

Genitourinary Oncology Highlights from the European Society for Medical Oncology Annual Meeting 2025: Advances in Renal Cell Carcinoma and Muscle-Invasive Bladder Cancer

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Abstract

Background: At ESMO 2025, practice-changing advances in genitourinary oncology emerged for renal cell carcinoma (RCC) and muscle-invasive bladder cancer (MIBC), highlighting a shift toward early systemic treatment and biomarker-driven treatment selection. **Summary:** In localized RCC, the NESCIO trial showed pathologic responses with short-course neoadjuvant checkpoint inhibition, while the RAMPART study supported adjuvant dual checkpoint blockade for high-risk disease. For advanced RCC, the KEYMAKER-U03 trial demonstrated improved progression-free survival with a novel HIF-2 α triplet regimen, and the LenCabo study supported the use of lenvatinib plus everolimus in later treatment lines. Conversely, the CALYPSO trial noted limited benefit when using empiric combinations without precise biomarker selection. In cisplatin-ineligible MIBC, the KEYNOTE-905/EV-303 trial

demonstrated a significant survival benefit with perioperative enfortumab vedotin plus pembrolizumab. Finally, emerging data from OPTIC RCC transcriptomic stratification and circulating markers like kidney-injury molecule type 1 and circulating tumor DNA strongly support a broader transition toward tailored therapy. **Key Messages:** Perioperative enfortumab vedotin plus pembrolizumab offers a major survival benefit for cisplatin-ineligible bladder cancer patients. Overall, early-stage RCC benefits significantly from perioperative immunotherapy, while managing advanced disease requires a decisive shift away from empiric combinations and toward biomarker-driven treatment selection.

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Introduction

At the European Society for Medical Oncology (ESMO) 2025 congress in Berlin, multiple pivotal trials for genitourinary tumors were presented. While some of the presented data are still early results, as for example

the first results of the RAMPART trial on durvalumab + tremelimumab as adjuvant treatment for RCC, other trials have already changed the clinical practice like the EV303-trial on neoadjuvant therapy with enfortumab-vedotin (EV) + pembrolizumab for cisplatin-ineligible MIBC, which has been approved by the FDA shortly after the congress in November 2025. This article outlines a selection of highlight-studies focusing on renal cell carcinoma (RCC) and muscle-invasive bladder cancer (MIBC). The trials discussed here cover the fields of perioperative treatment for both tumor entities, novel agents and treatment combinations to overcome resistance for metastatic RCC and finally, the latest studies on biomarker-guided treatment in RCC and MIBC.

Immunotherapy in Perioperative Management of RCC and MIBC

Renal Cell Carcinoma

Immunotherapy-based perioperative treatment strategies are increasingly being tested for high-risk localized RCC to reduce recurrence risk and improve overall survival (OS). So far, there is only scarce evidence for neoadjuvant treatment strategies in RCC. The phase II NESCIO trial [1] evaluated an ultra-short course of neoadjuvant immunotherapy before nephrectomy. Patients with intermediate- to high-risk resectable clear cell renal cell carcinoma (ccRCC; mostly T3 or node-positive) were randomized to receive either nivolumab alone, nivolumab + ipilimumab, or nivolumab + relatlimab (a LAG-3 inhibitor), with only two cycles of therapy given over 6 weeks pre-surgery. Despite the brief treatment window, NESCIO reported measurable pathologic tumor responses at surgery, particularly in the combination arms. Pathologic response (tumor necrosis/fibrosis indicating treatment effect) was observed in 2 of 14 patients receiving nivolumab + ipilimumab and 2 of 14 with nivolumab + relatlimab, compared to 1 of 15 with nivolumab monotherapy. Notably, the two patients in the nivolumab + ipilimumab arm achieved near-complete pathologic responses, and one patient in the nivolumab + relatlimab arm had a complete pathologic response. Radiographic tumor shrinkage was uncommon (RECIST objective responses occurred in only 1 of 14 nivolumab + ipilimumab patients and none in the other two arms), meaning most tumors remained stable in size preoperatively. However, the presence of pathological remission foci translated into promising early survival signals. At 18-month follow-up, the event-free survival (EFS) (freedom from progression or recurrence prior to or after surgery) was 93% in the nivolumab + ipilimumab arm, compared to 77% with nivolumab + relatlimab and 72% with nivolumab alone. Similarly, 18-month recurrence-free survival was highest with the nivolumab + ipilimumab regimen (93% vs. 83% and 77%). All patients

who achieved a pathologic response remained disease-free at last follow-up.

These trends suggest that even a short induction with dual checkpoint blockade might profoundly affect disease biology in aggressive RCC, potentially eradicating micrometastatic disease and preventing relapse. However, considerable toxicity was observed with dual checkpoint inhibition and should be weighed against efficacy. Grade ≥ 3 immune-related adverse events occurred in 43% of patients receiving nivolumab + ipilimumab, versus 14% with nivolumab + relatlimab and only 6.7% with nivolumab alone. Some patients in the combo arms required delays in surgery due to treatment side effects (e.g., one in the nivolumab alone arm had a ≥ 2 -week delay), and there was an increase in surgery-related complications in the combination arms (roughly 30% grade 3–4 surgical complications in nivolumab + ipilimumab and nivolumab + relatlimab arms). Despite these risks, the NESCIO investigators concluded that a short course of neoadjuvant immunotherapy is feasible and can induce pathologic responses in a subset of high-risk RCC patients. The nivolumab + ipilimumab doublet, in particular, showed the most favorable trend in preventing recurrences, albeit with more toxicity. This aligns with the paradigm seen in advanced disease that dual checkpoint blockade can produce deep responses, and suggests that for locally advanced RCC at high risk of relapse, an intensive immunotherapeutic approach before surgery might improve outcomes. Ongoing trials and longer follow-up will clarify if this translates into significant survival benefits. NESCIO adds evidence that neoadjuvant treatment of high-risk tumors may offer an opportunity of enhancing cure rates by treating micrometastatic disease at an early timepoint.

For adjuvant therapy, several clinical trials have tested checkpoint-inhibitor therapy for high-risk localized RCC. So far, the KEYNOTE-564 trial was the only trial demonstrating a disease-free survival (DFS) and OS benefit of adding pembrolizumab for 1 year as adjuvant therapy [2].

The RAMPART trial is a randomized, three-arm, open-label phase III trial comparing 1 year of active monitoring (arm A) to 1 year of adjuvant immunotherapy with either durvalumab monotherapy (arm B) or dual checkpoint-inhibition with durvalumab + tremelimumab (arm C) [3]. At ESMO 2025, first results of the dual checkpoint-inhibition arm (arm C) as compared to active monitoring (arm A) were presented. A total of 750 patients with intermediate or high-risk localized RCC as determined by the Leibovich risk score [4] or oligometastatic RCC following total tumor resection and metastectomy (M1 NED) were enrolled in this study and 3:2:2 randomized into the three arms. In arm C, patients were planned to receive two cycles of durvalumab + tremelimumab followed by 11 cycles of durvalumab

monotherapy. Notably, only 23% of patients received all intended treatment cycles in the dual checkpoint-inhibition arm with a median duration of treatment of 10.9 months. The initial analysis demonstrated a significantly improved DFS after durvalumab + tremelimumab treatment as compared to active monitoring (HR 0.65, CI 0.45–0.93, $p = 0.0094$) in the intention to treat population. Further subgroup analyses showed that this DFS-benefit could only be observed in the high-risk subgroup, but not in the intermediate-risk subgroup. Hence, the RAMPART trial is the second positive trial showing a clinical benefit of adjuvant immunotherapy for high-risk localized RCC. It remains to be clarified, whether the clinical benefit justifies the toxicity with 40% of grade 3 and higher adverse events caused by the dual checkpoint-inhibition in this therapeutic setting. Further results of this trial, particularly of the durvalumab monotherapy arm (arm B) are now being awaited to elucidate, whether there is an additional benefit of dual checkpoint-inhibition as compared to the anti-PDL1 monotherapy.

Muscle-Invasive Bladder Cancer

A parallel breakthrough has occurred in MIBC, where perioperative systemic therapy is critical but many patients cannot tolerate standard chemotherapy. The phase III KEYNOTE-905/EV-303 study [5] tested an immunotherapy-based regimen for cisplatin-ineligible MIBC. In this trial, patients with MIBC who were unable or unwilling to receive cisplatin were randomized to either surgery alone (radical cystectomy with lymph node dissection, plus standard-of-care which could include adjuvant nivolumab) or perioperative pembrolizumab (pembro) + EV in addition to surgery. EV is an antibody-drug conjugate targeting Nectin-4, which has become standard-of-care treatment for systemic therapy of metastatic urothelial carcinoma in combination with the PD-1 inhibitor pembrolizumab [6]. The first interim analysis of KEYNOTE-905, presented at ESMO 2025, demonstrated significantly improved survival outcomes with the use of perioperative EV + pembrolizumab. The primary endpoint, EFS, was markedly prolonged: median EFS was not reached in the immunotherapy arm versus 15.7 months with surgery alone (HR 0.40, 95% CI 0.28–0.57; $p < 0.0001$). OS, a key secondary endpoint, was likewise improved (median OS not reached vs. 41.7 months; HR 0.50, 95% CI 0.33–0.74; $p = 0.0002$). Pathologic complete response rates – a measure of eradication of tumor in the bladder and nodes at surgery – were 57.1% with neoadjuvant EV + pembrolizumab, showing a high activity in this setting. The abovementioned benefits were seen across all analyzed subgroups, and the addition of therapy did not compromise the feasibility of surgery. The EV + pembrolizumab arm showed high, but expected toxicity – grade ≥ 3 events in 71% vs. 46% of patients. The

most common serious toxicities included severe skin reactions from PD-1 therapy and EV-related rash or peripheral neuropathy. However, no new safety signals emerged and toxicities were generally manageable within known profiles. Given the significant gains in EFS, OS, and confirming its activity as shown by the pathologic complete response, KEYNOTE-905 establishes a new effective perioperative option for cisplatin-ineligible bladder cancer. For the first time, there is a treatment regimen available for patients who cannot receive chemotherapy that improves survival when added to local therapy. This is expected to change the standard of care in MIBC, pending regulatory approvals, by making curative-intent treatment more effective in this historically hard-to-treat group. More broadly, it highlights the expanding role of immunotherapy and targeted agents in earlier stages of GU cancers – moving from metastatic settings to neoadjuvant and adjuvant use to treat occult disease.

Strategies to Overcome Resistance in First- and Subsequent-Line Therapy for RCC

Current first-line therapy for metastatic or advanced localized RCC consists of either a combination therapy with an anti-VEGF tyrosine-kinase inhibitor (TKI) and an anti-PD-1 checkpoint-inhibitor (TKI/IO: cabozantinib + nivolumab, axitinib + pembrolizumab or lenvatinib + pembrolizumab) or a dual checkpoint-inhibition with ipilimumab + nivolumab (IO/IO). These treatment regimens have clearly improved outcomes for metastatic RCC in comparison to previous treatment strategies yielding an objective response rate (ORR) of up to 70% for TKI/IO and 40% for IO/IO and a median OS of up to 50 months. Despite these first-line advances, there are still many patients who do not respond due to primary resistance or eventually develop progressive disease, underscoring the need for further treatment strategies in first- and subsequent therapy lines.

For first-line therapy, novel molecular targets are being explored in combination with established standard therapy regimens. The phase I/II KEYMAKER-U03 platform [7] evaluated multiple pembrolizumab-based combinations in treatment-naïve ccRCC, including novel triplet regimens. Substudy 03A tested five arms, and notably the addition of the HIF-2 α inhibitor belzutifan to standard pembrolizumab + lenvatinib showed good efficacy; the belzutifan + pembrolizumab + lenvatinib triplet achieved a median progression-free survival (PFS) of 31.8 months – compared to 26.3 months with the pembrolizumab + lenvatinib control arm. Duration of response was similarly extended (33.4 vs. 25.6 months). These results suggest that a triplet targeting VEGF, PD-1, and HIF-2 pathways can deepen and lengthen responses in upfront ccRCC. However,

grade ≥ 3 toxicity remains a consideration: 24.4% in the triplet arm experienced anemia (control arm: 1.6%) and 8.9% hypoxia (control arm: 0%), underscoring the need to balance efficacy with tolerability.

Other arms of the study included an addition of favezelimab, a LAG3-inhibitor or quavonlimab, a CTLA4-inhibitor to the pembrolizumab + lenvatinib backbone. Both drugs did not show a significant benefit in terms of ORR or PFS. Overall, these findings reaffirm the established efficacy and safety of standard-of-care pembrolizumab + lenvatinib in advanced ccRCC and demonstrate the feasibility of evaluating first-line triplet regimens within a platform design using an active control arm.

As most metastatic RCC eventually progress on initial therapy, recent trials have explored how to best sequence or augment treatments in refractory disease. In this setting, the phase II LenCabo trial compares lenvatinib + everolimus vs. cabozantinib, two widely used treatment regimens in subsequent-line therapy [8]. A total of 90 patients were 1:1 randomized and received either lenvatinib + everolimus or cabozantinib in established standard dosing. The enrolled patients were allowed to have either one or two prior therapy lines including checkpoint-inhibition and/or anti-VEGF TKI; notably only 30% of the included patients received a prior TKI-therapy. This study showed a significant PFS benefit (HR 0.51, mPFS 15.7 months vs. 10.2 months, $p = 0.02$) and higher ORRs (52.6% vs. 38.6%) of lenvatinib + everolimus as compared to cabozantinib. However, these effects did not translate into an OS benefit (HR 1.05, $p = 0.86$) in these preliminary results. The higher efficacy of lenvatinib + everolimus also came at the cost of higher toxicities with 67.5% grade 3 and higher adverse events as compared to 50% for cabozantinib. The results of this study provide practice informing evidence and guide the treatment decision for subsequent-line therapy in RCC. Hereby, disease burden with a high need for treatment response and tumor size reduction needs to be weighed against toxicity for each patient individually.

Besides already established treatment strategies, further innovative regimens with novel molecular targets are also being explored and were presented at ESMO 2025. The phase II CALYPSO trial [9] examined whether adding a CTLA-4 inhibitor or a MET inhibitor could improve outcomes in ccRCC that had progressed after VEGF-targeted therapy. In this three-arm study, patients who were VEGFR-TKI pretreated but immunotherapy-naïve were randomized to durvalumab (PD-L1 inhibitor) alone, durvalumab + tremelimumab (CTLA-4 antibody), or durvalumab + savolitinib (MET TKI). The goal was to see if combination strategies could overcome resistance mechanisms after VEGF therapy – for example, MET pathway upregulation or insufficient immune response. Final results showed that adding savo-

litinib did not improve efficacy over PD-L1 monotherapy. The ORR was only 13% with durvalumab + savolitinib versus 10% with durvalumab alone, and median OS was actually shorter in the savolitinib arm (16.3 months) than with durvalumab alone (25.8 months). By contrast, the durvalumab + tremelimumab arm showed a higher ORR of 33%, nearly triple that of durvalumab monotherapy, although this did not translate into a meaningful PFS or OS advantage (median OS 24.2 months, similar to monotherapy).

In exploratory analyses, the only subset with a potential benefit from savolitinib were patients with MET-driven tumors. MET alterations were evaluated using next-generation sequencing and MET-driven status was defined as chromosome seven gain, MET amplification, MET kinase domain variations, or hepatocyte growth factor amplification. In this small subgroup, adding the MET inhibitor appeared to improve OS, although no statistics were presented. Outside of this niche, however, CALYPSO concluded that MET inhibition adds little value in unselected VEGF-pretreated ccRCC, and the combination of PD-1 plus CTLA-4 inhibitors, while somewhat increasing response rates, did not significantly prolong survival. These findings temper enthusiasm for routine triplet use (e.g., PD-1 + CTLA-4 + MET inhibition) in second-line RCC, and suggest that a broad phase III trial of savolitinib in this setting is unwarranted. Instead, clinicians may consider other sequential approaches after IO therapy.

Overall, the post-VEGF and post-IO space in RCC is still challenging, and CALYPSO's outcome directs future research toward biomarker-enriched trials (e.g., focusing on MET-altered tumors) or novel targets to overcome resistance. The consistent message is that adding agents without robust biological rationale did not yield benefit and cannot be recommended. Treatment decision should be guided by disease biology and prior treatment exposures. Upfront molecular profiling of RCC could be used for new clinical trials with stratified treatment options.

Biomarker-Guided Therapy in RCC and MIBC

Renal Cell Carcinoma

Modern management of metastatic ccRCC could be witnessing a shift toward biomarker-guided treatment selection. Traditionally, no genomic or transcriptomic marker has guided first-line therapy in RCC, despite extensive efforts [10]. The phase II OPTIC RCC trial [11] exemplifies a new approach: using RNA sequencing to subtype tumors and assign therapy accordingly. In OPTIC, treatment-naïve metastatic ccRCC patients were classified by a machine-learning model into molecular clusters derived from IMmotion151 transcriptomic

signatures [12]. Those with “angiogenic” gene expression (Clusters 1/2) were given the VEGFR-TKI cabozantinib plus PD-1 checkpoint-inhibitor nivolumab, hypothesizing this IO/TKI combo would be optimal for angiogenesis-driven tumors. Patients with “inflamed” tumors (Clusters 4/5) received ipilimumab + nivolumab (dual immunotherapy, ongoing), while cases falling into Cluster 3/6/7 were excluded. Early results in the Cluster 1/2 cohort are encouraging: among 26 treated patients, the ORR reached 76%, with no patients experiencing primary progression (24% had stable disease as best response). All evaluable patients showed some tumor shrinkage, and 100% achieved a tumor burden reduction on therapy. This exceeds historical first-line ORRs in unselected RCC and suggests that enriching for angiogenic tumors can improve response to cabozantinib + nivolumab. Although follow-up is still short (median 11.1 months) and these findings are not yet practice-changing, OPTIC demonstrates the feasibility of using transcriptomic biomarkers to guide initial RCC treatment – a notable step toward biologically driven therapy in a disease that has so far lacked predictive biomarkers.

In addition to tissue-based biomarkers, circulating biomarkers are an attractive alternative option as the blood-based detection supports an easier implementation in daily clinical routine. In RCC, the kidney-injury molecule type 1 (KIM-1) is a blood-based biomarker, which has been studied in retrospective exploratory analyses of several clinical trials in adjuvant and palliative therapy settings [13, 14]. Previous analyses showed that low levels of KIM-1 at baseline before treatment or an early decrease under treatment was associated with better treatment outcome. This effect was more pronounced for checkpoint-inhibition treated than for TKI treated patients [14]. A post hoc analysis of KIM-1 levels in the COSMIC-313 trial showed similar results to previous studies [15]. COSMIC-313 was a two-arm, randomized phase III clinical trial investigating the triplet combination with cabozantinib + ipilimumab + nivolumab in comparison to ipilimumab + nivolumab as first-line therapy for metastatic RCC [16]. The results of this trial demonstrated a PFS benefit, but no OS benefit of adding cabozantinib to the dual checkpoint-inhibition. To evaluate the association between KIM-1 levels and treatment outcome, KIM-1 levels of patients were measured at baseline and at week 4, 7, 10, and 14 after treatment onset. Higher baseline KIM-1 concentration correlated with worse clinical risk factors like IMDC poor risk subgroup, no prior nephrectomy or high disease burden as measured by total diameter of target lesions and with worse OS outcome across both treatment groups. Following treatment, there was an association between KIM-1 decline and ORR as well as PFS in both treatment groups, while the differences were

detectable earlier and more pronounced in the ipilimumab + nivolumab arm (week 4) than in the triplet therapy arm (week 7). In the ipilimumab + nivolumab arm, there was also a significant association between KIM-1 decline and OS. These results support the existing evidence of KIM-1 as a prognostic and predictive biomarker for checkpoint-inhibition treated patients in RCC. Prospective clinical trials are needed to further validate these findings and evaluate the potential of this biomarker to guide treatment decisions.

Muscle-Invasive Bladder Cancer

In bladder cancer, similar efforts have focused on investigating prognostic and predictive circulating biomarkers. In this regard, increasing evidence from exploratory analyses of the perioperative [17] and adjuvant immunotherapy trials [18, 19] support the usage of circulating tumor DNA (ctDNA) as a biomarker to select for patients who will benefit from adjuvant immunotherapy.

The randomized, phase III IMVIGOR-011 trial is the first clinical trial prospectively investigating this ctDNA-guided approach for adjuvant immunotherapy in bladder cancer [20]. The trial builds on the post hoc analysis of the IMVIGOR-010 trial. Here, adjuvant therapy with atezolizumab did not result in a PFS or OS benefit in the intention to treat group. However, in the subgroup of patients with positive ctDNA results after cystectomy, adjuvant atezolizumab resulted in a significant OS benefit (HR 0.59) [18]. Based on these results, IMVIGOR-011 was conducted to prospectively validate the potential of ctDNA as predictive biomarker in the adjuvant therapy setting. A total of 756 patients were enrolled in this trial and underwent ctDNA testing every 6 weeks in addition to radiographic imaging every 12 weeks for 1 year after cystectomy. Approximately 50% ($n = 379$) were tested ctDNA+ within this period and were then 2:1 randomized to receive either atezolizumab or placebo as adjuvant treatment for up to 1 year. The trial showed positive results after a median follow-up time of 16.1 months with a significant DFS (HR 0.64, mDFS 9.9 vs. 4.8 months, $p = 0.0047$) and OS (HR 0.59, mOS 32.8 vs. 21.1 months, $p = 0.0131$) benefit of adjuvant atezolizumab in the ctDNA+ patient subgroup. For ctDNA- patients, the DFS-rate was 95.4% after 1 year and 88.4% after 2 years, the OS-rate was 100% after 1 year and 97.1% after 2 years. These results provide high-level evidence for the usage of ctDNA as a biomarker to select patients at high-risk of recurrence, who need additional adjuvant immunotherapy. At the same time, this biomarker also detects the patients with favorable prognosis and low risk of recurrence, who do not need additional treatment. IMVIGOR-011 is a

pioneer study as one of the first prospective clinical trials evaluating ctDNA-guided therapy and paves the way for biomarker-guided patient stratification, which can select patients with a particular benefit from intensified therapy and at the same time spare treatment and toxicity for the other patients.

Conclusion

The ESMO 2025 meeting presented transformative advances in RCC and MIBC, highlighting progress in perioperative immunotherapy, treatment sequencing, and biomarker-guided strategies. While trials such as NESCIO, RAMPART, EV-303, and KEYMAKER-U03 reflect a growing emphasis on optimizing sequencing and intensification, CALYPSO, OPTIC, and IMVIGOR-011 highlight the expanding role of molecular and biomarker-driven treatment selection. One major challenge remains the translation of these insights into routine clinical practice. Together, these studies reflect a shift toward precision immunotherapy in GU oncology, with increasing emphasis on stage-adapted and biology-informed approaches.

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