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GSK1120212 for BRAF V600 mutation-positive unresectable or metastatic melanoma

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GSK1120212 for BRAF V600 mutation-positive unresectable or metastatic melanoma

Target group

- Melanoma: unresectable or metastatic; BRAF V600 mutation-positive; adults.

Technology description

GSK1120212 (trametinib, GSK-1120212B) is an inhibitor of mitogen-activated protein kinase/ERK kinase (MEK). Through binding to MEK 1 and 2, it inhibits growth-factor-mediated cell signalling and cellular proliferation. It is intended for the treatment of unresectable or metastatic melanoma in adult patients with a BRAF V600 mutation-positive tumour. GSK1120212 is administered orally at 2mg once daily until disease progression.

GSK1120212 is not currently licensed for any other indications in the EU or US. It is in phase II development for the treatment of leukaemia (relapsed/refractory disease) and pancreatic cancer, and in early development for solid tumours including non-small cell lung cancer.

Innovation and/or advantages

If licensed, GSK1120212 would provide an additional treatment option for advanced and/or metastatic malignant melanoma.

Developer

GlaxoSmithKline.

Availability, launch or marketing dates, and licensing plans

In phase III clinical trials.

NHS or Government priority area

This topic is relevant to Improving Outcomes: A Strategy for Cancer (2011).

Relevant guidance

- NICE technology appraisal in development. Ipilimumab for previously treated unresectable stage III or IV malignant melanoma. Expected February 2012[1].
- NICE technology appraisal in development. Ipilimumab in combination with dacarbazine for previously untreated unresectable stage III or IV malignant melanoma. Expected date of issue to be confirmed[2].
- NICE public health guidance. Skin cancer prevention: information, resources and environmental changes. 2011[3].
- NICE cancer service guidance. Improving outcomes for people with skin tumours including melanoma. 2006 (updated 2010)[4].
- NICE cancer service guidance. Improving supportive and palliative care for adults with cancer. 2004[5].

- American Academy of Dermatology (AAD). Guidelines of care for the management of primary cutaneous melanoma. 2011[6].
- British Association of Dermatologists. Revised UK guidelines for the management of cutaneous melanoma. 2010[7].

- Royal College of Physicians. The prevention, diagnosis, referral and management of melanoma of the skin: concise guidelines. 2007[8].
- SIGN. Cutaneous melanoma: a national guideline. 2003 (updated 2004)[9].

Clinical need and burden of disease

Malignant melanoma is the less common, but more serious type of skin cancer, representing approximately 4% of all cancers. The incidence rate of malignant melanoma in the UK has more than quadrupled over the last 30 years[10]. In 2008, the number of new cases of malignant melanoma registered was 10,295 in England and Wales. Incidence rates increase steadily with age, but are disproportionately high in young adults (15-34 years), with more than two people of this age group being diagnosed with malignant melanoma every day in the UK[10,11]. Between 2006 and 2008, 949 young adults were affected with an incidence rate range of 1.0-7.1 and 1.9-13.5 per 100,000 population in males and females respectively. In 2008, the overall age-standardised incidence rate for malignant melanoma in the UK was 15.9 and 16.5 per 100,000 population in males and females respectively[11]. BRAF-mutation positive tumours are seen in nearly 60% of cases of non-chronic sun damaged skin and 11% of cases of chronic sun damaged skin[12].

Survival rates have been continually improving for the last 30 years, with a 5-year survival rate of 81% for men and 90% for women[13]. Based on the updated AJCC[a] melanoma staging criteria, multivariate analysis shows a 97% 5-year survival rate for stage IA disease, but the prognosis for stage IV with visceral metastases is poor, with only a 33% 1-year survival[14]. Prognosis is even worse if serum lactate dehydrogenase is elevated. In 2008, there were 1,839 deaths from malignant melanoma in England and Wales[15].

Existing comparators and treatments

A variety of treatments may be used to treat malignant melanoma depending on the tumour stage and site among other factors. These include[4,16]:

- Surgery to remove melanoma, affected lymph nodes and secondary tumours.
- Chemotherapy with; dacarbazine (DTIC), temozolomide, carboplatin, paclitaxel, vinblastine, carmustine – standard therapy for non-resectable/metastatic melanoma.
- Isolated limb perfusion with melphalan – for recurrent disease within a limb.
- Radiotherapy.
- Biological therapy with interferon alpha and interleukin-2 – use varies in UK.

Although DTIC remains the UK standard therapy for non-resectable/metastatic melanoma it has very low response rates (<15%)[b,17]. Alternatives to DTIC, such as temozolomide, cisplatin and carboplatin, vinca alkaloids, taxanes and nitrosoureas, have also shown little improvement in response rate[c]. However, recent studies comparing ipilimumab and vemurafenib to DTIC have shown significant improvement in overall survival, leading to accelerated licensing[18,17]. Ipilimumab was licensed in the EU in July 2011 for the treatment of previously treated unresectable stage III or IV malignant melanoma and a NICE technology appraisal is currently in development. A Marketing Authorisation Application with the EMA was filed in May 2011 for vemurafenib for the treatment of patients with BRAF V600 mutation-positive metastatic melanoma.

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[a] AJCC – American Joint Committee on Cancer.
[b] Personal communication with expert.

Efficacy and safety

Trial	NCT01245062; GSK1120212 vs DTIC or paclitaxel; phase III.	NCT01037127; GSK1120212; phase II.
Sponsor	GlaxoSmithKline.	GlaxoSmithKline.
Status	Ongoing.	Ongoing.
Source of information	Trial registry[19].	Trial registry[20].
Location	EU (inc UK), USA, Canada and other countries.	USA and Australia.
Design	Randomised, active-controlled, double arm.	Open-label, double arm.
Participants and schedule	n=297 (planned); adults; cutaneous melanoma; stage III or IV, unresectable or metastatic; BRAF V600E/K mutation-positive; may or may not have received prior therapy, but not with BRAF or MEK inhibitors. Randomised to GSK1120212 2mg orally once daily or chemotherapy arm (DTIC 1000mg/m^2 IV or paclitaxel 175mg/m^2 IV, both given every 3 weeks).	n=110 (planned); adults; melanoma; metastatic; BRAF V600E/K mutation-positive; may or may not have received prior therapy with BRAF inhibitor; no previous treatment with MEK inhibitor. Patients receive GSK1120212 2mg orally once daily as one of two cohorts; previous treatment with BRAF inhibitor or previous treatment with chemotherapy/immunotherapy (no BRAF inhibitor).
Follow-up	Treatment given until disease progression, unacceptable adverse event or death. Patients discontinuing treatment will be followed-up every 12 weeks. Survival follow-up will continue until 80% of study subjects have died or been lost to follow-up.	Treatment given until disease progression, unacceptable adverse event or death. Survival follow-up 2 yrs after last enrolment or until 70% of events observed.
Primary outcome	Progression free survival (PFS).	Response rate.
Secondary outcomes	Overall survival (OS), overall response rate, duration of response.	Pharmacokinetics, safety, duration of response, PFS, OS.
Expected reporting date	Apr 2012.	Dec 2011.

Estimated cost and cost impact

The cost of GSK1120212 is not yet known. Comparator, dacarbazine, is given at 850-1,000mg/m^2 IV every 3 weeks (1 cycle); a cycle costs £55.46[c,21,22].

Claimed or potential impact – speculative

Patients

- ☑ Reduced mortality or increased length of survival
- ☑ Reduction in associated morbidity or Improved quality of life for patients and/or carers
- ☐ Quicker, earlier or more accurate diagnosis or identification of disease
- ☐ Other:
- ☐ None identified

Services

- ☐ Increased use
- ☐ Service organisation
- ☐ Staff requirements
- ☐ Decreased use
- ☑ Other: oral therapy.
- ☑ None identified

[c] calculated using an average surface area of 1.7m^2.

Costs

☐ Increased unit cost compared to alternative
☐ New costs
☐ Increased costs: more patients coming for treatment
☑ Savings: oral therapy.
☐ Increased costs: capital investment needed
☑ Other: uncertain unit cost compared to alternative treatment options.

Other issues

☑ Clinical uncertainty or other research question identified:
The most appropriate/effective sequence or combination of newer therapies is not yet established.
☐ None identified

References

[1] National Institute for Health and Clinical Excellence. Ipilimumab for previously treated unresectable stage III or IV malignant melanoma. Technology appraisal in development. Expected February 2012.
[2] National Institute for Health and Clinical Excellence. Ipilimumab in combination with dacarbazine for previously untreated unresectable stage III or IV malignant melanoma. Technology appraisal in development. Expected date of issue to be confirmed.
[3] National Institute for Health and Clinical Excellence. Skin cancer: how the NHS and local authorities can help prevent skin cancer using public information, sun protection resources and by making changes to the environment. Public health guidance PH32. London: NICE; January 2011.
[4] National Institute for Health and Clinical Excellence. Improving outcomes for people with skin tumours including melanoma. Cancer service guidance CSGSTIM. London: NICE; May 2010.
[5] National Institute for Health and Clinical Excellence. Improving supportive and palliative care for adults with cancer. Cancer service guidance CSGSP. London: NICE; March 2004.
[6] American Academy of Dermatology. Guidelines of care for the management of primary cutaneous melanoma. March 2011. http://www.aad.org/education-and-quality-care/clinical-guidelines/current-and-upcoming-guidelines/current-guidelines-and-guidelines-in-development Accessed 27 May 2011.
[7] Marsden JR, Newton-Bishop JA, Burrows L *et al.* Revised UK guidelines for the management of cutaneous melanoma 2010. British Journal of Dermatology 2010;163:238-256.
[8] Newton-Bishop JA, Bataille V, Gavin A *et al.* The prevention, diagnosis, referral and management of melanoma of the skin: concise guideline. Clinical Medicine 2007;7:283-290.
[9] Scottish Intercollegiate Guidelines Network. Cutaneous melanoma. National clinical guideline 72 Edinburgh: SIGN; February 2004 (update).
[10] Cancer Research UK. Skin cancer statistics – key facts. http://info.cancerresearchuk.org/cancerstats/keyfacts/skin-cancer/ Accessed 1 June 2011.
[11] Cancer Research UK. Skin cancer – UK incidence statistics. http://info.cancerresearchuk.org/cancerstats/types/skin/incidence/ Accessed 1 June 2011.
[12] Curtin JA, Fridlyand J, Kageshita T *et al.* Distinct sets of genetic alterations in melanoma. The New England Journal of Medicine 2005;353:2135-2147.
[13] Cancer Research UK. Skin cancer – survival statistics. http://info.cancerresearchuk.org/cancerstats/types/skin/survival/ Accessed 1 June 2011.
[14] Balch CM, Gershenwald JE, Soong S-J *et al.* Final version of 2009 AJCC melanoma staging and classification. Journal of Clinical Oncology 2009;27:6199-6206.
[15] Cancer Research UK. Skin cancer – UK mortality statistics. http://info.cancerresearchuk.org/cancerstats/types/skin/mortality/ Accessed 1 June 2011.
[16] Bhatia S, Tykodi SS and Thompson JA. Treatment of metastatic melanoma: an overview. Oncology (Williston Park) 2009;23:488-496.
[17] Chapman PB, Hauschild A, Robert C *et al.* Improved survival with vermurafenib in melanoma with BRAF V600E mutation. The New England Journal of Medicine 2011;364:2507-2516.
[18] Robert C, Thomas L, Bondarenko *et al.* Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. The New England Journal of Medicine 2011;364:2517-2526.
[19] ClinicalTrials.gov. GSK1120212 vs chemotherapy in advanced or metastatic BRAF V600E/K mutation-positive melanoma. http://www.clinicaltrials.gov/ct2/show/NCT01245062 Accessed 31 May 2011.
[20] ClinicalTrials.gov. Study to determine the effectiveness of GSK1120212 in BRAF mutation-positive melanoma previously treated with or without a BRAF inhibitor. http://www.clinicaltrials.gov/ct2/show/NCT01037127 Accessed 31 May 2011.

[21] electronic Medicines Compendium (eMC). Summary of product characteristics (SPC) – dacarbazine. http://www.medicines.org.uk/EMC/medicine/1088/SPC/Dacarbazine+100mg%2c+200mg%2c+500mg%2c+1000mg/#INDICATIONS Accessed 1 June 2011.

[22] British Medical Association and Royal Pharmaceutical Society of Great Britain. British National Formulary. BMJ Group and RPS Publishing. London; March 2011.

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