Slides for projector and public – CiC information redacted

Chair's presentation

Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine [ID1059]

3rd Appraisal Committee meeting

Committee D

AG: Liverpool Reviews and Implementation Group

NICE technical team: Nwamaka Umeweni, Lucy Beggs

Companies: Eisai, Bayer

15 May 2018

Issue for consideration

Overall, do the consultation comments and additional data provide sufficient evidence of the effectiveness of sequential treatment with lenvatinib and sorafenib?

History of the appraisal

Sep/Oct 2017

- **ACD1:** lenvatinib & sorafenib **not recommended**

Jan/Feb 2018

FAD: lenvatinib & sorafenib **recommended within their MA**

However,

- Section 3.6: *'insufficient evidence to draw conclusions on whether the treatments are effective when used sequentially after progression'*
- NHSE interprets decision as **optimised** (excluding people who have received prior TKI)
- Eisai lodge appeal

March 2018

- NICE retracts FAD and releases **ACD2** to enable consultation on sequential treatment → Section 1.1: **optimised** (excluding people who have received prior TKI)

Today

- Consider consultation response to ACD2

Technologies: lenvatinib & sorafenib

Lenvatinib	Sorafenib
• Lenvima (Eisai) 4mg & 10mg capsules • Inhibits multiple receptor tyrosine kinases including vascular endothelial growth factor (VEGF) receptors 1-3, • Recommended daily dose 24mg • Continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs • £1,437 for 4 and 10mg (BNF Apr 2018) • Cost per year: £52,307(assuming max starting dose, source: AR) • **Confidential PAS available**	• Nexavar (Bayer) 200mg tablets • Inhibits multiple receptor tyrosine kinases including VEGF receptors 2-3 • Recommended daily dose 800 mg • Continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs • £3,576.56 for 112 x 200mg tablets (BNF Apr 2018) • Cost per year: £38,746 (assuming max starting dose, source: AR) • **Confidential CAA available**
Marketing authorisation	
Patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine	

Changes in ACD2

Recommendation and clinical effectiveness

Optimised recommendation made explicit in Section 1.1: 'Lenvatinib and sorafenib are recommended…**only if [people] have not had a tyrosine kinase inhibitor before**'

Section 3.6 updated:

- Prior TKI treatment not allowed in DECISION (sorafenib trial)
- In SELECT (lenvatinib trial):
  - 24% had TKI (inc. sorafenib) before lenvatinib & some may have had sorafenib after progression on lenvatinib
  - Lenvatinib vs placebo subgroup PFS HR = 0.22 (95% CI 0.12 to 0.41)
  - OS not reported
  - Small numbers in this subgroup
- Lenvatinib delays disease progression in this subgroup but no evidence of OS benefit with lenvatinib or sorafenib
- '*Committee concluded… **insufficient evidence** to draw firm conclusions on whether the treatments are effective when used sequentially after progression'*

Changes in ACD2
Cost effectiveness

Additional paragraph → Section 3.21:

- Companies & AG did not present cost-effectiveness analyses based on previous TKI treatment
- Because previous TKI treatment was not allowed in DECISION, sorafenib only considered for 1L use
- Committee preferred to see separate cost-effectiveness results according to previous TKI treatment for lenvatinib because of uncertainty about the benefit of the drugs when used sequentially
- Recommendation for sorafenib and lenvatinib limited to people who have not had previous TKI treatment

ACD2 consultation responses

- Consultee comments from:
  - Bayer
  - Eisai
  - Royal College of Physicians
- Web comments from:
  - 1 healthcare professional
  - 14 patients/carers
  - 12 members of the public

Please note: Web comments were duplicates of comments from the previous consultation and did not address the specific issue being consulted on. For transparency, themes from these comments were:

- Importance of additional treatment options for this patient group
- Concern about potential for regional inequality in access to treatment
- Concern that people with rare cancers are disadvantaged compared to people with more common forms of cancer

Consultation comments

- Letter from clinical expert: '…*it is widely accepted practice elsewhere in the world to use these drugs sequentially.'*
- Royal College of Physicians: Request for cost-effectiveness analysis for prior-VEGFR subgroup
- Bayer: cost-effectiveness analysis could be done if OS data were available
- *'Given the small number of patients and high level of unmet need, sequential TKI treatment has the potential to offer significant benefit to patients, with modest budget implications.'*
- Web comments from member of Thyroid Cancer Alliance: Optimised recommendation prevents access to lenvatinib for any people who received sorafenib via the CDF
- Sequential treatment is available in Scotland & Wales → regional disparity

Eisai's comments

SELECT: subgroup analysis

- 25% lenvatinib & 20% placebo had prior VEGFR therapy → interpret with caution

SELECT subgroup	PFS (HR: lenvatinib vs placebo)	Median PFS
Prior VEGFR therapy	HR 0.22 (0.12 to 0.41)	15.1 months
No prior VEGFR therapy	HR 0.20 (0.14 to 0.27)	18.7 months

- Similar PFS benefit in both subgroups
- Refer to AG report (p154): *'lenvatinib is more effective when compared with placebo/BSC for all patients and… prior VEGFR-targeted therapy… does not influence the potential for a patient to benefit from treatment.'*
- 'Real world' evidence could help to address uncertainty arising from small subgroups

- Eisai provided additional evidence from a compassionate use programme (slide 10) and real world data (slide 11) to support sequential use of treatments
- However, it did not provide a cost-effectiveness analysis in line with committee's preference of section 3.21 of ACD2

Eisai's additional evidence

Compassionate use programme

- Data from compassionate use programme provided at consultation
- Between Feb 2017 & Apr 2018, 52 patients given lenvatinib through compassionate use programme
- All patients had previously received sorafenib
- 18 patients no longer on treatment; average time on treatment = 6.56 months
- Estimated time on treatment of up to [redacted] months (however, variable treatment starting and stopping times means benefit is hard to quantify)
- Consultation comment (Eisai)= *'Data on these patients currently available to Eisai is limited, but it is evident from the estimated time on treatment that there is a clear benefit of lenvatinib in second-line patients.'*
- Letter from Eisai after original FAD = Compassionate use programme included patients who had received sorafenib on the request of NHSE → indication that sequential therapy is standard practice

Eisai's additional evidence

- At consultation Eisai provided supplementary 'real world' evidence
- Lenvatinib audits in France (Berdelou et al. 2018), Switzerland (Balmelli et al. 2018) & Italy (Nervo et al. 2018) provide more information about prior-TKI subgroup (however, efficacy results presented for ITT population rather than subgroup)

	SELECT	Berdelou et al.	Balmelli et al.	Nervo et al.
Patient Characteristics				
Patients on lenvatinib (n)	261	75	13	12
Patients with ≥1 prior TKI	25.3%	42.7%	53.8%	66.7%
Efficacy results for ITT population				
Median PFS (months)	19.4	10	7.2	-
Median OS (months)	11.0*	Not met	22.7	-
Complete/partial response	64.8%	31%	30.8%	41.7%
Stable Disease	23.0%	51%	30.8%	16.7%
Dosing & duration of treatment				
Mean/median dose (mg)	16.3/15.5	-/20	-/-	18.2/-
Median (months)	16.0	6	5	-

*AG: SELECT data provided by company, OS<PFS → clinically implausible

AG comment

- PFS benefit is maintained in SELECT patients with & without prior TKI
- However, small numbers → subgroup results should be interpreted with caution
- Even if OS data available for subgroup, many limitations & uncertainties (e.g. violation of proportional hazards affects interpretation of hazard ratios)
- 'Real world' studies may not be generalisable as patients had worse prognosis than in SELECT
- Median PFS from 'real world' audits do exceed placebo arms of DECISION & SELECT but inappropriate to draw conclusions from naive comparison because audits and RCTs differ in setting & population
- Efficacy results not available for compassionate use programme & only presented for ITT population in 'real world' studies → SELECT is only trial that can be used to estimate relative effectiveness

Conclusion:

- New data no more conclusive than previously reported subgroup results
- If available, OS findings from SELECT subgroup may be informative BUT face same limitations as in ITT population
- **Even if additional subgroup data were available, this would not be enough to estimate cost-effectiveness robustly**

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