NICE National Institute for Health and Care Excellence

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Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma [ID3880] – CDF review of TA581

Lead team presentation

Chair: Amanda Adler
Committee B
Lead team: Nigel Westwood (lay), Charles Crawley (clinical), Laura Bojke (cost)
ERG: Liverpool Reviews and Implementation Group (LRiG)
Technical team: Heather Stegenga, Adam Brooke, Michelle Green, Richard Diaz
Company: Bristol Myers Squibb
8 December 2021

Key issues

Proportions of patients with intermediate risk or poor-risk

- Should model reflect Checkmate 214 or systemic anti-cancer therapy (SACT) data?

Effect modification

- Does NIVO+IPI compared with sunitinib have a different effect by subgroup?

Treatment crossover within trial

- Should analyses from trial for overall survival adjust for crossover within trial?

Treatments 2nd line and beyond

- Should model reflect Checkmate 214 or SACT data? If using trial data, should analysis adjust for non-NHS life-extending treatments 2nd line and beyond in trial?

Extrapolating survival

- Which model?

Majority of benefits accrue beyond observed data

- How to model treatment difference over the long-term? Would this also address non-NHS life-extending treatments 2nd line and beyond in trial?

Costs

- Duration of treatment differs by risk – should SACT data inform this?

Utility

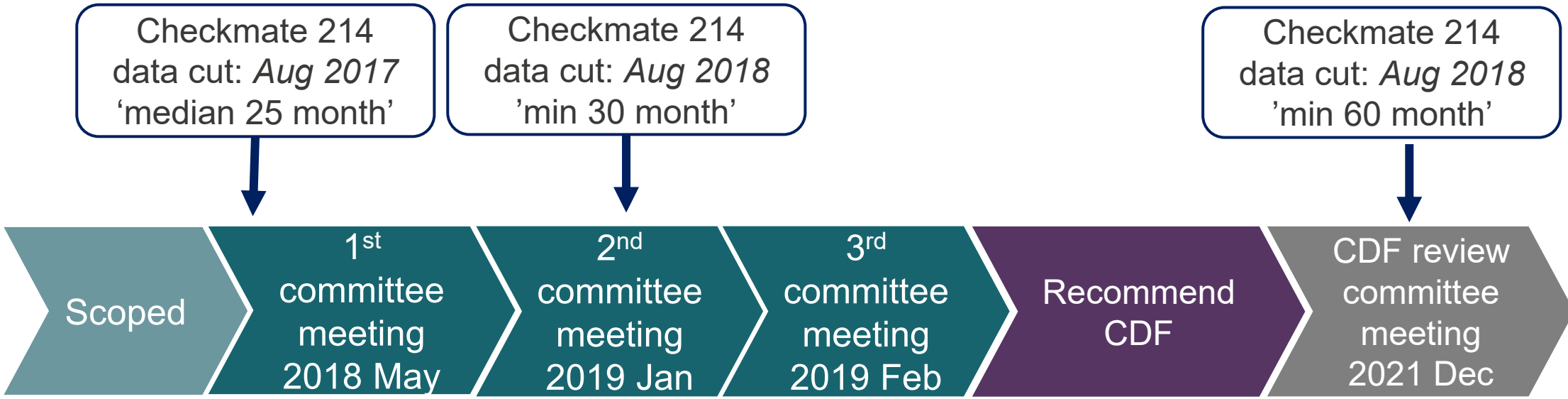
- Should NIVO+IPI utility values stay higher than sunitinib throughout modelled time horizon or to become equal to sunitinib? If so, at what timepoint?

Recommendation May 2019

Appraised by Committee B, Cancer Drug Fund = CDF

Nivolumab with ipilimumab is **recommended for use within the Cancer Drugs Fund** as an option 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

Summary of original appraisal TA581



CDF - managed access agreement with further data collection:

1. Checkmate 214: longer-term survival data adjusted for treatment switching
2. Systematic Anti-Cancer Therapy SACT:
   - % people with poor risk or intermediate risk
   - 2nd-line treatments and beyond
   - death rate
   - treatment duration

CDF review process

- A CDF review, following a period of data collection in managed access, is slightly different to a standard NICE guidance review
  - The comparators are the same as those in the original scope
  - The managed access agreement listed key uncertainties for which data have been collected. Key assumptions related to these should be revisited. For example approaches to extrapolate survival outcomes should be fully explored
  - Other key assumptions not addressed during the period of managed access remain unchanged

Note: The guidance update process following a period of managed access will be changing when the new NICE manual is launched in 2022, the process will include a re-scoping exercise to take account of changes to the treatment pathway that have occurred since the original recommendation.

Nivolumab + ipilimumab (Opdivo® +Yervoy®)

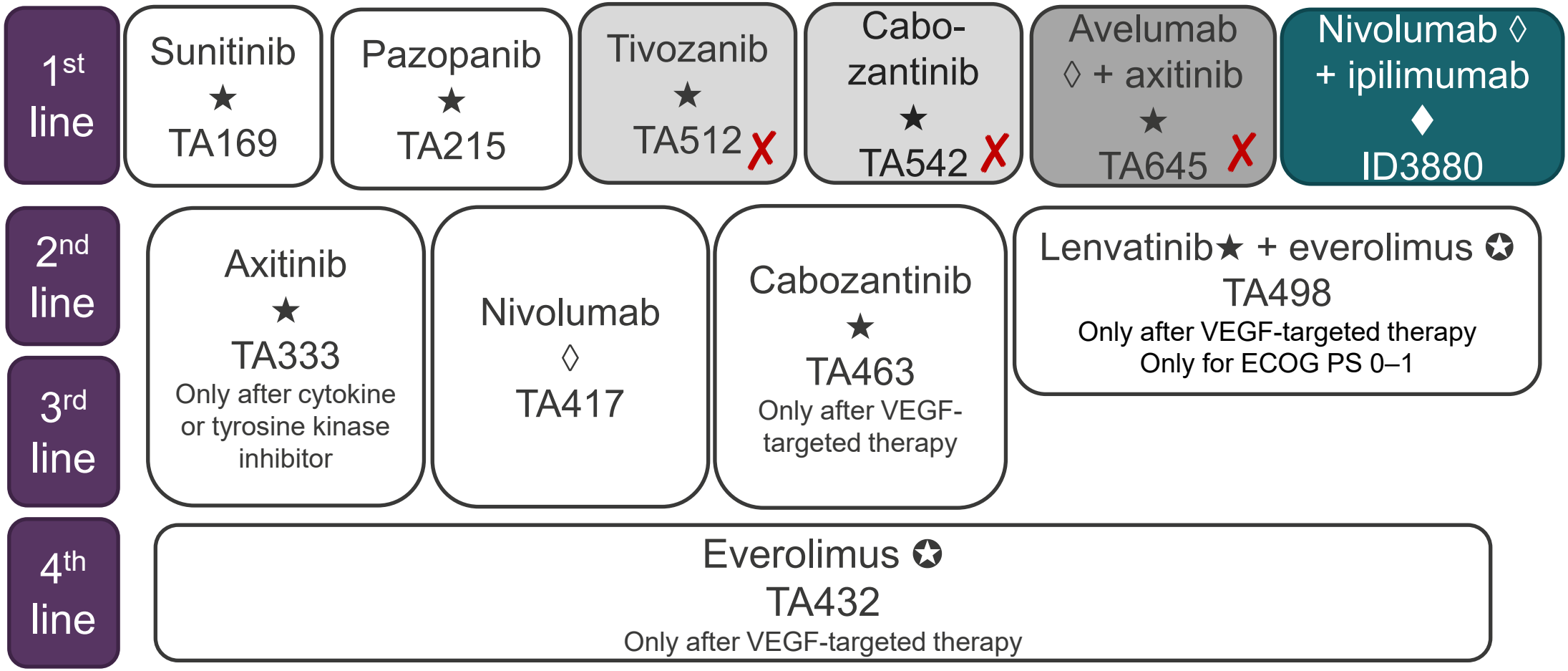
both Bristol-Myers Squibb; marketing authorisation narrower than trial

Marketing authorisation	1st-line treatment of adult patients with risk deemed intermediate (1 or 2) or poor (3 or 4) advanced renal cell carcinoma* *International Metastatic RCC Database Consortium risk based on Karnofsy performance, time from diagnosis to treatment, anaemia, hypercalcaemia, neutrophilia, thrombocytosis*
Mechanism of action	• Nivolumab: blocks PD-1 receptor • Ipilimumab: enhances T-cell mediated immune response
Administration & dose	*Induction phase* • Nivolumab: 3mg/kg IV every 3 weeks for 4 doses • Ipilimumab: 1mg/kg IV every 3 weeks for 4 doses *Maintenance phase* – previously weight based, now 480 mg IV every 4 weeks or 240 mg IV every 2 weeks until disease progression
Stopping rule	None
List price	• Per dose: **nivolumab,** £3,950; **ipilimumab,** £7,500. • Separate Patient Access Scheme (PAS discount) approved by Department of Health for both nivolumab and ipilimumab

* Checkmate 8Y8 (NIVO+IPI vs NIVO) conducted to examine contribution of ipi as per CHMP requirement. Results have not yet been reported.

Current treatment pathway

Intermediate-/poor-risk



✗ *= not a comparator in TA581 or here*

Note: Nivolumab is 2nd + 3rd line option

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; ♦: anti-CTLA-4 inhibitor

Patient perspective

Impact of disease:

- Symptoms include fatigue, depression, weight loss, anorexia, and pain
- Less energy to carry out activities of daily living and need time off work

Limited treatment options:

- Current treatments have adverse effects notably diarrhoea and fatigue
- Treatment options provide hope
- Most treatments aim to extend life; kidney cancer is a chronic disease with focus on quality of life

Nivolumab with ipilimumab:

- Improved adverse effect profile compared to other first line drugs
- But, some have colitis, pneumonitis and endocrine problems requiring hospitalisation
- ?What about people with non-clear cell renal cell carcinoma?

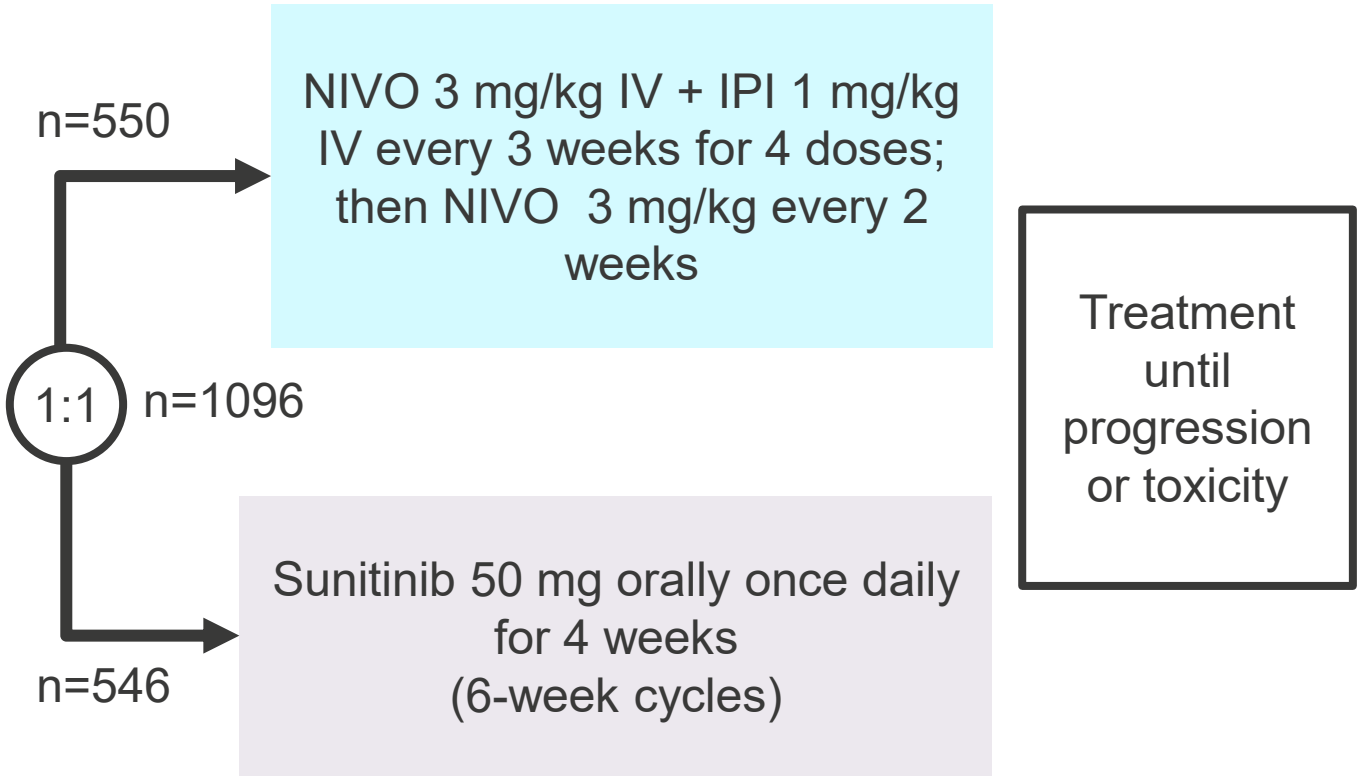
"current treatments work well for some … but not all…it is reassuring for patients having more treatment options "

Recap: CheckMate 214 trial active comparator

Trial broader than intermediate poor risk

Eligibility criteria:
- Advanced or metastatic RCC with clear-cell component
- Treatment-naïve
- Karnofsky Performance Status ≥70%
- ≥18 years old

Stratification by:
- Prognostic risk
- Region

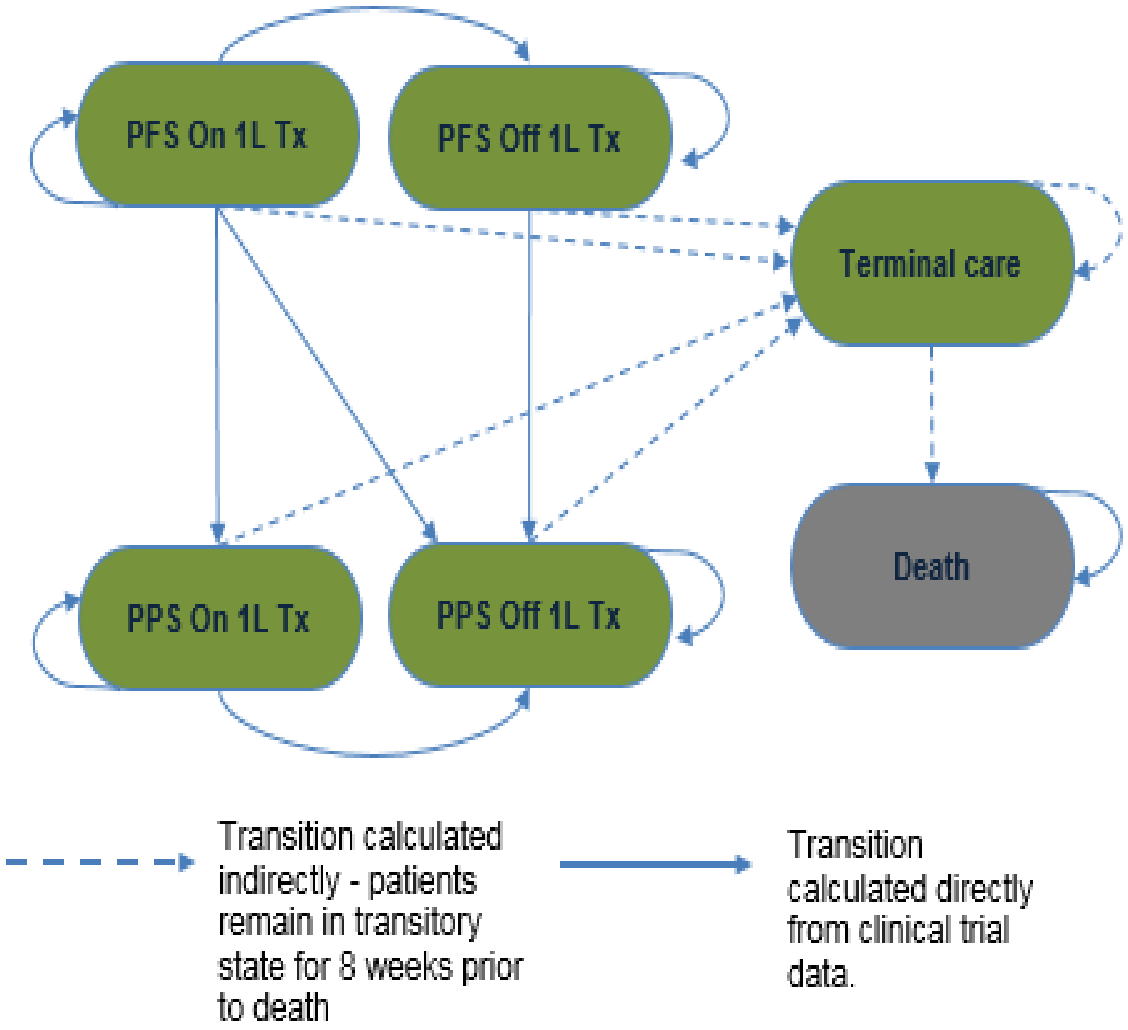


Trial powered for population with intermediate-/poor-risk (n=847):
- n=180 poor IMDC (3-6 prognostic factors)
- n=667 intermediate IMDC (1-2 prognostic factors)

NICE

Abbreviations: International Metastatic Renal Cell Carcinoma (IMDC) risk score

Recap company model: cohort-level partitioned survival



Efficacy	Trial
Cycle length	1 week
Time horizon	40 years
Treatment duration	Trial
Comparators	Sunitinib, pazopanib
Quality of life	Trial EQ-5D
Adverse events	Included (disutilities excluded)

Abbreviations: PFS: pre-progression state; PPS: post-progression state; 1L: 1st line; Tx: treatment

Key committee conclusions from TA581 1

Topic	Committee consideration from TA581 appraisal	FAD section
Prognostic risk scores	Not routinely used in practice, but no barriers to use them	3.2
Comparators	Sunitinib, pazopanib appropriate comparators, and clinically equivalent	3.3
Prognostic risk	CheckMate 214 generalisable to practice in England but more people would have poor-risk. The combined intermediate- or poor-risk group from trial is appropriate for decision making	3.4 and 3.5
Progression-free survival (PFS) definition	Prefer secondary definition of PFS which does not exclude patients once they move onto other treatments before disease progression, progress or die	3.6
Progression-free survival	Independent radiology review committee (IRCC)-assessed progression-free survival data should be used	3.13
Clinical effect vs sunitinib	Nivolumab with ipilimumab is more effective than sunitinib, but size of long-term survival unknown	3.7, 3.10
Adverse events	Safety profile preferable to tyrosine kinase inhibitors	3.9

Key committee conclusions from TA581 2

Topic	Committee consideration from TA581 appraisal	FAD section
Immunological effect 'cure'	Not appropriately modelled – cure fraction higher than number who remained on treatment	3.11
Stopping rule	Not appropriate to include	3.12
Weight-based vs flat dosing	Costs of treatment should reflect flat dosing and a maintenance dose for nivolumab of 480 mg every 4 weeks	3.14
Pazopanib and sunitinib	Time-to-stopping treatment with pazopanib or sunitinib equal	3.15
Quality of life	Estimates should reflect whether disease has progressed, on-off treatment, which treatment	3.16
Treatments after 1st line	Model should include treatments offered 2nd line and beyond in CheckMate 214	3.17
Extrapolation overall survival	Consider both company's and ERG's. Could not determine most appropriate in absence of evidence of long-term immunological effect.	3.18
Cost effectiveness	ERG's estimates more plausible than company's	3.19
End of Life	Life expectancy for combined intermediate- and poor-risk disease group likely >24 months. End-of-life criteria not met	3.20

CDF Review company response

Subject	Relayed to company	Company	Discuss?
Population	SACT should inform % with intermediate and % with poor risk	✗ did not provide	SACT reflects NHS – effect modification?
Comparator	Sunitinib + pazopanib clinically equal	✓ Base-case	No
Progression	Use 2º definition, independent review	✓ Base-case	No
Treatment switching	Trial stopped early; could switch to NIVO+IPI. Need more data to inform adjustment	✗ Didn't adjust: low % of patients switched	Unadjusted may favour sunitinib
Treatments after 1st line	Model 'supported' by SACT	Trial treatments in base case; SACT in scenario only	Do not reflect clinical practice
Extrapolating overall survival	Use more mature trial data to choose curve and address 'cure'	✓ Base-case did not incorporate separate immunological effect	ERG – most benefit accrues beyond observed data
Stopping rule	No stopping rule	✓ None in new base-case	No
Dosing	Per license	✓ In new base-case	No
Quality of life	Use mature trial data; ensure differences by treatment, on or off treatment, disease progression	✓ In new base-case	Likely minor impact on ICER

Updated clinical evidence after CDF

Post-CDF clinical evidence

SACT patients poorer risk that trial; SACT shorter follow-up than trial

	CheckMate 214 comparative Trial N=425	**Systemic Anti-Cancer Therapy (SACT) dataset** N=814*
Period	Oct 2014 to Feb 2021	Apr 2019 to Nov 2020
Follow-up in months, median, range	67.7, 60 to not reported	10.8, 5.0 to 24.7
Population: prognostic group	21% (91) poor-risk 79% (334) intermediate-risk	35% (281) poor-risk 65% (533) intermediate-risk
Comparator	Sunitinib	None
Company use of data in model	• overall survival • progression-free survival • time to discontinuing treatment • health-related quality of life • 2nd line treatments and beyond (distribution and cost)	2nd line treatments and beyond in scenario

* 99% of 821 who met inclusion criteria and were treated with nivo+ipi. (of 857 'cohort of interest')

Proportions of patients with intermediate risk or poor-risk

Should characteristics of patients in model reflect Checkmate 214 trial or SACT?

Which data source reflects population in NHS?

SACT have more poor-risk than CheckMate 214; company - caused by COVID-19

Committee TA581: more people in NHS than in CheckMate 214 have poor-risk. Treatment effect likely differs by risk. SACT should inform proportions with intermediate/poor-risk

Study / source	Proportion of patients with poor-risk disease
CheckMate 214 trial	NIVO+IPI and sunitinib: 21%
SACT registry	NIVO+IPI: 35%
KEYNOTE 426 trial	Pembrolizumab+ axitinib and sunitinib:17-19%
JAVELIN Renal 101 trial	Avelumab+axitinib and Sunitinib: 20- 21%
Registry study (Allison et al 2021)	NIVO+IPI: 28%

Company:

- Test for interaction showed [redacted] ([redacted] for overall survival, [redacted] for progression-free survival)
- Not powered for subgroup analysis
- More high risk patients because of pandemic -
  - CRUK: 29% delayed, cancelled or changed treatment
  - Nuffield Trust: 50% fewer urological cancer referrals, consultant appointments, diagnoses
  - Royal Free study: 50% fewer 2-week referrals, 47% fewer discussed at multi-disciplinary team meetings
- Online survey 41 clinical experts support company assertion that treatment of fit patients diverted leaving more unfit patients treated

Company clinicians:

- Some but not all referrals to SACT delayed

Which data source reflects population in NHS?

ERG consider SACT reflects NHS practice better than trial

ERG:

- SACT better reflects NHS patients who would be treated with NIVO+IPI
  - limited evidence that poor risk in SACT because of pandemic
  - Focus not on very unwell patients: 87% had ECOG performance 0 or 1
  - Clinical advice to ERG in TA581 - 30% have poor risk
- Even without effect modification by risk, ICERs across marketing authorisation would not apply to subgroup since costs and QALY would differ
- SACT data suggests overall survival and treatment duration lower for poor risk so cost-effectiveness may differ
- Company did not present outcomes from CheckMate 214 separated by subgroups even when requested 'trial not powered for outcomes by subgroups'

Clinical input:

- One expert expects 20% poor risk in clinical practice, another approximately 30%

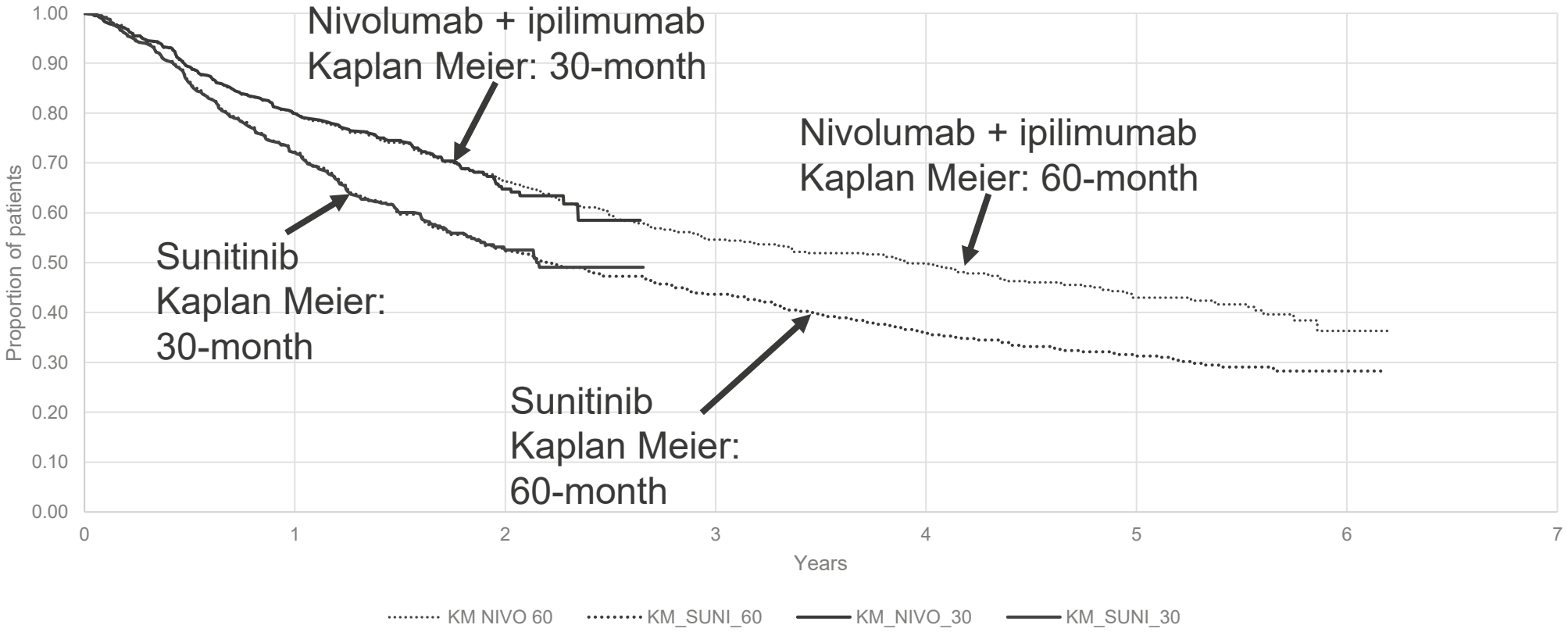
◉ *Should the model reflect the trial population or the NHS population?*

Abbreviations: ECOG, Eastern Cooperative Oncology Group

Checkmate 214: overall survival for NIVO + IPI vs sunitinib

Kaplan Meier data min 60 months. Company: benefit lasts

Hazard ratio not used in model but changed from 0.66 to 0.68

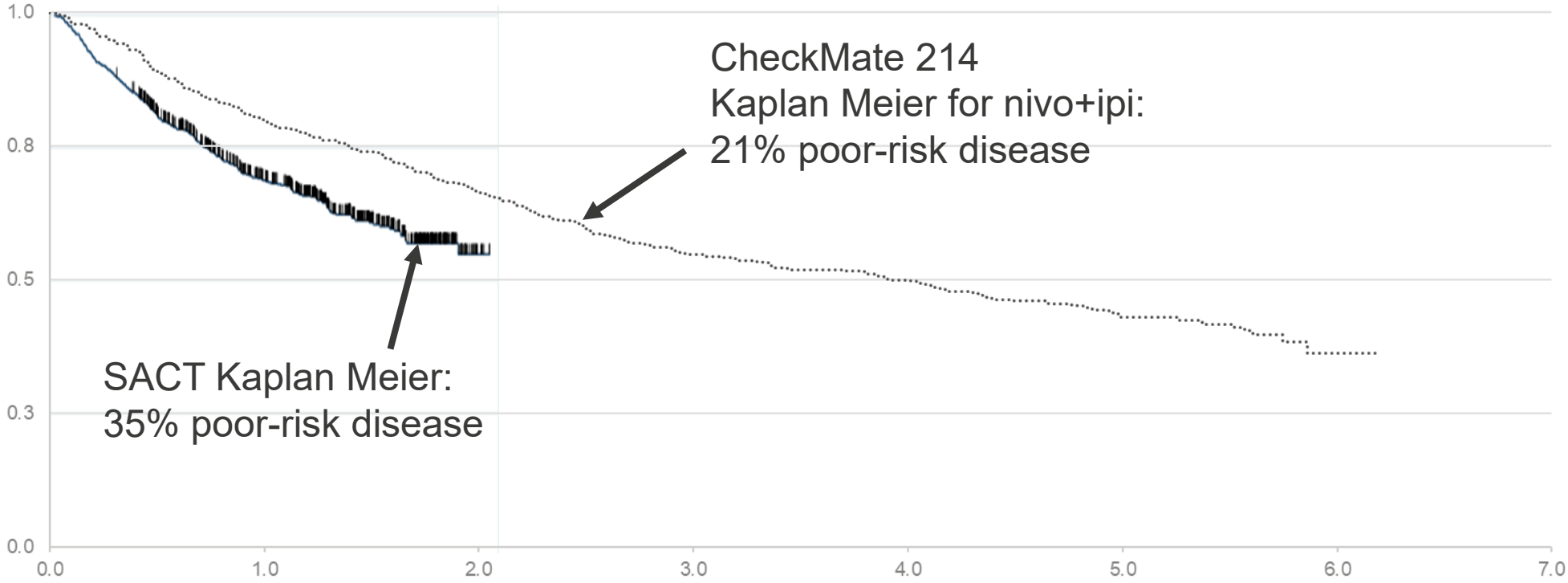


Data cut	Treatment	Median overall survival months (95% CI)	Hazard ratio (95% CI) unadjusted for switching
30-month	Sunitinib	27 (22 to 33) months	Reference
	NIVO+IPI	NA (36 to NA) months	0.66 (0.54 to 0.80)
60-month	Sunitinib	27 (22 to 34) months	Reference
	NIVO+IPI	47 (35 to 57) months	0.68 (0.58 to 0.81)

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival

SACT: overall survival for NIVO + IPI only

Naïve comparison; SACT data not for model, but for information



Time point	SACT overall survival, % (95% confidence interval)
6 months	80 (77 to 83)
12 months	69 (65 to 72)
18 months	61 (57 to 64)

SACT dataset:
58% (469/814) no longer on treatment*; of these outcome data complete for 64% (302/469)

* Patient outcomes only captured when patient has completed treatment because they have died, have an outcome in SACT stating why treatment stopped or have not received treatment in 3 months

Effect modification

Does NIVO+IPI compared with sunitinib have a different effect by subgroup?

CheckMate 214: overall survival by risk

Subgroup analyses in initial appraisal: visual inspection suggested differential treatment response; company does not present same analyses at 30- or 60-months

	Intermediate risk	Poor risk
Median 25-month data cut (Aug 2017)	[redacted]	[redacted]
Minimum 30- + 60-month data cuts (Aug 2018 and Feb 2021)	*Company does not provide results*	

◉ *Has committee seen further evidence to change its conclusion on effect modification?*

Histology – treatment effect modifier?

Clinician professional body submission: recent post hoc analysis from CheckMate 214 shows people with sarcomatoid disease have particular benefit with nivo+ipi

- Tannir et al 2021 reported analysis of people sarcomatoid disease and poor/intermediate risk (n=139) at 42 months' follow-up

Outcome	Treatment	Median, months (95% confidence interval)	HR (95% confidence interval)
Overall survival	NIVO+IPI (n=74)	Not reached (25 to not estimatable)	0.45 (0.3 to 0.7)
	Sunitinib (n=65)	14 (9 to 23)	
Progression-free survival	NIVO+IPI (n=74)	27*	0.54 (0.33 to 0.86)
	Sunitinib (n=65)	5*	

*Confidence interval not reported in publicly available abstract

◉ *Is histology a treatment effect modifier?*

Updated modelling and issues

Company model inputs

Model inputs	Company	ERG comment	Impact on ICER
Overall survival	Cure model no longer included	Company approach 'appropriate'	**Unknown**
Overall survival	Log-normal both treatments independently fitted*	NIVO + IPI mortality rates consistently higher than sunitinib – **data do not support this**	**Increases**
Progression-free survival	Hazard spline 2-knot for both treatments	None	**Unknown**
Time to treatment stopping	[redacted] for both treatments*	None	**Increases**
Utility benefit	NIVO+IPI values higher than sunitinib throughout modelled horizon	No evidence values higher than sunitinib beyond trial data	**Minimal**
Treatments after 1st line	From CheckMate 214 (SACT in scenario)	Uses trial but equalises hazards for OS because of 2nd and later line treatments	**Increases**
Subgroups by disease status and histology	Doesn't present subgroups in updated data	Prefers clinical and economic evidence by risk status	**Unknown**

Treatment crossover within trial

Should analyses from trial for over-all survival adjust for crossover within trial?

Treatment crossover: methods not used

Company says few crossover in Checkmate214

Committee TA581: company did not adjust… uncertainty in model around long-term survival predictions for nivolumab with ipilimumab **adjusted for treatment switching** which further data from CheckMate 214 would likely reduce.

Company:

- Did not adjust: switching treatments from sunitinib to nivo+ipi is low ([redacted])

ERG:

- Unadjusted results likely favours comparator

◉ *Should company have adjusted for crossover within trial?*

Treatment 2nd line and beyond

Should model reflect Checkmate 214 or SACT data? If using trial data, should analysis adjust for non-NHS treatments 2nd line and beyond in trial?

Treatments 2nd line and beyond

Company uses CheckMate 214 data on treatments after 1st line in base case; scenario SACT

Committee TA581: treatments 2nd-line and beyond in CheckMate 214 do not reflect NHS; prefer results using costs and clinical benefits that reflect NHS
CDF terms: explore appropriate modelling of 2nd-line treatments supported by SACT

Company:

- Follow-up differences between CheckMate 214 (min 60 months) and SACT (minimum 5 months) prevents comparing treatments used 2nd line and beyond

Clinical experts:

- SACT treatments match NHS practice
- After sunitinib, patients have nivolumab or cabozantinib
- After NIVO+IPI, patients have a tyrosine kinase inhibitor (TKI): cabozantinib but minority sunitinib, tivozanib or lenvantinib + everolimus (which TKI unlikely to make a difference)
- Nivolumab not available in UK after NIVO+IPI

ERG:

- Agree to use treatments from CheckMate 214 - longer period of time but NHS would not offer immunotherapy twice.
- For SACT, data on 2nd vs 3rd line presented separately; for trial, all lines combined
  - CheckMate214 patients heavily treated: [redacted]% in CheckMate 214 vs 29% in SACT

-Treatments 2nd line and beyond

In trial: most frequency 2nd line treatment after NIVO+IPI: sunitinib [redacted]

In trial: most frequency 2nd line treatment after sunitinib: NIVO [redacted]

In SACT: most frequent 2nd line treatment after NIVO+IPI: cabozantinib 59%

% treated after 1st line –some had >1	SACT	CheckMate 214	
Therapy 2nd line and beyond	NIVO+ IPI 29% (234/814)	NIVO+ IPI [redacted]	Sunitinib [redacted]
Nivolumab*	0	[redacted]	[redacted]
Sunitinib**	13	[redacted]	[redacted]
Cabozantinib	59	[redacted]	[redacted]
Pazopanib**	12	[redacted]	[redacted]
Tivozanib**	8	[redacted]	[redacted]
Everolimus and/or lenvatinib*	3	[redacted]	[redacted]
Axitinib*	3	[redacted]	[redacted]
Other/experimental (not modelled)	2	[redacted]	[redacted]

◉ *Are treatments aligned with NICE guidance? Which source of data, trial or SACT? Would nivolumab be offered 2nd-line after nivolumab + ipilimumab in the NHS? How do 2nd line treatments and beyond impact overall survival data?*

Note: some patients received more than one treatment; * NICE guidance recommends only after cytokine and/or tyrosine kinase inhibitors and/or VEGF-targeted therapy, **NICE guidance recommends 1st line only

Extrapolating survival

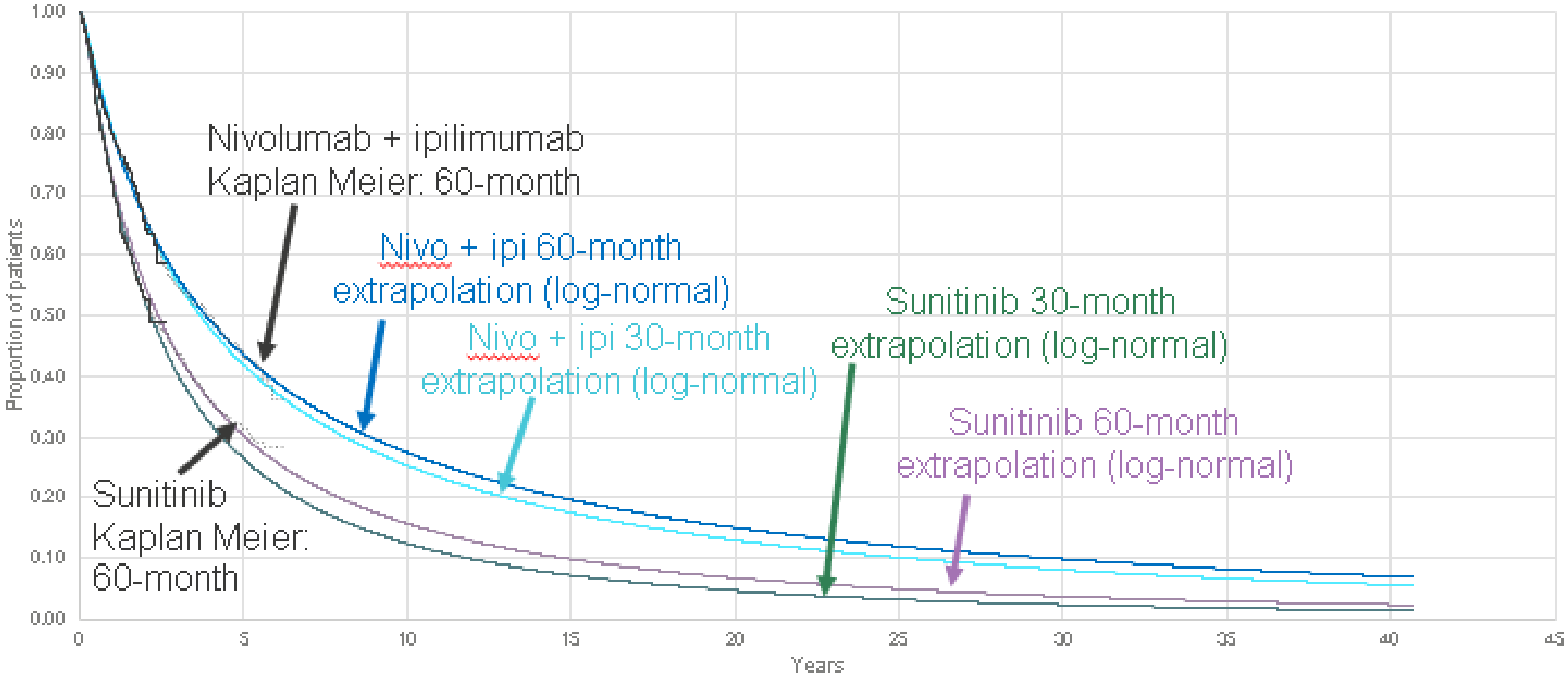
Which model?

Given majority of benefits accrue beyond observed evidence, how to model treatment difference over the long-term?

CheckMate 214: Extrapolating overall survival 60 month data

Lognormal also choice using 30 month data

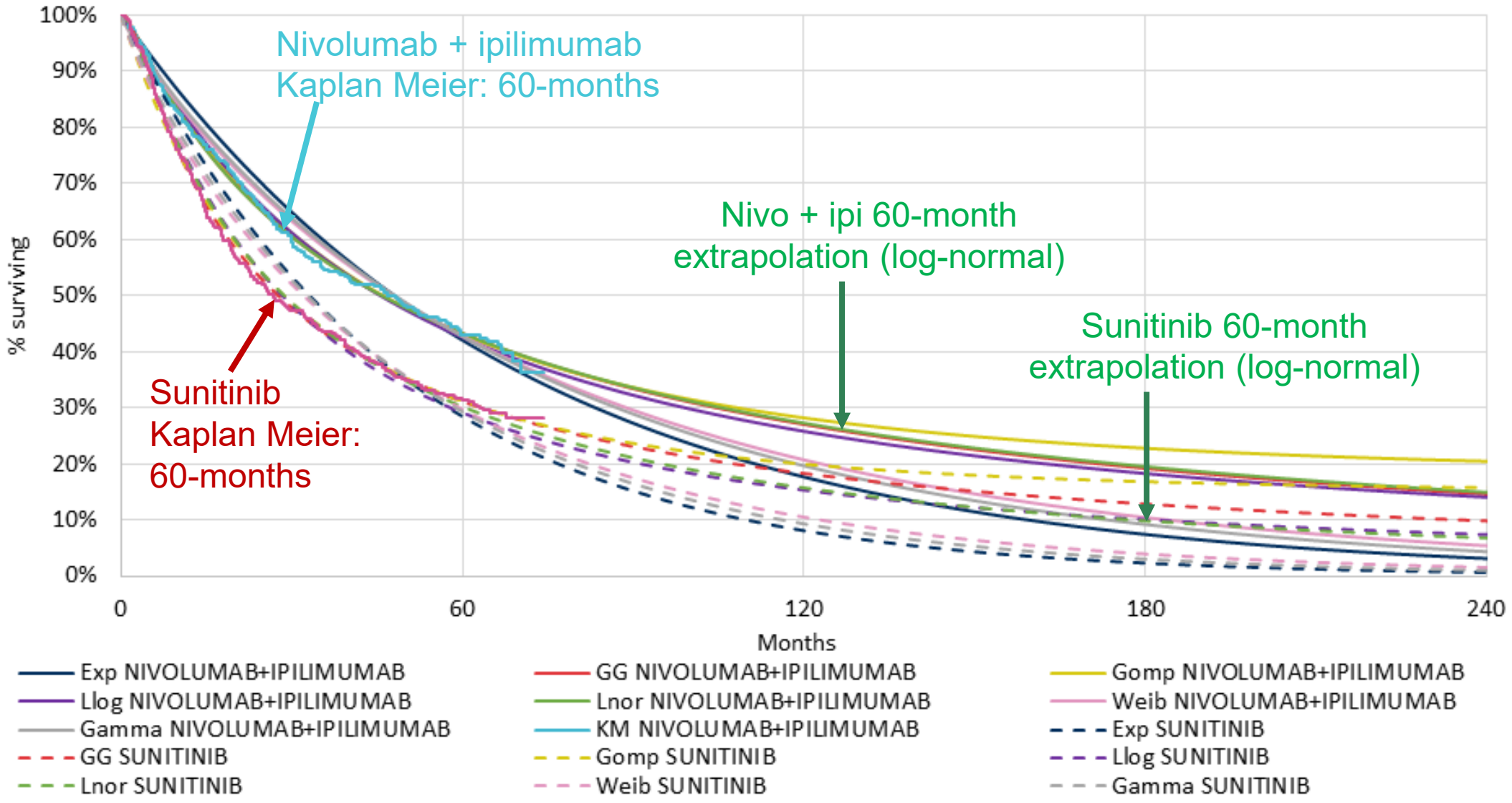
Company and ERG agree on lognormal



CheckMate 214: alternative curves for overall survival

Extrapolations based on 60 months data

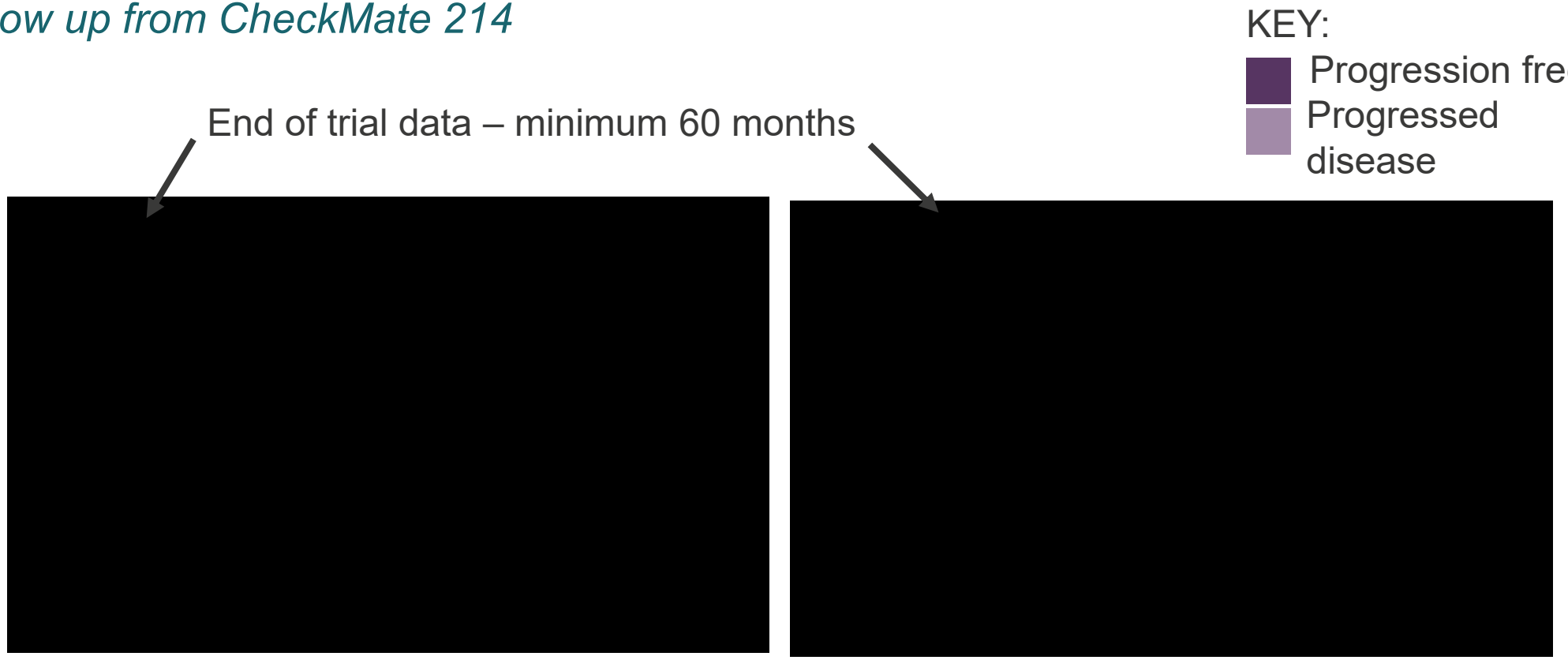
Scenario with generalised gamma chosen by company



◉ *Which model? Still log-normal for both treatment ? Results in part 2*

Mortality benefit predicted beyond observed data

ERG: vast majority of survival and QALY benefit is in the period beyond 60-month follow up from CheckMate 214



◉ *What is the committee's view of large proportion of benefits accumulated in the extrapolated period? Is it reasonable to 'mitigate' for this? ERG does scenario of equalising hazard?*

CheckMate 214: Crude mortality by 6 month intervals

ERG: Company's trial does not support company's model that predicts mortality NIVO+IPI< sunitinib up to 21 yrs. Treatments 2nd line+ – notably NIVO – may equalise hazards. ERG scenarios equalise hazard from 4.5 years when mortality hazard in CheckMate 214 similar between arms

◉ *Does the committee prefer company's base case or ERG scenarios assuming equalising of hazards from 4.5 years? Does this also 'mitigate' against non-NHS life-extending treatment used in trial 2nd line and beyond?*

Majority of benefits accrue beyond observed data

How to model treatment difference over the long-term? Would this also address non-NHS life-extending treatments 2nd line and beyond in trial?

CheckMate 214: Equalising hazards

Company: assuming equal hazard of death not clinically plausible or evidence-based; inappropriate to consider annual intervals as per ERG scenario

Company

- Time intervals chosen influence mortality rate trend observed – 6-monthly/annual hazard rates as per ERG analysis may not be granular enough
- Annual rates not established methodology for equalising hazard rates
- Choice of 4.5 year as the time point is inappropriate
- Smoothed graphs of other timepoints do not show evidence of equal effects

ERG

- Company's table providing CheckMate 214 mortality rates at other time intervals supports ERG's position of equalising mortality hazards from 4.5 year: from 4 years 6-month mortality rates slightly higher with nivo+ipi than sunitinib; ERG assumption may if anything be conservative
- Company's smoothed hazards do not refute direct trial evidence showing annual mortality rates unaffected by censoring or smoothing in 1st 5 years and converge by year 5

◉ *Does the committee prefer assuming mortality rate for nivo+ipi is lower than sunitinib until 21 years or ERG scenarios assuming equalising of hazards from 4.5 years?*

CheckMate 214: Company analysis of those alive at 5 years

Company: argue against equalising hazard of death for treatments

ERG: Does not support company. Many have 2nd line NIVO monotherapy and some sustain response to sunitinib

CheckMate 214	% alive 5 years	Of these, % progression free	Of these, % receiving 2nd line or beyond treatments	Of these, % receiving nivolumab monotherapy
NIVO+IPI	38.4%	[redacted]	39.3%	10.4%
		i.e. [redacted] of total	-	i.e. 27% of all treatments 2nd line +
Sunitinib	26.5%	[redacted]	75.0%	52.7%
		i.e. [redacted] of total	-	i.e. 70% of all treatments 2nd line +

Company: ERG assumes that those still responding have same risk of death as a patient on later line of therapy

ERG: clinically plausible that mortality hazards for both arms converge earlier than when curves meet general population mortality (at ~21 years). Suggest scenario based on evidence of convergence at 4.5 years. This is based on:

- Many alive at 5 years in sunitinib arm then had NIVO
- Many had sustained response to sunitinib

◉ *Should equalising hazards between treatments 'adjust' for life-extending non-NHS treatments?*

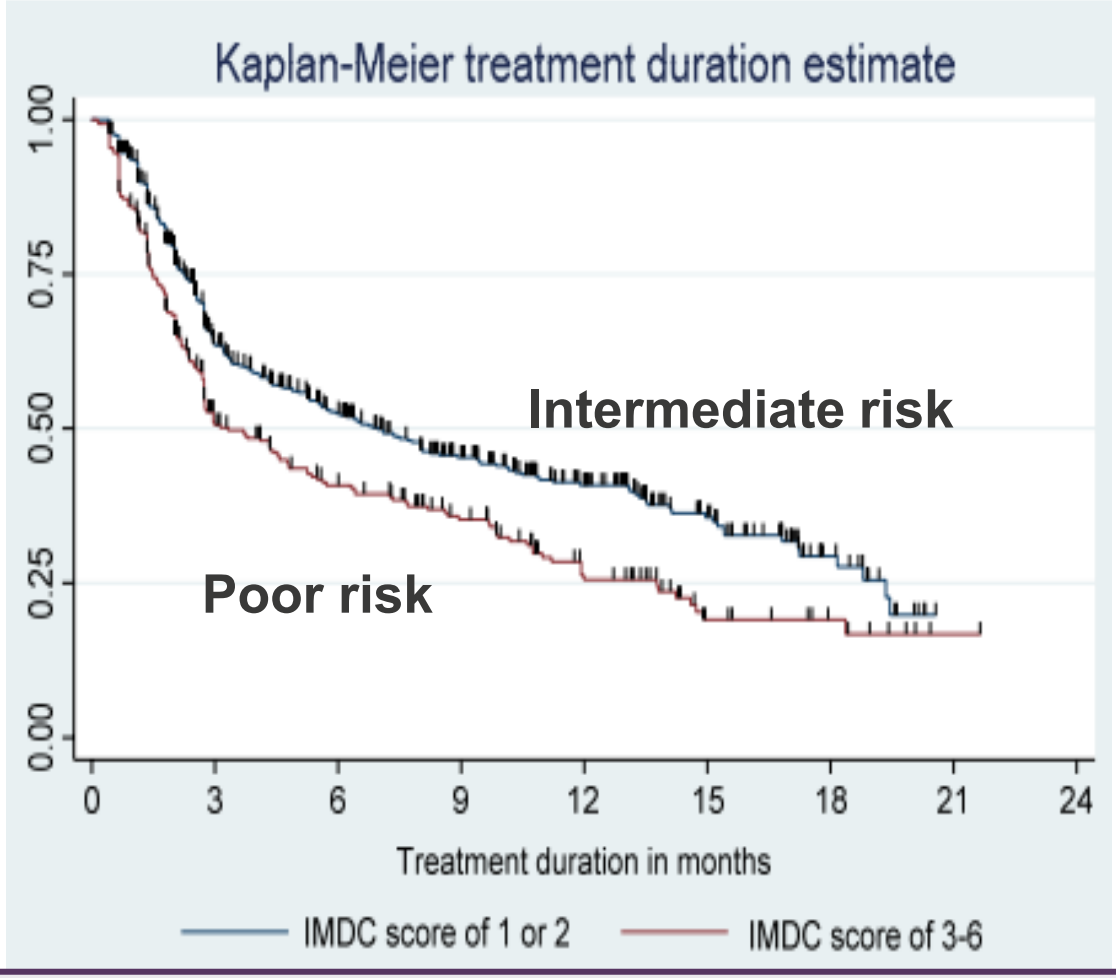
Costs

Duration of treatment differs by risk – should SACT data inform this?

SACT: Costs - Treatment duration by prognostic risk

No analysis for cost by subgroup

ERG: treatment duration lower for poor risk so cost-effectiveness may differ and hard to predict how; Company: CheckMate 214 not powered for subgroups so data not provided



Time period	Proportion still receiving treatment, % (95% confidence interval)	
	Intermediate risk	Poor risk
6 months	52 (48 to 57)	41 (35 to 47)
12 months	41 (36 to 46)	26 (20 to 32)
18 months	29 (23 to 35)	19 (13 to 26)

◉ *Since treatment duration differs by risk group, should SACT be used to inform duration of treatment in the model?*

Utility

Would committee prefer NIVO+IPI utility values to stay higher than sunitinib throughout the modelled time horizon or become equal to sunitinib at a certain time? If so, at what time?

Quality of life / utility

Company uses treatment-specific utilities for full model horizon even after stopping treatment

EQ-5D-3L values CheckMate 214 60-month data intermediate or poor risk	NIVO+IPI	Sunitinib
Progression-free on treatment, Post-progression on treatment	[redacted]	[redacted]
Progression-free off treatment	[redacted]	[redacted]
Post progression off treatment	[redacted]	[redacted]

ERG:

- Differential utilities by treatment years after patients stop treatment not justified
- More likely to assume values will become equal at some point
- Scenario: utility values of all health states equal in both arms from start of modelled time horizon (unlikely but extreme scenario) increases ICER by £1300

◉ *Which scenario company with utility based on both progression and which treatment or ERG based on progression only? If so, at what time?*

Estimates of cost effectiveness in part 2 which includes Discounts for:

1. NIVO+ IPI – separate confidential PAS (patient access scheme) for each

2. Comparators: Sunitinib, pazopanib – discounts in public domain so not confidential

3. 2nd line treatment and beyond: confidential PAS for axitinib and cabozantinib, Commercial Medicines Unit price for everolimus

END