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Original Research

Cost-effectiveness analysis of perioperative durvalumab plus platin-based chemotherapy in muscle invasive bladder cancer in Germany

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ABSTRACT

Background: The NIAGARA trial evaluated the efficacy of adding perioperative immunotherapy with durvalumab to standard gemcitabine/cisplatin chemotherapy in muscle-invasive bladder cancer (MIBC). In light of the rising financial burden associated with the treatment of urothelial carcinoma and the favorable clinical outcomes reported in the NIAGARA trial, we conducted a cost-effectiveness analysis based on clinical data to determine whether the inclusion of durvalumab is also justified from a socioeconomic standpoint in Germany.

Methods: We constructed a Markov model from the payer's perspective, incorporating clinical data derived from the NIAGARA trial. A Monte Carlo simulation was employed to determine the most cost-effective treatment strategy within the context of the German healthcare system. Lastly, we compared the incremental cost-effectiveness ratios (ICERs) of each treatment approach across varying willingness-to-pay (WTP) thresholds.

Results: The average cost associated with the standard of care (SoC) was €113,224, whereas the combination of durvalumab with gemcitabine/cisplatin resulted in an average cost of €126,386, leading to incremental costs of €13,162. The quality-adjusted life years (QALYs) gained were 3.16 for the SoC and 3.37 for the intervention, corresponding to an incremental effectiveness of 0.21 QALYs. The resulting ICER for the combination therapy was €61,006 per QALY. At a WTP threshold of €100,000, the addition of durvalumab to gemcitabine/cisplatin is the preferred treatment option, with a 76.5 % probability of being cost-effective. A significant proportion of the costs observed in the simulations was attributable to the expenses associated with subsequent therapies administered in the metastatic disease setting.

Conclusion: Based on our findings, the incorporation of durvalumab into the perioperative treatment regimen constitutes a cost-effective strategy, primarily due to its potential to reduce the need for high-cost subsequent therapies in a proportion of patients. Consequently, an intensified therapeutic approach for MIBC may confer not only oncological advantages but also notable socioeconomic benefits.

1. Introduction

Bladder cancer is the ninth most common malignancy worldwide, with an estimated 549,393 new cases and approximately 200,000 deaths annually [1, 2]. Around 25 % of newly diagnosed cases are detected at the muscle-invasive stage (MIBC), which requires a multimodal treatment approach consisting of neoadjuvant chemotherapy followed by radical cystectomy. Meta-analyses have demonstrated a mean overall survival benefit of approximately 8 % for neoadjuvant chemotherapy, which typically includes either gemcitabine/cisplatin or dose-dense MVAC regimens [3, 4]. Despite strong recommendations by leading international guidelines, the use of neoadjuvant chemotherapy remains markedly underutilized in many countries, with average utilization rates below 20 % [5, 6].

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The NIAGARA trial investigated the addition of perioperative immunotherapy with durvalumab to gemcitabine/cisplatin [7]. This combination demonstrated a significant survival benefit, with 82 % overall survival at 24 months compared to 75 % in the control arm. Furthermore, the pathological complete response rate (pCR) increased from 27 % to 37 %, prompting discussion of gemcitabine/cisplatin plus durvalumab as a potential new standard of care for patients with MIBC.

Bladder cancer accounts for approximately 2–3 % of total cancer-related healthcare expenditures and, due to costly interventions and intensive follow-up protocols, is considered as one of the most expensive cancer per capita over a patient's lifetime [8, 9]. Treatment costs rise significantly with disease progression. Radical cystectomy alone incurs costs ranging from $30,000 to $40,000, which can double in the event of perioperative complications [10].

Given the increasing financial toxicity associated with urothelial carcinoma and the promising results of the NIAGARA trial, we conducted a cost-effectiveness analysis based on the study data to assess whether the addition of durvalumab is also justified from a socioeconomic perspective.

2. Material and methods

2.1. Treatment arms

The objective of this study was to develop a cost-effectiveness model comparing two treatment strategies for patients with newly diagnosed MIBC, based on the population and treatment regimens reported in the NIAGARA trial.

The standard of care (SoC) comprised neoadjuvant chemotherapy with gemcitabine (1000 mg/m^2 on days 1 and 8) and cisplatin (70 mg/m^2 on day 1) administered for three to four cycles, followed by radical cystectomy. The intervention arm included the same neoadjuvant chemotherapy regimen in combination with four cycles of durvalumab (1500 mg). Postoperatively, patients in the intervention arm received adjuvant immunotherapy with durvalumab (1500 mg) for up to eight cycles.

As all clinical data were derived from previously published trial results, ethical approval was not required for this analysis

2.2. Markov model

To perform the cost-effectiveness analysis, we constructed a Markov transition model using TreeAge Pro (TreeAge Software, Williamstown, MA, USA) with a 5-year time horizon and a cycle length of 3 months. A short time horizon was selected due to the limited long-term follow-up data currently available. The model was initiated at the commencement of either SoC or the intervention regimen consisting of gemcitabine/cisplatin combined with durvalumab.

Fig. 1 illustrates the respective treatment pathways, which are based on current international guidelines for first-line therapies in metastatic urothelial carcinoma. In cases where metastasis occurs following SoC treatment with neoadjuvant gemcitabine/cisplatin and radical cystectomy, patients receive Enfortumab vedotin in combination with Pembrolizumab (EV + P), in accordance with data from the EV-302/KEYNOTE-A49 trial [11].

As no established treatment algorithms currently exist for patients who develop metastases following perioperative treatment with gemcitabine/cisplatin combined with durvalumab, the subsequent therapeutic strategy is based on investigator's choice. If disease progression occurs during therapy or within 12 months after completion of durvalumab, patients are treated with EV monotherapy, given the assumption that rechallenge with a checkpoint inhibitor would provide limited clinical benefit [12]. Conversely, if the interval between the last administration of durvalumab and the onset of metastasis exceeds 12 months, patients are likewise administered EV + P.

Multiple health states were incorporated into the model (see

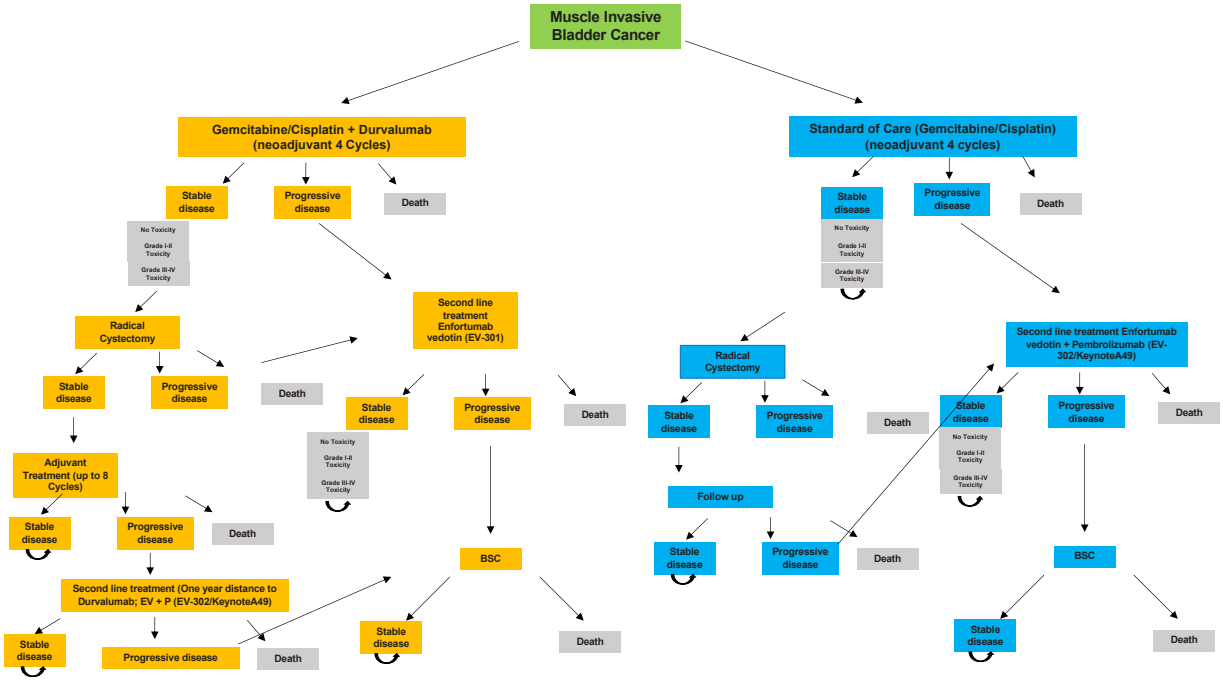

Fig. 1. Markov Model of the study. The figure illustrates the simplified Markov decision model utilized in our study. The model compares the two treatment arms evaluated in the NIAGARA trial: (left arm) gemcitabine/cisplatin (gemcitabine at a dose of 1000 mg/m^2 on days 1 and 8, and cisplatin at a dose of 70 mg/m^2 on day 1) in combination with durvalumab (1500 mg for four cycles), followed by radical cystectomy and adjuvant durvalumab (1500 mg for eight cycles), versus (right arm) gemcitabine/cisplatin followed by radical cystectomy alone. In the intervention arm, if disease progression occurs during treatment or within one year after the last administration of durvalumab, patients in our model receive monotherapy with enfortumab vedotin (EV), based on the assumption that re-administration of a checkpoint inhibitor is unlikely to offer additional benefit. If metastasis occurs more than one year after the final durvalumab dose, patients receive enfortumab vedotin in combination with pembrolizumab (EV + P). In contrast, patients in the standard-of-care (SoC) arm consistently receive EV + P upon metastatic diagnosis.

Table 1
QALYs.

State	Value	Standarddeviation (+/-)	Distribution	Horizon	Reference
Muscle invasive bladder cancer	0.95	0.2	Beta	Lifetime	[20]
Radical Cystectomy	0.8	0.2	Beta	90 days	[20]
mUCa (stable disease)	0.62	0.2	Beta	Lifetime	[20]

Table 1 shows the respective health value of each state based on publishes Cost-Effectiveness Analysis.

Table 1), including stable disease, metastatic disease, and radical cystectomy. Survival outcomes and adverse event data were derived from the NIAGARA trial. Adjusted survival data for overall survival (OS) and progression-free survival (PFS) are provided in the Supplementary Appendix. These clinical inputs were used to calculate transition probabilities for health state changes and adverse event occurrences.

In addition, the Supplementary Appendix includes the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist to ensure transparency and methodological rigor in the reporting of this cost-effectiveness analysis.

2.3. Primary outcome

The principal outcomes of this analysis included mean costs, mean effectiveness measured in quality-adjusted life years (QALYs), and the incremental cost-effectiveness ratio (ICER) for each treatment strategy. QALYs, representing one year of life in perfect health, served as the standard metric for quantifying health-related quality of life within the cost-effectiveness framework. The treatment regimen comprising gemcitabine and cisplatin was designated as the comparator or reference strategy.

To evaluate the economic value of the interventions, we adopted the concept of willingness-to-pay (WTP), which reflects the maximum cost society is prepared to bear for a health benefit of one additional QALY. In line with international standards and WHO recommendations (typically 2–3 × GDP per capita), WTP thresholds of €50,000/QALY, €100,000/QALY, and €150,000/QALY were applied in this study to account for variability across economic evaluations.

The net monetary benefit (NMB) for each strategy was derived by multiplying the incremental QALYs gained by the respective WTP threshold and subtracting the associated treatment costs. All cost estimations were conducted from the German payer's perspective, encompassing statutory and private health insurance systems. The analysis incorporated direct healthcare costs, including drug acquisition, procedural interventions, adverse event management, and costs of subsequent lines of therapy (see Table 2 and Supplementary Material). Unit costs were modeled using a non-commercial Diagnosis-Related Group (DRG) grouper specific to the German healthcare system (see Supplementary Material).

Table 2
Drug costs.

Treatment	Estimated Costs (€/Germany)	Standarddeviation (+/-)	Distribution
Gemcitabine (1000 mg /m^2) / Cisplatin (70 mg/m^2)	2500	250	Gamma
Enfortumab (100 mg)	3060	306	Gamma
Durvalumab 1500 mg	6462	646	Gamma
Pembrolizumab (200 mg)	5700	570	Gamma

The costs of each Treatment arm are presented. As Gemcitabine/Cisplatin is applicated in Germany in a hospital, the costs were simulated with non-commercial DRG Simulator. The other costs were from the Hospital Fee Schedule under the Hospital Fee Act.

2.4. Sensitivity analysis

To assess the robustness and uncertainty of our economic model, we performed both probabilistic and deterministic sensitivity analyses. A probabilistic sensitivity analysis was conducted using Monte Carlo simulation (1000 iterations) to explore the variability of outcomes across a wide range of parameter estimates. This simulation informed the construction of a Cost-Effectiveness Acceptability Curve (CEAC), which illustrates the probability of each strategy being cost-effective at WTP thresholds of €50,000, €100,000, and €150,000 per QALY gained.

Additionally, we conducted one-way (univariate) sensitivity analyses to examine the impact of individual parameters—such as drug costs and effectiveness—on model outcomes. These analyses helped identify thresholds at which the cost-effectiveness of each therapy may shift. A 3 % discount rate was applied as per standard health economic recommendations, and the range of values tested for each parameter is summarized in the corresponding tables. Detailed transition probabilities are provided in the supplementary material.

All probabilities were converted into 3-month cycle-specific transition probabilities to align with the structure of the Markov model. To ensure consistency between the clinical trial data and model estimations, tracker variables were incorporated for real-time comparison, as outlined in the supplementary materials.

3. Results

3.1. Cost-effectiveness-report

The average cost for the SoC was €113,224, compared to €126,386 for the combination of durvalumab with gemcitabine/cisplatin, resulting in incremental costs of €13,162 (Table 3). The QALYs were 3.16 for the SoC and 3.37 for the intervention, yielding an incremental effectiveness of 0.21 QALYs. The ICER for the new treatment was calculated at €61,006/QALY.

3.2. Probabilistic sensitivity analysis

According to the probabilistic sensitivity analysis (1000 iterations), gemcitabine/cisplatin is cost-effective in 59.4 % of simulations at a WTP threshold of €50,000. At a WTP of €100,000, the combination of gemcitabine/cisplatin plus durvalumab emerges as the preferred treatment strategy, with a probability of cost-effectiveness of 76.5 % (Figs. 2 and 3). This probability further increases to 94.2 % at a WTP threshold of €150,000.

3.3. One-way sensitivity analysis

Model sensitivity was highest with respect to the costs of the novel medications, particularly EV + P as second-line treatment in the metastatic setting, and durvalumab in the intervention arm. A cost reduction of approximately 17 % for EV + P would render the intervention arm no longer cost-effective at a WTP threshold of €100,000. Conversely, increasing the cost of durvalumab by 10 % per Markov cycle would also result in the intervention arm falling outside the cost-effectiveness threshold. In contrast, the costs of chemotherapy itself had a less pronounced impact, as demonstrated in the tornado diagram (Fig. 4).

According to our model, to consider gemcitabine/cisplatin plus

Table 3
Base Case Analysis.

Strategy	Costs				
(€)	Incremental costs (€)	Effectiveness (QALY) / estimated life years	Incremental effectiveness / estimated incremental life years	ICER (€)	
SoC	113 224		3.16		
Gemcitabine/Cisplatin + Durvalumab	126 386	13 162	3.37	0.21	61 006

The table summarizes the cost-effectiveness outcomes evaluated over a lifetime horizon. It outlines the mean cost and effectiveness per patient for each treatment strategy, along with the incremental cost and effectiveness relative to the Standard of Care. Furthermore, the table reports the corresponding Incremental Cost-Effectiveness Ratios (ICERs),

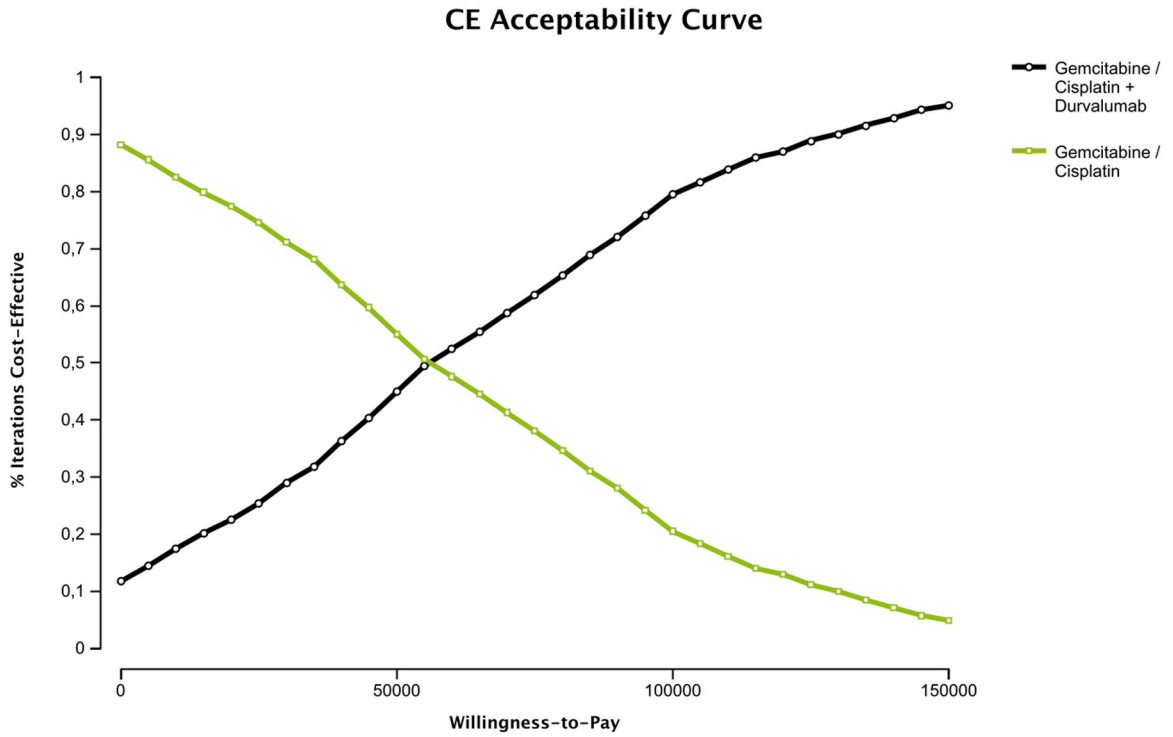

Fig. 2. Acceptability Curve. The x-axis represents varying willingness-to-pay (WTP) thresholds, while the y-axis denotes the probability that each treatment strategy is cost-effective at the corresponding threshold. Based on the probabilistic sensitivity analysis, gemcitabine/cisplatin alone is cost-effective in 59.4 % of simulations at a WTP of €50,000. At a WTP threshold of €100,000, the combination of gemcitabine/cisplatin plus durvalumab is favored, with a 76.5 % probability of being cost-effective. This probability further increases to 94.2 % at a WTP threshold of €150,000.

durvalumab not cost-effective in terms of QALYs, the treatment efficacy for MIBC would need to decrease by approximately 23 %, while the efficacy in mUCa would need to increase by around 52 %.

4. Discussion

Urothelial carcinoma is already considered is an expensive malignancy per capita when assessed over a patient's lifetime. Ongoing advancements in this field—while leading to significant improvements in clinical outcomes—are accompanied by rapidly escalating treatment costs, placing increasing pressure on healthcare systems worldwide. The addition of perioperative durvalumab, as investigated in the NIAGARA trial, has demonstrated a survival benefit over gemcitabine/cisplatin monotherapy. In this cost-effectiveness analysis, we aim to evaluate whether this oncological advantage is also accompanied by a justifiable socioeconomic value.

In our cost-effectiveness analysis, we demonstrated that the perioperative administration of durvalumab in combination with SoC chemotherapy can be a cost-effective strategy within a European healthcare system. At a WTP threshold of €100,000 commonly applied in cost-effectiveness analyses, the combination therapy proved to be cost-effective in more than three-quarters of simulations. While the overall costs in the base-case scenario were slightly higher, the total QALYs gained over the study period increased by 0.21.

Our analysis also identified the primary driver of cost justification, as illustrated by the tornado diagram. Notably, the costs associated with metastatic disease—particularly the use of EV + P—had a dominant influence. In the NIAGARA trial, Event-Free Survival (EFS) at 24 months was approximately 68 % in the intervention arm, compared to 60 % in the control arm [7]. Even this modest difference had a significant impact on downstream costs related to the expensive management of metastatic disease, which could be mitigated through the addition of durvalumab.

In a recently published study from our group, we previously demonstrated the high-cost burden of long-term treatment with EV+P in the metastatic setting. Although the QALYs were nearly doubled, EV+P did not meet cost-effectiveness thresholds [13]. These findings are consistent with other studies and emphasize the critical importance—not only from a clinical but also from a socioeconomic perspective—of preventing progression to metastatic urothelial carcinoma [14–17]. The difference in metastatic progression between the two treatment arms contributes to the cost-effectiveness in our model observed in the intervention arm.

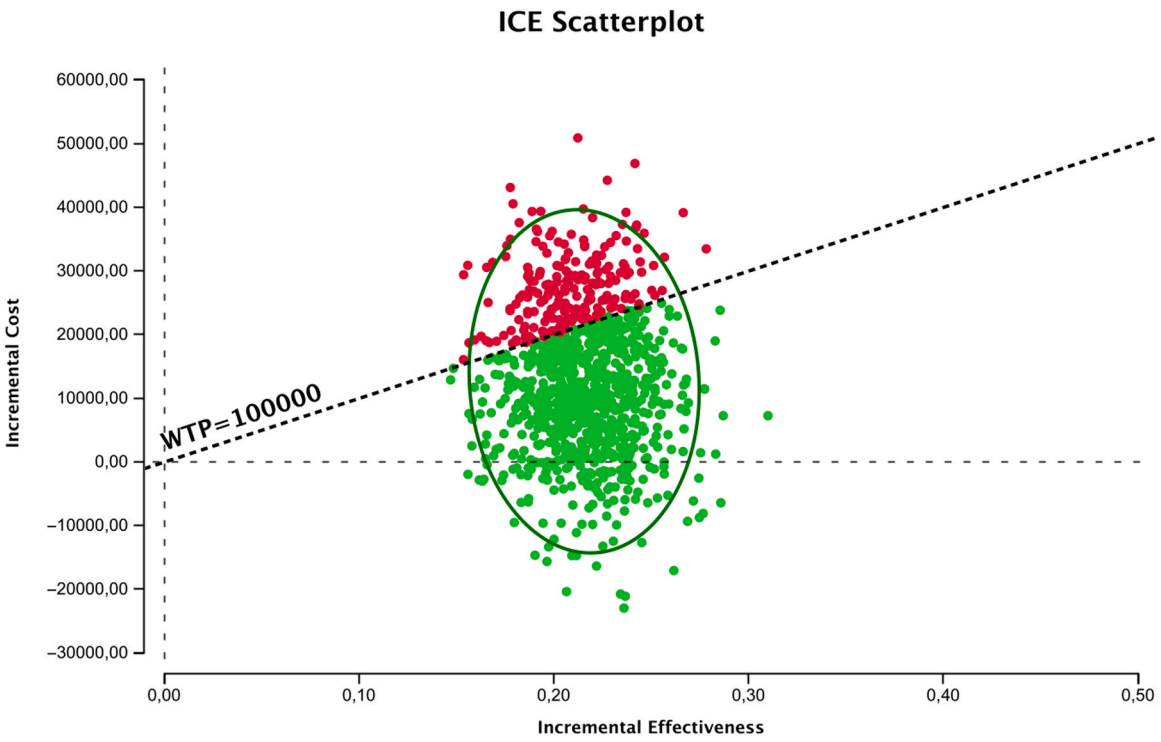

Fig. 3. ICE Scatterplot. The points represent the 1000 simulations generated from the probabilistic sensitivity analysis, with the ellipse indicating the 95 % confidence interval. The green points represent the probability of showing Gemcitabine/Cisplatin + Durvalumab being cost effective.

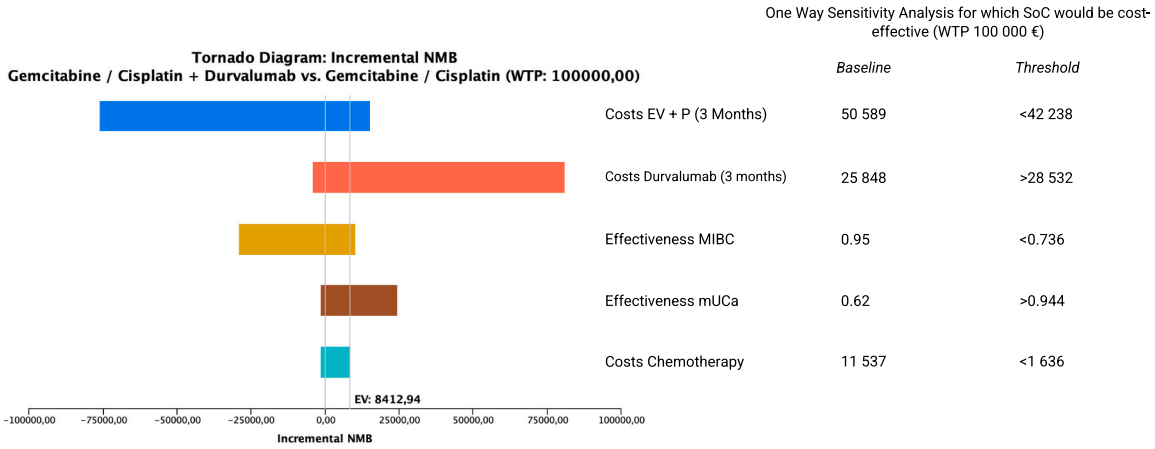

Fig. 4. Tornado Diagram with Incremental NMB. The EV line represents the incremental Net Monetary Benefit (NMB) at a willingness-to-pay (WTP) threshold of €100,000. The left portion of the input range illustrates the impact of varying a parameter from its lower bound up to the base case value, while the right portion reflects changes from the base case to the upper bound. This visualization indicates whether an increase or decrease in a given parameter would be required to improve the NMB, thereby informing which variables most influence the cost-effectiveness outcome.

The NIAGARA trial has recently demonstrated that the addition of durvalumab to neoadjuvant gemcitabine/cisplatin followed by adjuvant durvalumab provides a significant survival benefit compared to neoadjuvant gemcitabine/cisplatin monotherapy without adjuvant treatment. However, an important question remains as to whether gemcitabine/cisplatin truly represents the current standard of care for preoperative systemic therapy in MIBC. The VESPER trial, for instance, showed in the neoadjuvant subgroup analysis that dose-dense MVAC significantly improved survival outcomes [4]. Moreover, patients with locally advanced urothelial carcinoma now receive adjuvant nivolumab following radical cystectomy based on prospective data [18].

Both MVAC and adjuvant nivolumab have been evaluated in previous cost-effectiveness studies and have demonstrated justification of their associated costs [19, 20]. Taken together, our results can only support the cost-effectiveness of adding durvalumab to gemcitabine/cisplatin, relative to gemcitabine/cisplatin alone. Whether this combination represents a superior therapeutic approach—both oncologically and socioeconomically—compared to MVAC or to MVAC followed by adjuvant nivolumab, cannot be concluded from our analysis. We deliberately chose not to perform a cross-trial comparison, given the substantial methodological differences between the NIAGARA and VESPER trials. Furthermore, the results of the EV303 and EV304 trials are anticipated in the near future, which may potentially support the use of EV + P in the MIBC setting, thus expanding future treatment options [21].

In the intervention arm of the NIAGARA trial, all patients received

adjuvant therapy following radical cystectomy regardless of individual risk profiles. This raises the question of whether adjuvant treatment is necessary for all patients. Notably, as previously mentioned, a pCR was observed in 37 % of cases. In the context of a pCR following platinum-based chemotherapy without subsequent adjuvant immunotherapy, the five-year recurrence risk is only 9 % [22]. This could strengthen the opinion that the vast majority of patients would receive adjuvant treatment unnecessarily. In future treatment strategies, biomarker-based approaches should be employed to enable more precise patient selection, thereby potentially reducing the substantial financial toxicity associated with overtreatment. Circulating tumor DNA (ctDNA) has already demonstrated promising potential in other studies on MIBC as a stratification tool to identify patients who may not require adjuvant therapy [23]. According to retrospective studies, disease-free survival (DFS) reaches approximately 92 % in cases with undetectable ctDNA following radical cystectomy [24].

Naturally, our analysis is also subject to several limitations. First, our model is based on the clinical data reported in the NIAGARA trial, which currently has a relatively short follow-up period. Consequently, we selected a five-year time horizon for the cost-effectiveness analysis, aiming to maintain a realistic reflection of the available clinical data while acknowledging the temporal limitations. Second, we modeled subsequent treatment pathways according to current guideline-based standards, with EV+P representing the preferred first-line therapy in the metastatic setting. However, since the NIAGARA trial was initiated prior to the widespread approval of EV+P, not all patients in the trial would have received this combination upon disease progression. As a result, OS in the control arm may be slightly underestimated, potentially influencing our findings. In this context, it should be noted that patients who experience disease recurrence within 12 months after the last administration of durvalumab receive EV monotherapy in our model. This approach is based on the assumption that the EAU does not recommend re-challenging with immunotherapy in cases of recurrence within this timeframe [5]. However, clinical data supporting this treatment sequence are lacking. Nonetheless, we chose to align our analysis with the most up-to-date clinical guidelines to ensure contemporary relevance. Third, our study included only direct medical costs and did not account for indirect costs such as loss of productivity or caregiver burden, which may impact the broader economic evaluation. Fourth, our analysis was conducted within the framework of the German healthcare system, which we considered representative of broader European healthcare economics. However, generalizability to other countries, including those with different healthcare infrastructures such as the United States or China, remains uncertain. Even within Europe, substantial variations exist in the costs of bladder cancer medications. A recent analysis positioned Germany in the mid-range with respect to therapy-related expenditures [25]. Our study remains a model-based analysis, which may not fully capture the complexity and variability of real-world clinical scenarios. Despite the aforementioned limitations, we firmly believe that our cost-effectiveness analysis—being the first to evaluate the NIAGARA trial in this context—provides important and novel insights.

5. Conclusion

Based on our findings, the addition of durvalumab represents a cost-effective treatment strategy, as it may prevent the need for expensive subsequent therapies in a subset of patients. Thus, an intensified therapeutic approach in earlier stages of disease appears to yield not only oncological but also socioeconomic benefits. Future studies should focus on identifying which patients truly require adjuvant therapy. Optimized patient selection could substantially reduce treatment-related financial toxicity.

CRediT authorship contribution statement

Julian Heidenreich: Writing – review & editing. **Jörg Schlüchtermann:** Writing – review & editing, Methodology, Formal analysis. **Constantin Rieger:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Axel Heidenreich:** Writing – review & editing, Supervision, Investigation. **David Pfister:** Writing – review & editing. **Florian A Schmid:** Writing – review & editing. **Olivia Steenbock:** Writing – review & editing, Visualization. **Christian Bach:** Writing – review & editing. **Richard Weiten:** Writing – review & editing.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author used deepl write and ChatGPT only to improve language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Constantin Rieger**: Honoraria: Medac Germany, Astellas. **David Pfister**: Consulting Fees: MSD. Travel: Bayer, Janssen. Advisory Board: BMS, Janssen, MSD, Pfizer. Honoraria: Bayer, Pfizer, Janssen, AstraZeneca, MSD, BMS. **Axel Heidenreich**: Honoraria: Amgen, Astellas, AstraZeneca, Bayer, BMS, Clovis Oncology, Janssen, Pfizer, Takeda. Advisory Board: Astellas, Bayer, Janssen, MMS. Research Grant: BMS. **The remaining authors** declare no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115621.

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Further reading

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