ESMO 2025 Review: Bring me the horizon

ESMO and its US counterpart, ASCO, always trigger meaningful discussions among physicians, patients, and the industry; this year was no different. One theme that really came across over the various sessions was that we are rapidly moving toward new horizons in oncology. Although there are still meaningful data releases and findings on existing immune checkpoint inhibitors, these are quickly being supplanted by antibody-drug conjugates (ADCs) in terms of podium time. We are also seeing greater interest, excitement, and anticipation for the role of bispecific antibodies (bsAbs) and novel radioligands in the treatment of a broad range of cancers. So, although ESMO often feels like an exercise in peering over the horizon into the future of oncology, it certainly feels like we are rapidly bringing the future to life.

Key themes

→ At the horizon: ADCs continue their dominance

- ESMO and ASCO continue to be the launchpads for key ADC data releases, securing several keynote spots over the course of the weekend, with one in particular retaining its position on the mainstage for several years now: Enhertu (trastuzumab deruxtecan).
    - The double salvo of data from DESTINY-Breast05 and DESTINY-Breast11 have demonstrated a role for the ADC in earlier stages of HER2+ breast cancer across both adjuvant and neoadjuvant states.
    - Physicians were quick to note that Enhertu will become a new standard of care in the earlier disease setting, but questions still remain on when might be the best time to use it.
    - As with previous meetings in the US and Europe, physicians are keen to understand the optimal duration of treatment, and to avoid unnecessary clinical and financial toxicity—a trend that was reflected throughout ESMO again this year.
- We saw a similar pattern emerge from another ADC, Padcev (enfortumab vedotin), which has now demonstrated significant efficacy moving from metastatic urothelial cancer (mUC) into the muscle-invasive stage of disease.
    - As with the release of EV-302's data at ESMO 2023, the results of the combination EV-303/KEY-NOTE-905 trial this year was met with a round of spontaneous applause from the audience, driven by significant gains in event-free survival and overall survival (OS).
    - Attention will now turn toward its pricing and reimbursement process, following the ongoing successes being recorded in mUC across international markets.

- Finally, triple negative breast cancer (TNBC) continued to be a theme from this year's ASCO meeting by delivering important, potentially practice-changing results from sacituzumab govitecan (Trodelvy) in the 1L metastatic setting, this time in PD-L1 negative patients as a monotherapy (ASCENT-03).
    - The impact of this data release, however, was perhaps lessened by data from datopotamab deruxtecan (Datroway, in TROPION-Breast02) that was released in the same session, revealing a statistically significant and clinically meaningful improvement in overall survival, whereas Trodelvy's mature data was limited to a measure of progression-free survival (PFS).
    - Although at the naïve comparison level both led to similar PFS durations, Gilead's decision to permit crossover to Trodelvy in the 2L for those on the comparator arm may have led to a diminished OS difference between the two.
    - While the physicians in attendance applauded this trial design as being in the best interests of patients, this design may complicate any cross-trial comparisons and potentially impact pricing and reimbursement negotiations in this indication.

→ Over the horizon: The rise of bispecific antibodies

- Although not as numerous and clinically progressed as ADCs, bsAbs continue to make waves at ESMO, whether as part of the Presidential Symposia or among numerous other sessions over the weekend.
- Akeso's ivonescimab, one of the upcoming PD-(L)1 x VEGF bsAbs, was notable this year for its inclusion in the Presidential Symposia sessions, with data on show from its ongoing HARMONi-6 trial in 1L advanced squamous non-small-cell lung cancer (NSCLC).
    - Although OS currently remains immature, the molecule was able to prolong PFS when combined with chemotherapy versus BeOne's tiselizumab (Baizean in China, Tevimbra elsewhere) and chemotherapy.
- ESMO also saw considerable discussion of the role of tarlatamab (Imdelltra/Imdylltra), a CD3 x DLL3 bsAb, which has already begun to establish a standard of care role in the management of 2L ES-SCLC.
    - Phase 1 data from the DeLLphi-303 trial in 1L ES-SCLC were presented, which demonstrated encouraging early signs that the combination of this bsAb with existing PD-(L)1 molecules and chemotherapy could potentially lead to important survival outcomes.
    - Of course, drawing conclusions from early-stage data is problematic, but physicians viewed these advances as highly promising.
    - Further, it remains to be seen how Imdelltra fares in international markets in terms of its pricing and reimbursement success; this challenge becomes greater when combining with other products from different manufacturers.
- Beyond the multivalent bsAbs, there were also several sessions covering the potential role of combining the modalities with ADCs as part of a bigger regimen and also bispecific antibody-drug conjugates (bsADCs) focusing on a range of (co-)targets.

→ Exploring new horizons: The global fight against cancer

- What was particularly striking about ESMO this year was the volume of high-profile coverage afforded to molecules that are either not routinely used in Europe or the US, or where clinical trial data has been generated predominantly in Asia.
- Beyond ivonescimab's HARMONi-6, which was conducted in China, we also heard about sacituzumab tirumotecan (sac-TMT) in 2L advanced EGFRm NSCLC and disitamab vedotin plus toripalimab in 1L HER2+ locally advanced or metastatic UC, all three within the centerpiece Presidential Symposia sessions.
- These were not singular exceptions, as they were accompanied by many other presentations across the weekend's 2,927 discussed abstracts and speak to not only the pace of biotechnological innovation but also the increasing role of newly emerging centers for this innovation.
- While these developments are exciting, they must be tempered by the need for global confirmatory data, given the questions that currently exist on the transposability of data from individual ethnicities and geographies to a global patient community where both the pathology of the disease and response to drugs can be impacted.

CRA's strategic considerations

→ Clinical trial design pricing and market access trade-offs

- The positioning of the TROPION-Breast02 and ASCENT-03 readouts adjacent to one another during ESMO was a clear way of illustrating the complexities of modern clinical trial design.
- Whereas Datroway was able to show an OS benefit in 1L metastatic TNBC, it looks unlikely that Trodelvy will be able to mirror this, despite both targeting the same population with similar technologies.
- Although naïve comparisons are fraught with pitfalls, it would not be unreasonable to hypothesize that if both trials either did or did not permit crossover in 2L then it is plausible that both readouts would look more similar to one another.
- The downstream trade-offs of this decision remain to be seen in terms of pricing and market-access decisions, given some markets' preference for OS data over PFS, so although this crossover trial design brings tangible benefits to patients and is likely to drive up recruitment in doing so, it also may have commercial ramifications.

→ Today's challenges are tomorrow's trivialities

- A returning theme this year was tolerability and adverse event management for innovative medicines, notably the ADCs and bispecific T-cell engagers.

- Previously, at ASCO and ESMO, we have had discussions of the management of interstitial lung disease, stomatitis, peripheral neurotoxicity, and cytokine release syndrome, among other important safety signals.
- The continuing theme here, however, was the real-world reporting of adverse events, how to effectively manage them, and proactively mitigate risks to bring down the likelihood of a Grade 4 or 5 adverse reaction.
- We have previously discussed the importance of safety and tolerability in modern oncology decision-making, where physicians and patients often have multiple treatment options available to them, allowing a degree of preference and choice dependent on the individual reward-to-risk trade-offs stakeholders are willing to accept.
- It remains to be seen, however, how far this increased comfort permeates into the physician community, particularly among those in community or more rural hospitals where there may not be access to a multidisciplinary team or the equipment necessary to deal with adverse event emergencies.

→ Monitor an evolving clinical, regulatory, and policy environment

- The global policy environment, especially in terms of biopharmaceuticals, continues to evolve in both predictable and unpredictable ways that require stakeholders to be fully aware of this dynamic situation.
- Recent high-profile FDA rejections that have been made based on limited North American patient inclusion in pivotal trials starkly highlight this point.
- Given the volume of trials that were shown at ESMO, in which patient enrollment skews dramatically toward one geography over another, it will be critical that commercial planning and risk identification is conducted in a manner that is aware of the turbulent regulatory environment.
- Indeed, even views among the physician community are somewhat divided on this topic, with views aired at ESMO both for and against the need for international confirmatory trials in light of data from a single geography.

We invite you to reach out to members of CRA's Life Sciences Practice to share how advances seen at ESMO will impact your development, medical, commercial, and pricing and market access strategies. For assistance on critical questions for your early-stage, prelaunch, or inline oncology assets, pricing and market access considerations, value maximization, or understanding the commercial potential that exists for your asset in a rapidly evolving oncology therapeutic area, please contact us.

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