Public observer slides

NICE National Institute for Health and Care Excellence

Avelumab for metastatic Merkel cell carcinoma (CDF review of TA517)

Chair's presentation

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ERG: BMJ Technology Assessment Group

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Company: Merck Serono

2nd February 2021

Key clinical issues

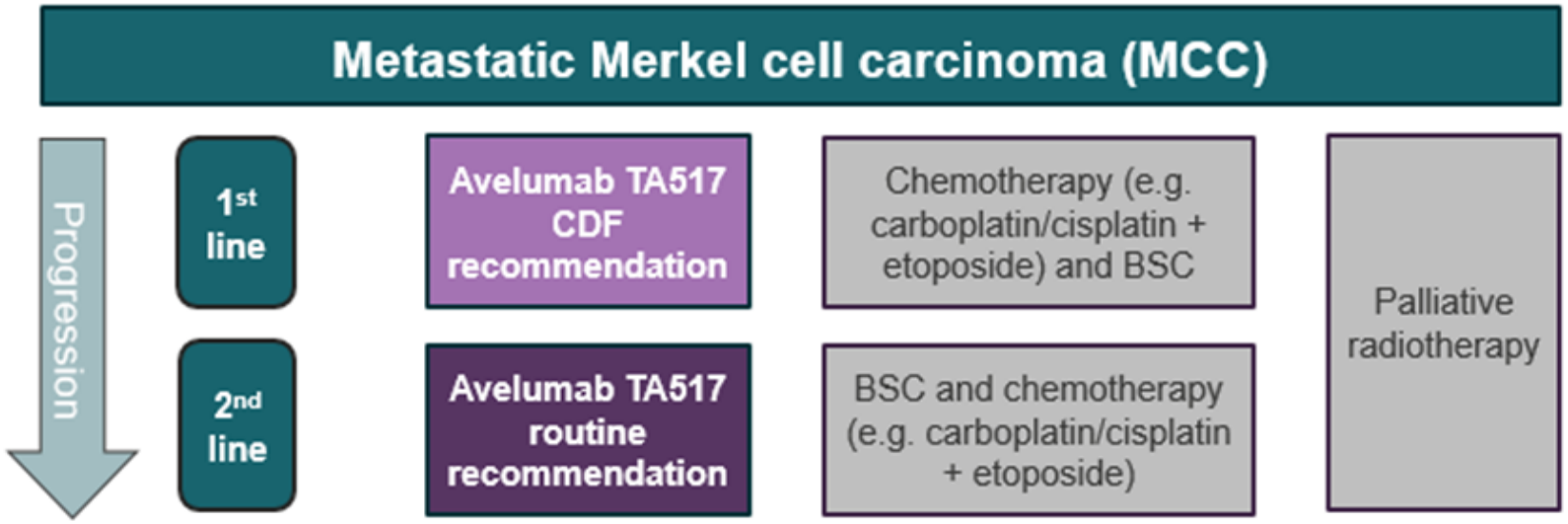
- **Generalisability of data**
  - Are the updated data from JAVELIN generalisable to clinical practice?
  - Are the SACT data more generalisable to clinical practice?
- **Indirect treatment comparison: avelumab vs chemotherapy**
  - Is the PSW4 analysis (preferred by the ERG) with adjustments for age, sex, and ECOG performance status more appropriate than the naive comparisons presented?

Key: SACT: Systemic Anti-Cancer Therapy PSW: propensity score weighted; ECOG: Eastern Co-operative Oncology Group

Merkel cell carcinoma (MCC)

- Merkel cell carcinoma (MCC) is a rare neuroendocrine tumour found in the skin
- Merkel cells are present in the top layer of the skin; carcinoma occurs when they grow out of control
- May be associated with immunosuppression
- Usually presents as a lump of unbroken skin, often in areas of the body that receive direct sun exposure
- MCC is symptomless in the initial stages and may be difficult to diagnose
- More common in older people and in those with fairer skin
- In 2010, 53 to 106 people were diagnosed in England
- Poor prognosis with a 5-year survival rate dependent upon stage
- Early stage disease treated with local surgery and radiotherapy
- Stage IV metastatic disease, 5-year survival around 11%

Treatment pathway for metastatic MCC (mMCC)



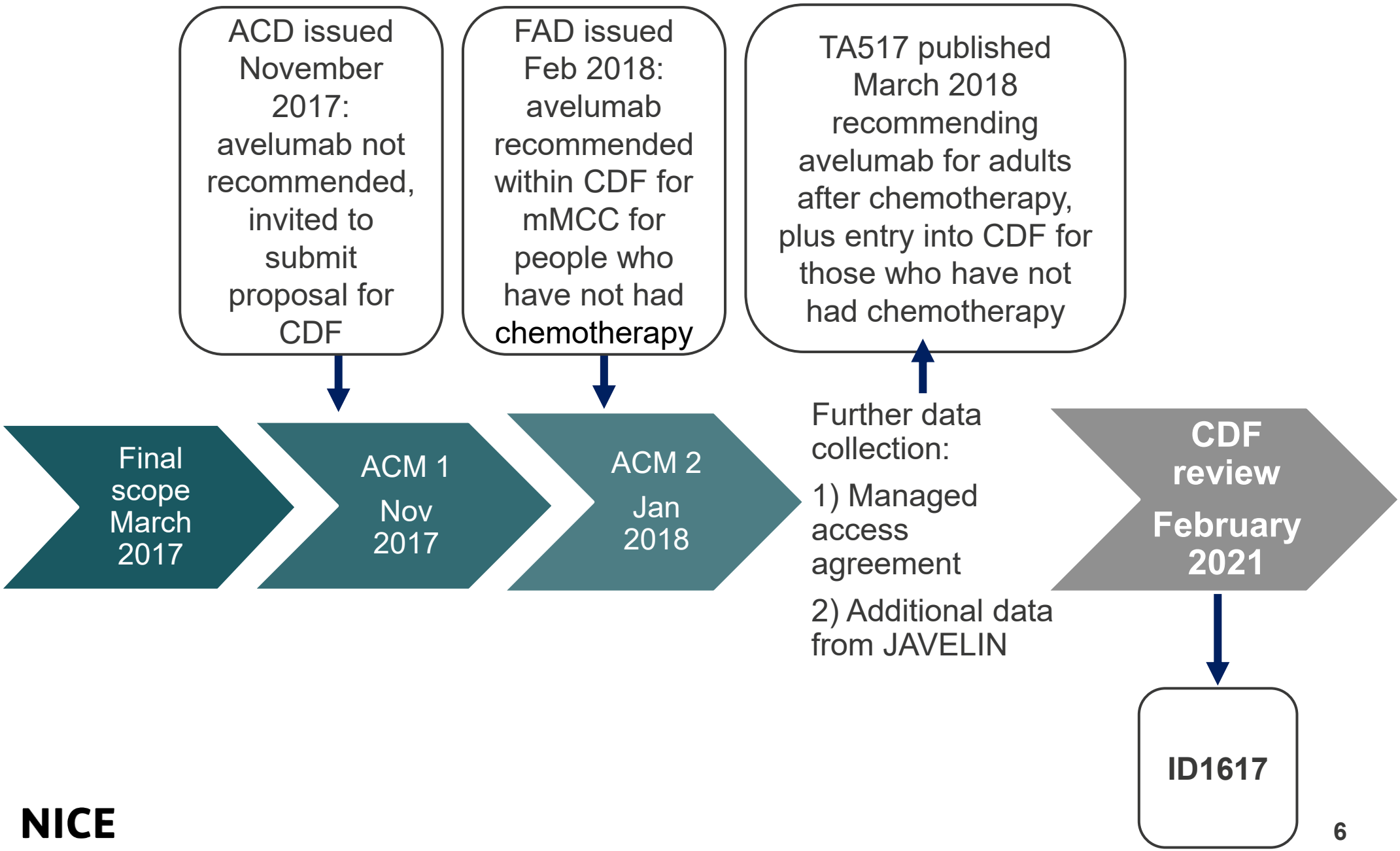
Key: BSC, best supportive care; CDF, Cancer Drug Fund

- **TA517:** The committee agreed that the appropriate comparator for first-line treatment is chemotherapy. However, it noted that some patients may be unable to have chemotherapy and are offered best supportive care instead

Avelumab (Bavencio, Merck Serono)

Marketing authorisation	Monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma
Mechanism of action	Immunotherapy drug that works by blocking a protein in tumour cells called PD-L1
Administration and dose	Administered at a flat dose of 800 mg intravenously over 60 minutes every two weeks. Dosage in JM200 clinical trial was 10mg/kg. In November 2019, the approved dose was changed to the flat 800 mg dose.
List price	£768 per 200 mg vial (excluding VAT; British National Formulary). The average cost of treatment per patient is £65,086 based on the list price. A confidential price discount has been agreed.

Summary of original appraisal TA517



Key conclusions from TA517

Avelumab is recommended as an option for treating metastatic MCC in adults, only if they have had 1 or more lines of chemotherapy for metastatic disease.
Avelumab is recommended for use within the CDF as an option for treating metastatic MCC in adults, only if:

- ***they have not had chemotherapy for metastatic disease and***
- ***the conditions in the managed access agreement for avelumab are followed.***

- The results for first line use are highly immature and should be interpreted with caution
- Key sources of clinical uncertainty in the treatment-naïve cohort data:
  - The absence of a randomised comparator arm in the JAVELIN trial
  - A naïve comparison with observational data
  - Small numbers of patients with short follow-up (specifically immaturity of progression-free and overall survival)
  - Acknowledged that the absence of a randomised comparator arm in the JAVELIN 200 study is a source of uncertainty, but this cannot be addressed by data collection in the CDF
- Avelumab as a first-line and second-line treatment meets NICE's criteria to be considered a life-extending end-of-life treatment

Patient and carer perspectives

Neuroendocrine Cancer UK

- *Family and friends describe hopelessness – as expressed in other cancer cohorts –but this is compounded by rarity – with limited accessible accurate and reliable information, expertise and support.*
- *Without Avelumab patients are faced with a decision to choose between chemotherapy or "doing nothing"*
- *Uncertainty abounds due to rarity of diagnosis, which not only limits clinical data and research – but also gives rise to the fear that lack of reaching target level of information will impact on decision-making about availability and accessibility of future treatment and options.*
- Key messages:
  - *Unmet need*
  - *Sustained response seen*
  - *Safe, effective and durable*
  - *Positive impact on quality of health for both patients and carers (families)*

Equality

Neuroendocrine Cancer UK

- *In rare cancers there remains a risk that measures used to assess evidence can determine weight allocated to it – in that small number populations may not have the equivalent numbers and protocols as those of higher number. This factor needs to be taken into account to ensure patients are not discriminated against due to limits in incidence and therefore eligibility for trial inclusion and / or treatment. We need robust evidence – and alternatives to RCTs as a measure of value of evidence - need to be explored. Or HST adapted to fit needs of rare cancers. But this may be a policy/processes issue rather than equality.*

Primary clinical evidence: JAVELIN Merkel 200

Design	Phase II, single arm, open-label
Population	Patients with metastatic MCC with no prior systemic therapy for metastatic disease (=1L) • Exclusion of immunosuppressed patients • no UK patients were included
N	TA517: [redacted] (still enrolling patients; target n=112) **CDF review of TA517: 116**
Median follow- up	TA517: 3 months (n=[redacted]) & 6 months (n=[redacted]) **CDF review of TA517: 16 months**
Outcomes	**Primary:** Durable response rate (DRR) defined as objective response [CR or PR] lasting at least 6 months **Secondary:** DoR, PFS, OS
Avelumab	Dose: 10mg/kg • Treatment should continue until disease progression or unacceptable toxicity

Key: CR, complete response; PR, partial response; OS, overall survival; PFS, progression-free survival; 1L, first line.

Note: new data in the CDF review of TA517 are highlighted in bold.

Updated baseline characteristics: JAVELIN & SACT

JAVELIN Part B data (May 2019 cut) now includes 116 patients and has a median follow up of 16 months

Characteristic		JAVELIN 200 Part B 1L (n=116)	SACT (n=52)
Follow-up: minimum/median		15 months / 16 months	5 months / 6 months
Sex	Male	81 (70%)	30 (58%)
Age	<40	0 (0%)	0 (0%)
	40-49	4 (3%)	1 (2%)
	50-59	7 (6%)	3 (6%)
	60-69	27 (23%)	8 (15%)
	70-79	46 (40%)	22 (42%)
	80+	32 (28%)	18 (35%)
	Median	74.0 years	75.5 years
ECOG PS	0	72 (62%)	7 (13%)
	1	44 (38%)	34 (65%)
	2	0 (0%)	4 (8%)
	3	0 (0%)	1 (2%)
	4	0 (0%)	0 (0%)
	Missing/ unknown	0 (0%)	6 (12%)

ERG: JAVELIN population may be slightly younger, comprise more males and have more favourable ECOG PS than in clinical practice

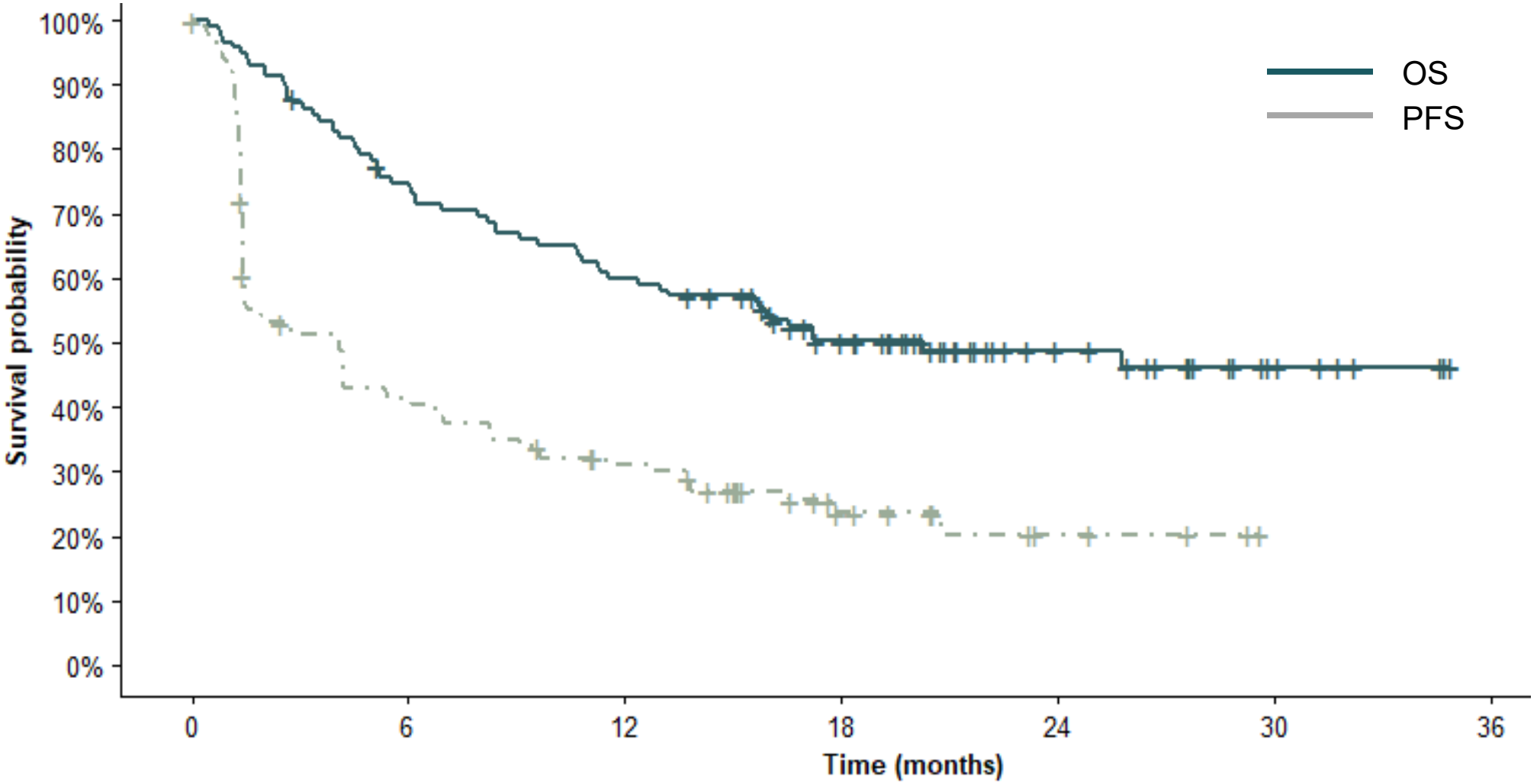
SACT data more closely match expected patient characteristics but **not** used in model

Updated clinical evidence: results

JAVELIN Part B data (May 2019 cut) now includes 116 patients and has a median follow up of 16 months

	JAVELIN 200 Part B: 1L only Avelumab			SACT Avelumab	Study 100070-Obs001 1L Part A – US only Chemotherapy	
	TA517 (n=39)		NEW data	NEW data		
	≥3-month FU (N=29)	≥6-month FU (N=14)	16-month FU (N=116)	6-month FU (N=52)	ITT (N=67)	Immunocompetent SG (n= 51)
ORR	[redacted]	[redacted]	39.7%	Not available	31.3%	29.4%
Median OS	[redacted]		20 months	11.8 months	10.2 months	10.5 months
OS at 6 months	[redacted]		75%	58%	70.1%	66.7%
OS at 12 months	-		60%	50%	44.0%	45.3%
Median PFS	[redacted]		4.1 months	Not available	4.6 months	4.6 months
PFS at 6 months	[redacted]		41%	Not available	44.8%	47.1%
PFS at 12 months	-		31%	Not available	21.8%	24.8%
Median ToT	-		[redacted]	6 months	2.5 months	[redacted]
on T 6 months	-		[redacted]	46%	-	[redacted]
on T at 12 months	-		[redacted]	31%	-	[redacted]

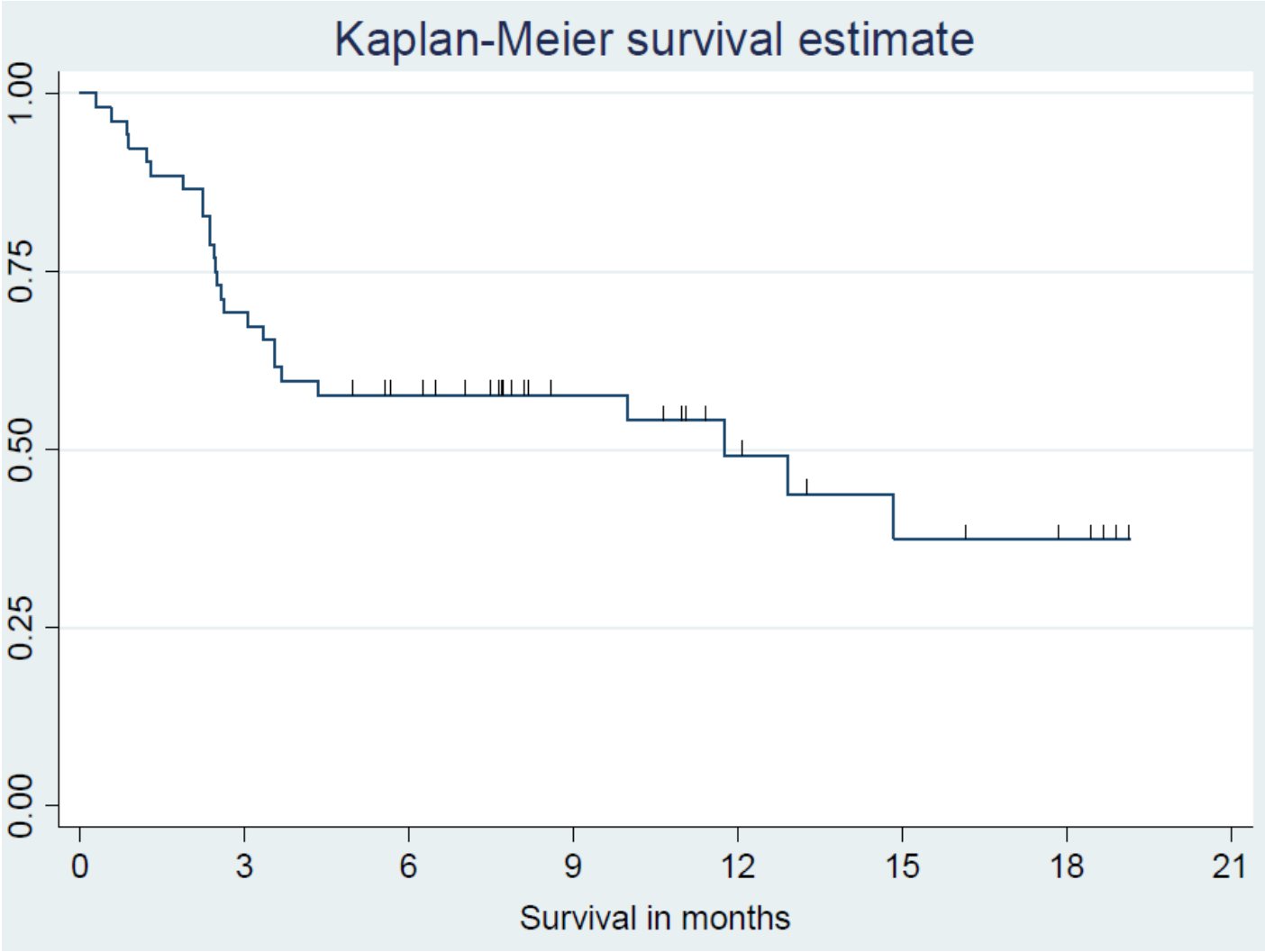
Updated PFS/OS JAVELIN results (May 2019)



At risk							
OS	116	85	68	45	20	7	0
PFS	116	45	31	12	4	0	0

Key: OS, overall survival; PFS, progression-free survival

Updated OS SACT results (November 2019)



NICE OS: overall survival; PFS not available for SACT data set

Systemic anti-cancer therapy (SACT) dataset

- **Company:** SACT data less suitable than JAVELIN Part B due to several limitations:
  - Small sample size (n=52 vs 116 in JAVELIN Part B)
  - Data are immature (median follow-up for OS: 6 months vs 16 in JAVELIN Part B)
  - No PFS, HRQoL, response rate or adverse events collected
  - Population limitations:
    - 10% of patients in SACT dataset had ECOG of 2 or 3, 12% of patients had unknown or missing ECOG
    - Some patients included may have poor prognosis due to being deemed ineligible for treatment with 1L chemotherapy owing to its associated toxicities, and therefore will have received BSC prior to avelumab
    - Patients need to have sufficient life expectancy to benefit from immunotherapies (e.g. avelumab) – initial drop in OS curve of SACT cohort indicates inclusion of patients who did not have sufficient life expectancy to benefit from immunotherapy
    - But provides an additional data source which can support decision-making

SACT dataset (2)

- **ERG**: agrees there are limitations with SACT data, however clinical advice is that they more closely match expected patient characteristics
  - The SACT population has the following characteristics:
    - Male to female ratio is closer to anticipated 50:50
    - A higher proportion of ≥ 80 years patients
    - A higher proportion of ECOG PS 1 and above
- ERG explored using SACT data in a scenario analysis. SACT time on treatment (ToT) data were used as a proxy for PFS in this scenario – increases company base case ICER of £17,947 to £23,485
- **Neuroendocrine Cancer UK**: Combination of trial and real world data available should provide a better understanding for decision-making
- **RCP**: JAVELIN population resembles patients treated in clinical practice but there is an excess of males and unusual that 80% of patients have a WHO performance score of 0

Issue 1: Are the updated data from JAVELIN (n=116) generalisable to clinical practice? Are SACT data (n=52) more generalisable to clinical practice and, given their limitations (immaturity, small sample size and no PFS data), can they inform decision making?

Indirect comparison of avelumab vs chemotherapy (Issue 2)

TA517

- Company used a naive pooled analysis of seven chemotherapy studies (observational Study 100070-Obs001 [n=67] considered best source of comparator data, conducted by company)
- Pooled chemotherapy data were used in a naïve comparison with avelumab JAVELIN data

CDF review of TA517

- Company updated the naive indirect comparison with the 2019 JAVELIN data (n=116) and the estimation of chemotherapy remained the same as in TA517. No new data for chemotherapy were identified. In addition, during clarification, the company:
  - Conducted a number of propensity score matching and weighting (PSM and PSW) analyses using updated data from JAVELIN Part B and Study 100070-Obs001 to adjust for key outcomes in the indirect comparison
  - Data were available for age, sex, ECOG PS and immunocompetency
  - Patients with missing ECOG PS (n=13 in the company's chemotherapy study) were removed from the analysis. Including immunocompetency was not considered suitable because only 13 patients were immunosuppressed in the company's chemotherapy study
  - In addition, as 8 patients reported ECOG PS >1, a dataset that removed these 8 patients was also considered in the analyses

Indirect comparison of avelumab vs chemotherapy (2)

ERG comments

- Naïve pooling of data from chemotherapy likely to introduce unnecessary heterogeneity
- Considers the immunocompetent subgroup (n=51) of Study 100070-Obs001 to be more appropriate than the pooled data for a naïve comparison with JAVELIN (JAVELIN only includes immunocompetent patients), but still potentially unreliable
    - Naïve comparison using this subgroup conducted by company at clarification – reduces ICER by £722
- From the options presented by the company, ERG prefers the PSW analyses using JAVELIN data and Study 100070-Obs001
- **PSW4 analysis** with adjustments for age (≥75 vs <75 years), sex (female vs male), and ECOG PS (0 vs 1) is most appropriate and included in ERG's preferred analyses
    - maintains all patients in the analysis and achieves the best balance in baseline characteristics
    - however, chemotherapy group still includes some patients who were immunosuppressed: imbalance likely to underestimate effectiveness of chemotherapy vs. avelumab

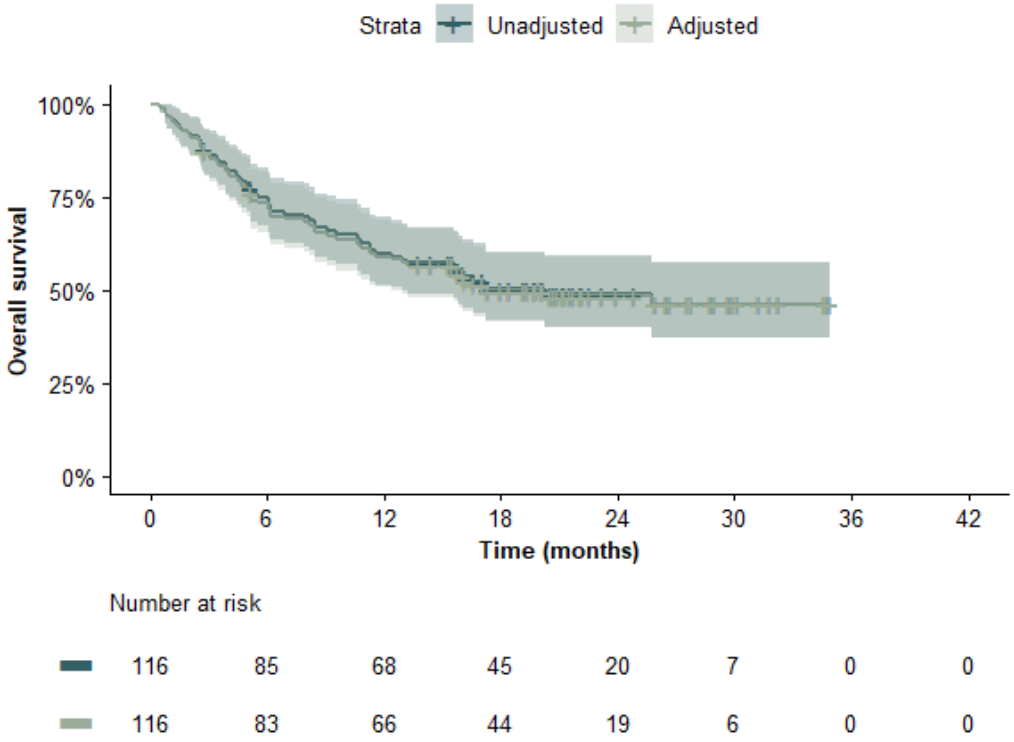
Propensity score weighting analysis: PSW4 adjusted PFS results for avelumab and chemotherapy

JAVELIN: avelumab

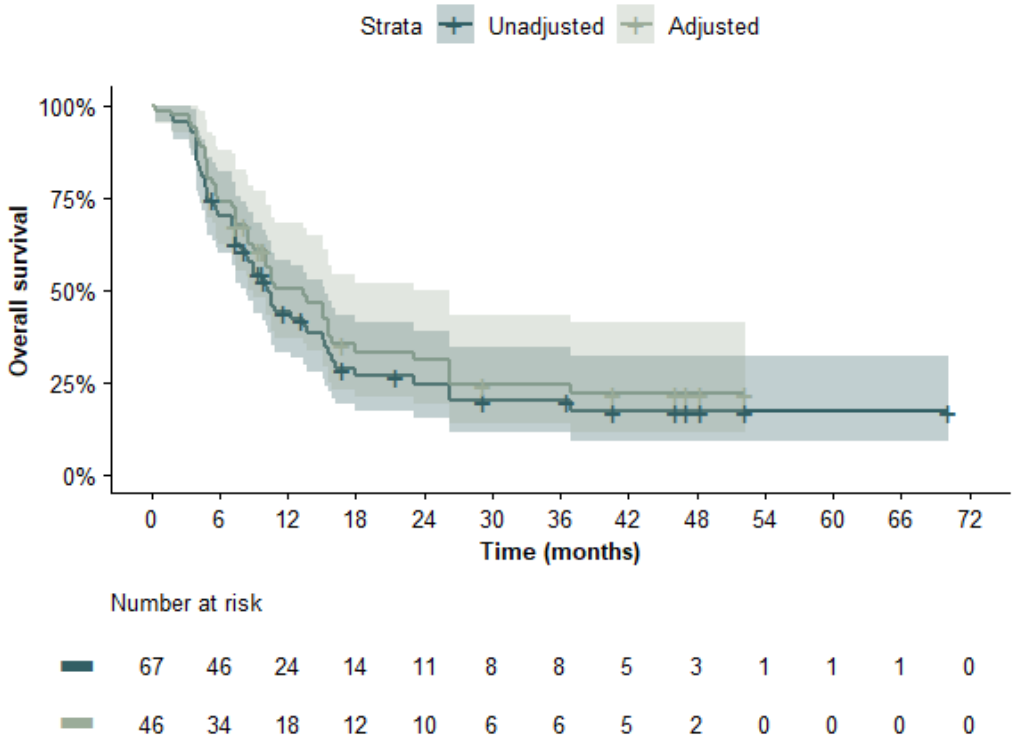
Study 100070-Obs001 (chemotherapy)

Propensity score weighting analysis: PSW4 adjusted OS results for avelumab and chemotherapy

JAVELIN: avelumab



Study 100070-Obs001 (chemotherapy)



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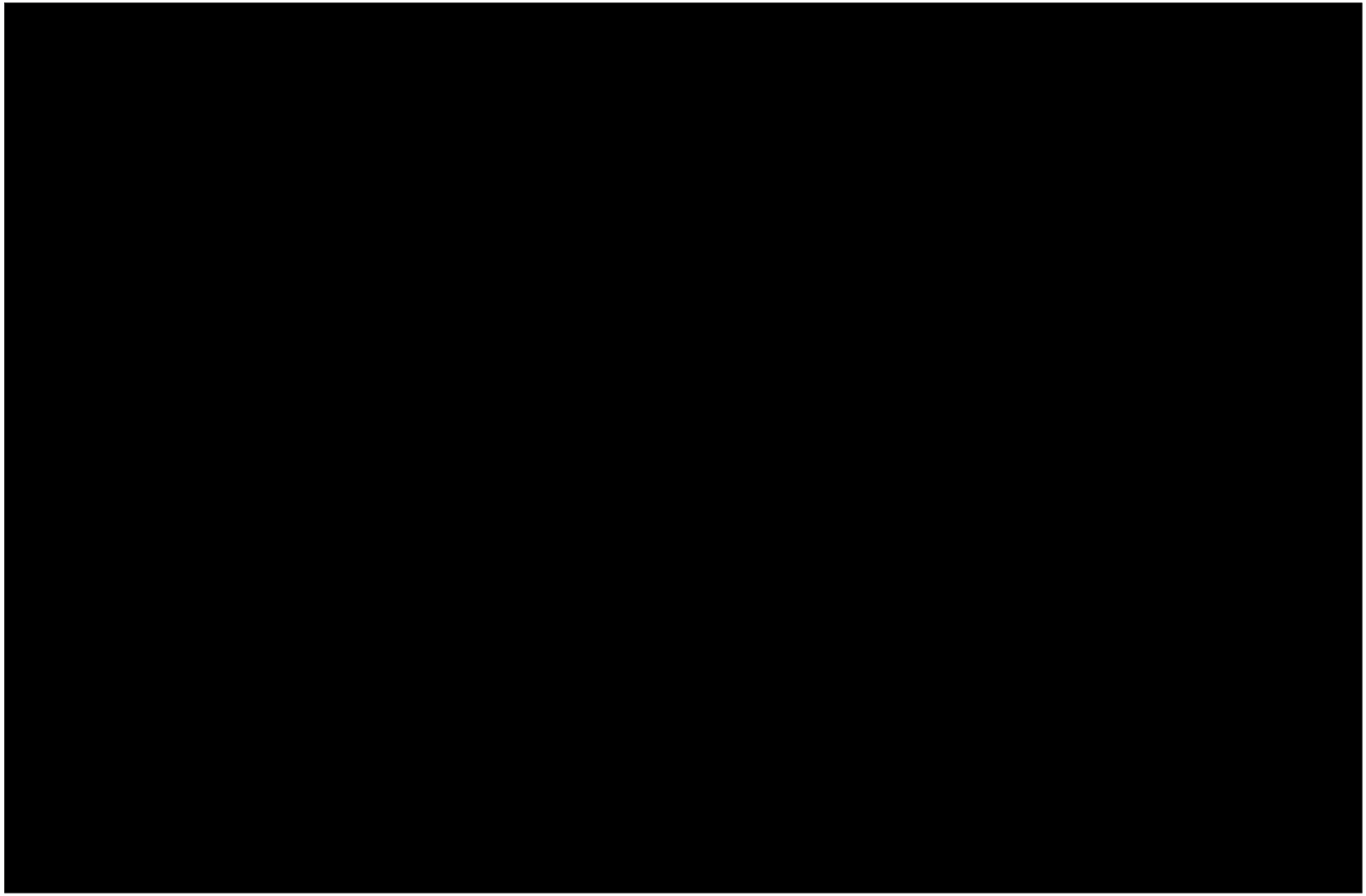
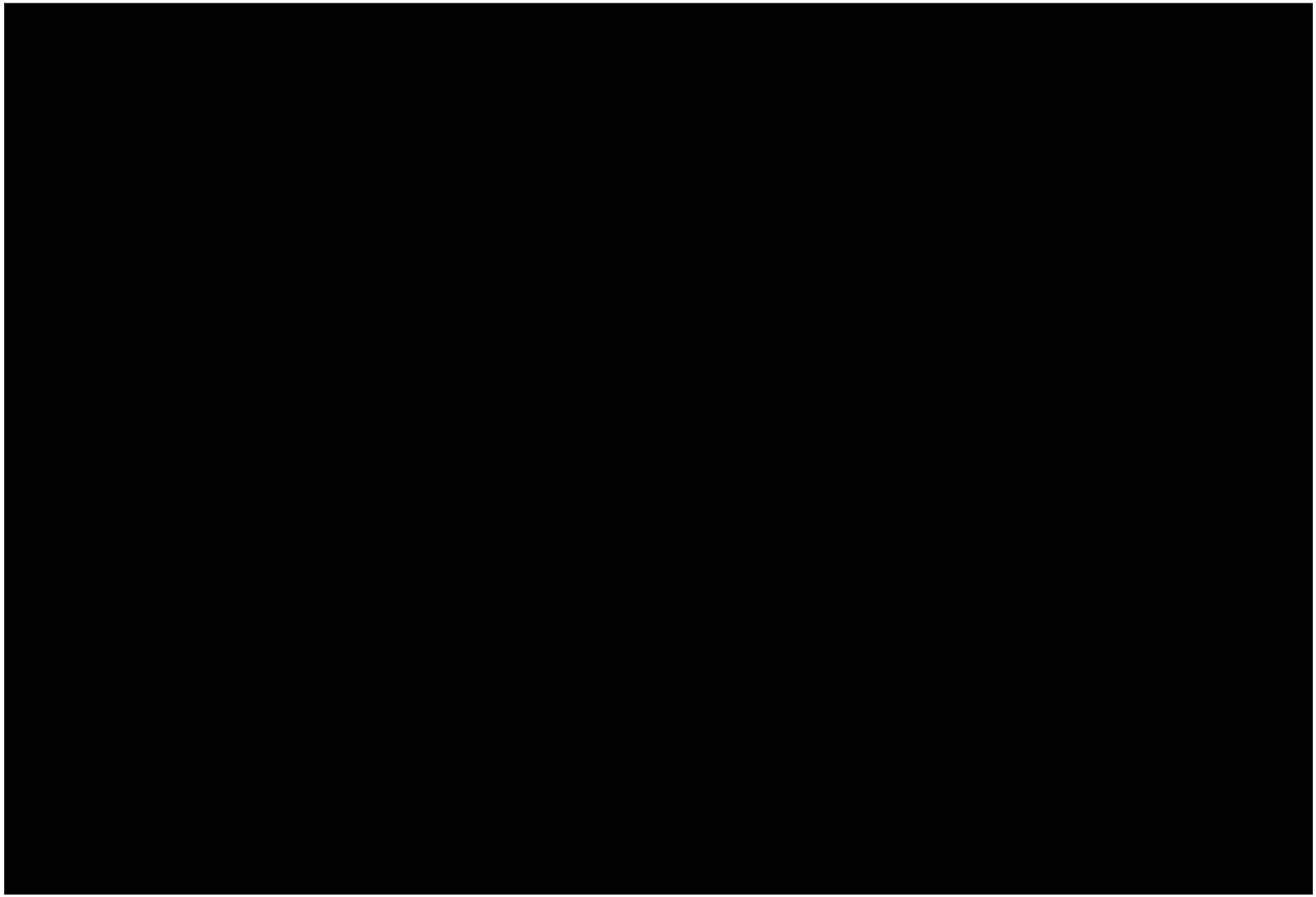
Propensity score weighting analysis: PSW4 adjusted PFS results for avelumab and chemotherapy



Adjusted progression-free survival plot for PSW4 analysis used in the ERG's preferred analyses, using updated JAVELIN data and Study 100070-Obs001

Propensity score weighting analysis: PSW4 adjusted OS results for avelumab and chemotherapy



Adjusted overall survival plot for PSW4 analysis used in the ERG's preferred analyses, using updated JAVELIN data and Study 100070-Obs001

Propensity score weighting analysis: TE comments

Company:

- Using propensity score weighting analysis has limited impact on cost-effectiveness
- Immunocompetency not expected to have a large impact on the outcome of treatment with chemotherapy within the context of mMCC, as patients were considered fit enough to receive chemotherapy

- **Is the PSW4 analysis (preferred by the ERG), with adjustments for age, sex and ECOG PS, the most appropriate to inform the avelumab versus chemotherapy comparison in the model?**
  - **Scenario analyses using the immunocompetent subgroup of Study 100070-Obs001 and SACT data instead of JAVELIN unlikely to influence decision making**

Key clinical issues

- **Generalisability of data**
  - Are the updated data from JAVELIN generalisable to clinical practice?
  - Are the SACT data more generalisable to clinical practice?
- **Indirect treatment comparison: avelumab vs chemotherapy**
  - Is the PSW4 analysis (preferred by the ERG) with adjustments for age, sex, and ECOG performance status more appropriate than the naive comparisons presented?

NICE

Key: SACT: Systemic Anti-Cancer Therapy PSW: propensity score weighted; ECOG PS: Eastern Co-operative Oncology Group

Key cost effectiveness issues

- **Extrapolation of overall survival and progression-free survival for avelumab**
  - Is the modelling appropriate?
  - Do the different models capture the range of possible outcomes for OS and PFS?
- **Extrapolation of time on treatment for avelumab**
  - Is the modelling appropriate?
  - Do the different models capture the uncertainty effectively?

Cost effectiveness results - summary

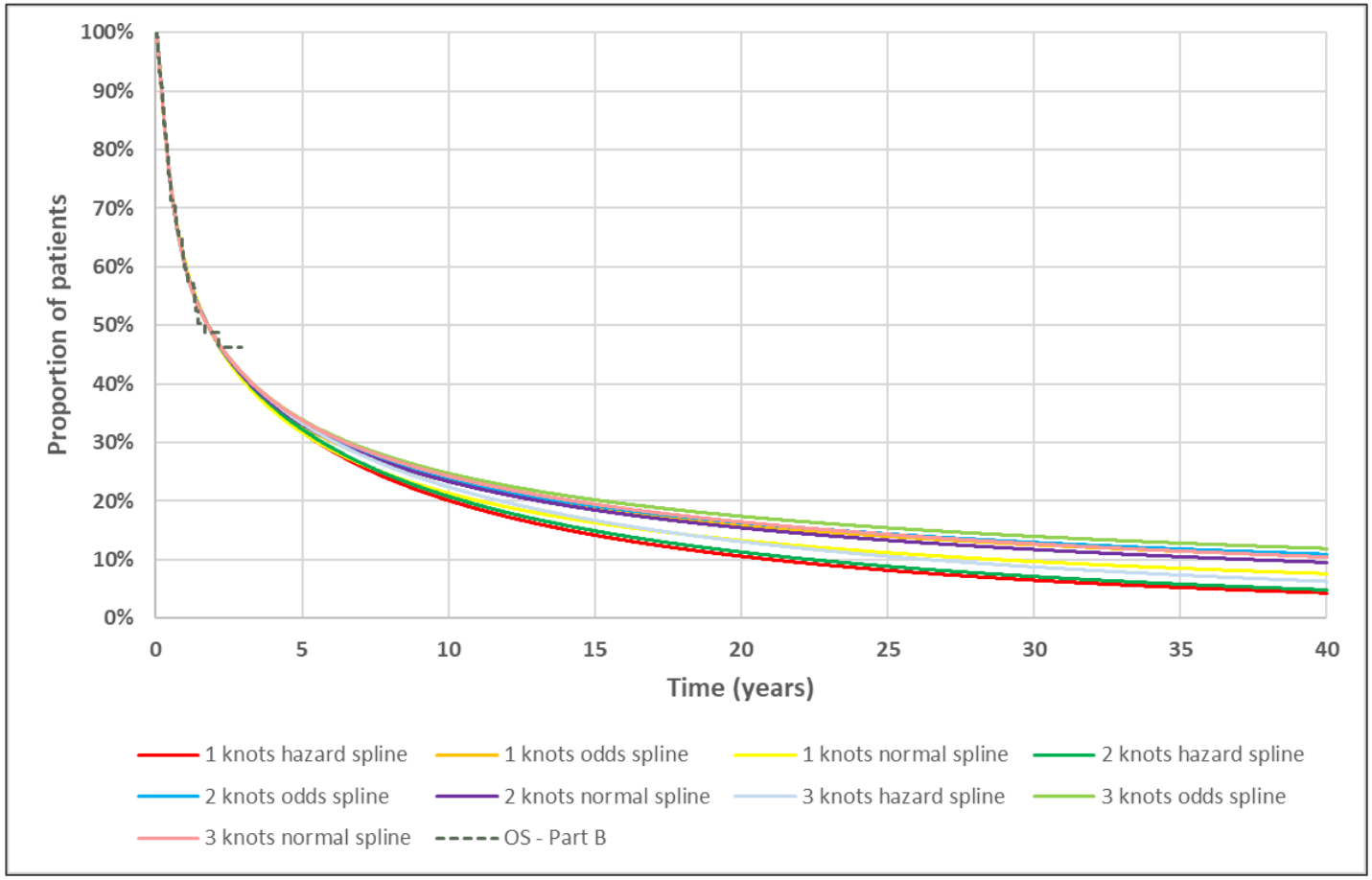
	Scenario	ICER (£/QALY)	+/- company base case
	Company base case	17,947	-
1	ERG curves for OS, PFS, ToT applied to SACT data instead of updated JM200: Part B	23,485	+ 5,538
2a	PSW analyses for OS and PFS for JM200: Part B data for avelumab and Part A for chemotherapy instead of naïve comparison	18,352	+ 405
2b	Using only immunocompetent patients in company's part A study for OS and PFS	17,225	- 722
3	Using 1-knot hazard spline for OS instead of 1-knot odds spline for JM200: Part B data	20,097	+ 2,150
4	Using 3-knot odds spline for PFS instead of 2-knot odds spline for JM200: Part B data	17,852	- 95
5	Using 3-knot hazard spline for ToT instead of Weibull of JM200: Part B data	18,290	+ 343
6	Removing the adjustment to ToT using JM200: Part A data	19,332	+ 1,385
7	Weight-based dose instead of flat dose	18,938	+ 991
8	**ERG preferred ICER following technical engagement:** Cumulative changes with PSW4: 2a + 3 – 6 (flat dose)	20,780	+ 2,833

Changes to model parameters in CDF review

	Original parameters TA517	Company base case in CDF review	Company justification for change
OS extrapolation	1-knot normal-based spline model fitted to interim JM200: Part B data	1-knot odds-based spline model, fitted to JM200: Part B data	Updated JM200: Part B data allows for a more robust estimation of parametric curves, as opposed to an assumed benefit or difference versus treatment-experienced patients. • For OS, a 1-knot odds model provides good visual and statistical fit, while also providing realistic long-term projections • For PFS, similar inferences may be noted, yet a 1- or 3-knot model did not provide as good of a fit versus a 2-knot model • For ToT, extrapolation was adjusted to make use of the longer-term data from Part A of JM200 to better reflect expected pattern (rate) of treatment discontinuation
PFS extrapolation		2-knot odds-based spline model, fitted to JM200: Part B data	
ToT extrapolation	Weibull model fitted to interim JM200: Part B data	Weibull model fitted to JM200: Part B data, adjusted in two aspects: estimated hazard of discontinuation based on JM200: Part A data after 15 months (min. follow up in Part B), and all patients assumed discontinued after 5 years	
Acquisition costs	Weight-based dose (10mg/kg)	Flat-dose (800mg)	Changed to align with updated product label. Not expected to affect NHS practice; dose banding guidance means majority of patients treated with 4 vials prior to label change

Extrapolation of avelumab OS (Issue 3)

- Company found that the spline-based models provided a good fit for the updated JAVELIN Part B 1L data while also producing plausible extrapolations that remained above the KM data for 2L+ data. Company considered the 1-knot odds spline (dark yellow) the most appropriate
- ERG: spline-based model appropriate but prefers more conservative 1-knot hazard based spline (red) due to uncertainty in naïve comparison of treatment effects between avelumab and chemo



- ERG also prefers the adjusted PSW4 analysis (Issue 2):
  - curves were refitted to the adjusted data and both the ERG and company chose the same curves as for the unadjusted data

Extrapolation of avelumab OS – TE comments

Company

- The difference in long-term survival is difficult to validate as all 3 models produce estimates that are broadly in keeping with clinical advice, and produce near-identical fits to the Kaplan-Meier curve
- Projected hazards produced by the ERG's preferred 1-knot hazard spline result in an extrapolation which eventually (at approx. 11 years) produces an estimated hazard of death which exceeds that of the base-case analysis in TA517 for the 2L+ population. Misaligned with clinical opinion that outcomes for patients treated in the 1L setting are expected to be better than those for a 2L+ population

ERG

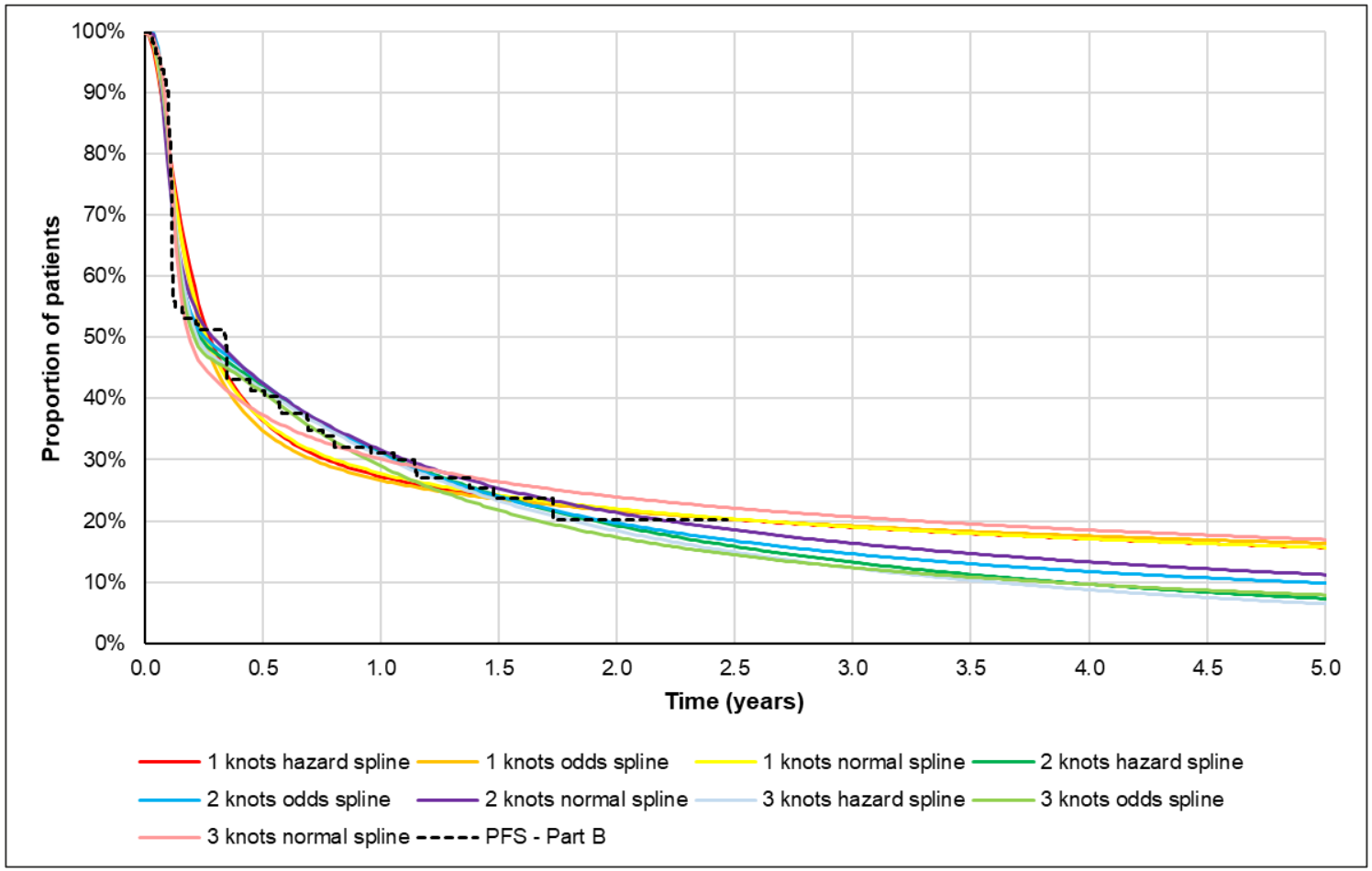
- Acknowledges that the three 1-knot models presented by the company are very similar and, on its own, the selection of model is unlikely to make a difference to decision making

RCP

- Not necessarily appropriate to choose most conservative model. Would be best to wait longer before re-evaluating to allow for more robust and reliable modelling

Extrapolation of avelumab PFS (Issue 4)

- Company applied the same general approach to estimate PFS outcomes as for OS. The spline-based models provided a good fit for the updated JAVELIN Part B 1L data.
- Company considered the 2-knot odds spline (blue) most appropriate; ERG considered the 2-knot spline to underestimate KM data between 0.5 and 1 year, and overestimate KM data for the tail. It considers the 3-knot odds spline (green) to provide better extrapolation and better fit to data



TE comments

Company: little evidence to reject one model in favour of the other, both approaches are suitable for decision making – small impact on ICER

Is the modelling of OS and PFS appropriate?

Do the different models capture the range of possible outcomes?

Extrapolation of avelumab time on treatment (Issue 5)

- Company chose parametric curves to extrapolate ToT using updated JAVELIN Part B 1L data. Clinical experts expected most patients to discontinue avelumab within 2 years of initiation, and all to discontinue by 5 years. As a result:
  - extrapolation beyond the minimum follow up period of 1L data (15 months) was informed by data from JAVELIN Part A 2L+ (n=88); minimum follow up = 36 months
  - at 5 years, all patients remaining on treatment are assumed to immediately discontinue
- Company chose Weibull curves for both 1L and 2L+ data

Extrapolation of avelumab time on treatment (2)

- **ERG** agrees with assumption to stop treatment at 5 years and uses this in its preferred analyses
- However, ERG considers that the curves fitted to 1L data should not be adjusted by 2L+ data as not reflective of treatment-naïve population
- Prefers 3-knot hazard spline for the 1L data (2L+ data are not used in ERG approach).

TE comments

Company: approach was taken to supplement limited JM200: Part B (1L) data with more mature JM200: Part A (2L+) data while maintaining a model based on 1L data for earlier part of curve

Both models result in similar mean ToT estimates (company: 12.59 months, ERG: 13.07 months) – small impact on ICER

Is the modelling of ToT appropriate? Do the different models capture the uncertainty effectively?

Key model parameters used in company's base case and ERG's preferred analysis

Assumption		Company's base case	ERG's preferred assumptions
1	OS extrapolation	1-knot odds-based spline model, fitted to JM200: Part B data	1-knot hazard based spline fitted to JM200: Part B data
2	PFS extrapolation	2-knot odds-based spline model, fitted to JM200: Part B data	3-knot odds spline fitted to JM200: Part B data
3	ToT extrapolation	Weibull model fitted to JM200: Part B data adjusted in two aspects; estimated hazard of discontinuation based on JM200: Part A data after 15 months (min. follow up in Part B) and all patients assumed discontinued after 5 years	3-knot hazard spline fitted to JM200: Part B data (Part A data not used in ERG approach)
4	Acquisition costs	Flat-dose (800mg) in line with licence change	

Cost effectiveness results: company base case

	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Deterministic	[redacted]	[redacted]	17,947
Probabilistic	[redacted]	[redacted]	17,939

Cost effectiveness results: ERG analyses

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