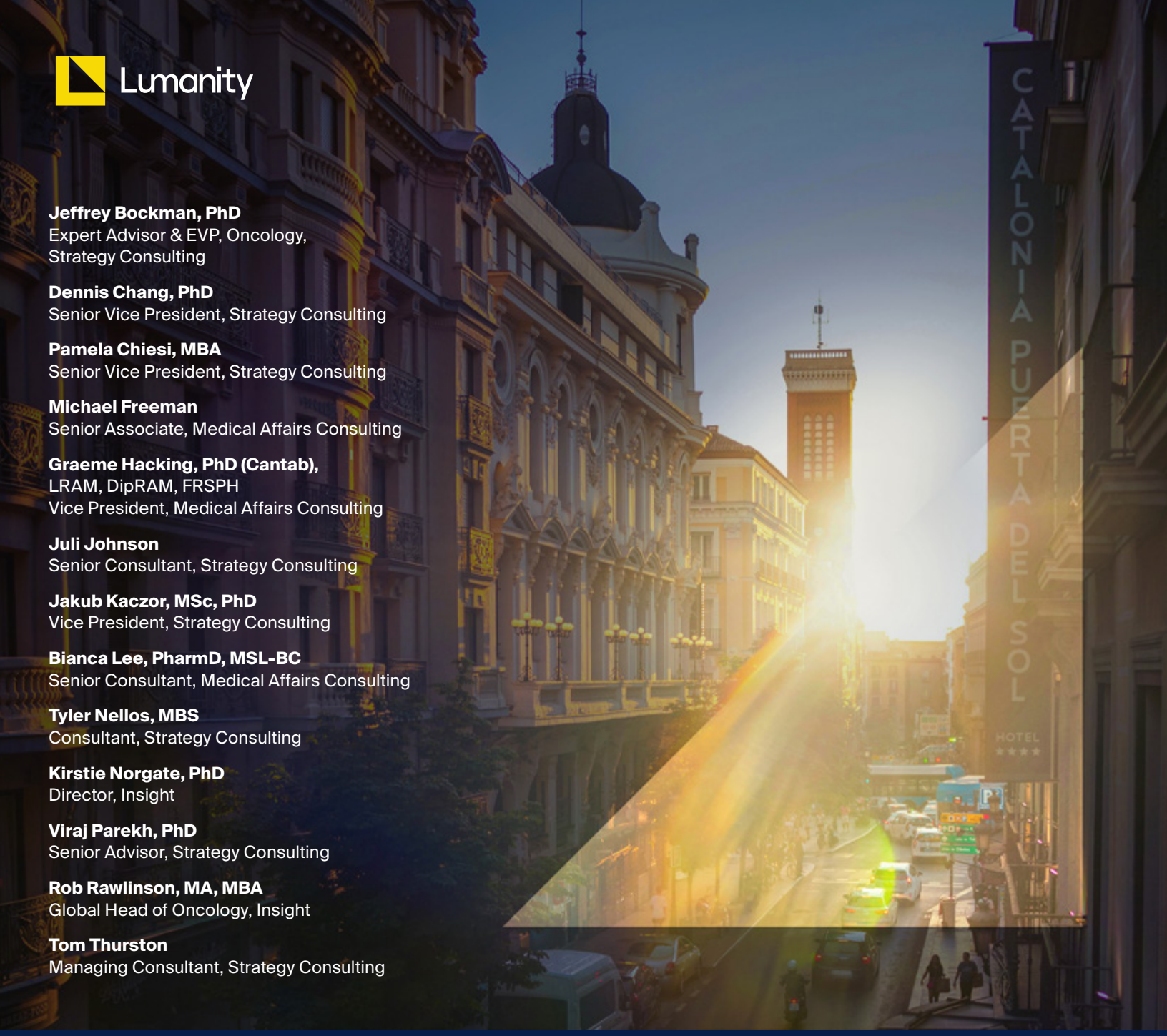



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# ESMO 2026 Insights from the Sessions and the Hallways

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# Introduction

In late October, Lumanity's oncology experts joined the crowds in Madrid for Europe's largest cancer conference. Across tumor types, we heard the central question shift from "*does it work?*" to "*where does it belong, for whom, and can patients get it?*" Potent new agents are moving into earlier lines of therapy. That makes patient selection, sequencing, evidence quality, pricing and access as important as efficacy.

Our experts joined the attendees to hear the data and the conversations around it. In this collection of takeaways and insight, we share what we heard in the sessions and in the corridors, and what to expect over the next 12–18 months.

# The Breakthroughs Continue in Pancreatic and Gastric Cancers: What ESMO 2026 Means for Their Future



**Jakub Kaczor, MSc, PhD**
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Across ESMO's pancreatic and gastro-esophageal sessions, the debate has moved past whether new agents work. The question now is whether their evidence will hold up with guideline committees, HTA bodies and payers.

## Pancreatic cancer: from "does it work" to "who gets it, and at what price"

**Eligibility is up for debate.** Additional analyses of daraxonrasib, the first approved pan-RAS inhibitor, reopened the question of who should receive it. Progression assessments differed between central review and investigators, and censoring was uneven between arms in an open-label trial. Together, these suggest the signal behind limiting European guideline recommendations to RAS G12-mutant disease may be an artifact. Overall survival benefit held across subgroups. Daraxonrasib significantly improved OS vs SOC chemo in patients with previously treated mPDAC overall (with or without an identified tumor RAS mut; mOS 13.2 vs 6.7 mo; HR, 0.40) and in patients with RAS G12 mut mPDAC (OS HR, 0.40; PFS HR, 0.45).

Narrow labels and guideline restrictions are now a commercial risk as well as a clinical one. Sponsors should ask early whether the data support a broad population. They should also be ready to challenge restrictive recommendations with the evidence-quality argument rather than accept them.

**The next wave will add biomarkers.** Early combination work pairs the PRMT5 inhibitor vopimetostat with daraxonrasib or the G12D-specific zoldonrasib in MTAP-deleted, RAS-mutant disease. Results are early, from a small, single-arm, sponsor-funded dose-escalation study. The commercial implications are worth noting:

- **Narrower populations.** A second biomarker, MTAP deletion, sits on top of RAS status. That means an extra testing step and a smaller addressable population.
- **Harder evidence design.** Choosing comparators and endpoints is difficult when the backbone drug, daraxonrasib, is itself still being assessed.
- **Higher access stakes.** Combinations built on premium-priced backbones will face affordability scrutiny from the outset.

**Price will shape access.** With a US list price of around $477,000 a year, daraxonrasib is already a test case for turning breakthrough value into broad access. EU reimbursement is decided country by country, and the Joint Clinical Assessment is ahead. Pricing strategy will therefore decide how many patients actually benefit.

## Gastric and GEJ cancers: Different modality, same dilemma

The same pattern appears in gastric and gastro-esophageal junction (GEJ) cancer, with two claudin 18.2 (CLDN18.2)-directed antibody–drug conjugates (ADCs):

- Arcotatug tavatecan is a novel CLDN18.2-targeted ADC that showed overall survival improvement over chemo (with 34.8% of events, median OS was 9.9 months vs 7.4 months). However, it raised questions about an Asia-only population, pending quality-of-life data, and CLDN18.2 expression falling below eligibility thresholds after prior claudin-targeted therapy.
- Results from a global phase 3 trial of sonesitatug vedotin ease the transferability concern. It showed an overall survival benefit across CLDN18.2 expression subgroups vs investigator's choice of therapy in both 3L+ (median 10.0 vs 5.0 mo, HR 0.47) and in 2L+ (median 10.6 vs 6.4 mo, HR 0.58). Progression-free survival in the intent-to-treat population did not meet the threshold for statistical significance.

Endpoints, comparators and sequencing will each shape how these claudin-directed agents are judged. A strong survival result alongside a missed co-primary progression endpoint gives HTA bodies room to challenge the evidence. The control arm is a mix of standard options, so payers may also probe how much of the gain reflects a weak comparator. As more claudin-directed

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agents arrive, biomarker re-testing between lines becomes a planning issue rather than an afterthought.

As transformative mechanisms reach some of oncology's hardest-to-treat tumors, efficacy alone will no longer decide uptake. Established players and newcomers alike will need to:

- Stress-test endpoint choices
- Plan bridging data beyond the regions where pivotal trials ran
- Build biomarker re-testing into sequencing strategies
- Set pricing strategy early

**Relevant trial and reference notes:**

- LBA82: **Daraxonrasib (Rasonque; Revolution Medicines)** subgroup analyses from the phase 3 RASolute 302 study for previously treated metastatic pancreatic adenocarcinoma (mPDAC)
- 3149P: **Vopimetostat (Tango Therapeutics)** + daraxonrasib or zoldonrasib (RevMed) in a phase 1/2 study for MTAP deleted RAS mutated (MTAPdel/RASmut) mPDAC and NSCLC
- LBA77: **Arcotatug tavatecan (IBI343/TAK-921; Takeda/Innovent)** in phase 3 G-HOPE-001 study for previously treated, advanced gastric or gastroesophageal junction adenocarcinoma (G/GEJA)
- LBA7: **Sonesitatug vedotin (Sone-Ve; AstraZeneca)** in phase 3 CLARITY-Gastric 01 (CG-01) study for 2L+ Claudin 18.2 (CLDN18.2)-positive gastroesophageal carcinoma (GEC)

## Takeaways

The new questions in GI oncology aren't about whether the drugs work. They're about whether the evidence holds up, whether the biomarker still applies, whether the data travel beyond the trial's region, and whether the price lets patients get the drug. Developers who plan for all four from phase 2 will set the terms; the rest will spend launch defending them.



# A New Wave of ADCs for Ovarian Cancer



**Dennis Chang, PhD**
Senior Vice President,
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Ovarian cancer is entering a new era of antibody-drug conjugates (ADCs). Currently only one ADC is approved specifically for ovarian cancer: AbbVie's Elahere (mirvetuximab sorvatansine) for platinum-resistant ovarian cancer (PROC) with high expression of folate receptor alpha (FRα). But during ESMO 2026, we saw a profusion of clinical data for new agents including a raft of new FRα-targeted ADCs as well as ADCs for new targets including CDH6 and B7-H4.

All of these new ADCs showed promising efficacy, apparently stronger than Elahere's based on cross-trial comparisons. The new FRα ADCs also seem to be able to do without FRα biomarker restriction. For example, AZ's Torvu-sam achieved an ORR of 57% and mPFS of 7.6 mo. for FRα-low PROC, better numbers than what Elahere had in FRα-high PROC (42%, 5.6 mo). The results for Torvu-sam in FRα-high PROC were even better (62%, 9.7 mo). Zymeworks's ZW191 does not have PFS data yet, but showed similarly favorable ORR across FRα expression levels. Genmab's Rina-S did not feature in presentations at the conference itself, but a positive phase 3 trial (RAINFOL-02) readout for PROC was announced by press release on Oct. 23 during the meeting, again without the need for FRα selection. Moreover, all of these FRα ADCs can be used after prior Elahere use, given they use a different class of payload: topoisomerase 1 (TOP1) inhibitors instead of Elahere's antitubulin DM4 payload.

Looking beyond FRα, Daiichi/Merck's R-DXd, which targets CDH6, showed an ORR of 50% at its go-ahead dose (in combination with bevacizumab) in PROC. GSK's Mo-rez targets B7-H4 and had ORR of 62% and mPFS of 11.1 mo at the highest dose level, with responses seen across B7-H4 levels.

All of these impressive efficacy findings point to a future where many strong ADCs will be available for ovarian cancer patients. However, there are two big caveats: toxicity and cross-resistance.

Grade 3+ TRAE rates ranged from 40% to over 70% across these studies. Major AEs included neutropenia and other hematologic AEs, as well as fatigue and GI AEs, in line with other ADCs using TOP1 payloads.

All of the new ADCs use a TOP1 inhibitor payload, which means their use will likely be limited by cross-resistance. They may be used before or after Elahere, but likely not after another TOP1-loaded ADC. Thus, these ADCs are now in a race to be used as early in the treatment algorithm as possible. At ESMO, Lilly's FRα ADC Sofe-M reported an impressive ORR of 79% in platinum-sensitive ovarian cancer (PSOC), but many other ADCs are also in ongoing PSOC trials.

The pipeline for ovarian cancer also has a variety of mechanisms besides ADCs, including novel immunotherapies and novel agents targeting DNA damage response (DDR), as well as other approaches.

### Takeaways

Ovarian cancer is the deadliest gynecologic cancer type, with limited treatment options especially in the platinum-resistant setting. However, data readouts at ESMO presage a much larger, more powerful, and more ADC-rich toolkit for treating ovarian cancer in the future, and these tools will be used in earlier lines of therapy.

**Relevant trial and reference notes:**

- 1245RO: **Torvutatug samrotecan (Torvu-sam; AstraZeneca)** in phase 1/2 FONTANA for PROC
- LBA40: **ZW191 (Zymeworks)** in phase 1 for PROC
- 1246RO: **Sofetabart mipitecan (Sofe-M; Eli Lilly)** in phase 1 for PSOC
- 1247RO: **Raludotatug deruxtecan (R-DXd; Daiichi/Merck)** + bevacizumab in phase 1/2 REJOICE-Ovarian02 for PROC
- 1248RO, LBA41: **Mocertatug rezetecan (Mo-rez; GSK)** in phase 1 BEHOLD-1 for PROC
- Genmab press release, Oct. 23, 2026, for **Rinatabart sesutecan (Rina-S)** in phase 3 RAINFOL-02 for PROC

# Breast Cancer at ESMO 2026: More Options, Harder Choices



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The breast cancer takeaways from ESMO 2026 center on three connected themes: Chinese innovation, antibody–drug conjugate (ADC) sequencing, and better patient selection. Together, they raise a question: how do more options become better treatment choices?

## Chinese innovation is expanding the possibilities but not clarifying which drug for which patient

China's role in oncology is expanding with each congress. The ESMO–CSCO joint session, "Navigating the development pathways of cancer therapeutics – From China to the world", brought this into focus: China-only studies accounted for 30% of ESMO 2026 late-breaking abstracts, with 18 phase 3 study results. Innovation is already reaching patients in China: CDK2/4/6 inhibitor culmerciclib gained first-line approval in May 2026 following CULMINATE-2.

## Breast cancer study presentations at the congress illustrated the clinical opportunities:

- **PANKU-Breast01:** Izalontamab brengitecan (iza-bren), an EGFR×HER3 bispecific ADC, improved median progression-free survival (PFS) to 8.2 versus 4.0 months with chemotherapy in previously treated HR+/HER2– advanced disease (HR 0.41). Overall survival (OS) remained immature.
- **APEX-Breast01:** The biparatopic HER2 ADC rolditamig deuderuxtecan (TQB2102) achieved median PFS of 16.4 versus 5.5 months with chemotherapy in the primary HR+/HER2-low population (HR 0.29).
- **HORIZON-Breast06:** Trastuzumab rezetecan improved median PFS to 16.4 versus 6.8 months overall (HR 0.27). The chemotherapy-naïve population, the source of the particularly striking HR 0.25, achieved median PFS of 16.6 versus 6.8 months.

Positive data, yet an elephant in the room remains: chemotherapy-controlled results cannot compare ADCs against each other. Toxicity matters too. Head-to-head trials are needed to inform these choices.

## The joint CSCO-ESMO session raises another question: what evidence is needed to translate these results into global access?

What matters is not only intrinsic biological differences between Chinese and non-Chinese populations, but also extrinsic factors. This includes comparator and subsequent treatments, concomitant medicines, and how clinicians and patients report toxicity.

Targeted bridging studies may help, but PK/PD alone cannot resolve an outdated comparator. HERTHENA-Breast04 makes this tangible by including trastuzumab deruxtecan (T-DXd) among its control options.

## ADC sequencing requires more than changing the antibody

SWITCH challenged target switching: among 54 ADC-pretreated patients, only two confirmed responses occurred, both after a different payload. None followed topoisomerase I (TOP1)-to-TOP1 switching. Small cohorts, but a concern for payload cross-resistance, not proof that changing payload works.

Separately, the Nectin-4/MMAE ADC bulumtatug fuvedotin achieved a 30% response rate and median PFS of 3.7 months in 60 evaluable, TOP1-ADC-pretreated TNBC patients. Encouraging phase 2 data, not a sequencing rule. Both reinforce the call for biomarkers of payload sensitivity, not just antigen expression—a theme highlighted in Professor Loi's discussion on these data readouts.

## Better selection matters for immunotherapy in HR+ disease

KEYNOTE-B49 already selected for PD-L1 CPS ≥1. Pembrolizumab plus chemotherapy improved median PFS modestly—6.7 versus 6.0 months (HR

**(Continued)**

**Relevant trial and reference notes:**

- ESMO–CSCO: Navigating the development pathways of cancer therapeutics – From China to the world
- LBA50: **Izalontamab Brengitecan (Iza-bren; BMS/Biokin)** in phase 3 PANKU-Breast01 for previously treated HR+/HER2- advanced breast cancer
- LBA27: **TQB2102 (Chia Tai Tianqing/Sino Biopharmaceutical)** in phase 3 APEX-Breast01 study for HER2-low advanced breast cancer
- LBA13: **Trastuzumab rezetecan (SHR-A1811; Jiangsu Hengrui)** in phase 3 HORIZON-Breast06 study for HER2-low advanced breast cancer
- 4640RO: **Bulumtatug fuvedotin (BFv, 9MW2821; Mabwell Bioscience)** in a phase 2 study for advanced triple negative breast cancer (TNBC) previously treated with topoisomerase I inhibitor-based ADCs
- 4RO: **SWITCH:** Target switching with conserved-payload novel ADCs in patients with metastatic breast cancer following prior ADC therapy, a phase 2 platform trial
- LBA51: **Pembrolizumab (Keytruda; Merck)** + chemotherapy in phase 3 **KEYNOTE-B49** study for previously treated HR+/HER2- advanced breast cancer.
- 1767RO: **Tucatinib (Tukysa; Pfizer)** + trastuzumab + pertuzumab in phase 2 **BRIDGET** study after isolated intracranial progression in HER2+ advanced breast cancer
- LBA49: **Trastuzumab deruxtecan (Enhertu; AstraZeneca & Daiichi-Sankyo)** + pertuzumab in patients with HER2+ advanced breast cancer and baseline brain metastases – an exploratory central nervous system (CNS) efficacy analysis of DESTINY-Breast09

0.74)—without improving OS (HR 1.04). The stronger numerical signal at CPS ≥10 (PFS HR 0.59; 72 patients) remains hypothesis-generating.

The question is whether more refined biological selection can identify a responsive subset, not broad immuno-therapy use. TroFuse-010, testing sacituzumab tirumotecan alone and with pembrolizumab against chemo-therapy, is one to watch.

## The plot thickens for HER2+ disease

After ASCO 2026, HER2CLIMB-05, PATINA and DESTINY-Breast09 were making HER2+ treatment choices more nuanced. ESMO added another layer: CNS disease.

In DESTINY-Breast09's exploratory subgroup of 61 patients with clinically inactive or treated, asymptomatic brain metastases, T-DXd plus pertuzumab improved systemic PFS (HR 0.30) and CNS PFS (HR 0.26) versus taxane/trastuzumab/pertuzumab. Impressive, but a small, selected subgroup.

BRIDGET addressed isolated CNS progression. After local treatment, tucatinib was added to ongoing trastu-zumab/pertuzumab or T-DM1 (Kadcyla); 18-month intracranial PFS was 59%. This was single-arm phase 2 evidence, not a randomized comparison.

Different situations, different decisions. Both sharpen the question: when would finding asymptomatic brain metastases change treatment choice? They do not establish universal MRI screening.

### The next challenge

From a strategic insight perspective, the questions are compelling: what changes an oncologist's preferred sequence, what uncertainty sustains established choices, and how do patients weigh benefit against toxicity and treatment burden? More options are welcome. Understanding how to choose is the harder task.



# Multiple Modalities Will Redefine Care in Lung Cancer



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ESMO 2026 saw substantial progress in lung cancer with T-cell engagers showing transformative promise in ES-SCLC and EGFRm NSCLC patients likely to benefit from both biomarker-selected and agnostic post-TKI treatment options.

## Tarlatamab sets a new bar in SCLC

Frontline ES-SCLC has historically been defined by modest gains, with chemo-immunotherapy delivering a median OS of roughly 12–13 months and most patients progressing soon after induction, leaving a substantial unmet need for more effective maintenance therapy. The phase 3 DeLLphi-305 study evaluated Amgen's tarlatamab (Imdelltra; DLL3 × CD3 T-cell engager) plus AstraZeneca's durvalumab (Imfinzi) as 1L maintenance after durvalumab plus platinum-etoposide induction. In 563 patients, the combination reduced the post-induction risk of death by 58% vs durvalumab alone (median OS 21.1 vs 12.7 months; HR 0.42) and nearly quadrupled the post-induction median PFS (7.4 vs 1.9 months; HR 0.34), with benefit across all subgroups, including patients with brain or liver metastases. The data earned a standing ovation at Presidential Symposium I and position tarlatamab plus durvalumab as a likely new standard of care in the 1L maintenance setting.

The caveats in this study are mostly practical. Survival was measured from maintenance randomization, so the trial captures only patients who did not progress during induction. Cytokine release syndrome occurred in half of patients (49.6%), although nearly all cases were grade 1–2. On-site monitoring is also required after the first two doses, which may slow uptake in community practices. Still, treatment-related discontinuations were low (3.2%). The next question is whether adding tarlatamab to induction as well can further improve outcomes for 1L ES-SCLC patients—a hypothesis being tested in the phase 3 DeLLphi-312 study.

## Options abound in EGFRm NSCLC post-TKI

MET overexpression (OE) or amplification is found in roughly a third of patients progressing on osimertinib, yet there are no approved therapies targeting this resistance mechanism outside China. ESMO 2026 delivered the data to change that. The global Ph3 SAFFRON trial enrolled 338 patients with MET-OE and/or amplification after osimertinib. HUTCHMED/AstraZeneca's savolitinib (Orpathys; MET TKI) plus osimertinib (Tagrisso) improved both PFS (7.6 vs 5.4 months; HR 0.55) and OS (17.8 vs 12.9 months; HR 0.68) vs platinum-pemetrexed, and it did so with fewer grade ≥3 TRAEs (40% vs 52%). SAFFRON is the first global Ph3 after 1L osimertinib to demonstrate a statistically significant OS benefit, confirming China-only SACHI results, and an NDA has already been submitted to the FDA. Discussant Dr. Natasha Leighl declared it a new standard of care.

However, Dr. Leighl raised questions on whether MET OE alone is enough for patient selection, noting that only 45% of patients were both IHC3+ and FISH-amplified, while the rest were positive by just one test (27% IHC3+ only; 28% FISH-amplified only). Drawing on prior EGFR + MET TKI studies, she argued that true MET "addiction" (i.e., high-level amplification) may be required for benefit. Patient selection depends on a tissue biopsy at progression, which is not yet routine. Also, the trial comparator was chemotherapy rather than newer regimens now approved in the post-1L osimertinib setting.

Two other phase 3 trials in the EGFRm setting after third-generation TKI treatment read out with impressive data, though both are China-only trials. PANKU-Lung01 pitted Biokin/BMS's izalontamab brengitecan (EGFR x HER3 bispecific ADC) against chemo and cut the risk of progression by 60%. In OptiTROP-Lung04, Kelun/Merck's sac-TMT faced chemo and reported a final OS benefit of 25.9 vs 17.4 months. Both ADCs are being evaluated in global trials in the hope that the China-only data translate to post-TKI benefits for biomarker-agnostic patients.

In 1L EGFRm NSCLC, the Ph3 China-only SANOVO trial tested the savolitinib plus osimertinib combination in 1L MET-OE patients where the all-oral regimen improved PFS over osimertinib (ITT population, 24.9 vs 13.8 months; HR 0.56) with an early OS signal (HR 0.48

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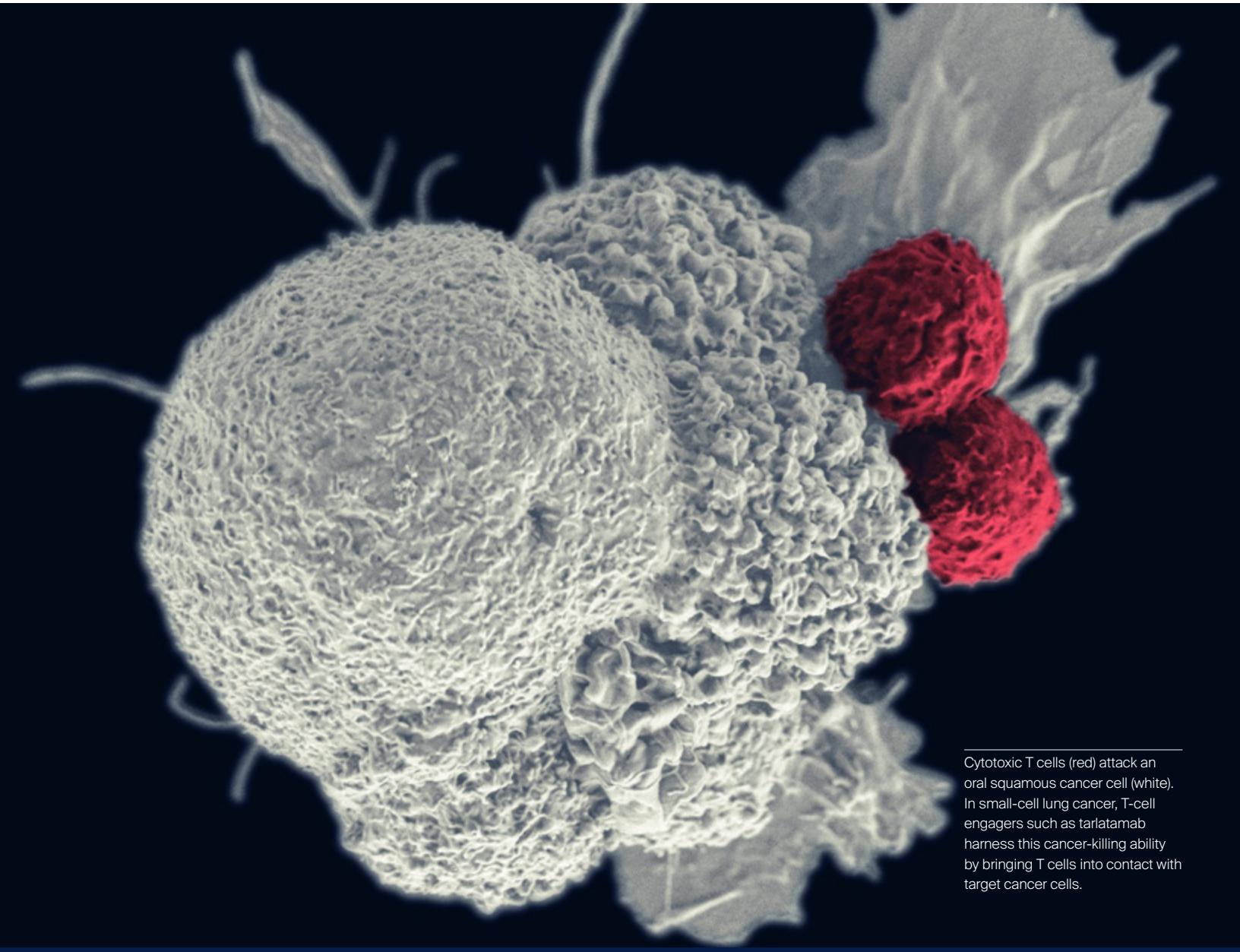
at 40.5% maturity). But grade ≥3 TEAEs nearly doubled (77% vs 38%), and patients with IHC2+ tumors showed no clear PFS benefit (HR 0.85). Discussant Dr. Rebecca Heist called it “a first step” toward a 1L practice change. To make an impact outside China, the regimen will need global data—likely against the 3rd generation TKI combinations that are replacing monotherapy as 1L standard of care.

**Relevant trial and reference notes:**

- LBA3: **Tarlatamab (Imdelltra; Amgen) + durvalumab (Imfinzi; AstraZeneca)** in phase 3 DeLLphi-305 as 1L maintenance for ES-SCLC
- LBA6: **Savolitinib + osimertinib (Tagrisso; AstraZeneca)** in phase 3 SAFFRON for 2L EGFR-mutant NSCLC
- LBA71: **Izalontamab brengitecan (Iza-bren; BMS/Biokin)** in phase 3 PANKU-Lung01 for 2L EGFR-mutant NSCLC
- LBA67: **Sacituzumab tirumotecan (sac-TMT; Merck/Kelun)** in phase 3 OptiTROP-Lung04 for 2L EGFR-mutant NSCLC
- LBA69: **Savolitinib + osimertinib** in phase 3 SANOVO for 1L EGFR-mutant NSCLC

## Takeaways

ESMO 2026 marked a shift toward more targeted and more potent strategies in lung cancer, with T-cell engagers moving into frontline ES-SCLC and biomarker selection extending MET targeting in EGFRm NSCLC. The next 12–18 months will test whether these gains translate into practice. Watch for regulatory decisions for tarlatamab maintenance and savolitinib plus osimertinib after osimertinib, and global ADC approaches that aim to transform lung cancer care.



Cytotoxic T cells (red) attack an oral squamous cancer cell (white). In small-cell lung cancer, T-cell engagers such as tarlatamab harness this cancer-killing ability by bringing T cells into contact with target cancer cells.

# Breaking the Undruggable: The Evolution of RAS Pathway Therapies



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As we've seen with earlier conferences like ASCO earlier this year, ESMO 2026 marked a significant milestone in targeting RAS in oncology, showcasing paradigm-shifting data for next-generation RAS pathway inhibitors. These presentations underscored a clear evolution and noteworthy progress from the 1st-gen KRAS G12Cs, sotorasib and adagrasib (approved in 2021-22), toward highly potent next-gen mutant-specific molecules, combination regimens, and pan-RAS coverage. These advancements offer the potential for robust survival advantages in late-stage settings while showing early-stage pipeline progress against previously untargetable alleles. However, as the field transitions into this next era, each breakthrough brings distinct clinical issues, sequencing challenges, and future operational considerations that drug developers must navigate to truly maximize patient benefit.

## Krascendo 1: Next-gen G12C inhibition for NSCLC

Headlining data from the registrational phase 3 Krascendo 1 trial established Roche's next-generation KRAS G12C inhibitor divarasib as the new benchmark in advanced 2L+ NSCLC. Divarasib demonstrated clear superiority over sotorasib (Lumakras; Amgen) and adagrasib (Krazati; BMS), extending median PFS to 9.8 months (vs. 5.7 months; HR: 0.58) and median OS to 17.7 months (vs. 12.0 months; HR: 0.56) with an impressive ORR of 58.6%. Another key differentiator was the doubling of DOR, indicating that the optimization in its biochemical design, structural binding kinetics, and target occupancy has paid off.

Importantly, key subgroup analyses from Krascendo 1 provide vital clinical clarity, proving that divarasib's structural modifications translate directly into meaningful neuro-oncological control and partial resistance bypass. Historically, significant CNS progression has been associated with KRAS G12Cm NSCLC, with sotorasib demonstrating poor BBB penetration. Divarasib's impressive intracranial ORR of 54.8% and median intracranial PFS of 10.4 months effectively match or exceed the CNS benchmarks previously established by adagrasib. By demonstrating such strong CNS disease control, divarasib may offer a viable systemic alternative that can defer or minimize the need for aggressive whole-brain radiation therapy, thereby directly preserving cognitive function and quality of life in this population.

However, the trial also highlighted the complex biological boundaries of single-allele mutant-selective inhibition when confronted with high-risk co-mutational profiles. While divarasib achieved a notable clinical victory by doubling median PFS to 6.4 months within the ultra-poor prognosis KEAP1/NFE2L2-mutant stratum, this sub-population still experienced rapid attrition compared to the overall intention-to-treat cohort. This discrepancy underscores the vulnerability of selective G12C inhibitors to rapid upstream reactivation and wild-type HRAS/NRAS bypass signaling. Furthermore, post-progression genomic profiling mapped clear structural acquired resistance limitations specific to divarasib monotherapy. Tumors ultimately escape target engagement via pocket-occluding Type I (Y96C, H95Q) and severe Type II (Y96D) structural mutations, alongside secondary KRAS-activating alterations (G12D, Q61H) in trans that reactivate downstream MAPK signaling and bypass direct G12C inhibition entirely. These subgroup dynamics suggest that the future of precision oncology will not belong to a single class; rather, clinical practice will require a nuanced, biomarker-driven triage to determine the utilization and combination of mutant-selective agents like divarasib and multi-RAS platforms for heterogeneous, bypass-prone co-mutational profiles.

Looking at the safety, while divarasib successfully minimized the severe liver toxicities common to first-generation drugs, it shifted the safety burden to the gut, with 9% grade 3/4 diarrhea (vs. 2.9% in the control arm) that places an additional supportive care and dehydration-management burden.

Furthermore, the trial protocol's lack of a crossover mechanism upon progression does not allow for evaluation of divarasib's

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efficacy post-progression. Additionally, from the trial design perspective, there appears to be a sharp control arm imbalance, with 91% of patients receiving sotorasib rather than providing a balanced head-to-head comparison against adagrasib, which historically tracks with slightly higher single-agent efficacy. Finally, the data are strictly from fit participants with stable, treated brain metastases, and will likely face performance attrition when translated to frailer, real-world oncology patients with active CNS disease. For divarasib, a primary future consideration will be determining optimal, data-driven sequencing strategies to manage this resistance, alongside determining how it will compete with emerging frontline combination regimens.

## Other data in KRAS-mutant NSCLC

Divarasib also faces significant competition from multiple KRAS G12C inhibitors in the 1L setting. One example showcased at ESMO was Lilly's olomorasib, which achieved durable, clinically relevant activity when paired with pembrolizumab and pembrolizumab + chemotherapy (LOXO-RAS-20001 [P1/2] & SUNRAY-01 [P3 lead-in] trials), which compared favorably with historical data for sotorasib/adagrasib. Additionally, the data demonstrate that KRAS G12C inhibitors can be safely combined with pembro and chemotherapy. The rate of severe liver toxicity (grade 3+ ALT elevation: 15.3%) appears to be manageable, potentially opening the door for a safe, dual-targeted frontline regimen in this high-unmet-need KRASm population. However, the critical issue here is potential long-term toxicity, and we do not yet know if low-grade liver inflammation will compound over time, possibly leading to late-stage drug discontinuations or permanent liver injury. Hence, future considerations for these early-stage frontline combinations must focus on identifying optimized dosing schedules, such as lead-in or intermittent dosing, to maintain a safe therapeutic index.

## Continued advances in KRAS-mutant PDAC

For KRAS G12D, in the phase 2 evaluation of Jiangsu Hengrui's HRS-4642, a liposomal nanoparticle-formulated non-covalent inhibitor, monotherapy yielded a 20.8% ORR and a 79.2% DCR in R/R KRAS G12Dm PDAC patients, with an ORR of 43.2%-48.5% when paired with anti-PD-L1. In the frontline PDAC setting, the agent plus gemcitabine/nab-paclitaxel produced a robust 63.3% ORR. Concurrently, FIH data for Incyte's INCB161734, an oral non-covalent dual "ON/OFF" state inhibitor, showcased a 37% monotherapy ORR and 78% DCR in R/R PDAC, and when combined with FOLFIRINOX in frontline PDAC, INCB161734 drove an impressive 89% ORR and a 100% DCR, paving the way for the global phase 3 DAWN-303 trial. Despite these encouraging responses, a central future hurdle remains navigating deep tissue drug delivery through the dense stroma of pancreatic malignancies to maximize target exposure and prevent the rapid activation of bypass signaling pathways like PI3K/AKT. Additionally, Revolution Medicines is already in phase 3 trials RASolute 305 and 309 for its KRAS G12D(ON) inhibitor, zoldonrasib, in 1L PDAC combinations, and has opened a phase 3 in 1L NSCLC as well.

Lastly, the late-breaking mature subgroup analysis of the phase 3 RASolute 302 trial establishes daraxonrasib as a pan-genotypic standard of care for R/R PDAC. The data demonstrate a consistent OS benefit across all major KRAS variants, including G12D (HR 0.49), G12V (HR 0.32), and G12R, validating the drug's multi-RAS targeted mechanism and potentially removing the need for mutation-specific patient selection. However, the mature data also highlight a critical efficacy imbalance between mutation variants, with exceptional survival outcomes in KRAS G12V patients (HR 0.32) contrasting against a more modest benefit in the highly prevalent G12D cohort (HR 0.49). Additionally, the drug's

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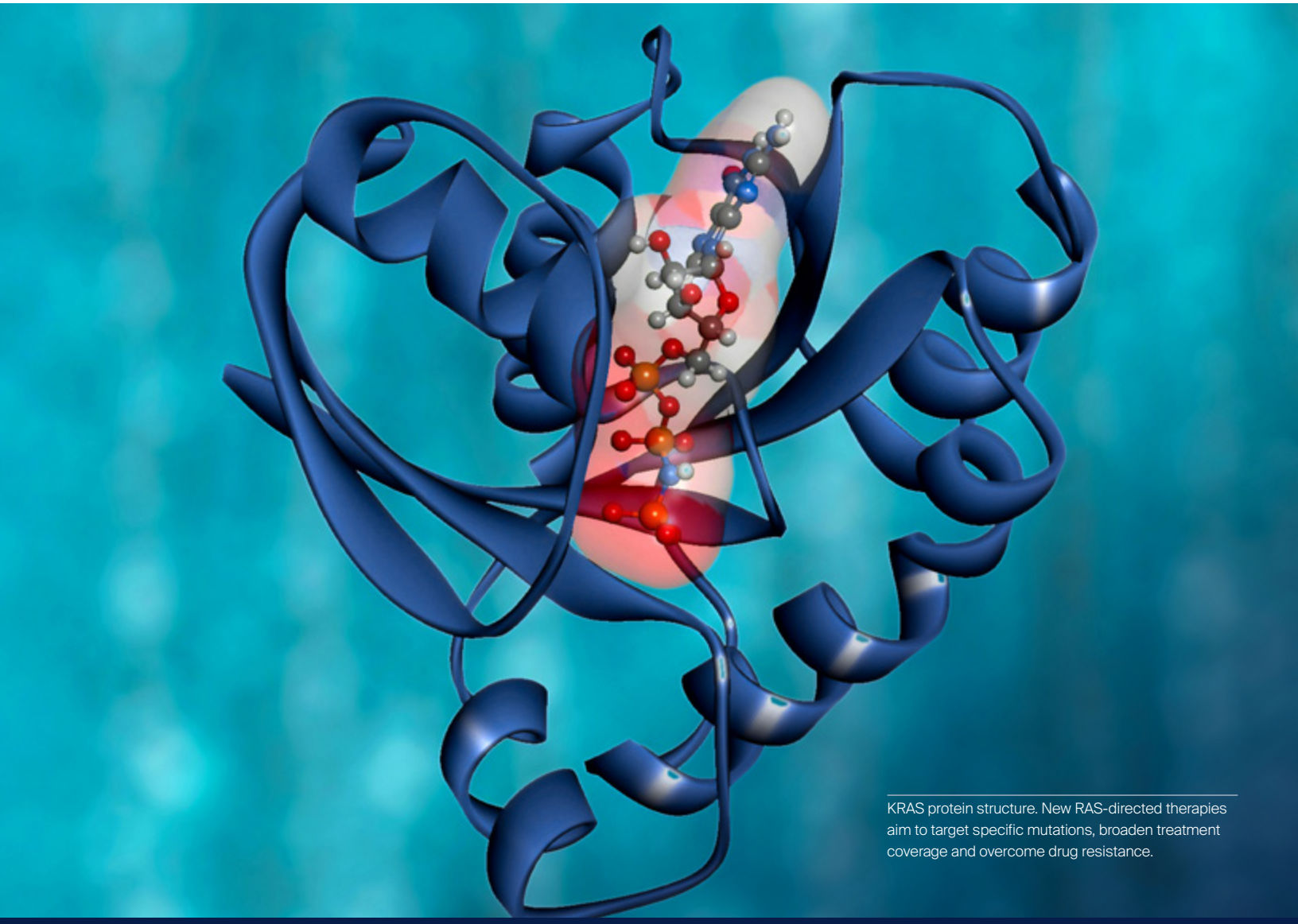
**Relevant trial and reference notes:**

- LBA5: **Divarasib (Roche)** vs sotorasib or adagrasib in phase 3 **Krascendo 1** study for previously treated advanced KRAS G12C-mutated NSCLC.
- 2652RO: **Olomorasib (Eli Lilly)** + chemoimmunotherapy updated results from the LOXO-RAS-20001 and SUNRAY-01 trials in 1L KRAS G12C-mutant NSCLC
- 2683P: **Olomorasib** + pembrolizumab updated results from LOXO-RAS-20001 and SUNRAY-01 trials in 1L KRAS G12C-mutant NSCLC
- LBA82: **Daraxonrasib (Rasonque; Revolution Medicines)** subgroup analyses from the phase 3 RASolute 302 study for previously treated metastatic pancreatic adenocarcinoma (mPDAC)
- 3157P: **HRS-4642 (Jiangsu Hengrui)** + dual immunotherapy and chemotherapy preliminary results from a phase 2 study for KRAS G12D-mutant advanced PDAC
- 3137RO: **INCB161734 (Incyte)** + chemotherapy in a phase 1 study for 1L/2L KRAS G12D-mutant advanced PDAC

multi-RAS mechanism triggers high rates of wild-type on-target toxicities, including an 85.5% rash rate and 58.1% diarrhea rate, which pose significant compliance challenges for future frontline combination regimens, affecting the drug's combinability potential. Ultimately, while the therapy near-doubles overall survival over historical chemotherapy, the median OS remained only 13.2 months, limited by downstream pathway bypass resistance. This leaves critical outstanding questions regarding optimal combination partners, cost-effectiveness, and efficacy in sicker patients (ECOG 2) or rare RAS genotypes.

## Takeaways

In summary, these datasets presented in Madrid this year demonstrate steady, tangible progress in dismantling the historic "undruggable" barriers of the RAS oncogene, incrementally refining the playbook for precision oncology, with a shifting focus in clinical design away from standalone single-mutation monotherapies in R/R disease toward rational, combination-first frameworks in earlier lines of therapy aimed at mitigating clonal escape.



KRAS protein structure. New RAS-directed therapies aim to target specific mutations, broaden treatment coverage and overcome drug resistance.

# Head and Neck Cancer: From Limited Options to Difficult Choices



**Juli Johnson**
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For years, progress in head and neck cancer has been slow, particularly once disease returns or spreads. At ESMO 2026, presentations spanning immunotherapy, antibody-drug conjugates (ADCs), surgery and quality of life pointed to a welcome change. But more options will bring a new challenge: deciding which treatment belongs where.

## Earlier treatment brings different questions

In locally advanced HNSCC, where cure is often the aim, the debate is as much about how much treatment patients need. Following KEYNOTE-689, research including OPTIMAL and circulating tumor DNA analyses from KEYNOTE-412 is exploring treatment intensity and ways to identify patients at greater risk.

In selected early-stage disease, the phase 3 'Best-of' trial found similar mean swallowing scores after surgery and radiotherapy at 12 months (83 versus 86), while the phase 2 QoLATI study also highlighted quality of life and patient preferences.

For companies, the lesson is not always to add treatment, but to prove when its benefit is worth the burden.

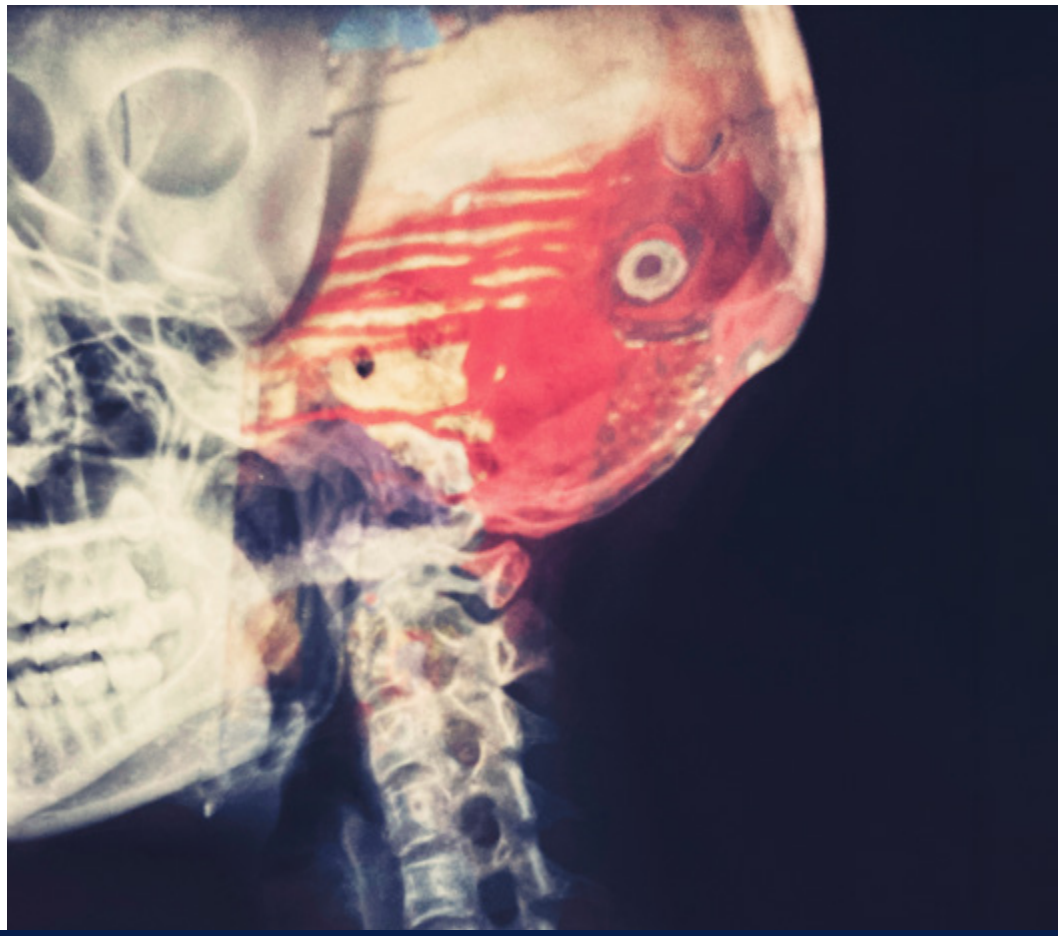
## A more crowded first-line R/M market

For recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), pembrolizumab-based regimens remain central to first-line treatment. Several studies offered a glimpse of a more competitive future.

In the phase 2 study HexAgon-HN, ordastobart plus pembrolizumab achieved a 48.3% response rate versus 26.5% with pembrolizumab alone in patients with high PD-L1 expression (CPS ≥20).

In a separate Chinese phase 2 study, the ADC iza-bren plus pembrolizumab produced a 47.4% confirmed response rate at the selected dose in 38 first-line patients.

**(Continued)**



**Relevant trial and reference notes:**

- LBA47: **Tislelizumab (Tevimbra; BeOne)** + chemo in phase 2 **OPTIMAL** study for perioperative treatment of locally advanced HNSCC
- 1536RO: **Pembrolizumab (Keytruda; Merck)** + CRT in phase 3 **KEYNOTE-412** for locally advanced HNSCC, ctDNA analysis
- 1535O: TOS (transoral surgery) vs DO (dysphagia-optimized)-IMRT in phase 3 **'Best-of'** (EORTC 1420) trial
- LBA45: TORS (transoral robotic surgery) vs IMRT (intensity-modulated radiotherapy) in phase 2 **QoLATI/DAHANCA34**
- LBA42: Ordastobart (INBRX-106; Inhibrx) + pembro in phase 2/3 **HexAgon-HN** for 1L PD-L1-high R/M HNSCC
- 1542RO: **Izalontamab brengitecan (Iza-bren; BMS/Biokin)** + pembro in phase 2 for 1L R/M HNSCC
- 1539RO: **Amivantamab (Rybrevant; J&J)** + pembro + chemo in phase 1/2 **OrigAMI-4** for 1L R/M HNSCC
- LBA43: **Tambotatug pelitecan (Tam-peli; Roche/MediLink)** in phase 3 **TAISHAN-301** for nasopharyngeal carcinoma (NPC)

Meanwhile, OrigAMI-4 investigated amivantamab, an EGFR/MET-targeting bispecific antibody, alongside pembrolizumab and up to six cycles of chemotherapy. Among 22 evaluable patients excluding HPV-associated oropharyngeal cancer, 77% achieved a confirmed response.

Importantly, across all these studies a promising response rate may get a drug noticed, but it will not, on its own, secure a place in treatment. Developers need to show which patients benefit most and what their regimen offers beyond existing options.

## Previously treated patients added another dimension

In heavily pretreated recurrent or metastatic nasopharyngeal cancer, phase 3 TAISHAN-301 reported a 50.8% confirmed response rate with the B7-H3-targeting ADC tambotatug pelitecan versus 25.8% with chemotherapy.

With survival data immature, the findings raise questions about treatment sequencing and how these therapies will fit into different regional treatment pathways.

### Takeaways

ESMO 2026 offered welcome momentum in head and neck cancers, a space which has had limited innovation for a decade, but greater choice will bring tougher decisions for clinicians, patients and payers. The real risk is developing against today's standard of care when the clinical landscape may look very different at launch. Companies need to anticipate future competitors, define the patients they can genuinely help and generate evidence that changes clinical decisions.



# When is Enough Enough in MIBC?



**Kirstie Norgate, PhD**
Director, Insight

ESMO 2026 shifted the conversation to perioperative muscle-invasive bladder cancer (MIBC). The question is no longer whether to add immunotherapy, but how much is needed, in which combination, and for which patients. The aim is to improve survival while limiting long-term toxicity.

Treatment has changed quickly in recent years. Perioperative pembrolizumab entered practice first. EV plus pembrolizumab (EV+P) is now replacing cisplatin-based chemotherapy in MIBC, following the same path as in locally advanced or metastatic urothelial cancer. The FDA approved EV+P for perioperative treatment of all MIBC on July 10, 2026. EV is highly effective but hard to tolerate, particularly because of skin toxicity and peripheral neuropathy.

## The promise of reduced EV exposure

VOLGA tested a reduced-EV approach. Patients received three cycles of EV plus the anti-PD-L1 agent durvalumab (EV+D) before surgery, then nine cycles of adjuvant durvalumab. The regimen cut the risk of an EFS event by 49% versus upfront cystectomy (HR 0.51). Median EFS was not reached versus 12.1 months, and 24-month EFS was 64% versus 45%. Median OS was not reached in either arm, but it favored EV+D (HR 0.58), with 24-month rates of 78% versus 69%. The pCR rate was 45% versus 10% by local review and 40% versus 8% by central review. That is a clear benefit from three neoadjuvant EV cycles. Adverse events were those expected with durvalumab or EV, including skin reactions. Immune-related events of any type occurred in 11% of patients and peripheral neuropathy in only 0.4%. This suggests that limiting EV exposure limited its long-term toxicity.

VOLGA also tested a triplet, EV+D plus the anti-CTLA-4 agent tremelimumab. It improved EFS (median not reached versus 12.1 months; 24-month rate 60% versus 45%) but was less compelling overall. Median OS was not reached, and unlike the doublet, the curves did not separate well (HR 0.77; p=0.1230). The triplet also added toxicity and more treatment discontinuations. In this setting, less may lead to more. As discussant Michiel van der Heijden noted, a lighter regimen could reduce the treatment burden for patients recovering from major cystectomy surgery.

## Finding the right combination

KEYNOTE-866 explored the same idea from the other direction by adding perioperative pembrolizumab to cisplatin/gemcitabine. The trial was negative. EFS did not improve significantly (HR 0.88; p=0.137), and five-year OS was 70.8% versus 70.9%. pCR was higher with pembrolizumab (44.4% versus 35.8%), but this did not carry through to EFS. Here, less was not more. A stronger immunotherapeutic effect appears to be needed, and the result is a useful caution about pCR as a surrogate. The investigators also noted that control-arm outcomes were better than historical expectations for neoadjuvant cisplatin/gemcitabine with radical cystectomy (RC) and pelvic lymph node dissection (PLND).

The KEYNOTE-905 ad hoc analysis reinforces the value of EV+P in the perioperative setting. The trial included patients who were ineligible for cisplatin as well as those who refused it, so its message applies beyond a narrowly defined group. The analysis compared all three arms in concurrently randomized patients (n=255). Pembrolizumab alone was active, with a pCR rate of 25.3% versus 10.3% with surgery alone. That is well below the 58.8% pCR reported with EV+P. The question is therefore not whether immunotherapy alone works, but whether it is enough. Discussant Min Yuen Teo argued that these data may mark the end of the neoadjuvant checkpoint inhibitor monotherapy era. Taken with the negative KEYNOTE-866 result, they strengthen the case that adding EV to immunotherapy, not adding immunotherapy to chemotherapy, is what moves outcomes.

## ctDNA may help define enough

KEYNOTE-B15 provides some additional insight and potential future treatment selection guidance through its ctDNA analysis. ctDNA is a strong prognostic

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marker, and it also shows how well treatment is working. With EV+P, ctDNA positivity fell from 52.4% at baseline to 13.0% presurgery and 4.8% postsurgery. With cisplatin/gemcitabine, it fell from 56.8% to 19.7% and 13.5%. Among ctDNA-positive patients, pCR was only 3.7% with EV+P and 2.2% with chemotherapy. Among ctDNA-negative patients it was 72.4% and 43.7%.

EFS followed the same pattern. At 24 months, EFS in patients who stayed ctDNA-negative was 94.6% with EV+P and 87.8% with chemotherapy. Patients who converted from positive to negative reached 81.1% and 63.2%. Those who stayed positive reached only 33.3% and 35.3%. Two points stand out. Clearing ctDNA is associated with good outcomes, and EV+P appears to clear it more often and with a better EFS result than chemotherapy. But persistent positivity carries a poor prognosis in both arms, and EV+P showed no clear advantage in that small group. That is a signal for escalation strategies and new agents.

The EFS HR favored EV+P in baseline ctDNA-positive patients (0.54). It also favored EV+P in ctDNA-negative patients (0.68), but that 95% confidence interval crosses 1 (0.37–1.26). While extremely promising, the data do not yet show that ctDNA-negative patients can safely avoid future treatment. As the discussant Teo noted, using ctDNA to select patients for bladder preservation or to omit adjuvant therapy needs further exploration and prospective validation.

### Takeaways

So, when is enough enough? ESMO 2026 suggests the answer is not one regimen but a threshold that differs by patient. For some, three cycles of EV with durvalumab appear to be enough. For others, enough has not yet been achieved.

ctDNA may eventually help define that threshold patient by patient. Patients who clear ctDNA do well. Patients who stay ctDNA-positive do poorly on either regimen, indicating new strategies are needed. Neither idea is proven. The ctDNA-negative subgroup data do not yet show that treatment can be safely omitted, and ctDNA's link to micrometastatic disease still needs validation. Together, though, these data give hope that bladder-sparing treatment may be achievable in the near future.

Answering the question will take trials designed for it. They need ctDNA-guided escalation and de-escalation arms, and endpoints such as bladder-intact EFS and patient-reported outcomes. The field's next task is to find out how much treatment each patient needs, not to keep adding more.

**Relevant trial and reference notes:**

- LBA2: **Perioperative durvalumab (Imfinzi) ± tremelimumab (Imjudo; AstraZeneca) + neoadjuvant enfortumab vedotin (EV, Padcev; Pfizer/Astellas)** interim data from phase 3 **VOLGA** trial for cisplatin-ineligible MIBC
- 4735O: **Perioperative pembrolizumab (Keytruda; Merck)** + cisplatin/gemcitabine in phase 3 **KEYNOTE-866** for cisplatin-eligible MIBC
- 4733O: **Perioperative pembro or enfortumab vedotin (EV) + pembro** analysis from **EV-303/KEYNOTE-905** for cisplatin-ineligible MIBC
- 4734O: **Perioperative enfortumab vedotin (EV) + pembro** ctDNA analysis from the phase 3 **KEYNOTE-B15** trial for cisplatin-eligible MIBC

# Glioblastoma at ESMO 2026: Turning Early Signals into Evidence



**Michael Freeman**
Senior Associate,
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More than two decades after the Stupp protocol became standard of care, glioblastoma (GBM) remains one of oncology's most stubborn challenges. Maximal safe resection followed by temozolomide (TMZ)-based chemoradiotherapy is still the backbone of treatment. Tumor Treating Fields is the only addition since then to show even a modest survival benefit. ESMO 2026 brought no practice-changing breakthrough. What it did offer was encouraging early-stage signals, a clearer view of where the field is heading, and data that reinforce the need to select the right patients for trial enrollment.

## Activity with Targeted Therapies

The randomized phase 2 trial adding the BET inhibitor trotabresib to chemoradiotherapy was another reminder that the Stupp protocol is hard to beat. Outcomes were not improved and toxicity was increased. It joins a long list of agents that have struggled to improve on the Stupp protocol. Like many GBM trials with targeted agents, it enrolled an unselected patient population.

The IMPRESS-Norway trial offers an alternative approach, molecularly profiling patients with advanced tumors who have exhausted standard-of-care treatment, and matching them with targeted agents approved in other indications. Among patients with CNS malignancies, 20 with GBM were evaluable for response and 30% experienced durable disease control ≥16 weeks, all using drugs with no GBM indication. While this activity is modest, the point stands: matching the drug to the patient got activity out of agents that have no established record in GBM.

## Immunotherapy Advances

GBM is a notoriously "cold" tumor, with low T cell infiltration and a highly immunosuppressive tumor microenvironment. However, encouraging data from novel immunotherapy targets and administration techniques were presented at ESMO. Preliminary results from a phase 1b/2 trial in China with ivonescimab and TMZ in recurrent GBM demonstrated:

- DCR of 95% (19/20)
- 6-month PFS of 77.8% (14/18)
- 12-month OS of 44.4% (8/18, mOS not reached)

Long-term follow-up from the GLITIPNI trial with intracerebrally injected ipilimumab, nivolumab, and autologous myeloid dendritic cells following maximal safe resection highlighted:

- 2-year PFS: 26% (5/19)
- 2-year OS: 42% (8/19)

While the ivonescimab and GLITIPNI trials are limited by small populations, both demonstrated manageable safety profiles and durable responses (18+ mo.) in certain patients. Investigation of both regimens is ongoing in larger, more diverse patient populations. If these signals are going to hold up, developers will likely need to identify which patient subgroups are receiving durable disease control.

During his keynote lecture on CNS malignancies, Prof. Wolfgang Wick highlighted the NeoVax trial at DFCI that combines a personalized neoantigen vaccine with pembrolizumab for newly diagnosed GBM (originally presented at ASCO 2026). The regimen induced neoantigen-specific intratumoral T cell responses and improved PFS and OS compared to propensity score-matched institutional controls. Patients with ex vivo neoantigen-specific T cell responses had significantly improved OS compared to non-responders (HR 0.26, p=0.015).

While validation of NeoVax is needed in a larger randomized trial, these data are promising, particularly in light of Moderna/Merck's phase 3 success with their personalized vaccine in melanoma. Notably, transcriptional analyses in the NeoVax study revealed that the mesenchymal subtype was associated with greater T cell infiltration and survival. While the transcriptional state of GBM is heterogeneous, deeper understanding of factors that improve T cell killing will guide future trials and research.

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## Developing Beyond Early Signals

ESMO 2026 points to a more selective development strategy in GBM: identify the right patient subgroup, demonstrate meaningful tumor exposure, and deliver benefit without compromising existing treatment. Across treatment modalities, a minority of patients achieve durable responses and long-term survival, emphasizing the need for further research to elucidate which treatments are effective in which patients.

The strongest opportunities remain developmental, and encouraging early signals must be distinguished from evidence that can support registration and adoption. GBM's unmet need is clear, but the investable opportunity lies in a precisely defined treatment proposition supported by comparative evidence and a deliverable care pathway.

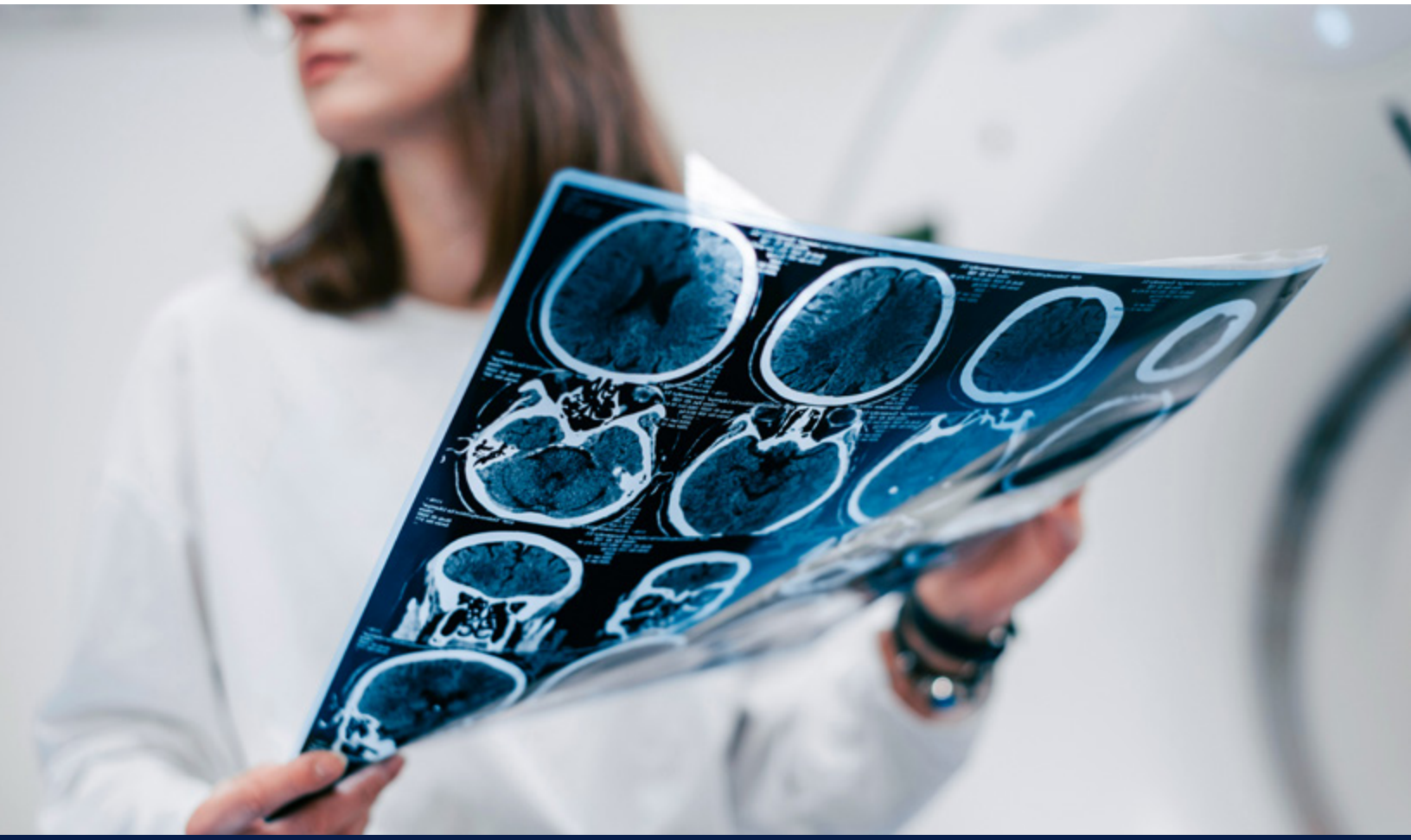
**Relevant trial and reference notes:**

- 692O: **Trotabresib (CC-90010; BMS)** + radiotherapy + temozolomide in a phase 2 trial for IDH wild-type (wt) newly diagnosed glioblastoma (GBM)
- 694O: **IMPRESS-Norway** phase 2 trial of matched therapy for GBM
- 700RO: Intracerebral **Nivolumab + Ipilimumab ± autologous CD1c+/CD141+ myeloid dendritic cells** in phase 2 **GLITIPNI** trial for resectable high-grade glioma (HGG)
- 706P: **Ivonescimab (Summit/Akeso)** + temozolomide in a phase 1b/2 trial for recurrent GBM
- Keynote lecture: Wick W. CNS disease as the next frontier in oncology care: Glioblastoma, metastases, and leptomeningeal disease
  - J Clin Oncol 44, 2026 (suppl 16; abstr 2006)

### Takeaways

GBM remains one of oncology's toughest challenges. Promising data were presented at ESMO from phase 1/2 trials testing targeted agents and immunotherapies, but encouraging early signals must be distinguished from evidence that can support registration and adoption.

ESMO 2026 points to a more selective development strategy in GBM: identify the right patient subgroup, demonstrate meaningful tumor exposure, and deliver benefit without compromising existing treatment.



# The Changing Paradigm in Diffuse Large B-cell Lymphoma (DLBCL) and Multiple Myeloma (MM): Beyond R-CHOP and Upfront Transplant



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Senior Consultant,
Medical Affairs Consulting

Lymphoma and myeloma discussions at ESMO 2026 highlighted a common shift towards earlier immune-based therapies and more personalized treatment selection, guided by tumor biology and MRD.

## DLBCL: Moving beyond R-CHOP

After approximately 50 years as the frontline backbone, R-CHOP is being challenged by targeted combinations. The following trials were highlighted during ESMO 2026 discussions to illustrate the evolving DLBCL treatment landscape. In POLARIX, polatuzumab vedotin plus R-CHP maintained a PFS benefit at five years (HR 0.77), while frontMIND reported improved PFS with tafasitamab plus lenalidomide and R-CHOP (HR 0.75) with added toxicity. Another strategy introduces bispecific antibodies into frontline treatment, with three phase 3 trials: OLYMPIA-3 (odronextamab), EPCORE DLBCL-2 (epcoritamab) and SKYGLO (glofitamab). EPCORE DLBCL-2 met its primary PFS endpoint in a topline announcement (HR 0.49; full data pending). Despite these advances, molecular heterogeneity remains important. Molecular profiling may guide treatment selection. ViPOR has shown preferential activity in MCD and EZB-MYC-positive subtypes, while tumor microenvironment and T-cell exhaustion signatures may help explain response variability to bispecific antibodies and CAR-T, respectively.

## MM: Rethinking transplantation

The question is shifting from whether to transplant to which patients benefit most. Anti-CD38 quadruplets are increasingly established in frontline treatment, while trials are exploring MRD-guided transplant strategies and earlier use of bispecific antibodies and CAR-T. Two ESMO 2026 abstracts explored belantamab-based combinations in transplant-ineligible patients. Early-phase belantamab combinations have shown encouraging activity: Bela-DRd achieved 81.3% MRD negativity among evaluable patients, while Bela-Rd reported a 97.6% overall response rate. Ocular toxicity remains an important management consideration. These early findings support further investigation of ADC-based combinations in patients unable to tolerate standard quadruplets.

### Takeaways

In DLBCL, targeted agents and bispecific antibodies are moving into frontline treatment. In MM, MRD-guided strategies are challenging the role and timing of upfront transplantation. Both diseases are moving towards earlier use of targeted immunotherapy and more individualized treatment. Molecular profiling in DLBCL and MRD assessment alongside cytogenetic risk in MM may help refine treatment selection and intensity; however, prospective validation and longer-term outcomes remain necessary.

**Relevant trial and reference notes:**

- Symposium presentation: Davies AJ. DLBCL is no longer a single disease with a unique therapy.
  - EPCORE DLBCL-2: NCT06037976. AbbVie and Genmab press release, October 5, 2026
  - POLARIX: J Clin Oncol. 2025;43:3698–3705
  - frontMIND: ASCO 2026, abstract LBA7000
  - OLYMPIA-3: NCT06091865
  - SKYGLO: NCT06047080
  - ViPOR: ASH 2023, abstract 434
- Symposium presentation: Gay F. Novel approaches challenging the role of transplantation in the treatment of frontline myeloma.
- 1454O: **Belantamab mafodotin (Blenrep; GSK)** + daratumumab, lenalidomide and dexamethasone in the phase 1/2 Bela-DRd study for transplant-ineligible, newly diagnosed MM.
- 1455O: **Belantamab mafodotin** + lenalidomide and dexamethasone in the phase 1/2 Bela-Rd trial for transplant-ineligible, newly diagnosed MM.

# Radiopharmaceutical Innovation Needs Evidence and Delivery Infrastructure to Translate into Commercial Success



**Graeme Hacking, PhD (Cantab), LRAM, DipRAM, FRSPH**
Vice President,
Medical Affairs Consulting

ESMO 2026 highlighted a radiopharmaceutical sector increasingly focused on treatment after lutetium-177, alternative tumor targets and the biology of resistance. For pharmaceutical companies, the commercial opportunity depends on establishing where each therapy belongs within the treatment pathway. Encouraging response rates can support investment, but meaningful differentiation will require evidence of durable benefit, acceptable cumulative toxicity and dependable delivery.

Early alpha-therapy findings illustrated both the promise and the uncertainty. TheraPb evaluated the PSMA-directed lead-212 agent ADVC001 in 22 patients. At the recommended phase 2 doses, the reported PSA50 response rate was 80% and median radiographic progression-free survival was 11.2 months. All five patients with RECIST-evaluable disease responded. That small denominator remains essential when interpreting the results; this uncontrolled study cannot establish superiority over existing therapies.

ProTACT addressed activity after lutetium exposure. At evaluated dose levels, actinium-225 PSMA agent FL-020 produced PSA50 responses in nine of nine lutetium-naive patients and six of eight previously exposed patients. These findings support further investigation of a potentially important sequencing opportunity. However, small subgroups and a PSA-based endpoint leave response durability and comparative clinical benefit unresolved. Companies pursuing this population will need prospective evidence that defines which patients benefit.

An alpha program pursuing treatment after lutetium will require a different comparator and evidence package from one seeking earlier use. This makes commercial positioning an early development decision, with trial design shaped by the population and clinical role the company intends.

Lead-212 also generated interest in neuroendocrine tumors. VMT-α-NET reported objective response rates, including unconfirmed responses, of 33% and 50% in two cohorts. Estimated progression-free survival at 18 months was 72% across 68 patients. Participants had received no previous radiopharmaceutical therapy, so these data cannot answer whether treatment works after earlier peptide receptor radionuclide therapy. No dose-limiting toxicities (DLTs), grade 4 or 5 treatment-emergent adverse events (TEAEs), or adverse event-related treatment discontinuations were reported. Continued renal safety assessment will also be important.

Sequencing may become more complex as retreatment develops. Re-LuPSMA reported interim safety findings in 20 patients selected for previous response to lutetium-PSMA. Two possibly treatment-related serious anemia events remained below the protocol stopping threshold; efficacy results were unavailable. For developers of subsequent therapies, selected patients receiving further lutetium could become a relevant comparator. Evidence generation must therefore anticipate how clinical practice may evolve.

Resistance biology strengthens the rationale for looking beyond PSMA. Exploratory studies found declining plasma-predicted PSMA expression at progression in 11 of 17 paired samples. Although this does not validate a treatment-selection assay, it supports investigating target reassessment. BActinium-1, targeting B7-H3, and ATNM-400, targeting HER3, illustrate alternative development strategies. Both were trials in progress, offering no clinical efficacy conclusions. Their potential commercial relevance lies in reaching patients poorly served by further PSMA-directed therapy.

These programs create opportunities for partnerships connecting target biology, therapeutic development and imaging. Imaging and biomarker research could help identify suitable patients and guide switching between targets. Investment decisions must nevertheless remain specific to each construct, including tumor retention, normal-tissue exposure and therapeutic window.

Intraperitoneal radium-224 in ovarian cancer illustrates another expansion route: regional treatment of residual disease after surgery, subject to future efficacy evidence and practical integration.

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Patient experience will also influence adoption. CCTG PR21 reported generally maintained quality of life with lutetium-PSMA compared with deterioration during docetaxel treatment. Such findings strengthen the case for collecting patient-reported outcomes alongside comparative efficacy and healthcare resource use. For payers and clinicians, value will depend on the overall treatment experience and outcomes achieved, making these measures commercially relevant throughout development.

**Relevant trial and reference notes:**

- 2253P: **$^{212}$Pb-ADVC001 (AdvanCell)** updated results from phase 1 TheraPb trial in PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)
- 2323eP: **$^{225}$Ac-FL-020 (Full-Life Technologies)**, targeting PSMA, in phase 1 ProTACT study in mCRPC
- 2396RO: **$^{212}$PbVMT-α-NET (Perspective Therapeutics)** in a phase 1/2 trial in advanced SSTR2+ neuroendocrine tumors (NETs)
- 2246P: **$^{177}$Lu-PSMA-617 (Pluvicto; Novartis)** interim safety analysis from phase 2 RE-LuPSMA trial of retreatment in mCRPC
- 8727P: **$^{177}$Lu-PSMA-617 (Pluvicto; Novartis)** plasma epigenomic profiling study in mCRPC
- 2390eTiP: **$^{225}$Ac-AKY-2519 (Aktis Oncology)**, targeting B7-H3, in phase 1b BActinium-1 study for mCRPC
- 2386eTiP: **ATNM-400 (Actinium Pharmaceuticals)** in phase 1 study for mCRPC
- 1446eTiP: Intraperitoneal α-emitting **Radium-224** in a phase 2 trial for homologous recombination proficient primary advanced epithelial ovarian cancer
- 2210RO: **$^{177}$Lu-PSMA-617 (Pluvicto; Novartis)** versus docetaxel in CCTG PR21 study; patient-reported quality of life in mCRPC

## Takeaways

Delivery capability must advance alongside clinical evidence. Isotope availability, manufacturing release, transport and treatment appointments must work together reliably. Partnerships with isotope suppliers, radiopharmacies and treatment centers can therefore contribute directly to commercial viability. Companies should assess whether the proposed regimen can be supplied consistently across intended markets and accommodated within available clinical capacity.

Medical Affairs should help connect these requirements through integrated evidence generation planning. Priorities include dose optimization, long-term safety, sequencing, patient selection and service capacity, with disease-specific questions addressed across indications. ESMO 2026 supports a broader radiopharmaceutical future, but commercial success will depend on resolving these practical and clinical uncertainties. Companies that define a specific unmet need, demonstrate meaningful benefit and establish a dependable route to treatment will be better positioned to translate early promise into sustained adoption.



# Beyond Checkpoint Blockade: New Modalities for Taking Control of Immune Responses



**Jeffrey Bockman, PhD**
Expert Advisor &
Executive Vice President



**Dennis Chang, PhD**
Senior Vice President,
Strategy Consulting

For years now, PD-(L)1 immune checkpoint blockade has dominated the immuno-oncology conversation. Even today, the "hottest" new class is based on the same backbone, the PD-(L)1×VEGF bispecifics. And in fairness, many other IO drug classes have risen to prominence over the years only to fail. But at ESMO 2026, we may be seeing a shift in immuno-oncology, with promising readouts across a diverse set of novel immunotherapy modalities.

## Personalized neoantigen mRNA vaccine

A phase 3 trial of Merck/Moderna's personalized neoantigen vaccine intismeran autogene was featured in the first Presidential Symposium of the conference, as an add-on to standard pembro for adjuvant treatment of melanoma. The vaccine combination significantly improved both relapse-free survival (RFS) and distant metastasis-free survival (DMFS) with hazard ratios ~0.6. Although this was not as impressive as the phase 2 data, it was still a definitive win, and with minimal added toxicity. The first personalized mRNA therapeutic vaccine for oncology will soon be approved and redefine the standard of care.

## In-situ vaccination

Syncromune's SYNC-T is a drug-device platform that relies on partial cryolysis of a target lesion to liberate patient-specific tumor neoantigens directly into the microenvironment. This is immediately followed by the intratumoral infusion of SV-102—a fixed-dose multi-target immunomodulator combining anti-PD-1, anti-CTLA-4, a CD40 agonist, and a CpG-ODN adjuvant. The intratumoral infusion also pushes the antigens and immunomodulators into the lymphatic system for increased immune cell access, following a biologic and immunologic rationale for local delivery of IO therapies that has been such an anathema to most large pharma.

The phase 1 trial of SYNC-T SV-102 showcased at ESMO focused on metastatic prostate cancer, a tumor type historically viewed as an immune desert. With 29.6 months of median follow-up, the trial confirmed durable systemic clinical responses well beyond the initial lesion site. Although the sample size was small, the 24-month OS was impressive at 80%: 70% for castration-resistant prostate cancer (mCRPC; n=10) and 100% for hormone-sensitive prostate cancer (mHSPC; n=5). Importantly, the localized delivery of this multi-agent cocktail averted the high-grade systemic toxicities (typically 42–53%) observed with systemic multi-checkpoint doublets: SYNC-T SV-102's grade 3-4 irAE rate was 0%.

## Selective T cell activation

Marengo's invikafusp alfa utilizes cooperative dual-binding to selectively target and expand Vβ6/Vβ10 T-cells—specific lineages heavily implicated in tumor infiltration—without altering other immune cell balances. Current immune checkpoint inhibitors (ICIs) are frequently limited by indiscriminate T-cell activation, where anti-tumor activity may come with severe immune-related adverse events. The first-in-human data for invikafusp presented at ESMO 2026 provided a meaningful clinical proof-of-concept for avoiding this pitfall.

In a heavily pretreated cohort of advanced solid tumors resistant to multiple lines of therapy, the agent yielded a 59.3% DCR and a 15% ORR at optimal doses. Crucially, it selectively drove both circulating and intratumoral expansion of the target T-cells with a highly tolerable safety profile, validating the mechanistic principle while opening the opportunity for immunotherapy combination.

## 4-1BB-based T-cell engager

Bispecific T-cell engagers (TCEs) are not new—the first (Blincyto) was FDA-approved in 2014—but thus far all approved TCEs have used CD3 as the T-cell target. In contrast, BeOne's BGB-233 (or BGB-B2033) is a GPC3 × 4-1BB bispecific antibody. The costimulatory molecule 4-1BB is a highly potent mediator for CD8+ T-cell activation, but historical systemic agonists like urelumab had to be discontinued due to severe hepatotoxicity. BGB-233 solves this through structural

**(Continued)**

strictness: it triggers 4-1BB signaling only upon cross-linking with GPC3 on the surface of tumor cells. Presenting early phase 1 data in hepatocellular carcinoma (HCC), where GPC3 is overexpressed in roughly 90% of cases, the molecule delivered marked CD8+ activation localized to the tumor landscape, with a rate of grade 3+ AEs of only 5%. The ORR at the recommended phase 3 dose was nearly 36%, in an HCC population where more than 90% of patients had previously been treated with a PD-(L)1 inhibitor. This TCE not only decoupled the anti-tumor potential of 4-1BB from its historical safety liabilities, but also could overcome at least a subset of ICI resistance mechanisms.

### Takeaways

The overarching theme of the next wave of immunotherapy is spatial and biological control. As showcased at ESMO 2026, various platforms may achieve tighter control of immune response, whether by restricting activation to a precise subset of tumor-reactive T-cells, engineering strict tumor-antigen dependency for costimulators, or using local delivery to modulate the TME. The lesson from Madrid amplifies what many in the IO space have believed and shown in models: that to overcome checkpoint resistance and mitigate immune toxicity, cancer immunotherapies must move past the standard systemic, global immune activation in favor of more localized precision.

**Relevant trial and reference notes:**

- LBA1: **Intismeran autogene (Merck/Moderna)** + pembrolizumab in phase 3 INTerpath-001 for adjuvant treatment of melanoma
- 2247P: **SV-102 (Syncromune)** in phase 1 for metastatic prostate cancer
- 1948O: **Invikafusp alfa (Marengo)** in phase 2 START-001 for high tumor mutational burden (TMB-H) solid tumors
- 1679O: **BGB-B2033 (BeOne)** in phase 1 for hepatocellular carcinoma (HCC)



# Conclusion

ESMO 2026 delivered practice-changing pivotal readouts alongside promising early signals for emerging therapies. The congress also highlighted novel mechanisms and modalities, next-generation versions of established drug classes, and valuable lessons drawn from trial failures, biomarker analyses, and subgroup data. This collection of insights and takeaways covers only a portion of the data presented, but the breadth and depth of findings were clear.

**Several themes stood out:**

- **Pivotal and early-stage progress:** Pivotal trial results are poised to change clinical practice, and early data point to promising new therapies.
- **Innovation across modalities:** Novel mechanisms and modalities are emerging. Existing drug classes are also being expanded and improved through next-generation chemistry and biologic engineering.
- **Learning from setbacks and subgroups:** Trial failures, biomarker analyses, and subgroup findings offered important insights to guide patient selection and future development.

# Lumanity at ESMO 2026

Lumanity co-authored several data presentations at this year's congress:

## 01

### 3315O (Paper)

When overall survival is not enough: The emerging need for context-sensitive endpoint frameworks in oncology.

- Lumanity co-author: Dan Gladwell
- This presentation supports formalizing the intrinsic value of endpoints beyond overall survival (OS) in Health Technology Assessments, clinical guidelines, and other data evaluations. Lumanity continues to advance this initiative, and further updates will follow.

## 02

### 2535P (Poster)

Global quantitative chart review of multidisciplinary team (MDT) care and treatment (Tx) in patients (pts) with stage (Stg) I-II, unresected non-small-cell lung cancer (urNSCLC).

- Lumanity co-authors: Rob Rawlinson & Florence Bulbrook
- This poster quantified the remaining gap in engaging multidisciplinary teams in NSCLC patient care.

## 03

### 3523eP (e-Poster)

The Hidden Toxicity: Measuring Cancer's Mental Health Burden in Real-World Data.

- Lumanity author: Josine Kuiper

## 04

### 4622eP (e-Poster)

Real-World Treatment Utilization in Biomarker-Positive Cancer Patients: Evidence from the Dutch PHARMO Data Network.

- Lumanity co-authors: Josine Kuiper and Naomi Reimes
- Together, these two e-posters draw on Lumanity's big-data analytical capabilities and the PHARMO dataset to generate real-world clinical insight.

# Looking Ahead

These presentations reinforce a broader point: the implications of the data shared at ESMO reach well beyond scientific understanding and clinical outcomes assessment. The findings shape decisions and policies on access, health economics, quality-of-life assessment, regulatory methodology, research funding, and more. As cancer treatment grows more complex, the systems that govern its use, and those that drive the development of future therapies, must evolve and innovate with it.

To help biopharma companies adapt to this evolution across functions and over time, Lumanity remains committed to staying at the forefront of the data and the discussions surrounding it. We welcome the opportunity to connect you with our experts.

Lumanity applies incisive thinking and decisive action to cut through complex situations and deliver transformative outcomes to accelerate and optimize access to medical advances. With deep experience in medical, commercial, and regulatory affairs, Lumanity transforms data and information into real-world insights and evidence that power successful commercialization and empower patients, providers, payers, and regulators to take timely and decisive action.

Contact us to learn more about how Lumanity can support your unique challenge.

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