National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Ipilimumab for previously treated unresectable malignant melanoma

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	Bristol-Myers Squibb	Accurate and complete	Comment noted. No action required.
	British Association of Dermatologists	We suggest including an additional sentence such as: "No licensed systemic therapy currently available as standard care for advanced disease has been shown to impact on overall survival."	Comment noted. The background of the scope highlights that there are limited treatment options available after first-line treatment has failed. No action required.
	CLIC Sargent	No comment	No action required.
	National Cancer Research Institute	The opening sentence of the background could be misinterpreted. As although '10% of cutaneous melanomas will have metastasised at presentation' the majority of cases of stage IV disease are patients diagnosed previously with early stage melanoma who subsequently relapse. Five year survival for stage IV disease is not as high as 20-30%. A more accurate figure would be 5-15%.	Comment noted. No action required. Comment noted. The scope has been amended accordingly.
	Royal College of Nursing	No comment	No action required.
The	Bristol-Myers	Please change the last sentence to 'It has been studied as monotherapy in	Comment noted. Scope has

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technology/ intervention	Squibb	clinical trials in people aged 16 years or older who have previously been treated **for stage III (unresectable) or IV malignant melanoma**'	been updated accordingly.
	British Association of Dermatologists	In contrast to some of the new biologicals, the duration of treatment with ipilimumab is defined: this may be helpful when considering cost implications. Perhaps this should be mentioned in the technology section. Treatment is delivered as an induction period of 4 intravenous infusions (1.5hrs every 3 weeks) over 12 weeks, before an assessment of response after an interval of 12 weeks. Only in patients who have responded at this time point is it appropriate to offer a further block of maintenance treatment comprising 4 x 3 weekly infusions.	Comment noted. The dosing frequency is not described in the scope. It will be considered during the appraisal. No action required.
	CLIC Sargent	Yes, appropriate	Comment noted. No action required.
	National Cancer Research Institute	Yes	Comment noted. No action required.
	Royal College of Nursing	No comment	No action required.
Population	Bristol-Myers Squibb	Accurate. No groups within this population should be considered separately.	Comment noted. No action required.
	British Association of Dermatologists	Appropriate population, but limited to ECOG/WHO performance status 0 or 1. No subgroups.	Comment noted. Guidance on the use of ipilimumab will only be considered in line with the UK marketing authorisation. No action required.
	CLIC Sargent	Yes, appropriate. 20% of cases occur in young adults between the ages of 15 - 39.	Comment noted. No action required.

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	National Cancer Research Institute	Yes	Comment noted. No action required.
	Royal College of Nursing	No comment	No action required.
Comparators	Bristol-Myers Squibb	There has been no standard treatment in this setting for at least for decades. Best supportive care (BSC) consists of a mixture of treatments that are used in current clinical practice, we need BSC defined more clearly. BSC may not be the only comparator. A more realistic situation in current clinical practice is that a certain proportion of patients receive BSC, and others receive active treatments within or outside clinical trials. Suggest we add comparators such as 'current clinical practice'. According to a UK survey conducted by Collinson and Marples (2010), carboplatin, with or without paclitaxel is the most commonly used regimen in the 2nd line setting for patients who fail dacarbazine. The authors concluded that **carboplatin-based treatment is a reasonable alternative to BSC.** An EU-based treatment pattern study also identified that various treatments are used in the UK (Middleton et al 2010) including dacarbazine, carboplatin, and paclitaxel.	Comment noted. The clinical and cost-effectiveness of ipilimumab will be considered in relation to current standard clinical practice in the UK. No action required. Comment noted. The scope has been updated to indicate that carboplatin-based treatment is sometimes considered for second-line therapy. Consultees indicated that best supportive care would be the primary comparator for this appraisal, however if evidence was available, a comparison with carboplatin-based chemotherapy or dacarbazine could be considered. The comparators in the scope have been updated to include these treatments.

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	British Association of Dermatologists	Perhaps treatment with dacarbazine as a single agent should be added to best supportive care as a standard comparator.	Comment noted. The scope has been amended to include dacarbazine as a comparator.
	CLIC Sargent	No comment.	No action required
	National Cancer Research Institute	Yes – best supportive care is the most appropriate comparator	Comment noted. No action required.
	Royal College of Nursing	Will this appraisal compare the effects of Ipilimumab with other drugs from the same background which are used in other cancers?	Comment noted. The clinical and cost-effectiveness of ipilimumab will be considered in relation to current standard clinical practice in the UK. No action required.
Outcomes	Bristol-Myers Squibb	Yes	Comment noted. No action required.
	British Association of Dermatologists	Yes – please assess median overall survival and improvement in 1 and 2 year overall survival	Comment noted. No action required.
	CLIC Sargent	No comment	No action required.
	National Cancer Research Institute	Yes – response rates for immunotherapies are less important than impacts on survival and progression free survival	Comment noted. No action required.
	Royal College of Nursing	How much will the Quality of Life measures include the effects of the drug on the terminal phase of the illness? We know that some of the newer drugs being used in what is a palliative stage of an illness, such as stage 111 and IV may initially be helpful but can have	Comment noted. The valuation of changes in HRQoL reported by patients should be based on public preferences elicited using a

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		unpleasant effects during the final stages of the illness, for example increased numbers of cerebral bleeds and intestinal bleeds.	choice-based method from a representative sample of the population. No action required.
Economic analysis	Bristol-Myers Squibb	Appropriate time horizon should be 10-20 year in order to take in to account long terms survival benefits	Comment noted. NICE 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. No action required.
	British Association of Dermatologists	This is appropriate	Comment noted. No action required.
	CLIC Sargent	No comment	No action required.
	National Cancer Research Institute	As described	Comment noted. No action required.
	Royal College of Nursing	No comment	No action required.
Equality and Diversity	Bristol-Myers Squibb	None	Comment noted. No action required.
	British Association of Dermatologists	We are not aware of any equality issues.	Comment noted. No action required.

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	CLIC Sargent	No comment	No action required
	National Cancer Research Institute	No issues	Comment noted. No action required.
	Royal College of Nursing	No comment	No action required
Innovation	Bristol-Myers Squibb	1) Mode of action: the technology is a novel immuno-oncologic agent that potentiates the immune system to destroy tumours 2) Survival benefits compared to existing treatments for advanced melanoma: a significant improvement in median overall survival (OS), 1- and 2-year survival rates, compared to other oncology agents, with approximately 20% of patients living over four years. Owing to the durability of the survival, conventional QALY measures based on median OS or mean OS do not fully demonstrate the long term benefit the technology may offer 3) Survival benefits compared to other existing oncology treatments which are considered as 'innovative' (e.g. Avastin, Nexavar, Revlimid, Sutent): the technology demonstrates significantly better median OS and mean OS, and the OS improvement at 1 year and 2 years	Comments noted. The Committee will consider the innovative nature of ipilimumab, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure. No action required.
	British Association of Dermatologists	No comment	No action required.
	CLIC Sargent	No comment	No action required.
	National Cancer Research Institute	Yes – there is a huge unmet need for patients with advanced melanoma. This technology is truly innovative	Comment noted. No action required.

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	Royal College of Nursing	No comment	No action required.
Other considerations	Bristol-Myers Squibb	None	Comment noted. No action required.
	British Association of Dermatologists	Toxicity can be significant for a small proportion of patients, warranting in-patient admission and supportive therapies including steroid treatment and, rarely, anti-TNF therapy. These cost implications should be considered in the economic modelling.	Comment noted. Adverse effects of treatment and their associated costs should be included within the economic evaluation. No action required.
	CLIC Sargent	No comment	No action required.
	National Cancer Research Institute	None	Comment noted. No action required.
	Royal College of Nursing	None	Comment noted. No action required.
Questions for consultation	Bristol-Myers Squibb	Yes, the technology is highly innovative in its potential to make a significant and substantial impact on health-related benefits. The technology represents a 'step-change' in the management of the condition in terms of survival benefits. In this setting, no other treatments have offered survival benefits for over 60 years Yes, we consider that the use of the technology can result in potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation, in particular: • **innovation:** (see Innovation section above) • **Unmet need/burden of disease:** 1) Advanced melanoma is an aggressive disease with increasing incidence	Comments noted. The Committee will consider the innovative nature of ipilimumab, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure. No action required.

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		and high mortality 2) There is no single standard of care, and current therapies have not demonstrated improved OS, as concluded below: *'… there is no impact of systemic therapy on survival in advanced [stage IV] melanoma patients…' (ESMO 2009)*; *'… little consensus currently exists regarding standard therapy for patients with metastatic melanoma, which most likely reflects the low level of activity of all available agents' (NCCN 2010)*; *British Association of Dermatologists Clinical Guidelines stated that for advanced melanoma, existing radiotherapy and chemotherapy only have a palliative role; patients with metastatic melanoma should be considered for entry into clinical trials of novel therapies (B.A.D 2010)* • **Unusual patterns of survival benefits:** As a result of the novel mode of action, it is observed in pivotal phase III clinical trials that the technology delivers sustainable survival: 20% patients are not progressed at the end of trial. This has also been shown to be the case in other phase II trials. Whilst longer follow-up is required, it is a challenge to capture such treatment effect with the conventional survival analysis in the economic modelling The following data is or will be available to enable the Appraisal Committee to take account of the benefits mentioned above: • **Innovation:** pivotal phase III trial -020, phase II trials, and BMS data on-file: analysis of comparative technologies • **Unmet need/burden of illness:** Epidemiology data has shown that the incidence of melanoma is increasing over years A systematic review of treatments for advanced melanoma noted that, despite current treatments, most patients progress quickly and decline in almost all of the major functional areas assessed by health-related quality	

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		of life (QOL) scales (Cashin 2008) In a meta-analysis of 42 phase II trials in 2,100 patients with metastatic melanoma: median overall survival was 6.2 months, 1-year survival rate was 25.5%, and 2-year survival rate was ~10% (Korn et al 2008) • **Unusual patterns of survival benefits:** phase II -024 for the first line indication, phase II trials, observational data	
	British Association of Dermatologists	Yes. This is the first systemic therapy that has been shown to offer a survival benefit in advanced melanoma in a well-conducted randomised trial. It therefore contributes significantly to a hitherto global unmet need in melanoma patient care. References: Hodi FS et al, NEJM 2010; 363:711-23 O'Day SJ et al, Ann Oncol 2010;21:1712-7	Comment noted. No action required.
	CLIC Sargent	No comment	No action required.
	National Cancer Research Institute	Yes – there is a huge unmet need for patients with advanced melanoma. This technology is truly innovative	Comment noted. No action required.
	Royal College of Nursing	As per our comment under comparators	Comment noted. No action required.
Additional comments on the draft scope.	Bristol-Myers Squibb	None	No action required.
	British Association of Dermatologists	None	No action required.

Section	Consultees	Comments	Action
	CLIC Sargent	None	No action required.
	National Cancer Research Institute	None	No action required.
	Royal College of Nursing	None	No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Marie Curie Cancer Care
MHRA
NHS Quality Improvement Scotland
Public Health Wales
Royal College of Pathologists
Welsh Assembly Government