Committee and public observer slides

Lead team presentation Cabozantinib for previously treated advanced renal cell carcinoma – STA

3rd Appraisal Committee B meeting, 23 May 2017

Lead team: Ken Stein, Mark Chapman, Danielle Preedy

Chair: Amanda Adler

ERG: BMJ Technology Assessment Group

NICE technical team: Aminata Thiam, Ahmed Elsada, Melinda Goodall

Company: Ipsen

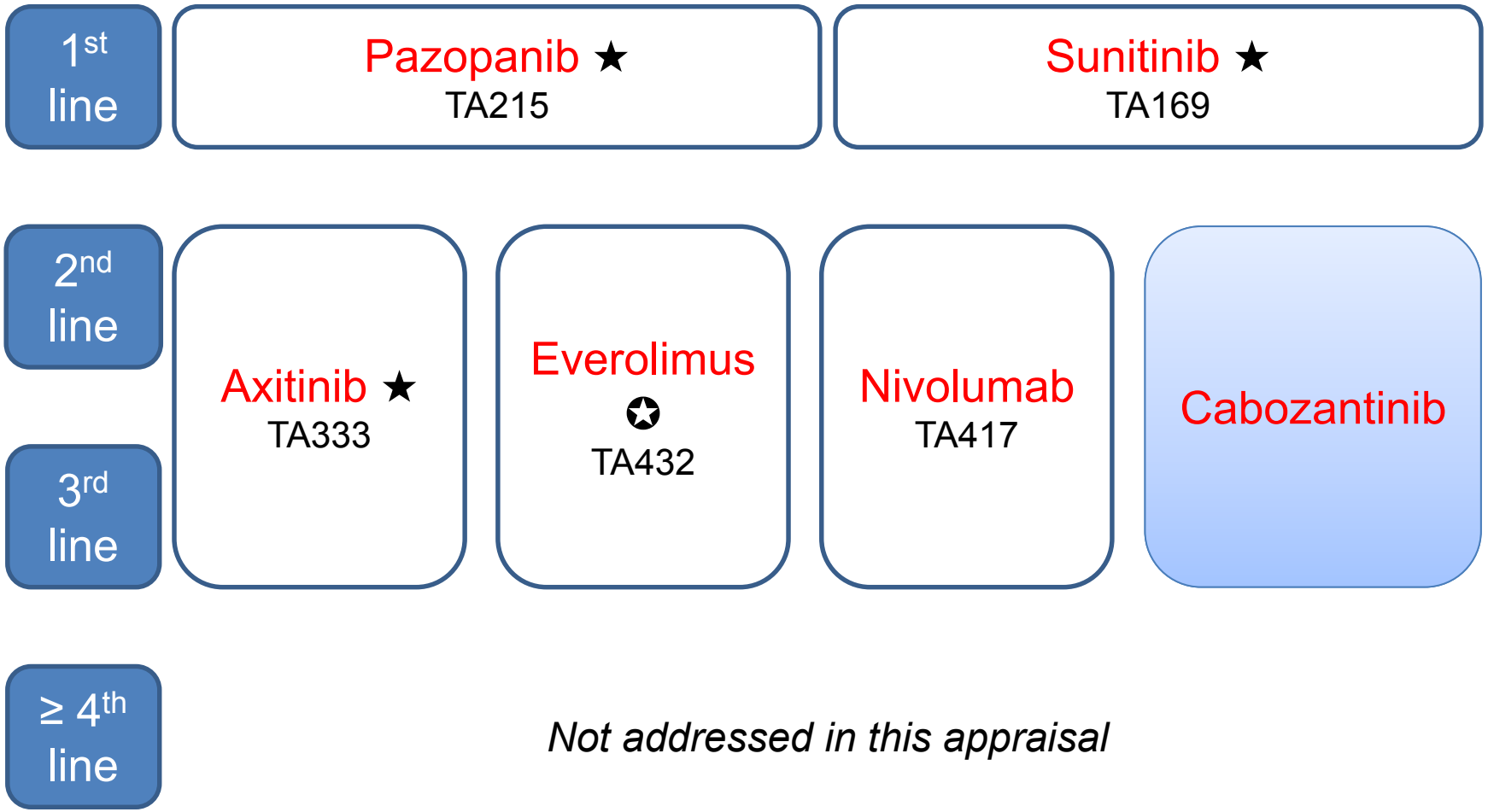
Appraisal consultation document (ACD) preliminary recommendation

Cabozantinib is not recommended within its marketing authorisation for treating advanced renal cell carcinoma in adults after vascular endothelial growth factor (VEGF)-targeted therapy.

Technology appraisals to date

Cabozantinib: 2nd or 3rd line (combined population)

Comparators: axitinib, everolimus and nivolumab but not best supportive care



★: oral tyrosine kinase inhibitors

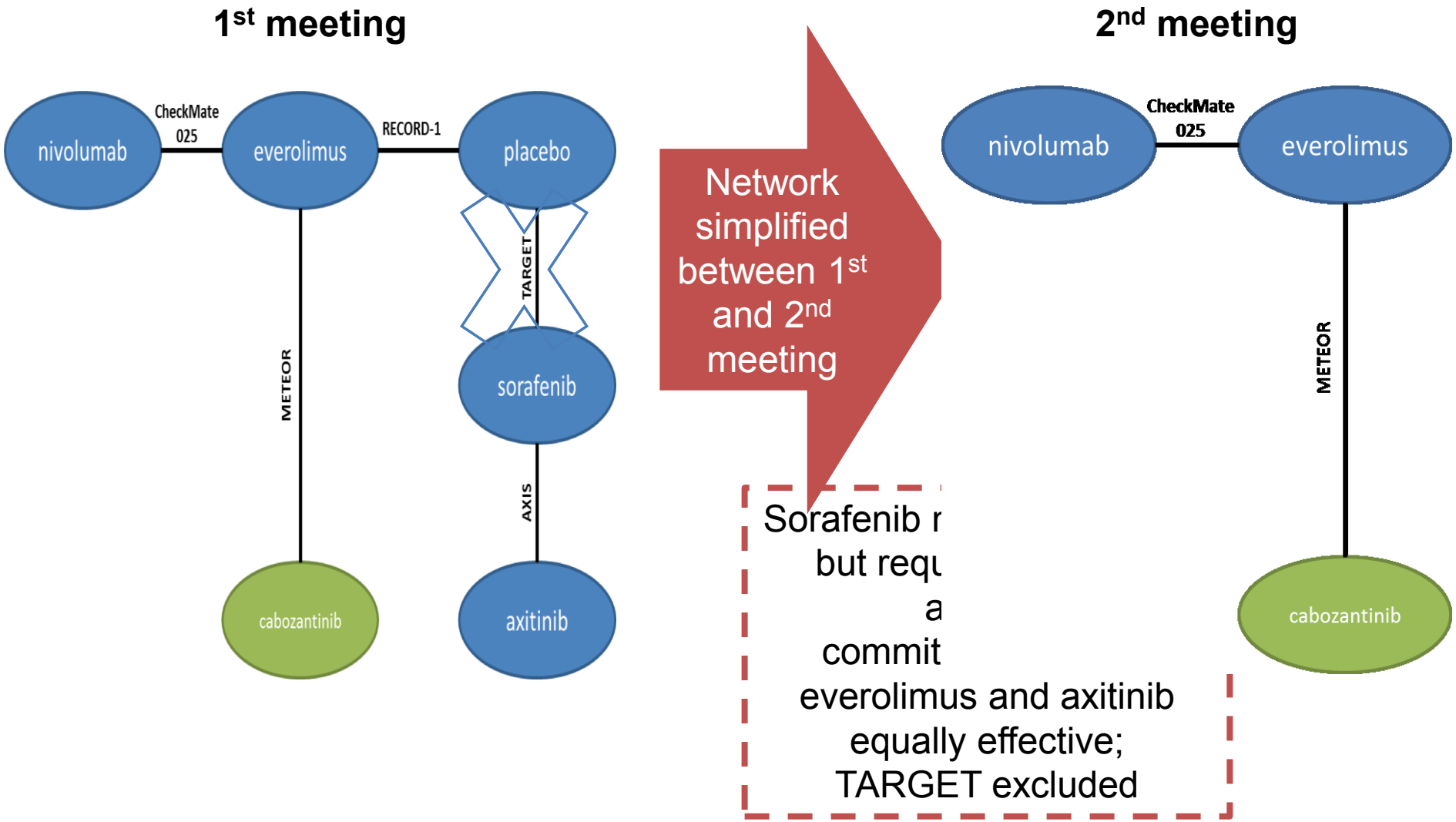
✪: oral mammalian target of rapamycin (mTOR) inhibitor

Evidence considered by the committee

- METEOR (n=658)
  - Open-label RCT
  - Cabozantinib vs. everolimus
- Network meta-analysis
  - Cabozantinib vs. comparators other than everolimus (axitinib and nivolumab)
- Analyses in economic model
  - Trial-based: METEOR data, comparison only with everolimus
  - Network-based: data from network, all comparators

Company's *network meta-analysis*

Cabozantinib vs. comparators other than everolimus



Committee's key conclusions

Population	Cabozantinib considered as 2nd or 3rd line treatment (combined population)
Comparators	Axitinib, nivolumab and everolimus
Everolimus	• Whether everolimus a comparator uncertain: – **At 1st meeting (Jan 2017)**: everolimus only available via CDF for 2nd line use if axitinib unsuitable – Clinicians could not use it beyond this setting – **Between 1st and 2nd meeting (Feb 2017)**: everolimus recommended for routine commissioning for 2nd line use and beyond (CDF reconsideration) with a drop in price (PAS discount) – Clinicians likely prefer to use it later than 2nd line in treatment – 2nd ACD sought comments on likely positioning of everolimus in treatment pathway

Committee's key conclusions

Duration of cabozantinib's effect	Model assumes effect continues up to 30 years… Highly uncertain as follow-up in trial under 2 years
Long-term survival of nivolumab	Model assumes people alive and on nivolumab 5 years after starting treatment remain progression-free until death… but no evidence to support this
Utility values	Committee preferred trial-based values (METEOR), but agreed to take into account values from AXIS (preferred by the ERG)
End of life	• Met when compared with axitinib and everolimus • Not met when compared with nivolumab
ICERs (incremental analysis)	• Everolimus dominated axitinib • Cabozantinib vs. everolimus > £60,000/QALY • Cabozantinib dominated nivolumab

Key issues for consideration

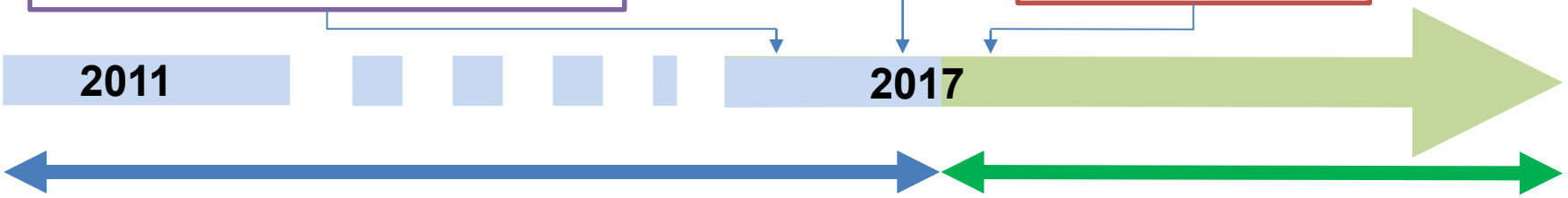
1. Position of everolimus in the treatment pathway
2. If everolimus is a relevant comparator, are there patient who cannot take everolimus (but can take cabozantinib)?
3. Cost effectiveness of cabozantinib beyond 3rd line
4. Most appropriate source of utility values

Appraisals of cabozantinib's comparators

Nov 2016: nivolumab recommended for 'previously treated advanced RCC in adults' (TA417), include **everolimus at list price**

Jan 2017: cabozantinib 1st meeting

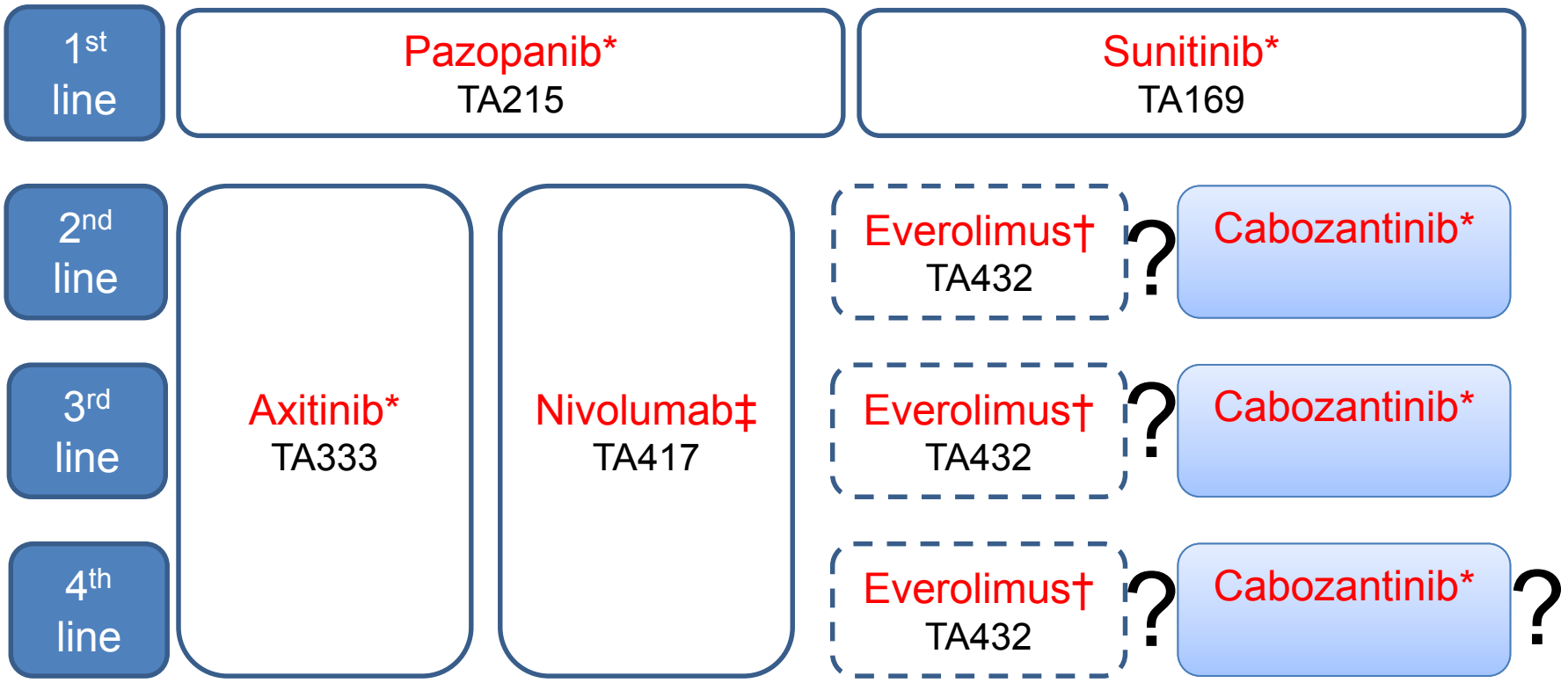
Mar 2017: cabozantinib 2nd meeting, include **everolimus at PAS price**



Apr 2011	Feb 2017
Everolimus **not recommended** for routine commissioning	Everolimus **recommended** for routine commissioning post CDF reconsideration (TA432)
Available through CDF	2nd or later line
Only 2nd line if axitinib unsuitable[1]	New PAS price

[1]Everolimus MA: treatment of patients with advanced RCC that has progressed during or after treatment with VEGF-targeted therapy

Uncertainty in current treatment pathway



* oral tyrosine kinase inhibitors
† oral mammalian target of rapamycin (mTOR) inhibitor
‡ PD-1 inhibitor

ACD consultation responses

- Ipsen (company)
  - New patient access scheme (PAS)
  - Scenario analyses using alternative utility values
- Patient/professional organisations
  - Kidney Cancer UK
  - Kidney Cancer Support Network
  - Kidney Research UK
  - NHS England
- Queen Mary University
- Clinical expert
- Web comment

General comments

- Hope NICE will recommend cabozantinib[1]
- Willingness for cabozantinib to be prioritized over other agents given its survival benefit[2]
- Clinicians should have the ability to choose the most cost-effective treatments[1]
- Call for “guidelines in the area of the sequencing of second-line treatments and beyond”[3]

[1]Kidney Cancer Support Network; [2]Queen Mary university; [3]Kidney Cancer UK

Benefits of cabozantinib

Response from consultees

- First drug to act on multiple tyrosine kinase receptors
- Designated a ‘promising innovative medicine’ by UK MHRA
- Addresses unmet need
- Additional alternative in 2nd line treatment and beyond
  - More choices allow individualised treatment
  - Enables the best possible quality of life for patients
- Particularly effective against bone metastases
  - Should be considered within CDF while further survival data are collected from cohort of patients with bone metastases

Key: CDF, Cancer Drug Fund; MHRA, Medicines and Healthcare products Regulatory Agency; TKI, tyrosine kinase inhibitor

Position of everolimus

Response from non-company consultees (I)

- Real-world evidence data in patients with advanced or metastatic renal cell carcinoma
  - Kidney Cancer UK annual patient survey (n=111)
    - ◊ Everolimus not taken once as a 2nd line or beyond
    - ◊ Only taken as a 1st line treatment as part of a clinical trial (2016)
  - Kidney Cancer Support Network data (n=1,000): everolimus taken by 2 patients, not used on a regular basis
- In clinical practice, it seems that everolimus is used as 4th line after failure of nivolumab and axitinib
  - Therefore, main comparators in 2nd line treatment are axitinib and nivolumab

Position of everolimus

Response from non-company consultees (II)

- NHS England* defines treatment algorithm (awaiting consultation):
  - 1st line: sunitinib or pazopanib
  - 2nd line: axitinib or nivolumab or everolimus
  - 3rd line: axitinib or nivolumab or everolimus depending on what was used as 2nd line treatment
  - 4th line: axitinib or nivolumab or everolimus depending on 2nd and 3rd line treatment
- Because of its different mechanism of action, there is a biological plausibility for everolimus to be active after nivolumab or axitinib, same applies for cabozantinib (multi-targeted TKI)

*In line with NHS England statement
Key: TKI, tyrosine kinase inhibitor

Position of everolimus

CDF reconsideration appraisal – 'unmet need'

- "Committee recognised that the treatment pathway for advanced RCC has changed since the publication of NICE's original technology appraisal guidance on everolimus. New treatments recommended by NICE are now available: axitinib is recommended as an option after treatment failure with a first-line tyrosine kinase inhibitor or a cytokine. This was reflected in the updated NICE scope for the Cancer Drugs Fund reconsideration. Axitinib and best supportive care were considered to be comparators for everolimus. In addition, nivolumab was recommended for previously treated advanced RCC in adults in November 2016 and can be now used at this place in the pathway. The committee heard from clinical experts that there is still unmet clinical need for some patients with advanced RCC. The committee agreed that everolimus remains a valuable treatment option for people with advanced RCC."

Position of everolimus

CDF reconsideration appraisal – consultees comments

- "NHSE considers that any NICE recommendation for nivolumab within its licensed indication is likely to result in considerable use of nivolumab either as 2nd line treatment with axitinib being used 3rd line (as there is as yet no biological reason shown why axitinib should not work as well post-nivolumab as pre-nivolumab) or nivolumab used as 3rd line post-axitinib. Either of these scenarios would displace any potential availability of everolimus to 4th line therapy." (NHS England)

- "Patients who are not responsive to VEGF TKIs, or who are unable to tolerate the side effects to VEGF TKIs, might benefit more from treatment with an mTOR inhibitor, such as everolimus." (Kidney Cancer Support Network)

Position of everolimus

Company response (I)

- Company approached 20 clinicians, 15 responded
  - 2nd line: none would use everolimus
  - 3rd line: 1 would use everolimus
- Scotland has had:
  - Axitinib since Nov 2013
  - Everolimus since Nov 2014
  - Only axitinib deemed a comparator for nivolumab and cabozantinib in meeting of Scottish Medicine Consortium[1]

[1]Company reports on 'meeting held in public', reference not provided

Position of everolimus

Company response (II)

- "… once everolimus is used in 2nd line, the comparator for 3rd line must be either nivolumab or axitinib. Similarly, if everolimus is considered to be the appropriate comparator in 3rd line, then the treatments which precede it would have to be nivolumab or axitinib."

⊙ *Where is everolimus positioned in the treatment pathway? Based on this, what should be the comparators for cabozantinib?*

Cost effectiveness

Company response

- It is illogical that “axitinib and nivolumab, which are confirmed by the ACD to be less cost-effective than cabozantinib, will be available for use while the more cost-effective drug (cabozantinib) will be rejected simply because it is not cost-effective against a drug (everolimus) that is not used in clinical practice in these lines of therapy. We understand that this is the product of sequential single technology appraisals in the same therapy area…”

Cost effectiveness

Clinician response

- "… I imagine everolimus has been approved as a result of a substantial discount that happened after the approval of nivolumab. It seems that cabozantinib is now being compared with reduced price of everolimus whereas nivolumab was compared with the full price – this potentially leads to the rejection of cabozantinib and the acceptance of nivolumab – this seems illogical since as I understand it, the NICE appraisal suggests cabozantinib is more cost effective than nivolumab?"

Cost-effectiveness

Kidney cancer support network response

- ICER decision rules used by NICE can be unfair to patients with rare cancers
  - N.b. cost effectiveness does not depend on size of population
- NICE and manufacturers should agree a price
  - "… to make this new and innovative drug available to the patients who need it; failure to do so would be seen as failure of professional competence. NICE and the manufacturer need to think outside the box to agree an alternative funding process, and work collaboratively to negotiate an acceptable patient access scheme."

Utility values

Company response

METEOR (EQ-5D-5L)

- Used in company base case
- Preferred by committee
- Considered high by ERG
- *Company*: EQ-5D-5L generates higher values than EQ-5D-3L (Devlin et al. 2016)

AXIS

- Preferred by ERG
- Committee agreed to take it into account
- *Company*: not appropriate as data aggregate values for 'prior-cytokine' and 'prior-VEGFR' (data not accessible to company)

CheckMate025 (everolimus arm)

- *Company*: if not METEOR, then everolimus arm of CheckMate025 (nivolumab)
- Not considered before by committee

	Progression-free survival	Progressed disease	NICE TA
METEOR	0.817	0.777	
AXIS	0.690	0.610	TA333
CheckMate025 (everolimus arm)	0.760	0.700	TA417

Key: TA, technology appraisal; VEGF, vascular endothelial growth factor

⊙ *Which source of utility does the committee prefer?*

CDF Recommendation Decision Pathway

Starting point: drug not recommended for routine use

Proceed down if answer to each question is yes

1. Why is drug not recommended? Is it due to clinical uncertainty?

2. Does drug have plausible potential to be cost-effective at the current price, taking into account end of life criteria?

3. Could data collection reduce uncertainty

4. Will ongoing studies provide useful data?

and

5. Is CDF data collection feasible?

Recommend enter CDF

Define the nature of clinical uncertainty and the level of it. Indicate research question, required analyses, and number of patients in NHS in England needed to collect data