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NICE National Institute for Health and Care Excellence

Ibrutinib for treating Waldenström's macroglobulinaemia (CDF review of TA491)

2nd Appraisal Committee meeting

Chair presentation

Chair: Jane Adam

ERG: ScHARR

Technical team: Sana Khan, Mary Hughes and Janet Robertson

Company: Janssen

15th March 2022

Key issues

- No new evidence has been presented in response to the ACD
- The ICER is well above the acceptable range. The company considers that an acceptable ICER should be around £30,000 per QALY (instead of £20,000 per QALY gained):
  - Given the high uncertainty in the evidence base, lack of further analyses that can resolve this uncertainty and difficulty in obtaining evidence, would the committee like to revisit that an acceptable ICER is around £20,000 per QALY gained?

History of appraisal

Marketing authorisation (July 2015)
Monotherapy for treating adults with Waldenström's macroglobulinaemia:
- who have had at least 1 prior therapy, or
- as first-line treatment in patients for whom chemo-immunotherapy is unsuitable.

Recommendations in TA491 (November 2017)
Ibrutinib is recommended for use in the Cancer Drugs Fund as an option for treating Waldenström's macroglobulinaemia in adults who have had at least 1 prior therapy, only if the conditions in the managed access agreement for ibrutinib are followed.

CDF data collection agreement data from:
- PCYC-1118E (single arm study of ibrutinib)
- ibrutinib arm of iNNOVATE (people who relapsed within 12 months of rituximab containing treatment)
- SACT data

Recommendations after 1st committee meeting for CDF review of TA491 (December 2021)
Ibrutinib is not recommended, within its marketing authorisation, for treating Waldenstrom's macroglobulinaemia in adults who have had at least 1 prior therapy.

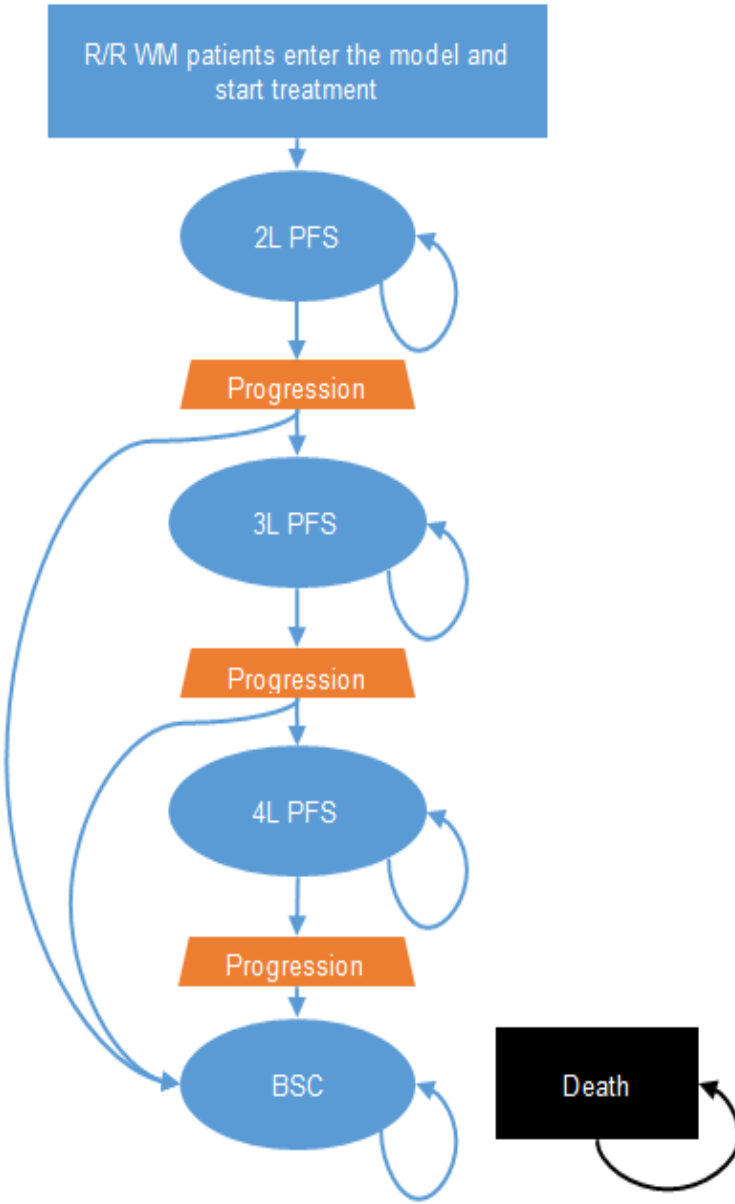
Economic model

Compares ibrutinib vs. standard therapies (blend of rituximab/chemotherapy options used at 2nd line)

Model driver is 2nd line time to progression which is modelled to differ between ibrutinib and standard therapies. All subsequent transition probabilities same in each modelled arm

Key model clinical inputs:

1) Estimate of PFS for ibrutinib
   - SACT data most relevant for population, but did not collect PFS. PFS indirectly estimated from SACT time to discontinuation data.
2) Relative treatment effect. Hazard ratio for progression free survival ibrutinib vs. standard therapies:
   - Estimated from indirect comparison of study 1118E (ibrutinib) vs. European Chart Review (standard therapies) HR = 0.25 (company base case – same as TA491)
   - Alternative estimate of 0.28 used updated data from study 1118E with same data for standard therapies and unanchored matching adjusted indirect comparison
3) Overall survival for ibrutinib calibrated to observed overall survival data from SACT



PFS, progression free survival; PC physician's choice; PPM, pre-progression mortality; PPS post-progression survival; TTD, time to treatment discontinuation; HR, Hazard ratio; ITC, indirect treatment comparison; 2L, 2nd line; 3L, 3rd line; 4L, 4th line; BSC, best supportive care

Key uncertainties in evidence

- **Indirectly estimating PFS using time to treatment discontinuation data from SACT** as no PFS data collected in SACT
- **High uncertainty** in the **HR for PFS** with ibrutinib vs standard therapies:
  - **Company base case**: indirect comparison of study 1118E with European Chart Review. Same as TA491. Conclusions in TA491 " [ibrutinib appears] more clinically effective than existing treatments [but] there remains considerable uncertainty about the size of the long-term benefit because of limitations in the data available".
  - Updated HR using unanchored matching-adjusted indirect comparison (MAIC) with full dataset from European Chart Review assumes that prognostic variables accounted for. Limited data on prognostic variables available; **HR from MAIC highly uncertain**
  - **ACD 3.5** there remains significant uncertainty around the extent to which ibrutinib improves progression-free survival
- **Plausibility of modelled outcomes (all dependent on progression free survival hazard ratio)**

Outcome	Model	Observed/expected in clinical practice
Time between stopping treatment and disease progression	6 months	Most people still on treatment when disease progresses or if stop before disease progresses soon after
Post-progression survival	1 year	Much longer – expected to respond to chemotherapy
Overall survival on standard therapy	<2 years with nearly all people dead by 6 years	Implausible. Indolent disease expected survival 4 years + (estimates of median survival range 4 to 12 years)

Company base case results (deterministic)

Includes patient access scheme for ibrutinib

Analysis	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Revised company base-case: includes ERG preferences (HR for PFS = 0.25)	2.88	[redacted]	[redacted]	[redacted]
Scenarios around assumptions on relative treatment effect of ibrutinib vs. standard therapies on PFS				
Revised company base-case with MAIC; HR for PFS =0.28	2.80	[redacted]	[redacted]	[redacted]
ERG: assumed HR for PFS = 0.50	2.34	[redacted]	[redacted]	[redacted]
ERG: assumed HR for PFS = 0.75	1.78	[redacted]	[redacted]	[redacted]
Note: * Undiscounted				

- ERG calculated a HR for PFS based on clinical expert opinion that survival at 6 years for standard therapies would be half of that for ibrutinib. The HR required in order for the model to predict a 6-year overall survival probability for standard therapies of 12.5% was estimated to be 0.74.
- ICER with this HR is [redacted]

Committee conclusions at ACM1

- All presented cost effectiveness estimates above a value considered cost effective use of NHS resources
- **ACD section 3.9** NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented.
  - Uncertainty around
    - The hazard ratio for PFS for ibrutinib compared with standard therapies estimated from an indirect comparison is uncertain
    - The revised approach for estimating ibrutinib PFS indirectly from SACT data is highly uncertain
  - Agreed an acceptable ICER would be around £20,000 per QALY gained.
- **Innovation ACD 3.11**
  - Ibrutinib has benefits including oral administration, manageable adverse reactions and low toxicity. Step change in managing the condition
  - Highly likely that that the clinical benefits had already been overestimated in the modelling
  - Highly unlikely any additional benefits not captured fully in the QALY calculation, would be enough to lower the ICER to within the range normally considered cost effective

ACD consultation responses

Professional/ patient organisations	• Royal College Pathologists and British Society Haematology
Company	• Janssen-Cilag
Public (web) comments	• **Patient perspective:** • This is a real kick in the teeth for me. Diagnosed with WM in 2001 at the age of 36. Treated in 2010 and 2015/16, followed up with a stem cell transplant to give a maximum treatment free period in the hope that a BTK inhibitor would have been recommended to be used when treatment required. Blood counts suggest treatment may be needed this year sometime. • It feels that WM being a rare condition is forgotten about as we have no treatments directly aimed at us. Likely will have to face toxicity of further chemotherapy (increasing risk of a 2nd cancer more likely, hence costing the NHS more). I know ibrutinib is expensive and money is limited, but it just feels like we don't matter • Not good from a mental health point of view either

Response to consultation- clinical expert

- SACT data is more generalisable to UK population than trial data but is limited in its use due to the lack of information regarding response and duration of response. Recent publication suggests that patients treated off trial in an academic centre with WM expertise have similar outcomes to trial data
- **Plausibility of modelled survival outcomes**: Patients will discontinue ibrutinib due to adverse events or due to progression. It is variable how long patients remain off treatment without disease progression. Patients who progress may not immediately discontinue treatment, and may stay on treatment for a period of time in the "progressed state" before proceeding to next treatment
- Provisional recommendation is a big backward step in treatment of patients with WM. Ibrutinib is a very effective treatment option for patients with WM, and not having this available would be very difficult for patients and clinicians alike:
    - Whilst many patients benefit from chemoimmunotherapy, repeated lines of chemoimmunotherapy leads to shorter responses, with increased risk of cumulative toxicities and risk of secondary malignancies.

Response to consultation- patient expert

- Patients with WM are clinically extremely vulnerable as they are immunocompromised. To have a negative recommendation especially in the COVID era serves only to increase patient and carer anxiety and fears.
- Ibrutinib is a “life transforming” drug; not being able to access it on the NHS seems to be a “death sentence” and the decision is against medical ethics. Ibrutinib should be made freely available to patients who benefit from its use.
- It is of limited comfort that company will fund supply after CDF funding ends as they are a commercial enterprise and may be forced to make decisions that take ibrutinib out of circulation with early mortality and life-changing repercussions for patients.
- Ibrutinib is approved for use by the Scottish Medical Council which will lead to health inequality for people unable to access in England.
- Zanubrutinib is an alternative treatment that will be considered by NICE shortly. It cannot be viewed as a straight alternative as targeted drugs are tailored to patient needs. To improve quality of life of patients, it is important to have more than one treatment option available especially for a rare disease like WM.
- Ibrutinib offers real hope and reduces anxiety about risk of relapse for patients especially when the relapse with toxic chemotherapy is higher
- Ibrutinib is an oral drug taken at home; its availability avoids hospital visits:
    - As patients with WM tend to be elderly, being able to avoid hospital visits is important from a cost and health perspective

Response to consultation – company

- Ibrutinib is a step-change treatment in a very rare condition; £20,000/QALY threshold does not account for the social value of treating very rare diseases
- £20,000/QALY threshold goes against precedents of previous appraisals for rare diseases with high unmet need. Recently published NICE manual places greater acceptance of uncertainty in rare diseases with high unmet need
  - In TA586, lenalidomide plus dexamethasone is recommended despite a most plausible ICER above £30,000 per QALY. Flexibility considered appropriate due to multiple myeloma's orphan status and unmet need for an alternative option to toxic chemotherapy.
- £20,000/QALY threshold does not account for aspects of health-related benefits and non-health factors that could not be accounted for in the ICER calculation
  - psychological benefit of availability of an effective treatment with manageable safety profile
  - Convenience of oral administration and avoidance of hospital visits for IV administration
  - Uncaptured non-health factors associated with treating WM patients with ibrutinib vs alternative IV therapies such as saved staff time and reallocated facilities not quantified by company but should be considered in decision-making
- Evidence collected in the CDF for ibrutinib in WM has significantly reduced uncertainty by improving maturity of data and generalisability to NHS clinical practice
  - Remaining uncertainty is residual and inherent to (i) defining SACT as the primary data source and (ii) appraising any very rare disease such as WM
  - PFS HR (0.25) is the most robust estimate to capture ibrutinib relative PFS benefit; clinical experts agree that a low HR is clinically plausible

ERG comments on company ACD response

ERG:

- No evidence presented to support other health and non-health benefits which have not been captured in company's cost-effectiveness estimates
- No additional analyses/evidence presented to reduce uncertainty for:
  - (i)absence of data on PFS from SACT
  - (ii) necessary reliance on estimates of relative treatment effects from unanchored indirect treatment comparisons (ITCs);
  - (iii) indirect approach to estimate outcomes for a SACT-like population receiving standard therapies
  - (iv) lack of clinical plausibility of model predictions based on company's original and updated ITC's

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Backup slide

2013 methods of technology appraisal: (in use for this appraisal)

- Above plausible ICER of £20,000 per QALY gained, judgements about acceptability of technology as effective use of NHS resources will consider following factors:
  - Degree of certainty around ICER. Committee will be more cautious about recommending a technology when they are **less certain** about the ICERs presented.
  - Whether there are strong reasons to indicate that assessment of change in HRQoL has been inadequately captured, and may therefore misrepresent the health utility gained.
  - Innovative nature of technology, specifically if innovation adds demonstrable benefits of a substantial nature which may not have been adequately captured in QALY measure.
  - technology meets criteria for special consideration as 'life-extending treatment at end of life'
  - Aspects that relate to non-health objectives of the NHS

2022 update of methods of technology appraisal

- Above a most plausible ICER of £20,000 per QALY gained, decisions about acceptability of the technology as an effective use of NHS resources will specifically consider the following factors:
  - Degree of certainty and uncertainty around the ICER.
  - Aspects that relate to uncaptured benefits and non-health factors.
- As ICER for a technology increases in the range of £20,000 to £30,000 per QALY gained, the committee's decisions about the acceptability of technology as an effective use of NHS resources will make explicit reference to the relevant factors listed above.
- Above a most plausible ICER of £30,000 per QALY gained, the committee will need to identify an increasingly stronger case for supporting the technology as an effective use of NHS resources, considering the factors listed above

Backup slide

Progression free survival: comparison of ibrutinib vs standard care from TA491

PFS curves of ibrutinib[redacted] vs. standard care [redacted]

Source: TA491 committee slides