Selumetinib for metastatic uveal melanoma – first line

SUMMARY

Selumetinib is an oral, potent selective mitogen activated protein kinase kinase (MEK) inhibitor, which has been shown to be effective against MEK-dependent tumours. It is intended to treat metastatic uveal melanoma, a rare malignancy that affects the eyes. It is the most common adult intraocular tumour; it arises from melanocytes in the uvea and affects mostly those from White ethnic groups, particularly those with light coloured irises.

Uveal melanoma tends to be asymptomatic initially, but as it enlarges, it may cause distortion of the pupil, blurred vision or a marked decrease in visual acuity.

Between 1995 and 2002, the crude incidence of uveal melanoma in European countries was 5.1 per million person years, with higher rates in those over 65 years of age, with the exception of iris melanoma which usually presents at a younger age. One and five year survival rates were 95.9% and 68.9%, respectively, in 2000-2002. For the same period, the 5 year survival rate in the UK and Ireland was 39.3%.

Once metastases to distant sites occur, median survival is 2-12 months with a 1-year survival of 10-15%. Fifty percent of cases metastasise to the liver only, and 90% of metastases to other sites also include liver disease. Liver involvement is the most common cause of death in metastatic uveal melanoma.

Treatment for uveal melanoma includes radiotherapy, phototherapy, and surgery. In metastatic disease, treatment options include resection for localised liver disease and intrahepatic therapy with isolated liver perfusion DELCATH and selective internal radiation therapy (SIRT). If miliary hepatic or extra-hepatic metastatic disease is present, patients should be offered dacarbazine or ipilimumab. Currently, selumetinib is in a phase III study in combination with dacarbazine comparing its effect on progression free survival vs placebo. This trial is expected to complete in February 2016.
TARGET GROUP

- Uveal melanoma: metastatic; stage 3 or 4 – first line; in combination with dacarbazine.

TECHNOLOGY

DESCRIPTION

Selumetinib (AZD6244, ARRY-142886, Hyd-Sulfate) is an oral, potent selective mitogen activated protein kinase kinase (MEK) inhibitor, which has been shown to be effective against MEK-dependent tumours. MEK is part of the mitogen activated protein kinases (MAPK) pathway, which is frequently activated and elevated in some solid tumours, including those with the Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation, which is present in about 20% of human cancers\(^1\). Selumetinib is administered at 75mg orally twice daily in combination with dacarbazine 1,000mg/m\(^2\) administered intravenously (IV) on day 1 of every 21 day cycle until disease progression is confirmed.

Selumetinib does not currently have Marketing Authorisation in the EU for any indication. Selumetinib is currently in phase III clinical trials for non-small cell lung cancer and thyroid cancer, and phase II clinical trials for acute myeloid leukaemia, biliary cancer, colorectal cancer, malignant melanoma, multiple myeloma, and pancreatic cancer.

INNOVATION and/or ADVANTAGES

If licensed, selumetinib will offer an additional oral treatment option for patients with uveal melanoma.

DEVELOPER

AstraZeneca UK Ltd.

AVAILABILITY, LAUNCH OR MARKETING

Selumetinib is a designated orphan drug in the EU, and is currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Uveal melanoma is a rare cancer that affects the eyes. It is the most common adult intraocular tumour, arising from melanocytes in the uvea\(^2,3\). The Uvea is composed of the iris, ciliary body and choroid\(^4\). It affects mainly those from White ethnic groups (incidence approximately 2-8 per million per year)\(^5\). Risk factors include light coloured irises, ability to tan\(^4\), congenital ocular melanocytosis, melanocytoma and neurofibromatosis\(^5\). The role of sunlight is uncertain\(^2,4,5\). Familial cases are rare, but some uveal melanoma patients have familial atypical mole and melanoma syndrome and may also develop cutaneous melanoma\(^5\). Those with a mutation of BAP1 on chromosome 3 are also predisposed to develop uveal melanoma, mesothelioma and other cancers\(^5\).
More than 90% of cases of uveal melanoma involve the choroid and less than 10% is confined to the iris and ciliary body. Those with iris melanoma have the best prognosis, while ciliary body melanoma has the worst outlook. Posterior (ciliary body or choroid) uveal melanoma tends to have a more malignant, histological appearance, is typically detected later and metastasises more frequently than iris melanoma.

Uveal melanoma tends to be asymptomatic initially, but as it enlarges, it may cause distortion of the pupil (iris melanoma), blurred vision (ciliary body melanoma) or a marked decrease in visual acuity caused by secondary retinal detachment (choroidal melanoma). Serous detachment of the retina may also occur. In cases of extensive detachment, secondary angle-closure glaucoma may develop.

Uveal melanoma is grouped by the thickness of the tumour into small (0-3mm thick), medium (3.1-8mm thick) or large (>8mm thick) tumours. Local recurrence of malignant uveal melanoma following initial treatment is infrequent but metastases can occur from initial diagnosis of primary tumour to several decades later. About 5% of primary uveal melanoma cases have metastases at presentation.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:

**CLINICAL NEED and BURDEN OF DISEASE**

For European countries, the crude incidence of uveal melanoma was 5.1 per million person years in 1995-2002, with higher rates in those over 65 years of age, except for iris melanoma which usually presents at a younger age. One and five year survival rates were 95.9% and 68.9%, respectively in 2000-2002, with the male survival rate slightly lower than that for females (66.5% vs 71.2%). For the same period, the 5 year survival rate in the UK and Ireland was 39.3%.

Once metastases to distant sites occur, the median survival is 2-12 months with a 1-year survival of 10-15%. The liver is the most common site of metastases, with 50% having only liver disease and 90% of those with metastases to other sites (bowel, bone, lung and lymph nodes) also having liver disease. Liver involvement is the most common cause of death in metastatic uveal melanoma.

In 2013-14, there were 652 admissions for choroid (ICD-10 code C69.3) and ciliary body (ICD-10 code C69.4) in England, resulting in 1,317 bed-days and 661 finished consultant episodes.

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* Expert personal communication.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal in development. Dabrafenib and trametinib for treating advanced unresectable or metastatic BRAFV600 mutation-positive melanoma (ID661). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Ipilimumab for previously untreated unresectable stage III or IV malignant melanoma (ID721). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Paclitaxel (as albumin-bound nanoparticles) for the first-line treatment of metastatic melanoma (ID570). Expected date of issues May 2015.
- NICE technology appraisal. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (TA321). October 2014.
- NICE technology appraisal. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma (TA269). December 2012.
- NICE technology appraisal. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (TA268). December 2012.
- NICE interventional procedures guidance. Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma (IPG446). March 2013.

Other Guidance


CURRENT TREATMENT OPTIONS

Current treatment for uveal melanoma includes:

- **Radiotherapy**
  - Ruthenium 106 or iodine 125 brachytherapy – for small to large uveal melanoma (<20mm in basal diameter).
  - Proton beam radiotherapy (PBR) – medium to large tumour that cannot be treated by brachytherapy.
  - Stereotactic radiosurgery – juxta papillary uveal melanoma; patients unsuitable for ruthenium plaque or unfit for surgery.
Phototherapy
  - Transpupillary thermotherapy – for local recurrence or adjuvant therapy (however, not recommended as a sole therapy).
  - Photodynamic therapy – for small melanoma. It is currently experimental, and not widely available.

Surgery
  - Exoresection with/without plaque – medium to large melanoma with a narrow basal diameter.
  - Endoresection with/without radiotherapy – medium sized uveal melanoma. Toxic tumour syndrome post PBR.
  - Enucleation – large uveal melanoma associated with neovascular glaucoma with/without extensive retinal detachment.
  - Exenteteration – large extra-ocular extension after uveal melanoma.

For metastatic disease, treatment options include:
  - For localised hepatic disease, resection with curative intent should be offered.
  - If liver only disease, some centres may also offer isolated liver perfusion DELCATH and selective internal radiation therapy (SIRT). These therapies provide treatment via injections into arteries that supply the liver, limiting damage to surrounding tissue.
  - If miliary hepatic or extra-hepatic metastatic disease present, patients should be offered dacarbazine based conventional chemotherapy. Following recent NICE approval of ipilimumab, most patients are now first offered ipilimumab to treat metastatic uveal melanoma.
  - Management of patients with oligometastatic disease should parallel that of cutaneous melanoma.
  - Best supportive/palliative care should be offered to patients not undergoing active treatment.

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>SUMIT, NCT01974752, D1344C00001; selumetinib with dacarbazine vs placebo with dacarbazine; phase III.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>AstraZeneca.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Trial registry.</td>
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<tr>
<td>Location</td>
<td>EU (incl. UK), USA, Canada and other countries.</td>
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<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=128 (planned); aged 18 years and older; histological or cytological confirmation of melanoma and eligible for dacarbazine chemotherapy; at least one lesion that can be accurately measured at baseline as ≥10mm in the longest diameter; ECOG (Eastern Cooperative Oncology Group) performance status 0-1; life expectancy &gt;12 weeks; normal organ and bone marrow function.</td>
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<td>Schedule</td>
<td>Randomised to: selumetinib 75mg or placebo, both oral, twice daily in combination with dacarbazine 1,000mg/m² administered intravenously (IV) on day 1 of every 21 day cycle. Treatment continues until radiological progression by Blind Independent Central Review (BICR) according to RECIST 1.1</td>
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<tr>
<td>Follow-up</td>
<td>Follow up to 18 months. Secondary outcomes followed up to 30 months.</td>
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<tr>
<td>Primary outcome/s</td>
<td>Progression free survival (PFS) assessed by BICR according to RECIST 1.1.</td>
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</table>

b Expert personal communication.
Secondary outcome/s | Objective Response Rate (ORR); duration of response; change in tumour size; overall survival; safety and tolerability. No quality of life measurement included in trial outcomes.
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Expected reporting date | Estimated study completion date January 2016.

**ESTIMATED COST and IMPACT**

**COST**

The cost of selumetinib is not yet known.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Other: *the need for treatment is high as there is no recognised standard of care based on clinical trials. The clinical impact is likely to be modest as phase II study suggests a doubling of progression free survival, i.e. only several months additional survival*.  
- Reduced symptoms or disability
- No impact identified

**Impact on Health and Social Care Services**

- Increased use of existing services: *oral treatment option.*
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other: *there is uncertainty as to the role of dacarbazine in this combination. There is also uncertainty as to the role and scheduling of ipilimumab if the trial is successful*.  
- None identified

**Impact on Costs and Other Resource Use**

- Increased drug treatment costs: *additional therapy.*
- Reduced drug treatment costs
- Other increase in costs:
- Other reduction in costs:
- Other:
- None identified

**Other Issues**

- Clinical uncertainty or other research question identified:
- None identified

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*Expert personal communication.*
REFERENCES


