Projector and public observer slides

Lead team presentation

Tivozanib for treating renal cell carcinoma

1st 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

Company: EUSA Pharma

19th July 2017

Key issues – clinical effectiveness

- Where will tivozanib be used in the treatment pathway?:
  - treatment-naive population (1st line)
- Is the clinical trial TIVO-1 generalisable to UK practice in terms of baseline characteristics?
- Is the analysis using treatment-naive patients or the whole trial population most relevant?
- Do overall survival results in geographical subgroups support effectiveness of tivozanib in NHS clinical practice?
- What is the most appropriate method for crossover adjustment (IPCW, RPSFT, other [MAIC])?
  - Does the proportional hazards assumption hold?
- What is the most appropriate approach for extrapolation (e.g. fractional polynomial method, other)?
- Are results from the network meta-analysis plausible?
  - Are the other trials in the network generalisable to NHS clinical practice?
  - Should the trials be adjusted for crossover?
- Is tivozanib clinically effective?

Key issues – cost effectiveness

- Which fractional polynomial-based extrapolation is most appropriate to use in the model? (from range of 1st and 2nd order options)
- Are the results from the model reliable without inclusion of crossover-adjusted data?
- How should subsequent therapy be accounted for in the model? (company's approach, ERG's approach, other?)
  - % of patients receiving each treatment, benefits and costs
- How should adverse effects be incorporated into the model?
  - Include utility decrements (company) or not (ERG)?
- Are the end-of-life criteria met?
- Is tivozanib an innovative treatment?
- Are there any equality issues?

Disease background and management

Kidney cancer

- More common in men than women
- Five-year survival is 56%, varying with age
- 86% of renal cancers are renal cell carcinoma

Renal cell carcinoma

- Estimated 9,045 new diagnoses in England per year
- Disease is often locally advanced or metastatic at point of diagnosis
- Early stage disease can be treated surgically – half of patients who have surgical treatment will develop metastatic disease
- Overall survival for people with metastatic disease is 8 months to 3.6 years

Tivozanib (Fotivda)
EUSAPharma

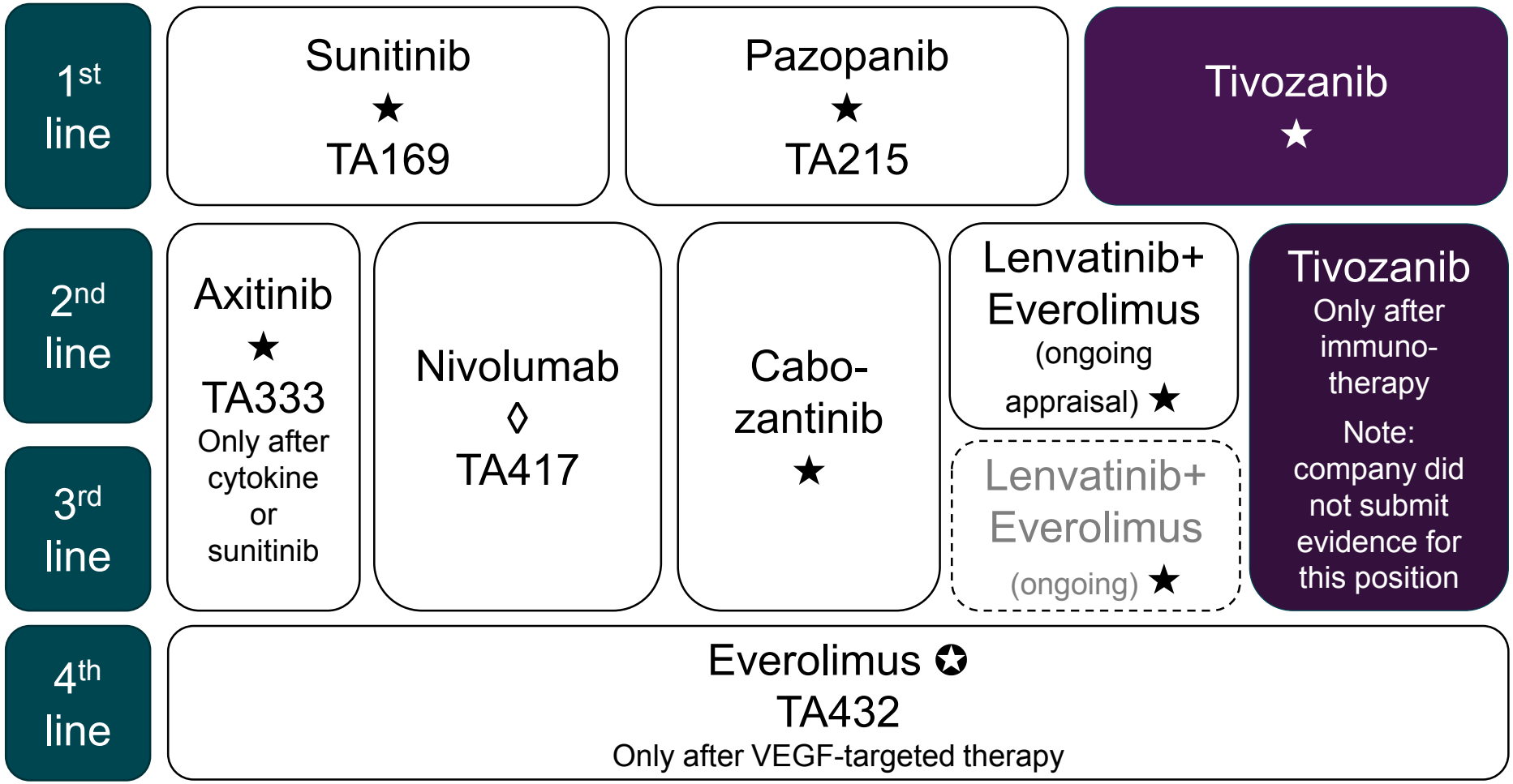
UK marketing authorisation	First line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGFR and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC
Administration	Administered as an oral therapy
Mechanism of action	Tyrosine kinase inhibitor with affinity for all three vascular endothelial growth factor receptors, leading to reduced vascularisation of tumours
Dosage	1,340 micrograms (one tablet) tivozanib once daily for 21 days, followed by a 7-day rest period 890 micrograms capsule is available so that the dose can be reduced if necessary

Comparators

	Final scope issued by NICE	Company's decision problem
Comparator	Untreated disease: • Sunitinib • Pazopanib • Immunotherapy (interferon-alfa, interleukin-2) Previously treated disease: • Axitinib • Nivolumab • Everolimus • Cabozantinib • Best supportive care	Untreated disease: • Sunitinib • Pazopanib • Immunotherapy (interferon-alfa, interleukin-2) (Immunotherapy not considered a comparator → rarely used in UK)

- Company: Tivozanib will not be used for previously-treated disease in NHS clinical practice
- Marketing authorisation for tivozanib as 2nd line is for use after immunotherapy, which is not used in the NHS

Current treatment pathway



ERG agree with company on positioning of tivozanib (1st line) and comparators

» Does the committee agree with position & comparators?

Key; VEGF, vascular endothelial growth factor

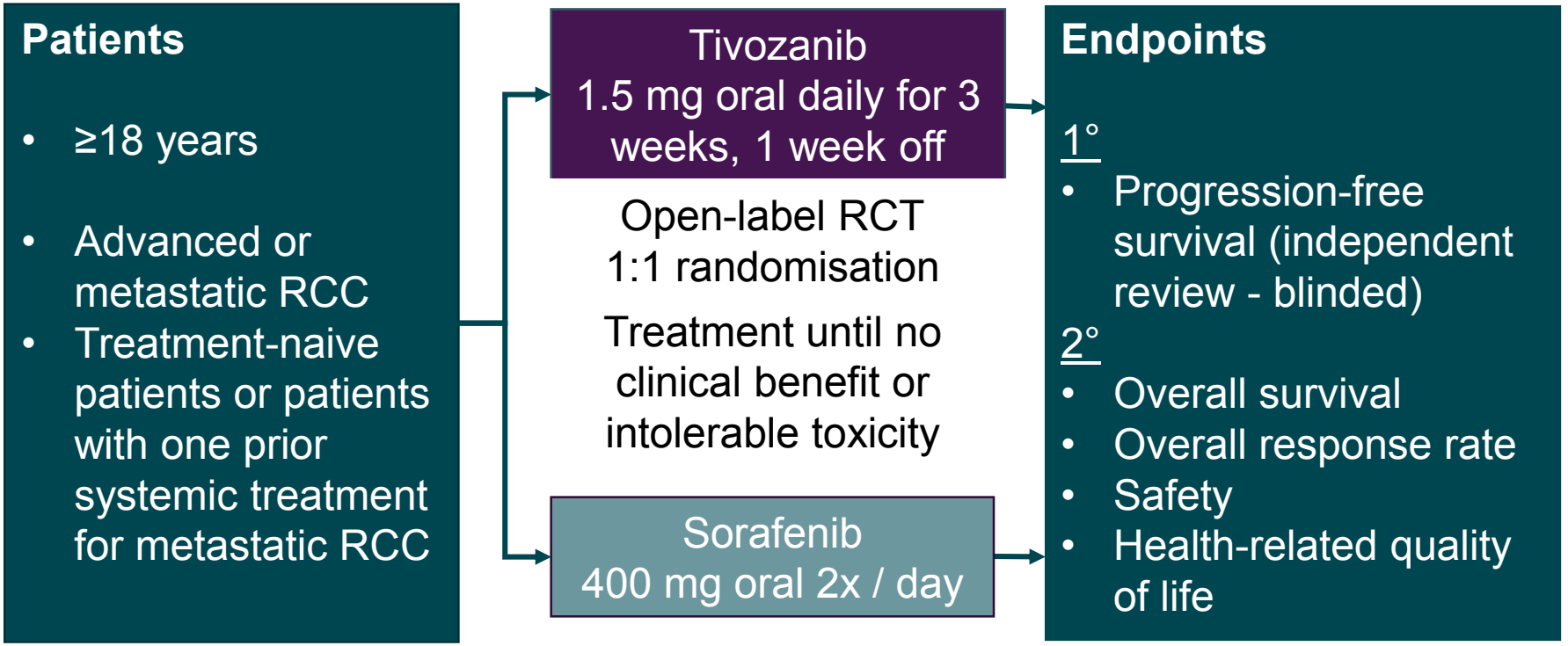
★: oral tyrosine kinase inhibitors; ✪: oral mammalian target of rapamycin (mTOR) inhibitor; ◊ : anti-programmed death 1 (PD-1) inhibitor

Comments from patient and professional groups

- Patient groups
  - People may experience constant pain as well as psychological effects e.g. depression, loss of confidence and self-worth
  - Many patients have to give up work due to debilitating effects of disease and treatments available – leads to financial pressures
  - Few treatment options available and adverse effects are significant e.g. extreme fatigue, severe hand and foot syndrome, chronic diarrhoea
  - No biomarkers to predict who will respond to each drug, therefore range of treatment options important
- Professional groups
  - Sunitinib or pazopanib currently used first line (sorafenib not used first line in UK)
  - Adverse event profile of tivozanib is comparable with other TKIs

Company's clinical evidence

Tivozanib vs sorafenib (not used in NHS): TIVO-1 trial (n=517)



RCT, randomised controlled trial; HR, hazard ratio; OR, odds ratio

Extension study:

- 65.8% of patients in sorafenib group crossed over to another targeted treatment (VEGF inhibitor or mTOR inhibitor) after progression (95.3% of these received tivozanib) (July 2013 data cut)
- 20.5% of patients in tivozanib group received 2nd-line targeted therapy (July 2013)

TIVO-1 baseline characteristics

Full population vs. treatment-naive

	Full population		Treatment-naive	
	Tivozanib	Sorafenib	Tivozanib	Sorafenib
N (% of randomised)	260 (100)	257 (100)	181 (70)	181 (70)
Median age (range)	59 (23-83)	59 (23-85)	59 (23-83)	59 (23-85)
Male, n (%)	185 (71)	189 (74)	134 (74)	135 (75)
ECOG performance status, n (%) 0	116 (45)	139 (54)	85 (47)	94 (52)
1	144 (55)	118 (46)	96 (53)	87 (48)
Region ……North America /Western Europe	22 (9)	18 (7)	19 (11)	15 (8)
Central/Eastern Europe	229 (88)	228 (89)	154 (85)	155 (86)
Rest of world	9 (3)	11 (4)	8 (4)	11 (6)
Number of organs with metastases, n (%) 1	76 (29)	88 (34)	53 (29)	65 (36)
≥2	184 (71)	169 (66)	128 (71)	116 (64)
MSKCC prognostic group, n (%) Favourable	70 (27)	87 (34)	48 (27)	60 (33)
Intermediate	173 (67)	160 (62)	121 (67)	112 (62)
Poor	17 (7)	10 (4)	12 (7)	9 (5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan Kettering Cancer Center.

» Is the clinical trial TIVO-1 generalisable to UK practice?

Clinical expert and NHS England statements

- Clinical expert
  - Interleukin-2 used rarely and interferon alpha even more rare – very few people eligible for 2nd line treatment with tivozanib in NHS
  - Efficacy of pazopanib, sunitinib and tivozanib at least equivalent; tivozanib may be superior – drug of choice will depend on tolerability
  - Patient may tolerate tivozanib better than pazopanib – should conduct a patient preference trial
  - If approved, tivozanib would replace sunitinib or pazopanib, so NHS would not need extra resources
- NHS England
  - Uncertainty because of design of TIVO-1 (prior nephrectomy required, significant crossover, and imbalance in performance status between treatment groups)
  - Tivozanib reasonably well tolerated but inconclusive whether it has fewer adverse effects than sunitinib or pazopanib
  - Potential therapy options at 2nd line and beyond: axitinib, nivolumab, cabozantinib and everolimus
  - Agree with ERG's modelling of subsequent therapies

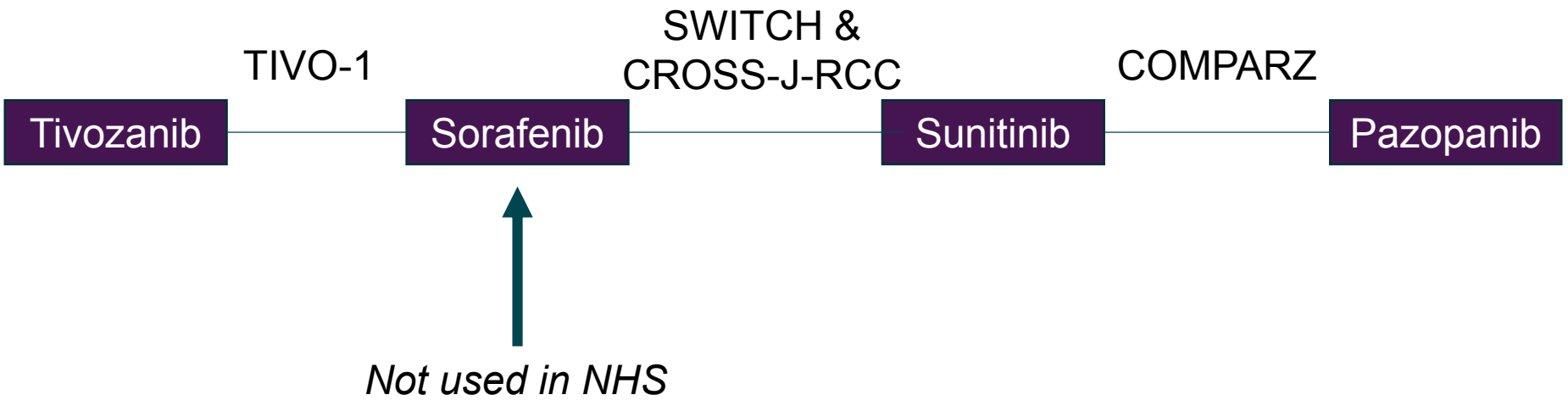
ERG comments on TIVO-1 trial

- Considerable uncertainty in estimate of OS because of subsequent therapies received
- Inconsistencies in reported results due to multiple data cuts
- Population is generalisable to a UK population likely to be eligible for treatment with tivozanib in NHS
- However, population enrolled in TIVO-1 study may have better prognosis than full population in scope due to trial inclusion criteria (clear cell component to RCC, ECOG score 0 or 1 and prior nephrectomy)
- ERG clinical experts consider only **treatment-naive** population relevant to population eligible for tivozanib in England

» Which population is most relevant for modelling, trial patients who are treatment-naive, or all patients in the trial?

Indirect comparison to compare tivozanib to sunitinib and pazopanib

(later slides)



- Company and ERG agreed that sorafenib is not used in the NHS
- Comparator in TIVO-1 may not be relevant, therefore, a network meta-analysis was also needed
- Results for tivozanib vs sorafenib & vs sunitinib and pazopanib follow…

History of company's analyses

Stage of process	**TIVO-1 analysis** for comparison to sorafenib (not used in the NHS)	**Network meta-analysis** for comparison to sunitinib or pazopanib or immunotherapy
Company's submission	• Full trial population • **PFS**: Kaplan-Meier with Cox hazard ratios, unadjusted and adjusted for baseline characteristics • **OS**: Kaplan-Meier with Cox hazard ratios and IPCW adjustment for crossover	• Complex network • Both treatment-naive only and full population analyses • Immunotherapy included as comparator • Calculated hazard ratios • No crossover adjustment
Clarification	• Treatment-naive population • **OS**: RPSFT adjustment for crossover	• Simplified network • Treatment-naive only • Immunotherapy not included • Based on Weibull parametric curves • No crossover adjustment
Final analysis	• No change from clarification	• Fractional polynomial curves ‡ • No crossover adjustment

‡, used in economic model; PFS, progression-free survival; OS, overall survival; IPCW, inverse probability of censoring weights; RPSFT, rank preserving structural failure time

Clinical effectiveness results – summary

Progression-free survival, December 2011 data cut

ERG considers these results from original PFS Cox analyses inappropriate as proportional hazards do not hold

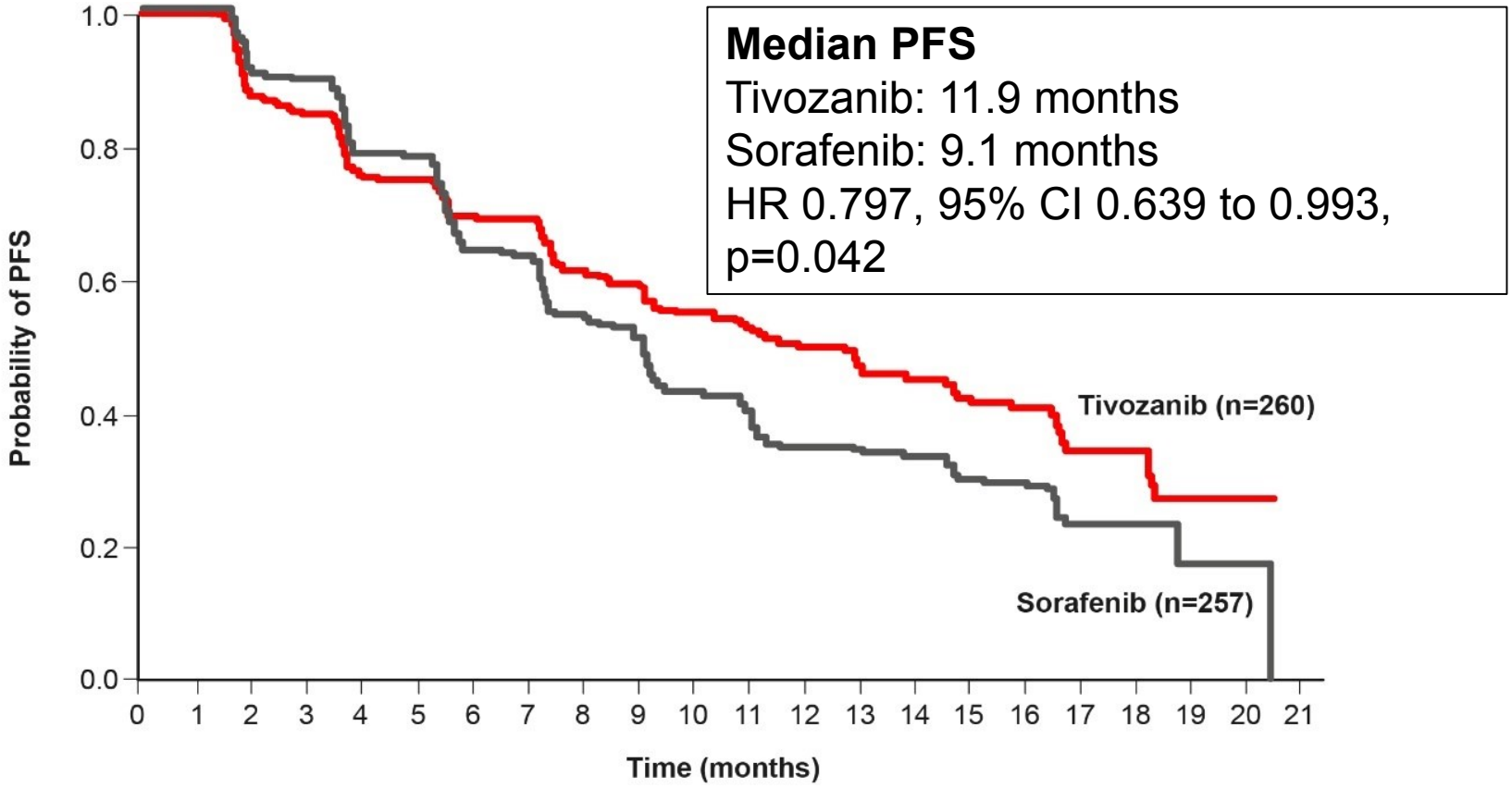
	Median, months		**Hazard ratio**	**95% confidence intervals**	**P value**
	Tivo	Sora			
Full population, unadjusted	11.9	9.1	0.797	0.639 to 0.993	0.042
Full population, adjusted for baseline demographics and geographical region; post-hoc analysis	NR	NR	0.725	0.58 to 0.91	0.006
Treatment-naive subgroup, unadjusted	12.7	9.1	0.756	0.581 to 0.985	0.037

NR, not reported

» Which analysis for PFS is most appropriate - full population (unadjusted, adjusted) or treatment-naive?

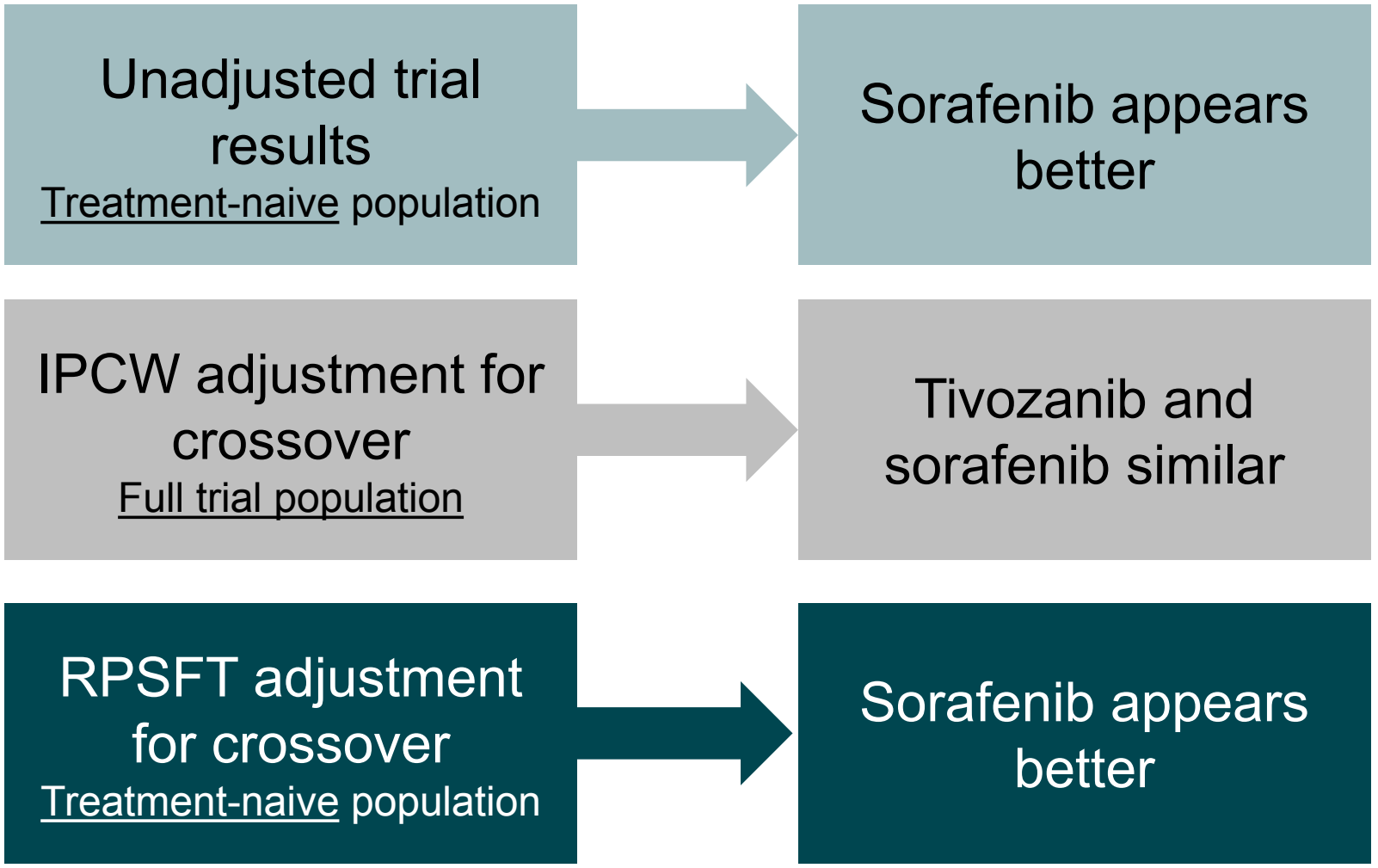
Progression-free survival

Full trial population, unadjusted



- Kaplan-Meier plot of PFS as determined by independent radiology review, December 2011 data cut
- Company did not provide KM plot for PFS in treatment-naive population

Summary of overall survival in TIVO-1



Clinical effectiveness results – summary

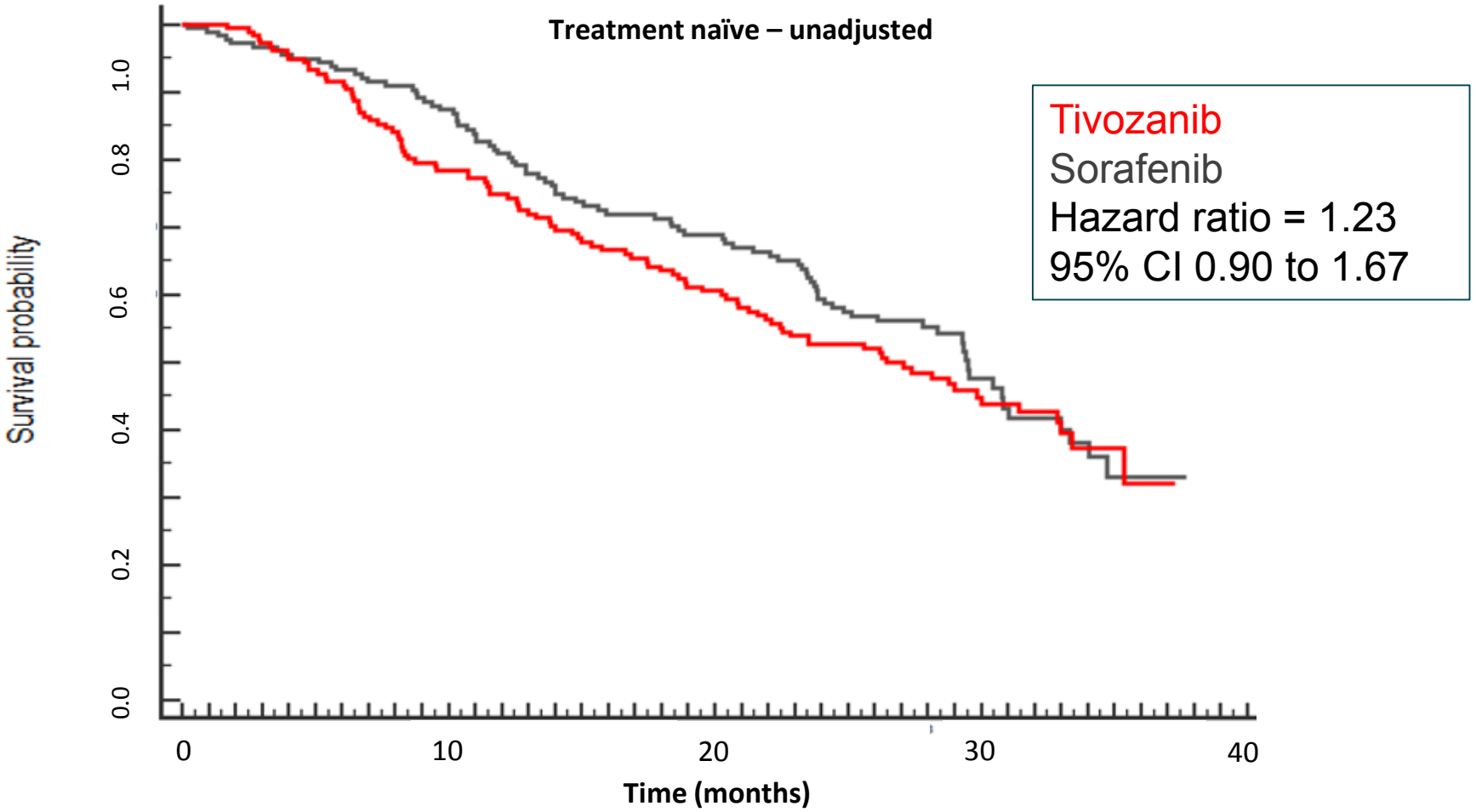
Overall survival

	Median, months		Hazard ratio	95% confidence intervals	P value
	Tivo	Sora			
Full population, Jan 2015 data cut, unadjusted for crossover	29.0	34.1	1.18	0.930 to 1.504	0.078
Full population, IPCW-adjusted*	NR	NR	1.021	0.671 to 1.553	0.923
Treatment-naive subgroup, unadjusted for crossover, Jul 2013 data cut	NR	NR	1.23	0.90 to 1.67	NR
Treatment-naive subgroup, RPSFT-adjusted*	Kaplan-Meier plots				
Pre-specified subgroup analyses by geographical location, full population July 2013					
N America & EU	32.9	29.5	0.846	NR	0.433
N America & EU5	NA	29.5	0.497	NR	0.136
Russia & Ukraine	26.3	32.0	1.383	NR	0.051

*Unclear which data cut company used. NR, not reported; NA&EU: US, Canada, Bulgaria, Czech Republic, France, UK, Hungary, Italy, Poland, Romania. NA&EU5: US, Canada, Italy, France, UK

Overall survival results

Treatment-naive population, unadjusted for crossover



Kaplan-Meier plot of overall survival, July 2013, unadjusted for crossover

Methods used to analyse overall survival
Substantial treatment switching causes confounding

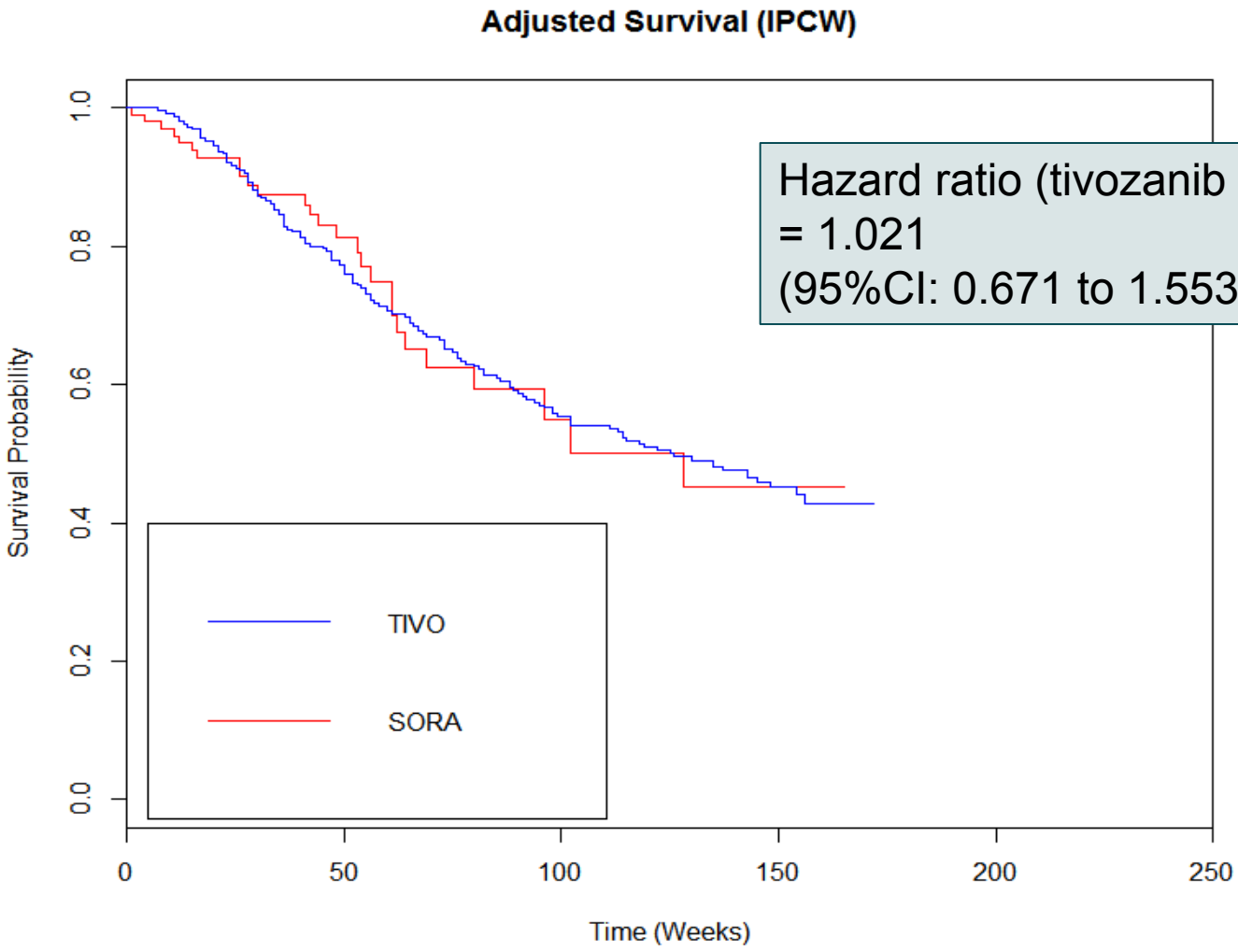
- 161 patients who progressed on sorafenib crossed over to receive tivozanib (62.6%)

	Inverse probability of censoring weights (IPCW)	Rank preserving structural time failure method (RPSFT)
Description of method	Patients artificially censored at point of switch and remaining observations weighted	Estimate effect of exposure to tivozanib on survival time and adjust sorafenib arm results accordingly
Population	Full trial	Treatment-naive
Criticisms	High weighting given to small numbers of patients who didn't cross over	Assumes treatment benefit with tivozanib is same regardless of patients' original randomisation, but patients who cross over are further along disease course
Preferred by	Company	ERG

IPCW method for overall survival

Results of adjusted analysis – full trial population

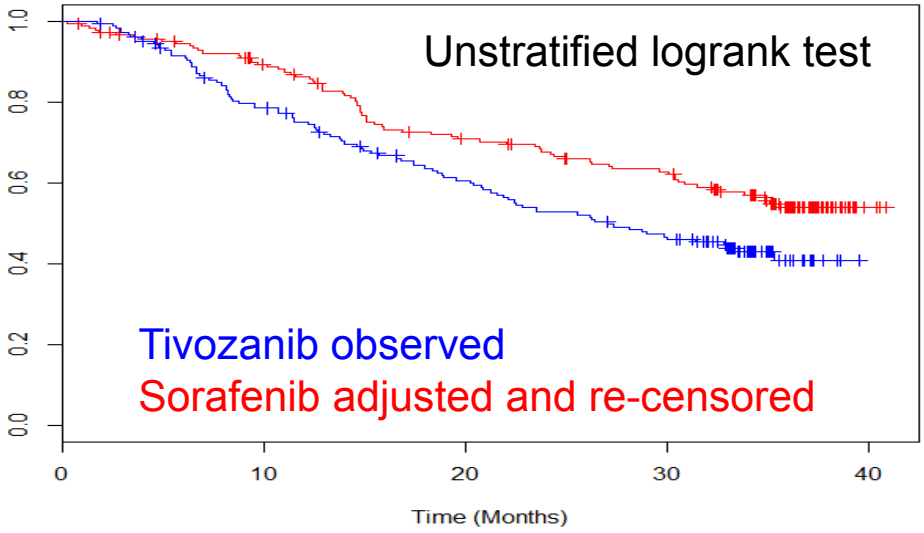
Company only carried out IPCW method in full trial population, not treatment-naive

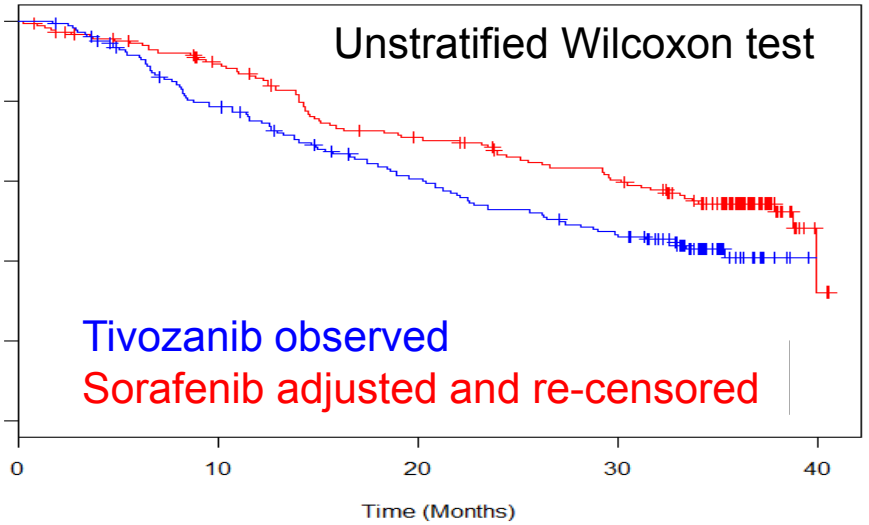


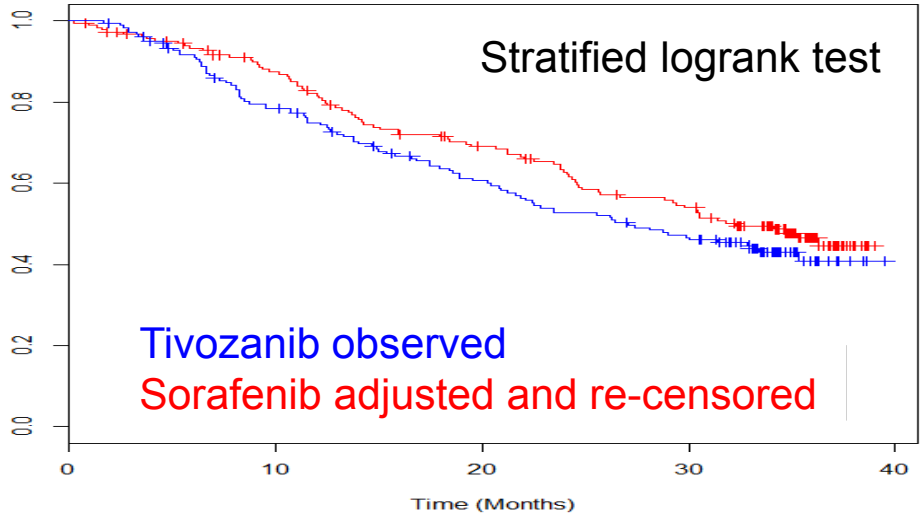
Hazard ratio (tivozanib v sorafenib) = 1.021
(95%CI: 0.671 to 1.553; p=0.923)

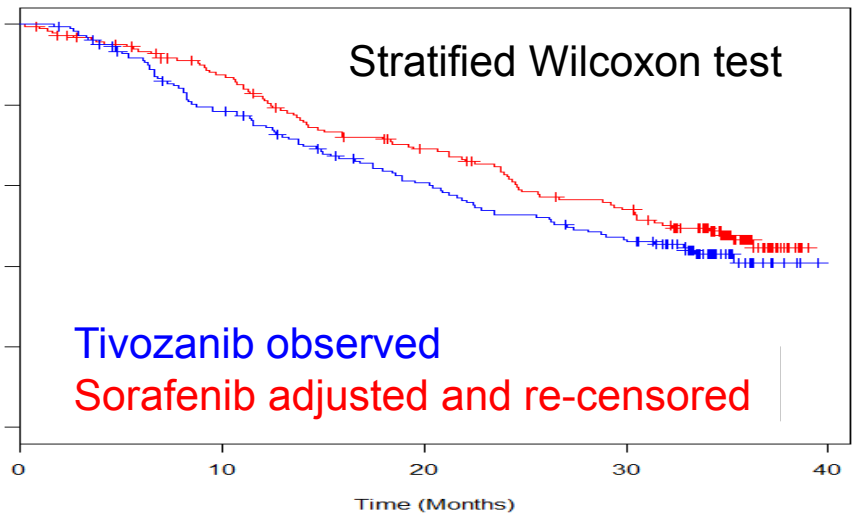
RPSFT method for OS

Adjusted survival distributions – treatment-naive population









Stratification based on patient baseline characteristics – ECOG performance status, MSKCC risk category and number of metastatic disease sites

ERG comments on results from crossover adjustment

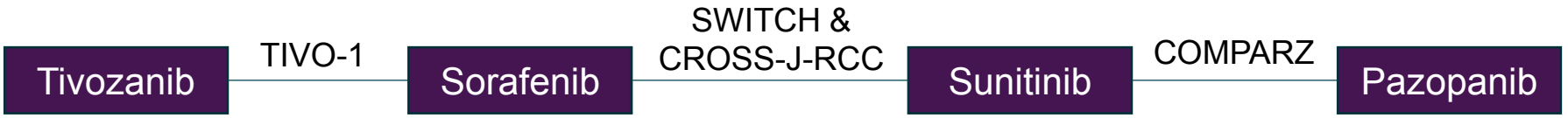
- Proportional hazard assumption does not hold for PFS
- RPSFT-adjusted analyses do not support the IPCW-adjusted analyses
- ERG: prefers RPSFT approach → more reliable when large proportion of patients switch treatments, as in TIVO-1
- OS estimate unreliable despite adjustments for crossover
- Company suggest imbalance in subsequent therapies biased OS against tivozanib, but ERG states the bias caused by this imbalance cannot be quantified
- **Crossover-adjusted results not used in NMA or model - ERG unable to predict direction and magnitude of bias**

» What approach to adjusting for crossover does the committee think is most appropriate (IPCW, RPSFT, other)?
» Is tivozanib associated with longer PFS than sorafenib? Longer OS?

Network meta-analysis

To compare tivozanib to comparators without direct trial evidence

Company only consider patients who are **treatment-naive** in base-case analysis



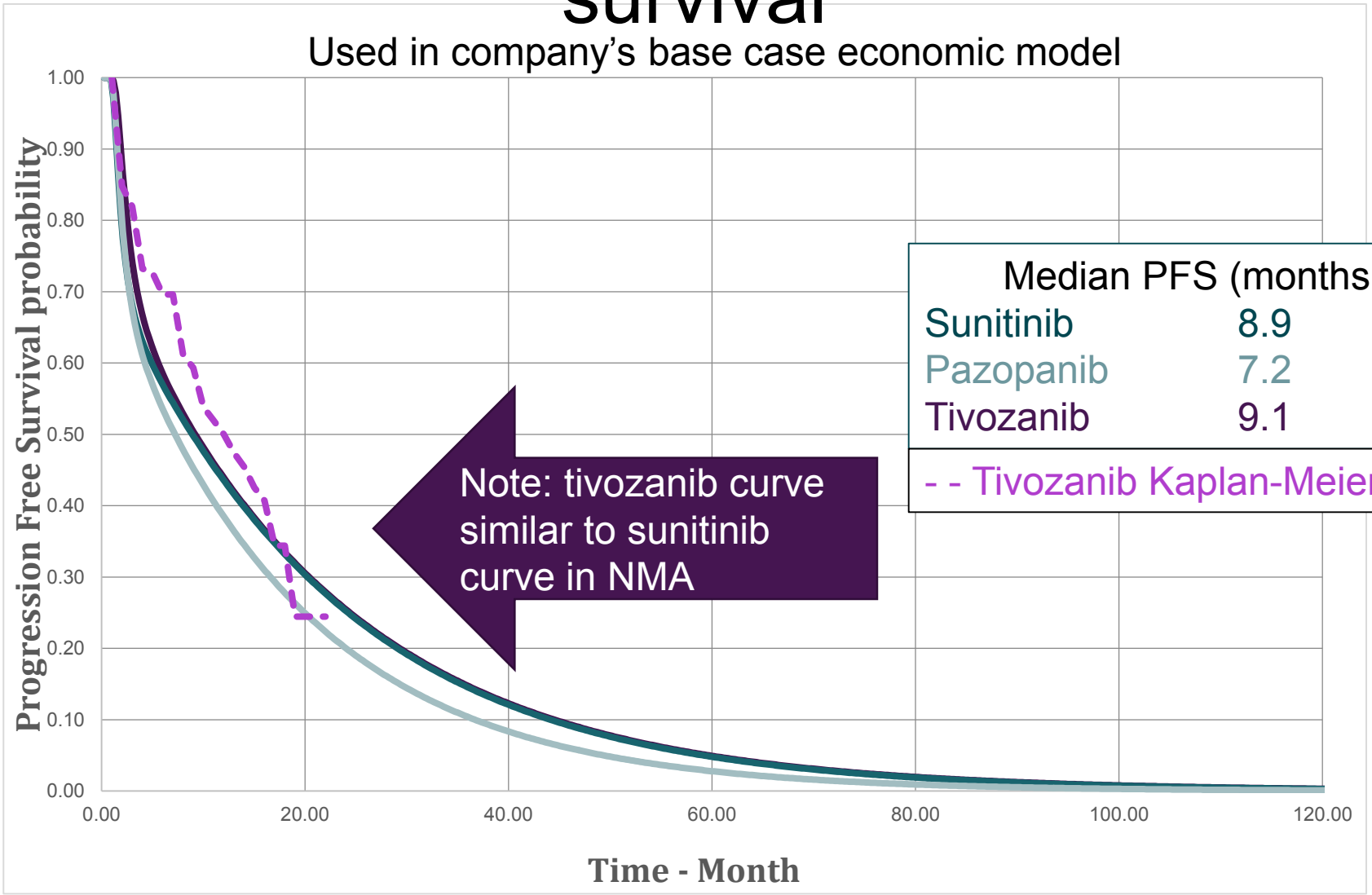
Trial	Population	Intervention	Comparator	Methodology
COMPARZ Motzer et al. 2013	Clear cell metastatic RCC, treatment-naive	Pazopanib (crossover not reported)	Sunitinib (crossover not reported)	Open label phase III RCT
Cross-J-RCC Tomita et al. 2014 and 2017	Clear cell metastatic RCC, treatment-naive	Sunitinib (53% switched to other VEGFR)	Sorafenib (75% switched to other VEGFR)	Open label crossover RCT
SWITCH Eichelberg et al. 2015	Advanced/ metastatic RCC, treatment-naive or prior cytokine therapy	Sorafenib (64% received 2nd line therapy)	Sunitinib (55% received 2nd line therapy)	Open label phase III crossover RCT
TIVO-1 Motzer et al. 2013	Clear cell recurrent/ metastatic RCC, treatment-naive or prior cytokines	Tivozanib (30% received 2nd line therapy)	Sorafenib (69% received 2nd line therapy)	Open label phase III RCT

Fractional polynomial method

- Used by company in network meta-analysis (PFS and OS) because proportional hazards assumption did not hold for progression-free survival
- Method uses parametric survival functions, including survival distributions such as Weibull or Gompertz, together with **more flexible** fractional polynomials (FP)
- Allows for **change of hazards over time** and offers more freedom in distribution selection
- With 1st or 2nd order fractional polynomials:
  - Model hazard functions of the interventions compared in a trial
  - Consider difference in the parameters of these fractional polynomials within a trial
  - Synthesise multidimensional treatment effect (and indirectly compare) across studies
- Therefore, treatment effects are represented with multiple parameters rather than a single parameter or outcome

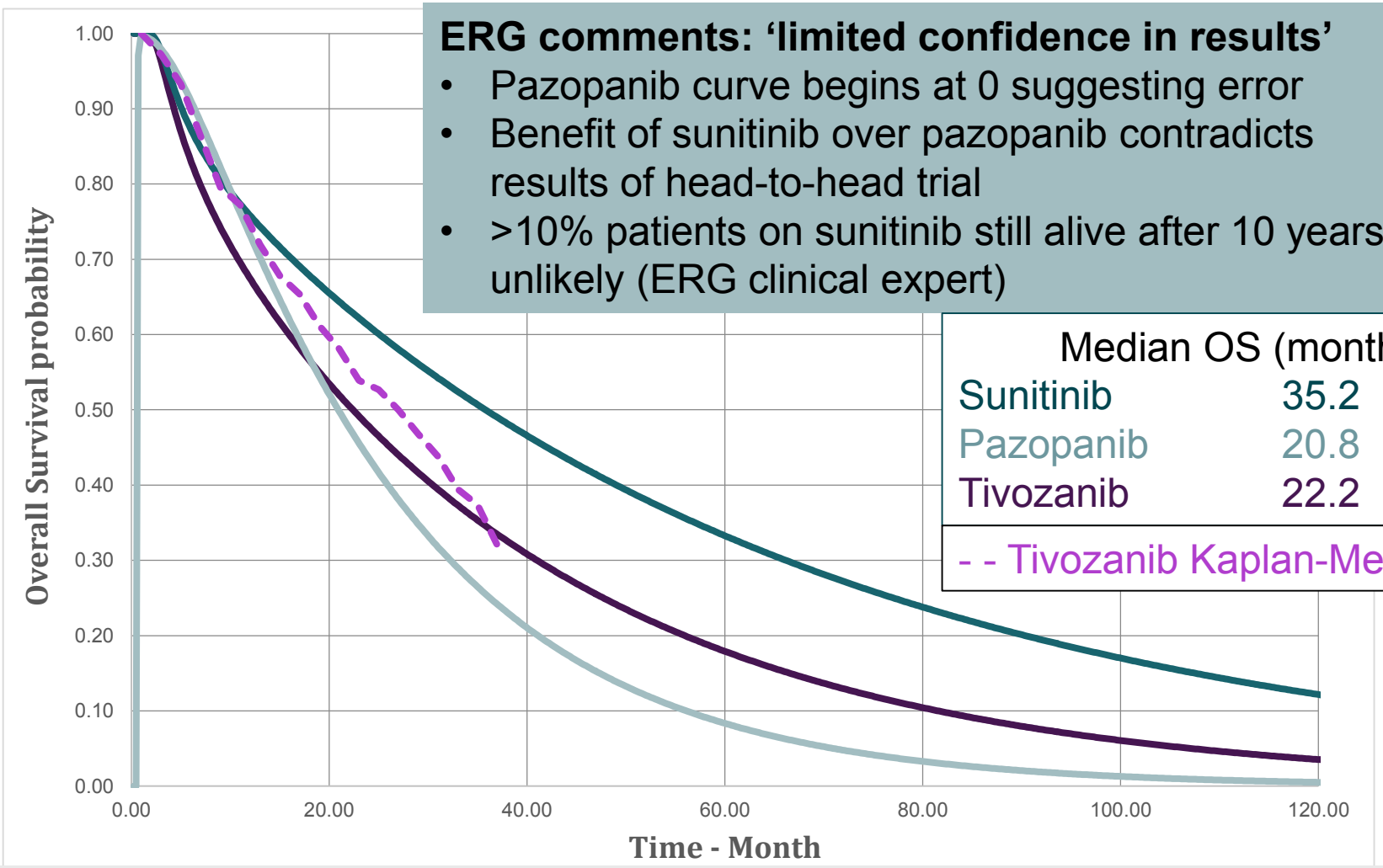
Company's fractional polynomial network meta-analysis for progression-free survival

Used in company's base case economic model



Company's fractional polynomial network meta-analysis for overall survival

Not adjusted for crossover - used in company's base case economic model



ERG comments: 'limited confidence in results'

- Pazopanib curve begins at 0 suggesting error
- Benefit of sunitinib over pazopanib contradicts results of head-to-head trial
- >10% patients on sunitinib still alive after 10 years – unlikely (ERG clinical expert)

Median OS (months)	
Sunitinib	35.2
Pazopanib	20.8
Tivozanib	22.2

- - Tivozanib Kaplan-Meier

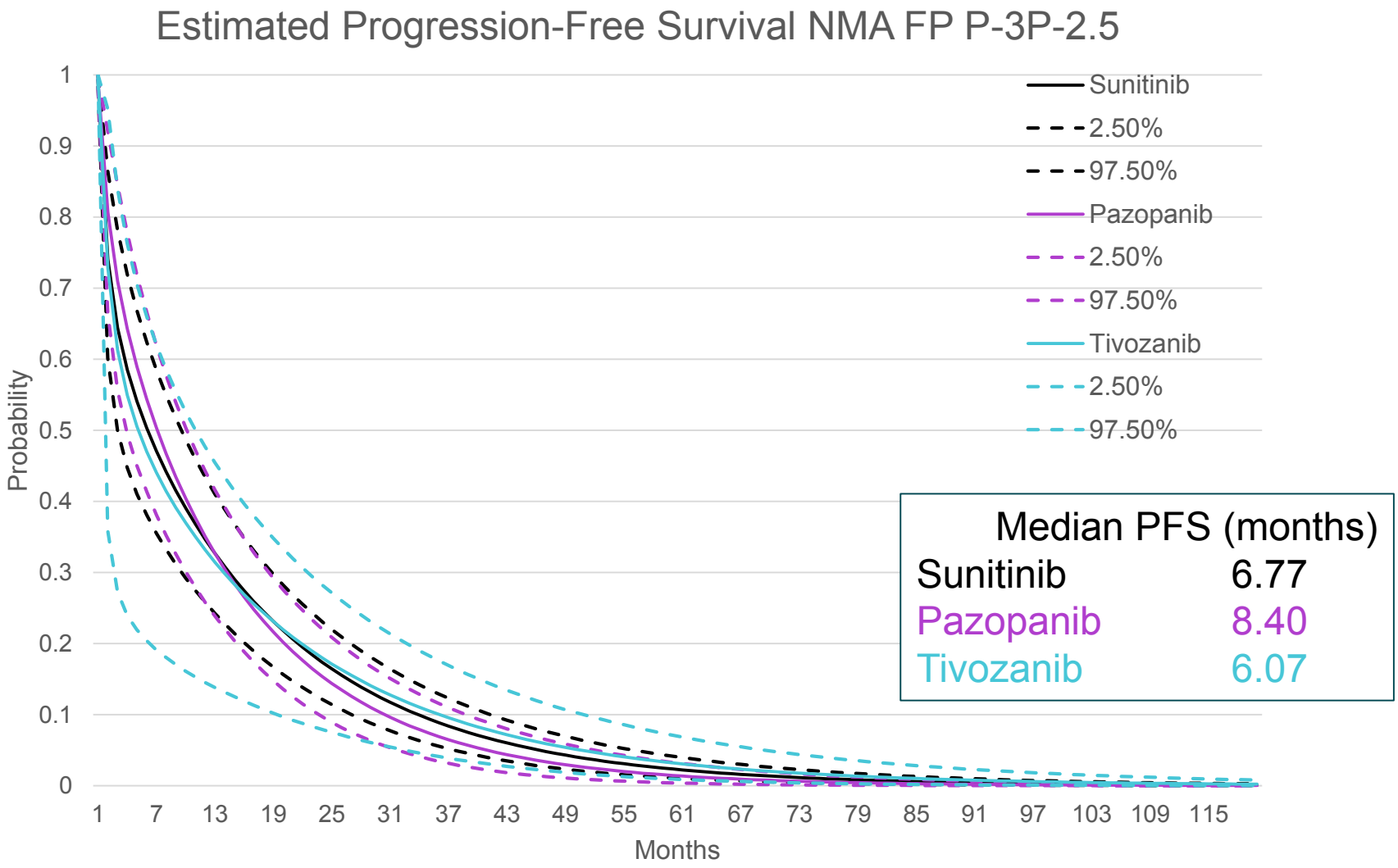
» Is it appropriate to use curves unadjusted for cross-over? Do the results have face validity?

ERG's comments on network-meta analysis and fractional polynomial approach

Issue	ERG's comments
Included trials	Inclusion criteria and population broadly similar
Crossover	• Company did not include crossover-adjusted data from TIVO-1 because it did not have crossover-adjusted data for SWITCH and CROSS-J-RCC • Treatment-switching more pronounced in TIVO-1 than in other studies • Incorporating RPSFT-adjusted results from TIVO-1 into the network would have been a useful scenario for comparison
Fractional polynomial method	• Fundamental flaw in calculation used to generate curves • Estimated within period hazard rather than cumulative hazard within model cycle → leads to implausible OS curves → **ERG corrects this** • Company only tested 1 second order fractional polynomial approach → **further scenarios conducted by ERG** • ERG's replication of the NMA did not match the company's results so additional exploratory analyses conducted

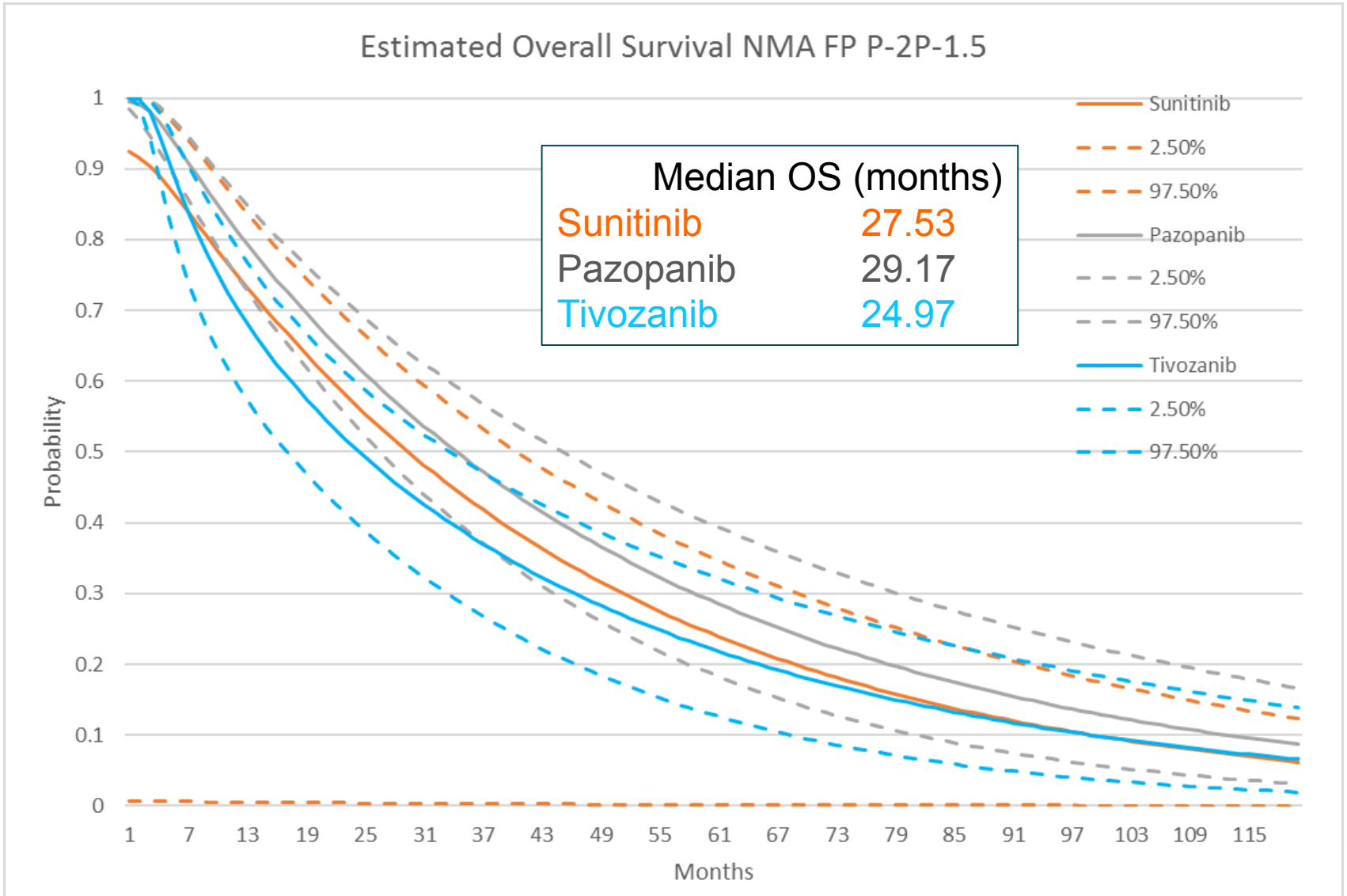
ERG's preferred NMA curves showing 95% credible intervals – PFS

Used in ERG's base case economic model



ERG's preferred NMA curves showing 95% credible intervals - OS

Used in ERG's base case economic model



ERG comments on preferred curves

- Crossover-adjusted results not included
- Therefore, confounding seen for OS in TIVO-1 still an issue
  - ERG suggests use of matched adjusted indirect comparisons (MAIC) to adjust tivozanib group in TIVO-1 to match characteristics of population in COMPARZ trial (sunitinib v pazopanib) would overcome issue as would not rely on within-study comparison with sorafenib
  - ERG recognises several limitations but prefers MAIC to all methods explored by company so far

» What is the most appropriate approach for extrapolation (e.g. fractional polynomial method, other)?
» Are results from the network meta-analysis plausible?
Are the other trials in the network generalisable to practice?
Should they be adjusted for crossover?
» Is tivozanib clinically effective?

Network meta-analysis results for adverse effects

- Pairwise estimates of treatment effects (odds ratios) for specific AEs from Bayesian NMA (treatment-naive patients)

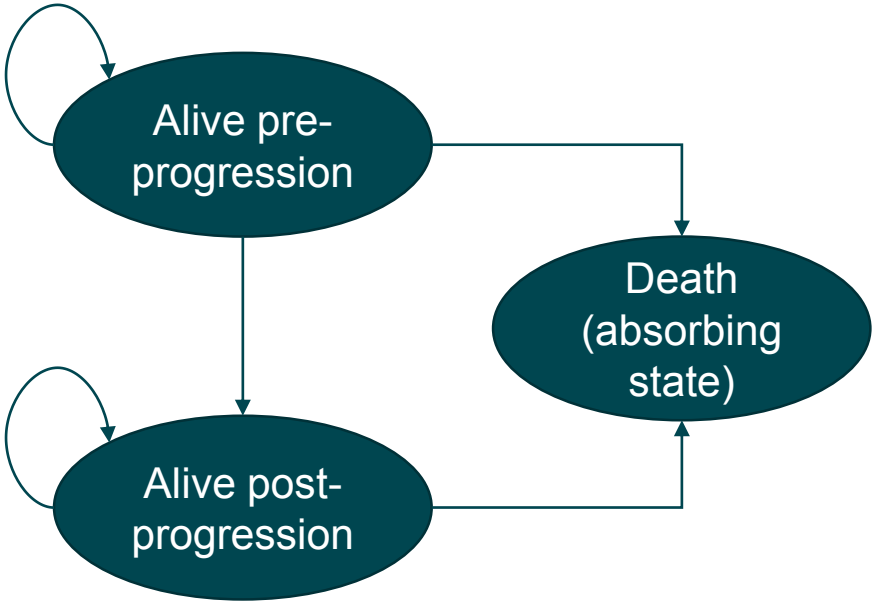
Treatment	Diarrhoea: Median [95% CrI]	Fatigue/ asthenia: Median [95% CrI]	Hypertension: Median [95% CrI]	ALT increased: Median [95% CrI]	AST increased: Median [95% CrI]
TIVO vs SUN	0.1131 [0.025; 0.43]	0.6846 [0.173; 2.849]	1.422 [0.639; 3.182]	0.2307 [0; 7.128]	0.134 [0; 3.215]
TIVO vs PAZ	0.09738 [0.02; 0.399]	1.22 [0.294; 5.294]	1.421 [0.598; 3.391]	0.05841 [0; 1.873]	0.0295 [0; 0.753]

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

ERG comments: results of NMA do not provide robust evidence to support company's assertion that tivozanib has a favourable safety profile compared with pazopanib and sunitinib

Cost effectiveness

Modelling approach and structure



- Partitioned-survival model
- Estimated proportions in each health state based on parametric survival curves fitted to clinical trial data on PFS and OS
- Based on NMA with fractional polynomial method
- Time horizon: 10 years
- Cycle length: 1 week

Treatment	Dosage regimen
Tivozanib (oral)	1,340 µg daily for 3 weeks followed by 1 week without treatment
Sunitinib (oral)	50 mg daily for 4 weeks followed by 2 weeks without treatment
Pazopanib (oral)	800 mg daily, continuously administered

ERG comments: appropriate structure, cycle length, time horizon

Model inputs
Utility values

- Utility values derived from health-related quality of life data from EQ-5D-3L questionnaires given to patients in TIVO-1 study
- Based on full trial population (not on treatment-naive population)
- Utility values assumed same for each treatment arm

	Utility value (mean)	Source	Measure
Pre-progression	0.726	TIVO-1	EQ-5D-3L
Post-progression	0.649	TIVO-1	EQ-5D-3L

ERG comments:
- assuming same utility values for each treatment → reasonable
- satisfied with company's approach of using conservative utility estimates → ERG base case is based on treatment-naive population

Model inputs

Utility values including decrements from adverse effects

- Decrements for adverse effects were derived from published cost-effectiveness analysis of pazopanib
- Each decrement applied to the pre-progression utility value estimate
- Incidence of AEs in tivozanib arm identified from TIVO-1 and odds ratio from NMA applied to calculate expected incidence in each comparator group

Adverse effect (all grade 3+)	Utility value including decrement
Anaemia	0.61
Asthenia/fatigue	0.60
Hand-foot syndrome	0.68
Hypertension	0.66

ERG comments

- Decrements for adverse effects were estimated from a sample from UK general population, **not** people with RCC → ERG removes in base case
- Odds ratios used to produce incidences of AEs were **not** taken from post-clarification NMA → ERG uses post-clarification NMA in base case, but notes odds ratios from both NMAs associated with uncertainty
- Odds ratios applied to incidence rates of AEs for tivozanib in the **overall** population instead of the treatment-naive population → ERG uses treatment-naive in base case

» Should utility decrements from pazopanib analysis be included?

Costs + resources used in company model

Drug costs

Treatment	Dose regimen	PAS discount	List price	Mean cost per week
Tivozanib	1,340 µg daily for 3 weeks followed by 1 week rest	None	XXXX	XXXX
Sunitinib	50 mg daily for 2 weeks followed by 2 weeks rest	No charge for first cycle. List price thereafter	50 mg caps x 28: £3,138.80[94]	First 6 weeks: nil Thereafter: £523.13
Pazopanib	800 mg daily administered continuously	12.5% discount on all doses	400 mg tabs x 30: £1,121[94]	£457.74

Costs and resources in company's model

Company includes only 1 2nd line therapy

- Pre-progression service/monitoring costs
  - consultant appointment on starting treatment
  - monthly outpatient follow-up
  - CT scan every 3 months
- Post-progression service/monitoring costs
  - 60% treated with axitinib (ongoing monitoring requirement same as in pre-progression state)
  - 40% receive supportive care only (same monthly follow-up but no CT scans)
- Adverse events: Company obtained advice from UK clinician to estimate resources for managing advserse events – anaemia, fatigue, hand-foot syndrome, hypertension and diarrhoea

» Is a model stopping at 2nd line therapy and reflecting that 60% receive active therapy realistic?

ERG comments on costs and resource use

- Month assumed to have 4 weeks when converting monthly to weekly disease management costs, instead of 4.35 (→ ERG corrected company's base case)
- Relative dose intensities (RDI) not included in company's model
  - ERG considers RDIs used in previous NICE technology appraisals to be relevant (→ included in ERG base case)
- ERG clinical experts
  - patients would have monthly blood tests – not included in company's model (→ included in ERG base case)
    - full blood count and liver function tests
    - thyroid function tests every 3 months
  - disagree with resource use assumptions for managing AEs
    - → included in ERG base case (but 'negligible impact on ICER')

» What costs and resources should be included in the model?

ERG comments on subsequent therapy costs

	Proportion of patients	
	Company's base-case assumptions (based on TA333 and expert opinion)	Proposed by ERG clinical expert* (→ included in ERG base case)
Axitinib	60%	50%
Everolimus	0%	10%
Nivolumab	0%	30%
Best supportive care	40%	10%

*in line with clinical experts views in NICE TA on cabozantinib [ID931]

- ERG's clinical experts disagree with company's assumption that all patients who receive axitinib will continue taking it until they die
- Company did not discount subsequent treatment disease management costs in the model (→ ERG corrected company base case)
- Modelling only includes 2nd line subsequent therapies and does not include any assumptions around the treatment effectiveness of subsequent therapies on OS

» How should subsequent therapies be incorporated into the model?

ERG's base case analysis

- Based on corrected company's base-case ICER and incorporates:
  - Alternative second order FP-based NMA (P1= -2, P2= -1.5) for OS
  - Alternative second order FP-based NMA (P1= -3, P2= -2.5) for PFS
  - Alternative modelling of adverse events (AE)
    - Treatment naive AE incidence rates for tivozanib from TIVO-1
    - ERG estimates of AE odds ratios based on network meta-analysis
    - ERG clinical expert resource use assumptions for AEs
    - Removal of AE health state utility value decrements
  - Inclusion of blood tests for disease management costs
  - Inclusion of relative dose intensities for treatments
  - Alternative modelling of subsequent therapy costs

» Which assumptions do the committee prefer?

Cost-effectiveness results

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

End of life considerations

- Company did not submit information about end of life considerations

Criterion	Data source	Sorafenib	Pazopanib	Sunitinib
		Median OS (months)		
Short life expectancy, normally < 24 months	TIVO-1 trial and extension study (unadjusted, full population)	34.1	-	-
	IPCW analysis (full population)	Not reported	-	-
	RPSFT analysis (treatment-naive): Unstratified logrank test Unstratified Wilcoxon test Stratified logrank test Stratified Wilcoxon test	Not reached 38.7 32.3 32.3	-	-
	Company's NMA	-	20.8	35.2
	Company's NMA - corrected	-	27.8	35.7
	ERG's NMA	-	34.8	33.1
Extension to life, normally of a mean value of ≥ 3 months		Median OS increase with tivozanib, (months)		
	Company's base case model	-	1.4	-13.0
	ERG base case model	-	-4.2	-2.6

Equality considerations & innovation

- No equality issues related to the use of tivozanib were identified
- Company stated innovation ‘not applicable’ to tivozanib
- Patient groups highlighted that tivozanib is thought to be more specific in targeting all 3 VEGF receptors and therefore to be more effective with fewer side effects than other treatments for metastatic renal cell carcinoma

Key issues – clinical effectiveness

- Where will tivozanib be used in the treatment pathway?:
  - treatment-naive population (1st line)
- Is the clinical trial TIVO-1 generalisable to UK practice in terms of baseline characteristics?
- Is the analysis using treatment-naive patients or the whole trial population most relevant?
- Do overall survival results in geographical subgroups support effectiveness of tivozanib in NHS clinical practice?
- What is the most appropriate method for crossover adjustment (IPCW, RPSFT, other [MAIC])?
  - Does the proportional hazards assumption hold?
- What is the most appropriate approach for extrapolation (e.g. fractional polynomial method, other)?
- Are results from the network meta-analysis plausible?
  - Are the other trials in the network generalisable to NHS clinical practice?
  - Should the trials be adjusted for crossover?
- Is tivozanib clinically effective?

Key issues – cost effectiveness

- Which fractional polynomial-based extrapolation is most appropriate to use in the model? (from range of 1st and 2nd order options)
- Are the results from the model reliable without inclusion of crossover-adjusted data?
- How should subsequent therapy be accounted for in the model? (company's approach, ERG's approach, other?)
  - % of patients receiving each treatment, benefits and costs
- How should adverse effects be incorporated into the model?
  - Include utility decrements (company) or not (ERG)?
- Are the end-of-life criteria met?
- Is tivozanib an innovative treatment?
- Are there any equality issues?

Additional slides

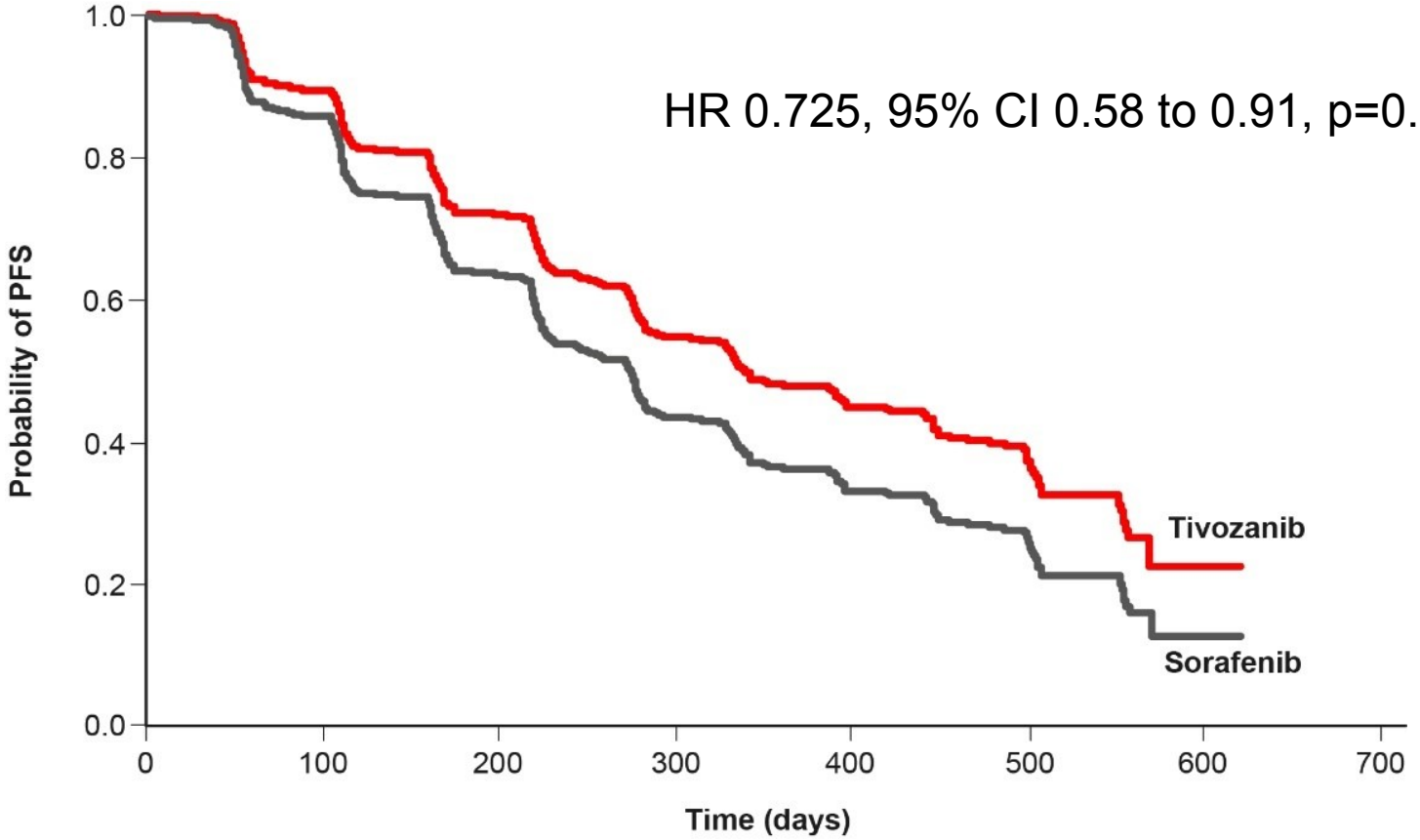
TIVO-1 baseline characteristics

	Full population		Treatment-naive	
	Tivozanib	Sorafenib	Tivozanib	Sorafenib
N (% of randomised)	260 (100)	257 (100)	181 (70)	181 (70)
Median age (range)	59 (23-83)	59 (23-85)	59 (23-83)	59 (23-85)
Male, n (%)	185 (71)	189 (74)	134 (74)	135 (75)
ECOG performance status, n (%) 0	116 (45)	139 (54)	85 (47)	94 (52)
1	144 (55)	118 (46)	96 (53)	87 (48)
Region				
……North America /Western Europe	22 (9)	18 (7)	19 (11)	15 (8)
Central/Eastern Europe	229 (88)	228 (89)	154 (85)	155 (86)
Rest of world	9 (3)	11 (4)	8 (4)	11 (6)
Number of metastatic organs, n (%)				
1	76 (29)	88 (34)	53 (29)	65 (36)
≥2	184 (71)	169 (66)	128 (71)	116 (64)
MSKCC prognostic group, n (%)				
Favourable	70 (27)	87 (34)	48 (27)	60 (33)
Intermediate	173 (67)	160 (62)	121 (67)	112 (62)
Poor	17 (7)	10 (4)	12 (7)	9 (5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan Kettering Cancer Center.

Clinical effectiveness results – PFS

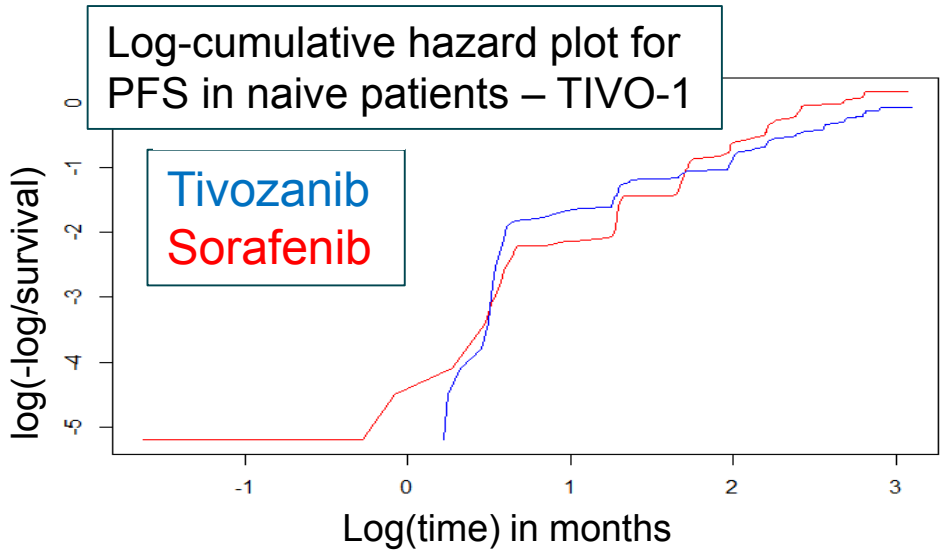
Full trial population, adjusted for baseline demographics and geographical region

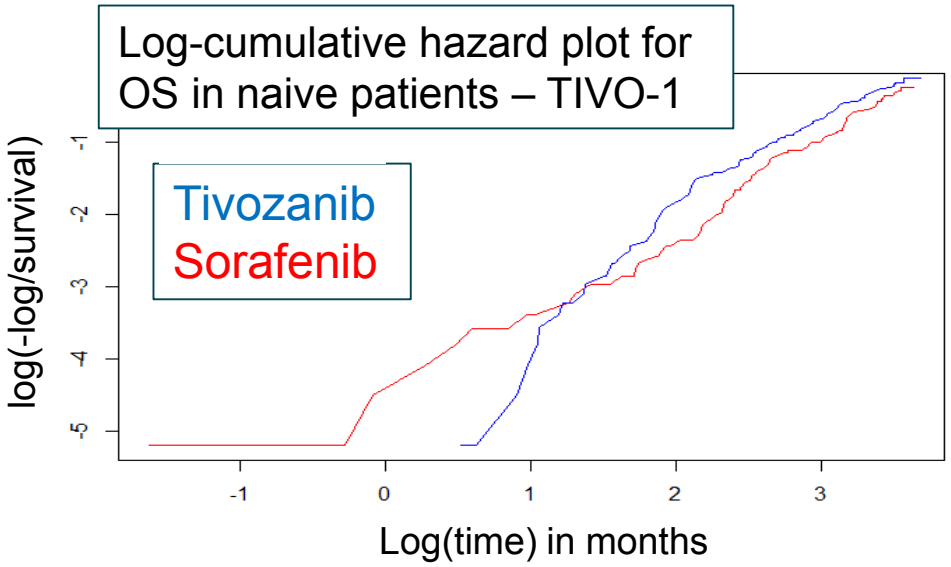


Kaplan-Meier plot of PFS as determined by independent radiology review, adjusted for baseline demographics and geographical region (post-hoc analysis, Dec 2011 data cut)

Extrapolation & proportional hazards

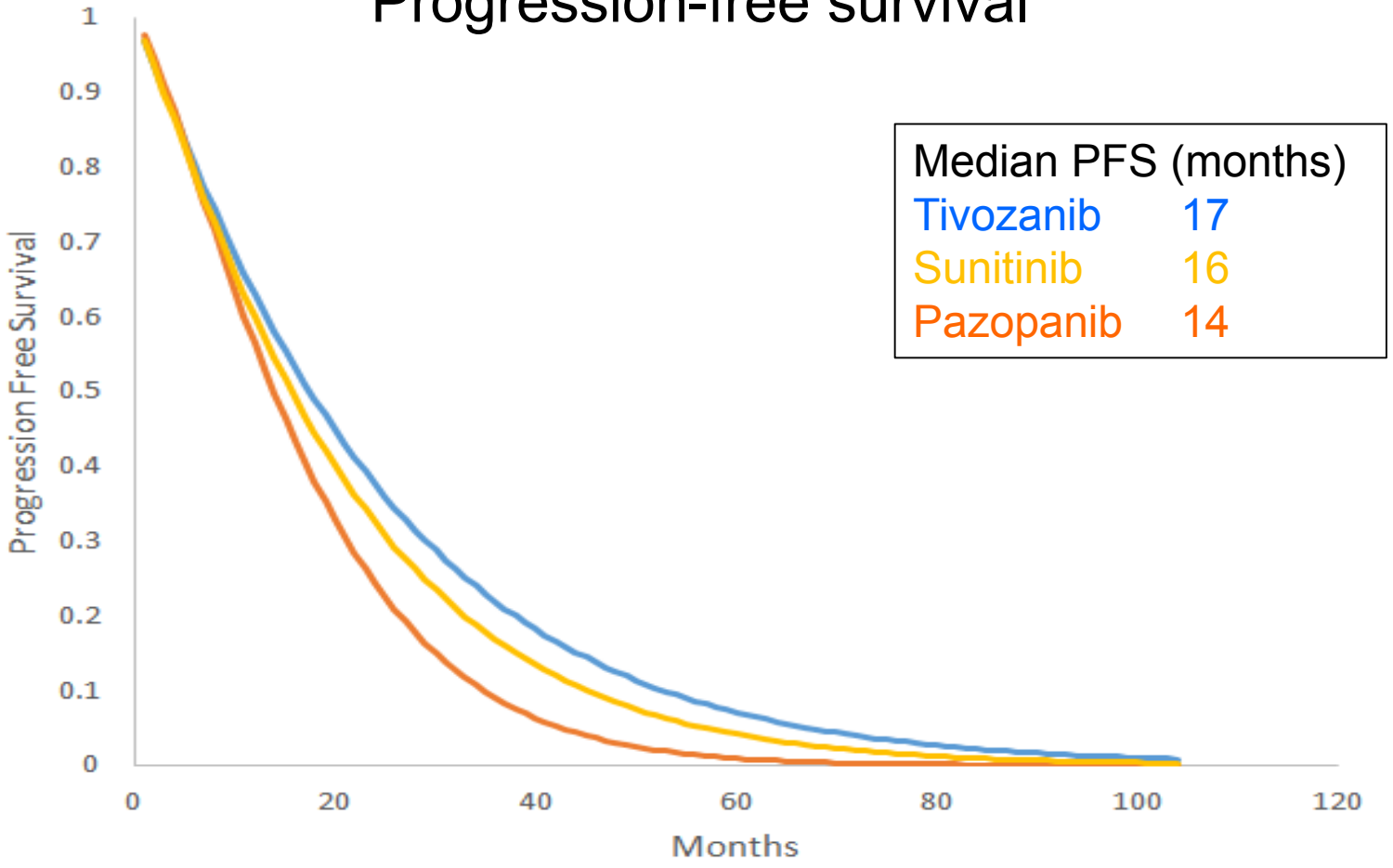
- Proportional hazards assumption does not hold for PFS in TIVO-1
- Curves cross at around 5-7 months of follow up in the trial
- **Company use fractional polynomial method for extrapolation of PFS**
- OS – curves cross but then appear to have a linear trend
- Company state violation of proportional hazards in first 2-3 months unlikely to have meaningful impact, but **use fractional polynomial method for extrapolation of OS**





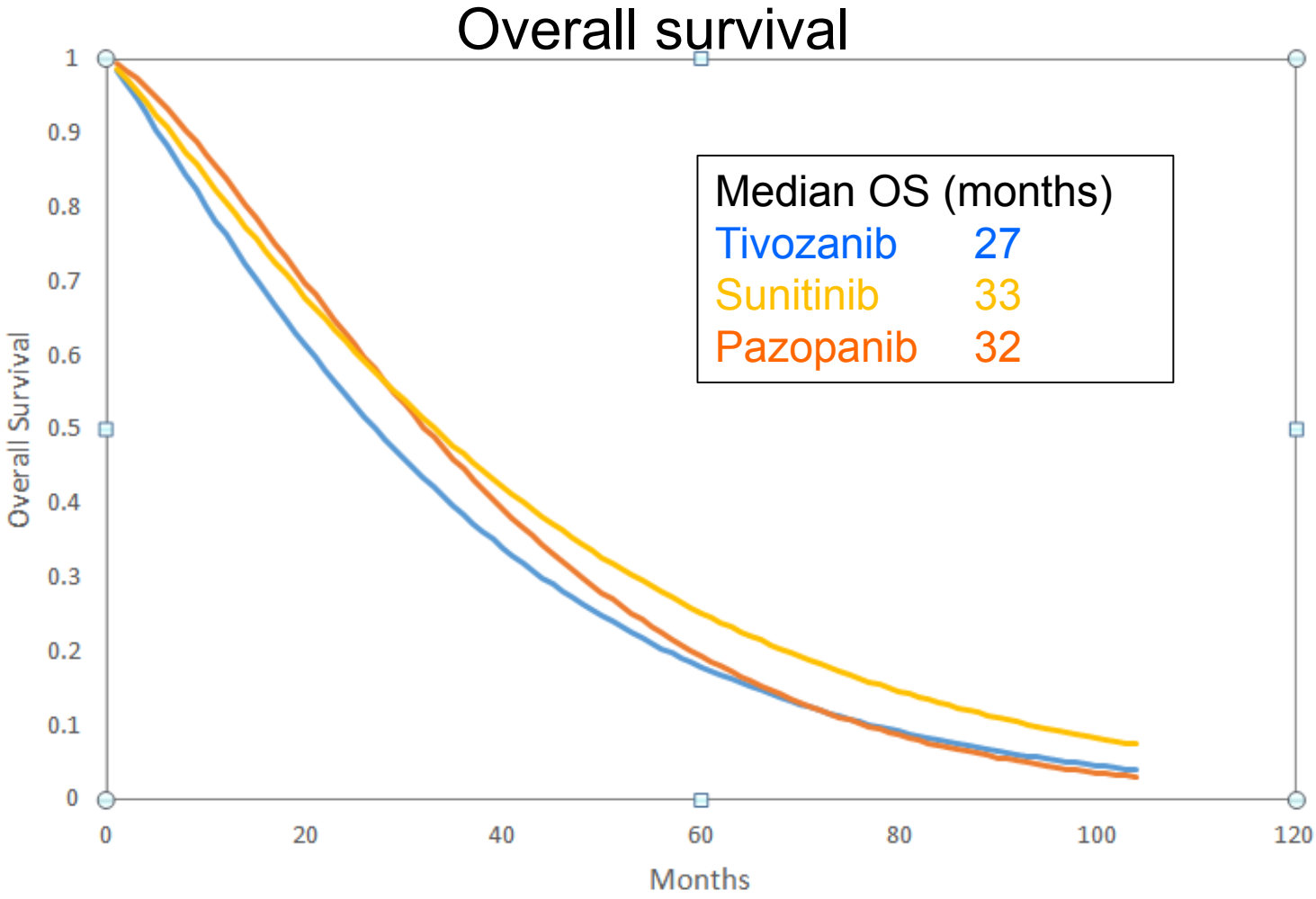
Company's Weibull network-meta analysis – original clarification response

Progression-free survival



- Average PFS adjusted to the baseline from CROSS-J-RCC study fixed effects (Weibull)

Company's Weibull network-meta analysis – original clarification response



- Average OS adjusted to the baseline from CROSS-J-RCC study fixed effects (Weibull)

Methods – using the fractional polynomial model (for extrapolation)

- Company use fractional polynomial method to allow for a change in hazards over time
- Deviance information criterion (DIC) used to compare goodness of fit of fixed effects models with 1st and 2nd order fractional polynomials
- 2nd order fractional polynomial had lowest DIC so was used in base case

Power P1	Power P2	DIC
-2	-	973.724
-1	-	1026.39
-0.5	-	1103.31
0	-	1178.43
-2	-1	**932.832**

Goodness-of-fit estimates for fixed effects fractional polynomial models for different powers P1 and P2: Progression-free survival

Power P1	Power P2	DIC
-2	-	864.418
-1	-	889.814
-0.5	-	921.329
0	-	957.12
-2	-1	**854.314**

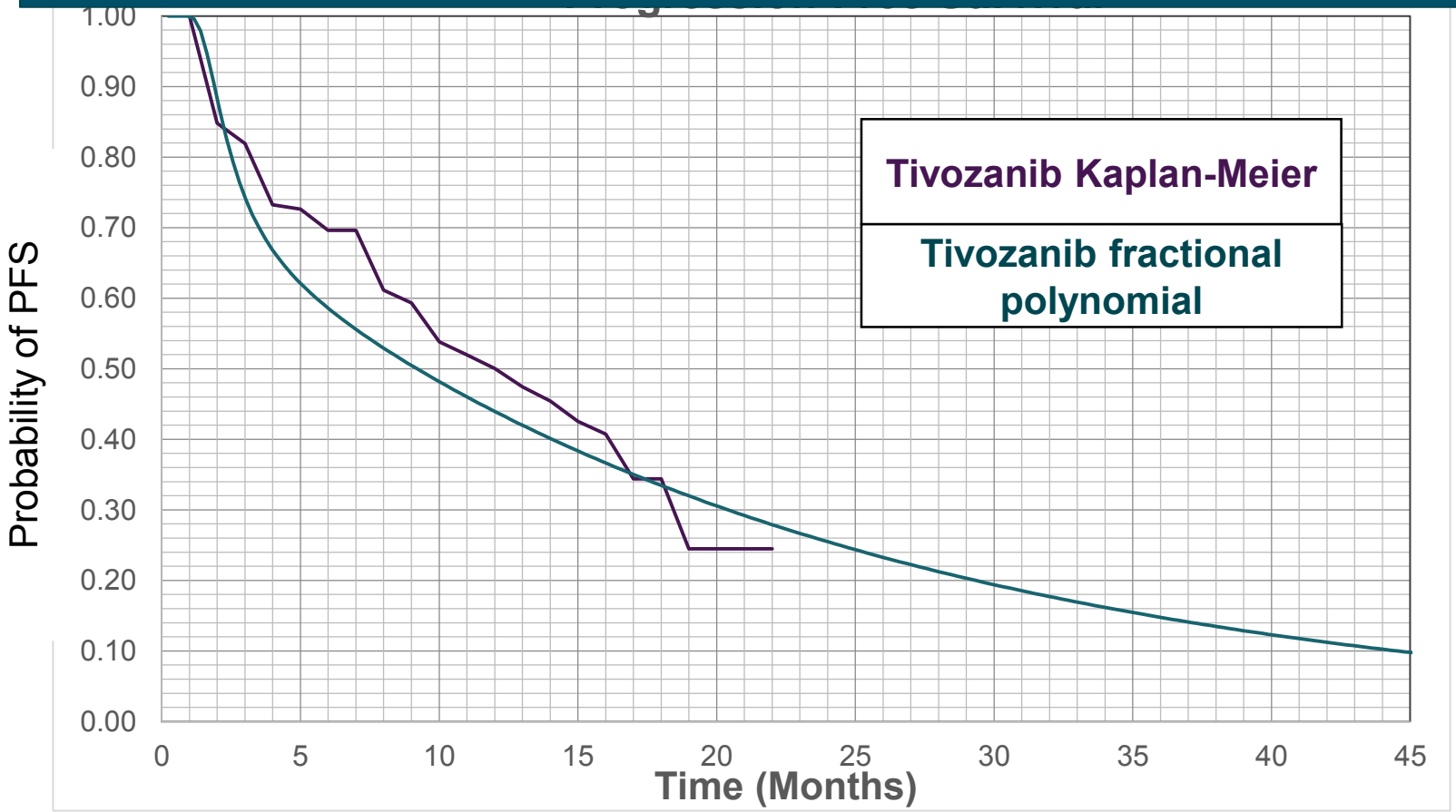
Goodness-of-fit estimates for fixed effects fractional polynomial models for different powers P1 and P2: Overall survival

Company's fractional polynomial model

Progression-free survival

- Company use fractional polynomial method to allow for a change in hazards over time
- Deviance information criterion (DIC) used to select curves

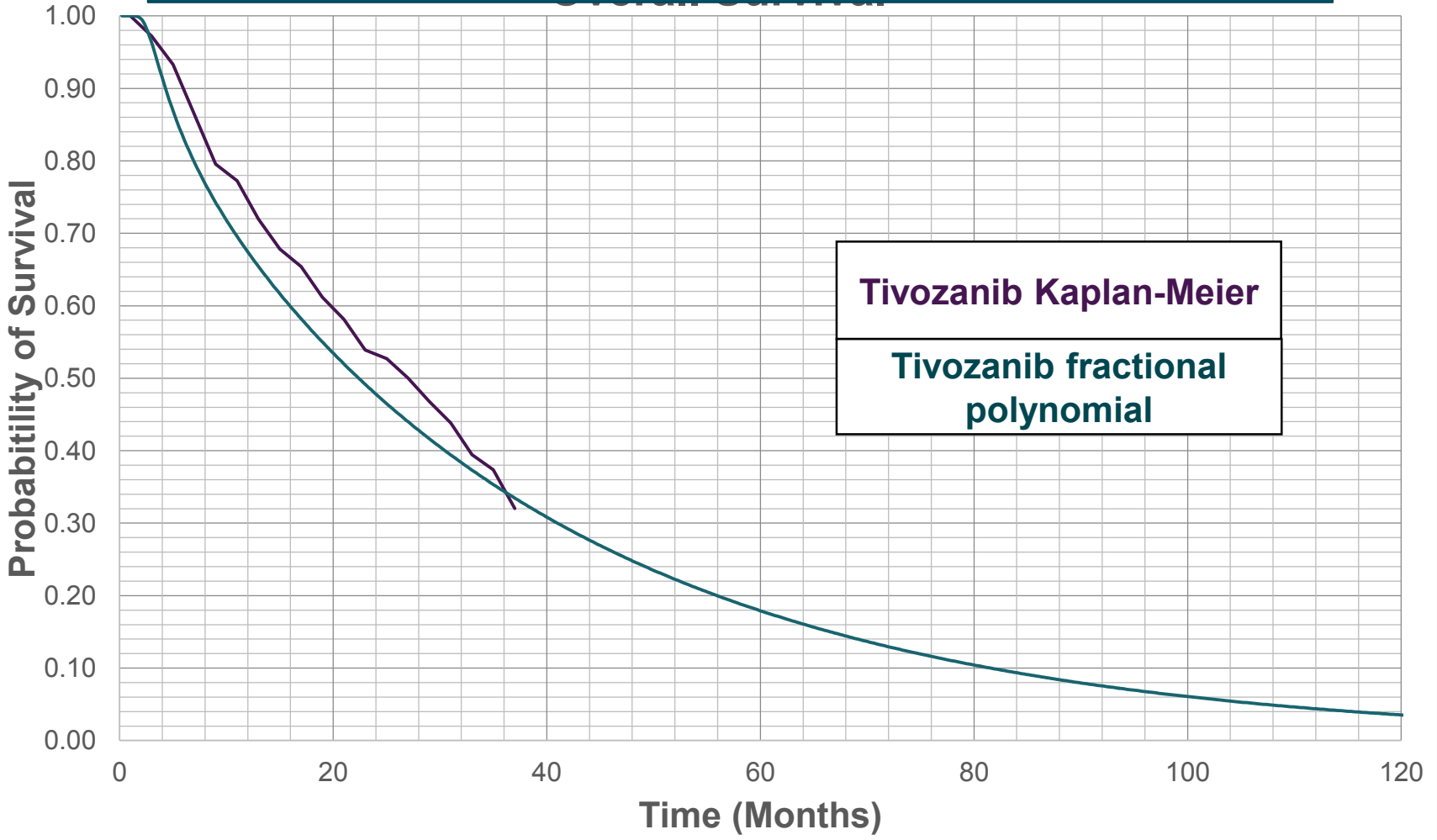
Fractional polynomial model (P= -2, P= -1) v original KM-curve for TIVO-1 study



Company's fractional polynomial model

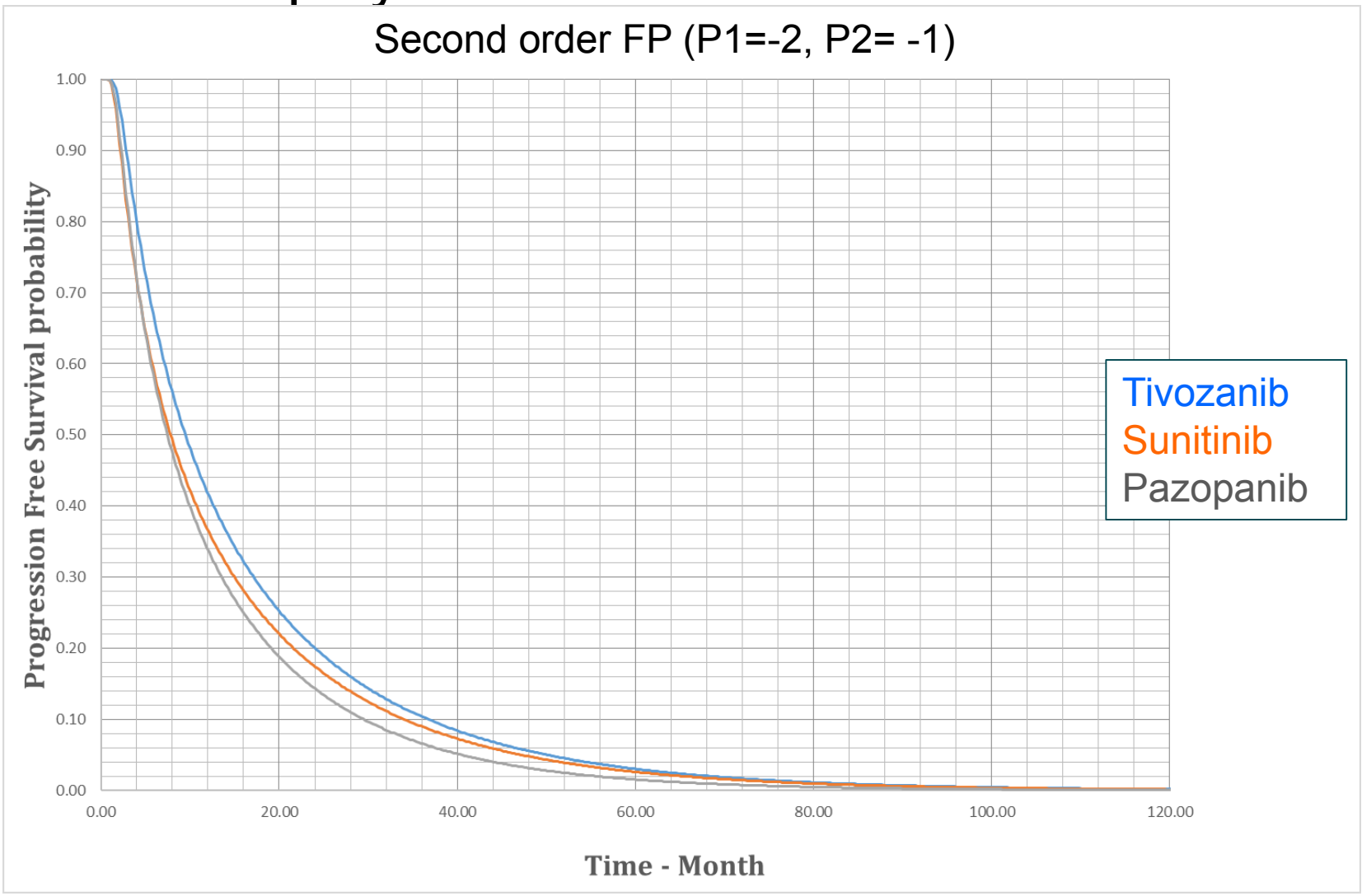
Overall survival, not adjusted for crossover

Fractional polynomial model (P= -2, P= -1) v original KM-curve for TIVO-1 study



Network meta-analysis

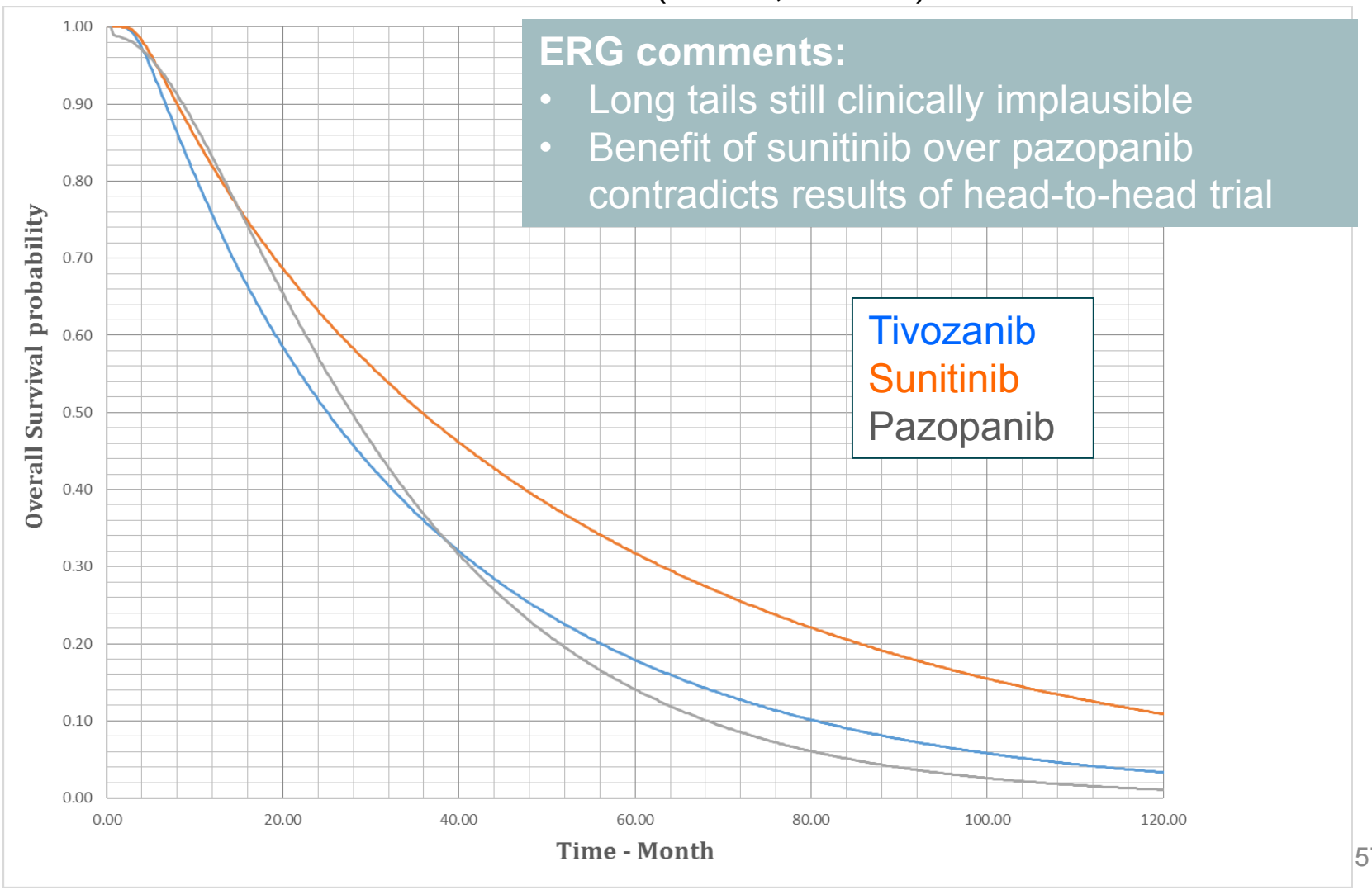
Company's results corrected by ERG – fractional polynomial method for PFS



Network meta-analysis

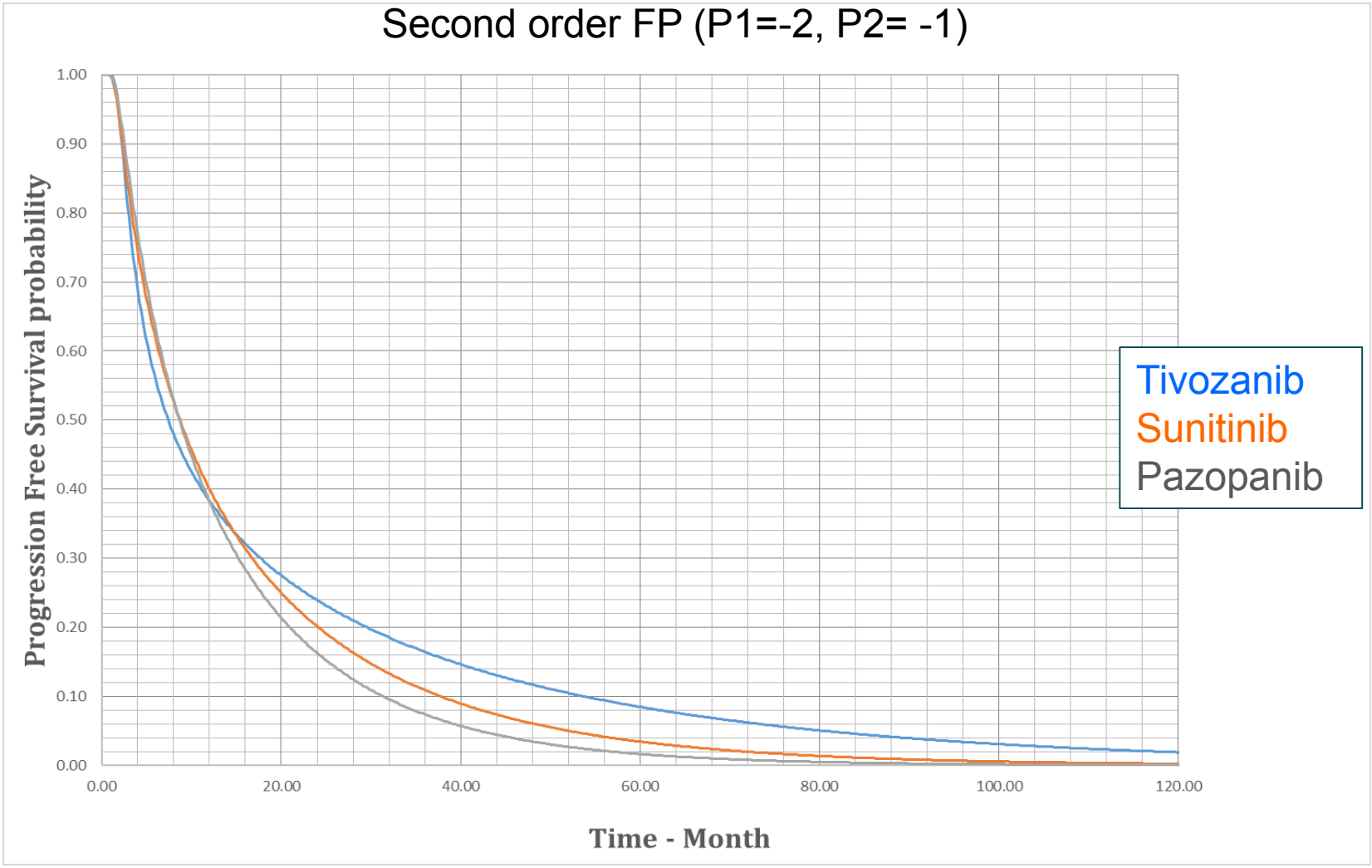
Company's results corrected by ERG – fractional polynomial method for OS

Second order FP (P1=-2, P2= -1)



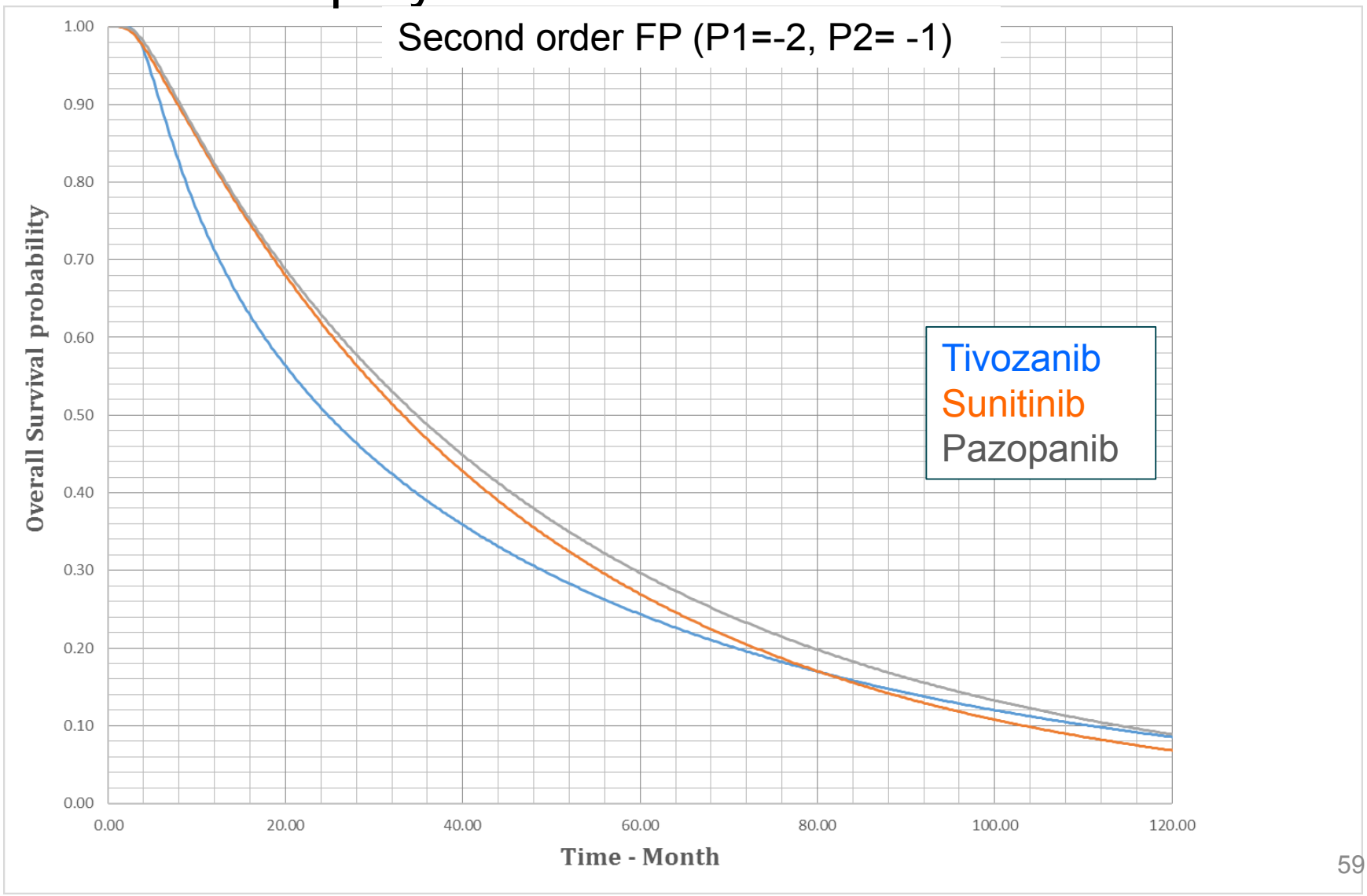
Network meta-analysis

Results using ERG's parameter estimates – fractional polynomial method for PFS



Network meta-analysis

Results using ERG's parameter estimates – fractional polynomial method for OS



ERG DIC statistics for second order FPs

- **PFS**

Power - P1	Power - P2	DIC
-3	-3	**781**
-3	-2.5	**781**
-3	-2	783
-3	-1.5	785
-3	-1	788
-3	-0.5	792
-2	-3	783
-2	-2.5	783
-2	-2	786
-2	-1.5	789
-2	-1	795

ERG

- **OS**

Power - P1	Power - P2	DIC
-3	-2.5	857
-3	-1.5	858
-3	-1	857
-3	-0.5	855
-3	0	853
-2	-3	858
-2	-2.5	857
-2	-2	858
-2	-1.5	855
-2	-1	855
-2	-0.5	852
-2	0	**849**
-2	0.5	850
-1	-1	851
-1	0	853

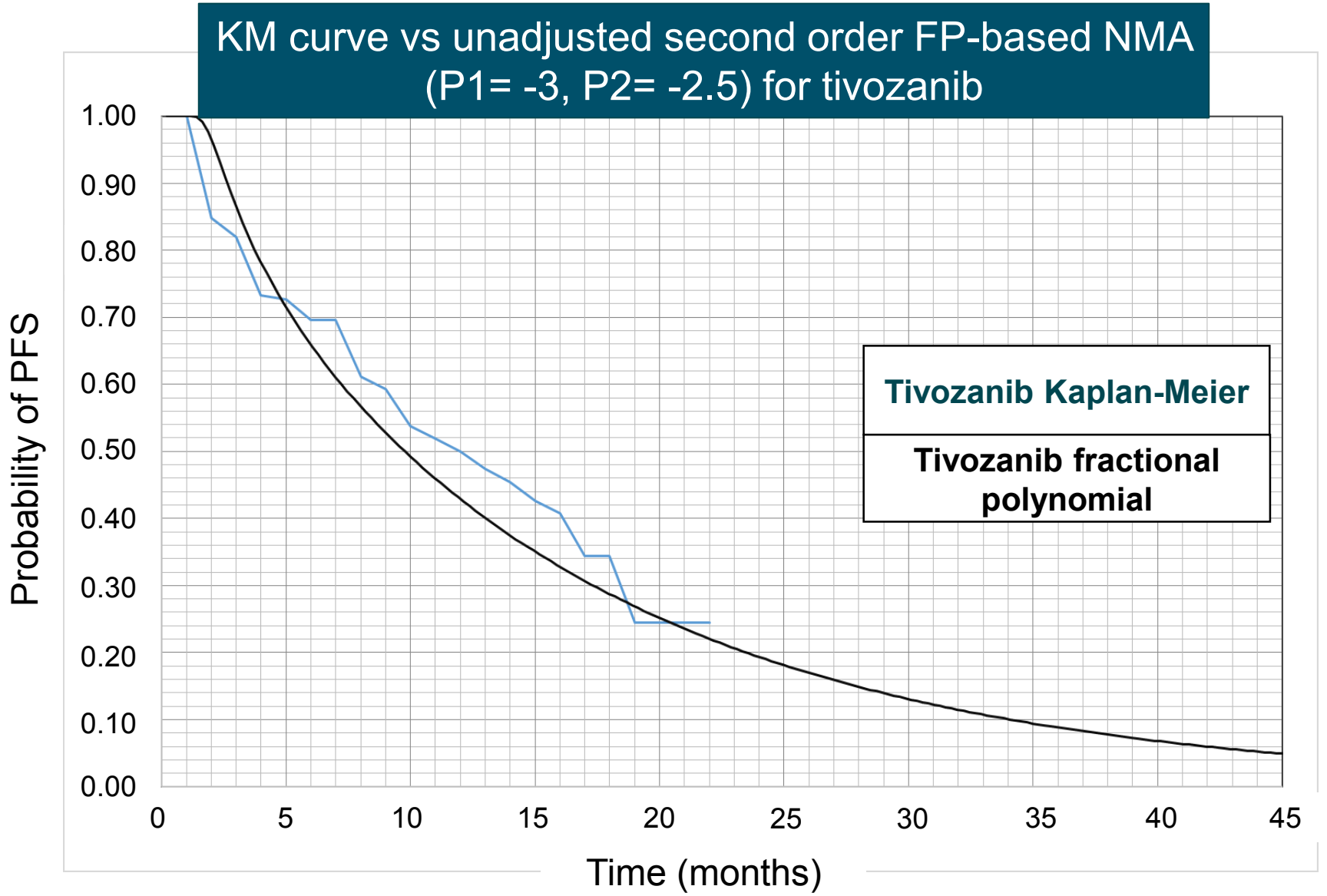
DIC, Deviance information criterion.

Note: Purple highlighted cells indicated company base case curve choice. Bold cells indicate lowest DIC. Blue rectangles indicate ERG curve choices.

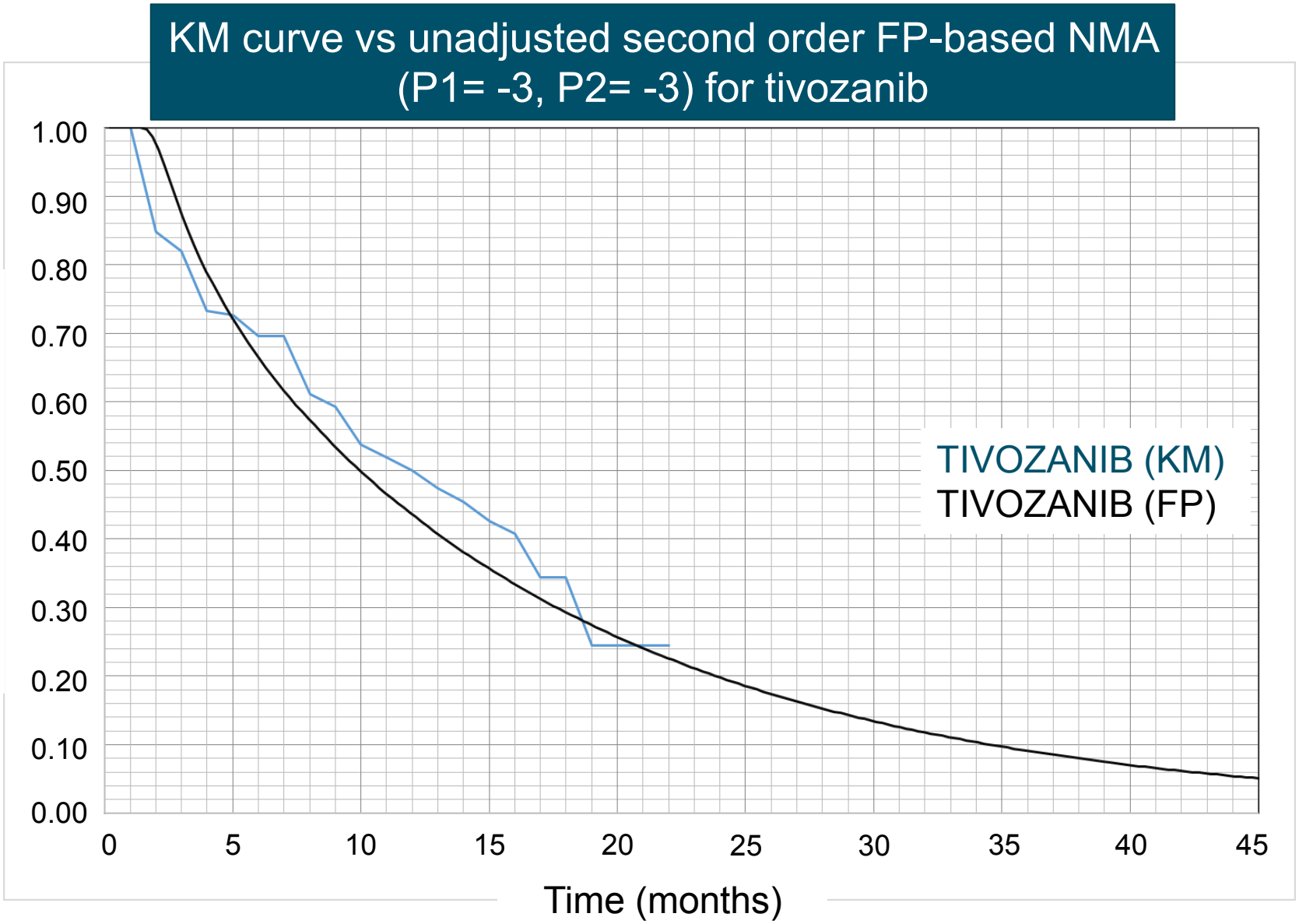
Summary of fractional polynomial NMA results

	Progression-free survival		Overall survival	
	Company	ERG	Company	ERG
Fractional polynomial order in base case	P= -2, P= -1	P= -3, P= -2.5	P= -2, P= -1	P= -2, P= -1.5
DIC statistic	795	781	855	855
Median (months)				
Tivozanib	9.1	6.1 ↓	22.2	25.0 ↑
Sunitinib	8.9	6.8 ↓	35.2	27.5 ↓
Pazopanib	7.1	8.4 ↑	20.8	29.2 ↑

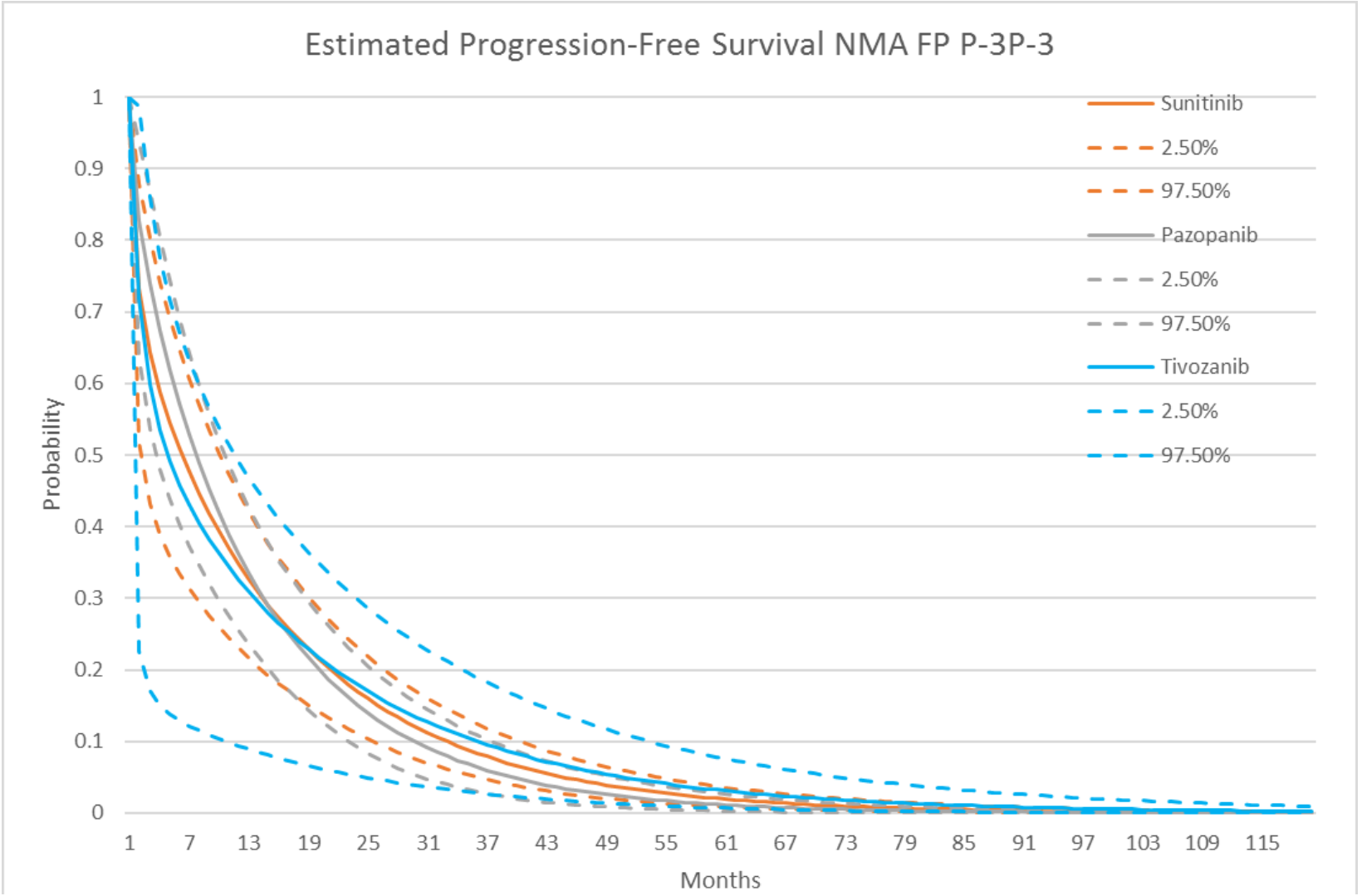
ERG's fractional polynomial curves - PFS



ERG's fractional polynomial curves - PFS

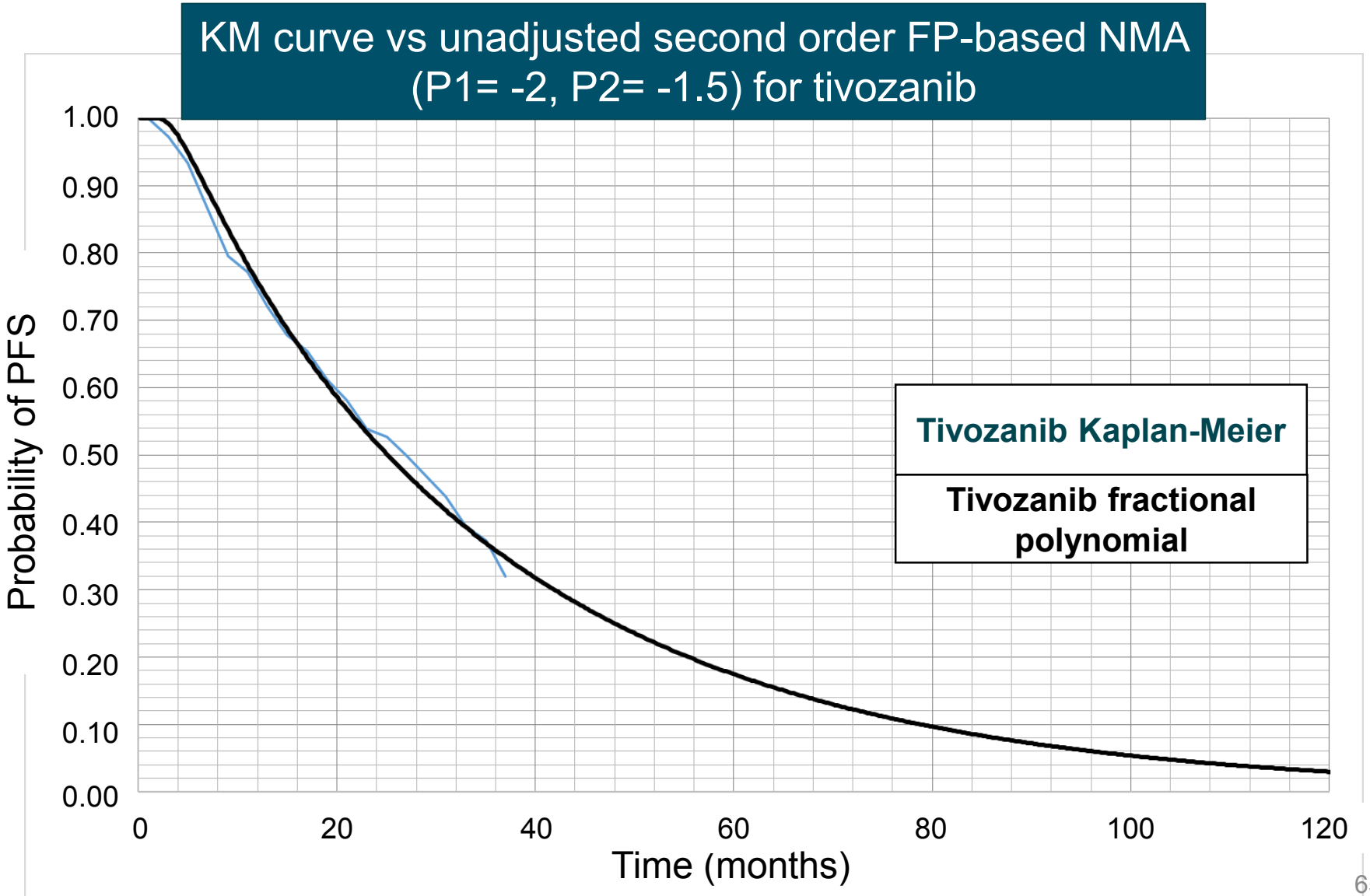


ERG's NMA curves showing 95% credible intervals - PFS



- Not included in base case but scenario analysis 2a

ERG's fractional polynomial curves - OS



Disease management costs in the model

Cost Item	Frequency – stable disease	Frequency – progressive disease	Unit cost	Reference
Oncologist Examination (first visit)	First visit	N/A	£197	NHS Reference Costs 2015/6 HRG WF01B: service code 370 Medical Oncology
Oncologist Examination (subsequent visits)	Monthly	Monthly	£163	NHS Reference Costs 2015/6 HRG WF01A: service code 370 Medical Oncology
CT Scan	Every 3 months	Every 3 months (for patients on subsequent active therapy only)	£115	RD27Z Computerised Tomography Scan of more than three areas (Source: NHS Reference costs 2015/16)

GP, General Practitioner; HFS: Hand-foot syndrome; HRG, Health Resources Group; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Adverse event costs in the model (1)

Adverse event	Service	Proportion of patients	Unit cost	Reference
Anaemia	Day case transfusion	50%	£306	NHS reference costs 2015/6
	Short stay transfusion	50%	£509	Weighted mean of HRG SA04G-SA04L[126]
	Mean expected cost:		£407.50	
Fatigue	Additional outpatient attendance	50%	£163	NHS Reference Costs 2015/6 HRG WF01A: service code 370 Medical Oncology[126]
	Mean expected cost		£81.50	

Adverse effects costs in the model (2)

Adverse event	Service	Proportion of patients	Unit cost	Reference
Hand-foot syndrome	Additional outpatient attendance	60%	£163	NHS reference costs 2015/6
	Short stay admission	30%	£526	NHS reference costs 2015/6
	Mean expected cost		£255.60	
Hypertension	GP attendance x3	100%	£109	PSSRU costs of health and social care 2016
	Treatment with antihypertensive	100%	£28	Assumes treatment with ramipril 5mg + bendroflumethiazide 2.5mg for 1 year
	Mean expected cost		£137	
Diarrhoea	Not reported	100%	£752	Not reported

Estimated resource use assumptions for managing adverse events

Company's and ERG's assumptions

Adverse event	Service	Company's assumption	ERG's clinical expert
Anaemia	Day case transfusion	50%	80%
	Short stay transfusion	50%	20%
Fatigue	Additional outpatient attendance	50%	20%
Hand-foot syndrome	Additional outpatient attendance	60%	60%
	Short stay admission	30%	0

ERG's modelling of subsequent therapies

- Calculated the proportion of newly-progressed patients in a cycle and multiplied by one-off total weighted cost of subsequent therapy
  - Weighted cost based on distribution of patients across second line treatments (clinical expert advice), mean duration, list price, recommended dose and RDI of treatments obtained from published literature
- One-off cost for disease management also applied to proportion newly-progressed in a cycle
  - Estimated based on company's original costs and mean duration of treatment
- Doesn't include any assumptions around treatment effectiveness of each of the subsequent therapies on OS for tivozanib, sunitinib or pazopanib