Modelling health-related outcomes with avelumab as a first-line maintenance treatment following chemotherapy vs best supportive care (BSC) for patients with locally advanced or metastatic urothelial cancer in the UK

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SCOPE

- The objective of this study was to model and evaluate health outcomes in patients with locally advanced (LA) and metastatic urothelial cancer (mUC) treated in the UK with avelumab as a first-line (1L) maintenance treatment following complete/partial response or stable disease with platinum-based chemotherapy

CONCLUSIONS

- Avelumab 1L maintenance immunotherapy represents a novel treatment strategy for patients with LA/mUC that has not progressed on or after 1L platinum-based chemotherapy
- Extrapolated progression-free survival (PFS) and overall survival (OS) outcomes consistently demonstrate life-year (LY) and quality-adjusted life-year (QALY) gains for patients on avelumab maintenance compared with BSC. Improved health-related quality of life (HRQOL) associated with avelumab also contributed to QALY gains
- Despite uncertainty, extensive scenario analyses around treatment waning indicate that avelumab offers an incremental benefit in both LYs and QALYs compared with BSC
- Given the poor prognosis associated with patients receiving BSC alone and the improved survival associated with avelumab, it is likely that avelumab would meet the end-of-life criteria established by the National Institute for Health and Clinical Excellence (NICE)

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BACKGROUND

- Bladder cancer is the tenth most common type of cancer in the UK and accounts for 3% of cancer-related deaths, with ≈90% of cases expected to be urothelial cancer (UC)[1-2]
- 1L treatment options for LA and mUC are limited in the UK, with platinum-based chemotherapy regimens being the current standard of care[3]
- Although response rates to 1L platinum-based chemotherapies may be high, durable responses are uncommon and most patients will ultimately experience disease progression after 1L treatment[4-5]
- The median OS for adult patients in England diagnosed with stage III-IV UC between 2013 and 2017 is estimated to be 9.47 months.[6] **Table 1** summarises various median OS estimates from real-world data and other sources
- With poor prognosis for patients with mUC, there is a clear unmet need for improved, effective therapies in the 1L setting to meet the 3 key goals of treatment: to delay disease progression, maintain HRQOL, and extend life expectancy
- Avelumab is a human immunoglobulin G1 monoclonal antibody directed against the PD-L1 molecule expressed by tumour cells and a number of immune cells.[7] It is approved in several regions, including the US, Europe, and Japan, as 1L maintenance treatment for patients with LA/mUC without disease progression following 1L platinum-based therapy, based on outcomes from the pivotal phase 3 JAVELIN Bladder 100 (JB100) trial comparing avelumab + BSC with BSC in 700 patients[8-12]
- The JAVELIN Bladder regimen of avelumab 1L maintenance in patients without diease progression with 1L platinum-based chemotherapy is a recommended standard of care in international treatment guidelines for LA/mUC[13-17]

METHODS

Model design

- A partitioned survival analysis was developed including 3 health states: PFS, progressed disease (PD), and death, as illustrated in **Figure 1**. The cycle length was 7 days and the time horizon considered was 25 years. The model compared outcomes between avelumab + BSC vs BSC alone using data from the JB100 trial, with a cutoff date of October 21, 2019

Survival

- Standard independent parametric survival and cubic spline curves were fitted to OS and PFS data
- It is common that some immunotherapies may have stopping rules in place, for which the loss of treatment effect may be apparent. To explore this, a gradual treatment waning effect was also applied as scenario analysis (varying between 2 and 10 years), where the avelumab PFS and OS trajectories were based on the hazards of the BSC arm in the longer term

HRQOL

- Utility data collected in JB100 were analysed by disease status (ie, progression-free or progressed), with scenario analysis also analysed by treatment arm (**Table 2**). Methodology of the approach taken to derive utilities has been presented previously[18]

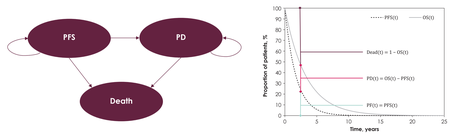
Safety

- The frequency of adverse events (AEs) was obtained from JB100, with the disutilities for each AE and assumed durations taken from the literature[19-24]. Disutilities associated with AEs were included within the model as a one-off disutility at the start of treatment

Outcomes

- Outcomes were reported in terms of LYs and QALYs gained

Figure 1. Model schematic



The partitioned survival model shown here is for illustration purposes only
OS, overall survival; **PD**, progressed disease; **PF**, progression-free; **PFS**, progression-free survival; **t**, time.

RESULTS

Base case results

- Using guidance from NICE's Decision Support Unit Technical Support Document 14, the generalised gamma was considered the most appropriate curve fit for both treatment arms to model OS, and the 3-knot normal cubic spline was considered most appropriate for PFS for both treatment arms (**Figure 2**)
- Base case results are presented in **Table 3** alongside scenario analyses. The base case shows that avelumab increased survival by 1.00 LY and 0.61 QALYs. For BSC, the model estimated a median OS of 15.9 months, similar to that observed in JB100 (14.3 months). **Table 1** summarises how these median estimates compare with the literature to date for BSC in a real-world setting

Scenario analyses

- Model results are robust when considering the PFS extrapolations, with results indicating a QALY gain ranging from 0.56 to 0.62
- Model results indicate that avelumab consistently offers an incremental OS gain compared with BSC, ranging from 0.28 to 1.00 LY and from 0.23 to 0.61 QALY gained

Utilities

- The model was not sensitive to changes in utility settings, with a QALY gain ranging from 0.56 to 0.61

Treatment waning

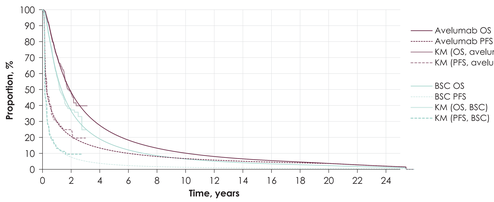
- Consistent gains in LYs and QALYs remained after application of treatment waning effects for patients treated with avelumab, with LY gains ranging from 0.71 to 0.99 and QALY gains ranging from 0.45 to 0.60 (**Table 4** and **Table 5**)

Table 1. Median OS in patients with LA/mUC in the JB100 trial and various real-world studies

Setting	Publication	Description	Population	Setting	N	Treatment	Median OS, months
JB100	Powles et al, 2020[8]	Phase 3 RCT	LA/mUC	Patients with CR, PR, or SD following 1L chemotherapy	350	BSC	14.3*
					350	Avelumab + BSC	21.4*
UK	Cheeseman et al, 2020[25]	Analysis of retrospective longitudinal cohort design from a UK NHS cancer centre	LA/mUC	1L	216	Mixed	16.2
	Davies et al, 2020[26]	Analysis of PLD from NCRAS in England	mUC	From diagnosis	2,543	Mixed	5.8†
	Kearney et al, 2020[27]	Analysis of PLD from NCRAS in England	LA/mUC	From diagnosis	14,548	Unknown	9.7‡
				From initiation of 1L systemic therapy	4,400	Unknown	14.0§
US	Geynisman et al, 2021[28]	Analysis of retrospective observational cohort data from the US Flatiron Health database	aUC	Stage IV UC or node-positive UC	5,855	≥1 systemic therapy	14.5‡
					2,328	No systemic therapy	6.8‡
	Miron et al, 2021[29]	Analysis of retrospective observational cohort data from the US Flatiron Health database	aUC	Patients diagnosed with mUC receiving 2L immunotherapy	399	Carbo/Gem	16.2‖
					381	Cis/Gem	18.0‖

Results presented here illustrate the low median survival for patients with mUC based on information found in the literature. The findings presented were not obtained through a thorough systematic review of the literature.
1L, first line; **2L**, second line; **aUC**, advanced urothelial carcinoma; **BSC**, best supportive care; **Carbo**, carboplatin; **Cis**, cisplatin; **CR**, complete response; **Gem**, gemcitabine; **JB100**, JAVELIN Bladder 100; **LA**, locally advanced; **mUC**, metastatic urothelial carcinoma; **NCRAS**, National Cancer Registration and Analysis Service; **OS**, overall survival; **PLD**, patient-level data; **PR**, partial response; **RCT**, randomised controlled trial; **SD**, stable disease; **UC**, urothelial cancer.
*In JB100, OS was measured from randomisation after completion of 1L chemotherapy; †OS was measured from mUC diagnosis; ‡OS was measured from aUC diagnosis; §OS was measured from initiation of 1L systemic therapy; ‖OS was measured from initiation of 1L therapy.

Figure 2. Model efficacy: base case settings compared with observed data from JB100



BSC, best supportive care; **KM**, Kaplan-Meier; **OS**, overall survival; **PFS**, progression-free survival.

Table 2. Utility values obtained from self-reported HRQOL data from JB100

Utility values	Pooled (base case)	Avelumab + BSC	BSC
PFS	0.77	0.77	0.77
PD	0.70	0.69	0.71

EQ-5D-5L responses were converted to EQ-5D-3L responses using the crosswalk by van Hout et al, 2012.[24]
BSC, best supportive care; **EQ-5D-3L**, 3-level EQ-5D; **EQ-5D-5L**, 5-level EQ-5D; **HRQOL**, health-related quality of life; **JB100**, JAVELIN Bladder 100; **PD**, progressed disease; **PFS**, progression-free survival.

Table 3. QALY and LY outcomes in scenario analysis

Category	Scenario	Incremental LYs	Incremental QALYs
Base case		1.00	0.61
PFS curves (selected curve applied to both PFS arms independently)	Exponential	1.00*	0.56
	Weibull		0.56
	Log-logistic		0.57
	Log-normal		0.57
	Generalised-gamma		0.62
	Gompertz		0.62
	1-knot hazard		0.61
	1-knot odds		0.61
	1-knot normal		0.62
	2-knot hazard		0.61
	2-knot odds		0.60
	2-knot normal		0.61
	3-knot hazard		0.61
	3-knot odds		0.61
OS curves (selected curve applied to both OS arms independently)	Exponential	0.86	0.56
	Weibull	0.50	0.35
	Log-logistic	0.86	0.55
	Log-normal	0.95	0.59
	Gompertz	0.28	0.23
Utilities	Treatment-specific utilities	1.00*	0.57
	Treatment-specific utilities for PFS		0.62
	Treatment-specific utilities for PD		0.56
	Exclusion of disutilities due to AEs		0.61

AE, adverse event; **LY**, life-year; **OS**, overall survival; **PD**, progressed disease; **PFS**, progression-free survival; **QALY**, quality-adjusted life-year.
*These scenarios only impact QALYs and not LYs; hence, incremental LYs remain the same as the base case.

Table 4. QALY outcomes associated with the application of a gradual treatment waning effect

		Incremental QALYs								
		End of treatment waning effect								
		2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
Start of treatment waning effect	2 years	0.45	0.48	0.51	0.52	0.54	0.55	0.55	0.56	0.56
	3 years		0.51	0.53	0.54	0.55	0.56	0.57	0.57	0.58
	4 years			0.55	0.56	0.57	0.57	0.58	0.58	0.59
	5 years				0.57	0.58	0.58	0.58	0.59	0.59
	6 years					0.58	0.59	0.59	0.59	0.59
	7 years						0.59	0.59	0.60	0.60
	8 years							0.60	0.60	0.60
	9 years								0.60	0.60
	10 years									0.60

This table illustrates incremental QALY results when varying the start of the treatment waning (where the modelled hazard of the avelumab OS and PFS are derived solely from the hazards estimated from the extrapolated avelumab data) and the end of the treatment waning (where the modelled hazard of the avelumab OS and PFS are derived solely from the hazards estimated from the extrapolated BSC data; ie, loss of a treatment effect). The relationship is linear such that the weighting is gradual and happens over a defined time period (eg, 2-10 years). As an illustrative example, a gradual treatment waning starting at 2 years and ending at 10 years would mean that the full implementation of the waning effect (and the avelumab OS and PFS being based on hazards from 100% of the BSC extrapolations) would take 8 years.
BSC, best supportive care; **OS**, overall survival; **PFS**, progression-free survival; **QALY**, quality-adjusted life-year.

Table 5. LY outcomes associated with the application of a gradual treatment waning effect

		Incremental LYs								
		End of treatment waning effect								
		2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years
Start of treatment waning effect	2 years	0.71	0.78	0.82	0.85	0.87	0.89	0.90	0.91	0.92
	3 years		0.83	0.86	0.89	0.90	0.92	0.93	0.94	0.94
	4 years			0.89	0.91	0.93	0.94	0.95	0.95	0.96
	5 years				0.93	0.94	0.95	0.96	0.96	0.97
	6 years					0.95	0.96	0.97	0.97	0.98
	7 years						0.97	0.97	0.98	0.98
	8 years							0.98	0.98	0.98
	9 years								0.99	0.99
	10 years									0.99

This table illustrates incremental LY results when varying the start of the treatment waning (where the modelled hazard of the avelumab OS and PFS are derived solely from the hazards estimated from the extrapolated avelumab data) and the end of the treatment waning (where the modelled hazard of the avelumab OS and PFS are derived solely from the hazards estimated from the extrapolated BSC data; ie, loss of a treatment effect). The relationship is linear such that the weighting is gradual and happens over a defined time period (eg, 2-10 years). As an illustrative example, a gradual treatment waning starting at 2 years and ending at 10 years would mean that the full implementation of the waning effect (and the avelumab OS and PFS being based on hazards from 100% of the BSC extrapolations) would take 8 years.
BSC, best supportive care; **LY**, life-year; **OS**, overall survival; **PFS**, progression-free survival.

Strengths

- The model created is simple yet intuitive to the nature of mUC. This allows for transparent presentation of health outcomes based on predictions using the JB100 trial, which is a large, well-conducted, international, randomised, controlled trial with an appropriate comparator generalisable to UK clinical practice
- Validation by clinical experts was undertaken to mitigate areas of uncertainty within the cost-effectiveness analysis and select UK representative base case assumptions
- Extensive scenario analyses were conducted using different survival curve extrapolation options to interpret clinical uncertainty in the modelled survival

Limitations

- The long-term effect of avelumab as a 1L maintenance treatment following chemotherapy is not yet fully understood. As long-term data from JB100 become available, the uncertainty regarding long-term survival outcomes for patients treated with avelumab will be reduced
- Like all clinical trials, JB100 was conducted in a selected patient population that met trial inclusion and exclusion criteria and may not reflect patients seen in real-world clinical practice

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