ASCO 2025: Driving Knowledge to Action in Cancer Care

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THE 2025 American Society of Clinical Oncology (ASCO) Annual Meeting underscored a key principle: in today's complex and rapidly evolving cancer landscape, the application of knowledge, not just its acquisition, is our most powerful tool for progress. Robin Zon's presidential theme, "Driving Knowledge to Action: Building a Better Future," was brought to life across the plenary sessions and data presentations that spanned tumor types, geographies, and therapeutic modalities. Two dominant motifs emerged from the most practice-changing studies: the use of large-scale, well-designed clinical trials to validate transformative interventions, and a growing effort to repurpose effective therapies earlier in the disease course, challenging historical treatment sequences. These principles reflect the essence of oncology's future: evidence-powered, patient-centered, and accessible to all.

GASTROINTESTINAL CANCERS

ASCO 2025 highlighted several practice-informing studies in gastrointestinal (GI) oncology. The Phase III CHALLENGE trial[1] demonstrated that structured exercise after adjuvant chemotherapy significantly improved disease-free survival (DFS) in Stage II–III colon cancer, a globally scalable, low-cost intervention with the potential to change standard survivorship care. In Stage III disease, the Phase II/III DYNAMIC-III trial tested circulating tumor DNA (ctDNA)-guided escalation with FOLFOXIRI versus standard therapy.[2] Escalation did not improve 2-year recurrence-free survival (RFS; 52% versus 61%), though ctDNA clearance remained a powerful prognostic marker (3-year RFS: 84% versus 12%), reinforcing its value for stratification but not yet guiding treatment decisions. The Phase III ATOMIC trial[3] showed DFS benefit with adjuvant atezolizumab in combination with chemotherapy in microsatellite instability-high (MSI-H) Stage III colon cancer, strengthening the rationale for immuno-oncology (IO) in early-stage disease. However, plenary discussants questioned whether adjuvant therapy is needed at all, or if neoadjuvant IO may provide greater benefit (i.e., NICHE-2). In metastatic colorectal cancer (CRC), the Phase III BREAKWATER (BRAF V600E)[4] and CheckMate 8HW (MSI-H)[5] trials confirmed new first-line standards, targeted triplet therapy, and dual checkpoint blockade, respectively.

In upper GI cancers, the Phase III MATTERHORN trial[6] demonstrated improved event-free survival with perioperative durvalumab plus 5-fluorouracil, oxaliplatin, and docetaxel (FLOT) in resectable HER2-negative gastroesophageal junction (GEJ) tumors. While subgroup and overall survival (OS) data are pending, D-FLOT met its primary endpoint and is expected to influence practice. Separately, the Phase III DESTINY-Gastric04 trial[7] showed that trastuzumab deruxtecan (T-DXd) significantly improved OS and progression-free survival (PFS) compared to ramucirumab plus paclitaxel in the second-line setting for HER2-positive unresectable or metastatic gastric/GEJ cancer, establishing a new standard of care.

In resectable or borderline resectable pancreatic ductal adenocarcinoma (PDAC), the Phase III CASSANDRA study[8] compared neoadjuvant PAXG (cisplatin + nab-paclitaxel + capecitabine + gemcitabine) to modified FOLFIRINOX. PAXG resulted in an improved event-free survival, a greater pathological response, and a signal toward OS benefit, raising the question of whether it will supplant FOLFIRINOX as the preferred neoadjuvant option. As PDAC remains one of the most lethal cancers, this data injects new optimism into early-stage management.

BREAST CANCER

The Phase III SERENA-6 trial[9] showed that switching to camizestrant plus cyclin-dependent kinase (CDK)4/6 inhibition at molecular progression (ESR1 mutation) delayed PFS-2 by nearly 7 months. However, the PFS-2 endpoint may have been biased by unequal treatment exposure across arms, limiting its interpretability and immediate clinical impact. VERITAC-2,[10] a Phase III trial of the oral proteolysis-targeting chimera (PROTAC) degrader vepdegestrant, demonstrated superior PFS over fulvestrant in *ESR1*-mutant estrogen receptor-positive (ER+)/HER2–metastatic breast cancer (MBC) (5.0 versus 2.1 months, hazard ratio [HR]: 0.58), supporting this novel mechanism of action as a viable endocrine strategy.

In ASCENT04,[11] the Phase III trial showed that sacituzumab govitecan plus pembrolizumab significantly improved PFS (11.2 versus 7.8 months; HR: 0.65) compared with chemotherapy plus pembrolizumab in PDL1-positive metastatic triple-negative breast cancer, supporting this antibody–drug conjugateIO combination as a potential new frontline standard. In early HER2-positive breast cancer, the neoCARHP trial[12] showed that omitting carboplatin (trastuzumab + pertuzumab + chemotherapy [THP] alone) yielded non-inferior pathologic complete response with fewer adverse events, supporting de-escalation in selected patients. Finally, in HER2-positive MBC, first-line T-DXd plus pertuzumab (DestinyBreast-09)[13] doubled complete response rates and significantly prolonged PFS compared to THP (40.7 versus 26.9 months). While OS data are still maturing, this combination is a strong contender to redefine front-line therapy.

LUNG CANCER

The lung cancer track was dominated by the long-term data from CheckMate 816,[14] showing a 5-year OS benefit with neoadjuvant nivolumab + chemotherapy in resectable non-small cell lung cancer (NSCLC; 65.4% versus 55.0%; HR: 0.72), reinforcing the shift toward neoadjuvant IO. Commentary highlighted that compared to KEYNOTE-671, CheckMate 816 achieved comparable OS outcomes while minimizing perioperative treatment burden. The IMforte study[15] was a milestone for small cell lung cancer (SCLC), reporting the first OS benefit from first-line maintenance therapy: lurbinectedin + atezolizumab prolonged OS to 13.2 months versus 10.6 months with atezolizumab alone. Additionally, the DeLLphi-304 study[16] showed that tarlatamab, a delta-like ligand 3 (DLL3)-targeted bispecific T cell engager, significantly improved OS over chemotherapy in relapsed SCLC, with benefit sustained across subgroups. NeoADAURA[17] also advanced the perioperative landscape by demonstrating significantly higher major pathologic response rates with neoadjuvant osimertinib, with or without chemotherapy, compared to chemotherapy alone in resectable *EGFR*-mutant NSCLC, although the survival benefit and added value beyond adjuvant osimertinib remain uncertain. Together, these data suggest a more nuanced, biomarker-informed, and immunotherapy-integrated future for both non-SCLC and SCLC.

GENITOURINARY CANCERS

In prostate cancer, the Phase III AMPLITUDE trial[18] was a landmark: the first biomarker-selected Phase III trial in metastatic hormone-sensitive prostate cancer showed that abiraterone + niraparib significantly improved radiographic PFS in patients with homologous recombination repair gene alterations, particularly *BRCA* mutations. This reinforces the value of routine genomic profiling in earlier prostate cancer settings. In clear cell renal cell carcinoma, the KEYNOTE-564 5-year update[19] confirmed sustained DFS and OS benefit with adjuvant pembrolizumab over placebo, with absolute gains of nearly 10% and 7%, respectively. These durable benefits further cement IO's role in early-stage renal cell carcinoma and validate long-term follow-up as essential to therapeutic confirmation. New strategies in urothelial cancer were also showcased. The JAVELIN Bladder Medley Phase II study[20] showed that maintenance avelumab combined with sacituzumab govitecan nearly tripled median PFS over avelumab alone (11.17 versus 3.75 months), though OS data remain immature. Together, these trials underscore the growing impact of biomarker-driven and immunotherapy-based strategies across genitourinary cancers.

NEURO-ONCOLOGY, SKIN CANCER, AND HEAD & NECK

Outside of high-incidence cancers, ASCO 2025 delivered compelling updates across several distinct disease areas. In neuro-oncology, the final results from the Phase III CATNON trial[21] confirmed that adjuvant temozolomide significantly improves OS in isocitrate dehydrogenase-mutant anaplastic glioma (HR: 0.54), while concurrent temozolomide with radiation offers no added benefit, refining standards for this molecularly defined subgroup. In skin cancers, the Phase III C-POST trial[22] showed that adjuvant cemiplimab improved DFS in high-risk cutaneous squamous cell carcinoma (HR: 0.32), reinforcing IO's role in curative-intent management. Conversely, in melanoma, RELATIVITY-098[23] found no RFS benefit from adding relatlimab to adjuvant nivolumab (HR: 1.01), though >60% major pathologic response in neoadjuvant settings suggests tumor presence may be essential for lymphocyte-activation gene 3 (LAG3) efficacy.

In head and neck cancer, two major trials advanced the role of perioperative immunotherapy. NIVOPOSTOP[24] showed improved DFS with postoperative nivolumab added to adjuvant chemoradiotherapy in resected high-risk disease (HR:

0.76), primarily by reducing locoregional recurrence. KEYNOTE-689,[25] recently granted FDA approval, demonstrated that perioperative pembrolizumab significantly improved event-free survival over standard chemoradiotherapy alone, with the greatest benefit in PD-L1 combined positive score of ≥10 patients (HR: 0.66). These results establish a new standard for operable, locally advanced head and neck squamous cell carcinoma and affirm the importance of treatment timing and immune priming. Lastly, a randomized trial examining the timing of chemoimmunotherapy infusions showed that patients treated earlier in the day had significantly improved OS (HR: 0.45), offering a novel, low-cost optimization strategy for daily oncology care.

CONCLUSION: NEW STANDARDS; CRITICAL QUESTIONS REMAIN

ASCO 2025 delivered clear advancements in multiple tumor types, from first-line T-DXd in HER2-positive MBC and D-FLOT in GEJ cancers to durable OS gains with neoadjuvant IO in lung and adjuvant IO in renal cell carcinoma. At the same time, several studies raised pivotal questions, such as: Does adjuvant IO offer added value over neoadjuvant alone in MSI-H colon cancer? Does ctDNA escalation improve outcomes or merely identify risk? Can biomarker-adaptive strategies like SERENA-6 truly alter long-term survival? Across these updates, the field continues to evolve toward earlier, biomarker-driven intervention. But translation into practice will require critical appraisal, long-term validation, and equitable access. In this, the theme of “Driving Knowledge to Action” remains not just aspirational, but essential.

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