National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ibrutinib for treating relapsed or refractory mantle cell lymphoma

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

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Janssen	The information reported in the draft scope for the second consultation is accurate.	Comment noted
	NCRI-RCP-ACP	Yes	Comment noted
	RCPath	Yes	Comment noted
The technology/ intervention	Janssen	There is limited information reported on ibrutinib, but what is reported is accurate.	Comment noted
	NCRI-RCP-ACP	Yes	Comment noted
	RCPath	Yes	Comment noted
Population	Janssen	Yes, appropriate.	Comment noted

Section	Consultee/ Commentator	Comments [sic]	Action
	NCRI-RCP-ACP	The population is defined appropriately, there are no special populations	Comment noted
	RCPath	Appropriate, there are no special populations	Comment noted
Comparators	Janssen	Janssen agree with the choice of multiple combination therapies as it reflects the lack of standard of care for this disease area in England. It should be noted that data for most regimens in relapsed/refractory (R/R) mantle cell lymphoma (MCL) are very sparse. Janssen believe that bendamustine and rituximab (BR) should not be considered a relevant comparator in England anymore. BR has been available in England till November 2015 via the National Cancer Drug Fund (NCDF) rather than routine baseline commissioning. The NCDF List of included drugs has been updated in November 2015 (version 6.0) and BR has been delisted for the treatment of R/R MCL, for which it was previously included. BR will not be available via any type of funding in England for R/R MCL.	Comments noted. Bendamustine has been removed from the comparators.
	NCRI-RCP-ACP	Relapsed / refractory covers a huge range of potential situations and as a consequence many potential therapies. Broadly speaking for first relapse an alternative rituximab containing combination chemotherapy is used, so if R-Bendamustine is front line then R-CHOP will be used and vice versa. There are a couple of regimens missing. Single agent lenalidomide can be used for relapse (it is licensed and used) the others are cytarabine with rituximab or velcade as a single agent or with rituximab.	Comments noted. As lenalidomide and bortezomib are not licenced for relapsed or refractory mantle cell lymphoma and are not available through the Cancer Drugs Fund, they are not considered appropriate comparators.

Section	Consultee/ Commentator	Comments [sic]	Action
	RCPath	Relapsed / refractory covers a huge range of potential situations and as a consequence many potential therapies. Broadly speaking for first relapse an alternative rituximab containing combination chemotherapy is used, so if R-Bendamustine is front line then R-CHOP will be used and vice versa. There are a couple of regimens missing. Single agent lenalidomide can be used for relapse (it is licensed and used) the others are cytarabine with rituximab or velcade as a single agent or with rituximab.	Comments noted. As lenalidomide and bortezomib are not licenced for relapsed or refractory mantle cell lymphoma and are not available through the Cancer Drugs Fund, they are not considered appropriate comparators.
	Roche Products Ltd	Bendamustine for 2nd and subsequent treatment lines of mantle cell lymphoma was recently delisted from the CDF. MabThera (rituximab) is not licensed in MZL. However, MabThera regimens are recommended in UK (BCSH) and European guidelines (ESMO). MabThera induction regimens may be followed by MabThera maintenance and both options may be an appropriate comparator.	Comment noted. Bendamustine has been removed from the comparators. Rituximab regimens are included as comparators.
Outcomes	Janssen	Yes, appropriate.	Comment noted
	NCRI-RCP-ACP	Yes	Comment noted
	RCPath	Yes	Comment noted
Economic analysis	Janssen	Yes, appropriate.	Comment noted
	NCRI-RCP-ACP	We believe the use of Ibrutinib for treating relapsed or refractory mantle cell lymphoma should be progressed as quickly as possible, such is the need for this agent.	Comment noted

Section	Consultee/ Commentator	Comments [sic]	Action
	RCPath	Needs to be as quick as possible such is the need for this agent	Comment noted
	NCRI-RCP-ACP	No issues with this.	Comment noted
	RCPath	No issues with this	Comment noted
Innovation	Janssen	Ibrutinib is a targeted, non-chemotherapy agent and first-in-class inhibitor of Bruton's tyrosine kinase (BTK). This is a novel therapeutic target and critical signalling kinase in the B cell receptor (BCR) pathway, whose activity is essential for tumour cell survival and proliferation. Regulatory approval in R/R MCL was based on a phase II single arm trial (PCYC1104) due to the high unmet need and unparalleled efficacy with ibrutinib, not observed with any other treatment for R/R MCL. Indeed, ibrutinib was granted US Food and Drug Administration (FDA) breakthrough status in R/R MCL in November 2013. The clinical assessment performed by the CHMP and reported in the European Public Assessment Report (EPAR) states that “the dramatic activity seen in terms of overall response rate (ORR) and DOR is unprecedented historically and considered sufficiently important in this heavily pre-treated patient population to support approval”. Data from the two main ibrutinib clinical trials, PCYC1104 (a phase II single arm study) and RAY (MCL3001, a comparative phase III trial versus temsirolimus), demonstrate that, in patients with R/R MCL, ibrutinib results in an unprecedented benefit in terms of progression free survival (PFS) compared to conventional treatment. Treatment with ibrutinib has been demonstrated to improve quality of life (QOL) as measured by the EuroQol - 5 dimensions (EQ-5D) scale and to also improve symptom control. These improvements are maintained throughout treatment. Anecdotal reports from patients receiving ibrutinib reveal that patients who	Comment noted

Section	Consultee/ Commentator	Comments [sic]	Action
		were confined to bed whilst receiving conventional chemotherapy showed a rapid response to ibrutinib treatment (within 10 hours in some cases). Patients were able to return to normal activities for example playing golf or attending work within weeks. Clearly, this evidence is anecdotal; however, it does suggest that treatment with ibrutinib results in an improvement in QOL. In these patients, ibrutinib enabled patients to contribute to society and improve their family functioning. Finally, ibrutinib is an oral treatment and unlike other treatment options does not require frequent hospital visits for infusion or monitoring. This is likely to improve carers' QOL as they will no longer be required to provide transport to hospital.	
	NCRI-RCP-ACP	This is an absolute step change in the management of this difficult disease. One of our experts has noted that this is the most impressive drug he has ever used or trialled in mantle cell NHL. The QOL data may not actually reflect how impressive this agent is from a patient perspective.	Comment noted
	RCPath	This is an absolute step change in the management of this difficult disease. The most impressive drug I have ever used or trialled in mantle cell NHL. I suspect that the QOL data will not actually reflect how impressive this agent is from a patient perspective.	Comment noted
Other considerations		None	
Questions for consultation		None	

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope		None	

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

Department of Health

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology Appraisal (MTA) (STA)

Ibrutinib for treating relapsed or refractory mantle cell lymphoma [ID753]

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	African Caribbean Leukaemia Trust	NICE Secretariat		Removed	This organisation's interests are no longer active/engaging with NICE. African Caribbean Leukaemia Trust has not been removed from the matrix of consultees and commentators under 'patient groups'.

2.	Aspen Pharma (chlorambucil)	NICE Secretariat		Removed	This organisation is not a comparator in the appraisal topic as per our inclusion criteria. Aspen Pharma (chlorambucil) has been removed from the matrix of consultees and commentators under 'comparator company.'
3.	Bloodwise	NICE Secretariat		Added	This organisation has an area of related to this appraisal topic and meets the selection criteria to participate in this appraisal. Bloodwise has been added to the matrix of consultees and commentators under 'patient groups'.

4.	Helen Rollason Cancer Charity	NICE Secretariat		Removed	This organisation's interests are not related to the appraisal topic and as per our inclusion criteria. Helen Rollason Cancer Charity has not been removed from the matrix of consultees and commentators under 'patient groups.'
5.	Janssen (bortezomib)	NICE Secretariat		Removed	This organisation makes the drug bortezomib which is not a comparator in the appraisal topic as per our inclusion criteria. Janssen (bortezomib) has been removed from the matrix of consultees and commentators under 'comparator company.'

6.	**Napp Pharmacuticals (bendamustine)**	NICE Secretariat		Removed	This organisation makes the drug bendamustine which is not a comparator in the appraisal topic as per our inclusion criteria. **Napp Pharmacuticals (bendamustine)** has been removed from the matrix of consultees and commentators under 'comparator company.'
7.	Rare Cancers Foundation	NICE Secretariat		Removed	This has disbanded and has been removed from the matrix of consultees and commentators under 'patient groups.'