

SUPPLEMENTAL MATERIALS

Benchmarking Maintenance Therapy Survival in First-Line Platinum-Based Chemotherapy–Treated Patients With Advanced Urothelial Carcinoma Using Simulated Disease Modeling

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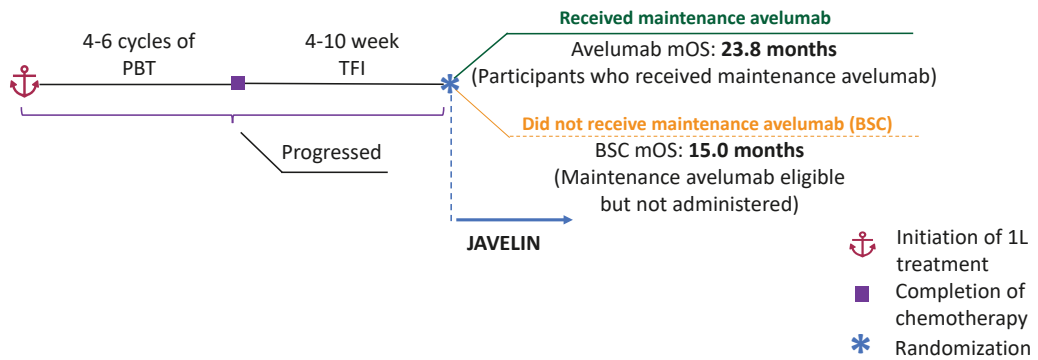
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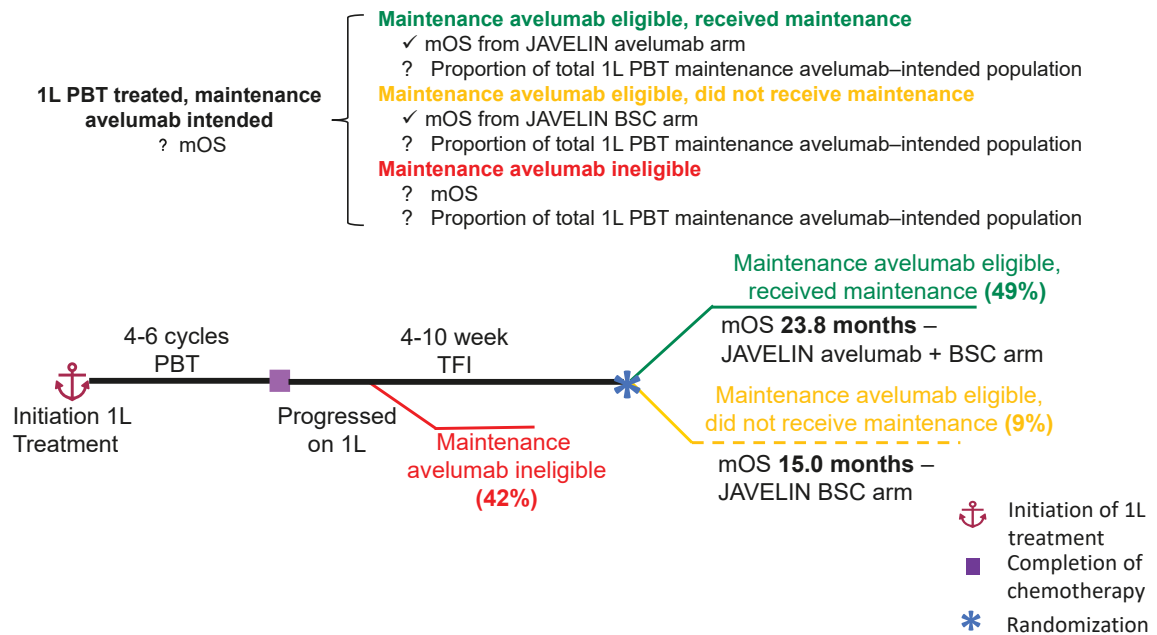
Supplemental Materials 1

Supplemental Figure 1. JAVELIN design overview.



Abbreviations: 1L, first-line; BSC, best supportive care; mOS, median overall survival; PBT, platinum-based therapy; TFI, treatment-free interval.

Supplemental Figure 2. The “unknown variable”: Unknown OS in patients with aUC.



Data with a “✓” are known and available in published literature. Data with a “?” are unknown and require estimation by the OSM.

Abbreviations: 1L, first-line; aUC, advanced urothelial carcinoma; BSC, best supportive care; mOS, median overall survival; OSM, oncology simulation model; PBT, platinum-based therapy; TFI, treatment-free interval.

Supplemental Materials 2

Statistical Analysis Methodology

The OS for the maintenance-avelumab ineligible, did not receive population and the overall first-line (1L) platinum-based therapy (PBT)–treated, maintenance-intended populations from 1L-treatment initiation were estimated with the OSM using the following methodology. Input values into the OSM to estimate the OS of the overall 1L PBT–treated, maintenance-intended population (base case) were taken from JAVELIN, KEYNOTE-361, and expert (MG and TP) clinical opinion.

Progression-free survival (PFS) data from the control arm of KEYNOTE-361 and treatment-duration data from JAVELIN were used to estimate the proportion of patients who were eligible for and received maintenance avelumab in the overall population. In JAVELIN, patients spent 4–7 months between initiation of PBT and the start of maintenance avelumab (≥ 4 cycles of PBT and a treatment-free interval [TFI] of 4–10 weeks); for simplicity, a 5.6-month interval between starting 1L PBT and commencing maintenance therapy was chosen. On the PFS curve of the KEYNOTE-361 chemotherapy arm, 58% of patients were progression free at 5.6 months, and, therefore, eligible for maintenance avelumab. Expert (MG and TP) clinical opinion indicated that 85% of eligible patients would receive maintenance avelumab. OS for the maintenance-eligible patients who received maintenance was then estimated using the reported 23.8 month OS for the maintenance therapy arm of JAVELIN + 5.6 months (PBT + TFI, **Supplemental Table 1**). OS for the maintenance-eligible patients who did not receive maintenance was estimated using the OS for the BSC arm of JAVELIN + 5.6 months (PBT + TFI, **Supplemental Table 1**).

Supplemental Table 1 Base case model inputs.

Population	mOS	Source
1L maintenance eligible with maintenance avelumab treatment	29.3 months ^a (23.8 + 5.6)	JAVELIN ⁴
1L maintenance eligible without maintenance avelumab treatment	20.6 months ^a (15.0 + 5.6)	JAVELIN ⁴
1L overall population (for calculating maintenance avelumab ineligible OS)	14.3 months	KEYNOTE-361 ¹³

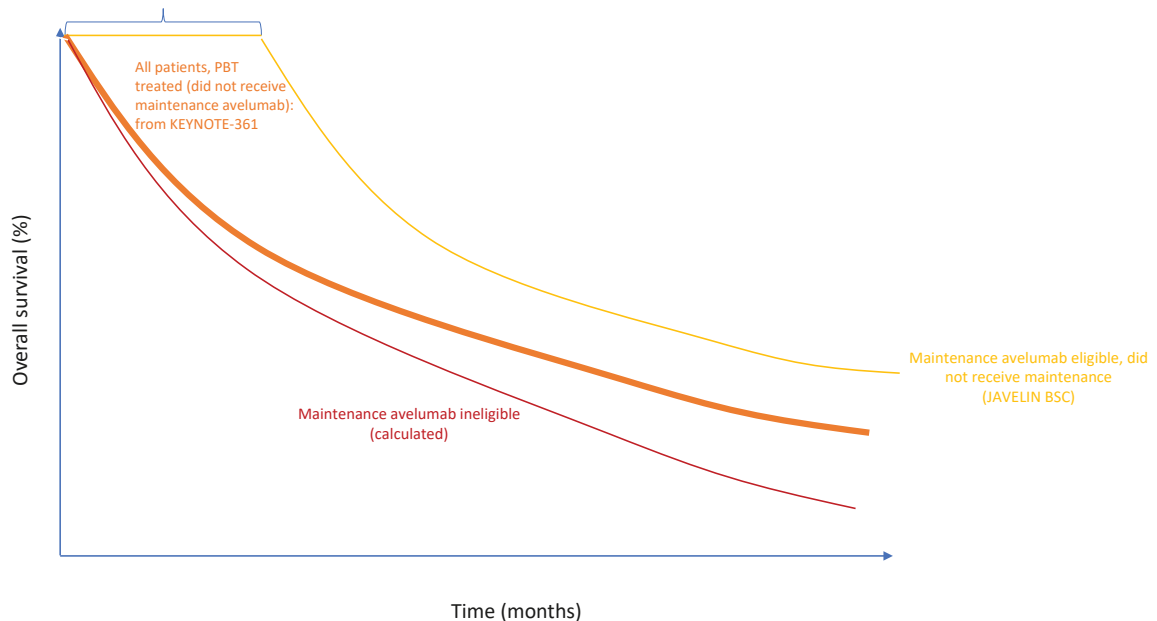
^amOS value includes the 5.6 months spent on 1L PBT treatment and the TFI.

Abbreviations: 1L, first-line; TFI, treatment-free interval; mOS, median overall survival; OS, overall survival.

The OS of 1L PBT–treated, maintenance-ineligible patients was calculated based on the difference in the OS curves of the JAVELIN BSC arm and the KEYNOTE-361 arm (**Supplemental Figure 3**).

Supplemental Figure 3. OS estimation of maintenance avelumab–ineligible patients.

4-6 cycles of PBT ± 4-10 weeks of TFI^a



^aThe horizontal portion of the maintenance avelumab–eligible (did not receive maintenance) line reflects the eligibility criteria of JAVELIN and shows the 5.6-month run-in (accounting for 6 PBT cycles and a nominal 6-week TFI) time interval during which a patient must remain progression free between PBT and the start of maintenance treatment in the JAVELIN trial.

Abbreviations: aUC, advanced urothelial carcinoma; BSC, best supportive care; OS, overall survival; PBT, platinum-based therapy; TFI, treatment-free interval

The model assumes the hazard of survival for the overall 1L maintenance–intended population is the linear combination of the hazards of each subpopulation, weighted by the size of each subpopulation, where n is the total number of subpopulations and w is the respective distribution of each subpopulation, as shown in the following equation:

$$\lambda_{overall} = \sum_i^n \lambda_i * w_i$$

OS for the maintenance-ineligible population was calculated as the linear combination of hazards between the maintenance avelumab eligible but did not receive avelumab (based on JAVELIN BSC arm) and all patients who did not receive maintenance avelumab (based on data from the KEYNOTE-361 control arm who received PBT without subsequent maintenance avelumab, including both maintenance avelumab–eligible and –ineligible patients):

- JAVELIN BSC mOS = 5.6-month run-in + 15.0 reported mOS = 20.6
- KEYNOTE-361 PBT arm mOS = 14.3 months.
- Based on KEYNOTE-361 PFS, 42% progress in 5.6-month run-in, so only 58% make it to maintenance
- Hazard of JAVELIN BSC = 0.034 (assuming constant hazard)
- Hazard of KEYNOTE-361 PBT arm = 0.048 (assuming constant hazard)

- (Hazard of JAVELIN BSC) * 58% + (Hazard of Maintenance Ineligible) * 42% = Hazard of KEYNOTE-361 PBT arm
- Solving for Hazard of Maintenance Ineligible = 0.069
- Assuming constant hazard, mOS of maintenance avelumab ineligible = **10.1 months**

OS for the overall, 1L PBT-treated, maintenance-intended population was calculated using a linear combination of hazards methodology:

- Estimated combined hazard = (Hazard of JAVELIN avelumab) * (% eligible and received maintenance) + (Hazard of JAVELIN BSC) * (% eligible but did not receive maintenance) + (Hazard of Maintenance Ineligible) * (% ineligible)
- Hazard of JAVELIN avelumab = 0.024 (assuming constant hazard, based on 5.6-month run-in + 23.8 reported mOS)
- Assuming 85% of those who are eligible actually receive maintenance avelumab
- **Estimated combined hazard = 0.024 * (58% * 85%) + 0.034 * (58% * 15%) + 0.069 * 42% = 0.044**
- Estimated combined effect of JAVELIN = **15.9 months**

For the Gem+Carbo subgroup:

- JAVELIN BSC mOS = 5.6-month run-in + 12.9 reported mOS = 18.5
- KEYNOTE-361 Gem+Carbo arm mOS = 12.3 months
- Based on KEYNOTE-361 Gem+Carbo PFS, 48% progress in 5.6-month run-in, so only 52% make it to maintenance
- Hazard of JAVELIN BSC = 0.037 (assuming constant hazard)
- Hazard of KEYNOTE-361 Gem+Carbo arm = 0.056 (assuming constant hazard)
- (Hazard of JAVELIN BSC) * 52% + (Hazard of Maintenance Ineligible) * 48% = Hazard of KEYNOTE-361 Gem+Carbo arm
- Solving for Hazard of Maintenance Ineligible = 0.076
- Assuming constant hazard, mOS of maintenance-avelumab ineligible = **9.1 months**
- Estimated combined hazard = (Hazard of JAVELIN avelumab) * (% eligible and received maintenance) + (Hazard of JAVELIN BSC) * (% eligible but did not receive maintenance) + (Hazard of Maintenance Ineligible) * (% ineligible)
- Hazard of JAVELIN avelumab = 0.027 (assuming constant hazard, based on 5.6-month run-in + 20.6 reported mOS)
- Assuming 85% of those who are eligible actually received maintenance avelumab
- **Estimated combined hazard = 0.027 * (52% * 85%) + 0.037 * (52% * 15%) + 0.076 * 48% = 0.052**
- Estimated combined effect of JAVELIN = **13.5 months**

For the Gem+Cis subgroup:

- Due to lack of subgroup data for Gem+Cis from KEYNOTE-361, IMvigor130 was used in its place
 - JAVELIN BSC mOS = 5.6-month run-in + 16.5 reported mOS = 22.1
 - IMvigor130 Gem+Cis arm mOS = 14.6 months
 - Based on IMvigor130 Gem+Cis PFS, 45% progress in 5.6-month run-in, so only 55% make it to maintenance
 - Hazard of JAVELIN BSC = 0.031 (assuming constant hazard)
 - Hazard of IMvigor130 Gem+Cis arm = 0.047 (assuming constant hazard)

- $(\text{Hazard of JAVELIN BSC}) * 55\% + (\text{Hazard of Maintenance Ineligible}) * 45\% =$
Hazard of IMvigor130 Gem+Cis arm
- Solving for Hazard of Maintenance Ineligible = 0.067
- Assuming constant hazard, mOS of maintenance-avelumab ineligible = **10.4 months**
- Estimated combined hazard = $(\text{Hazard of JAVELIN avelumab}) * (\% \text{ eligible and received maintenance}) + (\text{Hazard of JAVELIN BSC}) * (\% \text{ eligible but did not receive maintenance}) + (\text{Hazard of Maintenance Ineligible}) * (\% \text{ ineligible})$
- Hazard of JAVELIN avelumab = 0.022 (assuming constant hazard, based on 5.6-month run-in + 25.3 reported mOS)
- Assuming 85% of those who are eligible actually received maintenance avelumab
- **Estimated combined hazard = $0.022 * (55\% * 85\%) + 0.031 * (55\% * 15\%) + 0.066 * 45\% = 0.043$**
- Estimated combined effect of JAVELIN = **16.0 months**

Supplemental Materials 3

Supplemental Table 2. 1L therapy trials considered for inclusion in the OSM base case.

Trial name	Therapies investigated	Proportion of patients who received PD1/L1 immunotherapy in the 2L setting	Study used in base case or scenario
KEYNOTE-361 ¹³	<ol style="list-style-type: none">1. Pembrolizumab + PBT2. Pembrolizumab3. PBT	48%	Base case
IMvigor130 ¹⁵	<ol style="list-style-type: none">1. Atezolizumab + PBT2. Placebo + PBT3. Atezolizumab	20%	Scenario
DANUBE ¹⁷	<ol style="list-style-type: none">1. Durvalumab2. Durvalumab + tremelimumab3. PBT	31%	Scenario

Abbreviations: 1L, first-line; 2L, second-line; BSC, best supportive care; OSM, oncology simulation model; PBT, platinum-based therapy; PD1/L1, programmed cell death protein 1/ligand 1.

Supplemental Table 3. JAVELIN and KEYNOTE-361 baseline patient characteristics.

Parameters	PBT + avelumab (JAVELIN) ⁴	PBT + BSC (JAVELIN) ⁴	PBT Only (KEYNOTE-361) ¹³
Median age in years	68 (Range: 37–90)	69 (Range: 32–89)	69 (IQR: 61–75)
Site of primary tumor	Upper urinary tract: 30.3% Lower urinary tract: 69.7%	Upper urinary tract: 23.1% Lower urinary tract: 76.9%	Upper urinary tract: 23% Lower urinary tract: 77%
PD1/L1 status	Positive: 54.0% Negative: 39.7% Unknown: 6.3%	Positive: 48.3% Negative: 37.4% Unknown: 14.3%	≥10: 45% <10: 55%
Platinum received	Gem + Cis: 52.3% Gem + Carbo: 42.0% Gem + either platinum: 5.7% Not reported: 0%	Gem + Cis: 58.9% Gem + Carbo: 34.9% Gem + either platinum: 5.7% Not reported: 0.6%	Gem + Cis: 44% Gem + Carbo: 56%

Abbreviations: BSC, best supportive care; Carbo, carboplatin; Cis, cisplatin; Gem, gemcitabine; PBT, platinum-based therapy; PD1/L1, programmed cell death protein 1/ligand 1.

Supplemental Table 4. Modeling of proportion of 1L PBT maintenance–intended population who received maintenance avelumab.

		Base case	Scenario analyses		
KEYNOTE-361 ¹³ 14.3 mOS in control arm 58% eligible for maintenance ^a	mOS of 1L chemotherapy population with maintenance avelumab available ^b	15.9 mOS	15.5 mOS	15.2 mOS	14.9 mOS
	Change from KEYNOTE-361 control arm ¹³ 14.3 (months)	Δ1.6	Δ1.2	Δ0.9	Δ0.6
	% of eligible that received maintenance avelumab	85%	66%	50%	33%
IMvigor130 ¹⁵ 13.4 mOS in control arm 53% eligible for maintenance ^a	mOS of 1L chemotherapy population with maintenance avelumab available ^b	14.7 mOS	14.4 mOS	14.2 mOS	13.9 mOS
	Change from IMvigor130 control arm ¹⁵ 13.4 (months)	Δ1.3	Δ1.0	Δ0.8	Δ0.5
	% of eligible that received maintenance avelumab	88%	71%	53%	35%
DANUBE ¹⁷ 12.1 mOS in control arm 55% eligible for maintenance ^a	mOS of 1L chemotherapy population with maintenance avelumab available ^b	13.1 mOS	12.9 mOS	12.7 mOS	12.5 mOS
	Change from DANUBE control arm ¹⁷ 12.1 (months)	Δ1.0	Δ0.8	Δ0.6	Δ0.4
	% of eligible that received maintenance avelumab	85%	68%	51%	34%
Percentage of 1L PBT maintenance avelumab-intended population who received maintenance avelumab (% who were eligible) X (% who received maintenance avelumab)		~50%	~40%	~30%	~20%

^aProportion of 1L-treated patients eligible for maintenance avelumab (not progressed) at the time of maintenance avelumab eligibility assessment (5.6 months); ^bOS outcomes reported in months.

Δ, difference in mOS between a 1L chemotherapy–treated population and a 1L chemotherapy received maintenance population; “% of eligible” represents the proportion of the patients eligible for maintenance avelumab who received maintenance avelumab.

Abbreviations: 1L, first-line; mOS, median overall survival; PBT, platinum-based therapy.