NICE National Institute for Health and Care Excellence

Cabozantinib for untreated metastatic renal cell carcinoma

2nd appraisal committee meeting

Committee B, 10th July 2018 (previous meeting 6th March 2018)

Chair: Amanda Adler

ERG: Southampton Health Technology Assessments Centre

NICE technical team: Alan Lamb. Ahmed Elsada, Melinda Goodall

Company: Ipsen

Preview of key issues

1. **New** analyses by company incorporating committee's preferred assumptions, **new** Patient Access Scheme for cabozantinib
   - Key drivers of cost effectiveness
     - Price of cabozantinib
     - Costs and benefits of 2nd line (and beyond) treatments
     - Choice of OS extrapolation following new analyses based on most recent data available
2. Should cabozantinib be considered for inclusion in the Cancer Drugs Fund?

Recommendation in Appraisal Consultation Document (ACD)

‘Cabozantinib is not recommended, within its marketing authorisation, for adults with untreated advanced renal cell carcinoma that is intermediate- or poor-risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria.’

Cabozantinib (*Cabometyx*®)
Advanced renal cell carcinoma

UK marketing authorisation	Treatment-naive adults with **intermediate or poor risk** per International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria*
Administration	Oral
Mechanism	Inhibits multiple receptor tyrosine kinases.
Dosage	60 milligrams (1 tablet) once daily 40 and 20 milligram tablets Reduce dose as necessary
PAS	Simple PAS agreed with Department of Health as part of previous appraisal (2nd line treatment of renal cell carcinoma). Increase to PAS agreed – applies to 1st and 2nd line

**IMDC and other scores not used in clinical practice, but could be implemented*

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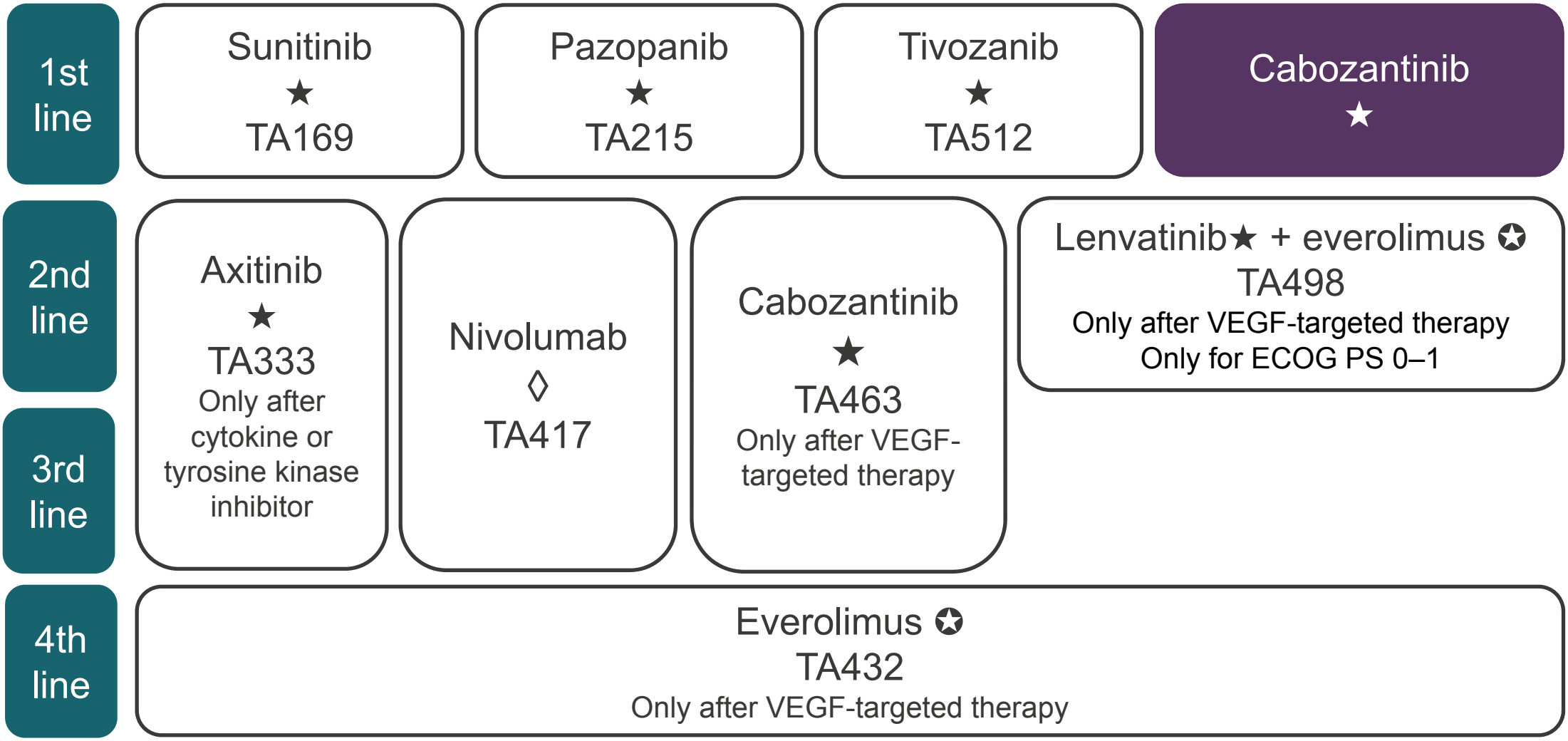
Proposed treatment pathway



Key; ECOG PS, Eastern Cooperative Oncology Group performance status; VEGF, vascular endothelial growth factor
★: oral tyrosine kinase inhibitors (TKI); ✪: oral mammalian target of rapamycin (mTOR) inhibitor;
◊ **:** anti-programmed death 1 (PD-1) inhibitor.

Decision problem

	Final scope from NICE	Company's decision problem
Population	People with untreated, intermediate or poor risk, locally advanced or metastatic renal cell carcinoma	Per scope
Comparators*	1. Pazopanib 2. Sunitinib	Per scope
Outcome	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment

*Tivozanib not recommended at time of scoping

Key clinical evidence for cabozantinib

Compared with sunitinib
Direct comparison

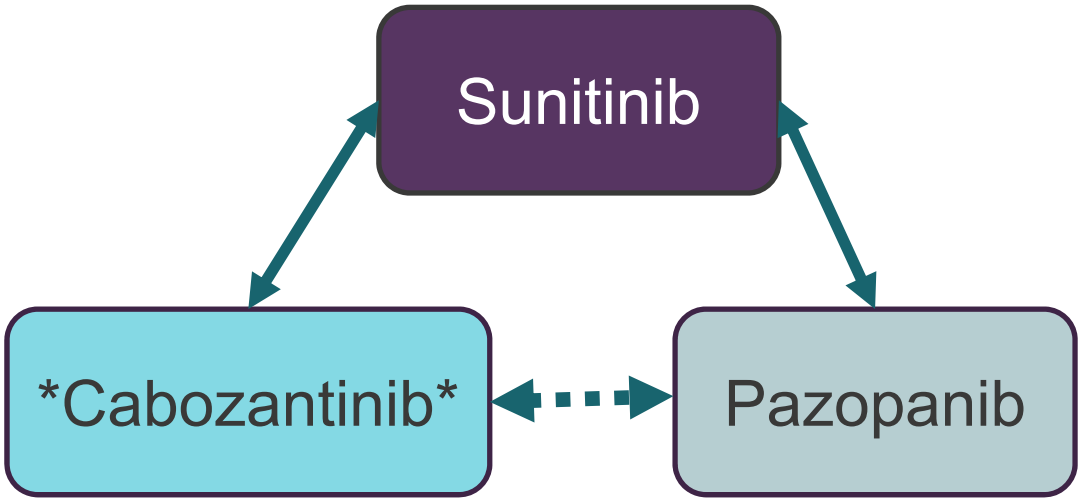
CABOSUN
Phase II
randomised controlled trial

Compared with pazopanib
Indirect comparison – network
Sunitinib is 'common comparator'

CABOSUN
cabozantinib vs. sunitinib

COMPARZ
pazopanib vs sunitinib

ACD: Committee considered sunitinib and pazopanib clinically equivalent in this and previous appraisals. No need for an indirect treatment comparison



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CABOSUN baseline characteristics

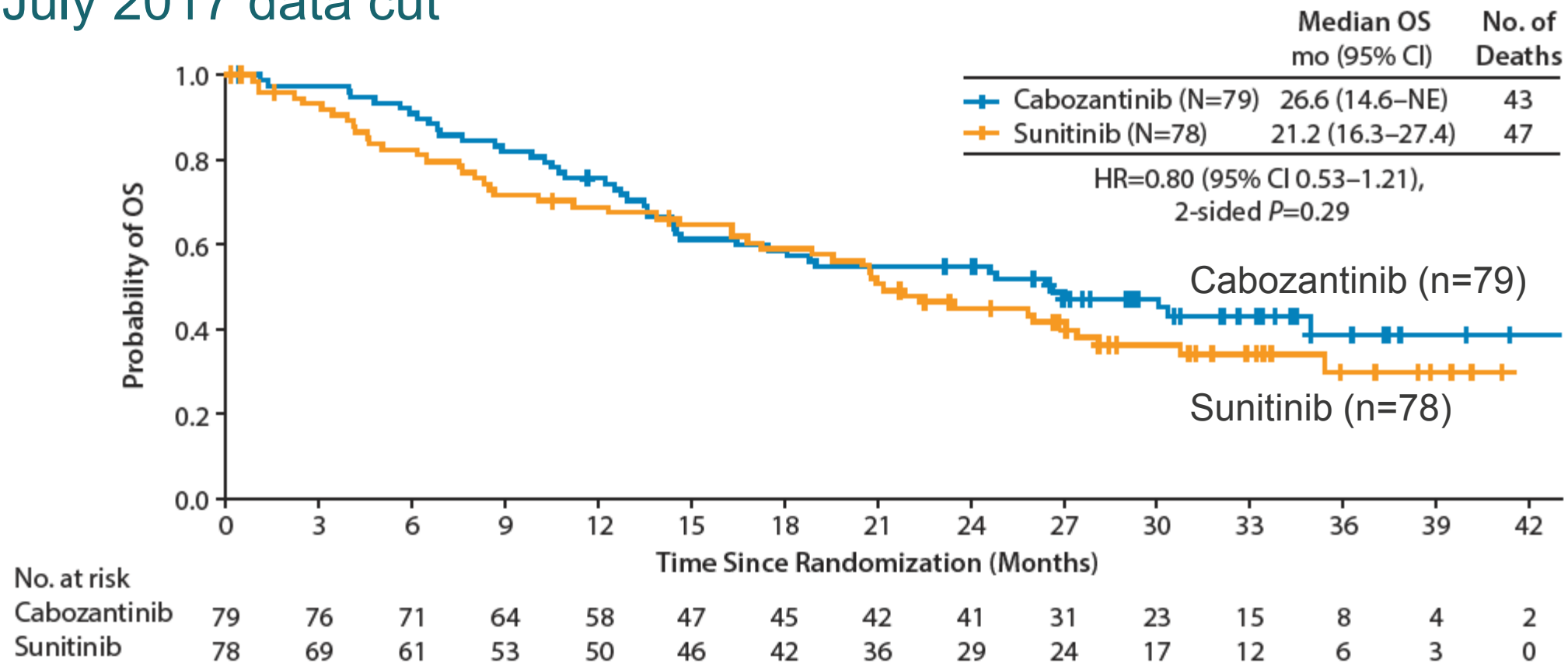
Characteristic	Cabozantinib n=79, n (%)	Sunitinib n=78, n (%)
Age, years		
Median (range)	63 (40-82)	64 (31-87)
Risk (per IMDC)		
Intermediate	64 (81)	63 (81)
Poor	15 (19)	15 (19)

ACD:

- *Committee*
  - *considered that it was possible that people in clinical practice have poorer health and a poorer prognosis than in the trial population;*
    it had not seen evidence to support this.
  - *concluded that the results of CABOSUN were generalisable to clinical practice in England*

Overall survival results

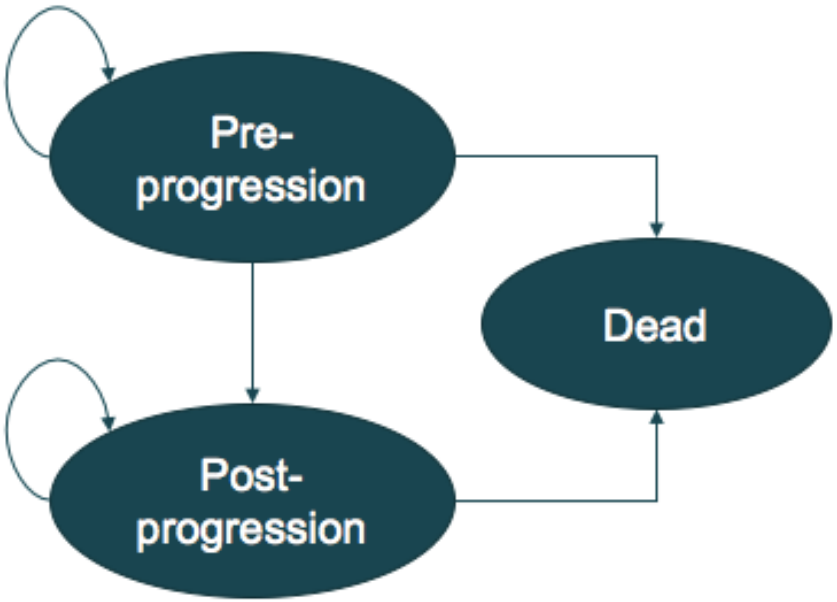
July 2017 data cut



ACD committee conclusions:

- *No conclusive evidence that cabozantinib prolongs life; unclear whether proportional hazards hold.*
- *Company used less mature data in model, committee preferred later (July 2017) data cut*

Company's model: approach + structure



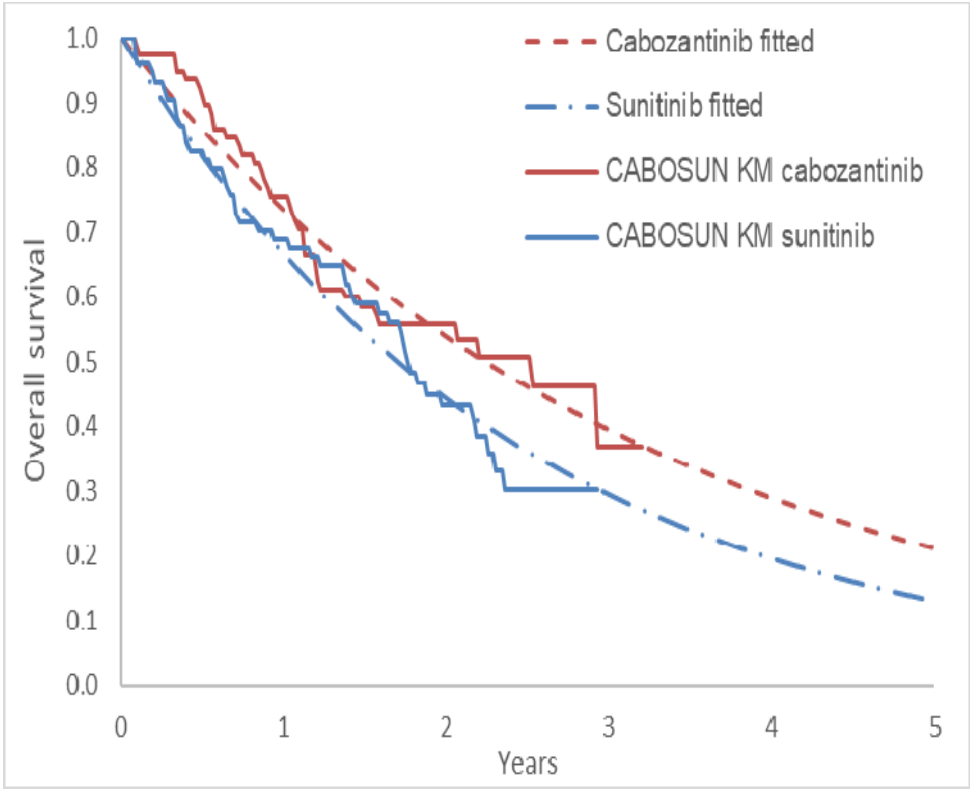
- Partitioned-survival model
- Fit parametric curve to trial data
- Estimated proportions in each health state based on curves
- Time horizon: 20 years
- Cycle length: 1 week

Efficacy	Trial-based
Treatment duration	**CABOSUN for cabozantinib and sunitinib (and pazopanib)**
Quality of life	Utility values from TA512 (appraisal of tivozanib, also 1st line)
Adverse events	Disutility values from Amdahl 2016 (based on COMPARZ, pazopanib vs. sunitinib), duration based on METEOR, a cabozantinib clinical trial
Costs – resources	TA512 (tivozanib) and TA215 (pazopanib)
Treatments 2nd line and beyond	**After cabozantinib and sunitinib - CABOSUN** **After pazopanib - COMPARZ**

Overall survival extrapolations company vs. ERG

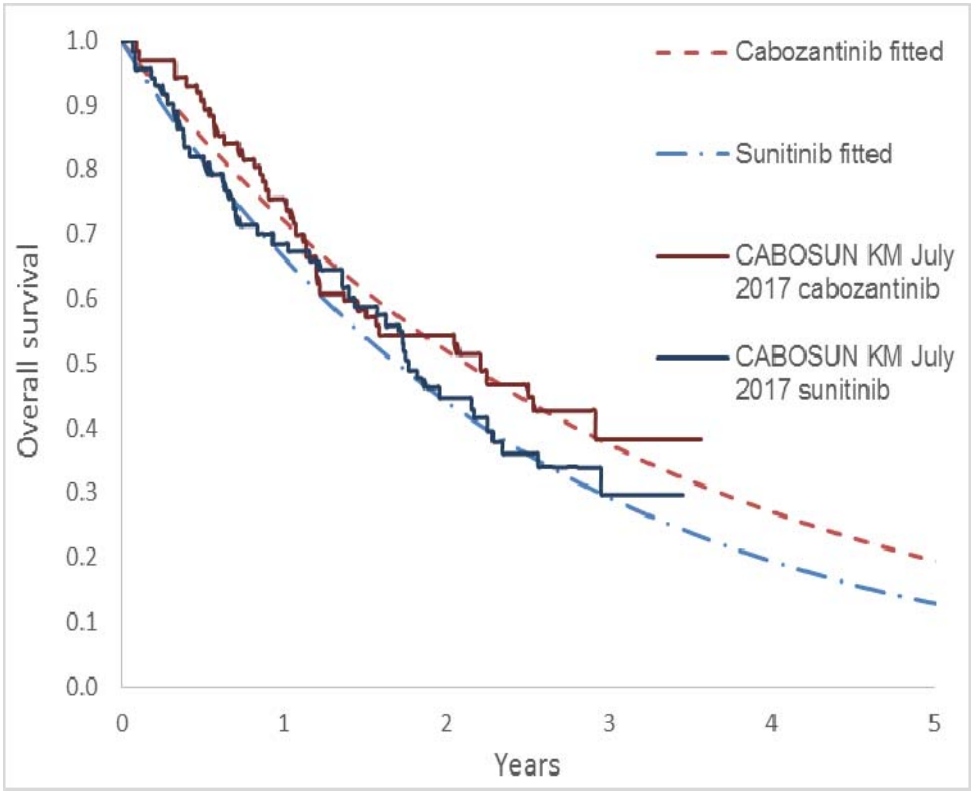
Trial-based analysis (CABOSUN)

Company base case
Jan 2017 data cut



Exponential curves fit separately to both arms

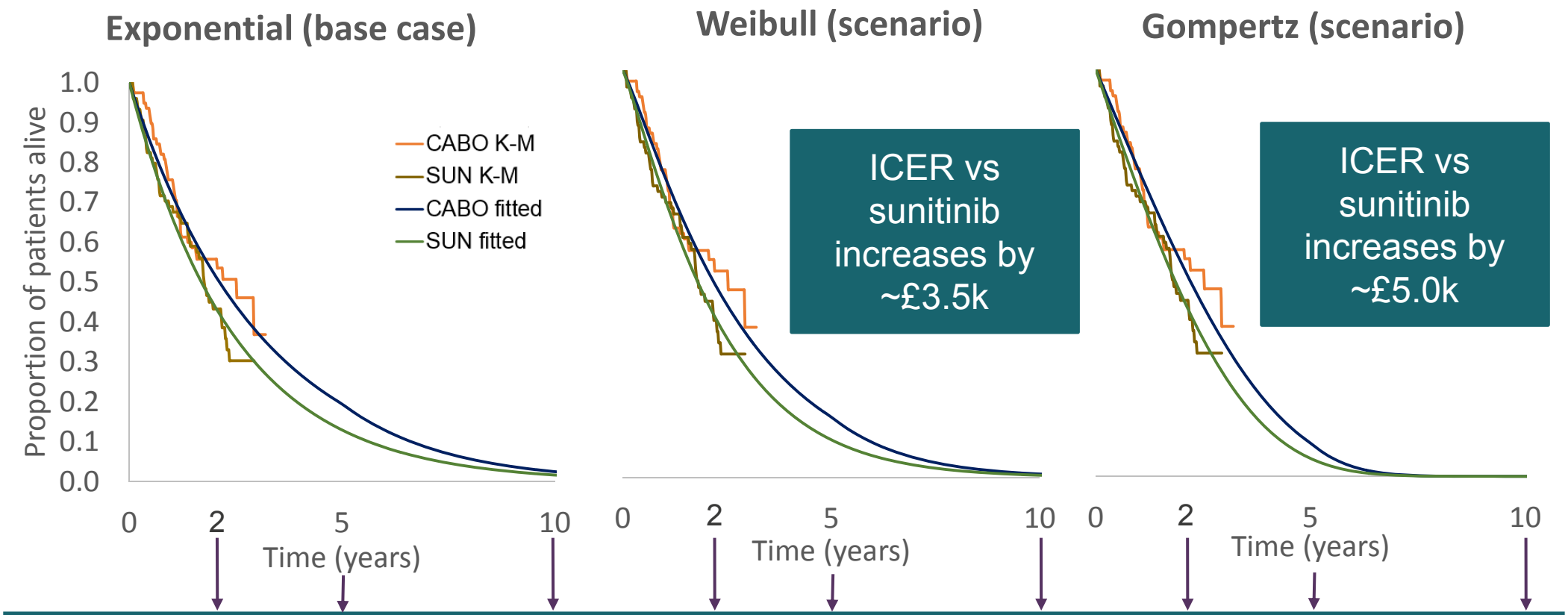
ERG base case
July 2017 data cut



Exponential curves fit to sunitinib then cabozantinib curve generated using

ACD: Committee: data immature; small numbers; projecting survival 'inherently uncertain; parametric distributions will fit data poorly given crossing curves. Unclear whether proportional hazards assumption holds or

Overall survival - ERG



Proportion of patients alive (%)									
CABO	52%	20%	3%	52%	15%	1%	52%	8%	0%
SUN	44%	13%	2%	44%	9%	1%	45%	4%	0%

ACD: clinical experts - not clear whether a survival benefit would continue after stopping treatment; committee - modelling should assume no treatment effect beyond the observed survival data

Other considerations

Topic	Committee conclusions
End of life	Criteria not met
Subsequent therapies	Committee would like to see cost and benefits of subsequent treatments
Innovation	No, no benefits not captured in QALYs
Cancer Drug Fund	Not discussed; not in ACD

End of life criteria

Criterion	Committee conclusions
Life expectancy of less than 24 months	• No robust evidence that life expectancy across marketing authorisation less than 24 months - **Criterion not met**
Life extension of more than 3 months	• No overall survival benefit for cabozantinib compared with sunitinib in CABOSUN trial • Company and ERG models estimated that cabozantinib extends life compared with sunitinib by 12 and 6 months respectively, **accepted criterion** across marketing authorisation

Committee's conclusions

Topic	Conclusion	Implication	Addressed by company?
Effectiveness of pazopanib	Same as sunitinib (control in key trial)	Don't need indirect comparison; treatment duration same; use pazopanib-specific adverse event rates, disutilities, costs	Yes
Maturity and extrapolation of OS data	Overall survival extrapolation based on the most recent data cut	Use July not January data cut	Yes
Duration of treatment benefit for cabozantinib compared with sunitinib	No evidence for benefit after end of trial	Model should assume treatment benefit for cabozantinib stops after end of trial follow-up (about 3.5 years)	Yes, 5 years (ERG consider scenarios of 3.5 and 7 years)
Treatments 2nd line and beyond	Must reflect both costs and effectiveness	Use CABOSUN trial data for both sunitinib and pazopanib as more up-to-date. Scenario analyses of NHS practice appropriate but does not reflect effectiveness.	Yes

Issues for discussion

- Committee' preferred assumptions
- Company has provided OS from a later data cut. So, Kaplan Meier curves reflect more mature data – committee must revisit which curve is best for extrapolating
  - Which curve fits the best
  - Dependent (on a hazard ratio – assumes proportional hazards) or separate
- Key drivers of cost effectiveness
  - Price of cabozantinib
  - Costs and benefits of 2nd line (and beyond) treatments
  - Choice of OS extrapolation

Contributing consultation comments

- Company (Ipsen):
  - Amended model incorporating committee's preferred assumptions
  - Proposed increase to Patient Access Scheme discount
- Patient Group
  - Kidney Cancer Support Network

Kidney Cancer Support Network comments

- "We are disappointed that yet again another drug for advanced RCC has been declined on the basis of the use of an unsuitable health economic assessment for small patient groups"
- Cabozantinib addresses unmet need … and expands the choice of treatments available to patients and clinicians
- Consider including cabozantinib within the Cancer Drugs Fund to address uncertainties around:
  - Magnitude of survival benefit in patients with bone metastases
    - *n.b. not a subgroup specified in scope or identified by company*
  - "KCSN urge NICE to consider funding for cabozantinib through the CDF to enable collection of real world survival data…"
- "If the government and the pharmaceutical industry cannot agree a price that allows the use of first-line cabozantinib on the NHS, we question whether patients will continue to support future research"

Company's revised model – choice of OS extrapolation

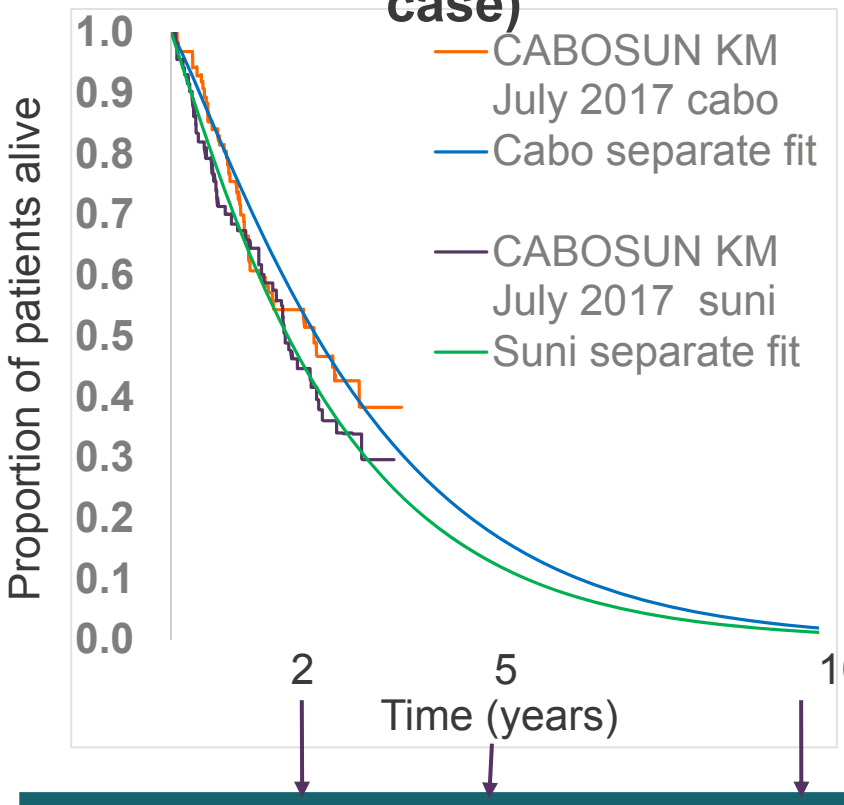
- Company update model to use most recent data cut (July 2017)
- Company presents both joint and separate fit to address uncertainty due to whether proportional hazards hold or not
- Company used **exponential separately fitted** in base case, included Weibull and Gompertz distributions as scenarios

ERG:

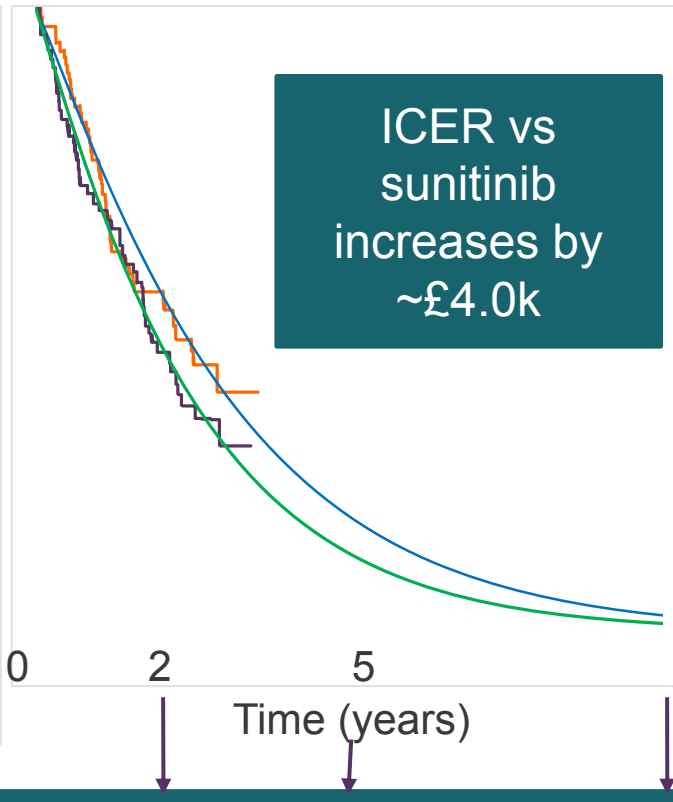
- *Presented additional scenarios; log-logistic, log-normal, gamma*
- *Uncertainty remains, ICERs vary by about £10,000 depending on distribution used*
- *No parametric curve fitted the data well*
- *Clinical experts agreed at first meeting that exponential curve used by ERG and company in base case produced plausible predictions of survival at 5 and 10 years*

Revised model – choice of OS extrapolation

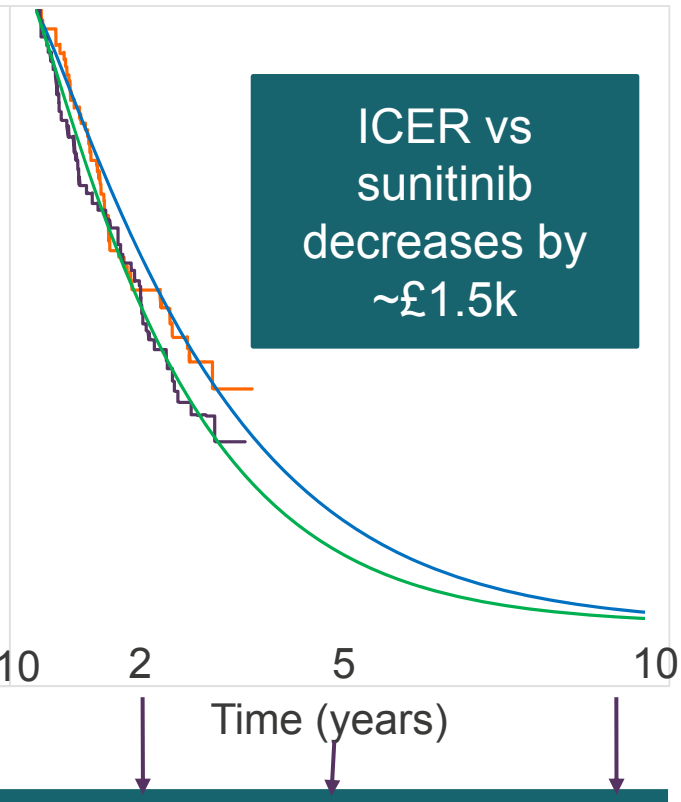
Exponential (base case)



Weibull (scenario)



Gompertz (scenario)



Proportion of patients alive									
CABO	54%	22%	5%	55%	18%	2%	54%	22%	5%
SUN	46%	15%	2%	46%	13%	1%	46%	13%	1%

⊙ ***Are any of the OS extrapolations presented plausible?***

Revised model – choice of PFS extrapolation

- Company used separately fitted lognormal curve (does not assume proportional hazards) in Appraisal Committee 1st meeting
  - ERG: exponential and Gompertz also reasonable fit
- Revised company base case uses **lognormal curve jointly fitted** (assumes proportional hazards) – in agreement with ERG

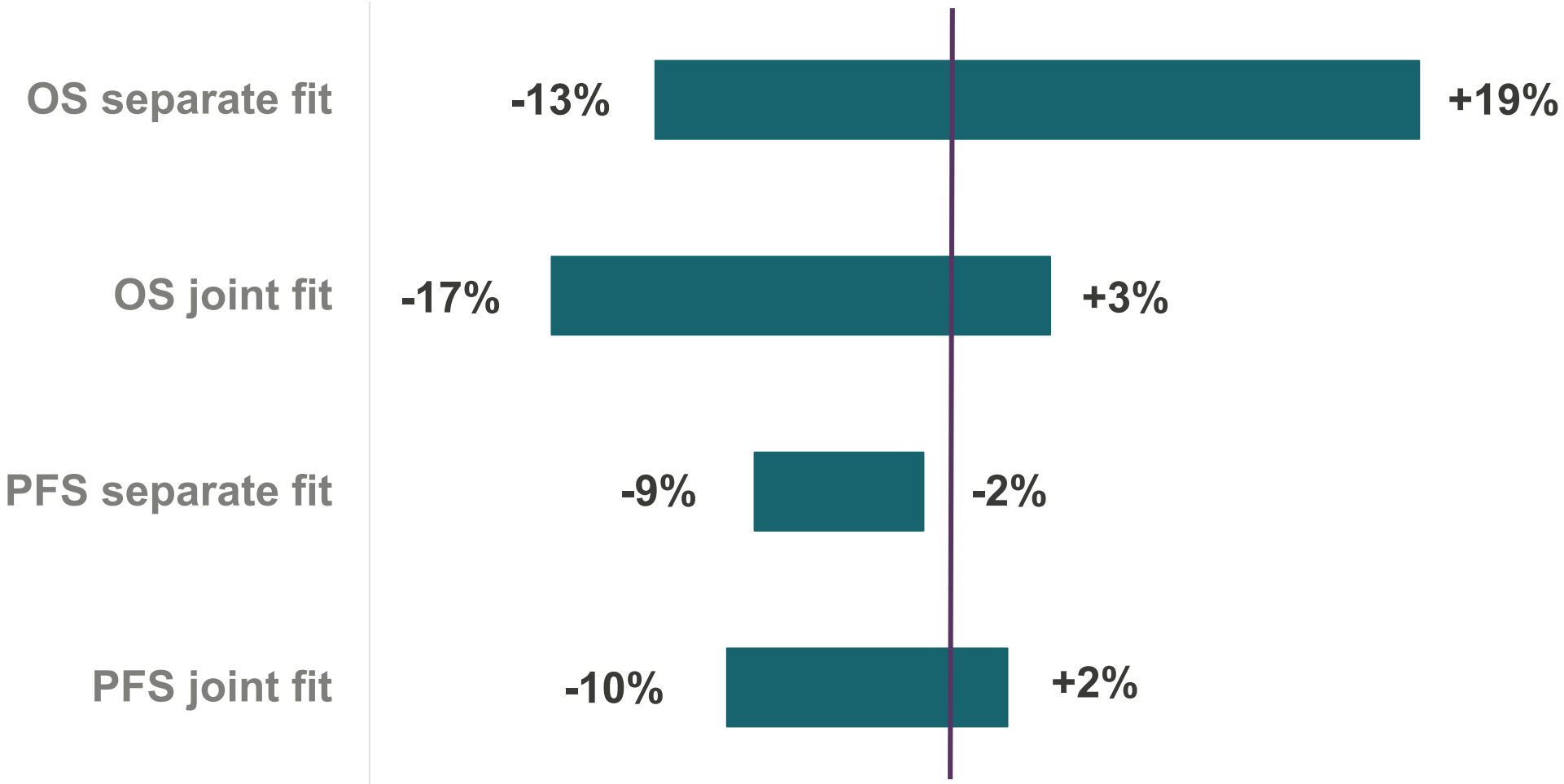
ERG:

- *No model-fit statistics presented for new PFS curves*
  - *For lognormal curve (revised base case) ICER not sensitive to choice of joint vs separate*
- *Included scenarios for additional choices of distribution for both jointly and separately fitted curves*

⊙ *Has committee seen any evidence to change preferred choice of PFS extrapolation?*

ERG scenario analyses – survival extrapolation

ERG scenario analyses – maximum percentage change in incremental cost effectiveness ratio (ICER) from base case



Company's amended model – results

- Amended model included an update Patient Access Scheme (PAS) for cabozantinib
- *Because PAS discounts exist for treatments received 2nd line and beyond, the estimates for cost-effectiveness which include these will be presented in the closed part 2 of this meeting*

Committee decision-making: CDF recommendation criteria

Proceed down if answer to each question is yes

Starting point: drug not recommended for routine use due to clinical uncertainty	TBD in Part 2
1. Is the model structurally robust for decision making? (omitting the clinical uncertainty)	⊙ *Agree?*
2. Does the drug have plausible potential to be cost-effective at the offered price, taking into account end of life criteria?	TBD in Part 2
3. Could further data collection reduce uncertainty?	⊙ *Are there any ongoing studies?*
4. Will ongoing studies provide useful data? and 5. Is CDF data collection via SACT relevant and feasible?	
Consider recommending entry into CDF (invite company to submit CDF proposal)	TBD in Part 2

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

NICE

Cancer Drugs Fund

- Plausible potential for cost effectiveness: To be determined in Part 2 (ICERs are confidential)

Summary of key issues

- Committee's preferred assumptions
  - ERG: Company implemented committee's preferred assumptions correctly (minor exceptions have little effect on base case results)
- KM curves now more mature – must revisit which curve is best for extrapolation
  - which curve fits the best
  - Separate or dependent (on a hazard ratio – assumes proportional hazards)
- Key drivers of cost effectiveness
  - Price of cabozantinib
  - Costs and benefits of 2nd line (and beyond) treatments
  - Choice of OS extrapolation

Backup slides

Subgroup analysis - Survival by risk group

	Cabozantinib Median, months (95% CI)	Sunitinib Median, months (95% CI)	HR (95% CI)
Intermediate	n=64	n=63	
Radiographic PFS – retrospective	11.4	6.8	0.52 (0.32 to 0.82)
Overall survival	30.3 (16.4 to NE)	23.5 (18.9 to 28.1)	0.80 (0.45 to 1.31)
Poor	n=15	n=15	
Radiographic PFS – retrospective	6.8	2.7	0.31 (0.11, 0.92)
Overall survival	18.4 (6.1 to NE)	6.4 (2.2 to 22.4)	0.51 (0.20 to 1.32)

ACD– Committee concluded cabozantinib prolonged PFS, but could not determine whether effectiveness of cabozantinib differed by subgroup

OS extrapolations – statistical fit

Distribution	AIC	AICC	BIC
Cabozantinib (separate fit)			
Lognormal	401.084	401.242	405.823
Loglogistic	401.670	401.828	406.409
Gamma	403.070	403.390	410.178
Exponential	403.733	403.785	406.103
Weibull	404.580	404.738	409.319
Gompertz	405.732	405.890	410.471
Sunitinib (separate fit)			
Exponential	418.862	418.915	421.205
Gamma	421.859	422.188	428.890
Gompertz	420.809	420.969	425.522
Loglogistic	420.599	420.761	425.286
Lognormal	420.380	420.542	425.068
Weibull	420.547	420.709	425.234
Joint fit			
Lognormal	819.769	819.927	828.919
Loglogistic	820.502	820.660	829.651
Gamma	821.606	821.871	833.806
Exponential	822.595	822.673	828.695
Weibull	823.296	823.454	832.446
Gompertz	824.576	824.733	833.745