NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of regorafenib within its marketing authorisation for unresectable or metastatic gastrointestinal stromal tumours in people whose disease progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib.

Background

Gastrointestinal stromal tumours (GISTs) are rare connective tissue tumours. Although GISTs can occur along the length of the gastrointenstinal (GI) tract, the majority arise in the stomach (60–70%) or small intestine (25–35%)[1]. GISTs are associated with overexpression of several tyrosine kinase growth receptors. Around 75–80% of GISTs have activating mutations in the c-KIT receptor (a tyrosine kinase receptor) and 5–10% in platelet-derived growth factor receptors[2]. These mutations are thought to affect tumour development.

There are approximately 900 new diagnoses of GIST per year in the UK and approximately half of these are likely to be resectable[3]. Although GISTs can occur at any age, the median age at presentation is 55-65 years and is more common in men than women[4].

Complete surgical excision is the current standard treatment for localised GISTs. The risk of recurrence after surgery varies by a number of factors including the size and anatomical location of the primary GIST. Disease can be classified by risk. A study on resected metastatic-only GIST patients reported a median survival of 19 months with a 41% 2-year survival and a 25% 5-year survival[5].

NICE recommends imatinib as a first-line treatment for people with c-Kit-positive unresectable and/or metastatic GIST (technology appraisal 86). However, imatinib at a dose of 600 or 800 mg a day is not recommended for people with unresectable and/or metastatic GISTs whose disease has got worse after treatment with imatinib at a dose of 400 mg a day (technology appraisal 209). NICE recommends sunitinib as a second-line treatment option after failure of imatinib because of resistance or intolerance (technology appraisal 179). Regorafenib has been available on the Cancer Drugs Fund for ‘adults with advanced (metastatic or unresectable) gastrointestinal stromal tumours after failure of at least previous imatinib and sunitinib’. The only available alternative at this stage is best supportive care.

The technology

Regorafenib (Stivarga, Bayer) inhibits angiogenic kinase receptors, such as the vascular endothelial growth factor and the TIE2 receptor, which play a role in angiogenesis. It also inhibits oncogenic kinases such as RAF, RET and cKIT, thereby preventing the proliferation of cancer cells. It is administered orally.

Regorafenib has a marketing authorisation in the UK for people with 'unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib'.

Intervention(s)	Regorafenib
Population(s)	People with unresectable or metastatic gastrointestinal stromal tumours whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib
Comparators	Best supportive care
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Adverse effects of treatment • Health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related technology appraisal guidance: 'Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours' (2010).

	NICE Technology appraisal 209 part review of NICE technology appraisal guidance 86' 'Sunitinib for the treatment of gastrointestinal stromal tumours' (2009). NICE Technology appraisal 179. Guidance on static list 'Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours' (2004) NICE Technology appraisal 86. This guidance has been partially updated by 'Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours' (NICE technology appraisal guidance 209) Related Cancer Service Guidance: Cancer Service Guidance, March 2006 'Improving outcomes for people with sarcoma' Cancer Service Guidance, March 2004 'Improving supportive and palliative care for adults with cancer' Related Quality Standards: Quality Standard 'End of life care for adults' Related NICE Pathways: NICE Pathway: Gastrointestinal cancers. Pathway created Feb 2016. http://pathways.nice.org.uk/pathways/gastrointestinal-cancers/stomach#content=view-node:nodes-gastrointestinal-stromal-tumours
Related National Policy	Manual for prescribing specialised services 2016/17 105. Specialist cancer services (adults): https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf The national cancer strategy: 4th annual report:https://www.gov.uk/government/publications/the-national-cancer-strategy-4th-annual-report Department of Health, NHS Outcomes Framework 2016-17, April 2016 . Domains 1, 2, 4 and 5:https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

References

1 Jakhetiya A, Garg PK, Prakash G, Sharma J, Pandey R, Pandey D. Targeted therapy of gastrointestinal stromal tumours. World J Gastrointest Surg 2016; 8(5): 345-352

2 Braconi C, Bracci R, Cellerino R Molecular targets in Gastrointestinal Stromal Tumors (GIST) therapy. Curr Cancer Drug Targets. 2008 Aug;8(5):359-66.

3. Kindblom LG, "Gastrointestinal Stromal Tumors Diagnosis, Epidemiology and Prognosis" in "Gastrointestinal Stromal Tumors: Current management and Future Challenges". Chair: Blanke CD. ASCO 2003

4. Kong S-H, Yang H-K. Surgical Treatment of Gastric Gastrointestinal Stromal Tumor. Journal of Gastric Cancer. 2013;13(1):3-18. doi:10.5230/jgc.2013.13.1.3.

5. Gold, J.S., van der Zwan, S.M., Gönen, M. et al. Outcome of Metastatic GIST in the Era before Tyrosine Kinase InhibitorsAnn Surg Oncol (2007) 14: 134. doi:10.1245/s10434-006-9177-7.