ESMO 2025 Reflections

Four potentially practice-changing bladder cancer papers

This year's ESMO congress delivered a wealth of impactful data across the bladder cancer spectrum, from muscle-invasive to metastatic disease. Here are four standout studies with potential to reshape clinical practice:

1. EV-P in perioperative MIBC: A new standard emerging?

EV-P has already shifted the landscape in locally advanced/metastatic urothelial cancer (la / mUC) – it looks like it's set to do the same in muscle-invasive bladder cancer (MIBC). The data presented for peri-operative enfortumab vedotin plus pembrolizumab demonstrates a significant step forward in survival post cystectomy. Raising more questions than it answers:

- Could this be the first, credible step toward bladder-sparing strategies?
- Will EV-P reduce progression to metastatic disease?
- What are the implications for sequencing therapies in those who do progress?

2. IMvigor011: ctDNA-guided adjuvant immunotherapy

The results of the IMvigor011 trial showed the survival benefits of atezolizumab in adjuvant MIBC. This was notable as it is the first trial to demonstrate the clinical utility of ctDNA in MIBC, perhaps paving the way for tailored escalation and de-escalation of adjuvant therapy in this setting.

3. RC48-C016: A second ADC in la/mUC

The RC48-C016 trial, from China, evaluated disitamab vedotin (DV) plus toripalimab in HER2-expressing la/mUC. Strong OS / PFS and ORR in this targeted population demonstrate the potential for a second ADC in La/mUC and being able to target ADC therapy to those most likely to respond.

4. DISCUS trial: Fewer cycles, same benefit

Whilst much of the focus in the bladder papers was about moving away from platinum chemotherapy, it was also good to hear the results of the DISCUS trial, which demonstrated that fewer cycles of platinum CT followed by avelumab maintenance in la/mUC improves tolerability whilst preserving efficacy. Providing an efficacious alternative where EV-P is not suitable.

TROP-2 ADCs turning the tide in TNBC

Among breast cancer subtypes, triple-negative disease remains the most aggressive, and for the 60–70% of patients who are PD-L1–negative, frontline options have long been limited. **But at ESMO 2025, the landscape shifted**. Two TROP-2 ADCs (sacituzumab govitecan and datopotamab deruxtecan) showed positive results in back-to-back presentations, offering long-awaited hope for patients who have had few options.

Considerations: Where do we go from here?

- TROP-2 ADCs are poised to **redefine first-line management** for PD-L1–negative TNBC, but the key question now is **how to choose between them**. Both agents carry a topoisomerase-1 payload, yet their pharmacokinetics — and therefore side-effect profiles — differ, as do their dosing schedules and trial designs.
- Overall survival is another important consideration. Twelve-month OS rates appear broadly comparable between trials, but the ASCENT-03 trial allowed patients to **crossover** to SG upon progression, which will influence the final analysis. This approach was widely applauded, though it may complicate the regulatory path for SG.
- With these differences in mind, clinicians will need to weigh disease burden, symptoms, and toxicity profiles when making treatment decisions. Although **forecasts estimate Dato-DXd will take the lead** owing to better tolerability and regulatory enthusiasm.
- Another consideration is how these agents will fit into the treatment algorithm for **BRCA-mutated patients**. Should a PARP inhibitor be prioritised over a TROP-2 ADC, or does the lack of clear survival benefit for PARP inhibitors (to date) mean ADCs should take precedence?

T-DXd steers toward early HER2+ breast cancer

The success of T-DXd in metastatic HER2+ breast cancer has set the stage for its next challenge: can it make a difference **earlier in the disease course**? At ESMO 2025, the spotlight turned to early breast cancer, with two key trials starting to reveal the answer. **DESTINY-Breast05**: evaluating T-DXd versus T-DM1 as adjuvant therapy in high-risk HER2+ eBC and **DESTINY-Breast11**: presenting initial data for T-DXd-THP versus ddAC-THP as neoadjuvant therapy in high-risk HER2+ disease.

Considerations: Where does this data leave us?

- Focus was on DESTINY-Breast05, the more mature dataset. The key question: does the risk–benefit profile of T-DXd justify replacing T-DM1 in this high-risk population? The answer is nuanced. While T-DXd halved recurrence risk, this must be weighed against ILD (and monitoring), higher side effects, treatment interruptions, and an unknown impact on overall survival. Dr. Sara Tolaney suggested the **risk–benefit favours T-DXd**, though broader opinion remains to be seen.
- The role of DESTINY-Breast11 is less clear. The trial is not powered for EFS, and questions remain about the comparator arm, particularly as some regions have moved away from anthracyclines.
- More broadly, these data raise questions about **sequencing** if T-DXd becomes available across both settings. Could T-DXd be repeated, or would T-DM1 with a different payload be preferred? Would HER2 expression remain sufficient to maintain response? The findings highlight the complexity of introducing ADCs earlier and underscore the need for clear guidance on resistance mechanisms and the potential value of retreatment to maximise benefit.

The next wave of radiopharmaceutical evolution

Radioligand therapy is making waves, with over 250 trials underway across 20 cancer types and dedicated sessions at ESMO 2025 highlighting the field's rapid evolution. Key papers showcased different avenues of progress and the expanding impact of this therapeutic class.

- **Evolution of beta-emitting therapies:** The PSMA-Addition trial explored Pluvicto earlier in the prostate cancer pathway (mHSPC). While positive, there was tempered enthusiasm regarding the magnitude of benefit. The results also highlighted broader questions, echoed across RLT sessions, about defining eligibility for PSMA-targeted RLT, therapy monitoring, and the personalisation of dosing, underscoring areas for refinement as the class continues to evolve.
- **Positioning alpha RLT in the treatment pathway:** A new generation of alpha-emitting radioligand therapies is emerging, offering short-range, high linear energy that induces double-stranded DNA breaks. A key question is how alpha emitters will be positioned relative to beta emitters - before, after, or alongside them. One presentation examined ^{212}Pb-DOTAMTATE in RLT-exposed GEP-NETs. Although a phase 2 study, it demonstrated that the therapy is safe and effective, and proposed retreatment with RLT as a viable treatment option.
- **Innovation continues to accelerate:** Sessions highlighted how the field is rapidly evolving, preparing medical oncology teams for the next wave of radioligand therapies. Developments include combination strategies, new radionuclides, next-generation ligands, albumin-binding strategies, and expansion into new tumor types. Case studies illustrated best practice, improved referral pathways, and streamlined turnaround times, emphasising that the pace of innovation shows no signs of slowing.

On the horizon: ambitions for the next era of personalised medicine

Discussions across ESMO 2025 pointed to a future in which personalisation in oncology extends beyond static, biomarker-based treatment selection. The focus is shifting toward a continuous, anticipatory model - one that adapts as the tumor evolves, aiming to outpace resistance rather than react to it.

Examples of what this next era could look like are already being explored:

- **Integrative predictive models:** Efforts are underway to develop tools that combine clinical, pathological, molecular, and radiographic factors to guide more dynamic decision-making - identifying which patients are most likely to benefit from certain treatments and opening new pathways, such as immunotherapy for pMMR mCRC.
- **Acting upon molecular progression:** The SERENA-6 trial exemplified how early intervention based on molecular, rather than radiographic, progression could help maintain disease control for longer.
- **Addressing residual disease more proactively:** In advanced NSCLC, future use of local consolidative therapy (LCT) following induction treatment (e.g., osimertinib) was discussed as a way to build on systemic response, guided by on-treatment evaluation and a deeper understanding of tumor and microenvironment dynamics.
- **Decoding resistance:** A recurring theme across tumor types was the need to deepen our mechanistic understanding of resistance - both to inform smarter sequencing today and accelerate the development of next-generation therapies.

Breaking the surface: the slow emergence of ctDNA in MRD

Using ctDNA to guide adjuvant therapy in solid tumours has long been the ambition, but progress has been slow and challenging. Test performance remains critical; for de-escalation studies, high sensitivity is essential to avoid false negatives, while for escalation trials, high specificity is key to prevent overtreatment.

CRC has primarily led the field, driven by the desire to spare patients unnecessary oxaliplatin. Yet this goal has remained elusive. Trials like **PEGASUS** and **DYNAMIC-III** have sought to advance ctDNA-guided de-escalation, but current test sensitivity is modest (around 40–50%). Estimates suggest that 80–90% sensitivity may be needed to safely implement de-escalation, meaning that next-generation testing will be critical to reach the next step.

On the other hand, **IMpower010** demonstrated how ctDNA can successfully identify patients most likely to benefit from adjuvant therapy, marking a milestone as the first IO to show an OS benefit in this population and setting. It's a meaningful advance for the ctDNA field, but even as this progress is celebrated, questions remain: how cost-effective is a ctDNA-guided approach versus treating all? And what will it take for ctDNA to truly become part of standard adjuvant decision-making?

We're ready to discuss how the latest oncology developments could shape strategy and decisions. Reach out to set up a conversation.

Paula Coyle

Siobhan Davies

oncology@beyondblueinsight.com