blood pressure, respirations and heart rate) and neurologic status
• The amount of oxygen in blood as measured by a non-invasive finger tip pulse oximeter
• Performance status check (Karnofsky scale): patients will be asked about the symptoms they are having from their cancer
• Collection of blood (approximately 4 teaspoons/20 mLs) for laboratory tests to measure blood chemistry, including kidney and liver function, count red and white blood cells and platelets, measure thyroid function, and check for

hepatitis B or C infection. Patients must not have HIV, hepatitis B, or hepatitis C in order to be able to participate in the study.
• A urine test (with dipstick) to check for any abnormalities
• Tumour tissue sample: If a patient has had cancer surgery in the past, study doctor will request the original samples from the medical facility where it was done. The patient will be asked to give permission for this sample to be sent to an additional laboratory for research testing
• Contrast enhanced magnetic resonance imaging (MRI) of the brain within 24-48 hours of your surgery
• A urine or blood pregnancy test for women of childbearing potential must be performed within 24 hours before the first dose of study medication is given. Results of the pregnancy test must be negative for you to participate in this study.
• Patients will be asked to complete a series of computer-based mental response and activity tests using a laptop. The testing will be completed at the clinic.

BASELINE VISIT
If based on the results of the screening visit tests and procedures, patient qualifies to participate in the study they will come for Baseline Visit. This may be done up to 3 days before first day of study treatment or the day patient receive study treatment
At the Baseline Visit the following tests and procedures will be performed:
• Review of any changes in patient*s health and medications since the last visit
• Measurement of weight and vital signs (including performance status)
• Collection of a urine or blood sample for a pregnancy test for women of childbearing potential. A pregnancy test must be performed within 24 hours before the first dose of study medication is given. Results of the pregnancy test must be negative for patients to participate in this study

TREATMENT PERIOD
Patients will be randomised in a 1:1 fashion to receive either Nivolumab plus Radiation Therapy and Temozolomide or Placebo plus Radiation Therapy and Temozolomide.
Chemotherapy is typically administered as a course of several cycles of treatment.

As described previously, subjects randomized to the radiation + nivolumab arm will receive nivolumab therapy for 16 weeks. Nivolumab will be administered at the dose of 240 mg every two weeks. Patients that remain on nivolumab therapy for 16 weeks will transition at Week 17 to nivolumab 480 mg administered every 4 weeks beginning at Week 17.
Nivolumab will be administered as an IV infusion over 30 minutes on Treatment Day 1. A Treatment will continue until documented disease progression, discontinuation due to toxicity, withdrawal of consent, or the study ends.
All subjects will receive Radiation Therapy and Temozolomide over a 6 weeks period. A total dose of 60 Gy will be administered in daily doses of 2 Gy,

typically on a 5 days on and 2 days off schedule as appropriate for scheduling, over 6 weeks. The therapy will be combined with temozolomide treatment. Patients will receive temozolomide (TMZ, Temodar®) daily for 6 weeks. Temozolomide will be dosed at 75 mg/m2 once per day continuously throughout Radiation Therapy. After completion of RT, there will be a 4 week break. Subjects will then receive 6 cycles of temozolomide daily x 5 days every 28 days.

During the Treatment period, patients will be asked questions about the state of their health including but not limited to the following questions:
• How their cancer is affecting their daily activities.
• What medications they took or are currently taking including herbal supplements and over-the-counter medicines.
• What side effects they experienced
• Patients will be asked to report the development of any new or worsening medical problems (since their last visit) to the study doctor/sire personnel

The following procedures/samples will be performed and/or collected at 1 or more treatment visits:
• A brief physical examination, including body weight and examination of performance status.
• Vital sign measurements (blood pressure, heart rate, breathing rate, and oxygen levels measured by a non-invasive finger tip pulse oximeter) will be assessed. If patients assigned to nivolumab develop a reaction during the infusion, they will continue to have their vital signs measured until the study doctor determines it is no longer necessary.
• Urine or blood pregnancy test for women of childbearing potential (result must be negative to receive study drug). During treatment, pregnancy test (urine or blood) will be done every 4 weeks.
• Blood samples will be drawn to assess 1 or more of the following: blood chemistry, including kidney and liver function, count your red and white blood cells and platelets and measure your thyroid function (about 2 1/2 teaspoons or 13 mLs)
• biomarker tests (about 8 to 12 teaspoons/40 to 59 mLs). These may be drawn at the following time points: Day 1 of Week 1, Week 3, Week 7 and Week 13. An optional sample may be taken if your disease worsens.
• For subjects receiving nivolumab, additional blood samples will also be drawn before some infusions to assess their immune response to nivolumab and to measure the levels of nivolumab in their blood. Patients will have from 1 1/2 teaspoons/8 mLs to 3 teaspoons/16 mLs of blood drawn at the following time points: Predose on Day 1 of Week 1, Week 5, Week 13, Week 17 (and at the end of the infusion), Week 21 and Week 33. Thereafter, every 16 weeks at predose until discontinuation or withdrawal of consent and first follow-up visit

Patients should not have more than about one third cup/88 mLs of blood drawn on any one single day for the purposes of this study.
• A contrast enhanced MRI of brain will be completed 4 weeks after completing

concurrent radiation therapy and then every 8 weeks (± 1 week) for up to 24 months and then every 12 weeks thereafter, until disease has worsened or study treatment stopped (whichever occurs later).
• At about the same visit as the MRI, study doctor will perform a neurologic assessment using the neurologic assessment in neuro-oncology (NANO) scale.
• Study doctor will document any radiation therapy patient has received.

Patients will be discontinued from receiving study treatment based on their disease assessments or if they are having side effects that make them unable to tolerate study therapy.

Radiation therapy
All patients participating in this trial will receive radiation therapy and temozolomide in combination with either nivolumab or placebo. Radiation therapy is given daily (usually Monday through Friday) for a total of 30 treatments and may last up to 7 weeks if doses are skipped. Treatments must be done at the same treatment center throughout the course of the study.

Health Related Questionnaires:
Patient will be expected to complete a serious of questions to assess their signs and symptoms and how the disease is affecting your daily activities. These questionnaires are called the EORTC QLQ-C30, BN20, and EQ-5D and will be completed prior to dosing Day 1 Week 1 and then with each MRI prior to tumor assessment discussion.

Cogstate Assessment
Patients will also be asked to complete Cogstate assessment. This series of computer-based mental response and activity tests completed using a laptop which the study personnel will show how to use. These will be obtained at screening and prior to dosing Day 1 Week 1, then at Months 6, 12, 18, 24 and 36.

END OF TREATMENT AND FOLLOW UP:
After stopping study treatment, patients will be asked to come back to the clinic after a month after they stop treatment and then about 2 1/2 months after the first follow-up visit.

Patients will be asked the same questions regarding the medical condition, side effects, medications etc. Also, the procedures/samples performed and /or collected while they were taking study treatment may be repeated at one or more of the visits.

Patients receiving nivolumab, will have more blood collected to measure immune response and the levels of nivolumab in blood (about 1 1/2 teaspoons = 8 mLs will be drawn)

Additional Follow Up/Survival Visits (after follow up visit 2)
The remaining follow up visits may be conducted over the telephone or at

doctor*s clinic. These visits will occur approximately every 3 months and potentially more frequently. Patients will be asked the same questions regarding their medical condition as described previously. During this period study doctor will continue to assess patients* health condition It may be necessary to have another MRI scan.
During the additional follow up visits patients will be asked to complete health related questionnaires EQ-5D, either via phone or at clinic visit.

BROAD TIMETABLE OF RESEARCH AND REPORTING:
The anticipated global first patient first visit is projected for Mid March 2016. End of recruitment is planned for March 2017 but it will close when the recruitment target is met.
The subjects* safety will be monitored on an ongoing basis by a Data Monitoring Committee. The DMC will meet at least every 6 months or more frequently as needed on an adhoc basis.

Intervention

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Nivolumab (BMS-936558) 240 mg IV or placebo as a 30 minute infusion every 2 weeks for 8 doses followed by nivolumab 480 mg as a 30 minute infusion every 4 weeks beginning after 8 doses until progression, unacceptable toxicity (or other reasons), and temozolomide 75 mg/m2 orally daily during radiation therapy followed by 4 week break then 6 (28-day) cycles temozolomide on Days 1-5 at 150 mg/m2 in cycle 1 increasing to 200 mg/m2 as tolerated up to 6 cycles.

All of these compounds will be supplied by the Sponsor. Due to significant issues with the provisioning of Temozolomide (TMZ), the site will be allowed to purchase and use TMZ (140 mg, 100 mg and 20 mg capsules) from the local markets until this shortage problem is resolved. It would be reimbursed by BMS.

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 females of childbearing potential) and monitoring for adverse events. In addition, every 8 weeks
patients will undergo radiographic assessment of their tumour(s) MRI up to 24 months and then every 12 weeks until disease progression or treatment discontinuation whichever occurs later.
Blood samples will be collected at certain visits for research purposes (PK and immunogenicity) including Biomarker
samples.

The frequency of visits and number of procedures carried out during this trial would typically be considered over and
above standard over care. These procedures are carried out by trained medical professionals and every effort will be
made to minimize any risks or discomfort to the patient.
Treatment for cancer often have side effects, including some that are life-threatening.
Because of the potential for clinically meaningful nivolumab related AEs requiring early recognition and prompt
intervention, management algorithms have been developed to assist investigators in assessing and managing the
following groups of Adverse Events: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathy, Skin and
Neurological.

Contacts

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Utrecht 3528 BD
NL
Scientific
Bristol-Myers Squibb

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Utrecht 3528 BD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Subjects must:
Provide signed written informed consent before the performance of any protocol related procedures that are not part of normal subject care.
Be willing and able to comply with scheduled visits, treatment schedule, lab tests, and other requirements of the study including disease assessment by MRI.
TARGET POPULATION
-Males and Females age >=*18 years old;
-Newly diagnosed histologically confirmed supratentorial glioblastoma (Grade 4 malignant glioma by World Health Organization including gliosarcoma)
a) No treatment for GBM other than surgery;
b) Postoperative baseline MRI within 72 hours of surgical resection
substantial recovery from surgical resection
a) No major ongoing safety issues following surgery
b) <=20 mg prednisone daily or <=*3 mg dexamethasone daily (or equivalent)
-Centrally confirmed methylated MGMT, partially methylated or indeterminate GBM
-Karnofsky performance status of >= 70
-Eligible for radiation therapy based on NCCN guidelines

Exclusion criteria

Subjects must not:
-Have had prior treatment for GBM (other than surgical resection)
-Have had recurrent GBM
-Have had biopsy only of GBM at surgery, defined as <20% resection
-Require ongoing treatment with supraphysiologic steroid defined as >20 mg prednisone daily or >3 mg dexamethasone daily (or equivalent), due to intracranial mass effect
-Have CNS hemorrhage of Grade >1 on baseline MRI scan, unless subsequently documented to have resolved.
-Have any known metastatic extracranial or leptomeningeal disease
-Have had diagnosis of secondary glioblastoma (i.e., progression from prior low-grade or anaplastic
astrocytoma)
- Subjects with prior hypersensitivity to dacarbazine (DTIC)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-07-2016
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	[18F]-BMS-986192
Generic name:	[18F]-BMS-986192
Product type:	Medicine
Brand name:	Nivolumab
Generic name:	BMS-936558
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Temozolomide SUN
Generic name:	Temozolomide
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	14-03-2016
Application type:	First submission

Review commission:	METC NedMec
Approved WMO Date:	03-06-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-07-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-08-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-01-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-01-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-02-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-03-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-08-2017
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	29-08-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-10-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-07-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-01-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-02-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-07-2019
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	08-10-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-03-2021
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	08-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-01-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-04-2022
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
EudraCT	EUCTR2015-004722-34-NL
ClinicalTrials.gov	NCT02667587
CCMO	NL56653.031.16