Slides for public observers

Chair's presentation
Midostaurin for untreated acute myeloid leukaemia

2nd appraisal committee meeting

Committee C

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ERG: CRD and CHE, University of York

NICE technical team: Kirsty Pitt and Sally Doss

Company: Novartis

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Midostaurin
Novartis

UK marketing authorisation	Indicated in combination with standard daunorubicin and cytarabine induction and high dose cytarabine consolidation chemotherapy, and for patients in complete response followed by midostaurin single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation positive
Mechanism of action	Multi-targeted kinase inhibitor, found to inhibit FLT3 and other receptor tyrosine kinases.
Administration and dose	Oral therapy taken as 50 mg twice daily (2 x 25 mg soft gel capsules) on days 8–21 of induction and consolidation chemotherapy cycles, and then twice daily as single-agent therapy for up to 12 months
Cost	List price: [redacted] for 56 capsules

ACD: preliminary recommendation

- Midostaurin is **not recommended** within its marketing authorisation (that is, with standard daunorubicin and cytarabine as induction and high-dose cytarabine as consolidation therapy, and alone after complete response as maintenance therapy) for treating newly diagnosed acute FLT3-mutation-positive myeloid leukaemia in adults.

Committee's considerations in ACD (1)

Issue	Committee's conclusion
Clinical evidence	Midostaurin increases overall and event-free survival compared with chemotherapy Midostaurin is well tolerated Mean age of people in the trial is lower than in NHS clinical practice in England
Model structure	People do not move from the relapsed state to remission • Most appropriate scenario: surviving patients with relapsed disease entering a cured health state after 3 years Implausible costs associated with complete remission after initial therapy and stem cell transplant recovery • Most appropriate scenario: no health state costs after the cure point
Survival after cure point	4-fold increase in mortality rate (lowest increase from literature) most plausible scenario

Committee's considerations in ACD (2)

Issue	Committee's conclusion
Duration of treatment	Maximum possible length of midostaurin monotherapy treatment in model should match RATIFY – 18 cycles maximum
Utility values	Should be adjusted for age Should include reductions for adverse effects of stem cell transplant
Cure point	Uncertain – but moving the cure point earlier or later than company's base case (6.2 years) increases the ICER
Mean age	45 in company's base case. Likely to be around 60 in England – increasing mean age significantly increases the ERG's base-case ICER.
Effect of midostaurin in older people	Company's analysis of single-arm phase 2 study propensity score-matched with historical controls – non-randomised comparison, susceptible to confounding, and not appropriate to use in the model in preference to trial-based data with an age adjustment

Committee's considerations in ACD (3)

Issue	Committee's conclusion
ICERs (midostaurin compared with placebo)	Company: £27,754/QALY gained ERG: £62,810/QALY gained Committee's preferred: over £62,818/QALY gained
Innovation	Midostaurin is innovative, but benefits are captured in cost-effectiveness analysis
End of life criteria	Met: >3 months extension to life Not met: life expectancy is over 24 months (range of life expectancy data provided in ACD)
Cancer Drugs Fund	Not suitable • no plausible potential to satisfy criteria for routine use • no clinical uncertainties that could be resolved through data collection in CDF

ACD consultation responses

- Consultee comments from:
  - Novartis (company)
  - National Clinical Research Institute, Association of Cancer Physicians and Royal College of Physicians (joint response) - endorsed by clinical experts Dr Steven Knapper and Dr Mike Dennis
  - Leukaemia CARE

- No comment response from:
  - Department of Health

Summary of consultation responses [1]

Patient and professional organisations

End of life criteria

- Believe midostaurin does meet end of life criteria
  - RATIFY trial had no UK sites – UK survival for AML is much lower than the European average
  - UK population older than population in RATIFY (trial of midostaurin vs standard of care) – would have a shorter life expectancy
  - Applying EUROCARE 5 (European cancer registry-based study) data to placebo group of RATIFY expect OS to be equivalent to 23.2 months in UK

Summary of consultation responses [2]

Patient and professional organisations

Cost-effectiveness model

- Joint response from professional groups accepts committee's preferred adjustments to model, except increasing maximum cycles of maintenance therapy from 12 to 18 (marketing authorisation is for 12 cycles)

Clinical benefit of midostaurin

- Separation of survival curves in early stages of chemotherapy treatment suggests that main clinical benefit of midostaurin is from initial induction and consolidation therapy
  - Midostaurin maintenance therapy: high costs, small number of patients in RATIFY
  - Committee should consider whether midostaurin would be cost-effective as induction and consolidation therapy, and not used as maintenance

Summary of consultation responses [3]

Company's response to ACD and new evidence

Response to ACD

- Corrected factual inaccuracies
  - Minor inaccuracies in a summary table in the slide set from the first committee meeting – figures correct in committee papers and on other slides
- Comments on end of life considerations
- Comments on the mean age of population

New evidence

- Changes to the economic model
- Proposed simple discount patient access scheme
  - See part 2

End of life considerations
Company's response

- Data from large UK registry: Haematological Malignancy Research Network (HMRN) – Yorkshire and Humber & Yorkshire coast
  - People newly diagnosed with AML between 2004 and 2015
  - 1,572 patients, 55.2% male

Population in the HMRN registry	Median overall survival (years, 95% CI)	Mean overall survival
People with AML	[redacted]	[redacted]
People with FLT3-positive AML who received daunorubicin plus cytarabine as induction chemotherapy	[redacted]	[redacted]

⊙ *Are end of life criteria met?*

Mean age of population
Company's response

ACD: *"it was likely the mean age of people eligible for midostaurin in England would be around 60."*

- Data from HMRN registry:
  - Mean age of overall population at diagnosis

    = [redacted]
  - Mean age of subgroup that received intensive chemotherapy and had FLT3 mutation-positive AML (corresponds to marketing authorisation for midostaurin)

    = [redacted]

⊙ *Should the mean age of people in the model be lower than 60 years?*

Company's new evidence: model changes
a. Survival after the cure point

ACD: [The committee] *concluded that…the most plausible* [analysis] *was the lowest increase in mortality rate from the literature, that is, a 4-fold increase in mortality rate.*

- In ACD, committee chose 4-fold increase in mortality rate from the scenarios presented, because it was the lowest value taken from literature, but acknowledged comments from clinical experts that this seemed high
- Company asked 7 UK clinical experts – responses ranged from [redacted]
  - Company use **SMR of 2** in revised base case

ERG comments

- Committee's preferred SMR of 4 derived from historic cohorts and may be overestimated compared with current practice
- Values from clinical experts more optimistic than published literature (range in literature 4 to 19.2)
- SMR is conceptually difficult to estimate – requires extensive follow up and comparison with general population

⊙ *Is it plausible that the standardised mortality ratio is 2 after the cure point?*

Company's new evidence: model changes
b. Utility value in relapsed health state [1]

Version	Utility value in relapsed health state
Company original base case	0.53: Company accept this may underestimate quality of life because model structure does not distinguish between people who achieve remission on secondary therapy from people with relapsed or refractory disease
Value used in committee's preferred model	0.83 after treatment: company consider an overestimate because some patients will have refractory disease
Company revised base case	0.655: midpoint of 0.53 (original base case) and 0.78 (Leunis et al. 2014)

Company's new evidence: model changes
b. Utility value in relapsed health state [2]

ERG comments

- Agree that 0.83 overestimates quality of life in short-term, but in the long-term, all alive patients in the relapsed health state will be in remission – relapsed or refractory disease will only be experienced for a short time
- Utility value should not be substantially lower than for patients with disease in remission after first-line treatment
- Company's argument that the value should be below 0.78 is reasonable, although utility values for remission after first-line and second-line therapy were not statistically significantly different in Leunis et al.
    - Applying 0.78 would have limited impact on the ICER

⊙ *Is a utility value of 0.655 for the relapsed health state plausible?*

Company's new evidence: model changes
c. Costs in the relapsed health state [1]

Committee's ACD considerations:

- *Routine care costs applied in the company's base-case model (£8,000 per year) too high*
- *Applying no costs after a certain point is implausible*
- *Scenario in which no health state costs were applied after the cure point was best to reflect clinical practice in England.*

- Company's revised base case includes costs of £2,000 per cycle for patients in the relapsed health state incurred until death (£4,884* in original base case)
- Estimated based on evidence from Wang et al 2014, although difficult to map exact costs to relapse health state that includes a mix of patients, and not all health states were reported in the study
- Company's exploratory analysis found that the ICER decreases when the cost of relapse increases (based on ERG base case, not committee's preferred assumptions)

*corrected after committee meeting

Company's new evidence: model changes
c. Costs in the relapsed health state [2]

ERG comments

- Wang study follow up is 6 years – may not be appropriate to extrapolate to a lifetime horizon
- Company's approach still assumes patients in the relapsed health state continue to incur substantial management and monitoring costs forever
- In the long-term, all alive patients will be in remission
- In the company's model, patients who achieve remission after first-line therapy do not incur any health state costs after treatment, so inconsistent to assume differently after second-line therapy
- When applied to committee's preferred model assumptions, the company's change increases the ICER

⊙ *Is it plausible that people in the relapsed health state have ongoing health costs of £2,000 per cycle?*

Company's new evidence: model changes
d. Alternative age-adjusted utility values

Committee's ACD considerations:

- Appropriate to adjust utility values in 2 health states *[complete remission after first-line therapy and post-stem cell transplant recovery]* for age

- Company has used a different method to adjust, basing the adjustment on the mean age of the patients in the utility value studies (older population), rather than mean starting age in the model

ERG comments

- Company's change accounts for utility values being sourced from older cohorts
- Adds computational complexity and means different age adjustments are used for difference utility values
- Marginal impact on ICER

⊙ *Are the company's age-adjustments for utility values appropriate?*

Company's new evidence: model changes

Summary – submitted by company, based on ERG base case

Amendment	ICER midostaurin (list price - NOT including PAS discount) vs standard of care	
	Individual change	Cumulative
ERG base case	£62,810	-
Correction of inconsistencies in ERG model*	£62,712	-
a. Survival after the cure point	£55,102	£55,102
b. Updated utility value in relapsed health state (0.655)	£55,579	£49,094
c. Costs in the relapsed health state (£2,000)	£42,869	£32,107
d. Alternative age-adjusted utility values	£61,904	£31,626
Company's revised base case	**£31,626**	**-**

*Corrections accepted by ERG

Changes to the economic model

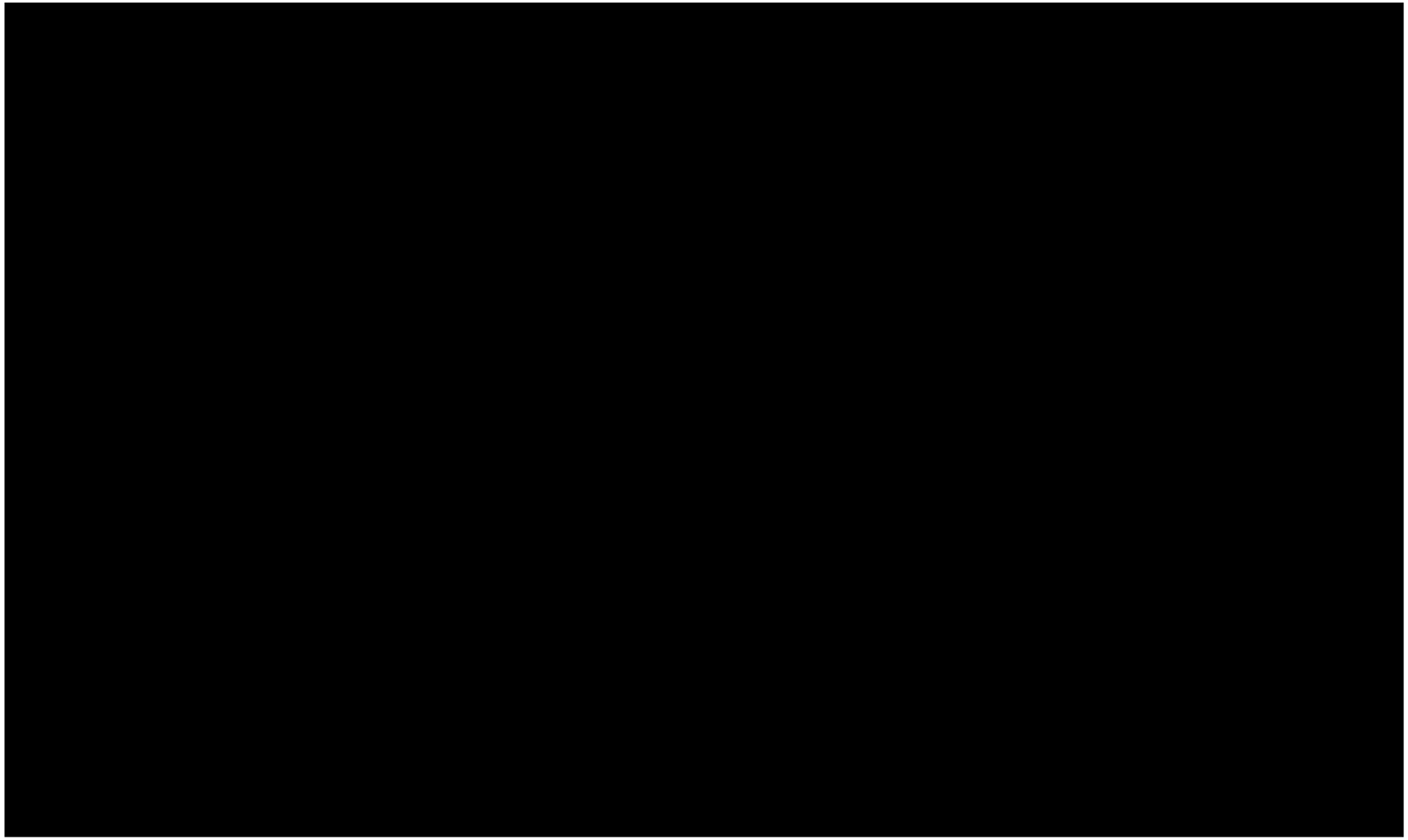
Summary – including committee's preferred assumptions*

Amendment	ICER midostaurin (list price - NOT including PAS discount) vs standard of care	
	Individual change	Cumulative
Committee's preferred assumptions in ACD	£62,818	-
Correction of inconsistencies in ERG model**	£63,488	-
a. Survival after the cure point	£53,695	£53,695
b. Updated utility value in relapsed health state (0.655)	£62,083	£52,126
c. Costs in the relapsed health state (£2,000)	£70,427	£56,740
d. Alternative age-adjusted utility values	£64,130	£56,749
Company's revised base case	**£56,749**	-

*Re-analysis carried out by the ERG. Age adjustment only applied when the alternative anchor proposed by the company exceeded the starting age of 60.
**Corrections accepted by the ERG.

End of life considerations

Company's response [2]



End of life considerations

Summary of ACD conclusions

Criterion	Data source	Indication	Age	Overall survival	
				Median (months)	Mean (months)
Short life expectancy, normally < 24 months	Maynadie (2013)	AML	15-70+	9.1	18
	Recher (2014)	AML	15-60	33	45
	Ohtake (2011)	AML	15-64	53	46
	Mandelli (2009)	AML	15-60	17	41
	Stone (2015) - RATIFY April 2015 cut off	FLT3+ve AML	18-60	26	[redacted]
	Company submission - RATIFY Sept 2016 cut off	FLT3+ve AML	18-60	[redacted]	[redacted]
	Knapper (2017) (highlighted by expert at first meeting)	FLT3+ve AML	5-68	>24 months	-

ACD: *The committee agreed that* [Maynadie] *was not likely to be representative of the UK population because it was based on relatively old registry data from 1995 to 2002, and included people from countries where life expectancy is lower than in the UK.*

Key issues for consideration

- Does midostaurin meet end of life criteria?
- Should the mean age of people in the model be lower than 60 years?
- Is it plausible that the standardised mortality ratio is 2 after the cure point?
- Is a utility value of 0.655 for the relapsed health state plausible?
- Is it plausible that people in the relapsed health state have ongoing health costs of £2,000 per cycle?
- Are the company's age-adjustments for utility values appropriate?