Single Technology Appraisal

Enfortumab vedotin with pembrolizumab for untreated unresectable or metastatic urothelial cancer when platinum-based chemotherapy is suitable [ID6332]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Enfortumab vedotin with pembrolizumab for untreated unresectable or metastatic urothelial cancer when platinum-based chemotherapy is suitable [ID6332]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Astellas Pharma Ltd**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Merck Sharp & Dohme

3. **Comments on the Draft Guidance received through the NICE website**

4. **External Assessment Group critique of company comments on the Draft Guidance**

5. **Systemic Anti-Cancer Therapy (SACT) data reports**
   a. Cohort 1
   b. Cohort 2
   c. Additional results from analysis
   d. Cohort 3

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. • The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Astellas Pharma Ltd.
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount	Not applicable

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• the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Time on pembrolizumab based on EV-302 trial** Astellas has now corrected the mistake in estimating the time on pembrolizumab treatment based on the EV-302 trial noted in the draft guidance document, and provided cost-effectiveness results using the full Kaplan-Meier curve for pembrolizumab, as per the committee's preference – see Appendix B at the end of this document.
2	**Data sources informing responses to NICE Committee requests** Section 3.18. of the draft guidance states: "The committee considered further data is needed to resolve the uncertainty in evidence required for decision making. It requested the following analyses: • **further information on time on treatment for avelumab maintenance in the NHS**, including mean time on treatment and justification for the choice of time-on-treatment model for avelumab, as well as the proportion of people having avelumab maintenance in the NHS, where available • **additional evidence on the overall survival of people having standard care treatments that are generalisable to NHS practice**, including the impact of avelumab maintenance treatment (where unavailable, additional evidence on overall survival for people having platinum-based chemotherapy without avelumab maintenance treatment may also be considered)."

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Astellas SACT analysis

In response to this request, Astellas has conducted a number of analyses using data on patients diagnosed with metastatic urothelial cancer (mUC) from the National Cancer Registration Dataset (NCRD) linked to the Systemic Anti-Cancer Therapy (SACT) dataset. Patients were selected to align with patient characteristics in the EV-302 trial as much as possible, and included two cohorts who initiated 1L platinum-containing chemotherapy between pre-specified dates:

- Cohort A received platinum-based chemotherapies from 1 April 2021 to 30 April 2022. This cohort reflects clinical practice prior to the recommendation of avelumab maintenance therapy, but in all other respects is similar to current clinical practice (i.e. after the NICE recommendation of atezolizumab [TA525] in June 2018 and pembrolizumab's exit of the Cancer Drugs Fund [TA692] in April 2021); N=431 patients.
- Cohort B received platinum-based chemotherapies after 1 May 2022, i.e. the cohort reflects clinical practice after the recommendation of avelumab; N=340 patients.
- A third set of analyses was performed on the pooled cohorts A and B (N=771 patients), given their similar survival outcomes.

Details of the study methods are provided in Appendix A at the end of this document. Information on overall survival was collected for both cohorts, while information of length of avelumab treatment was also collected for cohort B.

The results of the analysis are described in comment 4 (time on treatment with avelumab), comment 3 (proportion of patients receiving avelumab) and comment 6 (survival following platinum-chemotherapies).

NICE SACT analysis

NICE have also shared results of their own analyses based on SACT. Inclusion criteria in this study were broadly similar to Astellas' own analyses, with only a few exceptions:

1. NICE included patients with stage 4 disease (i.e., metastatic) plus either metastasis status M of 1 (distant metastasis) or M status unknown, whereas Astellas only included patients with stage 4 disease (see Appendix A for details).
2. NICE excluded patients if multiple tumours of interest were diagnosed between 2020 and 2022, which Astellas' analysis did not.
3. Avelumab regimens were only considered where initiated between one day after the start of the first-line platinum-based regimen and up to 43 weeks from the start of the first-line platinum-based regimen in Astellas' analysis. This is because platinum-based chemotherapy is given for up to six three-weekly cycles (although patients may have treatment spaced over a longer period to manage toxicities [e.g., the maximum duration of platinum-based chemotherapy in EV-302 was [redacted] months (approximately [redacted] weeks)], and avelumab can be started up to 10 weeks from the date of last chemotherapy. This restriction avoids the inclusion of off-label avelumab use and use

	of avelumab in other licensed indications. However, the NICE analysis did not include this restriction on avelumab use. 4. NICE did not apply an exclusion based on date of treatment with platinum chemotherapy, whereas Astellas' cohort B started the first platinum-based regimen between 01/05/2022 and 31/07/2024 – therefore fewer patients are necessarily included in the Astellas cohort B and the follow-up period is shorter. The NICE SACT analysis provides information for the following cohorts: • Cohort 1 received gemcitabine with platinum chemotherapies only, no avelumab maintenance therapy, N=642 patients. • Cohort 2 received gemcitabine with platinum chemotherapies plus subsequent maintenance avelumab, N=151 patients. • Cohort 3 comprises cohorts 1 and 2, N=793 patients. **Clinical expert consultation** To gain additional insight, Astellas consulted 7 clinical experts practising in the NHS in England (9 were contacted, 7 responded), using a structured questionnaire administered via video call. The completed, anonymised questionnaires are supplied in the reference pack. Summaries of responses are presented in the relevant sections of this document.[1]
3	**Proportion of patients initiated on avelumab in the NHS** **The committee concluded that the proportion of people who received avelumab from the EV-302 trial (30%) was plausible for the NHS and suitable for decision making, but would value further evidence.** The response below refers to the evidence included in the original Astellas submission, and new evidence based on analyses of avelumab use in the NHS, as described earlier and in detail in Appendices A and B. In summary: • Evidence included in the original Astellas submission suggested that 21%-31% of patients who started platinum-based chemotherapy subsequently had avelumab. • In the NICE SACT analysis of patients diagnosed with mUC between 2020-2022 and treated with platinum-based chemotherapy as first line, 19% of patients had subsequent maintenance avelumab. • In the Astellas SACT analysis of patients treated with avelumab after avelumab was recommended by NICE (Cohort B), 20% of patients had subsequent maintenance avelumab. **Evidence included in the original Astellas submission** The original Astellas submission included estimates from three alternative data sources that supported the 30% estimate as relevant to the NHS. These data sources suggest that 21-

	31% of patients who start platinum-based chemotherapy subsequently receive maintenance avelumab (details in Appendix T of original submission): - EVEREST-2 study reported a cross-sectional survey of physicians in Europe. Specifically regarding the UK, 41 UK physicians responded between December 2023 and May 2024, and reported that 21% of patients who had received platinum-based chemotherapy were started on avelumab maintenance. Overall, 28% of patients in the sample that received platinum-based chemotherapy were started on avelumab at any line. - Based on SACT data between April 2023 and March 2024 (patients with ICD10 code C67 [bladder cancer] without linkage to NCRD or restriction by stage at diagnosis), the ratio of 1st line platinum chemotherapy to avelumab is 31%. - Market research data from June 2024 from a panel of around 50 UK clinicians found that [redacted]% of patients who received 1st line platinum chemotherapy had avelumab subsequently. **Astellas and NICE SACT data analyses** In the NICE SACT analysis, 642 patients were included in Cohort 1 (patients who did not receive avelumab maintenance), while 151 patients were included in Cohort 2 (patients who did receive avelumab maintenance treatment after platinum-based chemotherapies). The two cohorts were captured during the same time period, which allows for the calculation that 19% of patients (=151/(642+151)) received avelumab maintenance treatment in England real life clinical practice. In the Astellas SACT analysis, 68 (20%) of the 340 patients included in Cohort B (captured during the period after avelumab became routinely available on the NHS) received avelumab maintenance treatment. The findings align with previous estimates and suggest that the estimate for the proportion of people who received avelumab from the EV-302 trial (30%) was plausible. If anything, the lower proportion of patients receiving avelumab in the SACT analyses further supports the claim that the economic evaluation may be conservative, since outcomes predicted by the model for the platinum-based chemotherapy arm based on the EV-302 trial may overestimate the health benefits experienced by patients treated with NHS standard of care in England.

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4	**Time on avelumab maintenance** **The committee requested (i) further information on time on treatment for avelumab maintenance in the NHS, including mean time on treatment; and (ii) more justification for the choice of time-on-treatment model for avelumab maintenance.** Astellas and NICE have conducted new analyses of NHS data, and Astellas sought additional evidence from the literature and clinical experts. The detailed response is below. In summary: • In the NHS, there is a considerable proportion of patients who remain on avelumab treatment in the long run (i.e., a plateau), suggesting lower hazard rates for discontinuation over time. • The existence of a plateau in the avelumab time on treatment (ToT) curve is supported by external literature and by most clinical experts consulted by Astellas. • Given this expected plateau, the exponential distribution is not supported to extrapolate avelumab ToT in EV-302. • The survival distribution that best fits the NHS SACT data on avelumab ToT is generalised gamma, therefore this is used for the cost-effectiveness scenarios based on this data. • The Astellas base-case continues to use the Weibull distribution, given its good alignment with clinical expert feedback and good statistical fit to the EV-302 avelumab ToT data. • Because it is not feasible to adjust the PBC arm survival outcomes to account for longer avelumab ToT in EV-302 trial compared to the NHS, it is inconsistent to adjust only ToT for costs. **Avelumab Time on Treatment (ToT) in the NHS** Figure 1 shows data from the NICE and Astellas SACT analyses overlaid with the observed time on avelumab maintenance treatment in EV-302. Table 1 shows the estimates of proportions of patients on treatment at 6, 12, 18 and 24 months, alongside the estimates from the Weibull and exponential models fitted to the EV-302 data.

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Figure 1: Avelumab time on treatment in EV-302 and requested SACT analyses

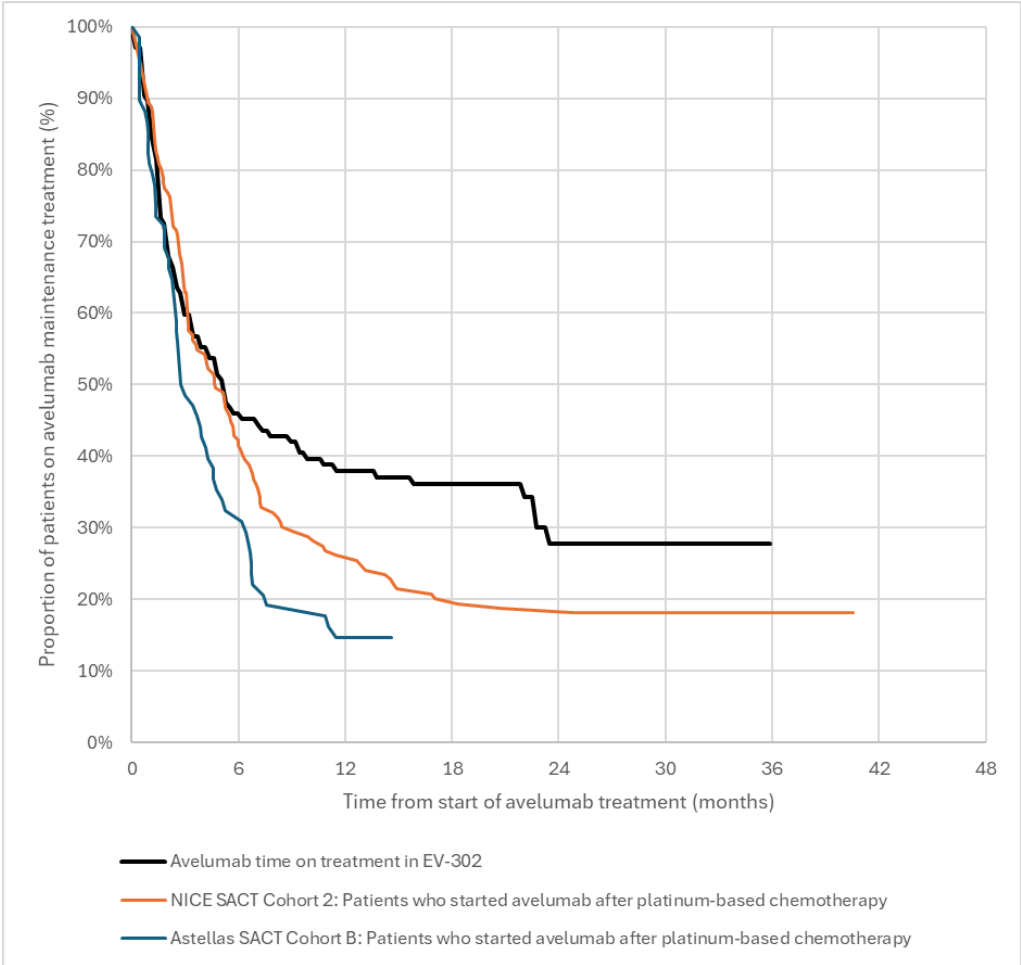

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Table 1: Landmark estimates of avelumab time on treatment in EV-302 and requested SACT analyses

Time, months:	6	12	18	24
EV-302, PBC arm patients who started avelumab	46%	38%	36%	28%
Astellas SACT analysis - Cohort B, subset of patients who started avelumab	32%	15%	n/a	n/a
NICE SACT analysis - Cohort 2 (patients who did have subsequent avelumab)	42%	26%	19%	18%
Weibull model fitted to EV-302 data	56%	41%	32%	26%
Exponential model fitted to EV-302 data	65%	43%	28%	18%

Note: Analyses include only patients who started avelumab, from the time of avelumab initiation.
Abbreviations: n/a, not applicable; PBC, platinum-based chemotherapy; SACT, systemic anti-cancer therapy
[1]Mean time on avelumab treatment according to the Weibull model is 16.9 months.
[2]Mean time on avelumab treatment according to the Exponential model is 13.9 months.

The Astellas SACT analysis in Cohort B found that median time on treatment with avelumab maintenance was 2.88 (95% Confidence Interval [CI] 2.43 - 4.8) months (see Appendix A for details), and in the NICE SACT analysis of Cohort 2 was 4.7 months, CI (3.3 months, 5.99 months; see Appendix B or details). These results confirm the clinical experts feedback that, in the NHS, median time on treatment with maintenance avelumab is well below one year.

In the NICE SACT analysis of Cohort 2, the restricted mean time on treatment with maintenance avelumab was 11.07 months. However, follow-up is not complete. At 36 months, 18% of patients are on avelumab (27 patients at risk), which appears to be constant up to approximately 40 months, when zero patients are at risk (see Appendix B, Figure 8). This suggests that, if follow-up was longer, the estimated mean time on treatment would likely increase.

The NICE SACT analysis of Cohort 2 suggests that there is a considerable proportion of patients who remain on avelumab treatment in the long run, which is also seen in EV-302 data. The follow-up of the Astellas SACT analysis is likely too short to capture this plateau in the proportion of patients remaining on maintenance avelumab, because Cohort B includes only patients treated with chemotherapy after 01/05/2022. **The plateaus observed in both the EV-302 data and the NICE SACT analysis of Cohort 2 mean that the hazards for treatment discontinuation reduce over time, therefore the exponential distribution is not supported.**

Figure 2 and Figure 3 show the survival extrapolations fitted to Astellas' SACT analysis and NICE's SACT analysis of avelumab time on treatment, respectively. The best fitting extrapolation to both the Astellas SACT analysis data and to the NICE SACT analysis is the generalised gamma. Based on these extrapolations, the estimated mean avelumab ToT is 8.2 months and 14.9 months, respectively.

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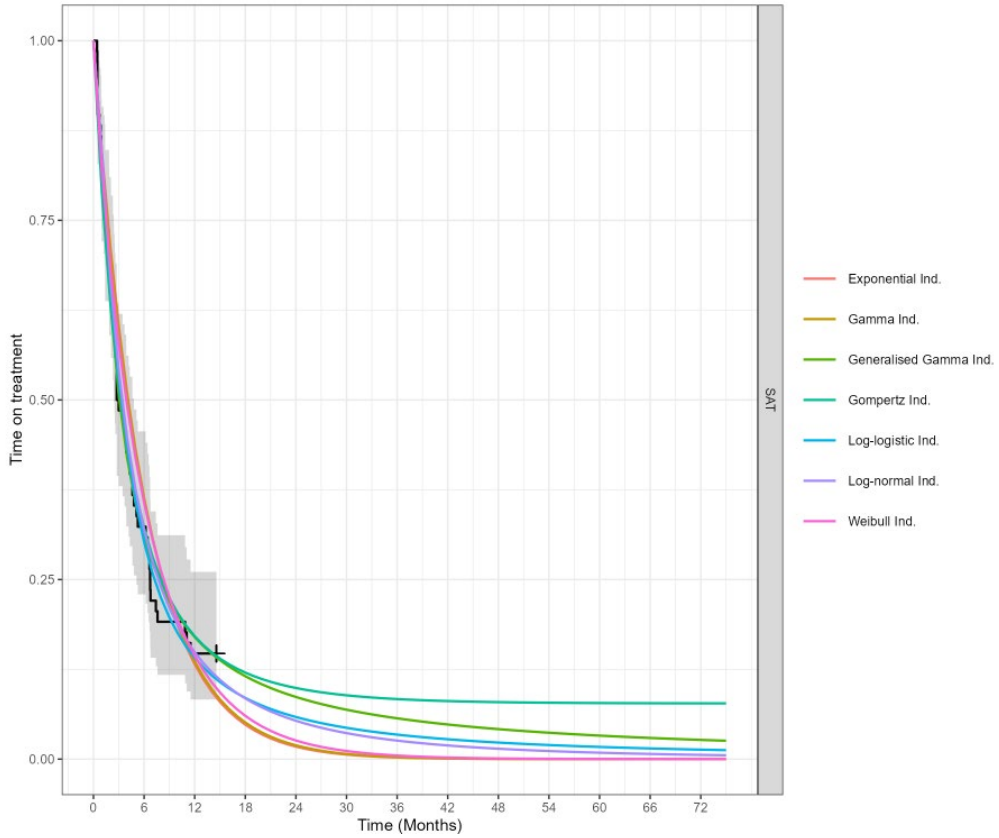
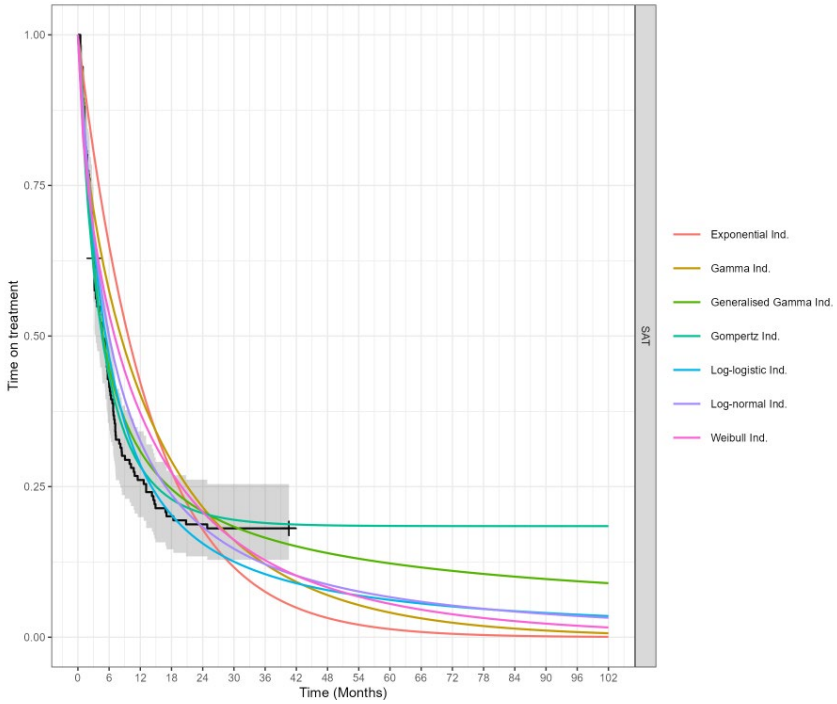
Figure 2: Avelumab time on treatment extrapolations based on Astellas' SACT analyses (Cohort B patients who had subsequent maintenance avelumab)



Abbreviations: Ind – independently fitted

Figure 3: Avelumab time on treatment extrapolations based on NICE's SACT analyses (Cohort 2)



Abbreviations: Ind – independently fitted

Supporting evidence from a recent published meta-analysis

A systematic review and meta-analysis of outcomes with avelumab first-line maintenance in this setting, published in April 2025 by Barthelemy et al.[2] covered real-world evidence studies of avelumab maintenance published from 1 January 2020 to 31 January 2024. Forty-five studies were identified. In the meta-analysis, 12-month PFS from avelumab start was 39% (95%CI 35–44%). The median PFS was 7.0 months (range 3.8-11.5 months) but the median duration of treatment was shorter at 4.8 months (range 3.8-7.1 months). This also supports a specific shape for the time on treatment curve such that many patients stop treatment after a relatively short time, but then the proportion stopping treatment likely gets smaller over time as indicated by the proportion of patients still progression-free at 12 months.

Estimates from clinical experts

The questionnaire asked clinicians to estimate the proportion of chemotherapy patients who are on avelumab maintenance treatment in the NHS at different time points. The average, minimum and maximum proportions estimated are shown in Table 2. Estimates varied, but suggest that the discontinuation rate slows over time and that a proportion of patients remain on treatment long-term. Five of the 7 experts expected a plateau in the curve depicting proportions of patients still on avelumab treatment over time from year 3 onwards.

Table 2 Estimates by clinical experts of proportion of patients still receiving avelumab maintenance at given time points.

	6 months	1 year	2 years	3 years	4 years	5 years
Model prediction based on EV-302	56%	41%	26%	18%	13%	10%
Average (mean) estimate	53%	30%	22%	8%	10%	8%
Minimum estimate	50%	20%	10%	5%	3%	0%
Maximum estimate	60%	40%	35%	10%	17%	16%

Note: Astellas received the SACT Avelumab time on treatment data during the HCP questionnaire process. Astellas therefore updated the questionnaire to only ask the remaining 4 HCPs their estimates for years 4 and 5 based on the SACT data to that point. This has resulted in the slight increase seen between years 3 to 4.

Conclusion

Both SACT analyses predict slightly lower proportions of patients to be on treatment in real life compared to what was observed in the EV-302 trial. However, both analyses align with the observation in the trial that the hazards for stopping treatment should decrease over time. The generalised gamma function provided the best fit for Astellas' own analysis and the second best fit for the NICE SACT data (however, the best fit Gompertz would predict patients to stay on treatment indefinitely, therefore it lacks clinical face validity). **Therefore, results for the scenarios incorporating information from SACT use the generalised gamma extrapolation for both data sources.** With this survival distribution, the estimated mean avelumab ToT is 14.9 months based on the NICE SACT analysis and 8.2 months based on the Astellas SACT analysis.

The base case (based on the trial data) continues to use the Weibull distribution. The Weibull distribution aligns with the range predicted by the clinical experts consulted by Astellas, and provides a better statistical fit to the observed data from EV-302 compared to the only other extrapolation choice (gamma) which would have aligned with the clinical experts' expectations. With the Weibull distribution fitted to EV-302 data, the mean avelumab ToT is 16.9 months.

As explained earlier, the exponential distribution is not appropriate because it assumes constant rate for stopping treatment, whereas both the NICE SACT analysis and the EV-302 data suggest that the rate reduces over time, and a proportion of patients remain on maintenance avelumab. Furthermore, most clinical experts consulted by Astellas agreed that a proportion of patients are likely to remain on maintenance avelumab.

While time on avelumab treatment is shorter in NHS clinical practice than in the EV-302 trial, **it is not appropriate to adjust the base-case for costs, given that survival outcomes in the chemotherapy arm also incorporate the effect of avelumab**. If avelumab ToT is shorter in the NHS than in the EV-302 trial, PFS and OS will likely be shorter too. Therefore, the QALY gain of EV+P vs PBC would be larger than what the model currently calculates based on the trial data. Because the trial data is insufficient to adjust the survival outcomes for shorter avelumab ToT, it is inconsistent to only adjust for shorter avelumab ToT in the costs. Although assuming a shorter avelumab ToT has a small impact on cost-effectiveness, doing so without adjusting survival outcomes in the chemotherapy arm would likely bias against the cost-effectiveness of EV+P.

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5	**Treatment effect waning** **The committee concluded that there is uncertainty in whether to apply an additional treatment waning assumption for pembrolizumab, given that enfortumab vedotin does not have a stopping rule (paragraph 3.12, p15).** Astellas considers that it is not appropriate to apply additional treatment effect waning in addition to what is already incorporated in the survival extrapolation, because: • The hazard rates of the log-logistic curves converge over time, therefore treatment effect waning is implicitly included. • The 5-year follow-up of the EV-103 Cohort A + dose escalation shows a sustained plateau in PFS and OS from 3 years onwards. • The choice of log-logistic survival extrapolation without additional effect waning is therefore supported by long-term follow-up from the EV-103 trial, and by clinical expert feedback. **EV-103 trial** EV-103 (NCT03288545) is a multi-cohort, non-randomised, open-label, Phase Ib/II trial.[3-5] It was designed to determine the safety and tolerability of enfortumab vedotin alone and in combination with pembrolizumab and/or chemotherapy for the treatment of locally advanced/metastatic UC and muscle-invasive BC. Patient populations and interventions varied by cohort. Both cohort A and K are relevant to this indication and were reported in the original submission (see Document B 2.3.2 EV-103 trial design p43-44, and 2.6.8 Study EV-103 p56-62). Cohort A with the dose escalation cohort provides long-term follow-up data (median follow-up 62 months) on previously untreated cisplatin-ineligible patients (N=45). Compared with EV-302, a greater proportion of patients were aged ≥75 years (35.6% vs 23.7%), fewer had ECOG PS 0 (33.3% vs 49.4%), more had EGOG PS 2 (17.8% vs 2.9%), and more had visceral metastases (84.4% vs 71.8%). All patients had discontinued EV+P at the time of the data cut. Median duration of treatment was 6.4 months (range: 0.7-32.9) and mean duration of treatment was [redacted] months for EV. For P median duration of treatment was 6.5 months (range: 0.7-28.1) and mean duration of treatment [redacted] months, respectively. Durable response rate, PFS and OS results for Cohort A + dose escalation cohort are shown in Table 3 and a Kaplan-Meier plots for PFS and OS in Figure 4 and Figure 5.[6] **EV-103 cohort A + dose escalation shows that PFS and OS rates after treatment with EV+P are sustained over time even though all patients stopped treatment by 32.9 months. For example, the 3-year OS rate was 49%, at 4-years was 44% and at 5 years 42%. The PFS rate has remained at 38% from year 3.**

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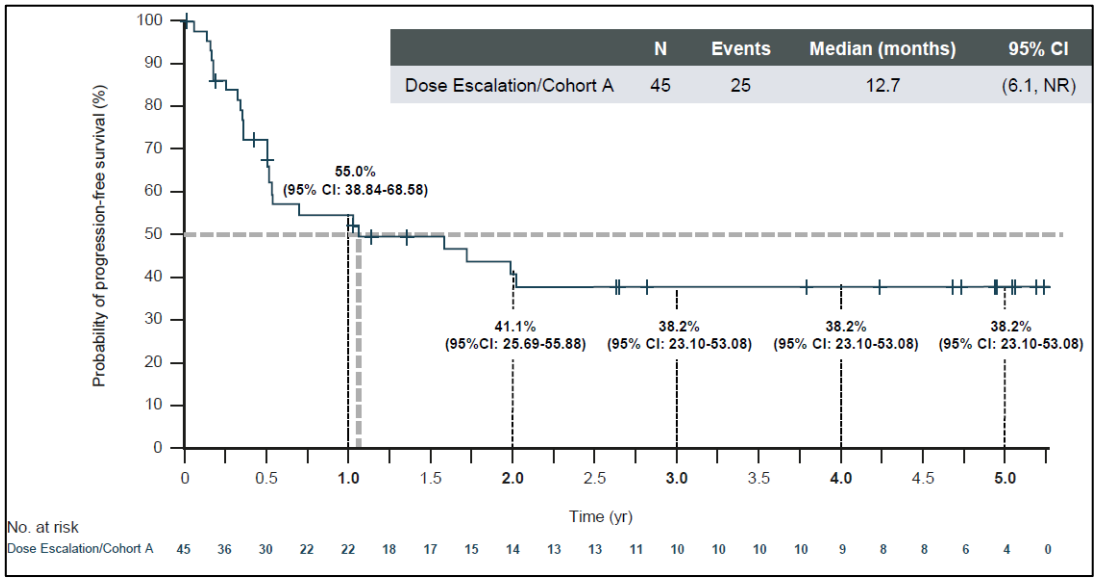
Table 3. Durable response rate, PFS (by BICR), and OS rates in EV-103 for Dose Escalation[a] + Cohort A (from original company submission)

% (95% CI)	12 mo	24 mo	36 mo	48 mo	60 mo
Durable response rate (n=33)[b]	63.9 (44.19-78.17)	47.0 (27.57-64.31)	47.0 (27.57-64.31)	47.0 (27.57-64.31)	47.0 (27.57-64.31)
PFS rate (N=45)	55.0 (38.84-68.58)	41.1 (25.69-55.88)	38.2 (23.10-53.08)	38.2 (23.10-53.08)	38.2 (23.10-53.08)
OS rate (N=45)	83.4 (68.25-91.72)	56.4 (40.03-69.91)	49.1 (33.16-63.15)	44.1 (28.76-58.48)	41.5 (26.45-55.99)

[a] Patients (N=5) assigned to EV 1.25 mg/kg + P on Days 1 and 8, and P 200 mg IV on Day 1 of every 3-wk cycle and for whom study treatment was administered as 1L therapy.[5] [b] Number of pts that responded to treatment. Abbreviations: BICR, blinded independent central review; CI, confidence interval; mo, months; OS, overall survival; PFS, progression-free survival. Source: Rosenberg et al. 2024[6]

Figure 4. Kaplan-Meier estimates of progression-free survival in Dose Escalation + Cohort A in the EV-103 trial (from original company submission).



Abbreviations: CI, confidence interval; Esc, escalation. Source: Rosenberg et al. 2024 (poster)[6]

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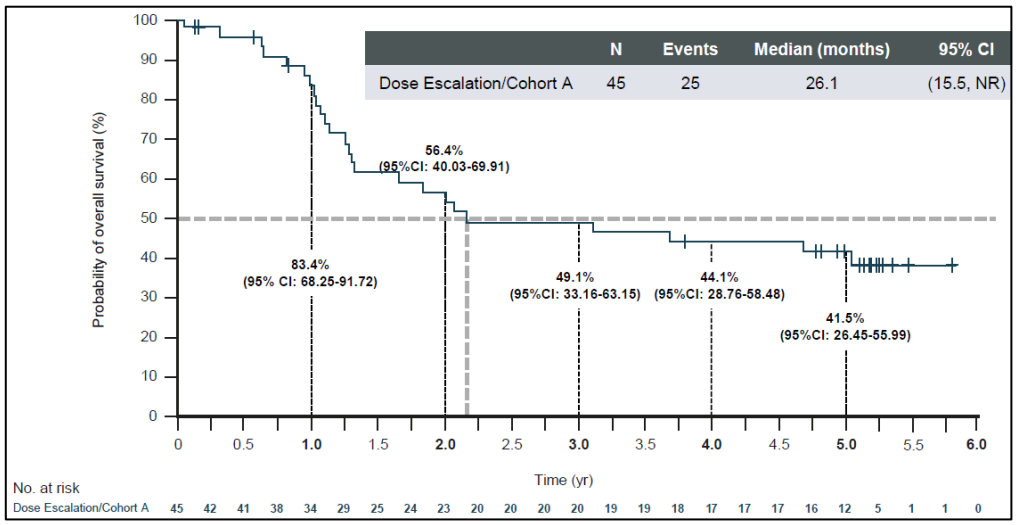
	Figure 5. Kaplan-Meier estimates of overall survival in Dose Escalation + Cohort A in the EV-103 trial (from original company submission).  *Abbreviations: CI, confidence interval; Esc, escalation Source: Rosenberg et al. 2024 (poster)[6]* **Evidence from clinical experts** In the questionnaire, clinical experts were shown the model predictions for OS at 5 and 10 years with EV+P, together with the EV-103 data above, and were asked whether the model predictions were reasonable. For the 5-year prediction (31% alive), five thought it was reasonable and two thought it was too low. For the 10-year prediction (16% alive), three thought it was reasonable, three thought it was too low, and one thought it was too uncertain to know. **Conclusion** **The log-logistic model, without any additional effect waning, is the most appropriate survival extrapolation model given the EV-302 data, EV-103 data and clinical expert feedback.** Imposing additional effect waning on the extrapolation is not appropriate, nor is selecting the generalised gamma model for extrapolation.
6	**Severity modifier** **The committee requested additional evidence on the OS of people having NHS standard of care treatments, including the impact of avelumab maintenance treatment if available (paragraph 3.14, p20).** To address this, Astellas has conducted an analysis of SACT data, and has elicited opinion from clinical experts using a questionnaire. Further to discussions of the severity modifier, Astellas notes that in NICE's recent (April 2025) appraisal of erdafitinib in the treatment of u/mUC in patients who had previously received at least one line of therapy containing a PD-1 or PD-L1

inhibitor, a severity modifier of 1.7 was accepted. The implications of this are discussed at the end of this section.

In summary:

- Using real-world data on survival outcomes from patients in the NHS in England (from the Astellas SACT analyses and the NICE SACT analyses), the 1.2 severity modifier is met in all scenarios, including a best-case scenario using data only from patients who all subsequently received avelumab.
- The application of the 1.7 severity modifier in the recent NICE appraisal of erdafitinib in the treatment of u/mUC after previous treatment with at least one line of therapy containing a PD-1 or PD-L1 inhibitor suggests that the 1.2 severity modifier would apply to EV+P in first line.

SACT data analysis

The full report of the SACT analysis by Astellas (methods and results) is provided as an appendix within this document (Appendix A). In addition to the analysis by Astellas, the results based on the SACT cohorts provided by NICE are also discussed below.

Figure 6, below, compares observed survival for patients receiving platinum-based chemotherapies based on NICE and Astellas's SACT analyses. The findings confirm that patients in England included in the SACT cohorts have worse survival outcomes compared to what was observed in the EV-302 trial (see also Table 4). NICE's SACT analysis for cohort 3 (all patients who received platinum-based chemotherapy as first line treatment for newly diagnosed mUC, and including patients who subsequently did and did not receive avelumab maintenance treatment), found that the median OS was 10.1 months (95% CI: 9.4 – 10.5 months). Astellas' SACT analysis found that the median OS was 11.02 months (95% CI: 10.13 – 12.2 months) in cohort A (time period before recommendation of avelumab) and 10.23 months (95% CI: 9.54 – 11.97 months) in cohort B (time period after recommendation of avelumab).

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Figure 6. Kaplan-Meier estimates of overall survival from EV-302, NICE and Astellas' SACT analyses

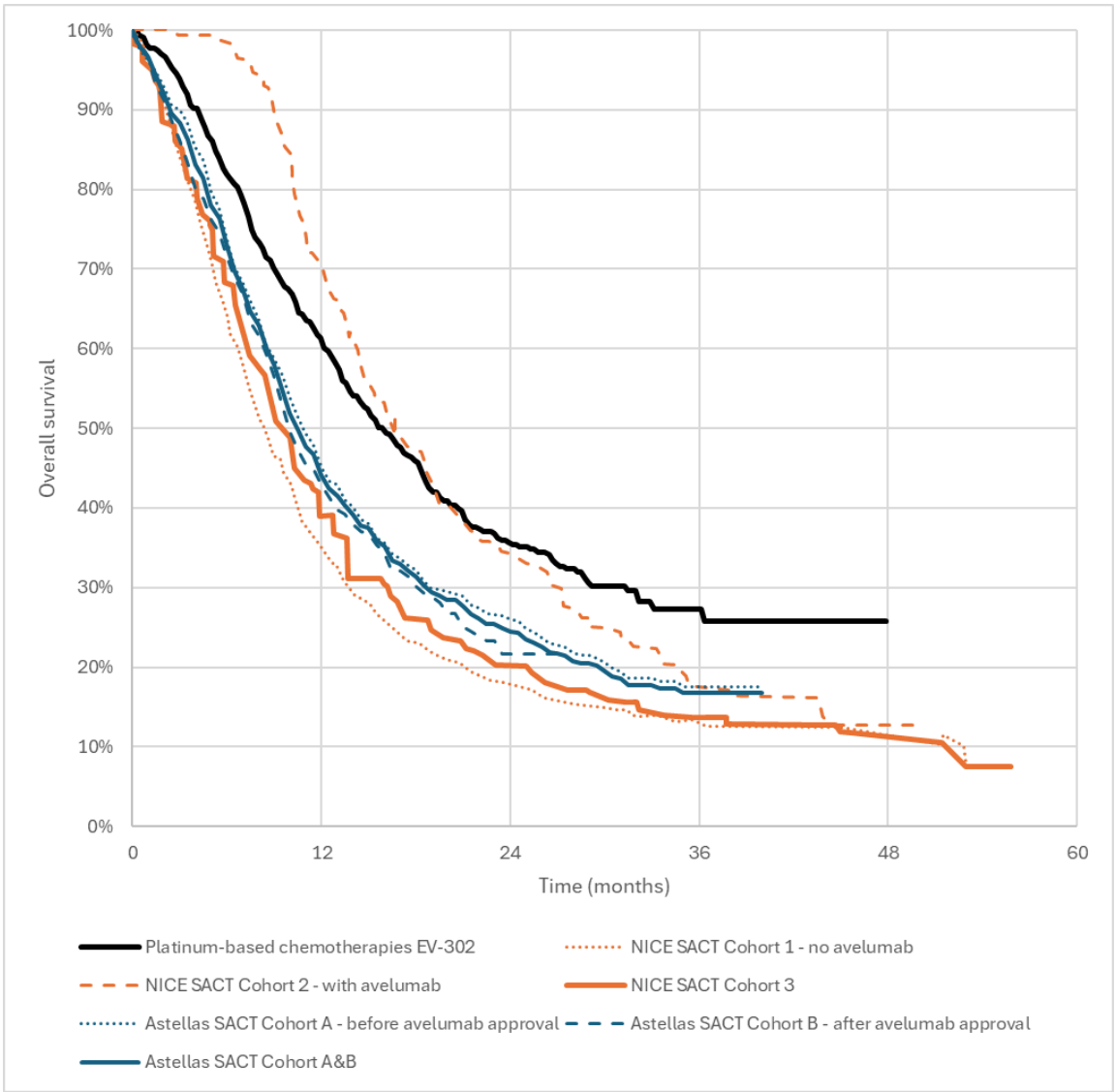

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Table 4: Landmark estimates of overall survival in EV-302 and requested SACT analyses

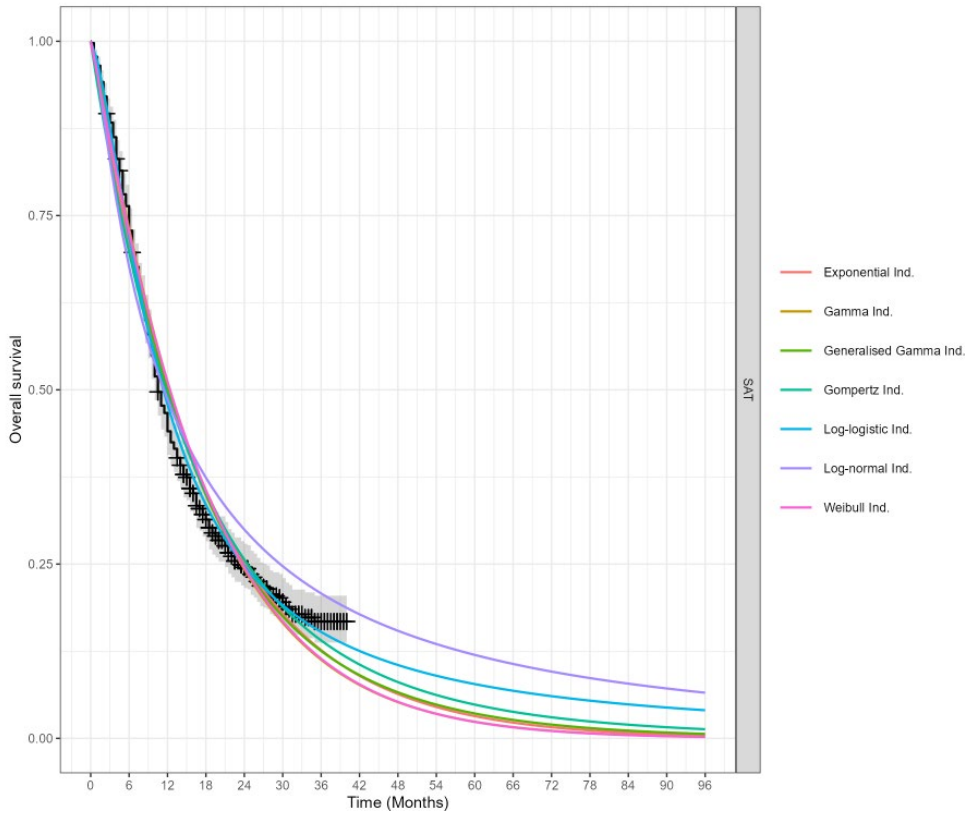
Time, months:	**6**	**12**	**24**	**36**
EV-302 PBC arm	82%	61%	35%	27%
Astellas SACT analysis – Cohort A (**before** avelumab becoming routinely available on the NHS)	75%	46%	26%	18%
Astellas SACT analysis – Cohort B (**after** avelumab becoming routinely available on the NHS)	73%	44%	21%	n/a
NICE SACT analysis – Cohort 1 (patients who did **not** have subsequent avelumab)	64%	35%	18%	13%
NICE SACT analysis – Cohort 2 (patients who did have subsequent avelumab)	98%	70%	34%	18%

Abbreviations: PBC, platinum-based chemotherapy; SACT, systemic anti-cancer treatment

Since in the Astellas SACT analysis estimates for overall survival between Cohort A and Cohort B were similar, and results also showed that the proportion of patients receiving avelumab maintenance treatment was already 18% before the time point of the recommendation of avelumab, which then increased to 20% after the recommendation of avelumab (i.e. the two cohorts were nearly identical), a combined analysis was undertaken.

Figure 7 and Table 5 show the survival extrapolations fitted to Astellas' SACT analysis of OS. Similarly to the EV-302 trial, hazards were initially increasing, then decreasing over time, and the log-logistic function provided the best statistical fit to the SACT data. Therefore, this was used to estimate survival and the severity modifier in the scenario presented below. Please see Appendix A for further details.

Figure 7: Overall survival for the combined cohort based on Astellas' SACT analyses



Legend: Ind – independently fitted

Table 5: Real-World overall survival and extrapolations of patients on platinum-based chemotherapies in Astellas' SACT analysis (combined cohort)

Model	AIC	BIC	Mean, months*	Timepoint			
				1 year	2 years	5 years	10 years
Astellas' SACT analysis			-				-
Exponential	4592.6	4597.3	17.54	50%	25%	3%	0%
Weibull	4591.0	4600.3	17.11	51%	25%	2%	0%
Log-normal	4738.1	4747.4	28.49	49%	30%	12%	5%
Log-logistic	4561.7	4571.1	23.41	48%	25%	8%	3%

Note: Only distributions that were also available in the NICE SACT analysis are presented here.

The log-logistic curve also provided the best statistical fit to the data from NICE SACT analysis cohort 1 (patients without avelumab maintenance treatment) and cohort 3 (the combined cohort including patients with or without avelumab maintenance treatment). The log-logistic was also the very close second best fit for cohort 2 (patients with avelumab maintenance treatment), and was used to generate results regarding survival, cost-effectiveness and weights for severity modifier for the scenario relying on NICE SACT data, as shown below.

Using the above information, a set of cost-effectiveness scenario analyses was undertaken using information available from the SACT analyses on proportions using avelumab, time on treatment with avelumab and overall survival from start of platinum-based chemotherapy, replacing data from the EV-302 trial control arm (see Appendix B for details). Please note that the economic model still relies on information from EV-302 and other sources as described in the company submission, using the settings preferred by the committee.

Table 5 shows the summary results (see Appendix B Tables 12-21 for full cost-effectiveness results). Under the corrected base case, which corresponds to the EAG's and the committee's preferred assumptions, the criteria for the severity modifier are not met. As discussed in the original submission, the cost-effectiveness model, based on the EV-302 data, is likely to overestimate survival with platinum-based chemotherapy given the likely impact of subsequent therapies used in the trial but not available in the NHS (e.g., EV monotherapy) and potentially longer avelumab ToT in the trial. Also as discussed in the original submission, it is not feasible to remove the effect of unavailable treatments or longer use of avelumab given data limitations (see Addendum to company evidence submission: response to NICE requests of 16 January).

However, **using real-world data on survival outcomes from patients in the NHS in England (from both Astellas and NICE SACT analyses), the severity modifier is met in all scenarios.**

Results using NICE SACT Cohort 2, comprising only patients who had subsequent maintenance avelumab, are shown in order to illustrate a best-case scenario where all patients have subsequent avelumab. This scenario aims to represent the upper bound of survival outcomes if avelumab uptake is in all patients, much higher than observed in the data. The results are illustrative only and are likely to be an overestimate of survival if avelumab uptake was 100%. This is because patients in Cohort 2 necessarily survived to receive avelumab (i.e., survival outcomes are subject to immortal time bias) and were selected to receive avelumab given their response to chemotherapy and other prognostic characteristics. Nevertheless, even in this selected NICE SACT Analysis Cohort 2, the 1.2 severity modifier is met.

Table 6: Estimates of proportional QALY shortfall and weights for the severity modifier using the requested SACT analyses

Scenario	Estimated proportional shortfall	Severity modifier	ICER without modifier	ICER with 1.2 modifier
Corrected base case (EAG and committee's preferred assumptions)	0.84	1.0	[redacted]	[redacted]
Scenario 1: Corrected base case (EAG and committee's preferred assumptions, except Weibull for avelumab maintenance ToT)	0.84	1.0	[redacted]	[redacted]
Scenario 2: Astellas' SACT analyses – Combined cohorts A+B	0.88	1.2	[redacted]	[redacted]
Scenario 3: NICE SACT analysis – Cohort 1 (patients who did not have subsequent avelumab)	0.90	1.2	[redacted]	[redacted]
Scenario 4: NICE SACT analysis – Cohort 2 (patients who did have subsequent avelumab)	0.87	1.2	[redacted]	[redacted]

Abbreviations: EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; SACT, systemic anti-cancer treatment; ToT, time on treatment

Evidence from clinical experts

In the questionnaire, clinical experts were asked to estimate OS rates with platinum-based chemotherapy in NHS practice (Table 7). Average estimates at 5 and 10 years were higher than the extrapolation based on SACT data, but somewhat lower than the model base-case based on EV-302 data. However, there was a considerable range in estimates, which indicates the difficulty estimating small proportions accurately. In addition, some respondents indicated that estimating long-term disease-specific survival is difficult due to the advanced age and comorbidity profile of the average mUC patient.

Table 7 Clinician estimates of OS for platinum-based chemotherapy patients in the NHS

	3 years	5 years	10 years
Cost-effectiveness model	[redacted]	[redacted]	[redacted]
Average (mean) estimate	16%	10%	5%
Minimum estimate	10%	1%	0%
Maximum estimate	20%	15%	12%

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	Severity modifier in the appraisal of erdafitinib Based on the public committee slides available for the appraisal of erdafitinib, expected discounted QALYs after at least one line of therapy containing a PD-1 or PD-L1 inhibitor were estimated to be 0.415. However, the current economic 1L model, using the committee's preferred assumptions, estimates 0.95 QALYs (discounted) to be accrued in the platinum-containing chemotherapies arm post-progression. Although the label population for erdafitinib does not fully overlap with the post-progressed population, this indicates that predictions based on the EV-302 trial may overestimate survival in England. As an illustration, if 0.415 QALYs were accrued in the PBC arm post-progression (as estimated in the erdafitinib appraisal) and all else was equal, the proportional shortfall would be 0.88 and EV+P would qualify for the 1.2 severity modifier.
7	**DG Page 4: Current text: "This is because people in the clinical trial had subsequent treatments that are not currently recommended in the NHS and this was not adjusted for in the economic model".** This should be changed to "not fully adjusted for", as the cost of treatments was adjusted, but it was not possible to adjust for the impact of subsequent treatments on overall survival.
8	**DG Page 19: Current text: "But the committee understood that the company's model included a round up function**". To clarify, the model included the "round" function, i.e. rounding either up or down to the nearest one hundredth, it did not round upwards. It included rounding to two decimal points, as the proportional shortfall categories are provided by NICE with a precision of two decimal points (e.g.0.85).
9	**DG Page 19: Current text: "The company provided additional data showing that overall survival was lower for people who had subsequent treatments with taxanes (such as paclitaxel) compared with enfortumab vedotin monotherapy. But the data did not include the impact of other subsequent treatments that are relevant to the NHS, such as atezolizumab, sacituzumab and erdafitinib."** Astellas' argument was that the survival estimates for the platinum-based chemotherapy arm of the model based on the EV-302 trial are likely to be higher than what is expected in real life clinical practice because some subsequent treatments (principally EV monotherapy) in the trial are not available in England. The aim of providing the additional subgroup data by subsequent treatment use from the EV-302 trial was to demonstrate the potential impact of the use of EV monotherapy as subsequent therapy. Regarding atezolizumab, sacituzumab govitecan and erdafitinib: • The full impact (on both costs and survival) of atezolizumab as a subsequent treatment is captured in the economic model, therefore no additional data was provided. • Sacituzumab govitecan is not recommended by NICE for use in the NHS, therefore is not relevant for the NHS. Its appraisal by NICE for treating unresectable metastatic urothelial cancer was suspended in June 2024.[7] • Erdafitinib was recommended on 10 April 2025, within its marketing authorisation, for treating unresectable or metastatic urothelial cancer with susceptible FGFR3 genetic alterations in adults after at least 1 line of treatment for unresectable or metastatic cancer that included a PD-1 or PD-L1 inhibitor.[8] However, the expected prevalence of FGFR3

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	alterations in the unresectable/metastatic UC population, as stated in the draft guidance document, is only 16.6%. Therefore, only a small proportion of patients treated with EV+P in 1L will be eligible to receive erdafitinib as a 3L treatment (after 2L treatment with platinum-based chemotherapy), and so the implications of erdafitinib's availability for the economic modelling would be limited. To clarify, EV-302 data includes the efficacy impact of the subsequent treatments referred to by the draft guidance: erdafitinib was used by [redacted]% of patients in EV-302 platinum-based chemotherapy arm; sacituzumab govitecan was used by [redacted]% of patients; and atezolizumab was used by [redacted]%. In addition, [redacted]% received pembrolizumab as subsequent therapy. As pembrolizumab is not recommended by NICE in this indication, the calculation of the costs of subsequent therapies in the economic analysis assumed that these patients would have received atezolizumab in the NHS.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Appendix A: Report of the Astellas SACT analysis

Real-world evidence generation for a cohort of patients in England with a diagnosis of metastatic urothelial cancer (mUC)

Introduction

Urothelial cancer (UC) affects the cells that line the urinary system, which includes the bladder, urethra, ureters, and renal pelvis, although bladder cancer accounts for 90-95% of UC at diagnosis. People with unresectable or metastatic urothelial cancer (u/mUC) may experience urinary symptoms, lower back or abdominal pain, fatigue, and a general feeling of illness,[i] as well as weight loss, lack of appetite, and pain specific to the site of metastasis (e.g. bone pain).[ii,iii,iv]

U/mUC can have a significant impact on people's physical, mental, and social quality of life.[v] The proportion of people with bladder cancer that will be alive after five years as estimated by the National Cancer Institute in the US is approximately 39.5% for locally advanced disease and 8.8% for metastatic disease.[vi] Of people diagnosed with BC in England in 2016-2020, 64.4% of those diagnosed with stage 3 were alive one year later, and 29.2% of those diagnosed at stage 4.[vii]

Platinum-based combination chemotherapy is the current standard treatment for u/mUC in the NHS.[viii] Cisplatin-based chemotherapy (usually cisplatin + gemcitabine) is the first choice treatment,[viii] but it is not suitable for everyone because of its side effects. Around half of patients with u/mUC are not eligible to receive it due to older age, poor general health, or other conditions such as kidney problems.[ix] Most patients who are not able to receive cisplatin receive carboplatin + gemcitabine instead, in line with NICE guidelines.[viii]

Enfortumab vedotin in combination with pembrolizumab is a new treatment option for adults with previously untreated u/mUC who are eligible to have platinum-containing chemotherapy. The main clinical trial studying this therapy was the study EV-302, which compared enfortumab vedotin in combination to pembrolizumab to platinum-based chemotherapy.[x] The EV-302 clinical trial found that EV+P almost doubled progression-free survival and overall survival, compared with platinum-based chemotherapy. Treatment with EV+P also resulted in a significantly higher response rate (percentage of patients whose cancer reduced [partial response] or disappeared [complete response] following treatment) compared with chemotherapy.[x]

The context for this real-world evidence generation is the technology appraisal by the National Institute of Health and Care Excellence (NICE) of enfortumab vedotin in combination with pembrolizumab.[xi] Two evidence gaps were identified: (i) the life expectancy of patients with this condition treated in England's NHS, and (ii) the extent to which avelumab maintenance treatment is used in clinical practice. Astellas wishes to investigate whether routinely collected NHS data could address these evidence gaps, and therefore better inform the recommendation decision.

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Objectives

The objectives are to:

- To estimate overall survival (OS) from the start of first-line therapy of patients with mUC, stratified by whether avelumab maintenance treatment was routinely available on the NHS:
    - Cohort A: Patients started first-line platinum-based systemic anticancer therapy between 1-April-2021 and 30-April-2022, to reflect clinical practice prior to avelumab recommendation but in all else similar to current practice (i.e., after NICE recommendation of atezolizumab [TA525] in June 2018 and pembrolizumab's exit of the Cancer Drugs Fund [TA692] in April 2021).
    - Cohort B: Patients started first-line platinum-based systemic anticancer therapy after 1-May-2022, to reflect clinical practice after avelumab recommendation.
- To estimate the number and proportion of patients in each cohort who received avelumab following first-line platinum-based chemotherapy.
- To estimate the time on avelumab maintenance treatment, in those patients in Cohort B who received avelumab following first-line platinum-based therapy
- To estimate baseline characteristics of patients in both cohorts.
- To report the attrition table.

Methods

The project will utilise the latest administrative data available at the time of analysis. Patients with mUC will be captured from the National Cancer Registration Dataset (NCRD), with data on systemic therapy then extracted from the Systemic Anti-Cancer Therapy (SACT) dataset. Vital status information will be obtained directly from the NCRD.

With analytical work set to start in April 2025, it is anticipated that finalised cancer registrations will be available up to the end of 2022, with vital status and linked SACT data both present to the end of July 2024. If linked datasets are refreshed by the time analysis starts, the end of patient follow-up will be extended accordingly.

Patient follow-up will run from entry into the cohort to the earliest of embarkation (i.e., movement of the patient outside England), death from any cause, or the end of the study period (July 2024).

Selecting patients

It is intended that **Cohorts A** and **B** will be composed of patients who were diagnosed with mUC and went on to initiate first-line platinum-based therapy between pre-specified dates. These two cohorts will be constructed by following the steps described below. Table 1 reports the inclusion/exclusion criteria and their rationale.

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Table 1: Inclusion/exclusion criteria and their rationale

Inclusion/exclusion criteria	Rationale
Adults (age ≥ 18 years)	To align with EV-302 trial
Diagnosed with de novo metastatic urothelial cancer (stage IV)	To align with EV-302 trial population, and because difficult to reliably identify patients with locally advanced unresectable urothelial cancer
Received platinum-based systemic anticancer chemotherapy after diagnosis or up to 30 days before diagnosis and as the first recorded treatment following diagnosis	To align with EV-302 trial population and ensure that the cohort includes only patients who received platinum-based chemotherapy for metastatic urothelial cancer as the first line treatment
Cohort A: Pre-avelumab recommendation and post-pembrolizumab exit from CDF	
Received platinum-based systemic anticancer therapy from 1-April-2021 to 30-April-2022	To reflect clinical practice prior to avelumab recommendation but in all else similar to current practice (i.e., after NICE recommendation of atezolizumab [TA525] in June 2018 and pembrolizumab's exit of the Cancer Drugs Fund [TA692] in April 2021)
Cohort B: Post-avelumab recommendation	
Received platinum-based systemic anticancer chemotherapy after 1-May-2022	To reflect clinical practice after avelumab recommendation

Creating an underlying cohort of patients with mUC

First, UC diagnoses will be defined in accordance with the site codes used by the NDRS Get Data Out programme (Table 2). There will be no requirement to consider morphologies.

Table 2: Get Data Out site definitions

Tumour type	Site code(s)
Renal pelvis*	C65 or D41.1 or (D09.1† with ICD-O-3 code C65).
Ureter	C66 or D41.2 or (D09.1 with ICD-O-3 code C66)
Bladder	C67 or D09.0 or D41.4
Urethra	C68 or (D09.1 with ICD-O-3.1 code C68)
*Historically, transitional cell carcinomas of the renal pelvis were occasionally miscoded to the kidney. This has been resolved for registrations from 2017 onwards. †ICD-10 code D09.1 refers to "Carcinoma in situ of other and unspecified urinary organs". To identify the specific site of these tumours, the accompanying ICD-O-3.1 site is used to give the location of the tumour.	

From here, patients will be selected into the underlying mUC cohort if diagnosed:

- Adults, aged at least 18 years at the time of diagnosis
- With any of the tumour types reported in Table 2;
- At stage IV (i.e., metastatic).[1]
- Between the years 2020 and 2022.
- By any route other than death certificate (i.e., had an opportunity to be offered treatment).
- Within a patient who was resident in England at the time of diagnosis.
- With robust vital status data (i.e. coded to A, D, or X and safe to use in survival analyses).

Should a patient have received multiple primary diagnoses of mUC between 2020 and 2022, the first such tumour will be selected.

[1] A restriction will not be applied by M stage given that NHS guidance for bladder cancer staging (which comprises the majority of patients with urothelial cancer) is that patients with M0 tumours are classified as stage four (IVA) if they have T4b and N0 tumours – see https://digital.nhs.uk/ndrs/data/cancer-data-training-materials/staging-sheets/urinary-bladder-tumours. Additionally, in the EV-302 trial of enfortumab vedotin with pembrolizumab, patients with only lymph nodes metastasis (i.e., N1 and M0) were considered metastatic, therefore inclusion of these patients aligns with the trial too.

Linking to the SACT dataset

The underlying table of mUC patients will be linked to the SACT dataset. As the SACT dataset is joined at a patient level, the following linkage rules will be applied in line with NDRS operating procedures:

- For mUC patients with no evidence of a primary non-UC cancer within +/- 18 months of the selected mUC, all SACT data will be extracted where dated between up to 30 days prior to diagnosis and the end of the study period (July 2024).

- For mUC patients with evidence of a primary non-UC cancer within +/- 18 months of the selected mUC, SACT data will be extracted where dated between up to 30 days prior to diagnosis and the end of the study period (July 2024) and recorded in SACT against an applicable ICD-10 code (i.e., C65, C66, C67, C68, D41, D09). This rule is applied to avoid extracting therapies that are associated with the treatment of a different primary diagnosis.

First-line platinum-based therapy

With SACT data having been extracted, mUC patients will be restricted to those whose first documented regimen was platinum based (i.e., contained the string 'PLATIN').

The start date of the platinum-based regimen will be equal to the earliest nested cycle or administration date, else the regimen start date. Cycle and administration dates are preferred over the recorded start date of the regimen as they offer a more accurate reflection of when therapy was delivered to patients.

If a patient switches from a cisplatin regimen to a carboplatin regimen and there is no other changes this will not be classed as a switch if this change happens within 4 weeks of the end of first line. 4 weeks were selected because the cycle length is 3 weeks, therefore allowing 1 additional week in case there are delays to initiating treatment.

Assigning patients to Cohorts A and B

Patients whose first documented regimen was platinum-based will then be assigned to Cohort A or Cohort B as follows:

- Cohort A: The first platinum-based regimen was dated between 01/04/2021 and 30/04/2022

- Cohort B: The first platinum-based regimen was dated between 01/05/2022 and 31/07/2024.

Study outputs

A series of outputs will be reported for the two cohorts. These outputs and their expected derivations are detailed below.

Overall survival (OS)

OS from the initiation of first-line platinum-based therapy will be reported at an aggregate level for both **Cohort A** and **B** per the definition in Table 3.

For each aggregate OS output, cumulative time at risk and a count of failure events will be reported alongside median survival. Point estimates and their 95% confidence intervals will be reported at 6, 12, 24, 36, 48, and 60 months following index and supplemented by accompanying Kaplan-Meier plots.

Table 3 Time to event statistics

Outcome	Time at risk	Failure
OS	From the start date of the first documented platinum-based regimen (T0) to the earliest of death, embarkation, or the end of the study period.	All-cause death.

Key: OS, overall survival

Alongside the release of aggregate data, an application will be made to the NDRS Caldicott Guardian for the release of an OS dataset that will contain the following individual patient data:

- A pseudonymised patient identifier
- Time at risk (months)
- A binary failure indicator (0,1).

The release of individual patient data is conditional on a privacy impact assessment and sign-off by NDRS via the Caldicott Guardian.

Should the Caldicott Guardian refuse the release of the individual patient data described above, OS survivor functions will be extrapolated within HDI using parametric survival models constructed in R using the *flexsurv* package.

The following standard parametric distributions will be applied: exponential, Weibull, log-logistic, log-normal, generalised gamma and Gompertz.

For each model, the parameterisation (point estimates, standard errors and variance-covariance matrix) will be reported alongside standard goodness of fit statistics (AIC and BIC). Kaplan-Meiers will also be produced with the parametric functions overlaid.

In line with NDRS anonymisation requirements, all time-at-risk outputs will be truncated when the at-risk population reaches n<10.

Receipt of avelumab

The planned treatment will necessitate the identification of avelumab therapy. Avelumab regimens will only be considered where initiated between one day after the start of the first-line platinum-based regimen and up to 43 weeks from the start of the first-line platinum-based regimen. This is because platinum-based chemotherapy is given for up to six three-weekly cycles although patients may have longer time between cycles to manage toxicities, and avelumab can be started up to 10 weeks from

the date of last chemotherapy.[xii] This restriction avoids the inclusion of off license avelumab use and use of avelumab in other licensed indications.

Following the same rules as for the platinum-based regimens, the start of each avelumab regimen will be equal to the earliest nested cycle or administration date, else the start date of the regimen. The end date of the regimen will be equal to the last observed cycle or administration date for the regimen.

If multiple consecutive avelumab regimens are documented within a patient, these will be merged and treated as part of the same course of avelumab treatment if the gap between the end of the former avelumab regimen and the start of the latter avelumab does not exceed 14 weeks. 14 weeks was selected given NHS England criteria that, where a treatment break of more than 12 weeks beyond the expected two-weekly cycle length is needed, a treatment break form should be completed.[xii]

Counts and proportions will be reported for the numbers of patients in **Cohort A** and **B** who received avelumab therapy.

Time on avelumab

Of the subset of patients in **Cohort B** who were found to have received avelumab after the start of first-line platin-based treatment, the following time-to-event analysis was conducted (Table 4).

Table 4: Time on avelumab treatment

Outcome	Time at risk	Failure
Time on avelumab	From the derived start date of the course of avelumab therapy (T0) to the earliest of death, embarkation, the end of the study period or the last known date of avelumab treatment.	End of avelumab treatment from any cause.

The same aggregate-level outputs will be provided for this output as for OS in Section 5.2.1.1 (i.e., tabular statistics and an accompanying Kaplan-Meier plot).

Attrition table and Baseline characteristics

Finally, the attrition table for the cohort definition and a series of patient and tumour characteristics will be reported for Cohorts A and B. These are summarised in Table 5 and include patient age, tumour site, Index of Multiple Deprivation (IMD) and performance status.

Table 5: Baseline patient and tumour characteristics outputs

Characteristic	Definition
Patient characteristics	
Age at index date	Obtained from the NCRD and reported both as a continuous measure (mean and standard deviation; median and range) and per the following categorisation:

	• <65 years • 65-74 years • ≥75 years
Self-reported gender	Obtained from the NCRD and represents self-stated gender at the time of diagnosis, categorised as: • Male • Female
IMD quintile of residence	The IMD ranks Lower Layer Super Output Areas (regions with an average population of circa 1,500 people or 650 households) in order of deprivation according to seven weighted area-level indices, including income, employment, education, health, crime and housing. Greater weight is placed on income and employment. These data will be obtained from the NCRD. For diagnosis years 2014 onwards, 2019 deprivation quintiles will be used in accordance with national guidance and coded as follows: • Quintile 1 (most deprived) • Quintile 2 • Quintile 3 • Quintile 4 • Quintile 5 (least deprived)
Performance status at index	ECOG performance status at index (i.e., at initiation of the first platin-based regimen) will be extracted from the SACT dataset. Performance status will be categorised as: • 0 • 1 • 2 • 3 • 4 • Unknown
Duration of follow-up (months)	Derived as the time (in months) between the date of cancer diagnosis and the end of follow-up.
Ethnicity	Extracted from the NCRD and categorised in accordance with the Office for National Statistics definitions: • Asian, Asian British, Asian Welsh • Black, Black British, Black Welsh, Caribbean or African • Mixed or Multiple • White • Other ethnic group
Tumour characteristics	

Tumour site	Extracted from the NCRD and to be reported to according to the following categories: • Renal pelvis • Ureter • Bladder • Urethra

Key: ECOG, Eastern Cooperative Oncology Group; IMD, Index of Multiple Deprivaiton; NCRD, National Cancer Registration Dataset.

Data protection and ethics

The project is descriptive in nature and involves a secondary use of data. No ethics approval is therefore required.

However, the analysis of NDRS-managed data is conditional on sign-off by the NDRS Project Review Panel. HDI will target the next available panel (03/04/2025). The subsequent panel may be too late in the month to turnaround any analytical milestones (18/04/2025), but it may be possible to obtain ad hoc sign-off via email if the 03/04/2025 panel is missed or cancelled.

It is anticipated that the underlying mUC population will be >1,000 patients. Consequently, no statistical disclosure control will be applied to any aggregate outputs beyond the truncation of time to event outputs once the at-risk population falls to n<10.

As previously mentioned, the release of individual patient data can only take place if approved by the NDRS Caldicott Guardian. The release is subject to a privacy impact assessment.

Survival analysis

Individual patient-level data was provided to Astellas. However, due to the requirement to preserve confidentiality of the data, survival times were rounded to the nearest 0.5 months.

Parametric functional forms

In line with guidance from National Institute of Care and Health Excellence (NICE) Decision Support Unit (DSU) Technical Support Document (TSD) 14, several standard parametric functional forms were used to model and extrapolate time to event (TTE) data for each outcome of interest:

- Exponential
- Gompertz
- Weibull
- Log-logistic
- Log-normal
- Gamma
- Generalised gamma

Each of the standard parametric models makes assumptions about the hazards over time:

- Exponential models assume that the hazard remains constant over time
- Weibull models assume that hazards monotonically increase or decrease; that is there are no turning points and as time increases the hazard either consistently increases or decreases for larger values of time
- Gompertz models assume that hazards monotonically increase or decrease, but the rate of change is assumed to be exponential
- Log-logistic, log-normal and generalised gamma models can represent hazards that monotonically decrease, or that initially increase and then decrease (one turning point). The generalised gamma can also represent hazards that initially decrease and then increase.

Selection of base case functional form

A model selection algorithm followed recommendations in NICE DSU TSD 14.

The selection of the base case functional form for each TTE outcome was based on the following criteria:

- Visual inspection of goodness of fit to observed data in Kaplan-Meier (KM) plots;
- Visual inspection of KM data and diagnostic plots, including the log-cumulative hazard plot;
- Objective statistical measures of goodness of fit to observed KM data: AIC and BIC statistics;
- The clinical plausibility of survival extrapolations beyond observed KM data, assessed through relevant published observational data and real-world evidence (if available);
- Consistency with external data and expert opinion (if available).

The following diagnostic plots also helped determine which parametric distribution best fits the observed data:

- Log(-log(S(t)) against log time
    - Labelled in figures as ‘Weibull and Exponential’.
    - If the plotted line is straight, a Weibull model may be appropriate.
    - If the slope of the line is one, an exponential model may be appropriate.
- Log(-log(S(t)) against time
    - Labelled in figures as ‘Gompertz’.
    - If the plotted line is straight, then a Gompertz model may be appropriate.
- Log odds of S(t) against log time
    - Labelled in figures as ‘Log-logistic’.
    - If the plotted line is straight, then a log-logistic model may be appropriate.
- Inverse standard normal (1-S(t)) against log time
    - Labelled in figures as ‘Log-Normal’.
    - If the plotted line is straight, then a log-normal model may be appropriate.

Statistical software

The analysis was conducted in R version 4.4.2. KM plots were produced using *survminer* package; and the package *flexsurv* was used for parametric survival analysis.

Results

Observed overall survival

Table 6 shows the descriptive statistics for OS by cohort, and Table 7 shows the Kaplan-Meier survival estimates. Figure 1 shows the Kaplan-Meier plot for OS for both cohorts. Cohort A (pre-avelumab) had the first platinum-based regimen dated between 01/04/2021 and 30/04/2022. Cohort B (post-avelumab) had the first platinum-based regimen dated between 01/05/2022 and 31/07/2024.

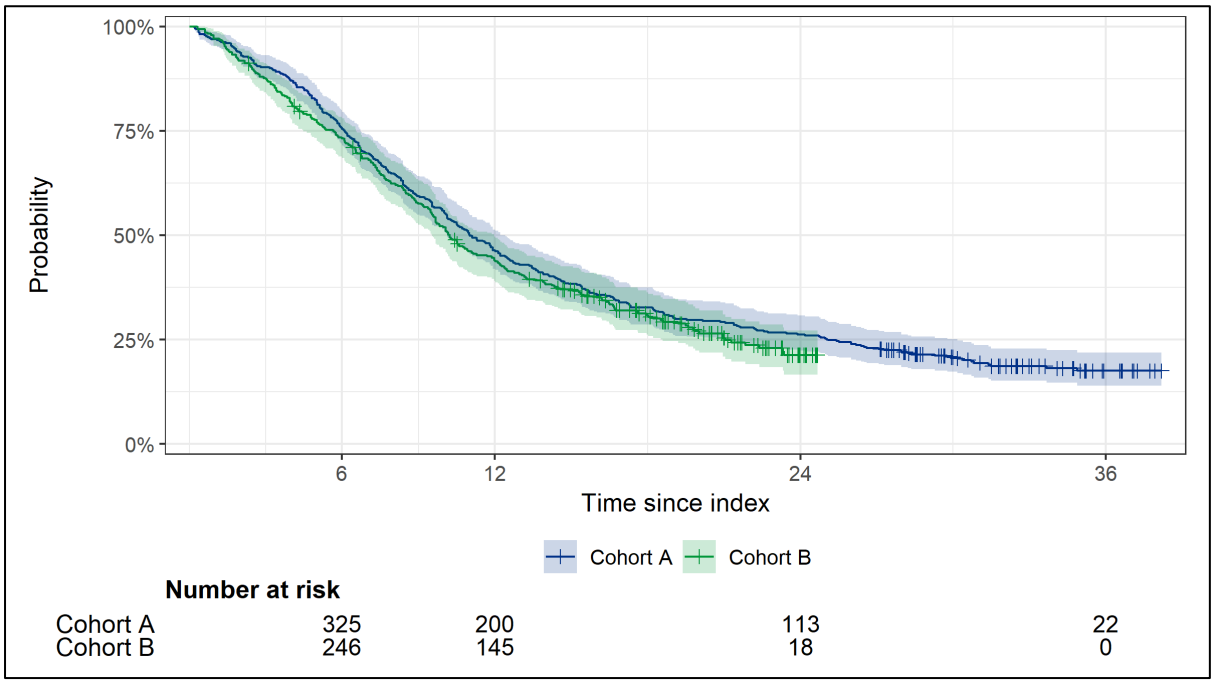
Table 6: Overall survival descriptives

Descriptives	Cohort A (N=431)	Cohort B (N=340)
Median (95%CI)	11.02 (10.13 - 12.2)	10.23 (9.54 - 11.97)
Mean (SE)	16.2 (0.6)	15.8 (0.8)
Min	0.2	0.33
Max	39.84	26.78

Table 7: Kaplan-Meier estimates for overall survival

Time point	Patients at risk	Events	Survivor function (95%CI)
Cohort A (N=431)			
Survival at 6 months	325	106	75.41 (71.45-79.58)
Survival at 12 months	200	125	46.4 (41.93-51.36)
Survival at 24 months	113	87	26.22 (22.38-30.72)
Survival at 36 months	22	30	17.52 (14.01-21.9)
Cohort B (N=340)			
Survival at 6 months	246	91	73.12 (68.55-78)
Survival at 12 months	145	97	44.01 (39-49.67)
Survival at 24 months	18	59	21.27 (16.63-27.2)

Figure 1: Kaplan-Meier plot of overall survival from initiation of first platinum treatment for both Cohorts A and B



Receipt of avelumab

Table 8 shows the count of patients started on avelumab after first line platinum-based chemotherapy.

Table 8: Patients started on avelumab after first line platinum-based chemotherapy

Cohort	Patients started on avelumab	
	Number	Proportion
Cohort A (N=431)	76	18%
Cohort B (N=340)	68	20%
Both cohorts (N=771)	144	19%

Time on avelumab

Table 9 shows the descriptive statistics for avelumab time on treatment for cohort B, and Table 10 shows the Kaplan-Meier estimates. Figure 2 shows the Kaplan-Meier plot avelumab time on treatment.

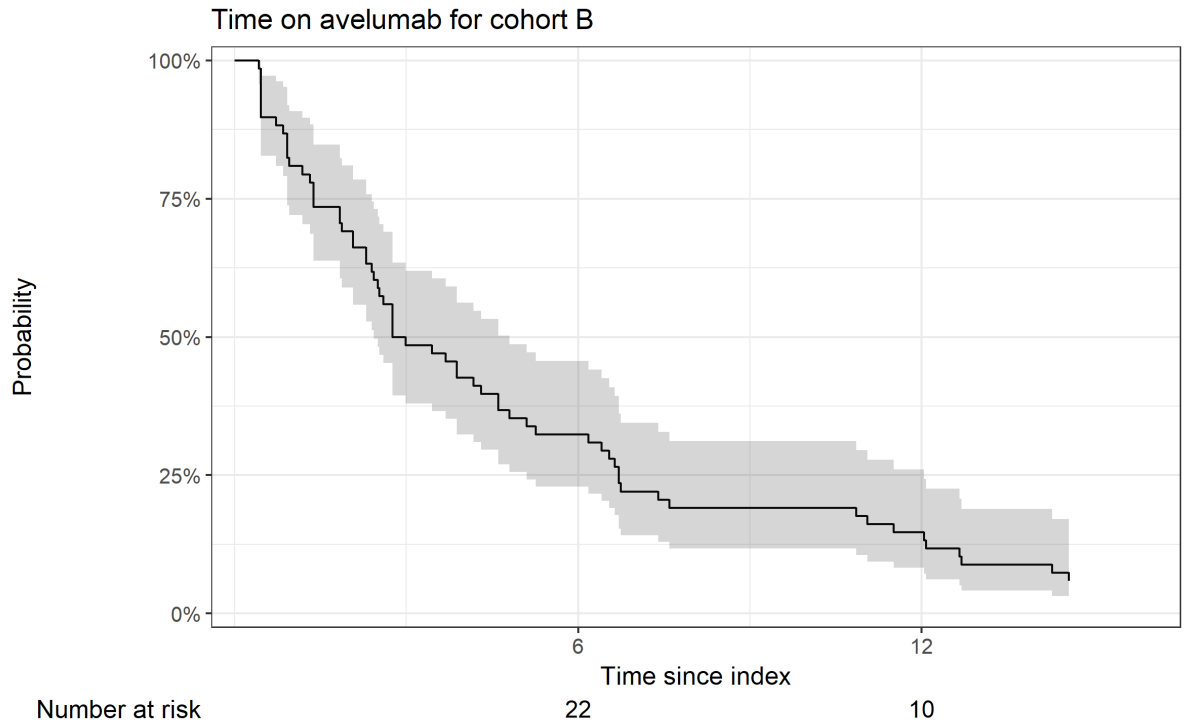
Table 9: Avelumab time on treatment descriptives (cohort B)

Descriptive	value
Median (95% confidence interval)	2.88 (2.43 - 4.8)
Mean (standard error)	5.1 (0.6)
Min	0.43
Max	20.72

Table 10: Kaplan-Meier estimates for time on avelumab (cohort B)

	Patients at risk	Events	Survivor function (95%CI)
Survival at 6 months	22	46	32.35 (22.94-45.62)
Survival at 12 months	10	12	14.71 (8.3-26.07)

Figure 2: Kaplan-Meier plot for time on avelumab (cohort B)



Baseline characteristics

Table 11 shows the characteristics of the cohort.

Attrition table

Table 12 shows the attrition table.

Switch between platinum-based therapies

Table 13 shows the descriptive statistics of patients who switched from cisplatin to carboplatin.

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Table 11: Cohort characteristics

Characteristic		Main Cohort		Subcohorts			
				Cohort A		Cohort B	
Total Patients; N		771		431		340	
Age	Mean, standard deviation	68.2	10.3	68.3	10.6	68.2	9.8
	Median	70		71		70	
	Q1, Q4	63	75	63	75.5	63	75
	Minimum, Maximum	24	88	24	88	29	87
Age group (years); N, %	<65 years	237	30.7	127	29.5	110	32.4
	65-70 years	314	40.7	177	41.1	137	40.3
	>= 75 years	220	28.5	127	29.5	93	27.4
Self-reported gender; N, %	Female	247	32	140	32.5	107	31.5
	Male	524	68	291	67.5	233	68.5
Index of Multiple Deprivation quintile of residence; N, %	1 - most deprived	133	17.3	68	15.8	65	19.1
	2	148	19.2	86	20	62	18.2
	3	162	21	94	21.8	68	20
	4	154	20	84	19.5	70	20.6

Characteristic		Main Cohort		Subcohorts			
				Cohort A		Cohort B	
	5 - least deprived	174	22.6	99	23	75	22.1
Performance status at start of first regimen; N, %	0	194	25.2	125	29	69	20.3
	1	403	52.3	216	50.1	187	55
	2	79	10.2	39	9	40	11.8
	3	3	0.4	1	0.2	2	0.6
	Unknown	92	11.9	50	11.6	42	12.4
Duration of follow-up (months)	Mean, standard deviation	13.5	9.8	15	11.1	11.5	7.3
	Median	10.5		11.0		10.1	
	Q1, Q4	5.9	19.4	6.1	25.1	5.3	17.6
	Minimum, Maximum	0.2	39.8	0.2	39.8	0.3	26.8
Ethnicity; N, %	Asian, Asian British, Asian Welsh	15	1.9	10	2.3	5	1.5
	Black, Black British, Black Welsh, Caribbean or African	15	1.9	7	1.6	8	2.4
	Mixed or Multiple	3	0.4	1	0.2	2	0.6
	Not stated	32	4.2	18	4.2	14	4.1
	Other ethnic group	48	6.2	20	4.6	28	8.2
	White	658	85.3	375	87	283	83.2

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Characteristic		Main Cohort		Subcohorts			
				Cohort A		Cohort B	
Tumour site; N, %	Bladder	415	53.8	239	55.5	176	51.8
	Renal pelvis	209	27.1	117	27.1	92	27.1
	Ureter	119	15.4	63	14.6	56	16.5
	Urethra	28	3.6	12	2.8	16	4.7

Table 12: Attrition

Inclusion criteria	2020-2021	2022	Combined	Proportion
Patients with a stage IV urothelial cancer diagnosis in England.	2632	1213	3845	100%
Had linkage to a Systemic Anti-Cancer Therapy record	839	432	1271	33%
Received a platinum-based regimen between one month prior and any point after diagnosis.	443	383	826	21%
Received platinum-based systemic anticancer chemotherapy as the first recorded treatment.	398	373	771	20%
Cohort A: Received platinum based systemic anticancer chemotherapy as the first recorded treatment between 2021-04-01 and 2022-04-30.	381	50	431	11%
Cohort B: Received platinum based systemic anticancer chemotherapy as the first recorded treatment between 2022-05-01 and 2024-07-31.	17	323	340	9%

Table 13: Descriptive statistics on the patients who switched from cisplatin to carboplatin

Quantity	**value**
Count of patients that had a switch between platinum-based therapies	178
Count of patients captured in the 4 week rule	145 (81%)
Mean time between the last dose of initial platinum-based therapy and the 1st subsequent platin therapy, in days	18.94
Median time between the last dose of initial platinum-based therapy and the 1st subsequent platin therapy, in days	16.5
Lower Quartile time between the last dose of initial platinum-based therapy and the 1st subsequent platin therapy, in days	14
Upper Quartile time between the last dose of initial platinum-based therapy and the 1st subsequent platin therapy, in days	27
Inter Quartile Range time between the last dose of initial platinum-based therapy and the 1st subsequent platin therapy, in days	13

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Survival curve fitting

OS (Astellas SACT cohort A)

Descriptive analysis

Figure 3 shows the Kaplan Meier plot for cohort A.

Figure 3: Kaplan Meier Plot: OS (Astellas SACT cohort A)

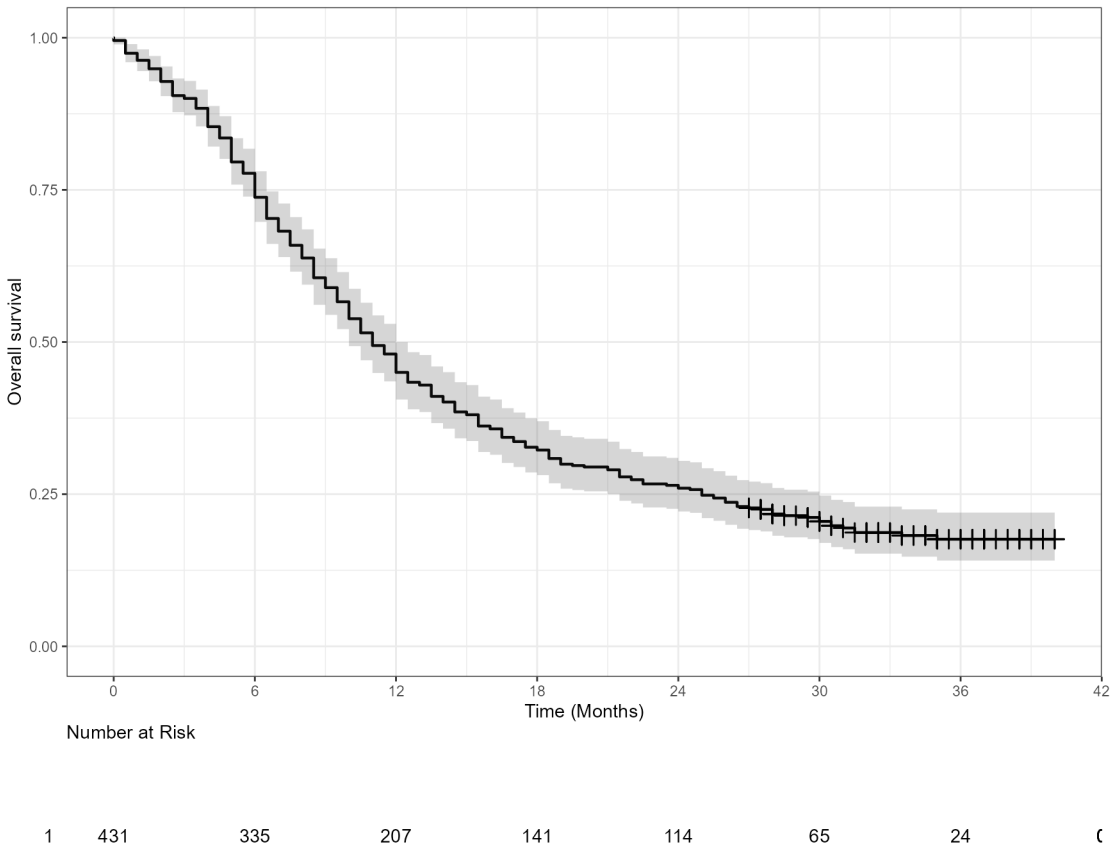

Table 14 shows the mean survival time (months) based on each fitted curve for Cohort A.

Table 14: Estimated mean overall survival time by survival distribution (Astellas SACT cohort A)

Distribution	Mean survival time
Exponential Ind.	18.44
Weibull Ind.	18.33
Gompertz Ind.	19.79
Log-logistic Ind.	21.05
Log-normal Ind.	25.45
Gamma Ind.	18.30
Generalised gamma Ind.	18.68

Abbreviations: Ind – individually fitted

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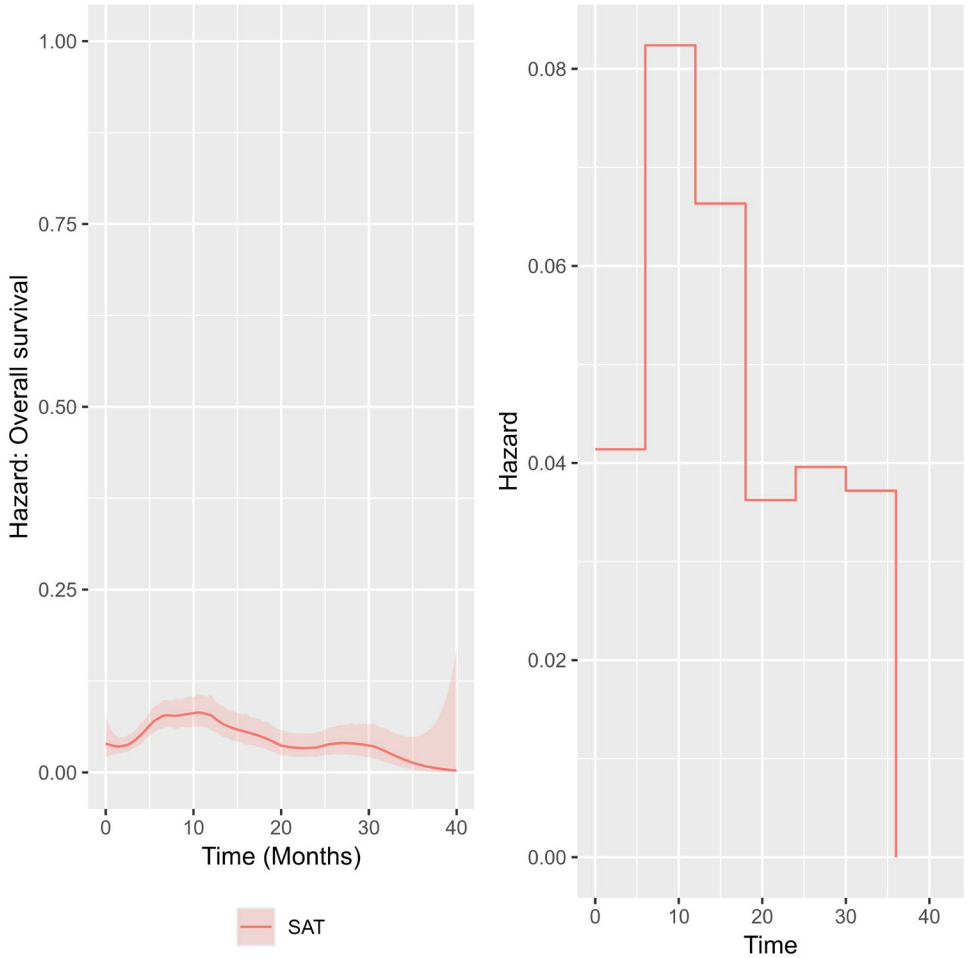
Hazards Assessment

Figure 4 shows the hazard plots.

Figure 4: Smoothed and piecewise hazard Plots OS (Astellas SACT cohort A)



Parametric Fit Diagnostics

Figure 5 shows diagnostic plots for treatment effects on various effect scales.

Figure 5: Individual Diagnostic Plots: OS (Astellas SACT cohort A)

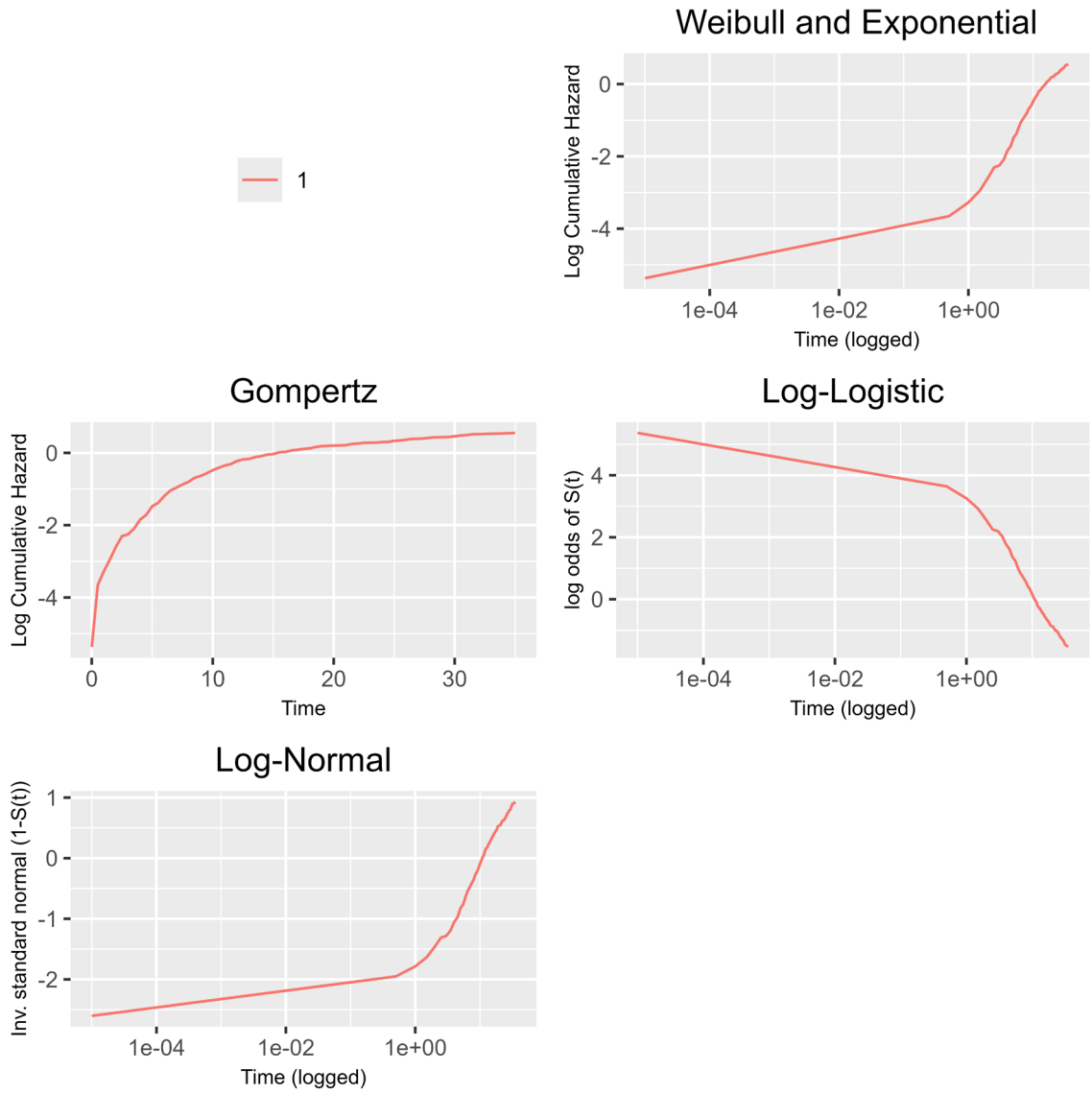


Figure 6 shows the fit for each parametric model to the observed data.

Figure 6: Parametric Fit Plots OS (Astellas SACT cohort A)

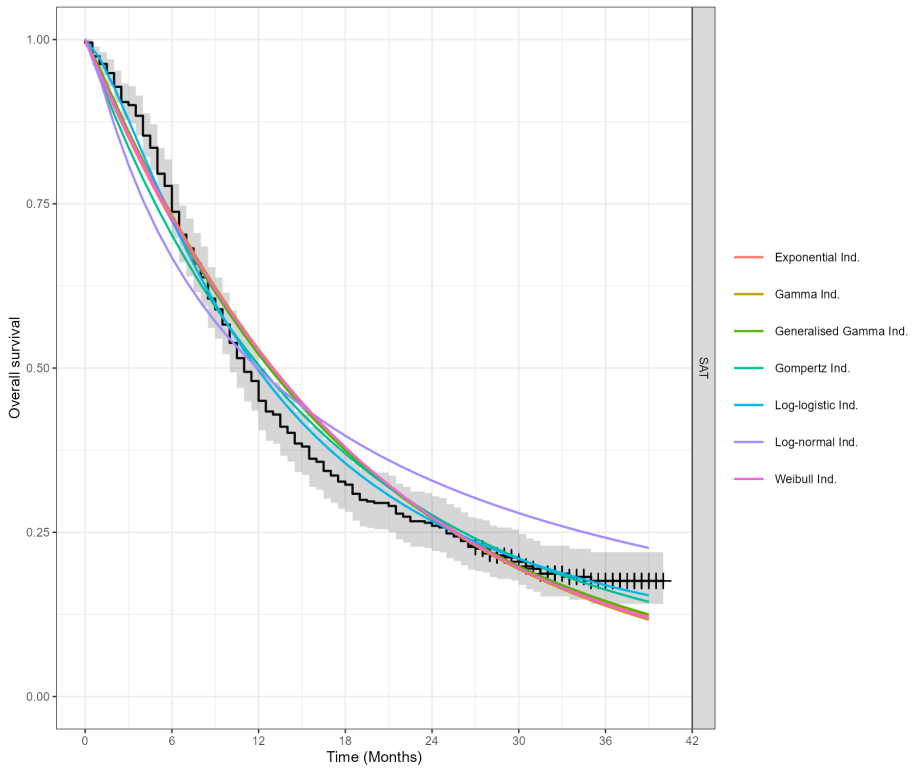


Figure 7 shows the predictions for each parametric model extrapolated beyond the observed data.

Figure 7: Parametric Fit Plots with Extrapolation OS (Astellas SACT cohort A)

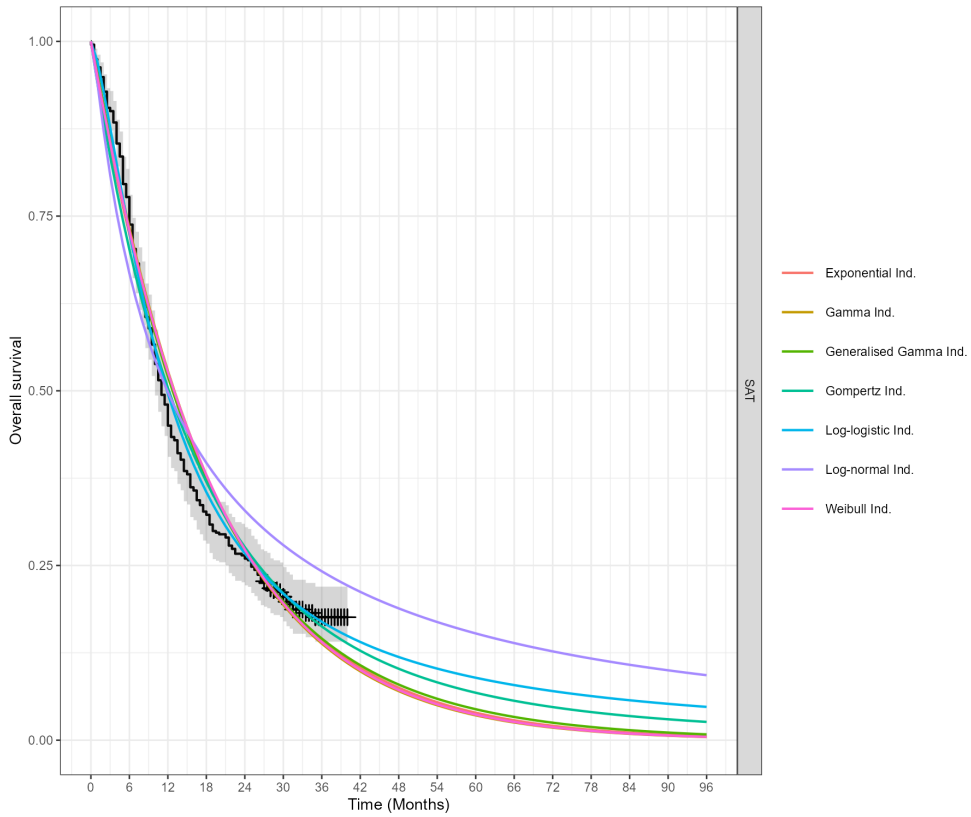


Figure 8 shows the hazards for each parametric model and the observed data.

Figure 8: Parametric Hazard Plots OS (Astellas SACT cohort A)

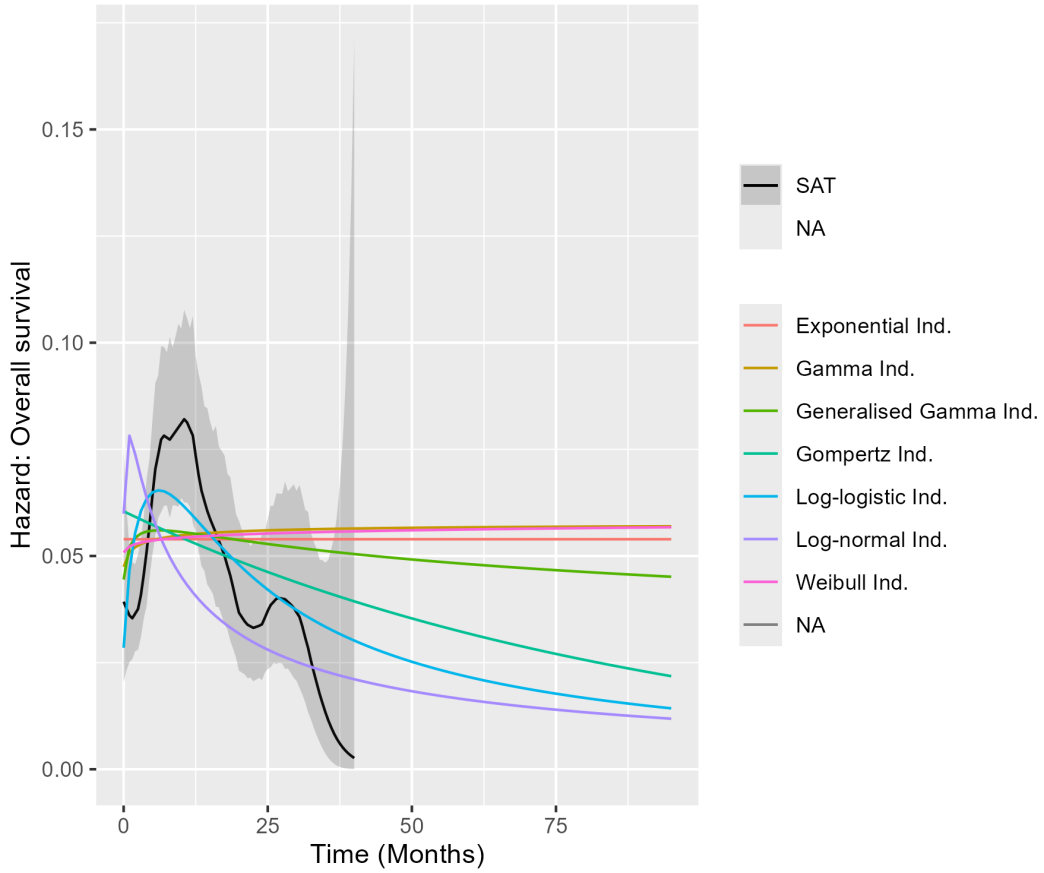


Table 15 shows the fit statistics for each parametric model.

Table 15: Parametric Fit Statistics OS (Astellas SACT cohort A)

Functional form	AIC	BIC
Exponential Ind.	2730.4 (3)	2734.5 (2)
Weibull Ind.	2732.2 (6)	2740.3 (5)
Gompertz Ind.	2729.2 (2)	2737.3 (3)
Log-logistic Ind.	2718.1 (1)	2726.2 (1)
Log-normal Ind.	2864.7 (7)	2872.9 (7)
Gamma Ind.	2731.7 (4)	2739.9 (4)
Generalised gamma Ind.	2732 (5)	2744.2 (6)

Bayesian Information Criteria (BIC), Akaike Information Criteria (AIC), Lower values indicate better fit for AIC and BIC. Rankings are given in parentheses.

OS (Astellas SACT cohort B)

Descriptive analysis

Figure 9 shows the Kaplan Meier plot.

Figure 9: Kaplan Meier Plot: OS (Astellas SACT cohort B)

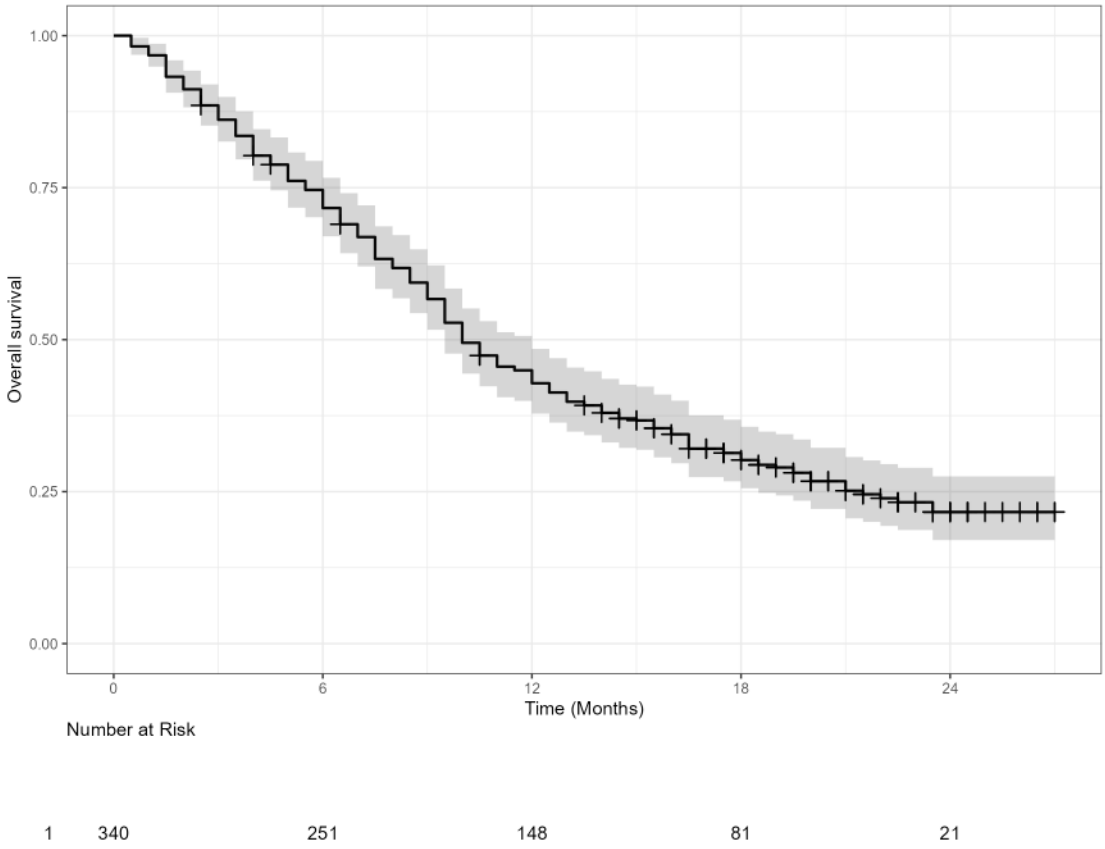


Table 16 shows the mean survival time (months) based on each fitted curve for Cohort B.

Table 16: Estimated mean overall survival time by survival distribution (Astellas SACT cohort B)

Distribution	Mean survival time
Exponential Ind.	15.76
Weibull Ind.	14.76
Gompertz Ind.	14.80
Log-logistic Ind.	17.76
Log-normal Ind.	17.79
Gamma Ind.	14.89
Generalised gamma Ind.	16.38

Abbreviations: Ind – individually fitted

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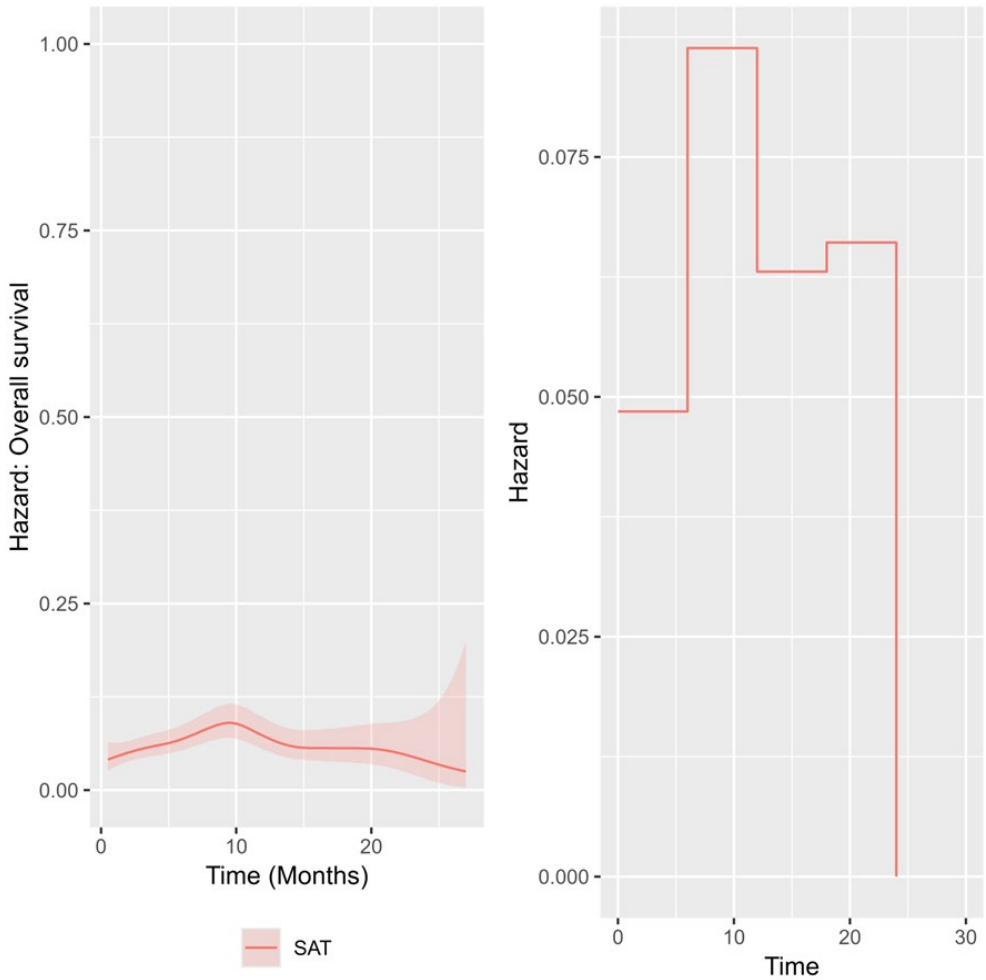
Hazards Assessment

Figure 10 shows the hazard plots.

Figure 10: Smoothed and piecewise hazard Plots OS (Astellas SACT cohort B)



Parametric Fit Diagnostics

Figure 11 shows diagnostic plots for treatment effects on various effect scales.

Figure 11: Individual Diagnostic Plots: OS (Astellas SACT cohort B)

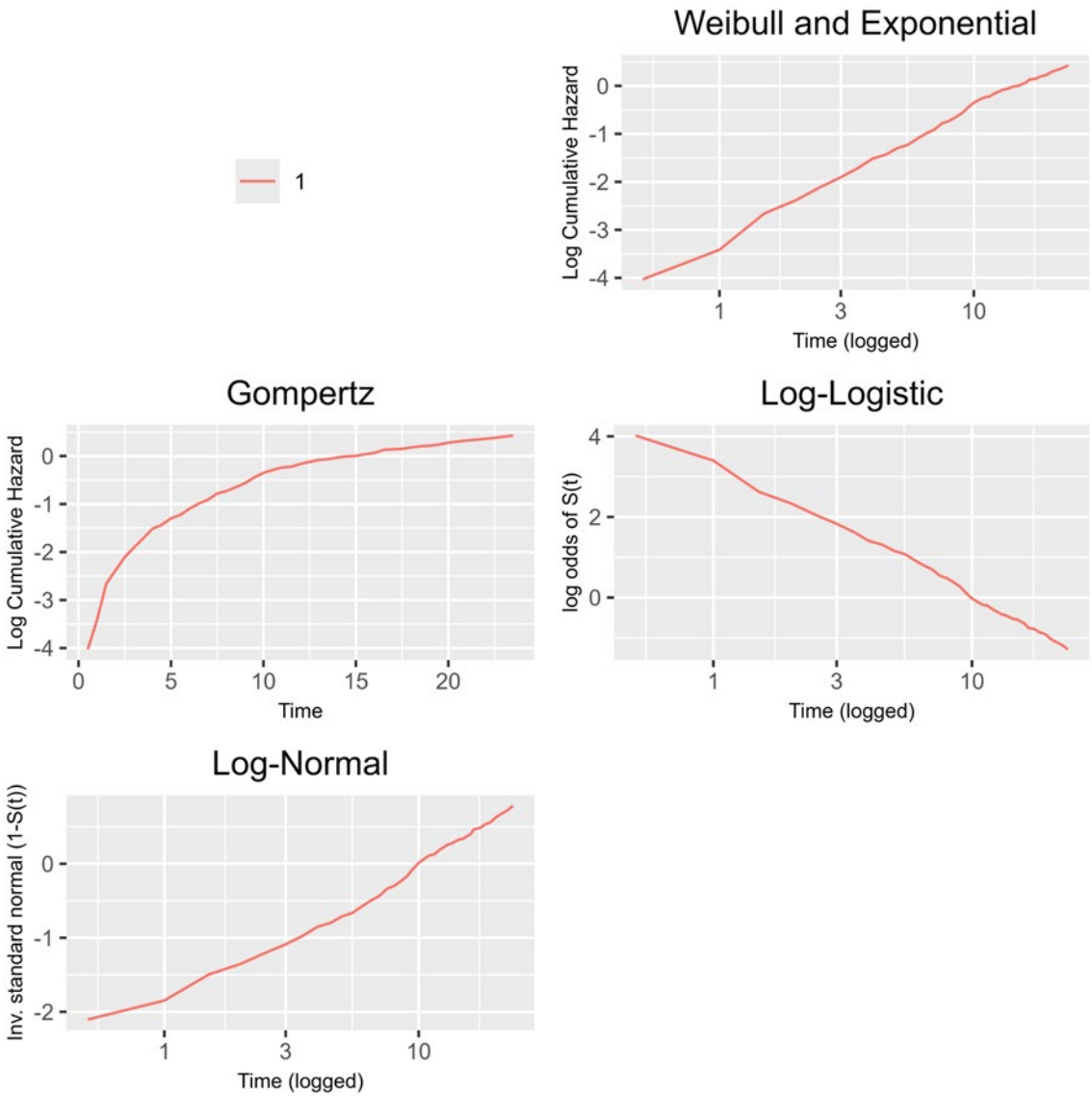


Figure 12 shows the fit for each parametric model to the observed data.

Figure 12: Parametric Fit Plots OS (Astellas SACT cohort B)

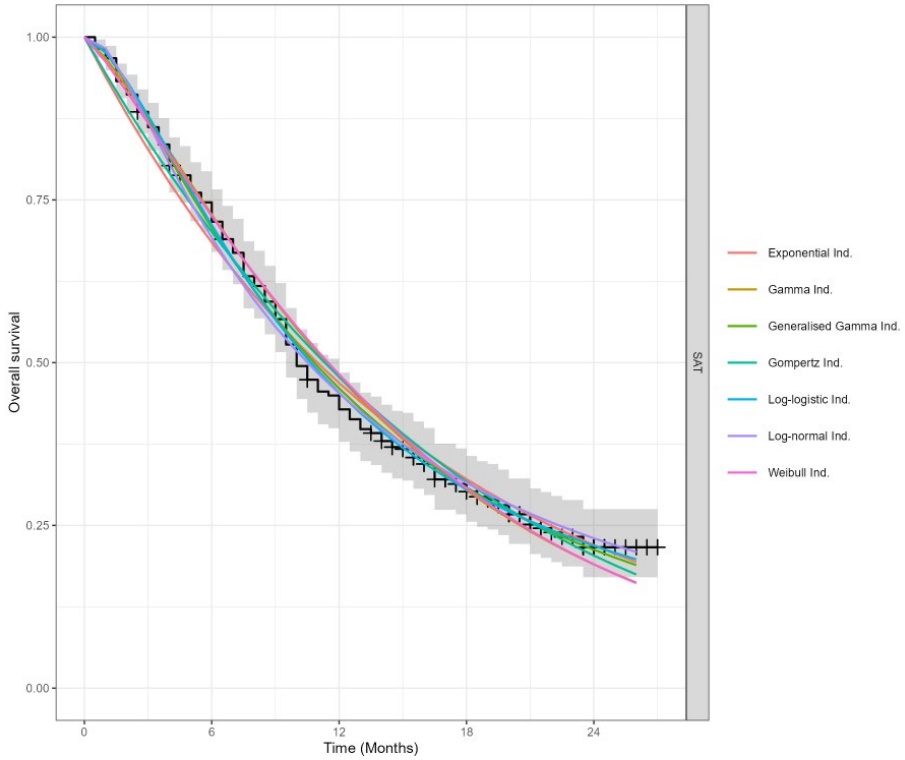


Figure 13 shows the predictions for each parametric model extrapolated beyond the observed data.

Figure 13: Parametric Fit Plots with Extrapolation OS (Astellas SACT cohort B)

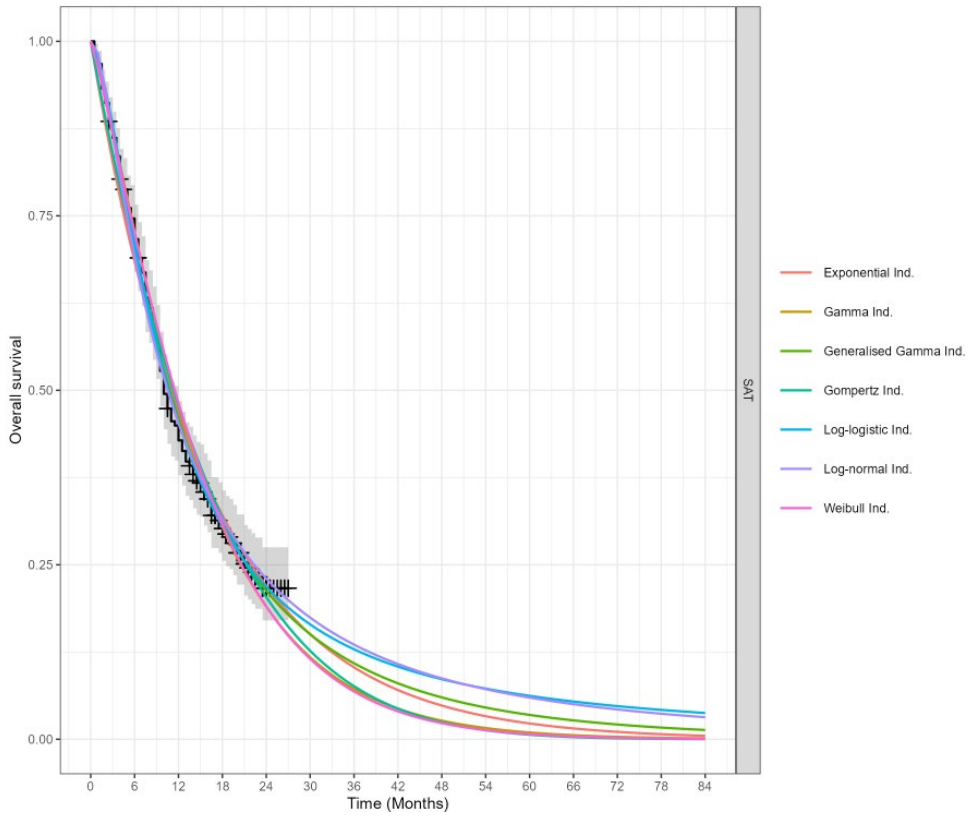


Figure 14 shows the hazards for each parametric model and the observed data.

Figure 14: Parametric Hazard Plots OS (Astellas SACT cohort B)

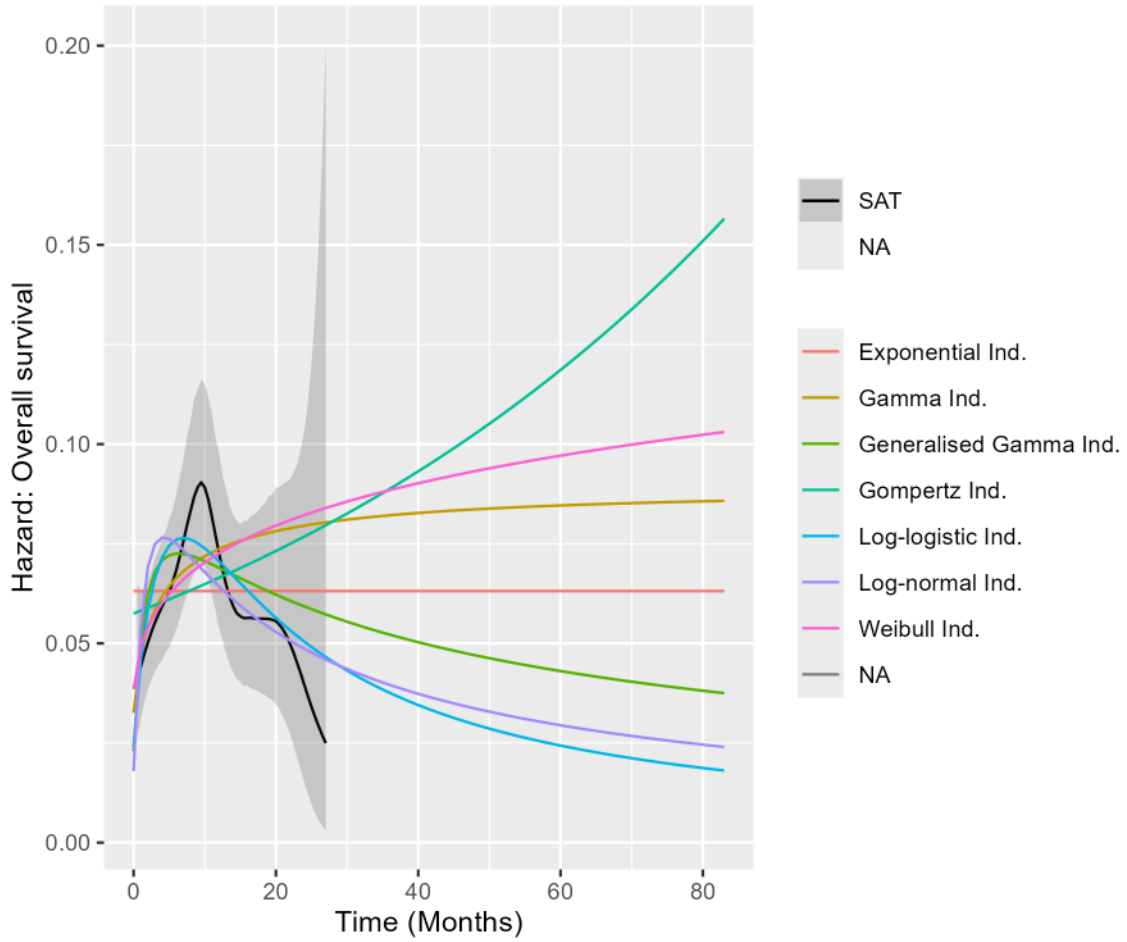


Table 16 shows the fit statistics for each parametric model.

Table 16: Parametric Fit Statistics OS (Astellas SACT cohort B)

Functional form	AIC	BIC
Exponential Ind.	1860.7 (6)	1864.5 (6)
Weibull Ind.	1853.6 (5)	1861.3 (5)
Gompertz Ind.	1861.4 (7)	1869 (7)
Log-logistic Ind.	1844.6 (1)	1852.2 (1)
Log-normal Ind.	1847.9 (3)	1855.6 (2)
Gamma Ind.	1850.8 (4)	1858.5 (3)
Generalised gamma Ind.	1847.1 (2)	1858.6 (4)

Bayesian Information Criteria (BIC), Akaike Information Criteria (AIC), Lower values indicate better fit for AIC and BIC. Rankings are given in parentheses.

OS (Astellas SACT cohort A&B)

Descriptive analysis

Figure 15 shows the Kaplan Meier plot.

Figure 15: Kaplan Meier Plot: OS (Astellas SACT cohort A&B)

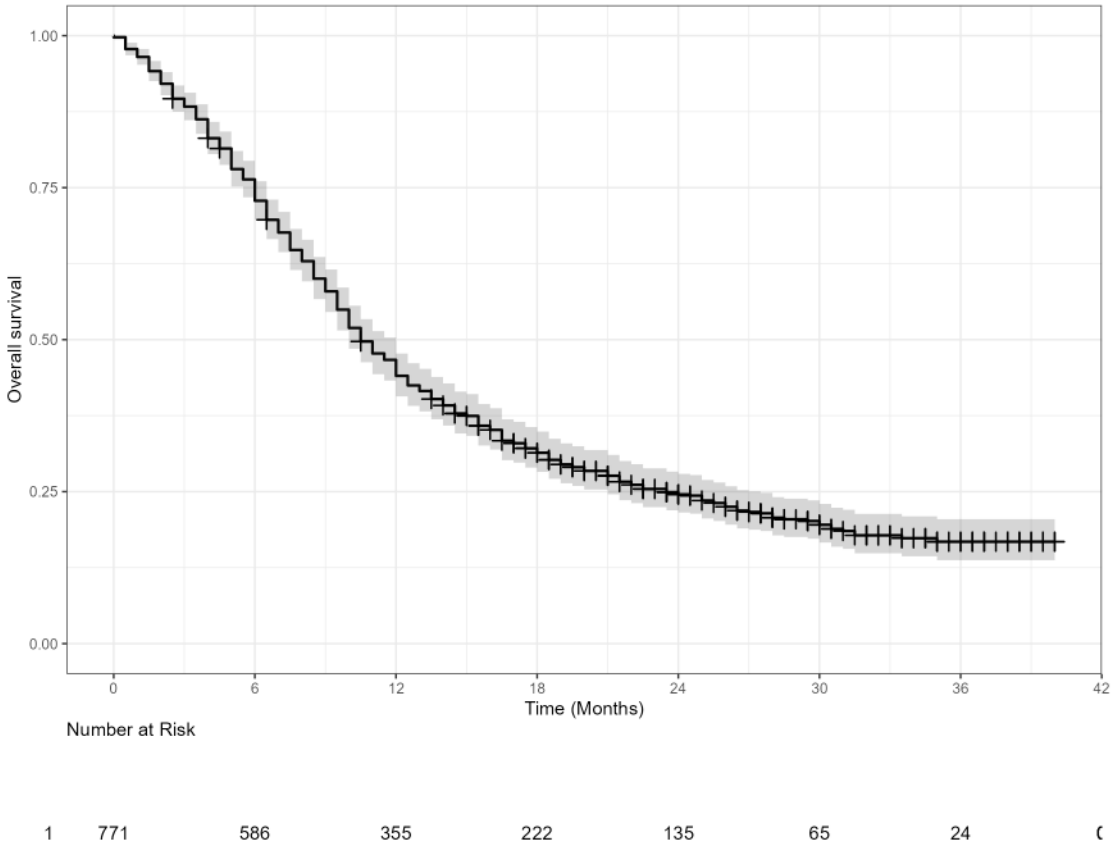


Table 17 shows the median time (months) for cohort A&B.

Table 17: Median Survival: OS (Astellas SACT cohort A&B)

Treatment	Median (months)	Lower CI	Upper CI
Platinum-based chemotherapies	10.5	10	12

Table 18 shows the mean survival time (months) based on each fitted curve for Cohort A&B.

Table 18: Mean Survival Time: OS (Astellas SACT cohort A&B)

Treatment	Platinum-based chemotherapies
Exponential Ind.	17.35
Weibull Ind.	16.97
Gompertz Ind.	18.18
Log-logistic Ind.	19.85
Log-normal Ind.	22.97
Gamma Ind.	16.96
Generalised gamma Ind.	17.55

Abbreviations: Ind – individually fitted
Extrapolations restricted to 5-years after end of follow-up in the data

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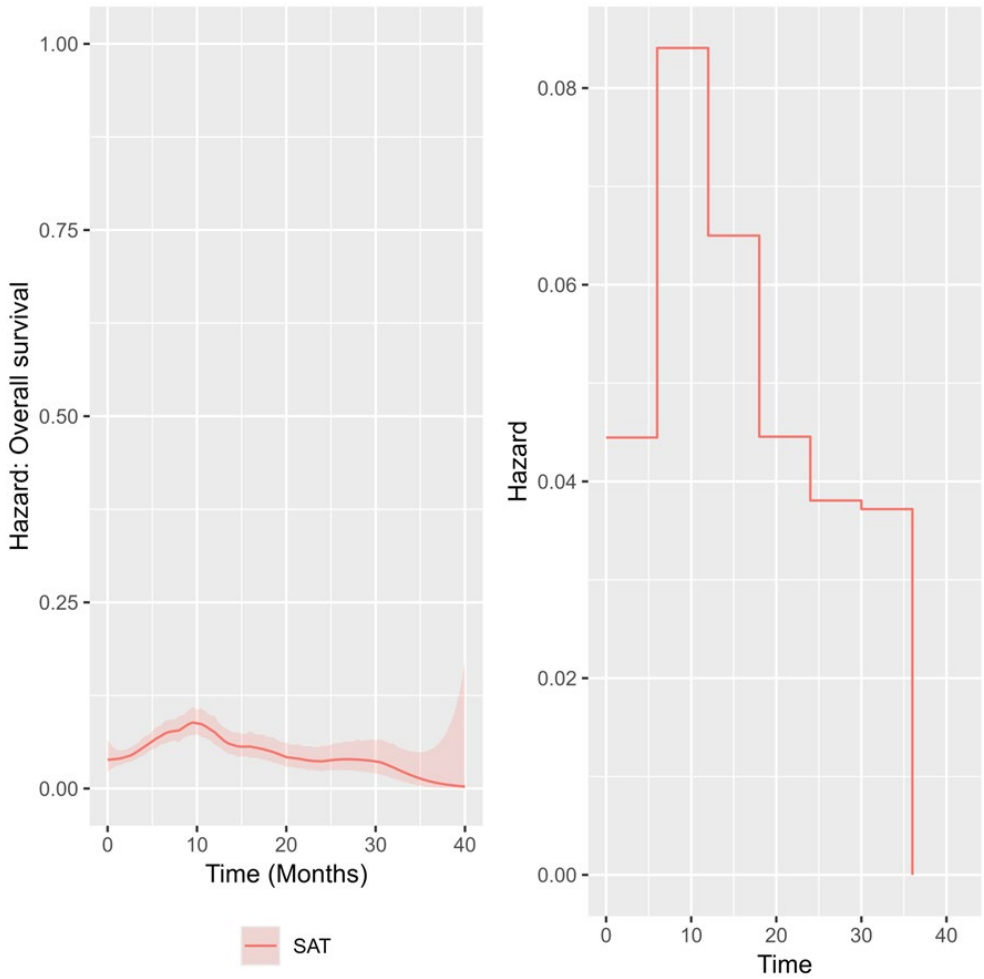
Hazards Assessment

Figure 15 shows the hazard plots.

Figure 15: Smoothed and piecewise hazard Plots OS (Astellas SACT cohort A&B)



Parametric Fit Diagnostics

Figure 16 shows diagnostic plots for treatment effects on various effect scales.

Figure 16: Individual Diagnostic Plots: OS (Astellas SACT cohort A&B)

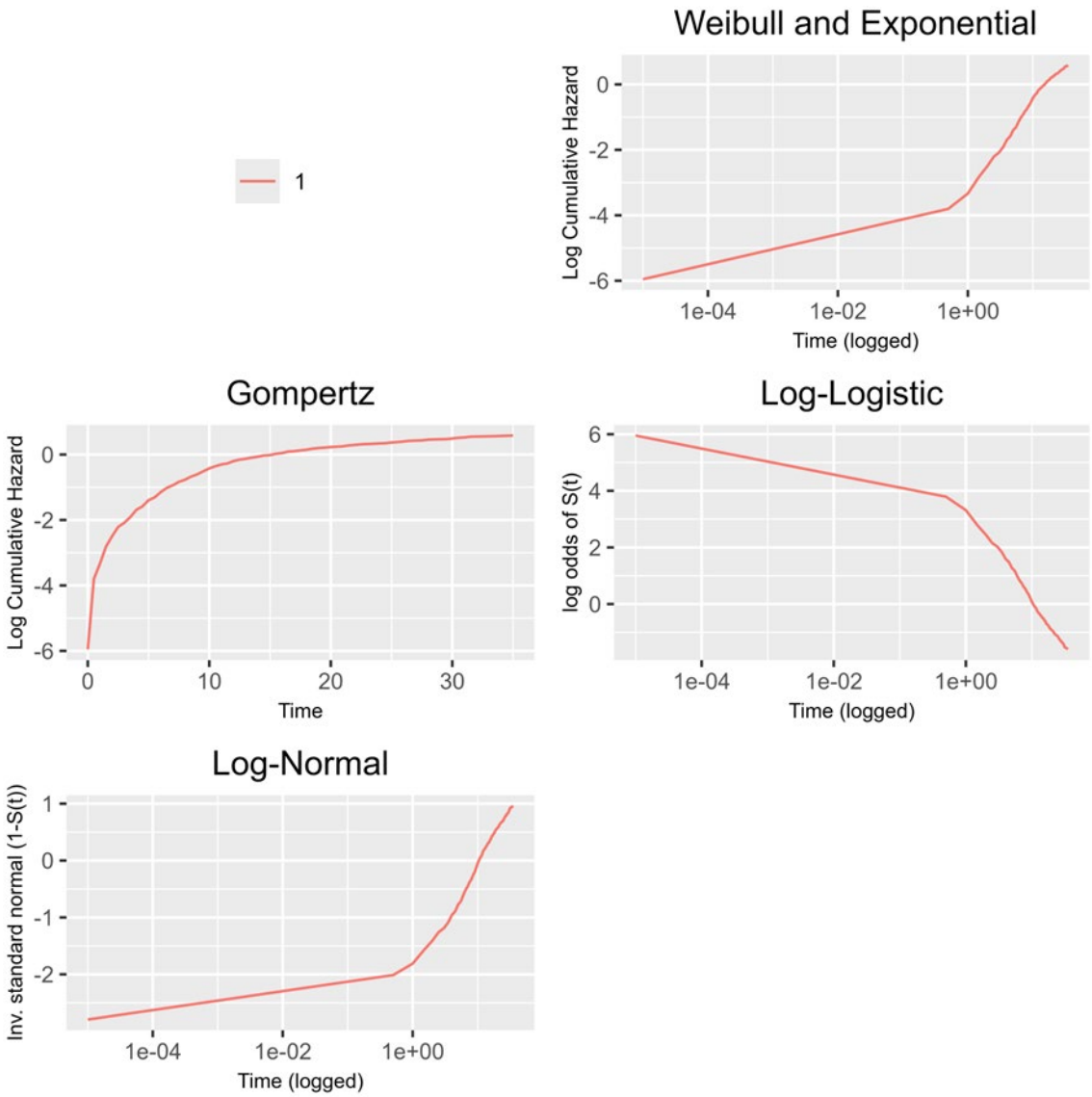


Figure 17 shows the fit for each parametric model to the observed data.

Figure 17: Parametric Fit Plots OS (Astellas SACT cohort A&B)

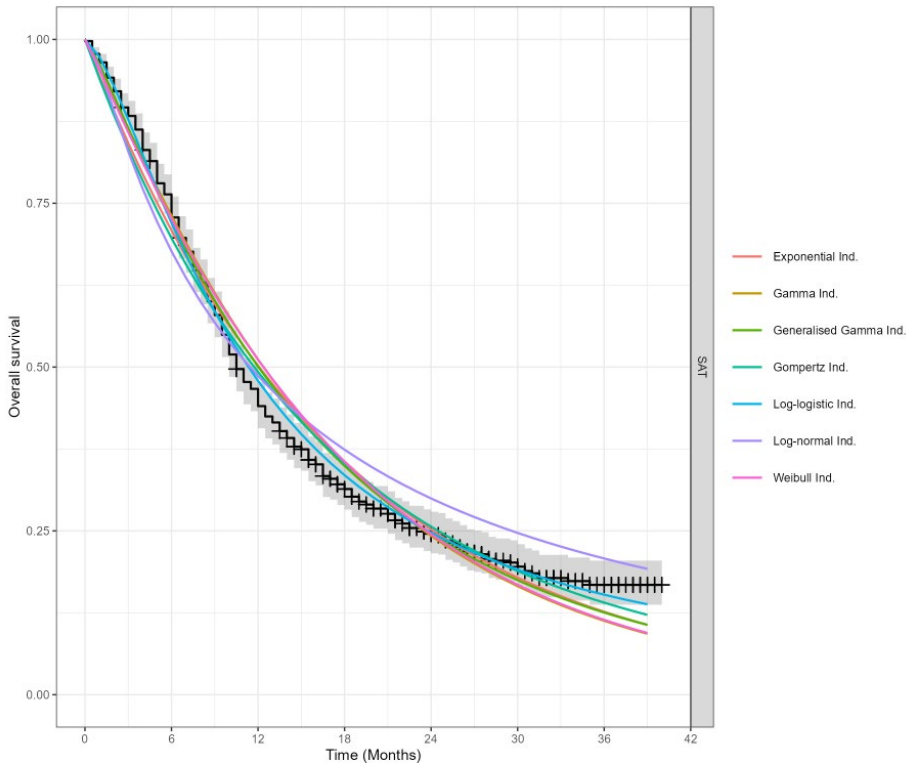


Figure 18 shows the predictions for each parametric model extrapolated beyond the observed data.

Figure 18: Parametric Fit Plots with Extrapolation OS (Astellas SACT cohort A&B)

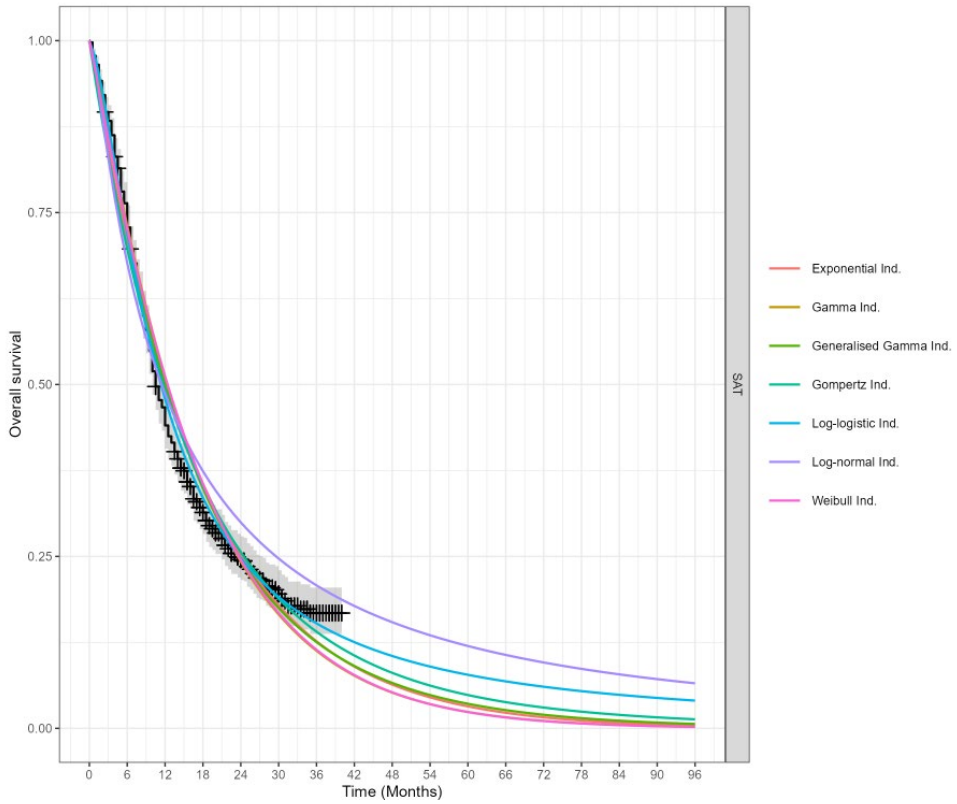


Figure 19 shows the hazards for each parametric model and the observed data.

Figure 19: Parametric Hazard Plots OS (Astellas SACT cohort A&B)

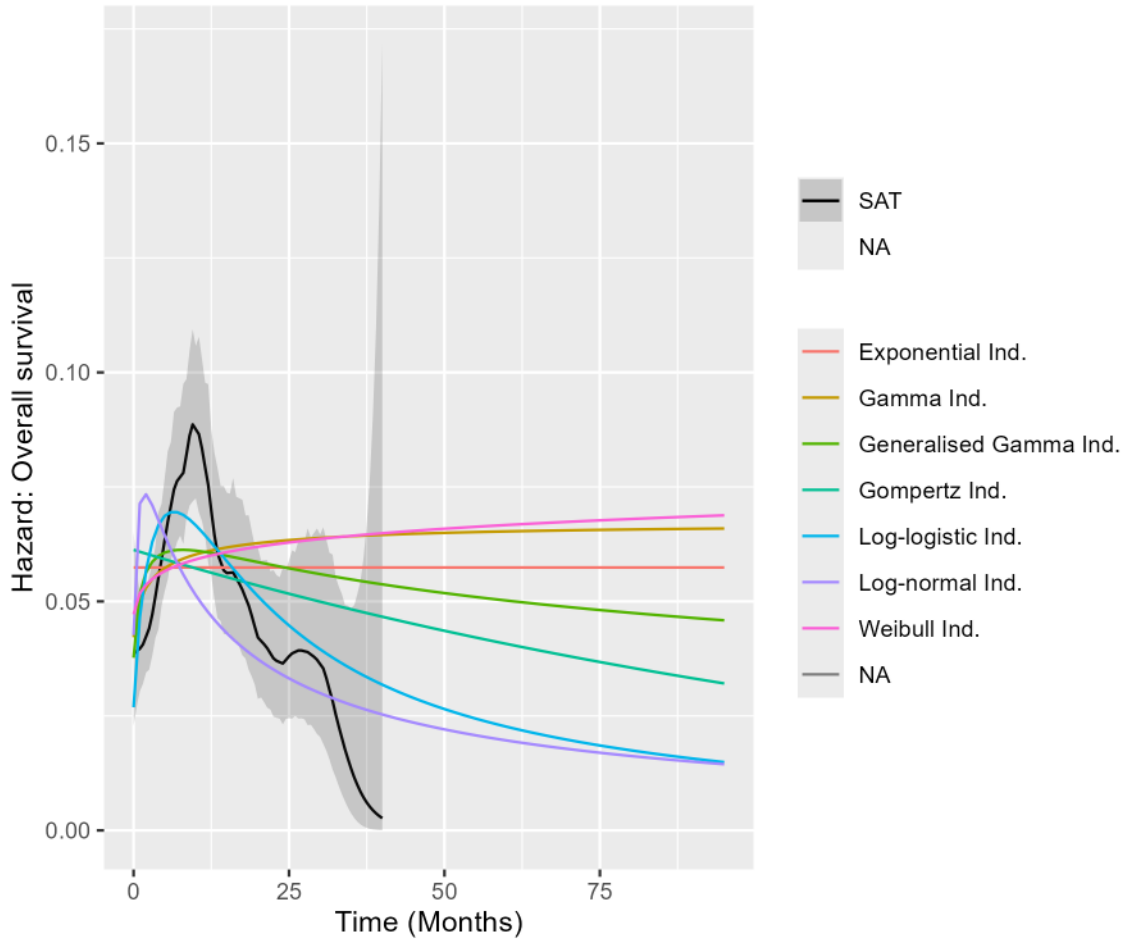


Table 19 shows the fit statistics for each parametric model.

Table 19: Parametric Fit Statistics OS (Astellas SACT cohort A&B)

Functional form	AIC	BIC
Exponential Ind.	4592.6 (5)	4597.3 (3)
Weibull Ind.	4591 (4)	4600.3 (5)
Gompertz Ind.	4592.8 (6)	4602.1 (6)
Log-logistic Ind.	4561.7 (1)	4571 (1)
Log-normal Ind.	4738.1 (7)	4747.4 (7)
Gamma Ind.	4588 (3)	4597.3 (2)
Generalised gamma Ind.	4584.2 (2)	4598.2 (4)

Bayesian Information Criteria (BIC), Akaike Information Criteria (AIC), Lower values indicate better fit for AIC and BIC. Rankings are given in parentheses.

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Time on avelumab treatment (Astellas SACT cohort B)

Descriptive analysis

Figure 20 shows the Kaplan Meier plot for time on treatment (ToT) for patients in Cohort B who went on to receive avelumab maintenance following platinum-based chemotherapies.

Figure 20: Kaplan Meier Plot: Avelumab ToT (Astellas SACT cohort B)

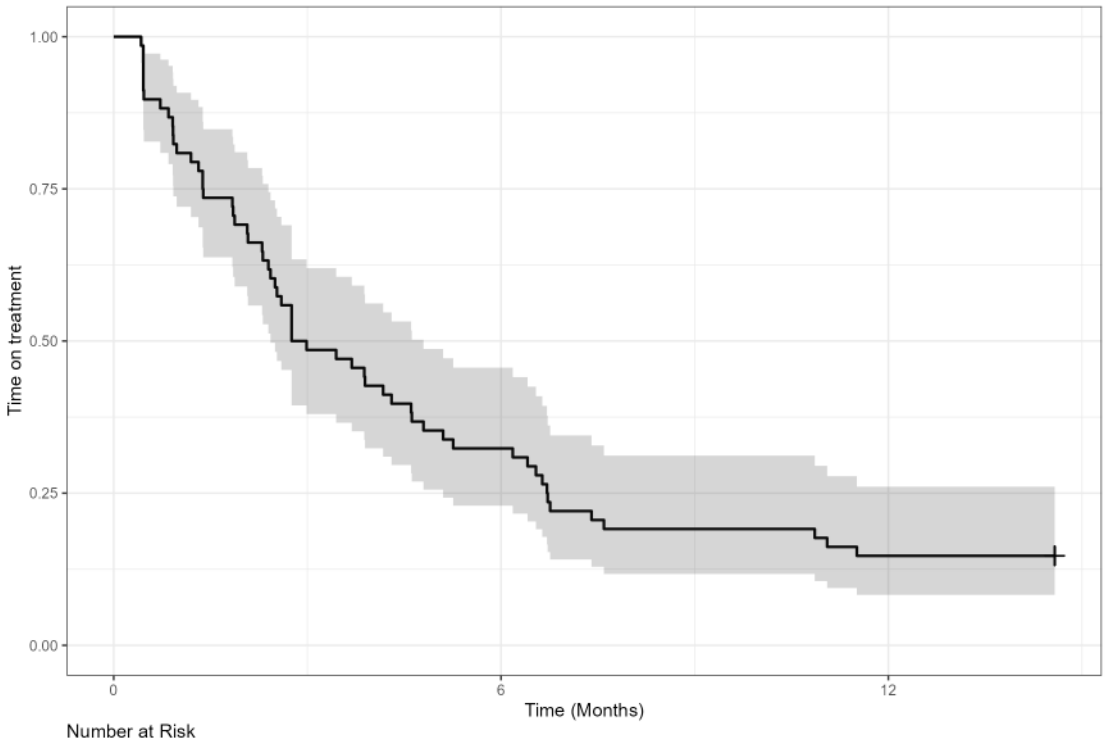

Table 20 shows the mean time on treatment (months) based on each fitted curve for those receiving avelumab in Cohort B.

Table 20: Mean Survival Time: Avelumab ToT (Astellas SACT cohort B) – without stopping rule

Functional Form	Mean Time on Treatment
Exponential Ind.	5.93
Weibull Ind.	6.07
Gompertz Ind.	10.45
Log-logistic Ind.	7.12
Log-normal Ind.	6.84
Gamma Ind.	5.96
Generalised gamma Ind.	8.51

Abbreviations: Ind – individually fitted

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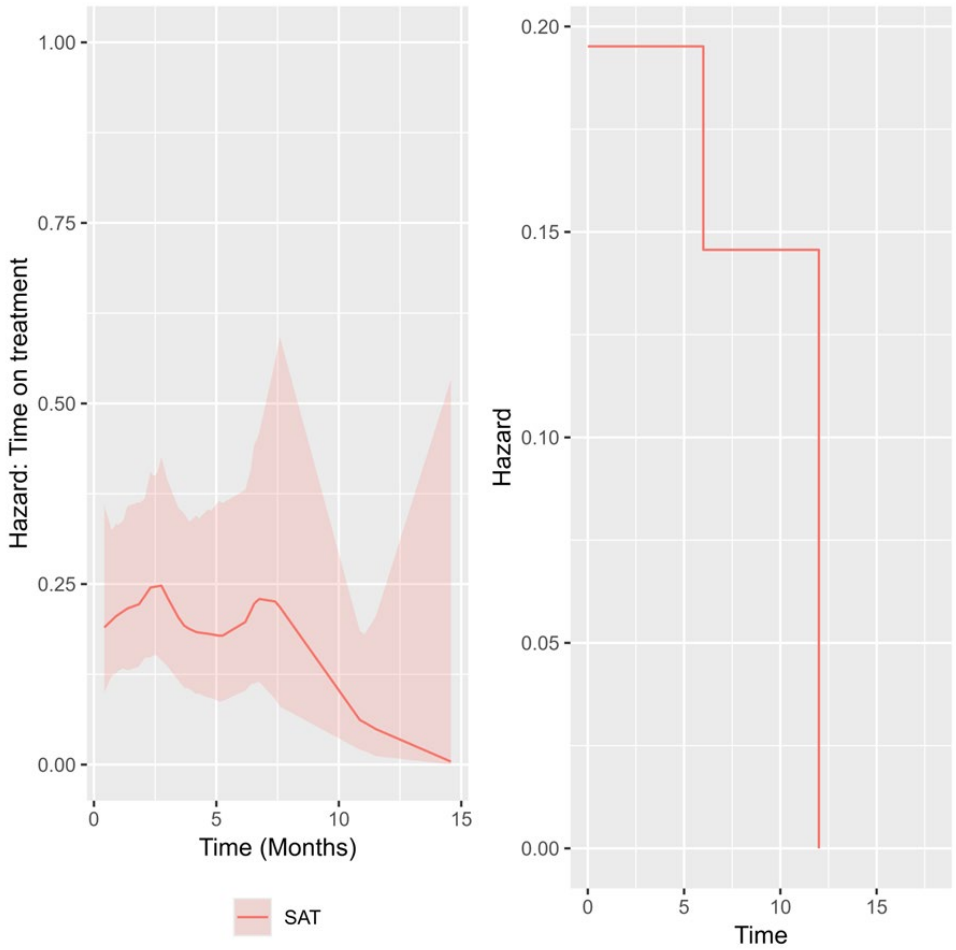
Hazards Assessment

Figure 20 shows the hazard plots.

Figure 20: Smoothed and piecewise hazard plots avelumab ToT (Astellas SACT cohort B)



Parametric Fit Diagnostics

Figure 21 shows diagnostic plots for treatment effects on various effect scales.

Figure 21: Individual Diagnostic Plots: Avelumab ToT (Astellas SACT cohort B)

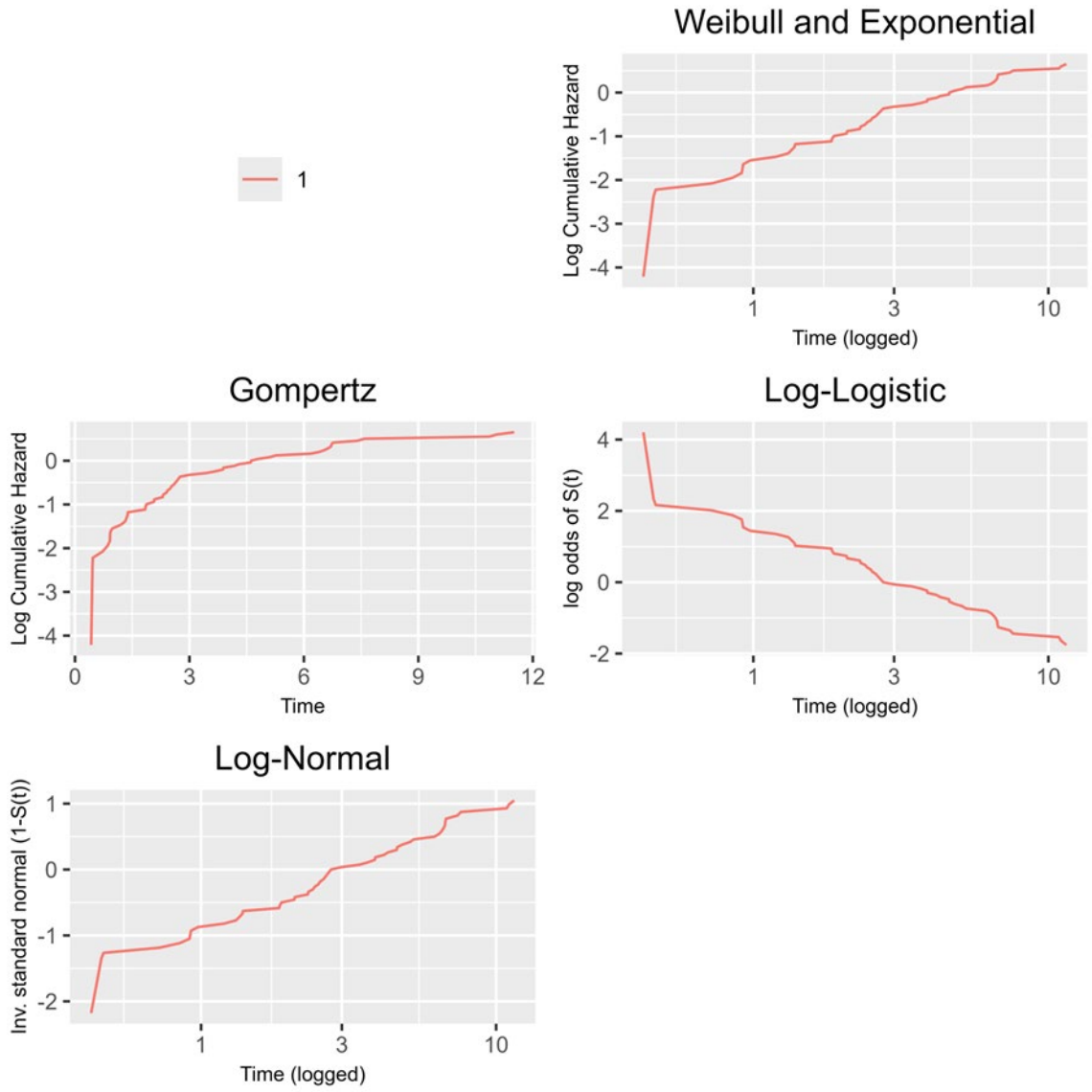


Figure 22 shows the fit for each parametric model to the observed data.

Figure 22: Parametric Fit Plots Avelumab ToT (Astellas SACT cohort B)

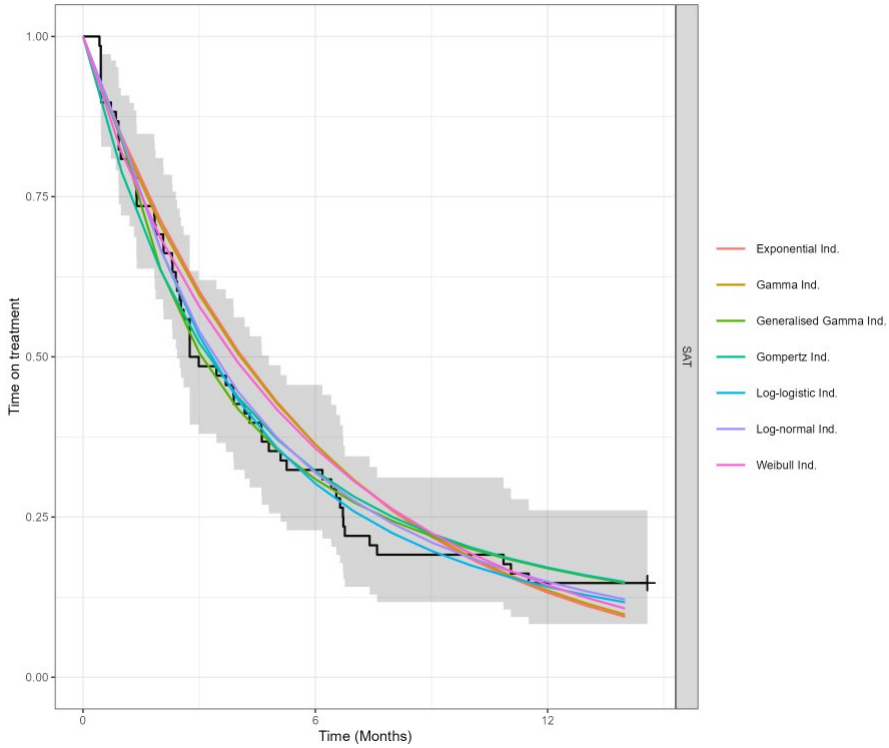


Figure 23 shows the predictions for each parametric model extrapolated beyond the observed data.

Figure 23: Parametric Fit Plots with Extrapolation Avelumab ToT (Astellas SACT cohort B)

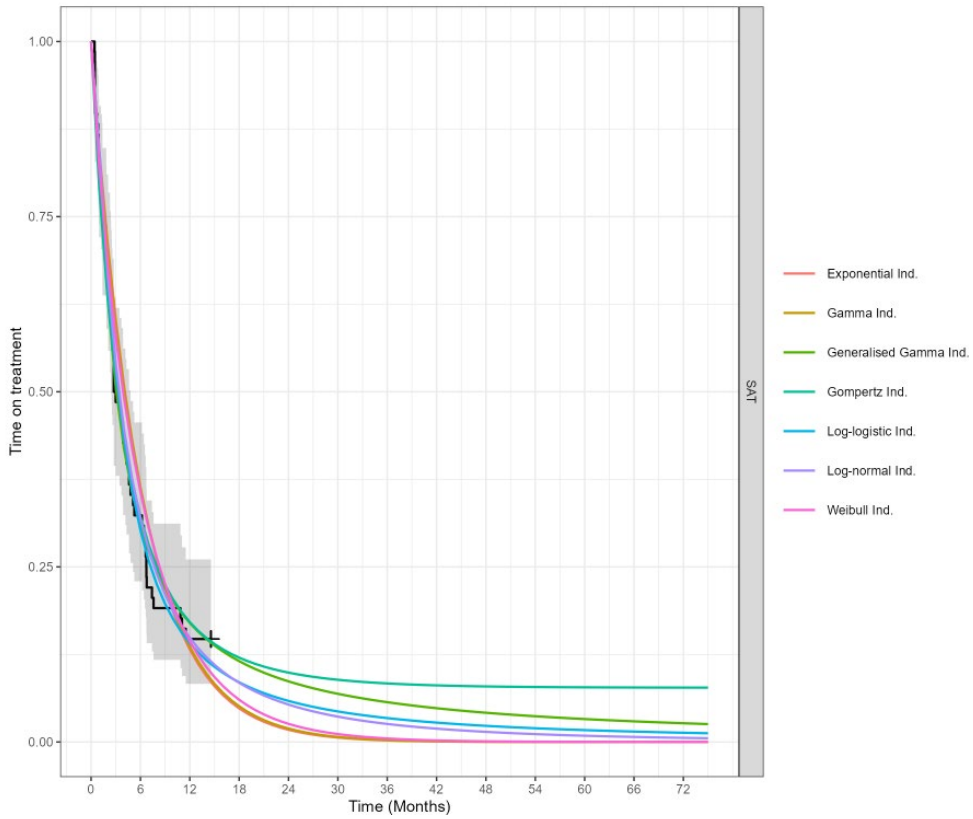


Figure 24 shows the hazards for each parametric model and the observed data.

Figure 24: Parametric Hazard Plots Avelumab ToT (Astellas SACT cohort B)

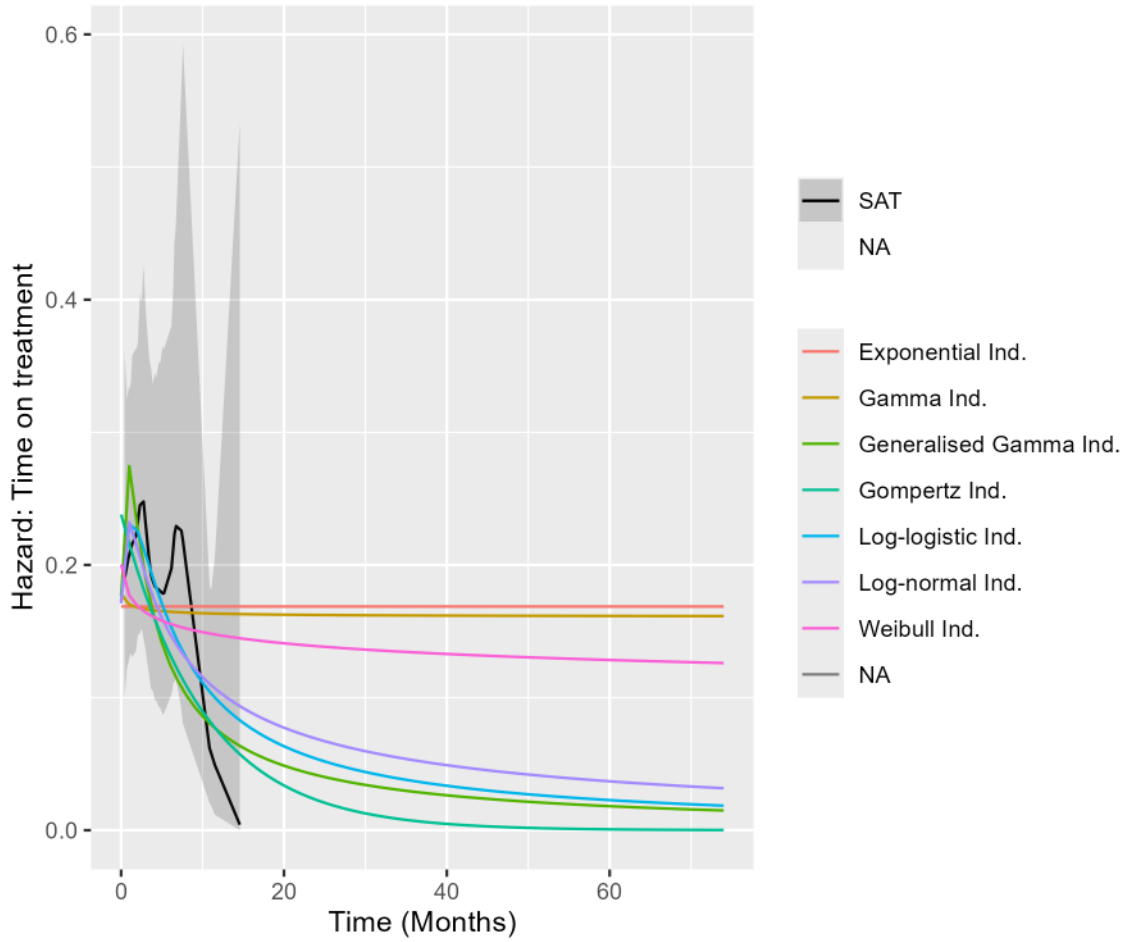


Table 21 shows the fit statistics for each parametric model.

Table 21: Parametric Fit Statistics Avelumab ToT (Astellas SACT cohort B)

Functional form	AIC	BIC
Exponential Ind.	324.5 (5)	326.7 (5)
Weibull Ind.	325.7 (6)	330.1 (6)
Gompertz Ind.	319.6 (4)	324 (4)
Log-logistic Ind.	315.8 (3)	320.2 (2)
Log-normal Ind.	314.7 (2)	319.2 (1)
Gamma Ind.	326.4 (7)	330.8 (7)
Generalised gamma Ind.	314.4 (1)	321.1 (3)

Bayesian Information Criteria (BIC), Akaike Information Criteria (AIC), Lower values indicate better fit for AIC and BIC. Rankings are given in parentheses.

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Appendix A.1: About Health Data Insight CIC

HDI is a social enterprise that has been set up to work as a trusted information broker for patients, the public and providers to give secure and supported access to healthcare information. All CIC's are overseen by the *Office of the Regulator of Community Interest Companies* which ensures we meet our social purpose and that the value we create is protected and used for social good.

Our aims are to:

- Create value for public sector organisations by finding new knowledge from both existing and new sources of information
- Provide a data management and linkage service that allows partners to access information in safe havens that guarantee the privacy of each individual patient.
- Create visual, internet-based information services and applications that can be easily accessed, used and understood
- Supply organisations with information and services that they can use to understand and help improve their services
- Inform patients to enhance their selection, access and use of healthcare services and improve their understanding of their clinical condition and care.

Our strategic objectives are aligned to NHS and wider government policy to improve transparency and access to data, encourage self-management, enable choice and foster the use of social enterprises to deliver public services.

HDI does three things:

1. Improve access to data and information to all existing and potential users, providers and commissioners of healthcare services
2. Help patients and the public to understand the value of their own and other healthcare data by providing guidance and interpretation that supports informed choice and access across healthcare providers
3. Support commissioners and providers in the delivery of improved care pathways and outcomes to ensure the community receives the best care

Those HDI works with use our expertise and knowledge of the UK healthcare system to help identify and gain access to the specific data they require. Yet as a social enterprise HDI is committed to protecting the public interest; HDI does not exist to make profit for personal gain but to deliver benefit to the community HDI serves.

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Appendix A.2: About the National Disease Registration Service (NDRS)

The National Cancer Registration and Analysis Service (NDRS), which is within NHS England (NHSE), provides intelligence to drive improvement in standards of cancer care and clinical outcomes. This is facilitated through a series of work programmes, utilising the healthcare data and information collected about cancer patients by multiple specialist organisations and collated within PHE. The NDRS builds on the work of partner organisations and teams to develop world class cancer intelligence for NHSE, partners – nationally and internationally - and the local public health system.

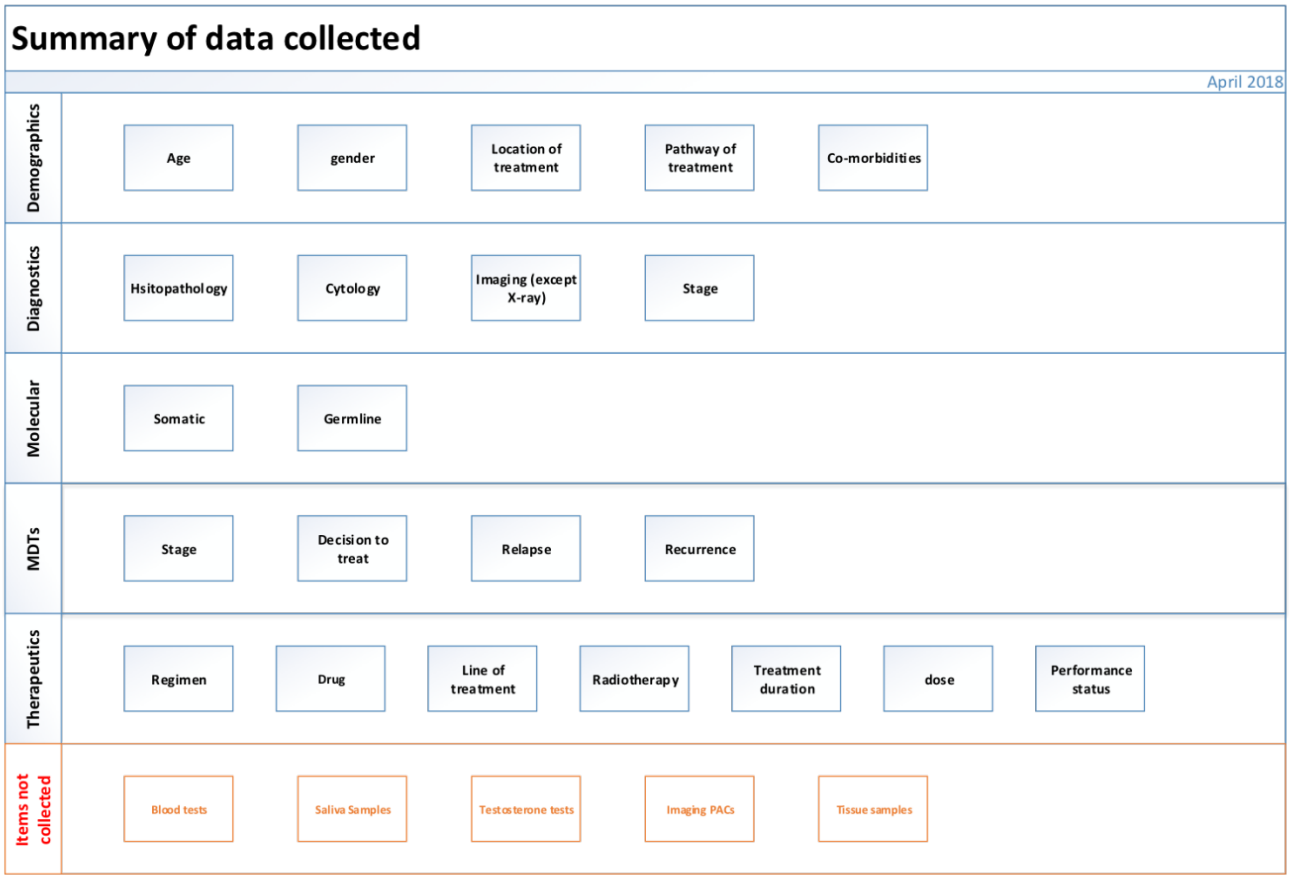
The NDRS leads on sharing high quality intelligence, knowledge, evidence and expertise to support the needs of stakeholders. It produces analyses, toolkits and reports which span both the Public Health and NHS agenda. New analyses include the number of people living with cancer, how outcomes vary between different patient groups and by stage at diagnosis, and an insight into cancer equality metrics.

The NDRS consists of cancer registration and intelligence teams in nine offices across NHSE. Each team will have national and local responsibilities and functions and will work closely with NHSE colleagues in other divisions, directorates, centres and regions.

HDI – NHSE Partnership

HDI has a Partnership Agreement with NHSE. The focus of the partnerships between NHSE's National Disease Registration Service (NDRS) and external organisations is to improve health outcomes using the real-world data collected by the National Disease Registration Service. These collaborative arrangements exist to support the development and application of innovative approaches and statistical techniques to the collection, quality assurance, data linkages and analyses of registry data. They are formed when an area that is deemed of significant benefit to patients is identified by both parties and when neither organisation would otherwise be able to progress individually.

Appendix A.3: Types of data collected by the NDRS



Appendix B: Updates to the economic evaluation of EV+P

Following the first committee meeting, feedback received from the EAG and the Committee's requests for additional information, the economic model evaluating EV+P has been updated. This appendix describes changed compared to the original version presented in the company submission and presents results with the new information obtained following the Committee's request.

Regarding specifically the NICE SACT analyses, NICE provided the parameters for the curves fitted to the overall survival data for all three cohorts. However, regarding time on treatment on avelumab in Cohort 2, only a graph depicting the Kaplan-Meier estimates for time on treatment was available in the reports shared with Astellas. This graph was digitised, and individual patient-level data was recreated using the Guyot algorithm[xiii] before survival curves were fitted using the same methods as described in Appendix A for Astellas SACT analyses.

Modifications to the economic model to include new scenarios based on SACT analyses

The updated economic model addresses all issues identified by the EAG and the Committee and allows for inclusion of the data obtained from both the Astellas and NICE SACT analyses.

The following changes were made to reflect the EAG base case:

- Correction to pembrolizumab time on treatment: calculations now reflect time on treatment as observed in the EV-302 trial, where patients stopped after 35 completed cycles, i.e. allowing patients to receive pembrolizumab after 24-months too if required due to previously missed doses.

- Discounting: discounting starts in the first cycle, rather than starting at end of first year.

- Pre-progression utilities: the treatment specific utility for platinum-based chemotherapy was applied for the first six months (u=[redacted]) and then the treatment independent utility thereafter (u=[redacted]). The treatment independent utility was used for enfortumab vedotin with pembrolizumab (u=[redacted]) throughout the pre-progression period.

- PFS for enfortumab vedotin with pembrolizumab and chemotherapy: the standard log-logistic distribution was used to extrapolate curves, rather than splines.

- Time on treatment for avelumab maintenance therapy: the EAG base case uses the exponential curve, rather than the Weibull distribution.

The following scenarios are presented to allow the Committee to explore scenarios based on new information from the SACT analyses:

- Scenario 1: the same as the EAG's preferred base case relying on data from the EV-302 trial, except for keeping the original assumption of using a Weibull function to extrapolate avelumab time on treatment curves. Both SACT analyses indicated a flattening of the ToT curves with a sharp decline in hazards and substantial proportion of patients remaining on treatment for long periods of time, i.e. an exponential curve assuming constant hazards for stopping treatment as preferred by the EAG would not capture trends in hazards as observed in real life.

- Scenario 2: replacing information from the EV-302 trial with information from Astellas' SACT analyses for OS, proportion of patients receiving avelumab and extrapolation of time on treatment with avelumab in the platinum-based chemotherapy arm using the combined Cohort A and Cohort B. Please note that the analysis found very little difference in the proportion of patients using avelumab and the survival outcomes between Cohort A (capturing patients from before avelumab was recommended for use and Cohort B (capturing patients from after the time point when avelumab was recommended for use), therefore the two cohorts were combined to provide more robust results.

- Scenario 3: replacing information from the EV-302 trial with information from NICE's SACT analyses for OS in Cohort 1, i.e. patients who did not receive avelumab maintenance treatment after platinum-based chemotherapy.

- Scenario 4: replacing information from the EV-302 trial with information from NICE's SACT analyses for OS, proportion of patients receiving avelumab and extrapolation of time on treatment with avelumab based on Cohort 2, i.e. representing patients who received avelumab maintenance therapy in the platinum-based chemotherapy arm.

Table 8 provides details of assumptions used in all scenarios based on information available from EV-302, and the Astellas and NICE SACT analyses applying the best fitting curves.

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Table 8 Assumptions in the economic evaluation of EV+P in the new scenarios

Scenario	Model location	EAG original base case	Scenario 1: updated avelumab ToT	Scenario 2: Astellas SACT cohort A&B	Scenario 3: NICE SACT Cohort 1 (no avelumab)	Scenario 4: NICE SACT Cohort 2 (with avelumab)
Proportion receiving avelumab	Sheet: Drug_costs_1L Cell: E17	30%	30%	20%	0%	100%
Avelumab ToT	Sheet: Efficacy_ToT Cells: F13:F15	Exponential based on EV-302	Weibull based on EV-302	Generalised gamma based on Astellas SACT	n/a	Generalised gamma based on NICE SACT
PBC OS	Sheet: Efficacy_OS Cells: E9:E10, E15	Log-logistic based on EV-302	Log-logistic based on EV-302	Log-logistic based on Astellas SACT	Log-logistic based on NICE SACT	Log-logistic based on NICE SACT

Abbreviations: OS – overall survival; PBC – platinum-based chemotherapies; ToT – time on treatment

Results

Survival curve extrapolations for time on avelumab treatment (NICE SACT cohort 2) based on digitization of graph provided

Descriptive analysis

Figure 8 shows the Kaplan Meier plot that was recreated via digitisation from the graph shared by NICE for time on treatment (ToT) for patients in Cohort 2 in NICE's SACT analysis, i.e. those who went on to receive avelumab maintenance following platinum-based chemotherapies.

Figure 8: Kaplan Meier Plot: Avelumab ToT (NICE SACT cohort 2)

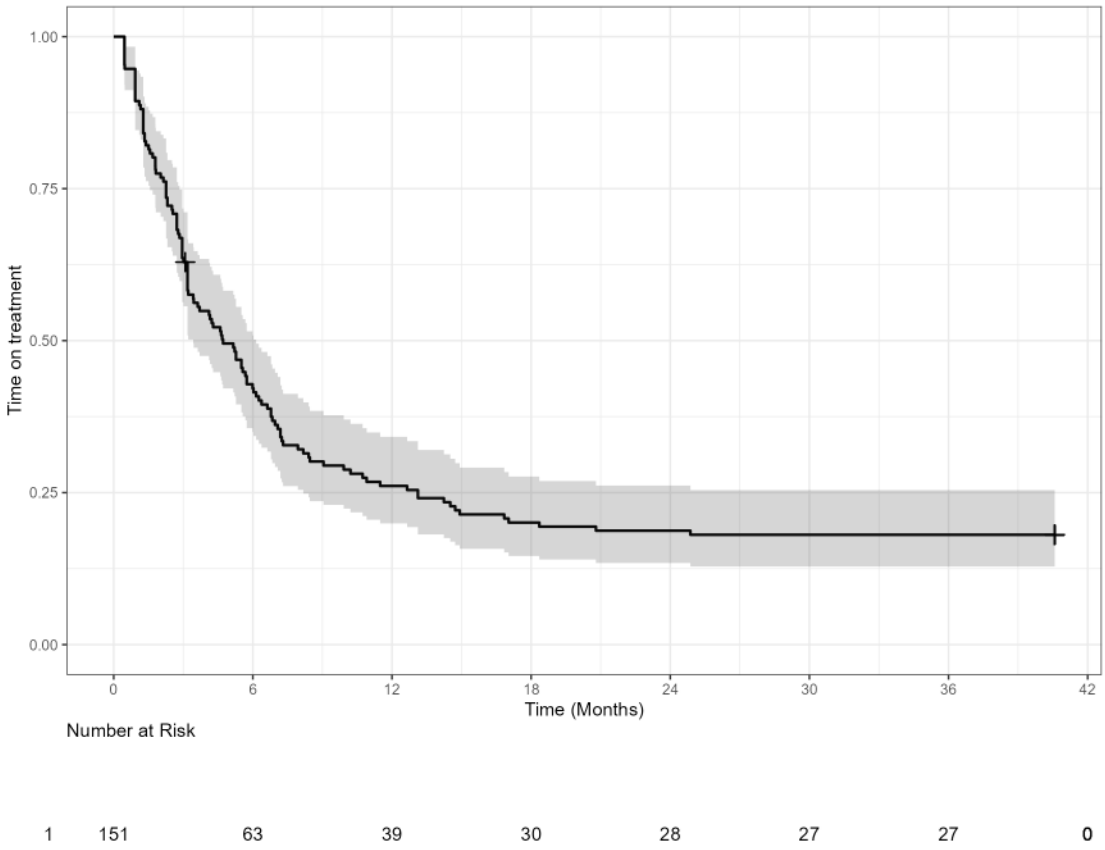


Table 9 shows the median time (months) for those receiving avelumab in cohort 2.

Table 9: Median Survival: Avelumab ToT (NICE SACT cohort 2)

Treatment	Median (months)	Lower CI	Upper CI
Avelumab	4.72	3.43	6.14

Table 10 shows the mean time on treatment (months) based on each fitted curve for those receiving avelumab in NICE SACT Cohort 2.

Table 10: Mean Survival Time: Avelumab ToT (NICE SACT cohort 2)

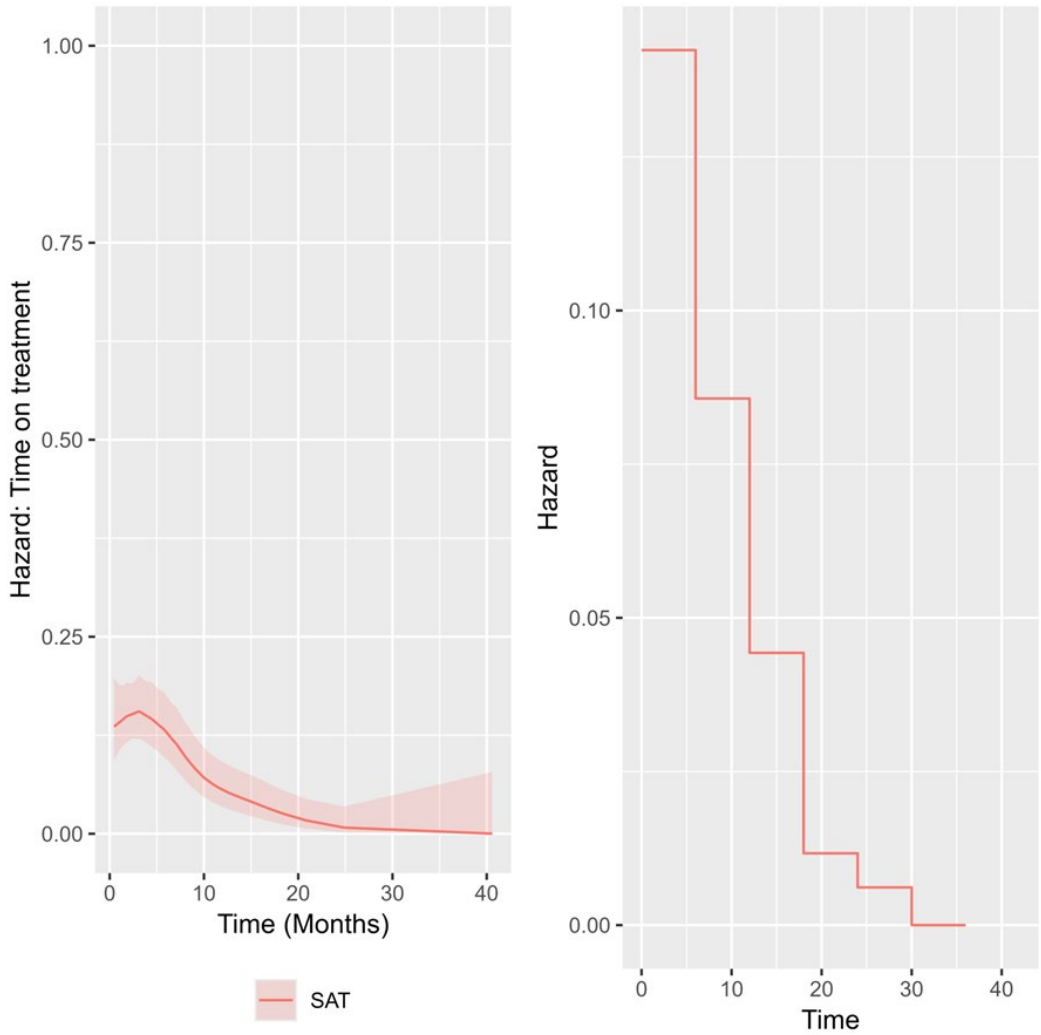
Distribution	Estimated mean time on treatment
Exponential Ind.	13.93
Weibull Ind.	15.55
Gompertz Ind.	23.33
Log-logistic Ind.	14.15
Log-normal Ind.	15.41
Gamma Ind.	15.34
Generalised gamma Ind.	19.19

Abbreviations: Ind – individually fitted

Hazards Assessment

Figure 9 shows the hazard plots.

Figure 9: Smoothed and piecewise hazard plots avelumab ToT (NICE SACT cohort 2)



Parametric Fit Diagnostics

Figure 10 shows diagnostic plots for treatment effects on various effect scales.

Figure 10: Individual Diagnostic Plots: Avelumab ToT (NICE SACT cohort 2)

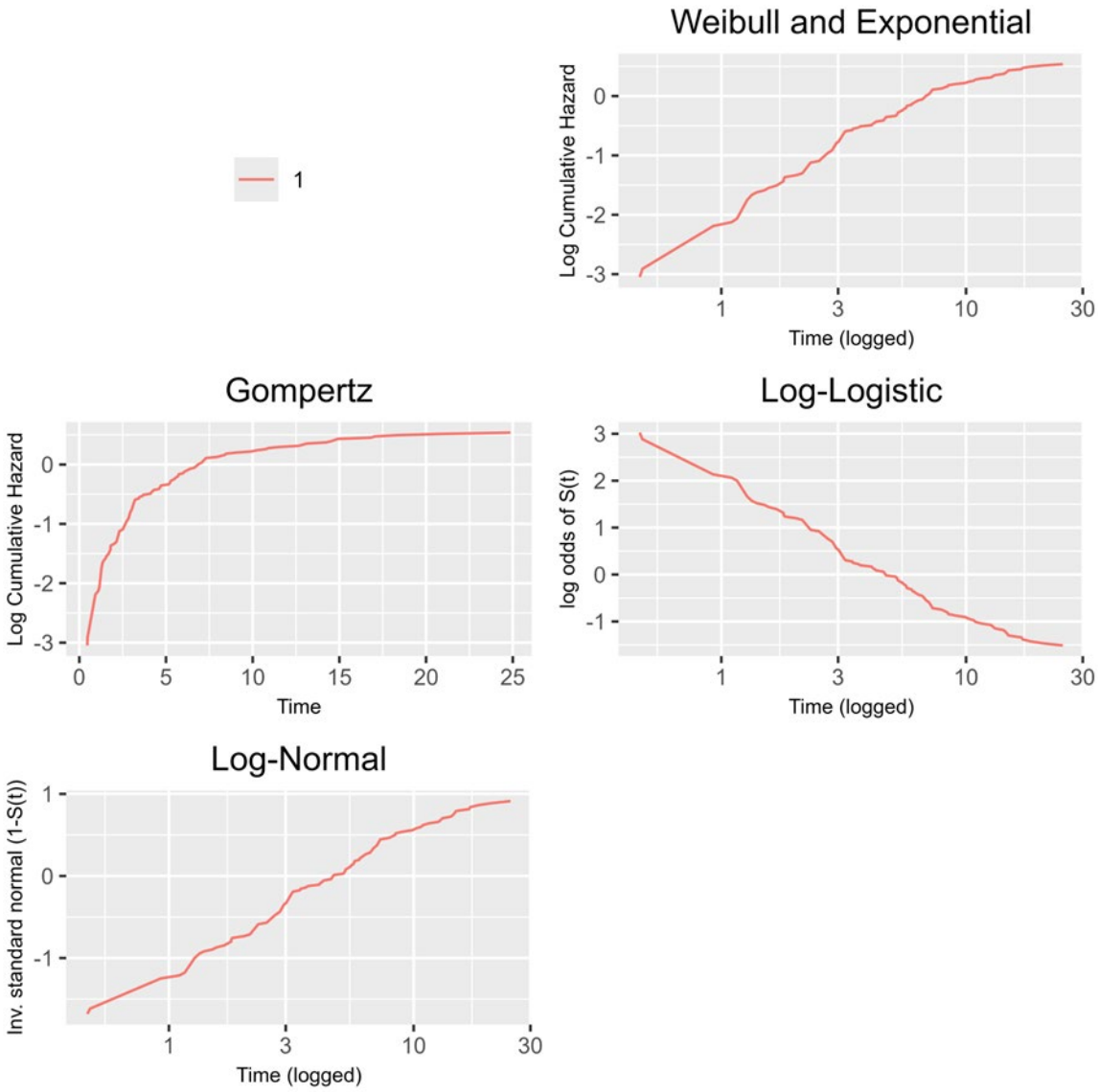


Figure 11 shows the fit for each parametric model to the observed data.

Figure 11: Parametric Fit Plots Avelumab ToT (NICE SACT cohort 2)

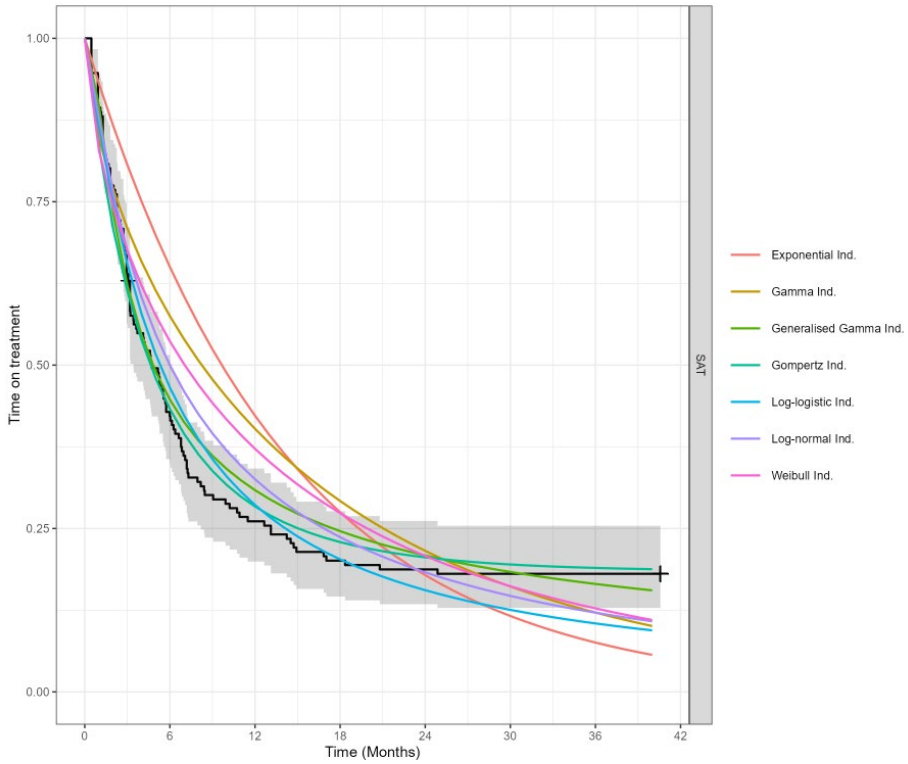


Figure 12 shows the predictions for each parametric model extrapolated beyond the observed data.

Figure 12: Parametric Fit Plots with Extrapolation Avelumab ToT (NICE SACT cohort 2)

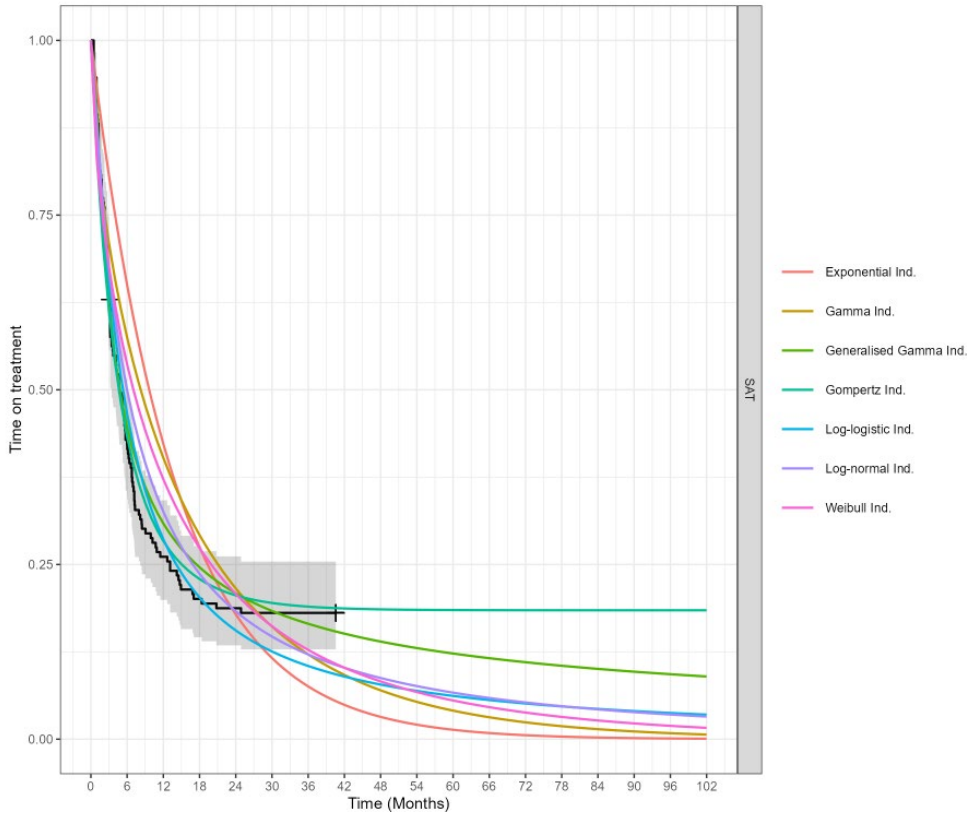


Figure 13 shows the hazards for each parametric model and the observed data.

Figure 13: Parametric Hazard Plots Avelumab ToT (NICE SACT cohort 2)

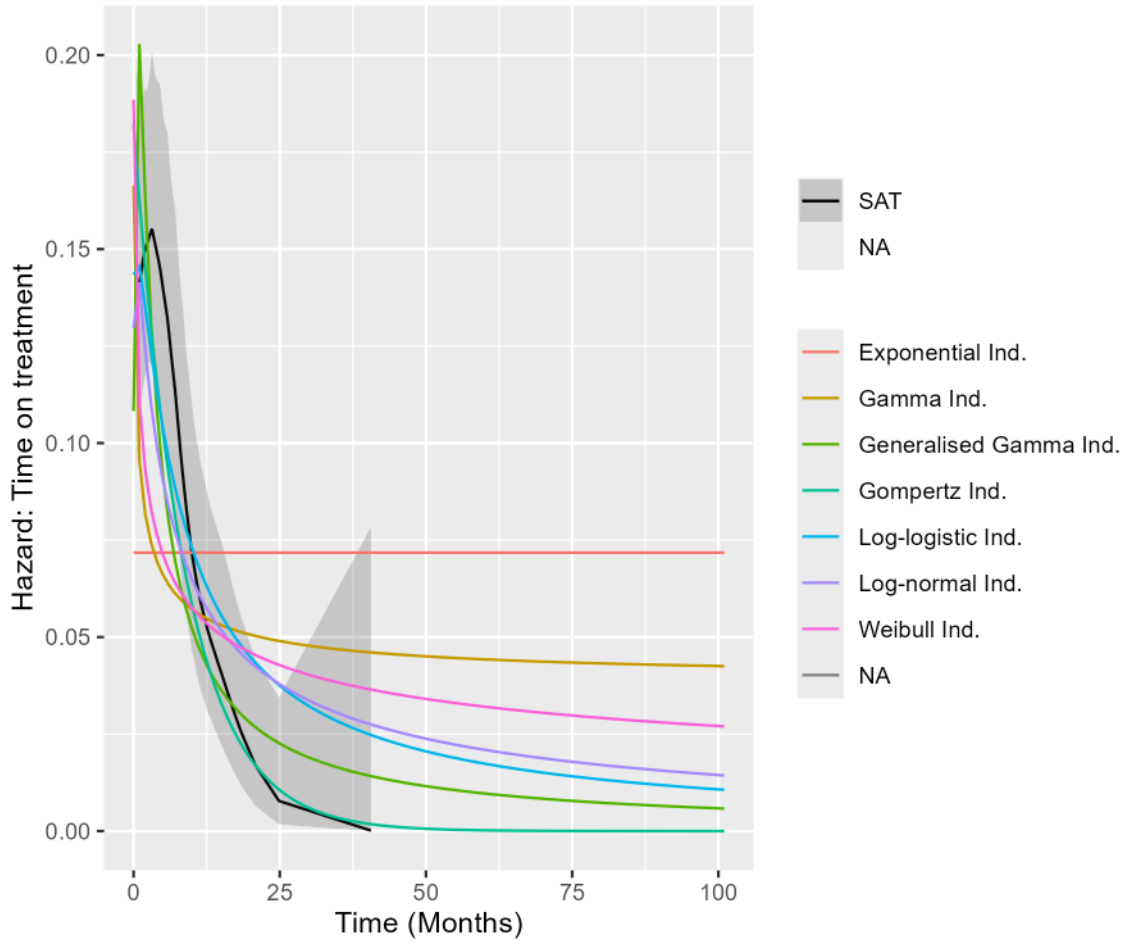


Table 11shows the fit statistics for each parametric model.

Table 11: Parametric Fit Statistics Avelumab ToT (NICE SACT cohort 2)

Functional form	AIC	BIC
Exponential Ind.	896.1 (7)	899.1 (7)
Weibull Ind.	858.6 (5)	864.6 (5)
Gompertz Ind.	795.4 (1)	801.4 (1)
Log-logistic Ind.	817.6 (3)	823.7 (3)
Log-normal Ind.	818.2 (4)	824.2 (4)
Gamma Ind.	873.5 (6)	879.6 (6)
Generalised gamma Ind.	795.5 (2)	804.6 (2)

Bayesian Information Criteria (BIC), Akaike Information Criteria (AIC), Lower values indicate better fit for AIC and BIC. Rankings are given in parentheses.

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Economic evaluation scenario results

Results of the economic evaluation and calculations for the severity modifier for each new scenario are presented in the tables below. Results are presented using [redacted] discount for EV and list prices for all other treatments.

EAG preferred assumptions

Table 12 Severity modifier calculations based on the EAG preferred assumptions with pembrolizumab time on treatment corrected

Comparative SOC intervention	Lifetime QALYs without disease (discounted)	QALYs with current standard of care (discounted)	Absolute QALY shortfall	Proportional shortfall
SOC: Gemcitabine + PBC	9.49	[redacted]	[redacted]	[redacted]

Table 13 Economic outcomes with EAG preferred assumptions with pembrolizumab time on treatment corrected

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Without severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.34	[redacted]
With 1.2 severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.60	[redacted]

Scenario A: EAG preferred assumptions except avelumab time on treatment using Weibull

Table 14 Severity modifier calculations based on the EAG preferred assumptions except for avelumab time on treatment

Comparative SOC intervention	Lifetime QALYs without disease (discounted)	QALYs with current standard of care (discounted)	Absolute QALY shortfall	Proportional shortfall
SOC: Gemcitabine + PBC	9.49	[redacted]	[redacted]	[redacted]

Table 15 Economic outcomes with EAG preferred assumptions except for avelumab time on treatment

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Without severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.34	[redacted]
With 1.2 severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.60	[redacted]

Scenario B: Astellas SACT analysis cohorts A and B combined

Table 16 Severity modifier calculations based on Astellas SACT analysis (cohorts A and B combined)

Comparative SOC intervention	Lifetime QALYs without disease (discounted)	QALYs with current standard of care (discounted)	Absolute QALY shortfall	Proportional shortfall
SOC: Gemcitabine + PBC	9.49	[redacted]	[redacted]	[redacted]

Table 17 Economic outcomes based on Astellas SACT analysis (cohorts A and B combined)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Without severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.73	[redacted]
With 1.2 severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.08	[redacted]

Scenario C: NICE SACT analysis cohort 1 (no avelumab maintenance)

Table 18 Severity modifier calculations based on NICE SACT analysis cohort 1 (no avelumab maintenance)

Comparative SOC intervention	Lifetime QALYs without disease (discounted)	QALYs with current standard of care (discounted)	Absolute QALY shortfall	Proportional shortfall
SOC: Gemcitabine + PBC	9.49	[redacted]	[redacted]	[redacted]

Table 19 Economic outcomes based on NICE SACT analysis cohort 1 (no avelumab maintenance)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Without severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.97	[redacted]
With 1.2 severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.36	[redacted]

Scenario D: NICE SACT analysis cohort 2 (with avelumab maintenance)

Table 20 Severity modifier calculations based on NICE SACT analysis cohort 1 (no avelumab maintenance)

Comparative SOC intervention	Lifetime QALYs without disease (discounted)	QALYs with current standard of care (discounted)	Absolute QALY shortfall	Proportional shortfall
SOC: Gemcitabine + PBC	9.49	[redacted]	[redacted]	[redacted]

Table 21 Economic outcomes based on NICE SACT analysis cohort 2 (with avelumab maintenance)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Without severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.66	[redacted]
With 1.2 severity modifier							
Gemcitabine + PBC	[redacted]	[redacted]	[redacted]				
EV + P	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.99	[redacted]

These analyses confirm the previous assumption that results generated using the platinum-containing chemotherapy arm of the EV-302 trial is likely to slightly overestimate the outcomes in real life clinical practice in England. The SACT data has shown that the proportions of patients receiving avelumab in England are lower compared to the trial and the amount of time patients spend on avelumab maintenance treatment is also lower than what was observed in the EV-302 trial. Furthermore, a number of treatments that were available for patients within the trial as subsequent treatment are not available in England, therefore the overall survival observed in the SACT data also predicts slightly worse outcomes compared to the trial. Despite these differences, the economic results were relatively robust, the ICER decreasing when information from the SACT analyses were applied. However, the SACT data has shown that patients suffering from u/mUC have a shortened lifespan and worse quality of life compared to the general population and that u/mUC should qualify for the 1.2 severity modifier

References for the appendices

[i] Cancer Research UK. Bladder cancer (2023). https://www.cancerresearchuk.org/about-cancer/bladder-cancer (accessed May 2024).

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[iii] Powles T, Bellmunt J, Comperat E, et al. ESMO Clinical Practice Guideline interim update on first-line therapy in advanced urothelial carcinoma. *Annals of Oncology* 2024

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[v] Smith AB, Jaeger B, Pinheiro LC, et al. Impact of bladder cancer on health-related quality of life. *BJU International* 2018;121(4):549-57.

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[ix] Milloy N, Kirker M, Unsworth M, et al. Real-World Analysis of Treatment Patterns and Platinum-Based Treatment Eligibility of Patients With Metastatic Urothelial Cancer in 5 European Countries. *Clinical Genitourinary Cancer* 2024;22(1):e136-e47.e1.

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[xiii] Guyot P, Ades AE, Ouwens MJNM, Welton NJ. Enhanced seconday analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Medical Research Methodology 2012;12, Article number 9. Available from: https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-12-9

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Merck Sharp & Dohme (MSD)

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Greater weight should be placed on the generalised gamma curve to model overall survival (OS) in the platinum-based chemotherapy with gemcitabine arm** Our comment is in response to Draft guidance, Section 3.7, Page 10 of 24:

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	"The clinical experts present during the committee meeting thought that the 10-year… results of the generalised gamma model (3%) was most plausible. The EAG explained that the generalised gamma model was plausible but it is more methodologically appropriate to apply the same type of model for both treatment arms." MSD are concerned the committee is overestimating modelled OS in the platinum-based chemotherapy with gemcitabine arm by placing greater weight on statistical methods than clinical plausibility. MSD acknowledges NICE DSU TSD 14 guidance that, "*fitting different types of parametric model (for example a Weibull for one treatment arm and a log normal for the other) to different treatment arms would require substantial justification, as different models allow very different shaped distributions*." (1) In response, MSD note the mechanism of action between platinum-based chemotherapy with gemcitabine and enfortumab vedotin with pembrolizumab is substantially different. Enfortumab vedotin is an anti-body drug conjugate which targets Nectin-4 on cancer cells and can activate immune system, while pembrolizumab is a PD-1/L-1 inhibitor which leads to durable immune response. The combination of them leads to a more potent and effective anti-tumour response. MSD consider this to be substantial justification to use the generalised gamma model in the platinum-based chemotherapy with gemcitabine arm and the log logistic model in the enfortumab vedotin with pembrolizumab arm. There is a precedent for the NICE committee to accept different OS models for each treatment based on clinical plausibility, hazard trends or differing mechanisms of action (TA983, TA992 and TA1027 are recent examples).(2-4) Additionally, there are reasons why OS in the platinum-based chemotherapy with gemcitabine arm is better predicted by the generalised gamma with shorter OS than the log-logistic: • If the time on treatment (ToT) for avelumab is shorter in the NHS than in the KEYNOTE-A39/EV-302 trial, the OS in clinical practice is likely shorter. • If enfortumab vedotin, pembrolizumab, erdafitinib and sacituzumab govetican are subsequent treatment options in the KEYNOTE-A39/EV-302 trial control arm and likely to improve OS, but do not represent options in the NHS, the OS in clinical practice is likely shorter; this point is discussed further in Comment 2 below. • RWE from NHS England reports 2-year OS of 17.6%, which suggests OS in clinical practice is likely shorter than in KEYNOTE-A39/EV-302; this point is discussed further in Comment 3 below. For these reasons, greater weight should be placed on the generalised gamma curve to model OS in the platinum-based chemotherapy with gemcitabine arm when considering the most plausible ICER and disease severity modifier in the base case.
2	**A QALY weighting of 1.2 is most plausible considering subsequent treatments in the UK** Our comment is in response to: Draft guidance, Section 3.14, Page 20 of 24: "*The committee noted that the point estimates of proportional QALY shortfall showed that a QALY weighting of either 1 or 1.2 may be plausible*." MSD has analysed the data in KEYNOTE-A39/EV-302 based on the final analysis database cutoff using APaT (All Participants as Treated) population. Over a quarter of patients in the control arm [redacted] received enfortumab vedotin monotherapy or pembrolizumab monotherapy as their first

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	subsequent therapy or second subsequent therapy (if avelumab maintenance was received as maintenance therapy counted as first subsequent therapy) and a small proportion of patients received erdafitinib monotherapy or sacituzumab govitecan monotherapy [redacted]; however, none of these treatments are options for patients in the NHS. [redacted] This finding is supportive to claim that if KEYNOTE-A39/EV302 patients only had taxanes, platinum-based chemotherapy and atezolizumab as patients in the NHS, their OS rates would be likely lower than the ones observed in the trial control arm. Of note, this comparison should be interpreted with caution given that the treatment groups may not be comparable at the time of initiation of these therapies, and their treatment initiation time point may also have been different. [redacted] [redacted] Additionally, the results of trials reporting >2 years' follow-up data are published (Rosenberg *et al* 2023(5), Fradet *et al* 2019(6)), demonstrating that enfortumab vedotin monotherapy and pembrolizumab monotherapy are associated with statistically significant improvements in OS with hazard ratios of 0.704 (0.581-0.852) and 0.70 (0.57-0.85) compared with chemotherapy (including taxane chemotherapy, which is commonly used in the NHS following progression). This is additional evidence to suggest the OS rates observed in the control arm of KEYNOTE-A39/EV-302 are likely to overestimate OS in NHS clinical practice, making a QALY weighting of 1.2 most plausible.
3	**A QALY weighting of 1.2 is most plausible considering real world evidence (RWE) for OS** Our comment is in response to: Draft guidance, Section 3.14, Page 20 of 24:

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	"To reduce the uncertainty, the committee requested additional evidence on the overall survival of people having standard care treatments that are generalisable to NHS practice." RWE data from patients with locally advanced/metastatic urothelial cancer attending the Leeds Cancer Centre between 2003 and 2017 has been published (Cheeseman et al. 2020(7)). For OS, the study reports 2-year survival of ~30% in the cisplatin sub-cohort, and ~5% in the carboplatin sub-cohort. RWE data has also been published from patients diagnosed with Stage 4 bladder cancer between 2016 and 2020 in England. This registry reports 2-year survival of 17.6%.(8) As avelumab maintenance was not an option at the time of these studies, they can be considered lower bounds for the extrapolation model for platinum-based chemotherapy with gemcitabine (with or without avelumab maintenance). The generalised gamma meets this validation test as it predicts 2-year survival above these estimates ([redacted] at 2 years). RWE data from patients with locally advanced/metastatic urothelial cancer treated in the US post avelumab approval between 2020 and 2023 has been published (Li *et al*. 2025).(9) For OS, they report 2-year survival of 35.7% in patients treated with platinum-based chemotherapy with or without avelumab maintenance. Avelumab maintenance was received by 40% of patients in the study. As more treatments are generally available and access was granted earlier to patients in the US, the proportion of patients on avelumab maintenance is likely to be less and achieve shorter OS in the NHS. If this study is considered an upper bound for the extrapolation model for platinum-based chemotherapy with gemcitabine (with or without avelumab maintenance). The generalised gamma would not meet this validation test as it predicts 2-year survival above 35.7% ([redacted]). Thus, the generalised gamma should be considered a conservative choice to model OS in the NHS. Considering the RWE above, a QALY weighting of 1.2 is most plausible and greater weight should be placed on the generalised gamma curve to model OS in the platinum-based chemotherapy with gemcitabine arm when considering the most plausible ICER.
4	**A QALY weighting of 1.2 is most plausible considering patient views** Our comment is in response to: Draft guidance, Section 3.14, Page 20 of 24: *"The committee recalled that a substantial burden of disease on people with urothelial cancer and their carers was reported by the patient experts (see Section 3.1). The committee noted that the point estimates of proportional QALY shortfall showed that a QALY weighting of either 1 or 1.2 may be plausible."* Given what is known about the significant burden of unresectable or metastatic urothelial cancer on mortality and morbidity, there is little doubt that unresectable or metastatic urothelial cancer meets the definition of severe conditions that the severity modifier has been designed to identify. Therefore, the cost-effectiveness results should be weighted using the 1.2 QALY weight. MSD wants to reiterate views previously provided by Fight Bladder Cancer which support this (Committee Papers, Page 336 of 527): *"The new NICE severity modifier may not fully address the needs of people with metastatic urothelial cancer. This group, often older and with limited treatment options, faces significant barriers to accessing innovative therapies like erdafitinib. The severity modifier, which replaced the end-of-life modifier, was designed to increase the value of treatments for severe conditions. However, it may fail to capture the full impact of therapies for patients in advanced cancer stages. For example, while erdafitinib clearly extends survival and improves quality of life, the weighting applied under the severity modifier might undervalue its benefits for this patient group. Older individuals with shorter life expectancy often achieve a lower QALY gain, potentially resulting in a lower score in NICE's cost-effectiveness*

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	assessments. This shift could reduce access to life-extending treatments that would have previously qualified for higher weighting under end-of-life criteria. Adjustments to the severity modifier's application are needed to ensure equitable access to innovative treatments" Additionally, MSD notes that other treatments recently appraised for metastatic urothelial cancer were assessed under the 2013 NICE Methods Guide and benefitted from end-of-life criteria (e.g., TA788 for avelumab and TA739 for atezolizumab). NICE's end-of-life threshold attributes 70% higher value to QALY gains (by increasing the willingness-to-pay threshold from £30,000 to £50,000), while the moderate severity modifier that should be applicable to enfortumab vedotin with pembrolizumab attributes 20% higher value to QALY gains. If no severity modifier is considered applicable to enfortumab vedotin with pembrolizumab, this exacerbates the question about the fairness of appraising treatments in the same disease and weighting QALY gains differently. Furthermore, a quantitative preference study undertaken by The Office of Health Economics (OHE) and funded by The Association of the British Pharmaceutical Industry (ABPI), concluded that NICE's current criteria for the severity modifier is not well aligned with the public's preference for prioritising health gains. If NICE seeks to align the value and priority assigned to enfortumab vedotin with pembrolizumab with societal preferences, a QALY weighting of 1.2 should apply.(10)
5	**Explicit treatment effect waning assumptions should not be added to the economic model** Our comment is in response to: Draft guidance, Section 3.12: • MSD agrees with the company that, "*because independently fitted overall-survival hazard models had been applied for both treatment arms, any treatment effect waning would already be incorporated*". • MSD agrees with the EAG that, "*treatment effect waning might already be accounted for in the model without an explicit treatment-effect-waning assumption being included*" and "*scenarios may overestimate the impact of treatment effect waning*". • MSD agrees with the clinical experts that, "*both treatments work synergistically to produce long-term immunological change in the body*" and "*there is some evidence showing long-term effect with pembrolizumab in people who had stopped treatment*". MSD considers there to be additional evidence for maintaining the treatment effect of enfortumab vedotin with pembrolizumab in the economic model without including additional waning assumptions: • **Study EV-103 provides 5-year follow-up data in patients treated with enfortumab vedotin and pembrolizumab.** The OS rate in Cohort A was estimated at 41.5% at 5 years, a survival rate that dramatically exceeds historical data (EORTC 30986). Additionally, 47% of patients have maintained a durable response at 5 years.(5) • **According to KEYNOTE-A39/EV-302 results and clinical experts advising the committee, a proportion of patients have been cured.** In KEYNOTE-A39/EV-302, [redacted] and [redacted] of patients treated with enfortumab vedotin and pembrolizumab had a complete response and partial response respectively. Furthermore, clinical experts advising the committee explained that "*the trial results suggest that a proportion of people may be*

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	considered clinically cured" (Draft Guidance, Section 3.5, Page 8 of 24). The submitting company's model structure is therefore conservative as it does not account for cured patients. Also, as the scenarios suggested by the EAG do not account for patients with a complete response or partial response and, as a result, dramatically overestimate the impact of treatment effect waning. • **Long-term data from trials of immunotherapy treatments have shown a sustained treatment effect post treatment discontinuation**. In previous NICE appraisals of immunotherapies, the committee have acknowledged that, "*in many trials of immunotherapies for metastatic NSCLC (which are now quite mature) there was no substantial evidence of treatment-effect waning*". The CDF clinical lead has also previously, "*agreed with the company that if waning of treatment effect were to occur it would likely be visible in the company's data."(11)* • **KEYNOTE-006 represents the longest follow-up (median 10 years) from a phase 3 trial of anti-PD-1/L1 therapy available to date.** The outcomes observed in KEYNOTE-006 with patients treated up to 2 years were generally consistent with those observed in the melanoma cohort of KEYNOTE-001 with similar underlying hazard pattern, which did not include a 2-year stopping rule.(12) • **In the most recent NICE appraisal that assessed pembrolizumab as part of a combination therapy (TA983), treatment effect waning was not discussed**. The Committee considered the plausibility of the extrapolated HRs for OS over time when using different survival curves, without imposing additional waning assumptions.(2) • **No treatment effect waning assumptions are imposed on the proportion of patients who receive avelumab maintenance despite it having a stopping rule**. Applying additional waning assumptions on enfortumab vedotin with pembrolizumab would lead to an inconsistency in the intervention and comparator arms. • **The mechanism of action of pembrolizumab supports a sustained treatment effect.** As immunotherapies act on the patient's immune system rather than directly on the tumour, the immune system will continue to recognise the cancer cells after treatment is stopped, which leads to durable responses and prolonged survival in some patients (Postow *et al*. 2015(13), Brahmer *et al.* 2010(14)). For these reasons, explicit treatment effect waning assumptions should not be added to the economic model or used in decision making for this appraisal.
6	**The committee's preferred approach to model ToT for pembrolizumab will overestimate treatment costs** Our comment is in response to: Draft guidance, Section 3.9, Page 12 of 24: *"The committee understood that the Kaplan–Meier curve for pembrolizumab was not properly applied in the company's revised model. This was because the 24-month stopping rule from the company's original base case was still functional."* MSD are concerned that the delayed dose in the KM curve for pembrolizumab will be double counted when a 24-month stopping rule is removed and this was not the committee's intention.

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	When the full KM curve is employed, it reaches maturity at [redacted] weeks, meaning a total of [redacted] Q3W or [redacted] Q6W treatment cycles will be costed in the model. If a ToT cap of 35 administrations for a Q3W regimen or a ToT cap of 18 administrations for a Q6W regimen is applied (starting with the first administration at Week 0 and ending at Week 102), patients who received delayed administrations are costed earlier than the actual timing in the trial. This is important for two key reasons: 1. When calculating discounted cost of treatment, costs applied at earlier cycles are discounted less heavily than costs in later cycles. Thus, costing delayed administrations earlier produces higher total costs, leading to a conservative estimate of treatment costs. 2. The proportion of patients on pembrolizumab for each protocol-specified administration in the model is likely higher than the actual proportion on pembrolizumab in the trial for a given administration because some patients may not receive pembrolizumab at protocol-specified treatment cycle length and delay receiving the administration in the trial. For example, based on pembrolizumab ToT KM, [redacted] of patients are on pembrolizumab at Week 39 (14th administration); however, the actual time in the trial when patients received the 14th administration is later than Week 39 and consequently the actual percentage receiving the 14th pembrolizumab administration in the trial should be lower than [redacted]. Pembrolizumab treatment was costed in the model based on protocol and thus leading to a conservative estimate of treatment costs. For these reasons, the company's model will overestimate the proportion of patients on pembrolizumab versus the trial and discount pembrolizumab costs earlier versus the trial, in which case it leads to a more conservative approach (higher pembrolizumab costs modelled than calculated using the treatment administrations observed in the trial). To mitigate this issue, the 24-month stopping rule should be included in the model to reflect accurately the total number of pembrolizumab administrations as per protocol.
7	**The company's approach to model ToT for enfortumab vedotin will overestimate treatment costs** MSD are concerned that a plausible and alternative approach to modelling ToT for enfortumab vedotin, suggested by the EAG, has not been considered by the committee. According to the EAG (Committee Papers, Page 415 of 527): *"Most of the company's time on treatment extrapolations for enfortumab vedotin in the ITT population (CS addendum (29 November 2024) Figure 13) predict that some patients will still be on treatment at five years. However, all patients had discontinued treatment by year 3 in Cohort A + dose escalation of the EV-103 trial (CS Figure 21). Clinical advice to the company was that the number of patients receiving enfortumab vedotin treatment would halve each year, and that no patients would be on treatment by Year 5."* MSD agrees with the EAG that the EV-103 trial should be used as supportive evidence to model ToT for enfortumab vedotin, and based on statistical fit, visual fit and clinical plausibility, the generalised gamma model (EAG report, Table 35) should inform the base case analysis. This assumption may have a significant impact on cost-effectiveness as the company's approach to use the log logistic based on statistical fit overestimates treatment costs.
8	**Pre-progression utility values according to treatment arm or response are plausible**

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	Our comment is in response to Draft guidance, Section 3.13, Page 17 of 24: *"The committee considered that sufficient justification would be needed for treatment-dependent utility values to be applied for the entire duration of the pre-progression health state."* MSD wants to reiterate evidence previously provided by Fight Bladder Cancer which supports treatment-dependent utility values (Committee Papers, page 330 of 527): *"In the EV-302 study, for the overall quality of life, pembrolizumab with enfortumab vedotin patients had a brief decline at week 3 but returned to normal afterward. In contrast, patients on chemotherapy experienced a steady decline from week 1 to week 17, with scores dropping between -1.2 and -7.1 below baseline. Although their condition stabilised at week 17, it remained at a worse level compared to patients on pembrolizumab with enfortumab vedotin, who had already recovered by then (Gupta S, Loriot Y, Van Der Heijden MS, et al. PROs from a phase 3 trial of enfortumab vedotin plus pembrolizumab vs. chemotherapy in advanced urothelial cancer. J Clin Oncol. 2024;42(16_suppl):4502. doi:10.1200/JCO.2024.42.16_suppl.4502.)"* Additionally, MSD considers the pre-progression utility values employed by Astellas and the EAG conservative. This is because, within the PFS health state, there are two groups of patients: responders to treatment who have high utility and patients with stable disease who have lower utility. It has been proposed that utilities reported by response may be appropriate to more accurately model immunotherapies (Gibson *et al.* 2018). (15) For this approach, patients with a complete response or partial response can be classified as a "responder" and those with stable disease as a "non-responder", and their utilities within the PFS health state were reported separately. Time to response or progression or death (RPFS) from KEYNOTE-A39/EV-302 (time from randomization to either response or progression or death) can then be modelled to estimate the proportions of PF patients who are non-responders (under the RPFS curve) and who are responders (between the RPFS and PFS curves). Given that [redacted] as many patients in the enfortumab vedotin with pembrolizumab arm had a complete response compared to the control arm ([redacted] versus [redacted]), this analysis would account for some benefits not captured in the current QALY calculation. Considering the points above, enfortumab vedotin with pembrolizumab offers the potential for better quality of life and is a considerable step forward compared with current standard of care. The company's approach to use treatment-dependent utility values for the pre-progression health state rather than response-based should be viewed as conservative.
9	**The company's administration cost codes overestimate treatment costs for pembrolizumab** MSD are concerned that the appropriateness of individual administration cost codes for enfortumab vedotin and pembrolizumab in combination and as monotherapies have not been considered by the EAG or the committee. To inform the unit costs of treatment administration in the economic model, the company employed currency code SB17Z with service code DCRDN (day case setting) for enfortumab vedotin and pembrolizumab in combination and as monotherapies. This is inconsistent with previous appraisals of pembrolizumab where currency code SB12Z with service code OP (outpatient setting) has been accepted (TA540/967, TA997 and TA1017 are recent examples).(16-18) Based on the National Schedule of NHS Costs, the unit cost of these different codes is different (£392 for SB17Z DCRDN versus £208 for SB12Z OP).(19)

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	According to the KEYNOTE-A39/EV-302 protocol, enfortumab vedotin will be administered as an IV infusion over approximately 30 minutes and pembrolizumab will be administered as an IV infusion over approximately 30 minutes. As such, the nurse time and chair time is aligned with previous pembrolizumab indications in an outpatient setting. MSD also consulted clinical experts in the field who advised that typical administration appointments would be held in the outpatient setting of the chemotherapy day unit. A "day case" refers to a procedural unit in the hospital, either for short surgeries or medical procedures and this would not be the clinical environment for the administration of systemic therapies for cancer. Administration costs are likely to have a large impact on cost-effectiveness and the company's approach to use SB17Z DCRDN overestimates treatment costs. To mitigate this issue, administrations of pembrolizumab should use SB12Z OP, as per previous appraisals of pembrolizumab. Committee should also reconsider the most appropriate administration cost codes for enfortumab vedotin. Given that both enfortumab vedotin and pembrolizumab are administered as IV infusions over approximately 30 minutes, MSD believes that SB12Z OP could be applicable to both treatments.
10	**Understanding of the patient population and unmet need** Our comment is in response to Draft guidance, Sections 3.1 to 3.2, Pages 5 to 6 of 24. MSD considers that, further to the details of the condition and treatment options, there is a substantial unmet need in bringing treatments to patients in the first-line metastatic urothelial cancer setting. A recent noninterventional study, published in 2024, showed that 69% of patients diagnosed with la/mUC in England did not access SACT.(20) When put into the context of a systematic literature review and meta-analysis, this study concluded that the proportion of patients not accessing SACT in England is above the median, but within the range, of real world evidence of other countries, suggesting England is lagging behind other countries in providing systemic anti- cancer treatments to patients in first-line metastatic urothelial cancer. When considering the eligibility of patients for standard of care chemotherapy, and bearing in mind the patient experts' description about the impact of chemotherapy on their quality of life, these real-world data demonstrate that the current standard of care is not accessed by many of the patients in England suggesting other treatments are much needed. Furthermore, the analysis from Mahmoudpour *et al.* highlighted that those in socio-economically deprived geographical areas, as well as other factors, were associated with lower SACT use in individuals, based on multivariable analysis. Further work is needed to understand the causes of such low SACT use in this setting, but MSD suggest that providing enfortumab vedotin with pembrolizumab as a treatment option could potentially increase the number of patients accessing SACT. Through our discussions with oncologists, we understand there are numerous reasons why large numbers of la/mUC patients do not access SACT, one of these reasons, for some patients, is likely to be a risk-benefit assessment of current SoC chemotherapy treatment and its associated side effects. Enfortumab vedotin with pembrolizumab has demonstrated a meaningful improvement in outcomes which changes that risk-benefit conversation with patients and oncologists and is likely to provide them with a suitable option where before no treatment would have been undertaken.
11	**Factual inaccuracy** Our comment is in response to Draft guidance, Section 3.14, Page 19 of 24:

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	"But the data did not include the impact of other subsequent treatments that are relevant to the NHS, such as atezolizumab, sacituzumab and erdafitinib." MSD considers the above statement to be erroneous as sacituzumab and erdafitinib are not subsequent treatment options in the NHS at the time of evidence submission and committee meeting. It is correctly noted on Page 18 of 24, "*subsequent treatments (such enfortumab vedotin monotherapy, erdafitinib and sacituzumab) that are not recommended in the NHS*."

Insert extra rows as needed

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Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 29 April 2025. Please submit via NICE Docs.

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Enfortumab vedotin with pembrolizumab for untreated unresectable or metastatic urothelial cancer when platinum-based chemotherapy is suitable [ID6332]

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Single Technology Appraisal

Enfortumab vedotin with pembrolizumab for untreated unresectable or metastatic urothelial cancer when platinum-based chemotherapy is suitable [ID6332]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	N/A
Conflict	N/A
Comments on the DG:	

Are the recommendations sound and a suitable basis for guidance to the NHS?

In my view the recommendations are not sound. This treatment is the new gold standard for the treatment of metastatic bladder cancer in Europe and the US due to 3 main factors
1. Its high response rates compared to the current standard treatment in England (described as being significantly better in the trial document)
2. The chances of a durable response - a complete response rate of almost 30% compared to a complete response rate of 12.5% with platinum based chemotherapy (according to the study report from the EV-302 trial). This complete response has been shown to be durable offering the hope of long term survival and much better quality of life for the patients
3. Good tolerance and fewer serious adverse effects than with chemotherapy.

I cannot understand why this new game changing treatment option should not be made available as it has been adopted as current best practice in so many other countries, offering hope and quality of life to patients who would otherwise face a severely shortened life expectancy and brutal side effects from the chemotherapy. The recommendation should be to use this treatment where suitable and to be funded by the NHS.

External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Enfortumab vedotin with pembrolizumab for first-line treatment of unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy [ID6332]

EAG critique of company's response to draft guidance

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Fay Chinnery, Research Fellow, Health economics Keith Cooper, Principal Research Fellow, Health economics Emma Maund, Research Fellow, Evidence synthesis Jonathan Shepherd, Principal Research Fellow, Evidence synthesis
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Date completed	08 May 2025

Confidential information from the company submission is highlighted in blue

1 INTRODUCTION

This document is the External Assessment Group's (EAG) critique of the response by the company, Astellas, to the NICE Draft Guidance Document (DGD), issued on 25th March 2025, following the NICE Advisory Committee Meeting (11th March 2025) for the technology appraisal of enfortumab vedotin with pembrolizumab for untreated unresectable or metastatic urothelial cancer when platinum-based chemotherapy is suitable (ID6332).

The EAG received the company's response documents and their revised economic model on 30th April 2025. In addition, the NICE technical team provided the EAG with additional evidence from the Systemic Anti-Cancer Therapy (SACT) data set on 16th April 2025.

In this addendum we present the following:

- The EAG's critique of the company's response and new evidence (section 2)
- Validation of the results of the company's updated cost-effectiveness analysis (section 3).
- The EAG's preferred assumptions and analyses (section 4).

2 EAG CRITIQUE OF THE COMPANY'S RESPONSE TO THE APPRAISAL CONSULTATION DOCUMENT

The following sections refer to items discussed in the company's response document (dated 29th April 2025).

2.1 Comment 1: Time on pembrolizumab based on EV-302 trial

The company's revised base case (dated 29th April 2025) uses the full Kaplan-Meier curve to estimate time on treatment for pembrolizumab in the EV-302 trial, rather than implementing a cut-off at two years (Figure 1). The company explains that this approach captures pembrolizumab use by patients who may have missed doses and reached the maximum allowable number of cycles later than 24 months. The EAG considers this change to be appropriate, because it likely better reflects what would happen in NHS practice compared with a treatment cut-off at two years.

Figure 1 Pembrolizumab time on treatment, Kaplan-Meier data from the EV-302 trial (no cut-off after 24 months of treatment)

2.2 Comment 2: Data sources informing responses to NICE Committee requests

The NICE appraisal committee requested further information on:

i) time on treatment for avelumab maintenance therapy in the NHS,
ii) the proportion of people having avelumab maintenance in the NHS, and
iii) the overall survival of people having standard care treatments that are generalisable to NHS practice, including the impact of avelumab maintenance treatment.

In response to these requests, both the company and NICE independently conducted a number of analyses using data on patients diagnosed with metastatic urothelial cancer from National Disease and Registration Service (NDRS) Systemic Anti-Cancer Therapy (SACT) dataset (hereafter referred to as "SACT"). The SACT dataset collects information on the use of systemic any-cancer therapies across all NHS England trusts.

SACT database inclusion/exclusion criteria

The inclusion and exclusion criteria applied to the SACT dataset by NICE and by the company were generally similar e.g. inclusion of adults aged at least 18 years at the time of diagnosis and who were diagnosed between the years 2020 and 2022. However, there a few differences, as shown in Table 1 below. Specifically, the company's inclusion criteria were designed to align with the EV-302 trial, which informs the company's economic model.

Table 1 Differences in NICE and the company's SACT inclusion/exclusion criteria

Characteristic	NICE analysis	Company analysis
Stage of disease	Stage 4 (metastatic) plus either M of 1 (distant metastases) or M status unknown	Stage 4 (metastatic) only
Multiple tumours of interest (bladder, renal pelvis and ureter) diagnosed between 2020 and 2022	Excluded	Included but should a patient have received multiple primary diagnoses of mUC between 2020 and 2022, the first such tumour will be selected.
Avelumab regimens	No restriction	Initiated between one day after the start of the first-line platinum-based regimen and up to 43 weeks from the start of the first-line platinum-based regimen (to avoid off-label use and for other licensed indications)
Platinum based chemotherapy (PBC) treatment date	No restriction	Cohort B started the first platinum-based regimen between 01/05/2022 and 31/07/2024

The EAG note that the NICE SACT dataset is similar in size to the company SACT dataset (N=793 versus N=771 patients respectively).

NICE and the company each constructed 3 cohorts of patients from their respective SACT datasets in order to provide the further information requested by the NICE appraisal committee. These cohorts are shown in Table 2 below:

Table 2 Overview of NICE and the company's SACT data set cohorts

	Cohort	Description	N
NICE analyses	Cohort 1	Received PBC only i.e. **did not have** subsequent avelumab maintenance therapy	642
	Cohort 2	Received PBC and **had** subsequent avelumab maintenance therapy	151
	Cohort 3	Cohorts 1 and 2 pooled	793
Company analyses	Cohort A	Received PBC prior to 1 May 2022 i.e. **before** avelumab becoming routinely available on the NHS (pre-avelumab recommendation TA788)	431
	Cohort B	Received PBC after 1 May 2022 up to 31 July 2024, i.e. **after** avelumab becoming routinely available on the NHS (post-avelumab recommendation TA788)	340
	Cohort A +B	Cohorts A and B pooled	771

Source: EAG-created table
Abbreviations: N, number of patients; PBC, platinum-based chemotherapy

There were differences in how NICE and the company constructed their cohorts, but overall the EAG considers that both sets of cohorts can provide the information the NICE committee requested.

Patient characteristics

The NICE analyses provided patient baseline characteristics of gender, and age by gender only. The company, in contrast, provided more detailed baseline characteristics including % aged ≥ 75 years, index of multiple deprivation quintiles, Eastern Cooperative Oncology Group (ECOG) performance status (PS), duration of follow up, ethnicity and tumour site.

The percentage of female patients was similar between the NICE cohorts and the company cohorts (range 29.1% to 32.7%) but slightly greater than the comparator arm of trial EV-302 (24.3%). Median and interquartile age range was also similar between the NICE and company cohorts (median age range from 68 to 71 years) and the comparator arm of trial EV-302 (median age 69 years).

With respect to the company cohorts only, the % aged ≥ 75 years ranged from 27.4% to 29.5%, which was slightly greater than the comparator arm of EV-302 (24.3%). ECOG PS was also similar between the company cohorts, with a similar proportion of patients having an ECOG PS of 2 (range 9% to 11.8%), in comparison to trial EV-302, where only 2.5% of patients in the comparator arm had an ECOG PS of 2. Furthermore, the percentage of White patients ranged from 83.2% to 87% in the company cohorts compared to 65.3% in the comparator arm of trial EV-302.

Clinical expert advice to the EAG is that the EV-302 trial population is younger, fitter and with fewer White patients than that seen in clinical practice. The EAG therefore consider the company cohorts to be more similar to the population seen in NHS clinical practice than the EV-302 trial population. Given that the NICE cohorts are also constructed from the SACT dataset, the EAG considers it reasonable to assume the NICE cohorts are also more similar to the population seen in NHS clinical practice than is the case for the EV-302 trial population.

Parametric survival distributions chosen to model overall survival in SACT cohort data analyses

The choice of the distributions chosen to model overall survival in the SACT cohort data analyses are shown in Table 3. The company prefers to use the log-logistic for all of the NICE cohorts (1-3), explaining that it was the best fit (using the AIC and BIC criteria) for cohorts 1 and 3, and a close second best fit for cohort 2. The EAG agrees with the company's conclusion (Table 4), and we consider the log-logistic a reasonable choice for modelling overall survival for all of the SACT cohorts.

Table 3 Distributions modelling overall survival in the SACT data cohorts

SACT data set cohort	Choice of parametric survival distribution	
	NICE	Company
Cohort 1	Log-logistic	Log-logistic
Cohort 2	Lognormal	Log-logistic
Cohort 3	Log-logistic	Log-logistic
Cohort A	n/a	Log-logistic
Cohort B	n/a	Log-logistic
Cohort A+B	n/a	Log-logistic

Source: EAG-created table
Abbreviations: SACT, Systemic Anti-Cancer Therapy

Table 4 Overall survival model fit, SACT cohort 2, NICE analysis

Distribution	AIC	BIC
Lognormal	928.90	934.93
Log-logistic	931.60	937.64

Source: EAG-created table
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; SACT, Systemic Anti-Cancer Therapy

2.3 Comment 3: Proportion of patients initiated on avelumab in the NHS

The committee considered the proportion of patients in the gemcitabine with PBC control arm receiving avelumab maintenance therapy in the EV-302 trial (30%), which is used in the economic model, to be relevant to the NHS, but requested the company provide further evidence. The company presented evidence from the data sources used in their original submission, and additional data from the SACT analyses undertaken by NICE and the company (Table 5).

Table 5 Evidence for the estimated proportion of patients receiving avelumab therapy

Proportion of patients receiving avelumab	Source
28%[a]	EVEREST-2 (Astellas Pharma Europe. Adelphi mUC Disease Specific Programme (EVEREST study), Data December 2023 to May 2024: Report in development, (2024).
31%	Company original SACT data analyses (April 2023 to March 2024)
[redacted]	Company market research data from a panel of around 50 UK clinical specialists
19%	NICE SACT analysis; cohorts 1[b] + 2[c] combined
20%	Company SACT analysis; cohort B[d]

Source: EAG-created table
Abbreviations: mUC, metastatic urothelial cancer; SACT, Systemic Anti-Cancer Therapy
[a] Patients who received PBC at first-line treatment and received maintenance avelumab (at any line) in the UK
[b] Cohort 1 received gemcitabine with platinum chemotherapies only, no avelumab maintenance therapy, N=642 patients.
[c] Cohort 2 received gemcitabine with platinum chemotherapies plus subsequent maintenance avelumab, N=151 patients.
[d] Cohort B received platinum-based chemotherapies after 1 May 2022, i.e. the cohort reflects clinical practice after the recommendation of avelumab; N=340 patients.
Differences between the inclusion criteria of the patient cohorts used in the NICE and company's analyses are described fully in the company's response document, comment 2, p.3-4.

The EAG notes that altering the proportion of patients receiving avelumab in the economic model affects the total costs in the gemcitabine with PBC control arm, but does not affect the QALYs gained in this arm i.e. it is only possible to change the costs for avelumab in the model, but using a lower proportion of patients on avelumab would also have an effect on the survival outcomes. Consequently, while the SACT data may provide an indication of the proportion of patients in UK clinical practice receiving avelumab, we prefer to continue to use the proportion of patients receiving avelumab from the EV-302 trial. However, we present a scenario where 20% of patients in the gemcitabine with PBC arm receive avelumab therapy, reflecting the proportion seen in the SACT data (section 4.2).

2.4 Comment 4: Time on avelumab maintenance therapy

In response to the committee's request for further information concerning time on treatment for avelumab maintenance therapy in the NHS, the company provided:

- Treatment duration estimates from the NICE and company SACT analyses (NICE cohort 2 and company cohort B, respectively)
- Evidence from a recent meta-analysis (Barthelemy et al. 2025)[1]
- Estimates from clinical experts

The company highlights that follow-up for the SACT cohort 2 data set is not complete and suggests that if it was longer, the estimated time on treatment would likely increase.

The company's base case continues to use the Weibull distribution to model avelumab time on treatment. However, we note that that this is presented as Scenario 1 in the results (Table 6 and Appendix B of the company response document). We agree with the company that the hazards for the exponential curve (as preferred by the EAG) do not predict an avelumab treatment stopping rate that reduces over time, as suggested by the company's clinical experts and observed in the EV-302 trial. However, the EAG considers that the Weibull model overestimates avelumab treatment duration (Table 6). We continue to use the exponential distribution to model avelumab time on treatment in our base case, because (of the extrapolations of the EV-302 trial data in the economic model) it produces the shortest time on treatment for avelumab therapy.

Table 6 Estimates of avelumab treatment duration

Source	Avelumab time on treatment (months)	
	Mean	**Median**
SACT cohort B[a]	8.20	2.88 (95% CI: 2.43 – 4.8)
SACT cohort 2[a]; NICE estimate of restricted mean	11.07	4.7 (95% CI: 3.3 – 5.99)
SACT cohort 2[a]; company estimate of mean	14.9	4.7 (95% CI: 3.3 – 5.99)
Barthelemy et al. (2025)	Not reported in source	4.8 (range 3.8 – 7.1)
Company's clinical experts	Experts estimated % patients receiving avelumab over time, not the mean or median treatment duration	
EV-302; Weibull distribution (company base case)	16.94	[redacted]
EV-302; exponential distribution (EAG base case)	13.94	[redacted]

Source: EAG-created table
Abbreviations: SACT, Systemic Anti-Cancer Therapy
[a] Cohort 2 received gemcitabine with platinum chemotherapies plus subsequent maintenance avelumab, N=151 patients.
Cohort B received platinum-based chemotherapies after 1 May 2022, i.e. the cohort reflects clinical practice after the recommendation of avelumab; N=340 patients

Using SACT data to model avelumab time on treatment in the economic model affects the total costs in the gemcitabine and platinum-based chemotherapy control arm, but does not affect the number of QALYs gained in this arm. We agree with the company that it is not appropriate to adjust avelumab time on treatment for costs only. Consequently, we prefer not to use SACT data to model avelumab time on treatment.

2.5 Comment 5: Pembrolizumab treatment effect waning

The company does not consider it appropriate to include an explicit treatment waning effect for pembrolizumab, because:

- The hazard rates of the log-logistic curves converge over time, suggesting treatment effect waning is implicitly included in the model (EAG report, Figure 8)
- The 5-year follow-up of the EV-103 Cohort A + dose escalation shows a sustained plateau in PFS and OS from three years onwards (company response document, Figure 4)

- The survival estimates produced by the log-logistic survival extrapolation, without additional treatment effect waning, are supported by clinical advice received by company (company response document, p.14)

The EAG agrees with the company, we consider that treatment effect waning has been adequately accounted for within the model and have no further comments on this issue.

2.6 Comment 6: Severity modifier

The company presents the estimated proportional shortfall for the severity modifier for their corrected base case, the EAG base case and the SACT data analyses in company response document Table 6. These indicate that, for the company and EAG base case, the proportional shortfall is 0.84 and the severity modifier is 1.0. For the SACT analyses, the proportional shortfall ranges between 0.87 and 0.9 and the severity modifier is 1.2.

The company also comments that a NICE appraisal of erdafitinib for patients who have had previous treatment accepted a severity modifier of 1.7 (NICE ID1333). They also note that the observed survival for patients receiving platinum-based chemotherapy have worse survival outcomes compared to what was observed in the EV-302 trial (company response document Figure 6).

The EAG has checked and confirmed the company's analyses. We acknowledge the variation in the proportional shortfall using different sources. As the SACT data appear more similar to UK clinical practice than the EV-302 trial, we consider it is reasonable to use a severity modifier of 1.2 for this population.

2.7 Comments 7 -9

The company describes text in the draft guidance document that they would like to amend (comment 7) or have provided additional clarification for (comments 8 and 9).

3 EAG VALIDATION OF THE COMPANY'S REVISED COST-EFFECTIVENESS RESULTS

In response to the draft guidance, the company have amended their base case. The following changes were made to reflect the EAG base case:

- Correction to pembrolizumab time on treatment: calculations now reflect time on treatment as observed in the EV-302 trial, where patients stopped after 35 completed

cycles, i.e. allowing patients to receive pembrolizumab after 24-months too if required due to previously missed doses (see section 2.1).

- Discounting: discounting starts in the first cycle, rather than starting at end of first year.
- Pre-progression utilities: the treatment specific utility for platinum-based chemotherapy was applied for the first six months (u=[redacted]) and then the treatment independent utility thereafter (u=[redacted]). The treatment independent utility was used for enfortumab vedotin with pembrolizumab (u=[redacted]) throughout the pre-progression period.
- PFS for enfortumab vedotin with pembrolizumab and chemotherapy: the standard log-logistic distribution was used to extrapolate curves, rather than splines.
- Time on treatment for avelumab maintenance therapy: the EAG base case uses the exponential curve, rather than the Weibull distribution.

The EAG has checked the revised company's model and confirms that the changes above have been implemented appropriately.

In Table 6 of the company response document, the company presents their corrected base case with the EAG and committee's preferred assumptions. However, the company also states on p.11 that they prefer to use the Weibull distribution to model time on treatment for avelumab in their base case (presented as scenario 1 in Table 6). The full results for the EAG base case and revised company base case are shown in Table 13 and Table 14 of the company response document, respectively.

4 EAG ANALYSES

4.1 EAG preferred assumptions

The EAG maintains the position that the Weibull distribution overestimates the time of treatment for avelumab and the exponential distribution is more appropriate in the circumstances (see section 2.4). The EAG's preferred base case is shown in Table 6 of the company response document and repeated below in Table 7 and shows an ICER of [redacted] and [redacted] per QALY, with and without the severity modifier for enfortumab vedotin, compared with gemcitabine with PBC.

Table 7 EAG preferred assumption with pembrolizumab amended time on treatment

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Without severity modifier					
Gemcitabine + PBC	[redacted]	[redacted]			
EV + P	[redacted]	[redacted]	[redacted]	1.34	[redacted]
With severity modifier of 1.2					
Gemcitabine + PBC	[redacted]	[redacted]			
EV + P	[redacted]	[redacted]	[redacted]	1.60	[redacted]

Source: Adapted from company response document Table 13
Abbreviations: EV+P, enfortumab vedotin with pembrolizumab; ICER, incremental cost effectiveness ratio; PBC, platinum-based chemotherapy; QALYs, quality adjusted life years

4.2 Scenario analyses on EAG's preferred assumptions

The EAG conducted a scenario using 20% of patients receiving avelumab in the chemotherapy arm and the ICER increased to [redacted] per QALY using the severity modifier of 1.2.

Table 8 EAG's scenario analyses with PAS for enfortumab vedotin

			ICER (£/QALY)	
Scenario	**Incr. costs**	**Incr. QALYs**	**No severity modifier**	**Severity modifier of 1.2.**
EAG base case	[redacted]	1.34	[redacted]	[redacted]
20% of patients receive avelumab in gem+ PBC arm	[redacted]	1.34	[redacted]	[redacted]

Source EAG created table
Abbreviations: EV+P, enfortumab vedotin with pembrolizumab; ICER, incremental cost-effectiveness ratio; incr., incremental; LYG, life years gained; OS, overall survival; PBC+gem, platinum-based chemotherapy (cisplatin or carboplatin) gemcitabine; PFS progression-free survival; QALYs, quality-adjusted life years;

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Age, Gender and Overall Survival for Gemcitabine + Platinum Chemo (no Avelumab)

Introduction

This report was produced in partnership by the National Disease and Registration Service (NDRS) and National Institute for Health and Care Excellence (NICE). It presents overall survival and patient characteristics among patients who have received platinum-based chemotherapy with gemcitabine for the treatment of metastatic urothelial cancer with no record of avelumab maintenance.

Method

A snapshot of SACT data was taken on 4th January 2025 and made available for analysis on 20th January 2025. SACT is only considered complete when 90% of trusts have submitted data. As a result, SACT is considered complete up to 31st March 2024. Patients were traced for their vital status on 5th October 2024.

Descriptive statistics of age and gender were computed, as well as overall survival (OS) Kaplan-Meier graphs and parametric fits.

Cohort inclusions / exclusions

Patients were included in this cohort where :

- Tumour site was consistent with the NDRS site groups 'Bladder', 'Renal pelvis and ureter', or 'Urethra'
- Country code was 'England'
- Age was 18 or over
- Gender field was known (male or female)
- Diagnosis occurred between 2020 and 2022
- Stage of 4 (4, 4A or 4B) at diagnosis
- M of 1 (distant metastases) or unknown
- First systemic treatment was Gemcitabine plus platinum chemotherapy (first regimen following diagnosis, identified using start date of regimen)

and excluded where:

- Multiple tumours of interest (bladder, renal pelvis and ureter) were diagnosed between 2020 and 2022
- Subsequent treatment (up to to 31st March 2024) included Avelumab

Patient Acknowledgement

This work uses data that has been provided by patients and collected by the NHS as part of their care and support. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of NHS England.

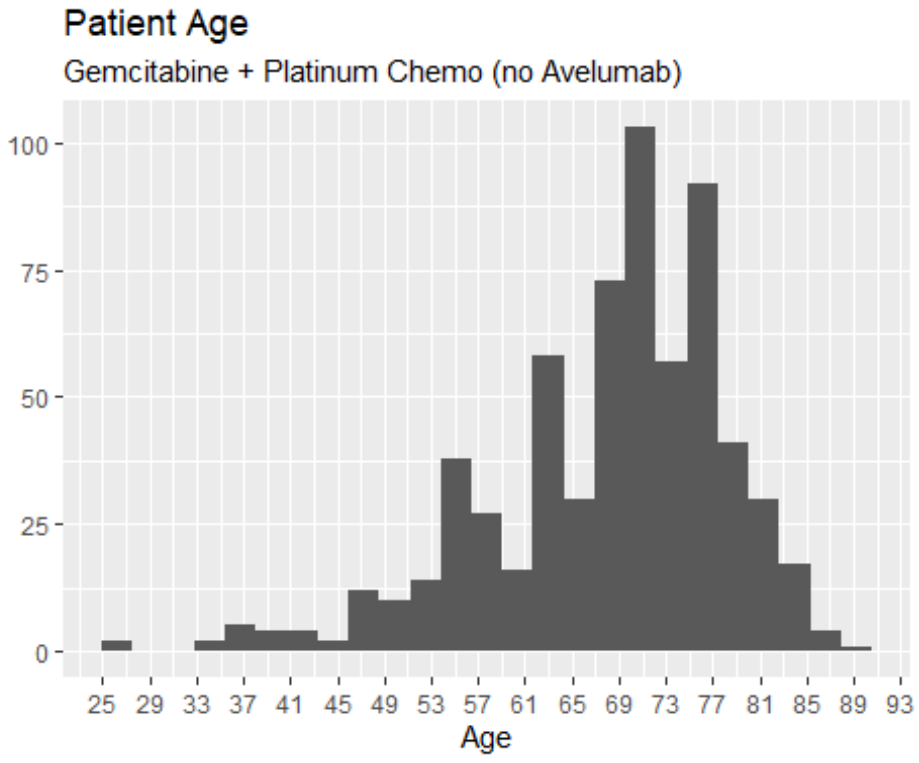
Results

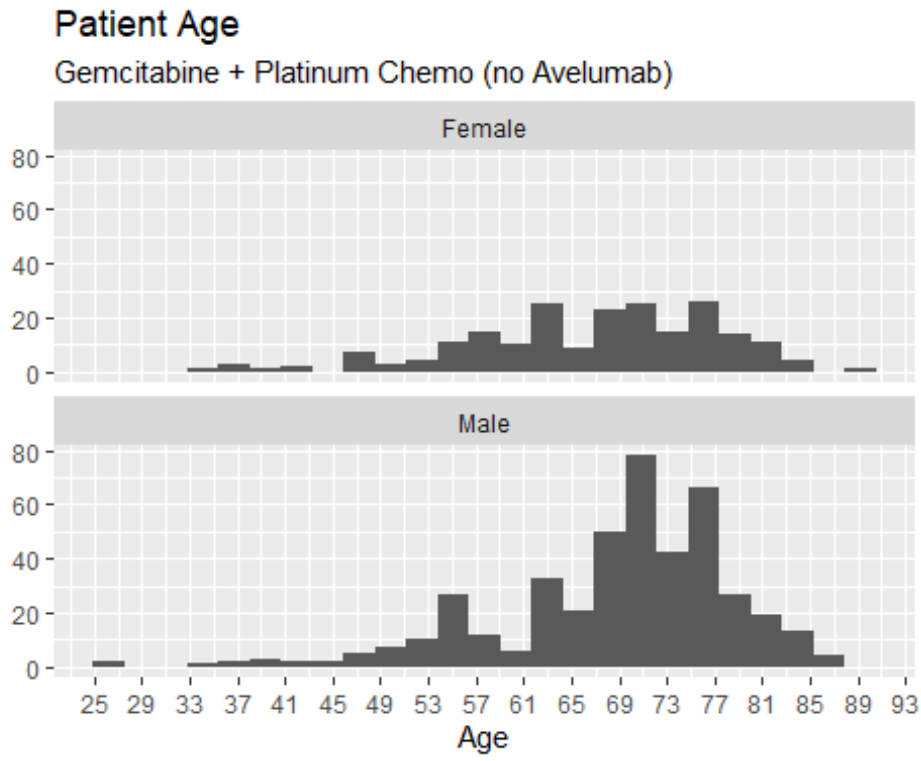
Age at start of treatment

The table below sets out the mean age, std. deviation, median age and IQR of patients who have received Gemcitabine + Platinum Chemo (no Avelumab). Age is measured at the commencement of the first treatment regimen.

Characteristic	**Female** N = 210[1]	**Male** N = 432[1]
Age at start of regimen	67, (10) : 68 (61, 75)	69, (10) : 71 (64, 76)

[1]Mean, (SD) : Median (Q1, Q3)

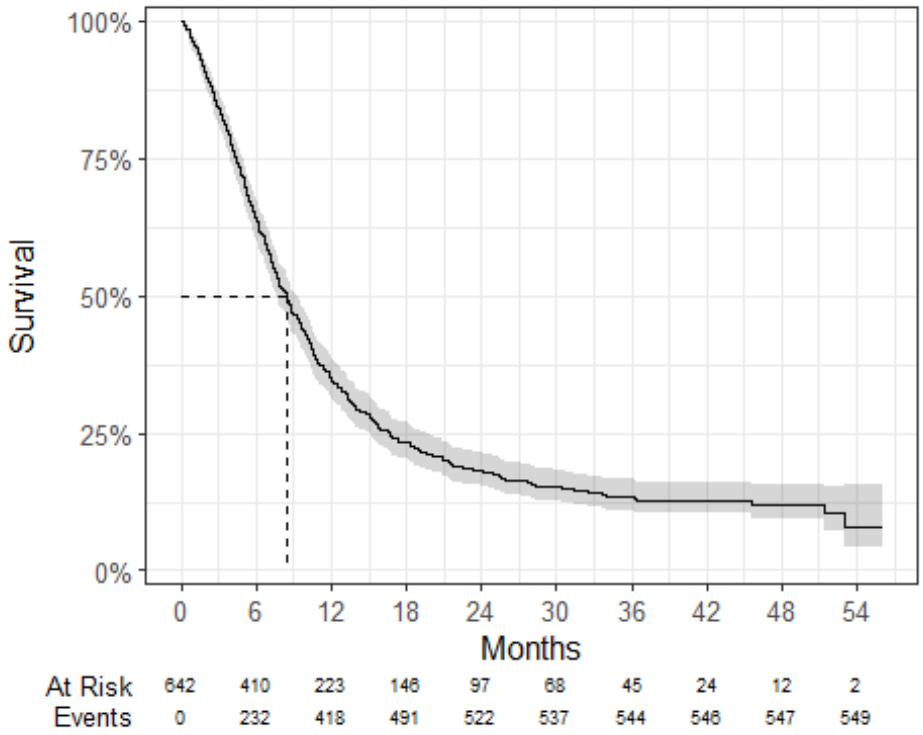



Patient Age
Gemcitabine + Platinum Chemo (no Avelumab)
Female
Male
80
60
40
20
0
25 29 33 37 41 45 49 53 57 61 65 69 73 77 81 85 89 93
Age

Overall Survival

Base K-M plot

The Kaplan-Meier plot below shows survival over time for those receiving a treatment regimen of Gemcitabine + Platinum Chemo (no subsequent Avelumab maintenance). The median OS was 8.4 months, CI (7.7 months, 9.3 months).



Exponential

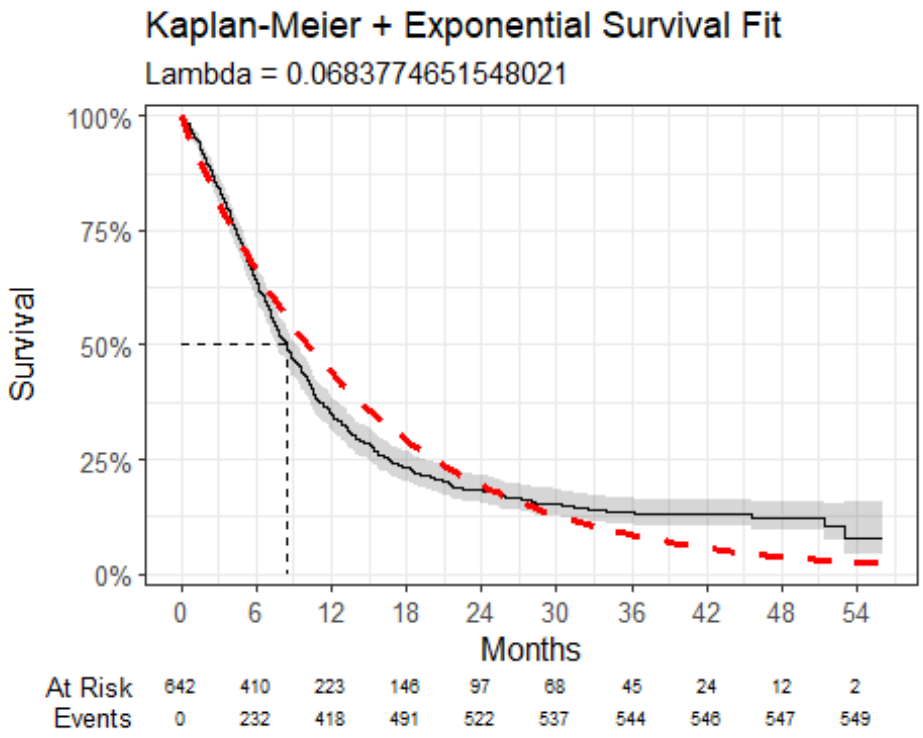


Table 1: Survival Model Fit Summary (Exponential distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	2.683	0.043	62.85795	0

log-likelihood = -2021.80886904916

AIC = 4045.617738

BIC = 4050.082326

Weibull

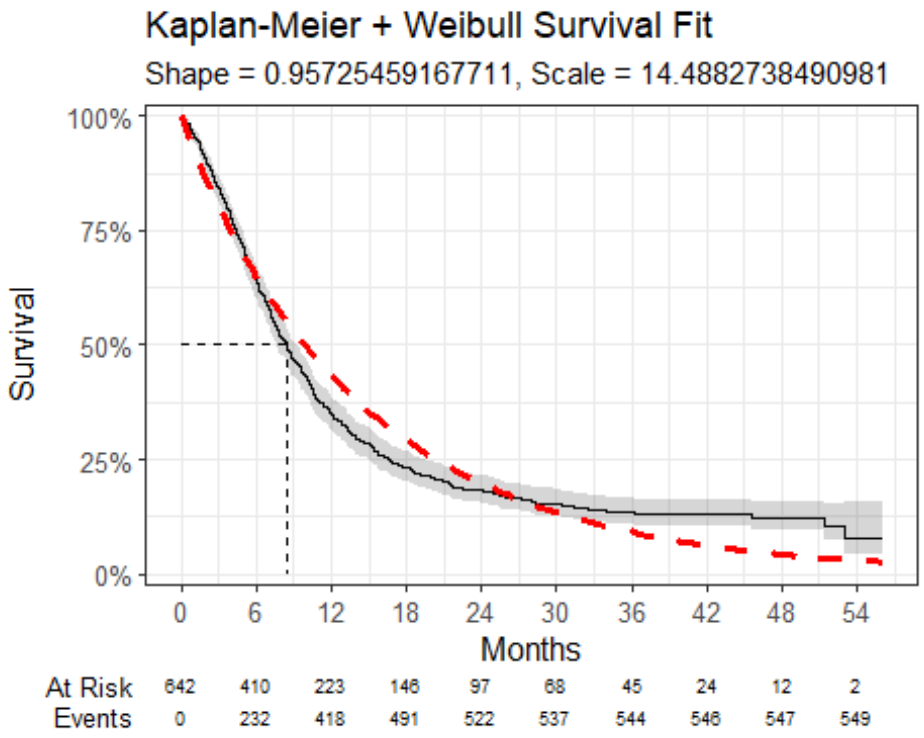


Table 2: Survival Model Fit Summary (Weibull distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	2.673	0.045	59.241789	0.0000000
Log(scale)	0.044	0.034	1.289564	0.1972022

log-likelihood = -2020.95852877918

AIC = 4045.917058

BIC = 4054.846234

Log-Normal

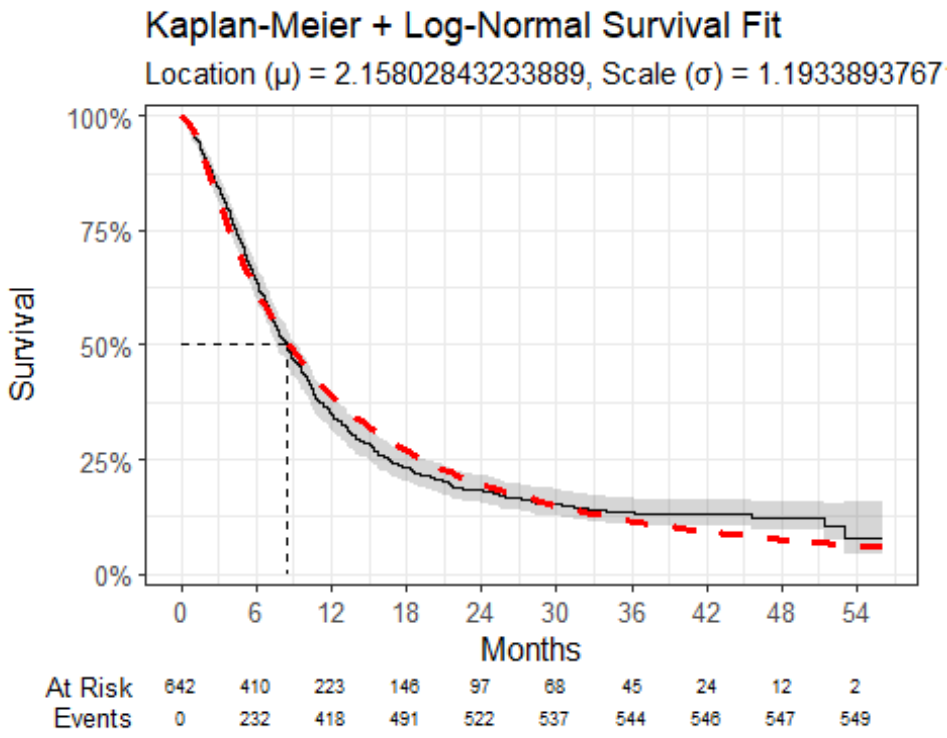


Table 3: Survival Model Fit Summary (Log-Normal distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	2.158	0.048	45.020112	0.00000e+00
Log(scale)	0.177	0.031	5.646022	1.64203e-08

log-likelihood = -1986.11899735246

AIC = 3976.237995

BIC = 3985.167171

Log-Logistic

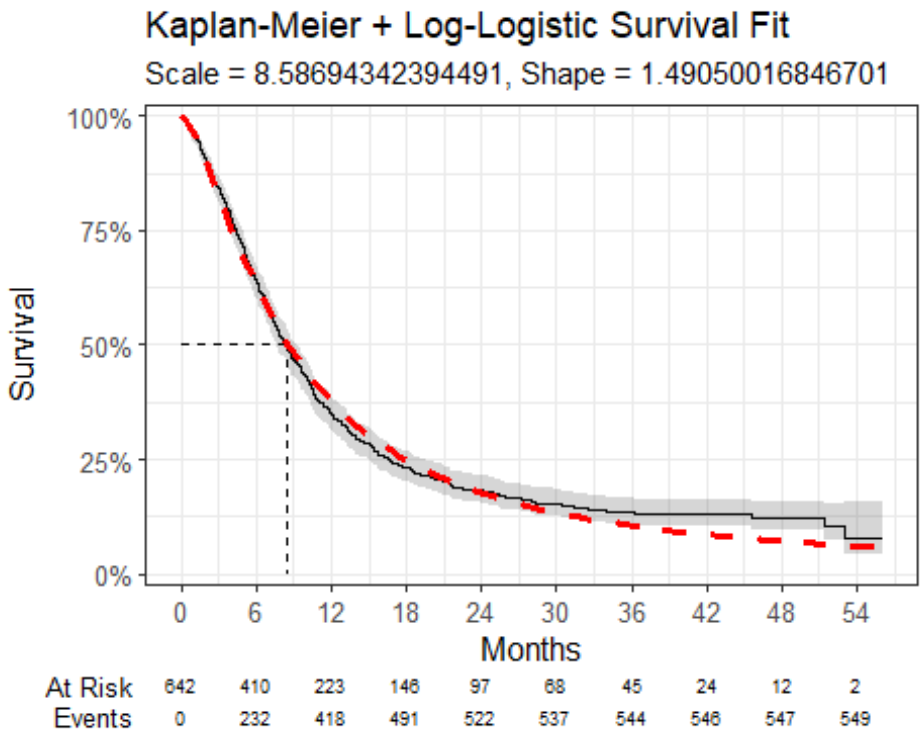


Table 4: Survival Model Fit Summary (Log-Logistic distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	2.150	0.046	47.09556	0.000000e+00
Log(scale)	-0.399	0.036	-11.10994	1.122319e-28

log-likelihood = -1977.03051896372

AIC = 3958.061038

BIC = 3966.990215

Gaussian

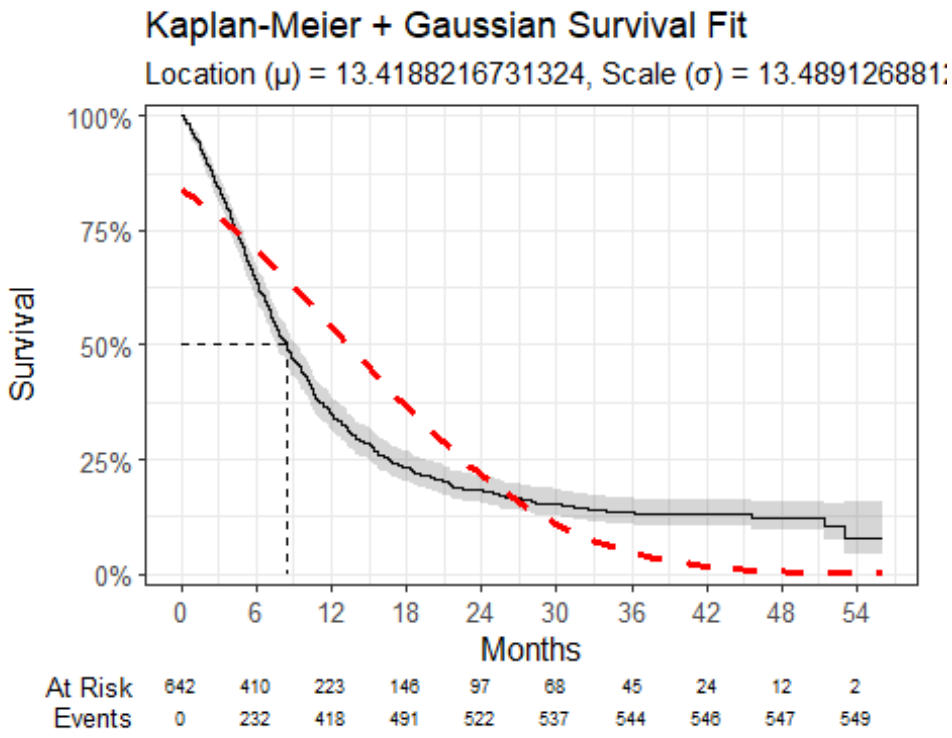


Table 5: Survival Model Fit Summary (Gaussian distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	13.419	0.541	24.82184	5.210194e-136
Log(scale)	2.602	0.032	82.54919	0.000000e+00

log-likelihood = -2321.95966636666

AIC = 4647.919333

BIC = 4656.848509

Age, Gender and Overall Survival for Gemcitabine + Platinum Chemo (with Avelumab maintenance)

Introduction

This report was produced in partnership by the National Disease and Registration Service (NDRS) and National Institute for Health and Care Excellence (NICE). It presents overall survival and patient characteristics among patients who have received platinum-based chemotherapy with gemcitabine and avelumab maintenance for the treatment of metastatic urothelial cancer.

Method

A snapshot of SACT data was taken on 4th January 2025 and made available for analysis on 20th January 2025. SACT is only considered complete when 90% of trusts have submitted data. As a result, SACT is considered complete up to 31st March 2024. Patients were traced for their vital status on 5th October 2024.

Descriptive statistics of age and gender were computed, as well as overall survival (OS) Kaplan-Meier graphs and parametric fits. Time on Treatment was measured by the difference between a patient's first and last avelumab administration date, plus a prescription length of fourteen days. If the patient had an administration date after 15 March 2024, the patient is assumed to still be on treatment and censored.

Cohort inclusions / exclusions

Patients were included in this cohort where :

- Tumour site was consistent with the NDRS site groups 'Bladder', 'Renal pelvis and ureter', or 'Urethra'
- Country code was 'England'
- Age was 18 or over
- Gender field was known (male or female)
- Diagnosis occurred between 2020 and 2022
- Stage of 4 (4, 4A or 4B) at diagnosis
- M of 1 (distant metastases) or unknown
- First systemic treatment was Gemcitabine plus platinum chemotherapy (first regimen following diagnosis, identified using start date of regimen)
- Subsequent treatment (up to to 31st March 2024) included Avelumab

and excluded where:

- Multiple tumours of interest (bladder, renal pelvis and ureter) were diagnosed between 2020 and 2022

Patient Acknowledgement

This work uses data that has been provided by patients and collected by the NHS as part of their care and support. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of NHS England.

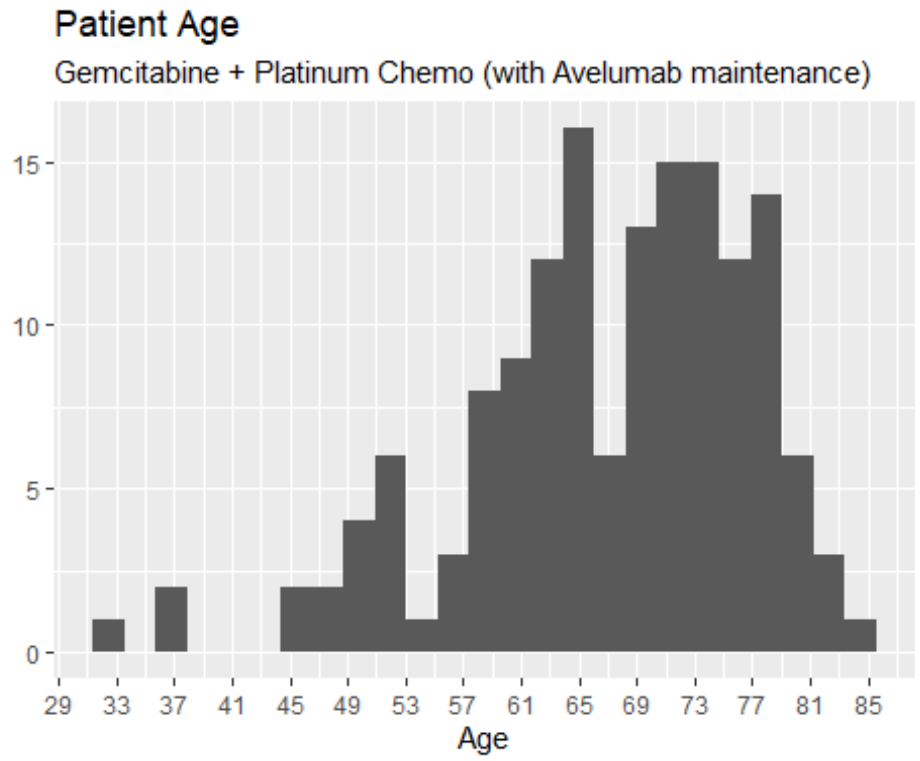
Results

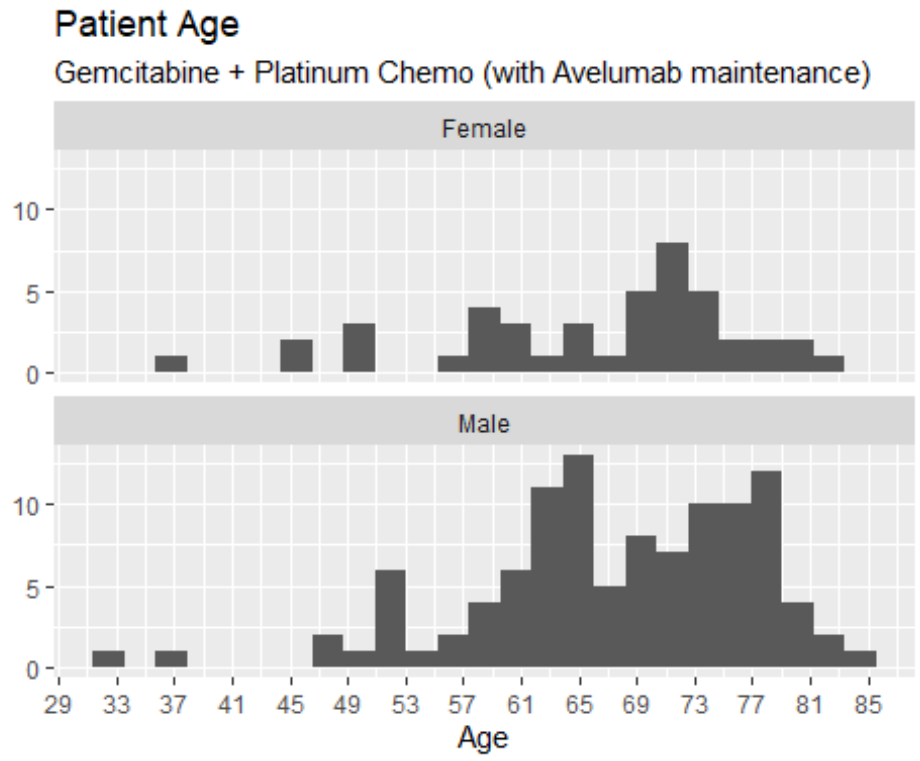
Age at start of treatment

The table below sets out the mean age, std. deviation, median age and IQR of patients who have received Gemcitabine + Platinum Chemo (with Avelumab maintenance). Age is measured at the commencement of the first treatment regimen.

Characteristic	**Female** N = 44[1]	**Male** N = 107[1]
Age at start of regimen	66, (11) : 70 (60, 73)	68, (10) : 69 (62, 75)

[1]Mean, (SD) : Median (Q1, Q3)

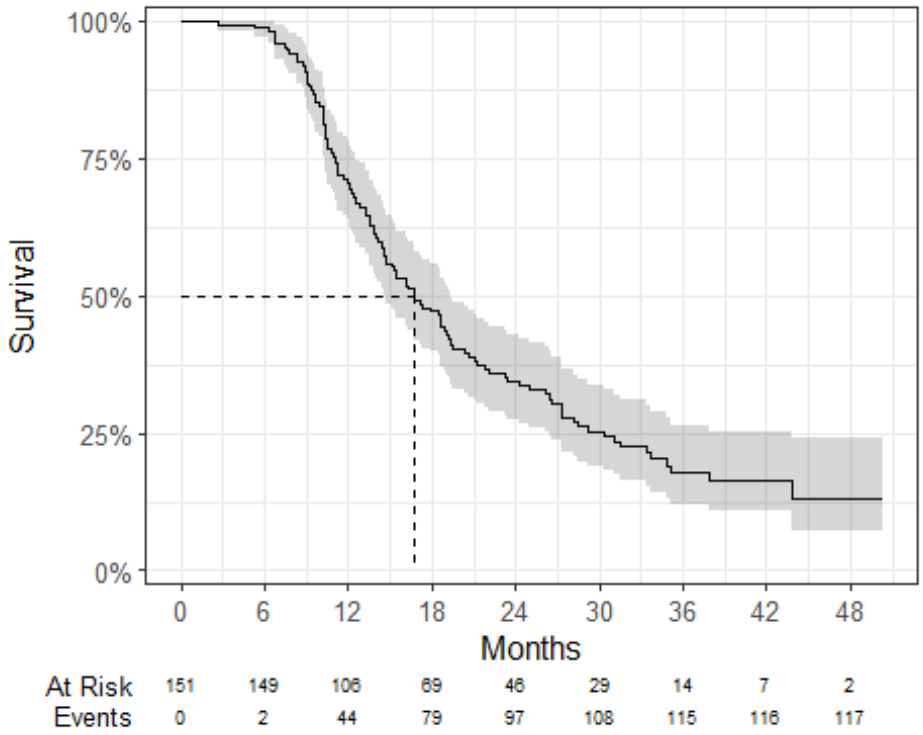



Patient Age
Gemcitabine + Platinum Chemo (with Avelumab maintenance)
Female
Male
10
5
0
29
33
37
41
45
49
53
57
61
65
69
73
77
81
85
Age

Overall Survival

Base K-M plot

The Kaplan-Meier plot below shows survival over time for those receiving a treatment regimen of Gemcitabine + Platinum Chemo (with Avelumab maintenance). The median OS was 16.7 months, CI (14.7 months, 19.4 months).



Exponential

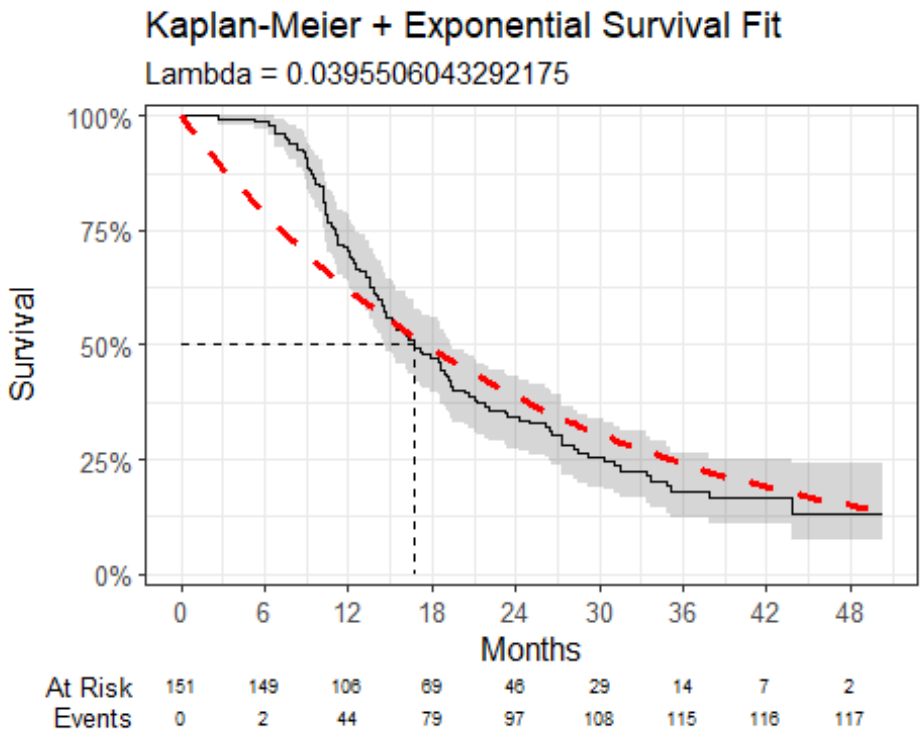


Table 1: Survival Model Fit Summary (Exponential distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	3.230	0.092	34.93968	1.857933e-267

log-likelihood = -494.930393656135

AIC = 991.8607873

BIC = 994.8780671

Weibull

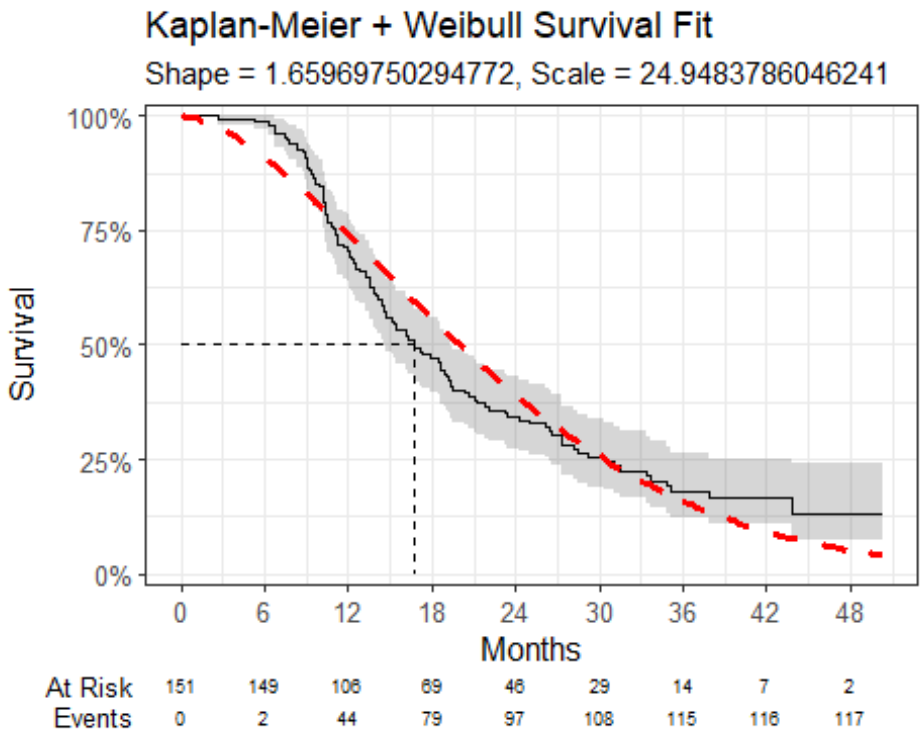


Table 2: Survival Model Fit Summary (Weibull distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	3.217	0.056	57.590691	0.000000e+00
Log(scale)	-0.507	0.073	-6.925757	4.336495e-12

log-likelihood = -476.229805857177

AIC = 956.4596117

BIC = 962.4941714

Log-Normal

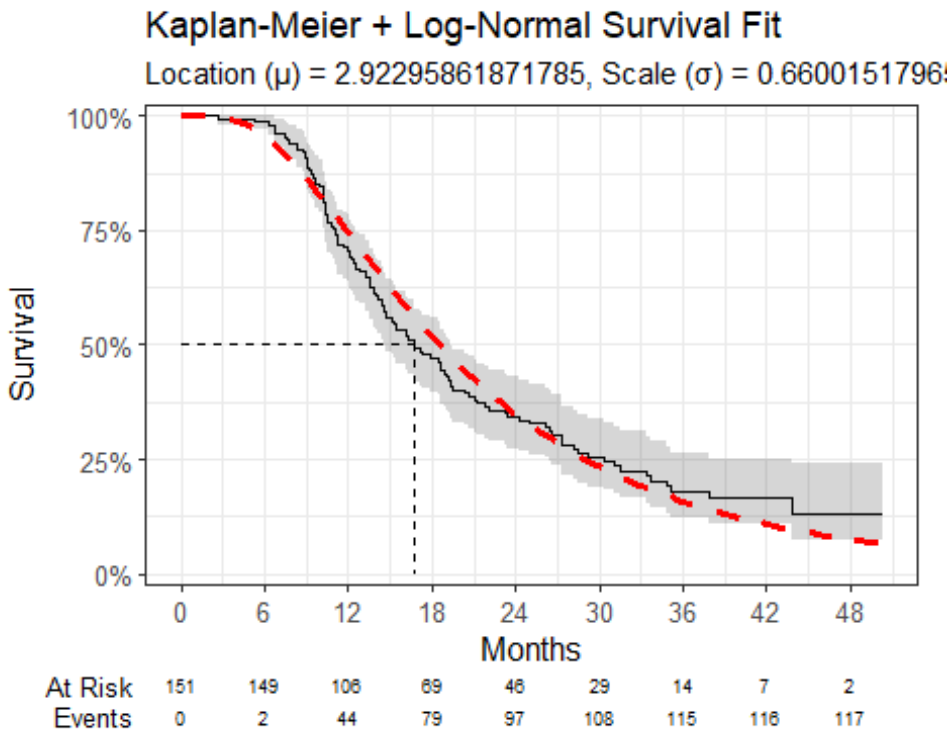


Table 3: Survival Model Fit Summary (Log-Normal distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	2.923	0.056	52.278668	0.000000e+00
Log(scale)	-0.415	0.069	-6.057438	1.383068e-09

log-likelihood = -462.448013222687

AIC = 928.8960264

BIC = 934.9305861

Log-Logistic

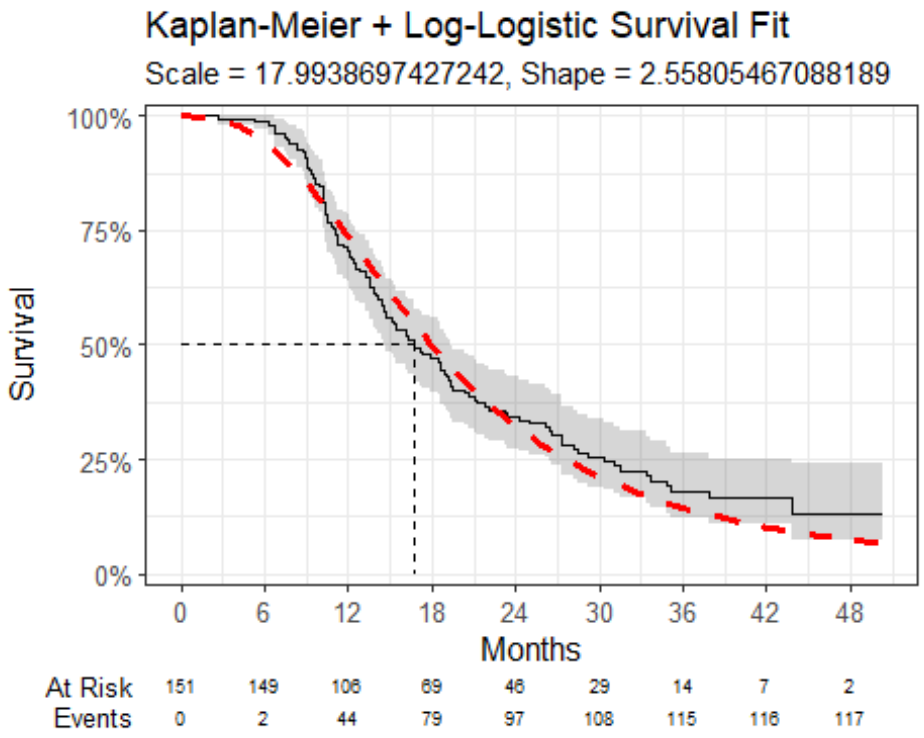


Table 4: Survival Model Fit Summary (Log-Logistic distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	2.890	0.057	50.98547	0.000000e+00
Log(scale)	-0.939	0.076	-12.33164	6.118534e-35

log-likelihood = -463.80042341938

AIC = 931.6008468

BIC = 937.6354065

Gaussian

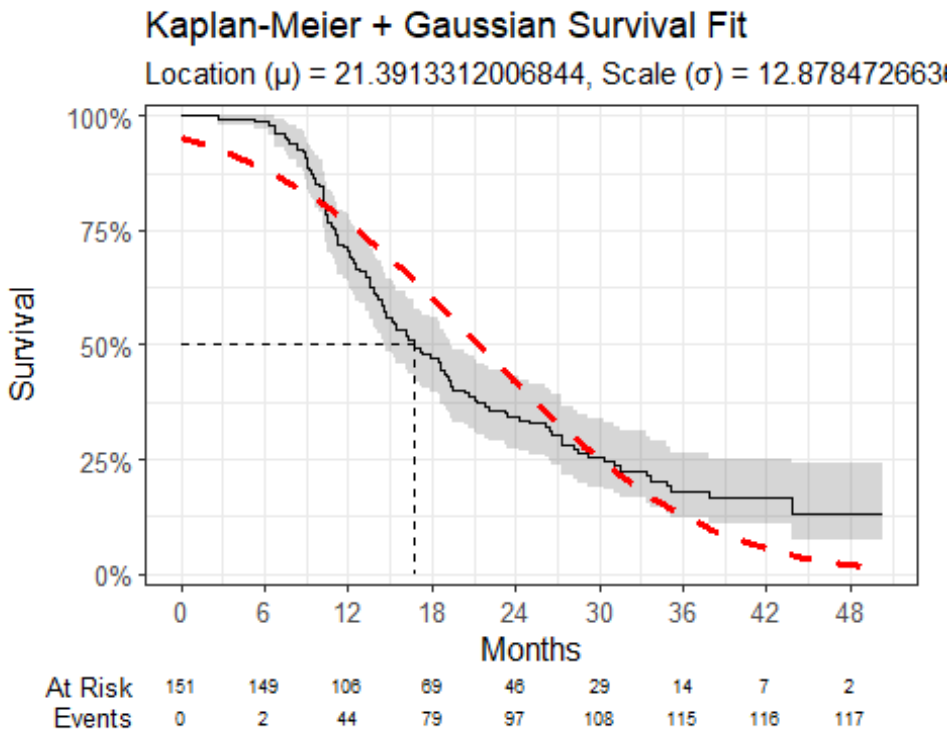


Table 5: Survival Model Fit Summary (Gaussian distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	21.391	1.090	19.61993	1.044982e-85
Log(scale)	2.556	0.069	37.21418	4.025581e-303

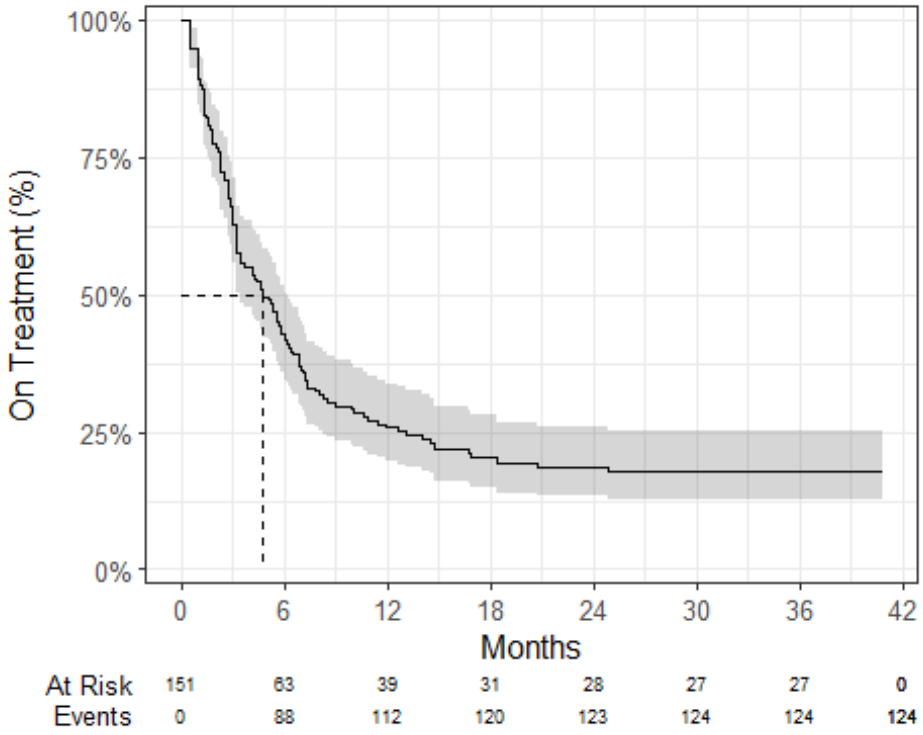
log-likelihood = -498.470041748085

AIC = 1000.940083

BIC = 1006.974643

Time on Treatment - Avelumab maintenance only

The Kaplan-Meier plot below shows Time on Treatment (ToT) for patients receiving Avelumab maintenance. The median ToT was 4.7 months, CI (3.3 months, 5.99 months).



Enfortumab vedotin with pembrolizumab for untreated unresectable or metastatic urothelial cancer when platinum-based chemotherapy is suitable [ID6332]

SACT data analysis

Cohort 3: OS prediction with log-logistic curve

Time	Survival
0	100.00%
6	69.04%
12	43.76%
18	29.59%
24	21.35%
30	16.21%
36	12.79%
42	10.40%
48	8.65%
54	7.34%
60	6.32%
66	5.52%
72	4.87%
78	4.33%
84	3.89%
90	3.52%
96	3.20%
102	2.93%
108	2.69%
114	2.48%
120	2.30%

Cohort 2: Mean time on treatment for avelumab

Parameter	Time (Months)
Restricted mean ToT time for the full length of the curve	11.066165

Age, Gender and Overall Survival for Gemcitabine + Platinum Chemo (irrespective of subsequent Avelumab maintenance)

Introduction

This report was produced in partnership by the National Disease and Registration Service (NDRS) and National Institute for Health and Care Excellence (NICE). It presents overall survival and patient characteristics among patients who have received platinum-based chemotherapy with gemcitabine for the treatment of metastatic urothelial cancer.

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Cohort inclusions / exclusions

Patients were included in this cohort where :

- Tumour site was consistent with the NDRS site groups 'Bladder', 'Renal pelvis and ureter', or 'Urethra'
- Country code was 'England'
- Age was 18 or over
- Gender field was known (male or female)
- Diagnosis occurred between 2020 and 2022
- Stage of 4 (4, 4A or 4B) at diagnosis
- M of 1 (distant metastases) or unknown
- First systemic treatment was Gemcitabine plus platinum chemotherapy (first regimen following diagnosis, identified using start date of regimen)

and excluded where:

- Multiple tumours of interest (bladder, renal pelvis and ureter) were diagnosed between 2020 and 2022

Patient Acknowledgement

This work uses data that has been provided by patients and collected by the NHS as part of their care and support. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of NHS England.

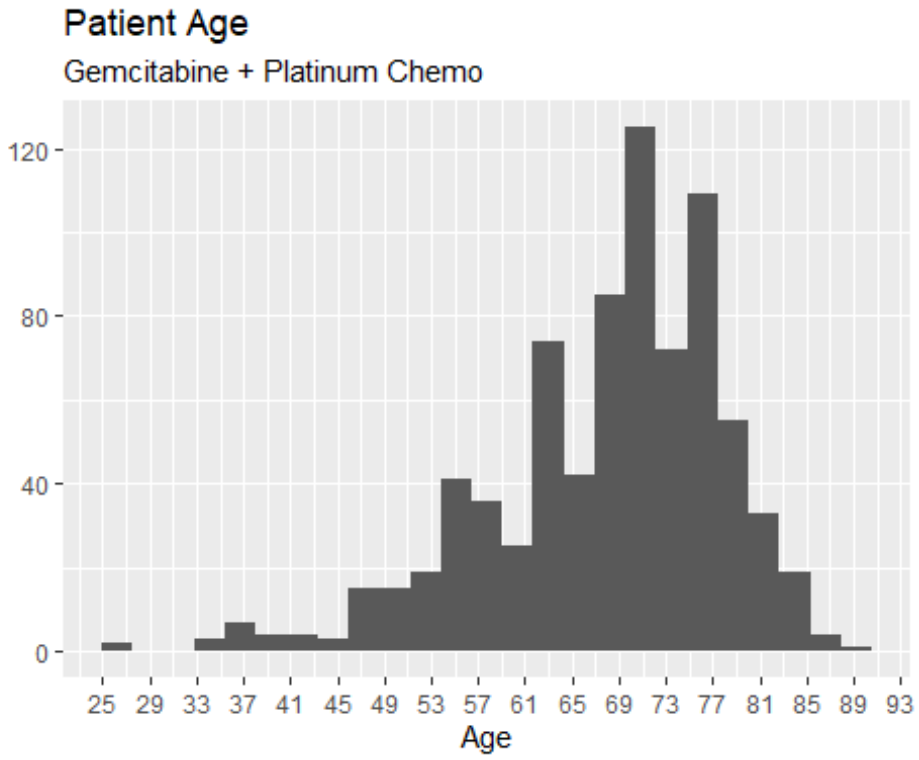
Results

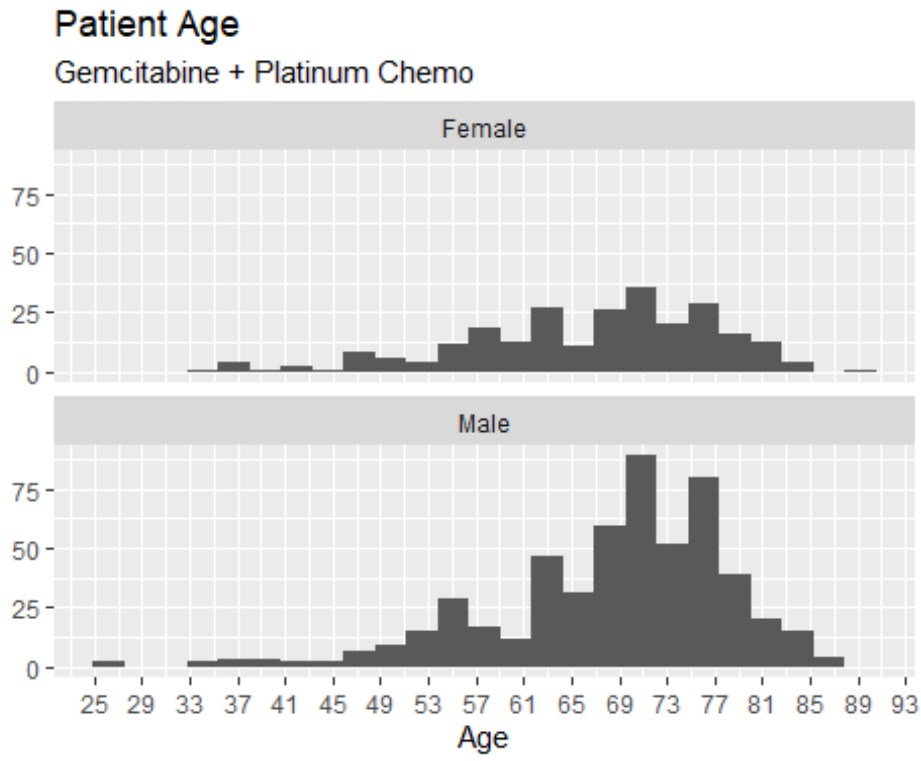
Age at start of treatment

The table below sets out the mean age, std. deviation, median age and IQR of patients who have received Gemcitabine + Platinum Chemo (with Avelumab maintenance). Age is measured at the commencement of the first treatment regimen.

Characteristic	**Female** N = 254[1]	**Male** N = 539[1]
Age at start of regimen	67, (10) : 68 (60, 74)	69, (10) : 71 (63, 75)

[1]Mean, (SD) : Median (Q1, Q3)

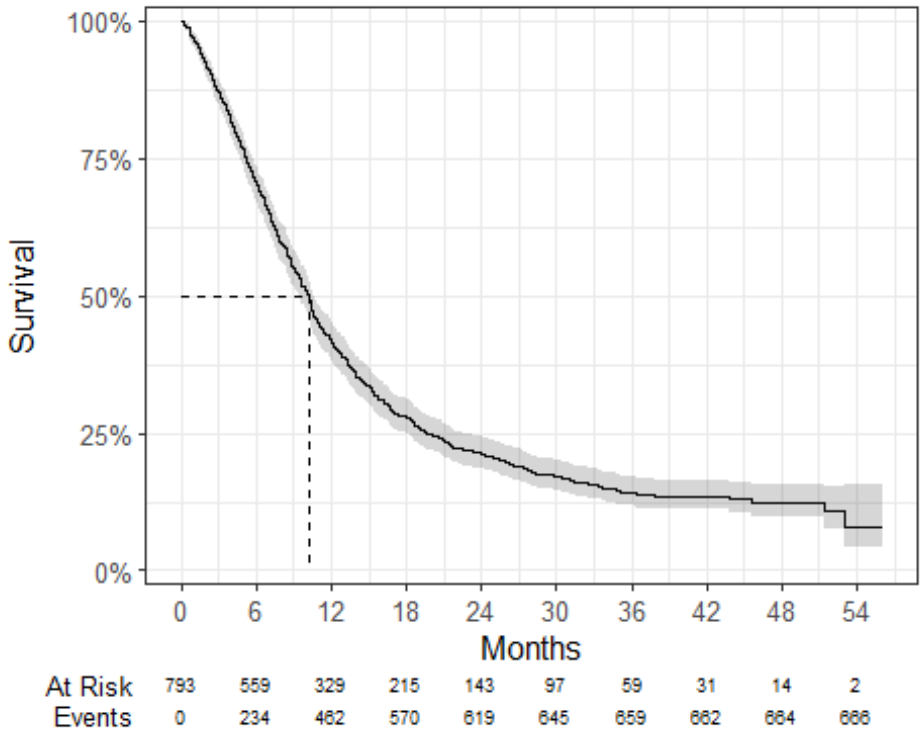



Patient Age
Gemcitabine + Platinum Chemo
Female
Male
75
50
25
0
25 29 33 37 41 45 49 53 57 61 65 69 73 77 81 85 89 93
Age

Overall Survival

Base K-M plot

The Kaplan-Meier plot below shows survival over time for those receiving a treatment regimen of Gemcitabine + Platinum Chemo (with or without Avelumab maintenance). The median OS was 10.1 months, CI (9.4 months, 10.5 months).



Exponential

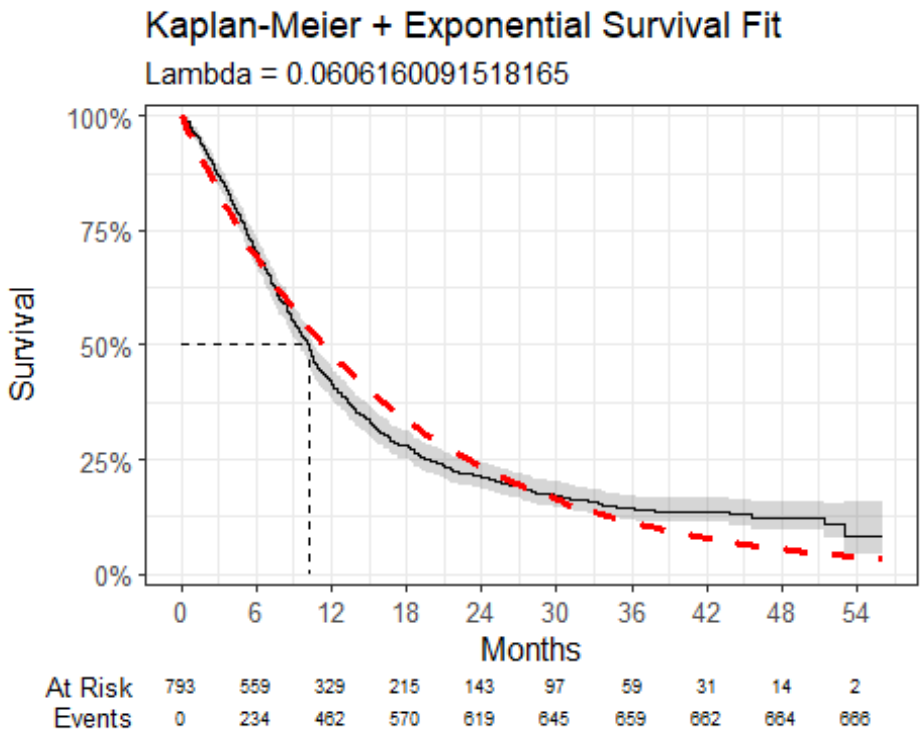


Table 1: Survival Model Fit Summary (Exponential distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	2.803	0.039	72.34202	0

log-likelihood = -2532.9286980943

AIC = 5067.857396

BIC = 5072.533219

Weibull

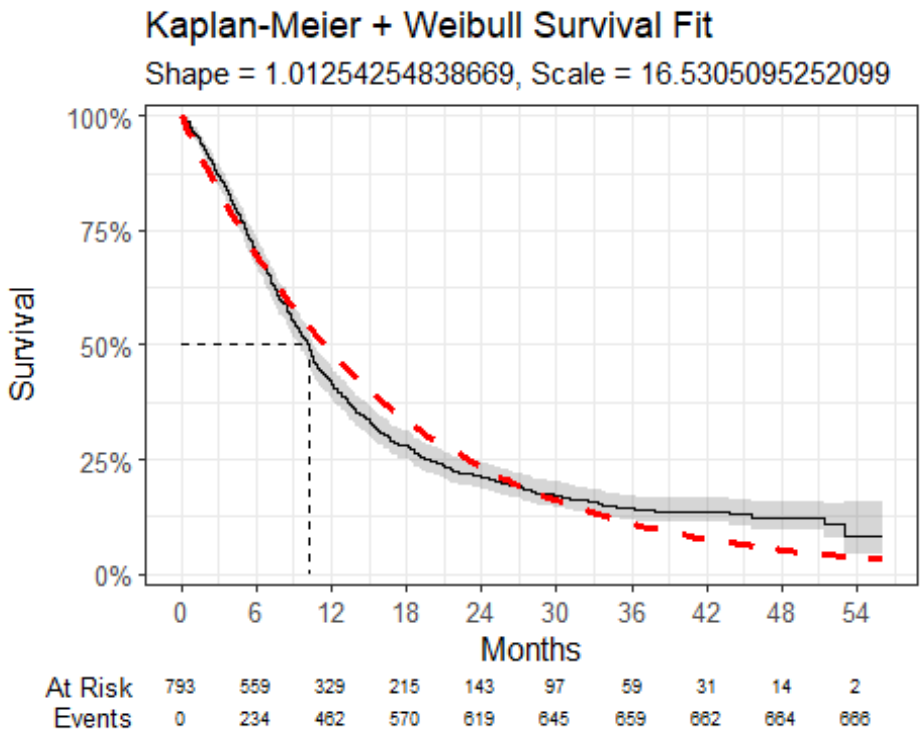


Table 2: Survival Model Fit Summary (Weibull distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	2.805	0.039	72.6587610	0.0000000
Log(scale)	-0.012	0.031	-0.3998801	0.6892448

log-likelihood = -2532.84923799132

AIC = 5069.698476

BIC = 5079.050122

Log-Normal

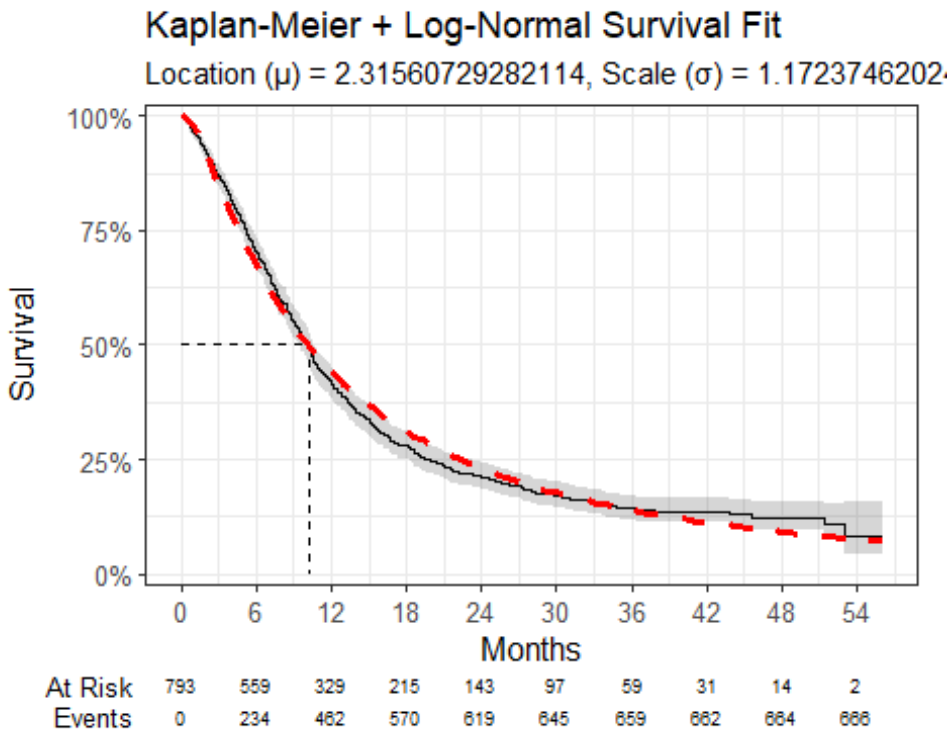


Table 3: Survival Model Fit Summary (Log-Normal distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	2.316	0.043	54.437483	0.000000e+00
Log(scale)	0.159	0.028	5.586773	2.313279e-08

log-likelihood = -2504.98961058149

AIC = 5013.979221

BIC = 5023.330868

Log-Logistic

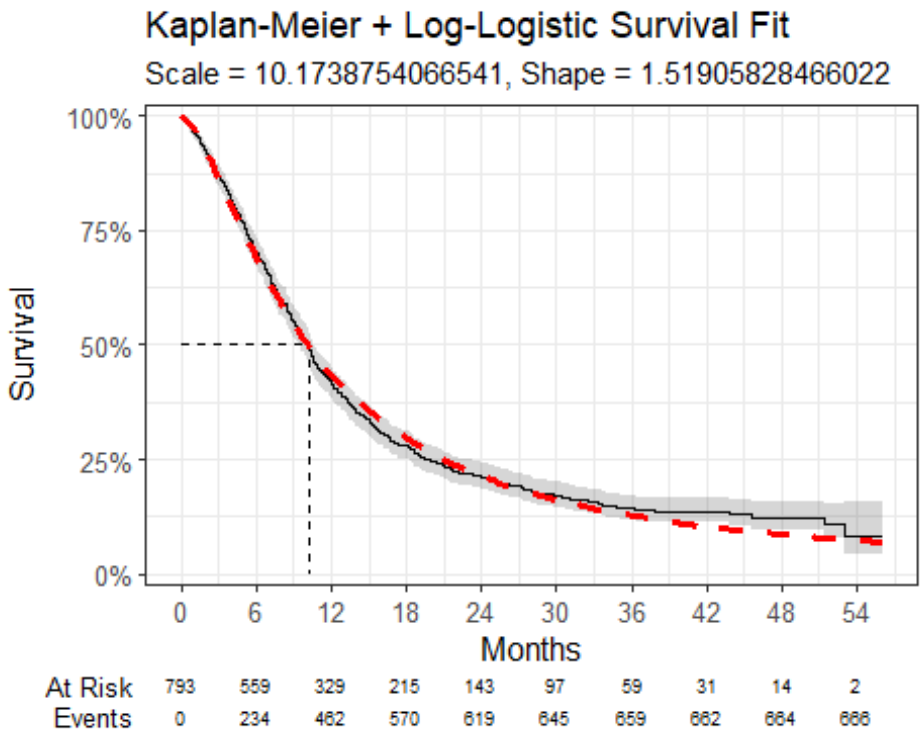


Table 4: Survival Model Fit Summary (Log-Logistic distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	2.320	0.040	57.42644	0.000000e+00
Log(scale)	-0.418	0.033	-12.81816	1.297507e-37

log-likelihood = -2493.60581656425

AIC = 4991.211633

BIC = 5000.56328

Gaussian

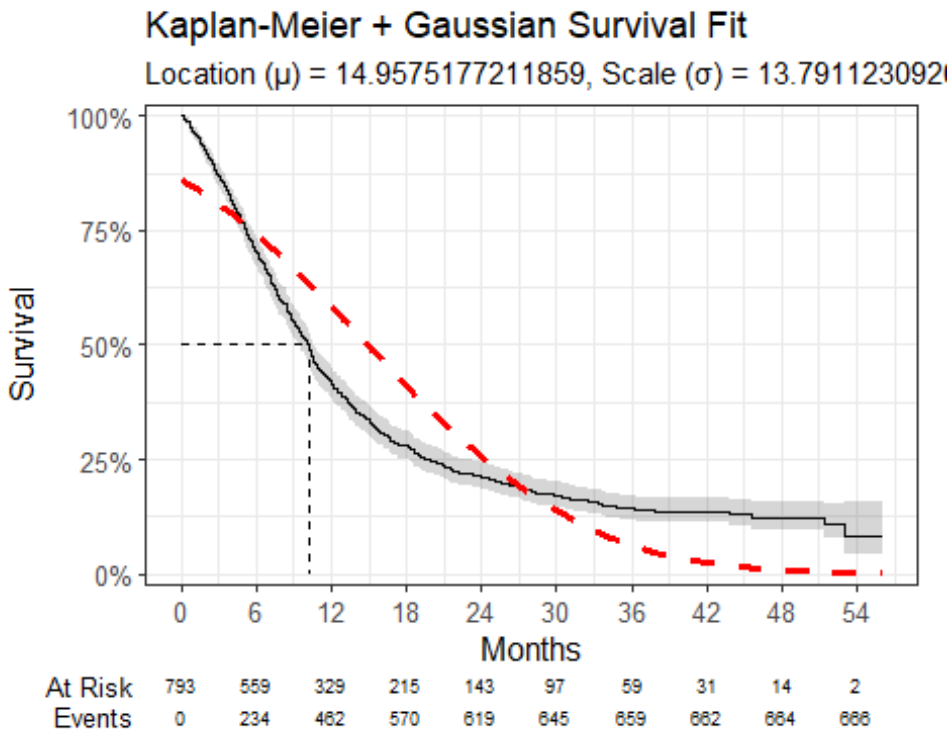


Table 5: Survival Model Fit Summary (Gaussian distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	14.958	0.499	29.96304	2.975834e-197
Log(scale)	2.624	0.029	91.55298	0.000000e+00

log-likelihood = -2841.21153862864

AIC = 5686.423077

BIC = 5695.774724