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ESMO 2025

The role of HER2-TKI in HER2-mutant, advanced NSCLC: A Comparative Review of Beamion-LUNG 1 and SOHO-01

HER2 belongs to the ERBB receptor family. HER2-mutated non-small cell lung cancer (NSCLC) accounts for approximately 2–4% of all cases and represents a distinct molecular subgroup with an unfavorable prognosis.

Most alterations are activating mutations, particularly exon 20 insertions fundamentally differing from HER2 overexpression or amplification in breast or gastric cancer (1–3). These biological differences explain the historically limited responses to conventional HER2-directed therapies and highlight the need for mutation-specific treatment approaches.

The current standard of care in the first line setting for advanced HER2-mutant NSCLC is pembrolizumab plus pemetrexed and platinum-based chemotherapy (KEYNOTE-189) (4). After disease progression, the HER2-directed antibody-drug conjugate (ADC) trastuzumab deruxtecan (T-DXd) is available in Switzerland (5). Data from DESTINY-Lung01 and DESTINY-Lung02 demonstrated robust activity in pretreated HER2-mutant NSCLC, with objective response rates (ORR) around 55–57%, a median progression-free survival (PFS) of roughly 8.2 months, and a median duration of response of approximately 9 months. Interstitial lung disease (ILD)/pneumonitis remains an important toxicity requiring close monitoring. Despite these challenges, T-DXd has become a key therapeutic option in the second-line setting.

Two next-generation, highly selective, covalent HER2 tyrosine kinase inhibitors (TKI) – sevabertinib and zongertinib – are now being evaluated and may shift treatment paradigms in the future. BEAMION-Lung1 and SOHO-01 are the respective trials that showed promising ORR. Both studies had multiple cohorts representing different treatment situations: untreated or pretreated, either with HER2-targeting ADC or with chemoimmunotherapy.

BEAMION-Lung 1 is a phase Ia/Ib study investigating the irreversible, selective HER2-TKI zongertinib. Primary endpoint was ORR. At the ESMO Annual Meeting, the results of cohort 2, including treatment-naïve patients, were presented. ORR was 77% with a rapid median time to response of 1.4 months (range, 1.1–6.9 months). Although PFS data remain immature yet, the 6-month PFS rate was 79%. The 6 month duration of response (DOR) was 80% with a median follow-up of 9.7 months. Responses were observed across different HER2 mutation types (6).

SOHO-01 is a phase I/II study of sevabertinib in advanced HER2-mutated NSCLC with ORR as a primary endpoint. Sevabertinib showed promising response rates in all cohorts, ranging from 38% in the HER2-ADC pretreated patients to 71% in untreated patients. In untreated patients PFS was not mature yet (with a median follow-up time of 9.9 months), the 12 months PFS was 55%. The median D0R was 11 months. In the cohort with pretreated patients who were naïve to an HER2-ADC, an exploratory biomarker analysis was performed as it was the largest cohort with the longest follow-up. This analysis indicated that patients with HER2-TKD mutations, especially YVMA exon 20 insertions, had higher response rates (7).

Both TKIs were associated with manageable toxicities. Diarrhea and rash were common adverse events (AEs). In both studies patients needed to have dose reductions to complete treatment (15% with zongertinib, 28% with sevabertinib). Diarrhea grade ≥ 2 occurred more frequently with sevabertinib (34% grade 2, 6.7% grade 3), as well as paronychia. This is probably due to a greater inhibition of EGFR wildtype. With dose reductions and treatment interruptions, the toxicities were manageable with supportive care in both studies.

Both trials underline that HER2-TKIs have the potential to transform the management of HER2-mutant NSCLC. Ongoing phase III studies (BEAMION-LUNG 2, SOHO-02, DESTINY-Lung 04) are ex-

pected to clarify optimal sequencing strategies – such as whether TKI- or ADC-based therapy should be used first – and help to define which approach offers the greatest survival benefit. □

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Trastuzumab Deruxtecan in the neoadjuvant and post neoadjuvant treatments

Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate (ADC) that has emerged as one of the most active HER2-targeted ADC, demonstrating superior survival outcomes compared with earlier HER2-directed therapies in metastatic disease.

Two major clinical trials, the DESTINY-Breast11 and DESTINY-Breast05 extend T-DXd evaluation into the neoadjuvant and post-neoadjuvant settings, respectively, addressing major unmet needs for patients with high-risk HER2-positive early breast cancer (eBC). This review summarizes the results for efficacy, safety and implications of these two pivotal trials, and proposes considerations for optimal integration of T-DXd in curative treatment strategies.

DESTINY-Breast11: Neoadjuvant T-DXd-THP versus ddAC-THP

Pathologic complete response (pCR) is a strong predictor of improved event-free and overall survival in HER2-positive eBC (1–3). Standard neoadjuvant regimens combining chemotherapy with HER2-targeted therapy achieve a pCR of about 39–69% (4–9), with lower rates in hormone receptor-positive and clinically high-risk patients (5,10). Traditional regimens also carry significant acute toxicities (9,11) and long-term risks such as cardiotoxicity (12,13), neuropathy (5) and secondary leukemias (12). Because T-DXd has already shown superior survival compared with prior standard therapies in metastatic disease (14,15), DESTINY-Breast11 was designed to explore whether incorporating T-DXd in the neoadjuvant setting could improve efficacy and safety.

DESTINY Breast11 compared neoadjuvant T-DXd combined with paclitaxel, trastuzumab, and pertuzumab (THP) versus dose-dense doxorubicin plus cyclophosphamide (ddAC) followed by THP, with patients receiving either 4 cycles of T-DXd followed by 4 cycles of THP, or 4 cycles of ddAC followed by 4 cycles of THP before surgery (16). A third arm evaluated T-DXd alone but was closed early following the independent Data Monitoring Committee recommendation, for several reasons, including a lower pCR rate. T-DXd-THP demonstrated a statistically significant improvement in pathologic complete response with a pCR rate of 67.3% and an improvement of 11.2% over ddAC-THP (95% CI 4.0–18.3%; p = 0.003). Benefits were seen in both hormone receptor (HR)-positive tumors (61.4% vs 52.3%; ΔpCR 9.1%, 95% CI 0.2–17.9%) and HR-negative tumors (83.1% vs 67.1%; ΔpCR 16.1%, 95% CI 3.0–28.8%). Also, early event-free survival (EFS) data (4.5% maturity) showed a hazard ratio of 0.56 (95% CI 0.26–1.17). This is the first phase III evidence showing that replacing chemotherapy with an ADC in a neoadjuvant setting improves pCR. Residual cancer burden analysis showed that more than 81% of patients in the T-DXd-THP arm had no or minimal residual invasive disease (RCB-0 or RCB-I), compared with 69% in the ddAC-THP arm. Of note, 78% of hormone receptor-positive tumors achieved RCB-0/I, highlighting the benefit in a group that traditionally responds less well. Importantly, the safety profile of T-DXd-THP was more favorable than ddAC-THP, with fewer grade 3 or higher adverse events, fewer serious adverse events, and reduced ventricular dysfunction (1.3% vs. 6.1%). Rates of interstitial lung disease were low and comparable between groups (4.4% vs. 5.1%).

DESTINY-Breast11 concluded that T-DXd-THP achieved higher pCR rates and a more favorable safety profile than ddAC-THP. However, the trial has important limitations: the comparator arm no longer reflects current standard-of-care chemotherapy (which is mainly carboplatin, a taxane plus HP[17]), and only about half of the patients without pCR received post-neoadjuvant trastuzumab emtansine (T-DM1), which is now recommended. Since the chemotherapy regimen in the standard arm does not meet current standards – which achieve pCR rates comparable to T-DXd-THP and are also anthracycline-free – the definitive role of T-DXd-THP in the neoadjuvant setting remains to be established.

DESTINY-Breast05: Adjuvant T-DXd Versus T-DM1 for Residual Disease

The DESTINY-Breast05 trial evaluated the use of adjuvant T-DXd in HER2-positive eBC patients who had residual invasive disease following neoadjuvant therapy (NAT) – a group known to have higher recurrence risk. In the earlier KATHERINE trial, T-DM1 had become the standard adjuvant therapy in this setting after showing significant improvements in invasive disease-free survival (IDFS) and overall survival (OS) (18,19) over trastuzumab. Still, outcomes in patients with advanced locoregional disease or positive nodal status remained modest (19,20), and CNS recurrence was not reduced (20). Given the superiority of T-DXd over T-DM1 in metastatic disease (21,22), DESTINY-Breast05 compared these two agents in patients with high-risk HER2 positive early breast cancer who had residual disease after neoadjuvant therapy. High-risk was defined as either inoperable disease prior to neoadjuvant therapy (cT4, N0–3, M0 or cT1–3, N2–3, M0) or operable disease (cT1–3, N0–1, M0) with axillary node-positive residual disease (ypN1–3) after neoadjuvant therapy. In the experimental arm, patients received

T-DXd every 3 weeks for 14 cycles, while in the comparator arm, patients received T-DM1 3.6 mg/kg IV every 3 weeks for 14 cycles. Notably, nearly half of the study population was of Asian descent.

DESTINY-Breast05 demonstrated that at 3 years, IDFS was 92.4% with T-DXd versus 83.7% with T-DM1, corresponding to a hazard ratio (HR) of 0.47 (95% CI, 0.34–0.66). The IDFS benefit was consistent across all prespecified subgroups, regardless of hormone receptor status, nodal involvement, baseline stage, or residual disease characteristics. Secondary endpoints also showed advantages for T-DXd. 3 year disease free survival (DFS) was 92.3% with T-DXd versus 83.5% with T-DM1 (HR 0.47; 95% CI, 0.34–0.66), and 3 year distant recurrence free interval (DRFI) was 93.9% versus 86.1% (HR 0.49; 95% CI, 0.34–0.71), favoring T-DXd. Notably, fewer central nervous system (CNS) metastases were reported in the T-DXd arm, with a 3-year brain metastasis-free interval of 97.6% versus 95.8% with T-DM1. Safety was considered manageable. Interstitial lung disease (ILD) occurred in 9.6% of patients receiving T-DXd, mostly grade 1–2. Three deaths occurred in the T-DXd arm (two due to ILD/pneumonitis and one due to unrelated respiratory infection), while five occurred in the T-DM1 arm from various unrelated causes. Cardiotoxicity was rare, occurring in 2.9% of T-DXd patients versus 1.7% of T-DM1 patients, with mostly asymptomatic left ventricular declines and no treatment-related heart failure. More than 72% of patients in both arms completed the full 14 cycles of therapy.

DESTINY-Breast05 concluded that adjuvant T-DXd showed better efficacy and a manageable safety profile in high-risk HER2-positive eBC patients with residual disease after NAT. High-risk was defined as either inoperable disease at presentation or residual axillary node-positive disease after neoadjuvant treatment; in this population, T-DXd represents a new post-neoadjuvant standard. For patients with residual disease who do not meet these high-risk criteria, T-DM1 remains the standard of care.

Discussion

When viewed together, DESTINY-Breast11 and DESTINY-Breast05 demonstrate that T-DXd has strong efficacy across both neoadjuvant and post-neoadjuvant settings. In the neoadjuvant trial, T-DXd-THP achieved high pCR rates with fewer severe side effects compared with an anthracycline-based chemotherapy backbone. In the post-neoadjuvant trial, T-DXd outperformed T-DM1, further reducing recurrence risk in a high-risk group. The optimal sequencing of T-DXd in early HER2-positive breast cancer remains an important unanswered question. Long-term outcomes with neoadjuvant T-DXd followed by THP are not yet known. In addition, the management of patients who receive neoadjuvant T-DXd-THP but still present with residual disease at surgery remains undefined. At the present time, it is unclear whether T-DXd should be preferentially used in the neoadjuvant setting, the post-neoadjuvant setting, or potentially both, leaving its optimal placement within the treatment sequence an active area of ongoing investigation. Continued follow-up is required to clarify long-term safety, survival outcomes, and the most effective therapeutic strategy for integrating T-DXd into curative-intent care.

Overall, these two trials show that trastuzumab deruxtecan is becoming an important component of curative-intent therapy in HER2-positive eBC and has the potential to redefine treatment strategies in both the neoadjuvant and post-neoadjuvant settings. □

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Highlights in Genitourinary Oncology

Last year's ESMO Congress featured numerous highlights in genitourinary malignancies. In the Presidential Symposium alone, four presentations focused on this field, underscoring the current dynamics in genitourinary oncology.

A particularly active area, as in the past few years, has been non-metastatic muscle-invasive urothelial carcinoma of the bladder (MIBC). The Keynote-905/EV-303 trial deserves particular attention: After the earlier EV-302 study had already redefined the new standard of care in advanced urothelial carcinoma with the combination of enfortumab vedotin and pembrolizumab (EV-P), this trial now evaluates the EV-P regimen in the perioperative setting for cisplatin-ineligible patients (1,2). According to current guidelines and due to insufficient data for neoadjuvant therapy, such patients usually undergo immediate cystectomy followed by adjuvant checkpoint inhibitor therapy in PD-L1 positive disease (3).

In Keynote-905, patients with MIBC (T2-T4a and N0 or N1) who were cisplatin-ineligible were randomized. The observational arm underwent upfront cystectomy followed by observation (17% received adjuvant nivolumab). The experimental arm received 3 cycles of neoadjuvant EV-P followed by cystectomy and postoperative enfortumab vedotin (6 cycles) and pembrolizumab (14 doses). The trial included an arm with pembrolizumab monotherapy, but this was discontinued in 2022, and no results were currently reported.

The baseline characteristics reflect the generally elderly and frail nature of the cisplatin-ineligible population, with median age of 74 years and ECOG performance status 2 in up to 15% of patients, respectively.

The primary endpoint event-free survival (EFS) was significantly improved by the addition of perioperative EV-P (hazard ratio [HR] 0.40; $p < 0.0001$), as was overall survival (OS) (HR 0.50; $p = 0.0002$). Furthermore, nearly 60% of patients treated with EV-P achieved a pathological complete response. As expected, toxicity was higher in the EVP group (71% vs. 46% grade ≥ 3); however, this did not appear to lead to a clinically relevant compromise of surgical feasibility.

In summary, EV-P represents a safe and effective perioperative treatment option for cisplatin-ineligible patients and will likely become the new standard of care in this population. Some questions and limitations should be addressed: only 17% of patients in the control arm received adjuvant nivolumab. Moreover, it would be interesting to know whether patients with a pathological complete response truly require adjuvant therapy.

This leads directly to the next MIBC study presented at ESMO: the IMvigor011 trial, which evaluated ctDNA-guided adjuvant therapy with atezolizumab in patients with MIBC.

Following a post-hoc analysis of its predecessor trial, the IMvigor010, which had suggested a possible benefit of adjuvant atezolizumab in ctDNA-positive subgroups, IMvigor011 enrolled patients after cystectomy and without any evidence of distant metastasis (4,5). Patients were monitored for one year with serial tumor-informed ctDNA assessments. If ctDNA became detectable in the absence of radiologically evident metastases, patients were randomized to receive atezolizumab vs. placebo for one year. ctDNA-negative patients were observed without systemic therapy.

The results highlight the strong prognostic value of postoperative ctDNA detection. In ctDNA-positive patients, the primary endpoint, disease-free survival (DFS), favored the atezolizumab arm (HR 0.64; $p = 0.005$); however, the median DFS of 9.9 months (vs. 4.6 months with placebo) still indicates a high relapse rate despite adjuvant treatment. As expected, outcomes for patients who remained ctDNA-negative were excellent, with a 12-month DFS of 95%.

The immediate impact of these findings on everyday clinical practice remains uncertain due to several limitations: Atezolizumab is not currently the standard of care for adjuvant treatment of MIBC, and the data cannot be directly extrapolated to the perioperative setting, which now defines the standard of care. Ongoing and future studies will further clarify how ctDNA can be integrated both for treatment escalation and de-escalation, including assessments of cost-effectiveness.

Several important trials were presented in prostate cancer. The PSMAddition investigated the addition of radioligand therapy with Lu-PSMA-617 in patients with metastatic hormone-sensitive prostate cancer (mHSPC). After confirmation of PSMA-positive disease, patients were randomized to receive current standard therapy with androgen deprivation therapy (ADT) and an androgen-receptor pathway inhibitor (ARPI), whereas the experimental arm received six cycles of Lu-PSMA-617 in addition to ADT + ARPI. The primary endpoint, radiographic progression-free survival (rPFS), was positive (HR 0.72; $p = 0.002$). However, at the current median follow-up of 23 months, there is no statistically significant difference in OS. Moreover, quality-of-life (QoL) analyses did not show an inferior outcome in the experimental arm. Toxicity was higher in the investigational arm, including a higher rate of secondary malignancies and renal adverse events even with short follow-up.

Thus, routine use of radioligand therapy already in the hormone-sensitive setting needs to be discussed critically, given the increased toxicity and lack of QoL benefit, and is probably not a «one size fits all» approach. It also remains unclear whether an OS benefit can ultimately be demonstrated, particularly in the context of the crossover design.

Another important study in the field of mHSPC is the CAPItello-281 trial: patients with phosphatase and tensin homolog (PTEN) deficiency were randomized to receive capivasertib or placebo in combination with ADT and an ARPI. Capivasertib is a protein kinase inhibitor targeting downstream effectors in the PTEN pathway and is therefore considered a promising targeted agent (6). In the trial, the primary endpoint of rPFS was significantly improved in the capivasertib arm (HR 0.81; $p = 0.034$), corresponding to a median rPFS extension of approximately 7.5 months (7). Mature OS data are not yet available. Patients on capivasertib experienced higher rates of severe toxicity, especially diarrhea, hyperglycemia, rash and anemia. Whether this regimen will be adopted into routine practice in view of the modest magnitude of benefit and side effect profile remains unclear.

The list of impactful trials presented at ESMO 2025 in the genitourinary field could easily be extended. Overall, the data presented reflect the remarkable dynamism of the field and the substantial

progress being made for patients. We eagerly await future trials and datasets that will continue to reshape the therapeutic landscape of urogenital malignancies. □

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Highlights in Gastric and Gastroesophageal Junction Adenocarcinoma

Gastric and Gastroesophageal Junction Adenocarcinoma (GC/GEJA) remain a major global health concern, with poor survival despite aggressive treatment. Molecular insights have enabled the integration of immunotherapy and targeted agents into advanced disease treatment, guided by biomarkers such as HER2, PD-L1, MSI and CLDN18.2 (1–5). Explorative biomarkers such as FGFR2b are being investigated with targeted therapies in development.

MATTERHORN

Curative surgical resection remains the cornerstone of localized GC/GEJA management. Perioperative chemotherapy improves prognosis with the FLOT (fluorouracil, leucovorin, oxaliplatin, docetaxel) regimen widely recognized as the standard of care (6,7). To further improve the efficacy of perioperative treatment, two trials presented at the 2025 ESMO Congress assessed novel regimens with already proven benefit in the palliative setting. The final overall survival (OS) results from the Phase III MATTERHORN trial were presented, comparing perioperative PD-L1 inhibitor durvalumab plus FLOT with placebo plus FLOT in 948 patients with resectable, locally advanced GC/GEJA (8). At a median follow-up of 43 months, durvalumab plus FLOT reduced the risk of death by 22% (HR 0.78; 95% CI 0.63-0.96; p = 0.021) regardless of PD-L1 status. Three-year OS was 69% with the durvalumab-based regimen compared to 62% with FLOT. 5% of patients had MSI(microsatellite instability)-high tumor tissue, evenly distributed between arms. However, MSS (microsatellite stability) status was unknown in around 30% of patients. HER2 was not assessed. 20% of patients died within 15 months in both arms, underscoring the need for biomarker-driven approaches to tackle the problem of early mortality.

PHERFLOT/IKF-053

A biomarker-driven strategy in the same setting was chosen in the phase II, single-arm PHERFLOT/IKF-053 trial for patients with HER2-positive GC/GEJA. This trial evaluated the efficacy and safety of combining FLOT, trastuzumab, and pembrolizumab in the perioperative setting in 31 patients with resectable, locally advanced HER2-positive GC/GEJA (9). This trial follows the KEYNOTE-811 trial that established this combination for advanced disease (10). The pathological complete response rate was 48.4% (15 of 31), meeting the co-primary endpoint and exceeding historical FLOT benchmarks of 15–20%. Two-thirds of patients achieved major pathological response. The safety profile aligned with expectations, except for the elevated grade 3 diarrhea (12 of 31) and reoperation rate (8 of 30). No 30-day postoperative mortality occurred. The long-term results — particularly the 2-year disease-free survival data (co-primary endpoint) — will determine whether this perioperative approach should be further explored in larger trials aiming for a new benchmark for this molecular subgroup.

FORTITUDE-101

Shifting focus to an emerging biomarker in a palliative setting: the randomized, placebo-controlled Phase III FORTITUDE-101 trial evaluated bemarituzumab, a first-in-class anti-FGFR2b antibody, added to mFOLFOX6 (fluorouracil, leucovorin, oxaliplatin) in 547 patients with unresectable or metastatic FGFR2b-expressing (2+/3+ staining in ≥ 10% of tumor cells), non-HER2-positive GC/GEJA. At the primary analysis (median follow-up 11.8 months), median OS was 17.9 months with bemarituzumab and 12.5 months in the placebo arm (HR 0.61; 95% CI 0.43– 0.86; p = 0.005). With a longer median follow-up of 19.4 months, no OS benefit was observed (14.5 months versus 13.2 months; HR 0.82; 95% CI 0.62–1.08). Grade ≥ 3 treatment-related adverse events occurred in 60% of patients receiving bemarituzumab, mainly reversible corneal events, compared with 18.4% in the placebo arm. The converging OS curves suggest a limited efficacy, likely due to data maturity and biomarker heterogeneity rather than treatment imbalance, as treatment exposure and subsequent therapy were similar between arms. Preclinical studies showed bemarituzumab sensitizes tumors to anti-PD1 antibodies by modulating the microenvironment (11). The ongoing phase Ib/III FORTITUDE-102 trial is exploring mFOLFOX6 plus nivolumab and either bemarituzumab or placebo in patients with advanced FGFR2b-expressing GC/GEJA.

These trials highlight the evolving landscape of GC/GEJA research with a move toward precision-based medicine. Furthermore, it is crucial to develop strategies targeting tumor heterogeneity and biomarker-based focal positivity, as these could significantly impact treatment responses. □

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Advancing Precision in Adjuvant Treatment of Colorectal Cancer: Progress Made, No Breakthrough Yet

Although the European Society For Medical Oncology (ESMO) Congress 2025 in Berlin did not present practice-changing studies in colorectal cancer (CRC), several findings offered valuable insights.

Standard management of high-risk stage II (pT4) and stage III (pN+) colon cancer involves surgical resection followed by adjuvant chemotherapy, which typically consists of a fluoropyrimidine such as 5-fluorouracil or capecitabine, administered either alone or in combination with oxaliplatin for three to six months. However, nearly half of the patients may be cured with surgery alone and could therefore avoid adjuvant chemotherapy, whereas a substantial proportion will relapse despite receiving chemotherapy. Recent efforts to improve risk stratification, including the DYNAMIC-III trial using circulating tumor DNA (ctDNA) and approaches integrating artificial intelligence with digital pathology, highlight ongoing strategies to individualize adjuvant therapy in CRC.

DYNAMIC-III Trial: ctDNA-Guided Adjuvant Therapy in Stage III CRC

ctDNA is a strong prognostic marker for relapse in colorectal cancer (1). The DYNAMIC trial, published in 2022 with recent updates, randomized stage II colon cancer patients to ctDNA-guided adjuvant chemotherapy or standard management. Only ctDNA-positive patients received chemotherapy, reducing treatment rates from 28% to 15% without compromising 2-year recurrence-free survival (RFS). At a median follow-up of 60 months, 5-year RFS was similar between groups (88% vs. 87%, 95% confidence interval [CI] –5.8% –8.0%). The trial met its primary endpoint, supporting ctDNA-guided therapy as a strategy to safely limit overtreatment in stage II CRC (2).

2025, from the same group, the ctDNA-negative arm of the DYNAMIC-III trial was presented at ESMO, and the ctDNA-positive arm at the American Society of Clinical Oncology (ASCO) Annual Meeting (3). This multicenter, randomized, phase 2/3 study enrolled 968 patients with stage III colon cancer who underwent ctDNA testing 5–6 weeks post-surgery and were randomized to ctDNA-guided or standard management. A tumor-informed personalized approach for ctDNA analysis was used (SaferSeqS targeted CRC panel). In the ctDNA-guided arm, ctDNA-negative patients received de-escalated therapy, whereas ctDNA-positive patients received intensified therapy. Primary endpoints were 3-year RFS for ctDNA-negative patients and 2-year RFS for ctDNA-positive patients, with secondary endpoints including hospitalization and ctDNA clearance.

Among 702 ctDNA-negative patients (72.5%), de-escalation reduced oxaliplatin use (34.8% vs. 88.6%) and hospitalizations (8.5% vs. 13.2%), with slightly lower 3-year RFS (85.3% vs. 88.1%, 95% CI of the difference –8% – +2.5%), though non-inferiority criteria were not met (non-inferiority was defined as the lower bound of the one-sided 97.5% CI for the difference at 3 years not crossing –7.5%). In ctDNA-positive patients, higher ctDNA levels were associated with increased recurrence risk (3-year RFS 77% to 23%; $p < 0.001$). Escalated therapy did not improve outcomes (2-year RFS 51% vs. 61%), and persistent ctDNA after treatment predicted markedly worse prognosis (3-year RFS 14% vs. 79%).

Overall, these findings confirm ctDNA as a strong prognostic tool in colon cancer; however, the trial was formally negative for the primary endpoints. Considering that the non-inferiority design is the appropriate approach to assess these questions, and that the subgroup analysis did not substantially contribute to hypothesis generation, the study leaves open questions regarding clinician-driven therapy selection, the choice of de-escalation strategies, and whether the SaferSeqS targeted CRC panel used was the most optimal and precise assay.

Prognostic value of the Combined Analysis of Pathologists and Artificial Intelligence in high-risk stage II-III colon cancer treated without chemotherapy

In the Netherlands, the Combined Analysis of Pathologists and Artificial Intelligence (CAPAI) was developed to refine prognostic assessment and guide ACT in high-risk stage II and III colon cancer. CAPAI combines histopathologic features from H&E slides, analyzed using the DoMore-v1-CRC deep learning biomarker, with tumor stage (pT/pN) and lymph node count to classify patients into low-, intermediate-, or high-risk groups. DoMore-v1-CRC was previously optimized and validated in large European cohorts, demonstrating superior prognostic performance compared with traditional morphological and molecular markers, stratifying patients into good, uncertain, or poor prognosis categories with 3-year cancer-specific survival (CSS) up to 97% in low-risk patients and hazard ratios exceeding 10 for high- versus low-risk groups (4). Leveraging the Netherlands' restrictive ACT practices, a nationwide cohort of 453 patients under 70 years, with good performance status and R0 resection, who did not receive neoadjuvant or adjuvant therapy, was analyzed. CAPAI effectively stratified patients, identifying nearly half as low-risk (3-year CSS 93.7%), 34% as

intermediate-risk (87.5%), and 18% as high-risk (60.4%), with statistically significant differences (log-rank p < 0.001). These findings suggest that integrating DoMore-v1-CRC with conventional staging enables precise identification of patients who may safely avoid adjuvant chemotherapy (ACT) while highlighting those who might benefit from treatment intensification (5).

Outlook

Taken together, these findings underscore the need to reassess clinical trial designs and refine diagnostic and prognostic tools, with the ultimate goal of delivering adjuvant therapy only to patients most likely to benefit. The rapidly evolving landscape of emerging biomarkers presents an opportunity for coordinated evaluation. For ctDNA, the proliferation of assays in clinical investigation brings several key questions to the forefront, including whether systematic cross-assay comparisons are needed to establish analytical validity and clinical utility and whether sequential measurements can provide additional insight into residual disease and relapse risk. Concurrently, advances in artificial intelligence (AI) applied to digital pathology suggest that AI-derived biomarkers may play an important role, particularly when integrated with established molecular and clinical markers. Incorporating these complementary, question-oriented approaches into future trials holds strong promise for improving patient stratification and advancing toward true precision in adjuvant colorectal cancer therapy. □

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Perioperative vs Adjuvant Immunotherapy in locally advanced Head and Neck Cancer: Lessons from KEYNOTE-689 and ADRISK Trial

Head and neck cancers are a heterogeneous group of tumors arising from the nasopharynx to the larynx. The majority are histologically classified as head and neck squamous cell carcinoma (HNSCC).

Approximately 50–60% of patients present with locally advanced HNSCC (LA-HNSCC) at diagnosis (1,2). For decades, the standard of care (SOC) was surgery followed by adjuvant radiotherapy (RT), with the addition of concurrent chemotherapy based on pathological risk factors (3). The combined analysis of RTOG 9501 and EORTC 22931, recently updated by Zumsteg et al., confirmed that adding cisplatin to postoperative RT significantly improves overall survival (OS) in patients with high-risk features such as positive margins and/or extracapsular extension (ECE) of positive lymph nodes (4). Despite multimodal therapy, 5-year OS remains below 50%, highlighting the need for treatment intensification. Immunotherapy, particularly PD-1 inhibition (e.g. pembrolizumab), has demonstrated efficacy in recurrent and metastatic HNSCC. Based on promising phase II and III data (5), there has been growing interest in integrating pembrolizumab into the primary management of resectable LA-HNSCC.

The phase III KEYNOTE-689 trial evaluated perioperative pembrolizumab in resectable LA-HNSCC (oral cavity, larynx, hypopharynx, or oropharynx; stages III–IVA, AJCC 8th edition) (6). Patients (n = 714) were randomized 1:1 to either perioperative pembrolizumab or SOC. In the experimental arm, patients received two cycles of neoadjuvant pembrolizumab prior to surgery, followed by adjuvant pembrolizumab administered concurrently with RT (with or without cisplatin) for three cycles, and subsequently up to twelve cycles of maintenance therapy. In the control arm (SOC), patients underwent surgery followed by postoperative RT with or without concomitant cisplatin, according to high-risk features. Patients with high-risk disease, defined as positive margins and ECE-positive lymph nodes, received RT (33 × 2 Gy) with concomitant cisplatin. Patients with low-risk disease were treated with RT alone (30 × 2 Gy). Most patients in the study had oral cavity carcinoma (60.3% in the pembrolizumab arm versus 60.7% in the control arm) and were HPV-negative (> 95%). At the time of the first interim analysis, with a median follow-up of 38.3 months, the 36-month event-free survival (EFS) rate was 59.8% in the pembrolizumab arm versus 45.9% in the control arm among patients with a CPS ≥ 10 (HR 0.66; 95% CI, 0.49–0.88; p = 0.004). In the CPS ≥ 1 population, the corresponding EFS rates were 58.2% and 44.9% (HR 0.70; 95% CI, 0.55–0.89; p = 0.003). In the overall study population, EFS at 36 months was 57.6% with pembrolizumab compared with 46.4% in the control group (HR 0.73; 95% CI, 0.58–0.92; p = 0.008). Major pathological response occurred in 9.4% of patients, including 3% with complete pathological response. The incidence of grade ≥ 3 treatment-related adverse events was similar between arms, though immune-mediated toxicities were higher with pembrolizumab (43.2% vs. 10.2%).

Compared to the Keynote-689, the ADRISK phase IIb trial examined pembrolizumab exclusively in the adjuvant setting (7). Patients with intermediate and high-risk LA-HNSCC were randomized after surgery if they had a close resection margin (R0 < 5 mm), a microscopic residual tumor (R1) or ECE-positive lymph nodes. All patients received adjuvant cisplatin-based chemoradiotherapy (CRT), with or without concomitant and maintenance pembrolizumab. Approximately two-thirds of the patients were diagnosed with an HPV-positive oropharyngeal carcinoma. After a median follow-up of 30 months, pembrolizumab addition did not significantly improve EFS (HR 0.812; 95% CI, 0.487–1.353; p = 0.423) or OS (HR 0.85; 95% CI, 0.46–1.57; p = 0.591). Subgroup analyses showed that p16-positive oropharyngeal carcinoma had the

most favorable 2-year EFS with 89.9%, whereas oral cavity cancers had the poorest 2-year EFS with 41.3%.

Both trials explored pembrolizumab integration into multimodal therapy for resectable LA-HNSCC but differed substantially in design and patient populations. KEYNOTE-689 assessed pembrolizumab in the perioperative setting, incorporating neoadjuvant and adjuvant treatment, whereas the ADRISK trial assessed pembrolizumab exclusively in the adjuvant setting. ADRISK enrolled patients with more advanced pathological features (close surgical margins [R0 < 5 mm], microscopic residual disease [R1], and/or ECE-positive lymph nodes), with all participants receiving adjuvant cisplatin-based CRT. Despite these high-risk criteria, approximately two-thirds of patients had HPV-positive oropharyngeal carcinoma, a subgroup generally associated with favorable outcomes. In contrast, KEYNOTE-689 included mainly HPV-negative tumors (> 95%), with only a small proportion of oropharyngeal cancers. This trial also enrolled some lower-risk patients treated with postoperative RT alone, while high-risk patients received concurrent cisplatin. Notably, only 38.9% of patients in the pembrolizumab arm and 50.5% in the control arm received concurrent CRT. Taken together, ADRISK focused on intermediate- and high-risk patients uniformly treated with adjuvant CRT ± pembrolizumab, and its population predominantly comprised tumors with favorable HPV-associated biology. Conversely, KEYNOTE-689 addressed a broader and biologically more aggressive cohort, largely HPV-negative, which may explain the differing clinical outcomes observed between the two trials.

Overall, the available data suggest that the therapeutic benefit of pembrolizumab in LA-HNSCC may be confined to specific subgroups (particularly patients with HPV-negative tumors and higher PD-L1 scores). In contrast, those with HPV-positive oropharyngeal carcinoma generally exhibit a favorable prognosis and are unlikely to benefit from additional treatment intensification. Furthermore, the timing of immunotherapy appears to play a critical role, with perioperative administration demonstrating greater potential to improve outcomes compared to adjuvant-only use. Nevertheless, treatment escalation involving immunotherapy must be carefully balanced against the increased risk of immune-related adverse events. □

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EHA 2025

Novel Genetic Insights in Lymphoma Biology: Follicular Lymphoma Subtypes and ASXL1-Related Disease

Review paper on ESID EHA SIOPE Focused Symposium 2025, Vienna, November 18–20. The scientific meeting was dedicated to the interplay of immunology and haematology, with particular emphasis on the somatic and germline genetic landscapes shaping malignancies.

Whole-genome sequencing reveals three follicular lymphoma subtypes with distinct cell of origin and patient outcomes

Follicular lymphoma (FL) is a malignancy of germinal-center B-cells and a common non-Hodgkin lymphoma subtype in Western Europe (1). While FL typically follows an indolent course and recent advances in treatment avenues have significantly improved patient survival, the disease remains incurable and demonstrates a considerable clinical heterogeneity. A patient subset experiences early progression, treatment refractoriness, or histological transformation (2).

The WHO 2022 classification recognizes four FL subtypes: classical FL, FL with unusual cytological features, follicular large B-cell lymphoma and FL with a predominantly diffuse growth pattern (3). Although, this classification enhances our understanding of FL biology, genetic-based subclassification remains challenging. The m7-FLIPI risk model integrates seven somatic mutations with clinical parameters to predict progression free survival (4); however, the algorithm does not incorporate FL hallmark translocations (*BCL-2::IGH, BCL-6* associated rearrangements).

The work by Ren et al. aimed to define clinically relevant genetic FL subtypes, through whole-genome and transcriptomic sequencing of 131 primary FL samples (5). Using integrated clustering of copy number variants (CNVs), somatic mutations, and structural variants, they identified three genetic subtypes. Cluster 1 (C1) was characterized by recurrent *BCL-6* translocations and mutations in NOTCH and NF-κB. C2, on the other hand, was defined by a high frequency of *BCL2* translocations and genetic alterations in chromatin modifier genes (*CREBBP, KMT2D, EZH2*). C3 lacked *BCL2/BCL6* translocations but exhibited a high CNV burden. Clinically, C1 was associated with a favourable prognosis, while C3 correlated with inferior progression-free survival and overall survival.

In summary, the work by W. Ren and colleagues proposes three genetic FL subtypes with distinct biological features, genetic propensities, and clinical outcomes. Future work will have to validate the proposed risk stratification and define its clinical use in view of the current and future therapeutic options.

ASXL1 deficiency causes epigenetic dysfunction, combined immunodeficiency, and EBV-associated lymphoma

Inborn errors of immunity (IEI) are germline disorders affecting immune system development and/or function (6). Malignancy is

the second leading cause of death in IEI patients (7). Notably, one third of newly identified monogenetic disorders are established by studying a single case (8), following methodical validation to establish causality.

Fu and colleagues described a female patient with recurrent pneumonia requiring hospitalization, including one severe EBV-related episode. At the age of three, she developed vaccine-strain rubella-positive granulomas following live-attenuated MMR vaccination that persisted over 10 years. Laboratory findings revealed erythrocytic macrocytosis, T-cell lymphopenia, and hypogammaglobulinemia. Chronic EBV replication was noted. At the age of 14 years, she developed EBV-associated advanced Hodgkin lymphoma (stage IVA, mixed cellularity subtype). Following polychemotherapy and checkpoint inhibitors, persistent disease necessitated allogeneic hematopoietic stem cell transplantation from a matched-unrelated donor. The patient remained well 18 months post-transplantation.

Given the severe clinical phenotype and young age, a genetic cause was assumed, and whole genome and exome sequencing was performed. Two novel compound heterozygous missense mutations in *ASXL1* were identified. While somatic alterations in the epigenetic modifier *ASXL1* are well-characterized in clonal hematopoiesis and hematological malignancies, germline variants have not been previously associated with immune dysfunction.

The authors demonstrated reduced *ASXL1* protein levels in patient-derived T-cells and fibroblasts. Cells transfected with the *ASXL1* variants recapitulated the low protein levels. This was paralleled with the loss of differentially methylated sites and accelerated epigenetic aging compared to healthy controls. To address causality, the authors transduced patient-derived T-cells with wild-type *ASXL1*, partially rescuing the methylation defects and epigenetic aging.

Profound T-cell exhaustion, reduced T- and NK-cell numbers, as well as impaired cytotoxicity, suggested that chronic viral replication and impaired immunosurveillance lead to Hodgkin lymphoma development.

In summary, the authors identified biallelic germline *ASXL1* missense mutations as a novel IEI (9). They suggest genetic testing in patients with chronic viral infections, viral-associated malignancy, and combined immunodeficiency. Allogeneic bone marrow transplantation in such rare cases will likely cure the immunodeficiency and the related haematologic malignancy. □

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Filling the gap for CAR T-cell therapy

Chimeric antigen receptor (CAR) T-cell therapy for hematological malignancies continues to expand rapidly, both in terms of approved products and new clinical indications. However, as applications broaden, the field increasingly faces delays in production and limited accessibility due to the constraints of current manufacturing processes.

Most approved CAR T-cell therapies are autologous – generated from a patient's own T lymphocytes. This approach presents several challenges. In heavily pretreated patients or those with a high circulating tumor burden, it can be difficult to obtain enough viable T cells to expand and meet manufacturing requirements. In addition, CAR T-cell production usually takes several weeks, exposing patients to the risk of disease progression before infusion. The process is also costly, labor-intensive, and centralized in a few specialized facilities, leading to long waiting times, logistical bottlenecks, and limited treatment availability as demand increases.

At the 2025 Annual Meeting of the European Hematology Association (EHA), part of the cell therapy session focused on these manufacturing challenges, with a focus on the need to treat high-risk patients (i.e. those heavily pretreated, with high tumor burdens, or rapidly progressing) and to make therapy accessible to more centers. Two presentations were particularly noteworthy in proposing innovative solutions to these problems.

The first, presented by Dr. Long and colleagues from Beijing (Abstract S283) (1,2), reported the phase I/II clinical trial results on allogeneic universal anti-CD7 CAR T-cell for T-cell acute lymphoblastic leukemia (T-ALL). Unlike autologous products, a total of eight healthy donors provided all the batches for this «off-the-shelf» CAR T-cells. To prevent CAR T rejection, graft-versus-host disease (GvHD), and fratricide among CAR T-cells, the team used genome editing to eliminate surface expression of HLA molecules, the T-cell receptor, and CD7. This allogeneic approach dramatically shortened production timelines: the median time from screening to infusion was approximately three weeks, eliminating the need for bridging therapy. Because the therapy did not depend on harvesting viable T-cells from each patient, no manufacturing failures occurred, and even patients with high circulating blast counts could be treated successfully. Safety remains a key concern for allogeneic CAR T products, given potential risks of immune rejection and off-target effects. Dr. Long's team reported a safety profile comparable to approved autologous CAR T-cell therapies, including manageable rates of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and immune effector cell-associated hematotoxicity (ICAHT).

Long-term safety assessment was limited, as all patients underwent consolidative allogeneic stem cell transplantation about 60 days post-infusion, but no unexpected toxicities were observed. The combined CAR T-cell plus transplant approach achieved complete remission (CR) in approximately 60% of patients with a median follow-up of two years. Importantly, efficacy was maintained in patients with extramedullary disease – a subgroup typically associated with poor prognosis – with a 57% CR rate at the full therapeutic dose. These encouraging results represent a major milestone for allogeneic CAR T-cell therapy, supporting its feasibility, safety, and potential scalability.

The second notable presentation (Abstract S281) (3), delivered by Dr. Mutsaers, focused on accelerating and decentralizing autologous CAR T-cell production. The team introduced a novel manufacturing platform capable of generating a CAR T-cell product within seven days of leukapheresis, significantly faster than the traditional multi-week process. This was achieved by shortening the culture period and decentralizing production, thereby eliminating the need for shipping of patient material to the production centre. The resulting CAR T-cells maintained an early T-cell memory phenotype, which may contribute to improved persistence and long-term disease control. Early clinical results showed a favourable safety profile, with low rates of severe CRS and ICANS, possibly reflecting the slower, more sustained cytotoxic activity of memory T-cells. Efficacy was evaluated in patients with both aggressive (DLBCL, MCL) and indolent (FL, MZL) B-cell non-Hodgkin lymphomas. At dose level 2, responses in DLBCL were comparable to those seen with approved CAR T-cell products, while outcomes in indolent lymphomas were particularly favourable. Whether these superior responses are due to enhanced CAR T-cell persistence remains under investigation, as longer-term follow-up is needed, especially in indolent lymphomas where relapses can occur months or years after treatment.

Together, these two studies exemplify the innovation currently shaping the CAR T-cell field. The allogeneic «off-the-shelf» approach offers a scalable solution to production bottlenecks, while accelerated, decentralized manufacturing could make autologous therapies faster and more widely accessible. The findings presented at EHA 2025 underscore the field's ongoing evolution toward making CAR T-cell therapy not only more efficient but also more clinically impactful. Continued research will determine how these advances translate into broader real-world adoption and improved patient outcomes. □

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EHA 2025 Highlights on Myeloproliferative Neoplasms

Chronic myeloid leukaemia: ASC4START-Trial

Chronic myeloid leukaemia (CML) has entered a new era of treatment with the introduction of tyrosine kinase inhibitors (TKIs), which have led to a near-normalization of life expectancy for most patients (1). Despite their remarkable efficacy, currently available TKIs all target the ATP-binding site of BCR::ABL1 and are associated with off-target toxicity. Asciminib represents a novel agent that targets the myristoyl pocket of BCR::ABL1, providing a new mechanism of action and the potential for an improved safety profile (2). In the ASC4FIRST trial, investigators evaluated whether asciminib achieved superior 48-week major molecular response compared with investigator-selected standard TKIs in newly diagnosed chronic-phase CML and found that asciminib demonstrated comparable – but not superior – efficacy relative to second-generation TKIs. Although a statistically significant advantage in efficacy over second-generation TKIs was not shown, asciminib appeared to offer a more favourable safety profile – an essential consideration in a chronic disease requiring lifelong therapy – thereby paving the way for a dedicated tolerability-focused trial.

The phase IIIb ASC4START trial (3) evaluated the safety and efficacy of asciminib versus nilotinib as first-line therapy in adults with newly diagnosed chronic-phase CML. Patients were randomized to receive either asciminib 80 mg once daily or nilotinib 300 mg twice daily. The primary endpoint of the study was the time to treatment discontinuation due to adverse events – both hematologic and non-hematologic (including gastrointestinal, cardiovascular, and general symptoms such as fatigue) – or death. Key secondary endpoints included type of adverse events and molecular response rates. This abstract presents data from an interim analysis conducted after 50 treatment discontinuations due to adverse events and/or death. At a median follow-up of 9.7 months, asciminib was associated with a significantly lower risk of treatment discontinuation due to adverse events compared with nilotinib (HR 0.45; 95% CI 0.25–0.81; p = 0.004). Overall, asciminib seemed to demonstrate superior tolerability compared with nilotinib, leading the authors to advocate for its use as a frontline therapy for newly diagnosed chronic-phase CML. A limitation of this analysis is that asciminib was only compared to nilotinib, rather than to all second-generation tyrosine kinase inhibitors, limiting the generalizability of the findings. As the study primarily focused on tolerability, it does not yet demonstrate an improvement in overall survival, underscoring the need for further long-term investigations to establish the full clinical benefit of asciminib in the first-line setting.

Essential thrombocythemia: Evaluation of INCA33989

Essential thrombocythemia (ET) is the second most common myeloproliferative neoplasm, yet its treatment remains largely nonspecific and is currently limited to hydroxyurea, anagrelide, and off-label interferon (4). In recent years, JAK inhibitors have introduced the possibility of targeting driver pathways. Unfortunately, JAK inhibitors failed to demonstrate clinical efficacy in ET in the

MAJIC-ET trial (5). These findings paved the way toward the search of novel therapeutic agents, including targeting alternative pathways.

In their work, J. Mascarenhas et al. evaluated INCA33989, a monoclonal antibody targeting mutant CALR (6). This first-in-human, open-label, dose-escalation study enrolled patients with high-risk CALR-mutated ET and therapy refractoriness and/or intolerance. 49 patients were included and received monoclonal antibody doses ranging from 24 mg up to 2500 mg intravenously every two weeks. Median treatment exposure was 22.6 weeks. No dose-limiting toxicities were identified, and serious treatment-emergent adverse events were only reported in 6.1% of the patients (n = 3). Those events were asymptomatic lipase increase (n = 1), visceral venous thrombosis (n = 1), and diverticulitis (n = 1). Thrombocytopenia was not observed amongst the studied population. Higher haematologic response was observed in patients receiving higher doses of treatment (doses ranging from 400 mg to 2500 mg). A reduction in the variant allele frequency (VAF) of mutated CALR was observed in 89% of evaluable patients with 47% of patients reaching a VAF reduction of over 20% and 21% of the patients reaching a VAF reduction of over 50%. These early-phase data suggest a good tolerability and efficacy of this new monoclonal antibody against mutated CALR, introducing a novel mutation-targeted approach for patients with ET. Further data and longer follow-up will have to assess the durability of responses, impact regarding thrombosis and cardiovascular risk, risk of transformation, and overall survival. □

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ESP 2025

Liquid Biopsy in the Clinic – My Highlights from the European Congress of Pathology 2025

In recent years, it has been evident that pathology is in a state of profound change. The advent of novel molecular and digital methods has influenced pathology substantially. This was also demonstrated at this year's European Congress of Pathology in Vienna, which took place under the motto «Tradition meets Future».

I would therefore like to give a brief insight into the session on liquid biopsy in solid tumors and introduce an exciting analysis method and its potential applications in Ewing sarcoma. This review has been adapted from a presentation given to the SCI Sarcoma Interest Group.

Liquid biopsy is a procedure that extracts molecular information from bodily fluids. Tumor cells release their molecular signature in various forms, whether as circulating tumor cells (CTCs), in exosomes, or as free DNA (circulating tumor DNA, ctDNA) after apoptosis. ctDNA is a part of cell-free DNA (cfDNA). The majority of cfDNA consists of leukocyte residues. Blood is typically used as the fluid for liquid biopsy, but other body fluids (e.g. pleural effusion, ascites, cerebrospinal fluid) can also be employed.

This «liquid» molecular tumor analysis has a wide range of applications, but includes mainly the analysis of mutational signatures, methylation, and changes in fragmentation.

The ease with which samples can be obtained also highlights their greatest advantage over traditional tissue biopsies: low invasiveness. In addition, multiple metastatic sites can be detected in their entirety, as can the reflection of a tumor's heterogeneity. On the other hand, ctDNA maybe completely absent or only present at low concentrations in liquid samples. This makes the samples very sensible and requires highly sensitive detection methods (e.g. digital droplet PCR, next-generation sequencing [NGS]). In addition, some analyses, such as fusion analyses, copy number variation (CNV), and tumor mutational burden (TMB), are more challenging. ctDNA levels can also vary greatly within and between tumor types. Consequently, the use of liquid biopsy is not yet widely adopted.

However, there are various established applications of liquid biopsies. Examples include ESR1 testing in breast cancer and resistance mutation testing in lung cancer.

Liquid biopsy is not yet widely used in soft tissue tumors. Ewing sarcoma is a tumor that develops in bones and soft tissues. It has a low mutational rate and highly fragmented DNA. Its detection in liquid biopsies proves difficult. Peneder et. al. developed a bioinformatic tool, called LIQUORICE, to detect ctDNA using fragmentation patterns. Interestingly, DNA methylation influences fragmentation patterns by affecting chromatin structure. Their developed algorithm uses epigenetic signals and fragmentation patterns for determining the tumor of origin. With this they were able to dis-

tinguish liquid biopsies from Ewing sarcoma patients from other sarcomas, quantify tumor burden, and track treatment response.

In summary, liquid biopsy is an exciting analytic method. Combining it with digital solutions opens up new possibilities for its broader application. □

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