Slides for committee, projector and public – no confidential information

Chair's presentation

Tivozanib for treating advanced renal cell carcinoma

2nd appraisal committee meeting

Committee B

Lead team: Stephen Palmer, Sanjay Kinra, Nigel Westwood

Chair: Amanda Adler

ERG: BMJ Technology Assessment Group

NICE technical team: Kirsty Pitt, Jasdeep Hayre, Ross Dent, Ahmed Elsada

Company: EUSA Pharma

20th September 2017 at NICE, London

Issues for discussion

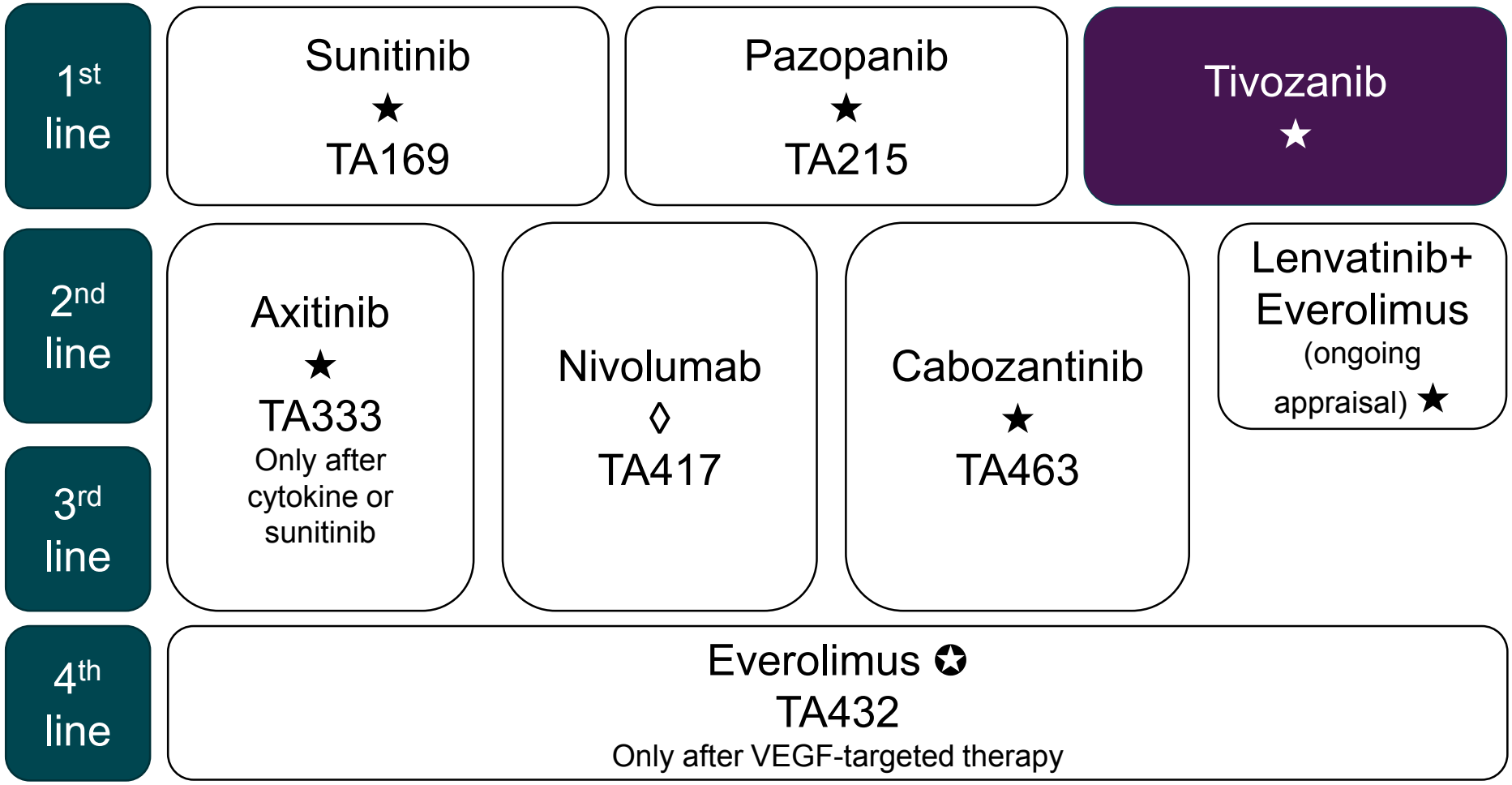
- Has the committee heard evidence to change its decision on ‘innovation’?
- Does tivozanib cause fewer, less severe adverse events than sunitinib or pazopanib?
- Does the ERG’s modelling appropriately capture the impact of any differences in a) quality of life benefits and b) outcomes from greater adherence to treatment?
- Has the committee heard evidence to change its conclusion that the simplified network meta-analysis is appropriate for decision-making?
- Does the committee agree with the company’s reasons for not including all the committee’s preferred assumptions in its revised modelling?

Tivozanib (Fotivda)
EUSA Pharma

Anticipated UK marketing authorisation (CHMP positive opinion issued)	First line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGF receptor and mTOR pathway inhibitor-naive following disease progression after one prior treatment with cytokine therapy for advanced RCC
Administration	Oral therapy
Mechanism of action	Tyrosine kinase inhibitor with affinity for all 3 VEGF receptors, leading to reduced tumour vascularisation
Dosage	1,340 micrograms (1 tablet) once daily for 21 days, followed by a 7-day rest period 890 micrograms capsule is available so the dose can be reduced if necessary

Abbreviations: VEGF, vascular endothelial growth factor; mTOR, oral mammalian target of rampamycin

Current treatment pathway



Key; VEGF, vascular endothelial growth factor
★: oral tyrosine kinase inhibitors; ✪: oral mammalian target of rapamycin (mTOR) inhibitor; ◊ **:** anti-programmed death 1 (PD-1) inhibitor

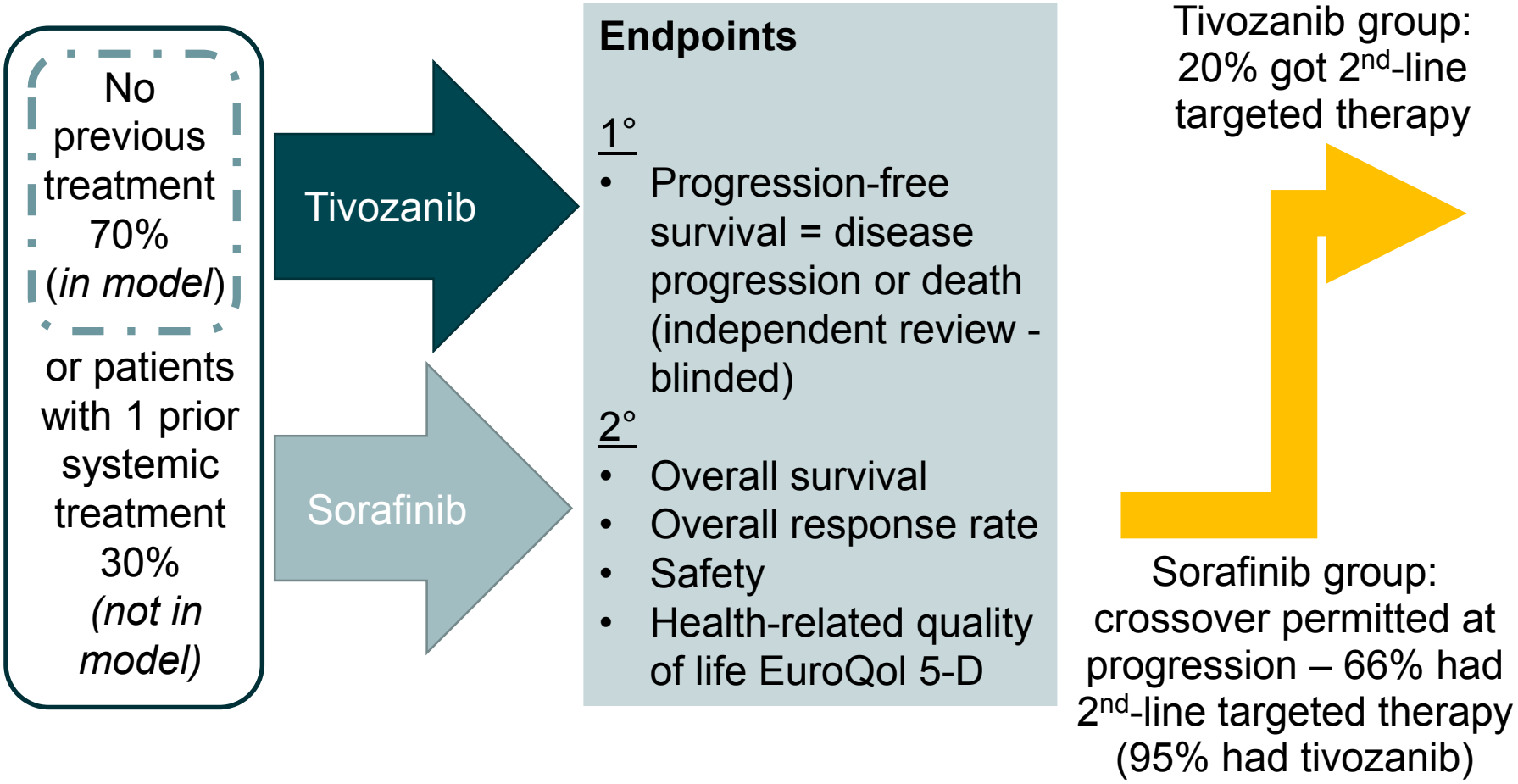
TIVO-1 trial: tivozanib vs. sorafenib

	Committee's considerations
Comparator	Sorafenib not recommended by NICE (TA178); not used in NHS
Population	Only previously untreated population relevant
Generalisability	Most patients enrolled in Central or Eastern Europe – may have poorer access to subsequent therapies than patients in England
Subsequent treatments and crossover	After progression, patients in tivozanib group received another targeted treatment (VEGF inhibitor or mTOR inhibitor) as did patients in sorafenib group who also crossed over to tivozanib
Statistical analysis	2 analyses to adjust for crossover: • Inverse probability of censoring weights • Rank preserving structural time failure Both have limitations and results inconsistent

Key trial: TIVO-1

517 patients, open-label, Phase III, 70% untreated, 6 data cuts

Extension study: July 2013 data cut



Results: TIVO-1
progression free and overall survival

	Median, months		Hazard ratio	95% confidence intervals
	Tivozanib	Sorafenib		
Progression-free survival				
Previously untreated subgroup (Dec 2011 data cut)	12.7	9.1	0.76	0.58 to 0.99 p=0.04
Overall survival				
Previously untreated subgroup, unadjusted for crossover (Jul 2013 data cut)	Not reported	Not reported	1.23	0.90 to 1.67 p=not reported
Previously untreated subgroup, RPSFT adjusted*	Results presented in Kaplan-Meier plots tivozanib appears worse than sorafenib			
Full population, unadjusted for crossover (Jan 2015 data cut)	29.0	34.1	1.18	0.93 to 1.50 p=0.08
Full population, IPCW-adjusted*	Not reported	Not reported	1.02	0.67 to 1.55 p=0.92

*data cut unclear

Evolution of network meta-analyses

Company original submission

Company response to "request for clarification"

Overall survival*
Untreated population:
13 studies, 11 therapies

Progression-free survival*
Untreated population:
15 studies, 11 therapies

Overall survival/ progression-free survival
- Simplified structure:
  4 studies, 4 therapies (next slide)
- Fractional polynomial model

Adverse events*
Untreated population: multiple networks for 8 adverse events, grade 1 and 2 and grade 3+
(up to 12 studies comparing 11 therapies)

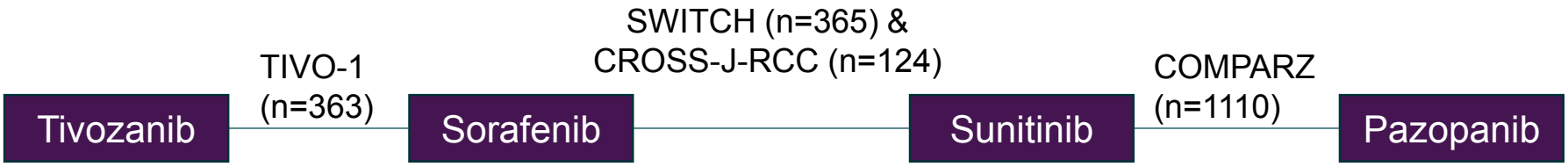
Adverse events
- Simplified structure:
  4 studies, 4 therapies
- Grade 3+ diarrhoea, fatigue, hypertension and liver disorder

★ used in company base case
● used in ERG base case

*network meta-analyses for mixed pretreated population also submitted

Network meta-analysis

- To compare tivozanib with relevant comparators: sunitinib and pazopanib



- Company used fractional polynomial in network meta-analysis for PFS and OS because for PFS, proportional hazards assumption did not hold
- Committee preferred ERG's choices of fractional polynomial curves

ERG's preferred results from network meta-analysis		
	Median PFS (months)	**Median OS (months)**
Tivozanib	6.1	25.0
Sunitinib	6.8	27.5
Pazopanib	8.4	29.2

Committee conclusion: At best, tivozanib may be similar to pazopanib and sunitinib in extending OS and PFS, but OS could be shorter with tivozanib

⊙ *Does the committee maintain this conclusion?*

Network meta-analysis results for adverse effects

- Pairwise estimates of treatment effects (grade 3+) - odds ratios

Tivozanib vs…	Diarrhoea	Fatigue/ asthenia	Hypertension	ALT increased	AST increased
Sunitinib Median (95% CrI)	0.11 (0.03 to 0.43)	0.69 (0.17 to 2.85)	1.42 (0.64 to 3.18)	0.23 (0 to 7.13)	0.13 (0 to 3.22)
Pazopanib Median (95% CrI)	0.10 (0.02 to 0.40)	1.22 (0.29 to 5.29)	1.42 (0.60 to 3.39)	0.06 (0 to 1.87)	0.030 (0 to 0.75)

CrI, credible interval; ALT, alanine aminotransferase; AST, aspartate aminotransferase

ERG comments in original report: results do not provide robust evidence to support company's assertion that tivozanib safer than pazopanib and sunitinib

	Committee's considerations (1)
Treatment effects against NHS comparators	Treatment effects uncertain in network meta-analysis: • 95% credible intervals wide • Company's OS curves for sunitinib and pazopanib lack clinical face validity - inconsistent with direct results from COMPARZ • Did not adjust for crossover in trials Choice of PFS and OS curves has a **large** effect on ICERs – Committee prefers ERG's approach
Utility values	**Small** effect on results; committee prefers ERG's approach: • Utility values from trial for untreated (not full) population • No utility decrements for adverse effects; likely already captured
Adverse events	**Small** effect on results; committee prefers ERG's approach: • Odds ratios from 'post-clarification' network meta-analysis and adverse event incidence rates from trial for untreated population
Relative dose intensities*	**Large** effect on results: ERG included (94% for tivozanib, 86% for sunitinib and pazopanib), company assumed 100% for all. Committee considered likely closer to ERG's estimates
Subsequent therapies	**Large** effect on results: ERG's modelling better reflects current treatment pathway Company included only costs– prefer including benefits also

** Amount of drug given relative to amount that reflects standard treatment*

	Company base-case	ERG base-case
Progression-free survival	Fractional polynomial (FP)-based network meta-analysis P1=-2, P2=-1	FP-based network meta-analysis P1=-3, P2=-2.5
Overall survival	FP-based network meta-analysis P1=-2, P2=-1	FP-based network meta-analysis P1=-2, P2=-1.5
Utility values	TIVO-1 full population	TIVO-1 untreated population
Adverse events	• Rates from TIVO-1 **full** population • Odds ratios from 'pre-clarification' network meta-analysis • Utility decrements	• Rates from TIVO-1 **untreated** population • Odds ratios from 'post-clarification' network meta-analysis • No adverse event utility decrements
Resource use	Monthly blood test omitted	Monthly blood tests included
Relative dose intensity	100% for all therapies	Different for each therapy
2nd line therapies	60% axitinib, 40% BSC	Reflect current treatment pathway

Cost-effectiveness results

Committee preferred ERG's base-case model:

- Same QALY gain for pazopanib and sunitinib– reflects results of COMPARZ trial which compared pazopanib and sunitinib directly
- Discounts **not** confidential for pazopanib and sunitinib, but **are** confidential for 2nd line therapies and beyond
- With these discounts, **pazopanib + sunitinib dominate tivozanib**
- Remained concerned about uncertainty in size of treatment effects and that model did not capture benefits of subsequent therapies

Committee considered scenario analysis:

- Assumed all 3 treatments equally effective
  - Likely very optimistic as network meta-analysis suggests tivozanib may be less effective than either pazopanib or sunitinib
- Including confidential discounts of subsequent therapies, **modelled costs of tivozanib remain higher than pazopanib and sunitinib**

Other considerations

Tivozanib did not meet end of life criteria

Tivozanib not considered innovative

Tivozanib not appropriate for Cancer Drugs Fund which does not collect data on pazopanib and sunitinib to compare effectiveness

ACD: preliminary recommendation

Tivozanib not recommended for treating advanced renal cell carcinoma in adults who have had no previous treatment, or who have had 1 treatment with a cytokine

ACD consultation responses

- Consultee comments from:
  - Kidney Cancer Support Network
  - Company (EUSA Pharma)

ACD comments: unmet need and innovation

Patient and professional organisations:

- Tivozanib is an innovative treatment with a different mode of action to existing treatments
- There is unmet need for effective treatments
- Quality of life and overall survival are important
- Treatment options allow more individualised treatment

Company

- Unmet need for more acceptable treatments
- Tivozanib offers an important alternative to pazopanib and sunitinib because of “its preferential adverse event profile”

⊙ *Has the committee heard evidence to change its decision on ‘innovation’?*

ACD comments: adverse events (1)

Company: tivozanib has better adverse event profile than comparators

Company:

- Adverse events which have biggest impact on quality of life were less frequent and less severe with tivozanib in TIVO-1 than sunitinib and pazopinib in COMPARZ

	Tivozanib*	Sunitinib	Pazopanib
Fatigue	19%	63%	55%
- grade 3 or above	*5%*	*17%*	*10%*
Diarrhoea	23%	57%	63%
- grade 3 or above	*2%*	*8%*	*9%*
Hand and foot syndrome	14%	50%	29%
- grade 3 or above	*2%*	*11%*	*6%*

**full population*

- Mohamed et al. (2011) study suggests that increasing PFS by 10 months is almost as important as avoiding severe fatigue
- Wong et al. (2012): patients willing to forgo 4.4, 3.5 and 2.1 months PFS to reduce fatigue, 'stomach problems' and hand and foot syndrome respectively from severe to mild-moderate

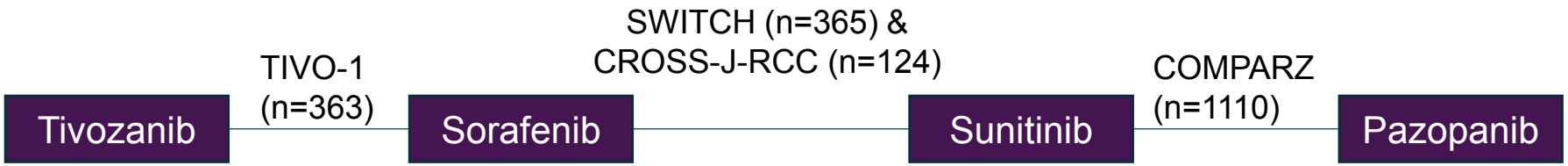
ACD comments: adverse events (2)

ERG: Network meta-analysis does not support view that tivozanib has favourable safety profile

ERG:

- Both the company and ERG model include the impact of adverse events on quality of life and costs
- Company comparison is naive and breaks with-in trial randomisation
- Network meta-analysis results are more appropriate as:
  - benefits of randomisation are maintained
  - includes additional adverse event data for sunitinib from the other trials in the network rather than just data from COMPARZ
  - variation in the estimates is reflected in credible intervals
- Results of network meta-analysis do not support view that tivozanib has a favourable safety profile compared with pazopanib and sunitinib (next slide)

Adverse events network meta-analysis



- Pairwise estimates of treatment effects (grade 3+) - odds ratios

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CrI, credible interval; ALT, alanine aminotransferase; AST, aspartate aminotransferase

⊙ *Does tivozanib cause fewer, less severe adverse events than comparators?*

ACD comments: Adverse events and treatment effectiveness (1)

Company: fewer dose reductions/interruptions and less stopping treatment with tivozanib lead to better outcomes

Company: more people remain on a full dose compared with sunitinib and pazopanib - this means people tolerate tivozanib better

Adverse events leading to:	Tivozanib	Sunitinib	Pazopanib
Reducing dose	14%	51%	44%
Interrupting treatment	19%	49%	44%
Stopping treatment	4%	20%	24%

- Retrospective study: people taking sunitinib with dose intensity <70% or who stop treatment do not live as long as people taking intended dose
  - company states that this shows importance of maintaining full dose
  - tivozanib relative dose intensity (94%) higher than sunitinib (86%)

ACD comments: Adverse events and treatment effectiveness (2)

ERG: Modelling already reflects impact on outcomes of differences between treatments in dose reductions/interruptions and stopping treatment

ERG:

- Open-label design of TIVO-1 and COMPARZ increases potential for investigator bias when deciding to interrupt/stop treatment or reduce dose
- Doses of tablets and protocol may influence the decision to reduce dose:
  - sunitinib and pazopanib can be reduced and increased in increments
  - tivozanib available only in 2 doses and in TIVO-1, dose could not be increased again if reduced
- Different drug regimens may 'define' dose interruptions differently
  - tivozanib taken 3 weeks in 4-week cycle, sunitinib 4 weeks in 6-week cycle
- Clinical benefit observed in trials reflects actual doses, so any differences in progression-free or overall survival already accounted when estimating effectiveness estimates for each drug

⊙ *Does the ERG's modelling appropriately capture the impact of any differences in a) quality of life benefits and b) outcomes from greater adherence to treatment?*

ACD comments: network meta-analysis(1)

Company: ERG's network meta-analysis is not robust

Company:

- ERG network meta-analysis included inappropriate studies (small numbers, heterogeneous populations) which it should have excluded
- "*Committee would have been more inclined to support the company's model and results if they had considered the integrity of the network meta-analyses provided as a source of data for the various models*"
- "*We appeal to the committee to consider this point carefully, as the safety of its judgement may be seen to hang on a technical issue that could be considered unsafe*"

ERG:

- In clarification response, company accepted simplified network suggested by ERG to minimise heterogeneity and did not raise any concerns about the 4 included trials
- All subsequent company and ERG analyses based on simplified network

⊙ *Has the committee heard evidence to change its conclusion that the simplified network meta-analysis is appropriate for decision-making?*

Company Patient Access Scheme proposal

- Company has proposed a Patient Access Scheme (PAS) for tivozanib
- New base case reflects some of committee's preferred assumptions

Committee preferred assumption	Included in updated company model?
Adverse event modelling from ERG including utility and resource assumptions	✓
Subsequent therapies - ERG modelling	✓
Relative dose intensities – by drug	✓
Overall and progression-free survival based on ERG preferred fractional polynomial model	✗ Original 2nd order fractional polynomial ERG estimates
Cost of monthly blood tests	✗

⊙ *Does the committee agree with the company's reasons for not including all the committee's preferred assumptions in its revised modelling?*

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential PAS discounts for subsequent therapies axitinib, nivolumab and everolimus