# Cost effectiveness analysis of pembrolizumab in combination with enfortumab-vedotin for first-line treatment of previously untreated locally advanced or metastatic urothelial carcinoma patients in Greece

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The International Society for Pharmacoeconomics and Outcomes Research, 17th -20th November 2024, Glasgow, Scotland

EE162

## BACKGROUND

- Bladder cancer is the 11th most common cancer worldwide and the 14th leading cause of cancer death worldwide, accounting for 2% of all cancer-related deaths in 2022. [1]
- The prognosis for advanced/metastatic bladder cancer patients is poor, with 5-year observed survival below 10% for distant metastatic disease.[2]
- The most common malignancy of bladder cancer- with more than 90% of all cases- is urothelial carcinoma. Urothelial Carcinoma refers to carcinomas that arise from the urothelial endothelium of renal pelvis, ureter, urethra and bladder with more than 90% of UCs originating in the latter.[3]
- It is important for urothelial cancer patients to have access to the Pembrolizumab+ EV(enfortumab-vedotin) treatment combination because it almost doubled overall survival (31.5 months vs 16.1 months) and progression free survival (12.5 months vs 6.3 months) compared to the previous standard of care (SoC); [4] which had remained in place for four decades. Thus, the efficacy of the Pembrolizumab+EV combination provided a practice changing paradigm shift which immediately became the new recommended SoC across the treatment guidelines of EAU and ESMO.[5,6]

## AIM

The present study aims to estimate the cost-effectiveness of pembrolizumab in combination with enfortumab-vedotin (EV) for first-line treatment of previously untreated locally advanced or metastatic urothelial carcinoma in Greece.

## METHODOLOGY

A partitioned survival model with three health states (Progression-free, Progressed Disease, Death), was adapted to a Greek payer perspective over a 32-year time horizon. The model schema is shown Figure 1. Efficacy and safety data applied in the model were extracted from the KN-A39 clinical trial.[7] Utility values used in the model were retrieved from KN-A39. Utilities were estimated using the health-states approach, based on KN-A39 data, to calculate time spent in each dynamic and mutually exclusive health state. The EQ-5D-5L instrument was used to capture patients' utilities values within the KN-A39 clinical trial. Greek inputs based on Greek DRG's (Diagnosis-Related Groups) and costs data, were used to populate the model, in order to have representative data of the day-to day clinical practice. The parametric extrapolations used in the model have been reviewed and validated by external clinical experts. Primary outcomes were quality-adjusted life-years (QALYs), total costs and incremental cost-effectiveness ratios (ICER)s per Life Years and QALY's gained. Both costs and QALY's were discounted at 3.0% per annum.

### Comparators and administration scheme within the model

The administration scheme was scheduled in 21-day cycles. All first-line treatment schemes included in the model were administered intravenously.

The compared interventions in the model are pembrolizumab + enfortumab vedotin (PEM+EV) and GP/GC (Gemcitabine plus cisplatin/ Gemcitabine plus carboplatin) followed by maintenance treatment with avelumab for the eligible patients, after GP/GC discontinuation or completion. EV was administered at a dose of 1.25 mg/kg on Days 1 and 8 of the three-week cycle. Pembrolizumab was administered at a flat does of 200mg, on day 1 of the three-week cycle. In alignment with the KNA39 clinical trial, the comparators of GP/GC, included Gemcitabine 1,000 mg/m2 in days 1 and 8 of the cycle, combined with 70 mg/m2 of Cisplatin in day 1 of the cycle for GC and 4.5 or 5 AUC of Carboplatin in day 1 of the cycle for GP. Avelumab was administered as 800mg flat does every 2 weeks, after completion of the GP/GC scheme.[7]

## RESULTS

### Description of the model base case results

The total cost of the PEM+EV combination and the comparators was assessed. Table 1 shows the results of the cost-effectiveness analysis in detail. The costs were estimated at €152,741 for PEM+EV and €43,626 for GP/GC +/- Avelumab. The PEM+EV intervention arm was more effective than the comparator with 5.04 LY's gained which translated to 3.07 QALY's gained; compared to 2.10 life years gained and 1.35 QALY's gained for GP/GC +/- Avelumab. The incremental analysis showed that PEM+EV resulted in an ICER of €37,200 per LY gained and €63,639 per QALY gained compared to GP/GC +/- Avelumab. Thus, it fell within the Greek unofficial threshold of €64,926 per QALY gained; and was deemed to be a cost-effective intervention.[7] These results are shown in Table 1. One of the limitations of the model is that the indirect costs have not been included in the model and hence the value of the treatment is underestimated; especially given the significant burden of UC in informal care costs.

### Deterministic Sensitivity Analysis

A deterministic sensitivity analysis was run to estimate the parameters with the biggest impact on the ICER. The results are presented in Figure 2. The parameters with the biggest impact on the ICER were, the expected percentage of patients receiving subsequent treatment with avelumab, and the duration of therapy for subsequent treatment with PEM, within the model. The variation in the results presented in the deterministic sensitivity analysis did not significantly vary from the base case analysis.

### Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis was run to assess the sensitivity of the model outcomes to the parametric uncertainty. The analysis showed that PEM had a 50.5% probability of being cost effective at a threshold of 64,926 per QALY € (3x Greece 2023 GDP per capita).[8] The results are shown in Figure 3.

## CONCLUSION

- This analysis presents the value of PEM+EV which provide cancer patients the opportunity to spend more time in the health-states with better quality of life.
- Based on the results of the model, we conclude that PEM+EV has the potential to be a cost-effective intervention, which doubles incremental predicted Life Years and QALY's, compared to the previous SoC.

## REFERENCES

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6. Rouprêt, M., et al., European Association of Urology guidelines on upper urinary tract urothelial carcinoma: 2022 update. 2022. 79(1): p. 62-79.
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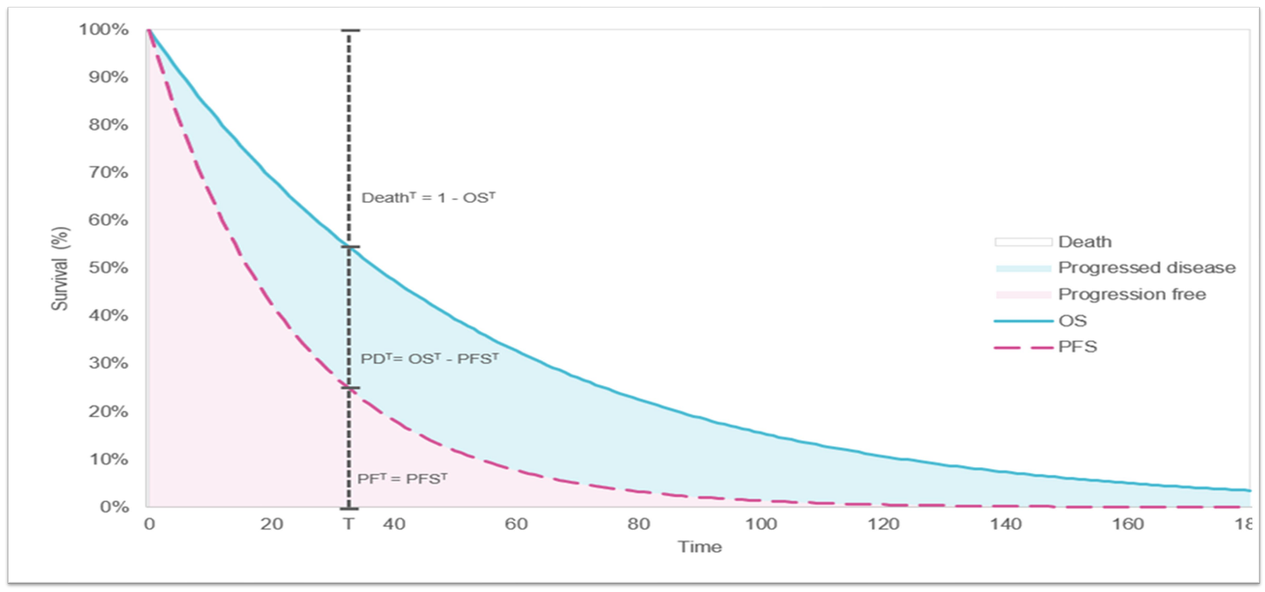
### Figure 1: Model Schema




### Table 1: Base Case Results of the Cost-Effectiveness Analysis

| | Total | | | Incremental | | | |
|---|---|---|---|---|---|---|---|
| | Costs | Life Years | QALY's | %Δ Life Years | %Δ QALY's | ICER per LYg (€) | ICER per QALY g (€) |
| Pembrolizumab+ EV | 152,741 | 5.04 | 3.07 | - | - | - | - |
| GP/ GC +/- Avelumab | 43,626 | 2.10 | 1.35 | - | - | - | - |
| Incremental Cost/ Outcomes | 109,115 | 2.93 | 1.72 | **+139%** | **+126%** | **37,200** | **63,639** |

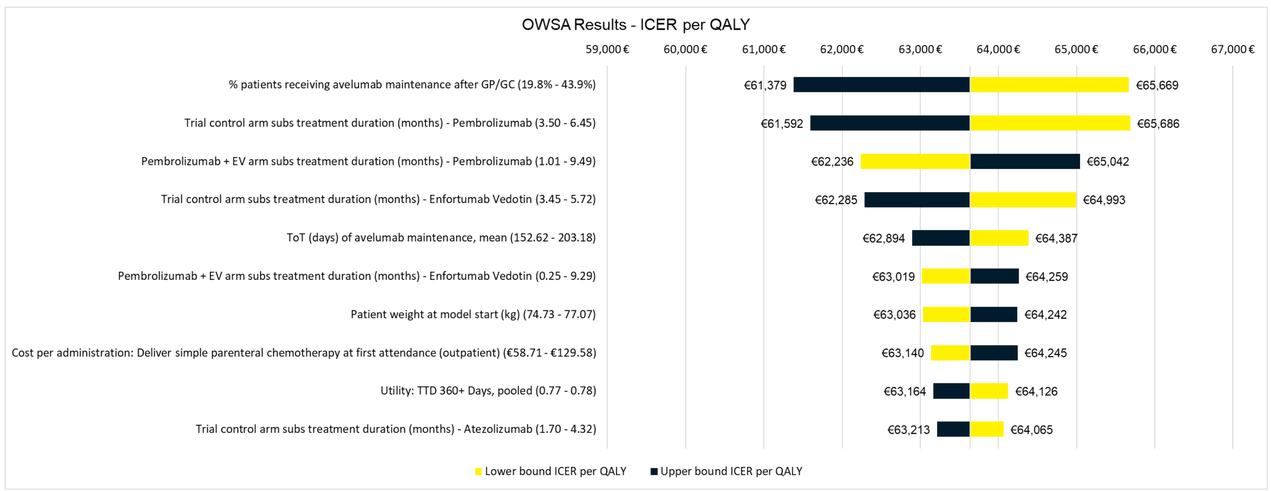
### Table 2: Life Years Breakdown per Health State

| Pairwise: Disaggregated Life Years (undiscounted) | | | | |
|---|---|---|---|---|
| Health-state | Pembrolizumab + EV | GP/ GC +/- Avelumab | Incremental | |
| *Pre-Progression* | *3.47* | *0.837* | *2.636* | **+315%** |
| *Post-Progression* | *1.564* | *1.267* | *0.297* | *+24%* |
| **Total LY's** | **5.037** | **2.104** | **2.933** | ***+139%*** |

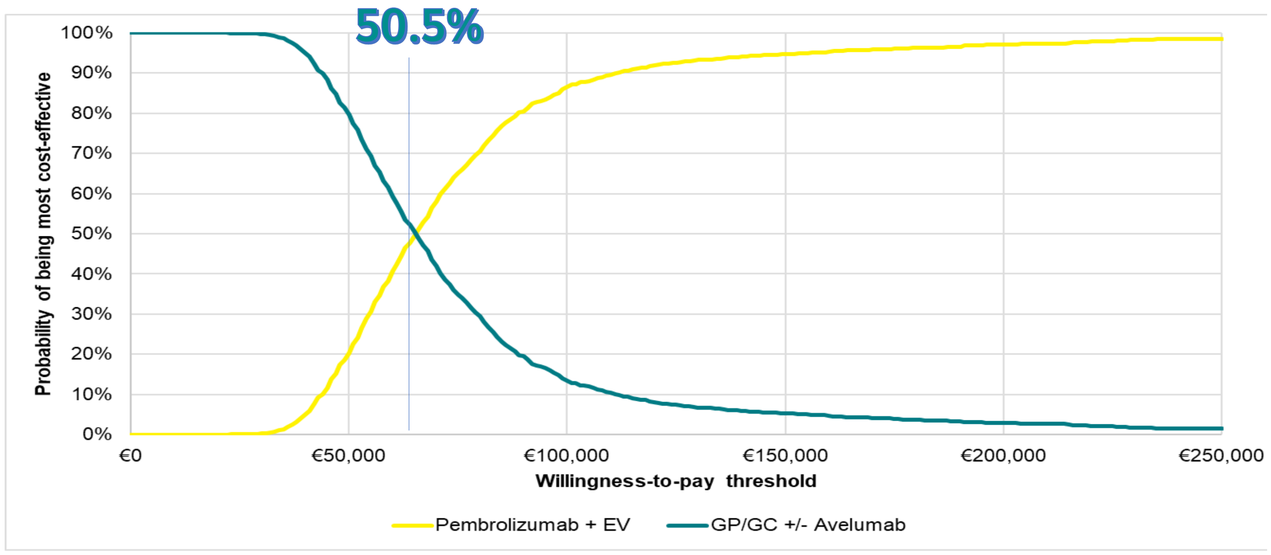
### Table 3: QALY's Breakdown per Health State

| Pairwise: Disaggregated Quality Adjusted Life Years (discounted at 3.0%) | | | | |
|---|---|---|---|---|
| Health-state | Pembrolizumab + EV | GP/ GC +/- Avelumab | Incremental | |
| *Pre-Progression* | *2.151* | *0.607* | *1.544* | **+255%** |
| *Post-Progression* | *0.838* | *0.738* | *0.100* | *+14%* |
| *AE disutility* | *-0.009* | *-0.022* | *0.13* | *-59%* |
| **Total QALY's** | **1.715** | **1.323** | **1.657** | ***+126%*** |

### Figure 2: Deterministic Sensitivity Analysis




### Figure 3: Probabilistic Sensitivity Analysis- Cost Effectiveness Acceptability Curve




Funding source: This work was funded by Merck Sharp &Dohme LLC, a subsidiary of Merck & Co., Inc.