A Randomised, Double-Blind Study to Assess the Efficacy of Selumetinib (AZD6244, Hyd-Sulfate) in Combination with Dacarbazine Compared with Placebo in Combination with Dacarbazine as First Systemic Therapy in Patients with Metastatic Uveal Melanoma (SUMIT)

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ObjectivesPrimary objective1. To assess the efficacy of selumetinib in combination with dacarbazine compared with placebo in combination with dacarbazine in terms of Progression Free Survival (PFS) assessed by blinded independent central review (...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Ocular neoplasms
Study type	Interventional

Summary

ID

NL-OMON44683

Source
ToetsingOnline

Brief title
SUMIT

Condition

- Ocular neoplasms
- Ocular neoplasms

Synonym
eye cancer, ocular or choroidal melanoma

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: industry

Intervention

Keyword: Efficacy Selumetinib, Metastatic Uveal Melanoma, Systemic Therapy

Outcome measures

Primary outcome

Progression Free Survival (PFS) using blinded independent central review (BICR)

according to RECIST 1.1

Secondary outcome

• ORR, DoR and change in tumour size at Week 6 using BICR according to RECIST

1.1

• OS

Safety:

• AEs

• Clinical chemistry, haematology and urinalysis

• Vital signs

• Electrocardiogram

• Echocardiogram/Multi Gated Acquisition Scan (MUGA)

• Ophthalmologic examination

Exploratory Outcome variables:

• HRQL using EORTC-QLQC30 v3

• Number, type and reason of hospitalisations and hospital attendances, procedures undertaken and hospital length of stay. Health state utility derived from the HRQL instrument, the EORTC-QLQC30 v3

• Output from both graphical and/or appropriate pharmacokinetic (PK)/pharmacodynamic (efficacy and safety variables) correlation or modelling techniques

• Correlation between efficacy observed in patients with tumours harbouring mutations in GNAQ and GNA11

• Biomarkers to response or development of cancer

• Host genetic polymorphisms

• By comparing (for example) relevant tumour genetics or signal transduction pathways between the baseline and the disease progression tumour biopsy, the evolution of the tumour biology in response to treatment with selumetinib in combination with dacarbazine can be assessed.

Study description

Background summary

Uveal melanoma (also known as ocular or choroidal melanoma) is the most common primary tumour of the eye.Uveal melanoma has a distinct molecular profile with the vast majority (80%) harbouring mutations in either the guanidine nucleotide binding protein (G protein), Q polypeptide 1 (GNAQ) or the G protein alpha 11

(GNA11) gene. Currently, there are no effective or approved therapies for metastatic uveal melanoma. Dacarbazine is the most commonly prescribed chemotherapy for both metastatic cutaneous and uveal melanoma. However, pre-clinical studies with selumetinib and clinical experience to date suggest that cell lines and tumours with activating mutations in RAS/RAF/MEK/ERK transduction pathway may be particularly sensitive to MEK inhibition. Selumetinib (AZD6244; ARRY 142886) is a potent, selective, uncompetitive inhibitor of the mitogen-activated protein kinase (MEK). Therefore, selumetinib in combination with dacarbazine may offer superior clinical benefit to patients with advanced uveal melanoma compared with dacarbazine alone.
Protocol "Introduction" section 1.1.1 - 1.3.2 page 20 - 25

Study objective

Objectives
Primary objective
1. To assess the efficacy of selumetinib in combination with dacarbazine compared with placebo in combination with dacarbazine in terms of Progression Free Survival (PFS) assessed by blinded independent central review (BICR)
Secondary objectives
1. To assess the efficacy of selumetinib in combination with dacarbazine compared with placebo in combination with dacarbazine in terms of:
* Objective Response Rate (ORR) by BICR
* Duration of Response (DoR) by BICR
* Change in tumour size at Week 6 by BICR
2. To assess overall survival (OS) in patients taking selumetinib in combination with dacarbazine compared with those taking placebo in combination with dacarbazine
3. To assess the safety and tolerability profile of selumetinib in combination with dacarbazine compared with placebo in combination with dacarbazine
Exploratory objectives
1. To explore the efficacy of selumetinib by assessment of OS adjusting for the impact of treatment options available post-progression as confirmed by BICR
2. To explore symptoms and health-related quality of life (HRQL) in patients treated with selumetinib in combination with dacarbazine and in patients receiving placebo in combination with dacarbazine using the European Organization for Research and Treatment of Cancer 30-item core quality of life questionnaire version 3 (EORTC-QLQC30 v3)
3. To investigate the health economic impact of treatment and the disease on hospital related resource use and health state utility
4. To investigate the relationship between selumetinib and/or N-desmethyl selumetinib plasma concentrations/exposure and clinical outcomes, efficacy, adverse events (AEs) and/or safety parameters if deemed appropriate
5. To explore mitogen-activated protein kinase (MEK) pathway mutations in GNAQ and GNA11
6. Future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to

include efficacy, tolerability or safety) may be performed on the collected and stored archival tumour samples (if available) and blood samples at baseline and on treatment discontinuation (mandated)
7. To collect and store DNA according to each country*s local and ethical procedures for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to study treatments and/or susceptibility to disease (optional)
8. To collect a tumour biopsy at the treatment discontinuation visit following confirmation of objective disease progression by BICR to allow assessment of the biology of resistance (optional)

Study design

This is a randomised, double-blind, placebo-controlled study assessing the efficacy and safety of selumetinib (75 mg, twice daily on a continuous oral administration) in combination with dacarbazine (1000 mg/m2, intravenously (iv) on Day 1 of every 21-day cycle) compared with matching placebo in combination with dacarbazine (1000 mg/m2, iv on Day 1 of every 21-day cycle) in patients who have not previously had a systemic therapy for metastatic uveal melanoma. Patients who fulfil all the eligibility criteria will be randomised in a ratio of 3:1 to receive:
• Selumetinib 75 mg twice daily in combination with dacarbazine 1000 mg/m2 (on Day 1 of every 21-day cycle)
Or
• Placebo twice daily in combination with dacarbazine 1000 mg/m2 (on Day 1 of every 21 day cycle)
Patients will be stratified based on the presence or absence of liver metastases (yes/no) at randomisation.
Following randomisation, patients will attend scheduled study visits as outlined in the study plan (Table 3). All randomised patients will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) at screening, Week 6 and every 6 weeks thereafter, relative to the date of randomisation. The same method for imaging tumours (ie, CT or MRI scan) should be used throughout the study. Tumour evaluation will be performed according to the Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) guidelines.
It is important that patients are assessed according to the intended scanning schedule to prevent the bias in analysis that can occur if one treatment group is assessed more often or sooner than the other. All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to an AstraZeneca appointed central imaging vendor for BICR.
Up to the data cut-off for the primary analysis, patients must be followed until evidence of RECIST 1.1-defined objective disease progression as confirmed by BICR. If a patient discontinues study treatment (selumetinib/placebo and/or dacarbazine) for reasons other than objective disease progression, RECIST 1.1 assessments should continue according to the original schedule until BICR confirmed objective disease progression occurs. Evaluation of CT/MRI scans according to RECIST 1.1 will be used to derive the primary variable of PFS and

secondary variables of ORR, DoR and change in tumour size at Week 6. BICR of CT/MRI scans will continue until confirmation of objective disease progression. Following confirmation of objective disease progression by BICR, patients will be unblinded to identify whether they were receiving selumetinib or placebo.
All patients, regardless of initial treatment, will have three options for post-progression therapy to consider:
1. Receive alternative treatment approach at the investigative site
2. Receive open-label selumetinib monotherapy
3. Receive open-label selumetinib in combination with dacarbazine.
Patients may receive any post-progression therapy that is, in the opinion of the Investigator, providing clinical benefit without significant toxicity concerns and it does not contravene local practice.
Patients who opt to receive an alternative treatment approach at the investigative site will be seen for the 30-day follow-up visit and will then be followed for survival every 8 weeks (with any subsequent therapies documented) until death, withdrawal of consent or the end of the study, whichever occurs first.
Patients who opt to receive open-label selumetinib as post-progression therapy will need to sign a separate Informed Consent Form (ICF) and will follow one of two assessment schedules depending on whether they received selumetinib in combination with dacarbazine or placebo in combination with dacarbazine in the main study. During the open-label extension phase, tumour assessments will be performed in accordance with local practice at the investigational site and will not be sent for BICR.
Once a patient has had objective disease progression confirmed by BICR, discontinued all study treatment and received their 30-day follow-up visit, they are to be followed up for survival status every 8 weeks (with all subsequent therapies documented) until death, withdrawal of consent or the end of the study, whichever occurs first.
After the data cut-off for the primary analysis, BICR of tumour assessments (CT or MRI scans) will no longer be performed and confirmation of objective disease progression will be by investigational site review of CT or MRI scans only. However, following confirmation of objective disease progression by investigational site review, the patients will still have three options for post-progression therapy as described above including the option to receive open-label selumetinib.
If a patient wishes to withdraw their consent to further participation in the study, including survival follow-up (which could be conducted by telephone) this should be clearly documented in the patient notes and in the clinical study database.

Intervention

At each dispensing visit, patients will receive sufficient selumetinib/placebo capsules for 21 days treatment, plus overage. Individual bottles will be dispensed in accordance with the medication identification numbers provided by the IVRS/IWRS.

Patients should swallow three selumetinib/placebo 25 mg capsules twice daily, commencing on Day 1 after the required Day 1 assessments are completed.
Capsules should be taken whole and with approximately 240 mL water.
The initial dose of selumetinib/placebo can be reduced/adjusted in accordance with the circumstances described in Section 5.5.6.

Study burden and risks

Currently there are no effective systemic treatments for uveal melanoma. In Study ISS62440007, selumetinib monotherapy demonstrated a promising therapeutic effect in patients with uveal melanoma.
Although used and prescribed for patients with uveal melanoma, the activity of non-targeted medicines approved for cutaneous melanoma have not been characterised for patients with uveal melanoma. As discussed above, there are pre-clinical and clinical data to support the use of selumetinib in combination with dacarbazine in patients with uveal melanoma. Results from the phase II Study D1532C00006 in patients receiving first line treatment for BRAF mutation positive advanced cutaneous or unknown primary melanoma showed the combination of selumetinib and dacarbazine had a safety profile consistent with monotherapy profiles with AEs managed in accordance with routine clinical practice. Study D1532C00006 also showed that the combination significantly improved PFS and ORR compared with dacarbazine alone (Robert et al 2013). The combination of pre-clinical and clinical experience to date indicates an acceptable benefit:risk ratio to explore the use of selumetinib in combination with dacarbazine in patients with uveal melanoma.

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

1.Clinical diagnosis of metastatic uveal melanoma
2.Written consent from female or male patients aged 18 years or older
3.Histological or cytological confirmation of melanoma who are suitable for treatment with dacarbazine chemotherapy
4.At least one lesion that can be accurately measured at baseline as >=10 mm in the longest diameter (except lymph nodes which must have short axis >=15 mm) with CT or MRI and which is suitable for accurate repeated measurements
- ECOG Performance Status 0-1
- Life expectancy >12 weeks
- Normal organ and marrow function
5.Patients should be able to swallow selumetinib/placebo capsules

Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:;1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site);2. Previous randomisation in the present study;3. Patients cannot have been previously treated with a systemic anti-cancer therapy. Patients can have prior intra-hepatic or non-systemic therapy;4. Having received any of the following within the specified timeframe:
* Any prior systemic anti-cancer therapy for the treatment of this current diagnosis
* An investigational drug within 30 days of starting treatment or within five halflives of the compound (whichever is the most appropriate is at the discretion of the Investigator), or have not recovered from side effects of an investigational drug
* Any non-systemic anti-cancer therapy which has not been cleared from the body by the time

of starting study treatment
* Radiation therapy within 4 weeks prior to starting study treatment, or limited field of radiation
for palliation within 7 days of the first dose of study treatment
* Major surgery within 4 weeks prior to entry into the study (excluding the placement of vascular
access) which would prevent administration of study treatment
* Any prior investigational therapy comprising inhibitors of RAS, RAF or MEK at any time
* Previous treatment with dacarbazine.;5. Any unresolved toxicity >CTCAE grade 2 from previous anti-cancer therapy, excluding alopecia;6. History of allergic reactions attributed to compounds of similar chemical or biologic composition to selumetinib or dacarbazine;7. Symptomatic brain metastases or spinal cord compression (patients must be treated and stable off steroids and anti-convulsants for at least 1 month prior to entry into the study);8. Cardiac conditions as follows:
* Uncontrolled hypertension (BP >=150/95 mmHg despite medical therapy)
* Acute coronary syndrome within 6 months prior to starting treatment
* Uncontrolled Angina - Canadian Cardiovascular Society grade II-IV despite medical therapy
* Symptomatic heart failure (New York Heart Association [NYHA] Class II-IV,
* Prior or current cardiomyopathy
* Baseline LVEF below the LLN (defined for this protocol as <55% on
echocardiography or institution*s LLN for MUGA)
* Severe valvular heart disease
* Atrial fibrillation with a ventricular rate >100 bpm on ECG at rest
* QTcF >450 ms or other factors that increase the risk of QTc prolongation;9. Any evidence of severe or uncontrolled systemic disease, active infection, active bleeding diatheses or renal transplant, including any patient known to have hepatitis B, hepatitis C or human immunodeficiency virus (HIV);10. Refractory nausea and vomiting, chronic gastrointestinal diseases (eg, inflammatory bowel disease), or significant bowel resection that would preclude adequate absorption;11. History of another primary malignancy within 5 years prior to starting study treatment, except for adequately treated basal or squamous cell carcinoma of the skin or cancer of the cervix in situ and the disease under study;12. Ophthalmologic conditions:
* Current or past history of retinal pigment epithelial detachment
(RPED)/central serous retinopathy
* Current or past history of retinal vein occlusion
* IOP >21 mmHg or uncontrolled glaucoma (irrespective of IOP);13. Female patients who are breast-feeding a child and male or female patients of reproductive potential who are not employing an effective method of birth control (see Section 5.1);14. Judgement by the Investigator that the patient should not participate in the study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-04-2014
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	Selumetinib

Ethics review

Approved WMO

Date:	17-02-2014
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	03-04-2014
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	10-04-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	28-05-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	01-09-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	24-09-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	13-01-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	17-02-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	17-06-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	15-07-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	12-10-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	18-11-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	22-03-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	09-06-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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	EUCTR2013-003545-41-NL
ClinicalTrials.gov	NCT01974752
CCMO	NL47183.058.14