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Targeted Cancer Therapy PERSPECTIVE

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Navigating the crossroads in gastric cancer therapy: New horizons and unresolved challenges

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Treatment of gastric cancer is rapidly evolving from conventional chemotherapy toward biomarker-guided care. In perioperative and metastatic settings, immunotherapy and treatments targeting HER2 and claudin 18.2 (CLDN18.2) have expanded therapeutic options, while antibody-drug conjugates, bispecific antibodies, and cellular therapies are reshaping later-line management. These advances also create challenges in patient selection, toxicity management, and treatment sequencing, particularly when biomarkers overlap or change during therapy. This perspective summarizes recent progress across the disease course and discusses the major unresolved questions in optimizing treatment strategies for gastric cancer.

Gastric cancer (GC) remains a major global health burden, particularly in East Asia. In recent years, its therapeutic landscape has expanded rapidly with immunotherapy, HER2-targeted treatment, claudin 18.2 (CLDN18.2)-directed therapies and other biomarker-guided approaches. Emerging modalities, including antibody-drug conjugates (ADCs), bispecific antibodies, and cellular therapies, are further broadening the therapeutic options. However, these advances have also increased the complexity of clinical decision-making. Here, we discuss recent progress and unresolved challenges in perioperative and metastatic GC. Figure 1 summarizes a biomarker-guided treatment algorithm across perioperative and metastatic GC.

PERIOPERATIVE TREATMENT: TOWARD BIOMARKER-SELECTED INTENSIFICATION

Early perioperative immunotherapy studies in GC were conducted largely in unselected populations. In KEYNOTE-585, the addition of pembrolizumab to perioperative chemotherapy improved pathological response but did not meet the prespecified thresholds for event-free survival (EFS) or overall survival (OS) benefit, whereas ATTRACTION-5 was negative in the adjuvant setting. A clearer positive signal emerged in 2025 with MATTERHORN, in which durvalumab added to perioperative fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) improved both EFS and OS over chemotherapy alone.[1] These mixed results likely reflect not only drug activity, but also differences in chemotherapy backbone, patient biology, and trial design.

In East Asia, FLOT has been less widely adopted than in Western practice, while doublet regimens such as S-1 plus oxaliplatin (SOX) and capecitabine plus oxaliplatin (XELOX) remain common perioperative backbones. Against this background, the phase III ASTRUM-006 study, published in 2026, evaluated neoadjuvant serplulimab plus SOX followed by adjuvant serplulimab in patients with PD-L1 CPS ≥5. The regimen improved EFS compared with perioperative chemotherapy alone and increased the pathological complete response (pCR) rate (21.6% vs 6.4%), without increasing severe treatment-related toxicity. These data support a biomarker-selected perioperative strategy and raise the possibility that postoperative chemotherapy intensity could be reduced in selected patients, although longer OS follow-up is needed to define the safest de-escalation strategy.[2]

In HER2-positive locally advanced GC, perioperative HER2-targeted therapy plus chemoimmunotherapy has also shown encouraging activity. In multicenter phase II studies, atezolizumab plus trastuzumab plus XELOX (in a randomized setting) and pembrolizumab plus trastuzumab plus FLOT (single-arm trial) produced pCR rates of approximately 40%. These promising findings support the clinical potential of perioperative HER2-directed chemoimmunotherapy and warrant further validation in phase III trials.

Despite recent progress, the optimal perioperative immunotherapy model in GC remains undefined. Current development has increasingly moved toward a sandwich strategy, with preoperative chemoimmunotherapy followed by postoperative systemic treatment. However, the optimal number of preoperative cycles, the duration of postoperative immunotherapy, and the need for postoperative chemotherapy remain unclear. The current evidence base is also uneven across biomarkers. Most perioperative immunotherapy data have been generated in biomarker-unselected or PD-L1-selected populations, predominantly in HER2-negative disease, whereas HER2-positive data are mainly from phase II HER2-directed chemoimmunotherapy studies and prospective CLDN18.2-positive perioperative data remain sparse. Benefit is therefore unlikely to be uniform across biological subsets. PD-L1 CPS ≥5 identifies a population more likely to benefit, and intestinal-type tumors may be more responsive to perioperative immunotherapy than diffuse-type adenocarcinoma. Whether CLDN18.2 targeting should be introduced preoperatively remains uncertain, as treatment-related gastric toxicity could affect nutritional status, surgical timing, and perioperative tolerance.

Response assessment and postoperative management also remain unresolved. Although pCR is an accepted surrogate in chemotherapy-based treatment, its value as a surrogate endpoint for long-term survival after immunochemotherapy remains unvalidated in gastric cancer. Whether patients with a clinical complete response could undergo less extensive surgery or modified lymphadenectomy requires further study. Postoperative liquid-biopsy assessment may refine risk stratification, but its role in guiding adjuvant treatment is not yet defined. Prospective studies should determine whether circulating tumor DNA (ctDNA)-guided escalation or de-escalation improves outcomes, when postoperative blood sampling should be performed, how long ctDNA positivity precedes radiographic relapse, and whether minimal residual disease (MRD) positivity should trigger a specific therapeutic intervention.

FIRST-LINE TREATMENT FOR METASTATIC GC

Redefining the HER2 paradigm: intensified HER2 blockade and ADC-based expansion

After ToGA established trastuzumab plus chemotherapy as first-line therapy, later studies, including LOGiC and JACOB, failed to deliver clear additional benefit. The field was reactivated by KEYNOTE-811,[3] which established pembrolizumab plus trastuzumab and chemotherapy as the current standard for HER2-positive GC with PD-L1 CPS ≥1. Translational studies further suggest that HER2-targeted therapy may enhance PD-1 blockade through immune remodeling, providing a mechanistic rationale for this combination strategy.

More recently, first-line HER2 development has moved in two related directions: intensified HER2 blockade and ADC-based expansion. HERIZON-GEA-01 evaluated zanidatamab, a biparatopic anti-HER2 antibody, with tislelizumab and chemotherapy. The regimen showed encouraging efficacy, but diarrhea requires active monitoring and early management. Steroid premedication is also a practical concern in chemoimmunotherapy, although available results have not indicated a major loss of immunotherapy efficacy. HLX22 represents another strategy, as it binds a distinct HER2 ECD4 epitope and can be paired with trastuzumab. After promising phase II activity, the phase III HLX22-GC-301 trial is evaluating HLX22 plus trastuzumab and XELOX versus trastuzumab and XELOX in the first-line setting, with pembrolizumab incorporated as an option in the control arm.

First-line HER2-directed ADCs may further expand options for tumors with heterogeneous HER2 expression, but they also raise sequencing and safety questions. For trastuzumab deruxtecan (T-DXd), interstitial lung disease and cumulative myelosuppression limit high-intensity combinations and support dose-optimized or platinum-sparing strategies. RC48, which uses a different payload and has shown activity across variable HER2 expression, is being

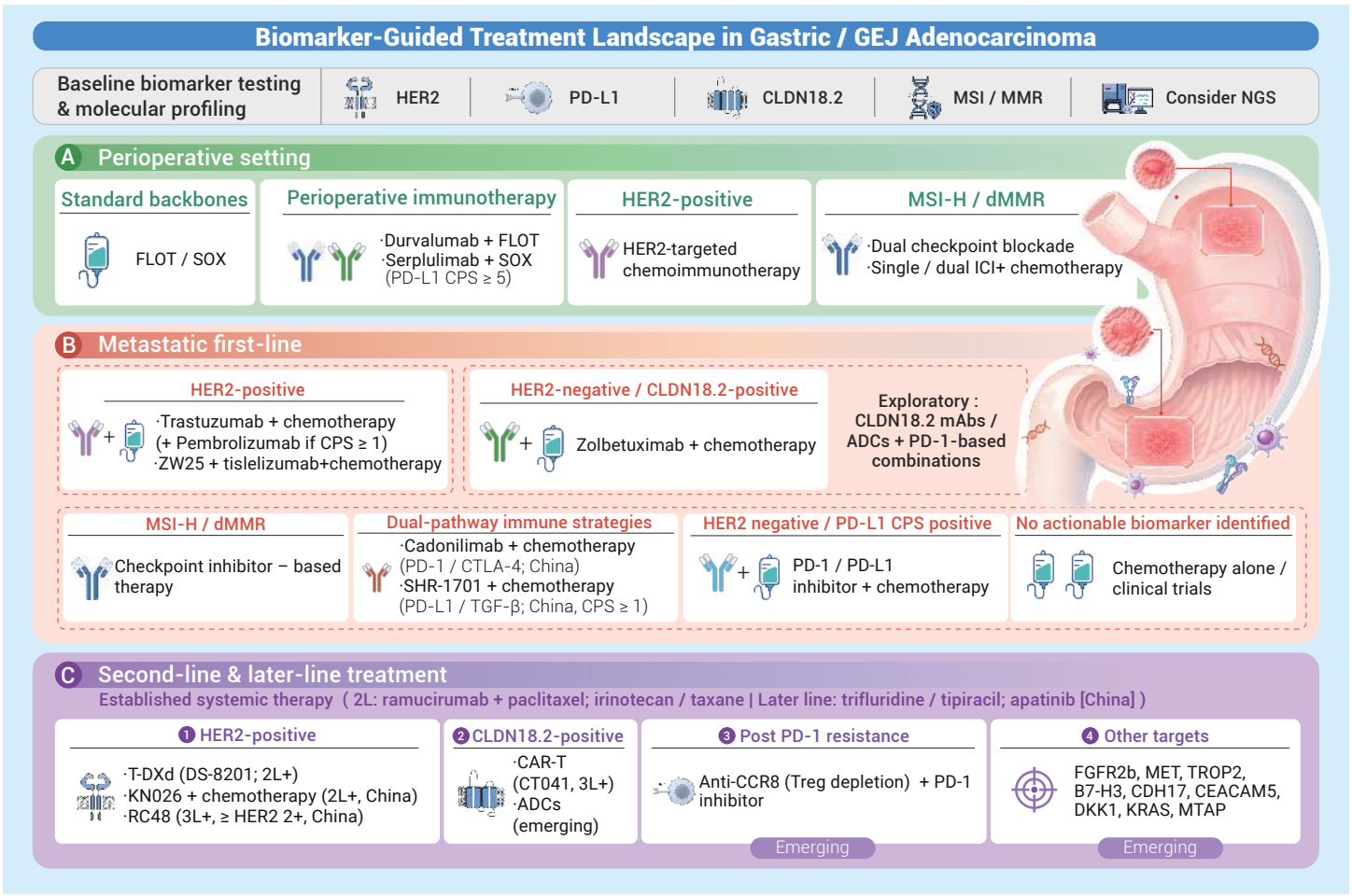

Figure 1. Biomarker-guided treatment algorithm for perioperative and metastatic gastric/gastro-oesophageal junction adenocarcinoma. HER2, human epidermal growth factor receptor 2; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; CPS, combined positive score; CTLA-4, cytotoxic T-lymphocyte-associated protein 4);TGF-β, transforming growth factor beta; CLDN18.2, claudin 18 isoform 2; MSI-H, microsatellite instability-high; dMMR, deficient mismatch repair; NGS, next-generation sequencing; 2L, second line; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel;SOX, S-1 plus oxaliplatin; DOS, docetaxel, oxaliplatin, and S-1; ADC, antibody-drug conjugate; TCE, T-cell engager; CAR-T, chimeric antigen receptor T-cell; T-DXd, trastuzumab deruxtecan; RC48, disitamab vedotin.

explored both as an alternative ADC and in combination with trastuzumab. These approaches suggest that ADCs may intensify, rather than simply replace, HER2 blockade in heterogeneous HER2-expressing tumors. ADC-immunotherapy combinations remain attractive, but their use will require careful balancing of efficacy, toxicity, chemotherapy backbone, and patient selection. After potent ADC-containing induction, prospective studies should define whether trastuzumab-based maintenance, immunotherapy maintenance in selected patients, or reduced-intensity combinations can preserve benefit while limiting toxicity.

CLDN18.2: synergistic strategies in a landscape of biomarker overlap

CLDN18.2 expression frequently overlaps with HER2 and PD-L1 positivity; in a recent European cohort, CLDN18.2-high expression was observed in 41.9% of HER2-positive tumors and 47.2% of tumors with PD-L1 CPS ≥5.[4] Such biomarker overlap complicates treatment selection and challenges a purely hierarchical approach to target prioritization. Although SPOTLIGHT and GLOW demonstrated survival benefit and have supported the incorporation of zolbetuximab into clinical practice, the similar objective response rates between zolbetuximab plus chemotherapy and chemotherapy alone (GLOW: 42.5% vs 40.3%; SPOTLIGHT: 48.1% vs 47.5%) indicate that its incremental value should be interpreted alongside contemporary chemoimmunotherapy and biomarker overlap.[5]

In this context, combining CLDN18.2-targeted agents with immunotherapy and chemotherapy may represent a more effective strategy. Early-phase studies have provided preliminary support for this combinatorial approach, with CLDN18.2 monoclonal antibodies (e.g., zolbetuximab, osemitamab), CLDN18.2×4-1BB bispecific antibodies (e.g., givastomig), and CLDN18.2-directed ADCs (e.g., JS107) showing encouraging activity when added to chemoimmunotherapy.

However, on-target gastrointestinal toxicities, including nausea, vomiting, and protein loss, particularly in patients who have not undergone gastrectomy, may compromise nutritional status, increase susceptibility to infection, and limit treatment tolerance. These toxicities could constrain the feasibility of intensive combinations and necessitate close multidisciplinary management.

Immunotherapy: bispecific agents beyond conventional PD-1 blockade

For HER2-negative advanced GC, phase III trials have established chemoimmunotherapy as a first-line standard.[6] However, benefit is limited in PD-L1 CPS-low disease and tends to be less pronounced in patients with liver or peritoneal metastases. In current practice, PD-1-based chemoimmunotherapy is generally considered for patients with PD-L1 CPS ≥1.

These limitations have strengthened interest in next-generation bispecific agents that may broaden immune activation through dual-pathway blockade. COMPASSION-15 showed that cadonilimab (PD-1/CTLA-4) plus chemotherapy improved survival in an unselected population. Similarly, the PD-L1/TGF-β fusion protein SHR-1701 improved survival in patients with PD-L1 CPS ≥1. Notably, SHR-1701 was associated with lower incidences of severe chemotherapy-related thrombocytopenia (grade ≥3, 19.0% vs 28.1%) and neutropenia (grade ≥3, 12.1% vs 16.4%), suggesting clinically meaningful mitigation of hematologic toxicity. Favorable signals in clinically difficult subgroups, including patients with peritoneal metastases, further support focused evaluation of dual-pathway strategies. However, because these studies used chemotherapy-only control arms, the value of bispecific or dual-pathway regimens relative to current PD-1-based chemoimmunotherapy remains uncertain. Head-to-head comparisons against contemporary chemoimmunotherapy will be needed to define their incremental clinical value.

SECOND-LINE AND LATER-LINE TREATMENT: EVOLVING STANDARDS AND NOVEL MODALITIES

HER2-positive

In HER2-positive disease, the phase III DESTINY-Gastric04 trial has moved HER2-directed ADC therapy from the third-line setting into second-line treatment.[7] T-DXd outperformed ramucirumab plus paclitaxel, prolonging median OS (14.7 vs 11.4 months; HR 0.70) and increasing ORR from 29.1% to 44.3%. The phase III KC-WISE study also showed that the bispecific antibody KN026 plus chemotherapy improved survival after prior trastuzumab treatment compared with chemotherapy alone. Together, these data establish T-DXd and KN026 as key second-line options for HER2-positive GC. Several ADCs, including SHR-A1811, BL-M07D1, and the EGFR/HER3-directed BL-B01D1, are now being evaluated in phase III trials.

CLDN18.2-positive

For CLDN18.2-positive disease, the incorporation of monoclonal antibodies into first-line treatment has shifted later-line development toward therapeutic modalities with distinct administration approaches, including ADCs, T-cell engagers (TCEs), and cellular therapy. Early-phase studies of ADCs (e.g., IBI343, SHR-A1904, and SKB315) and TCEs (e.g., ASP2138 and IBI389) have demonstrated efficacy in heavily pretreated patients. The phase II CT041-ST-01 trial further showed that satri-cel improved median progression-free survival (3.25 vs 1.77 months; HR 0.36) over physician's choice therapy in patients with CLDN18.2-positive GC after failure of standard treatment.[8]

Two practical questions may be more informative than a single CLDN18.2 positivity cut-off. As treatment expands from monoclonal antibodies to ADCs, TCEs and CAR-T cells, biomarker requirements will probably differ by modality. Patient selection should therefore consider antigen intensity, spatial heterogeneity and the therapeutic window of each platform, rather than relying on one uniform immunohistochemistry threshold. When feasible, reassessment at progression may help distinguish target persistence from antigen loss or patchy residual expression, particularly when selecting among subsequent ADCs, TCEs and cellular therapies. The second question is how to position cellular therapy. For satri-cel, efficacy has been shown, but the patients most likely to achieve durable benefit remain to be defined. Future selection should integrate CLDN18.2 expression with disease burden, immune context, T-cell fitness and lymphodepletion strategy to balance efficacy with tolerability.

Immunotherapy-based strategies after prior PD-1/PD-L1 blockade

Reversing resistance following PD-1/PD-L1 blockade remains a major challenge. Current strategies can be grouped into two broad approaches. One involves augmenting immunotherapy with antiangiogenic agents; triplet regimens combining checkpoint inhibitors such as cadonilimab or adebrelimab with chemotherapy and antiangiogenic agents have shown encouraging results. The other approach targets alternative immunosuppressive pathways. For instance, early data with the anti-CCR8 antibody LM-108 suggest that targeting intratumoral regulatory T cells (Tregs) may help overcome resistance to PD-1/PD-L1 blockade, particularly in tumors with high CCR8 expression. Further progress will depend on defining the dominant mechanism of resistance and matching treatment accordingly.

Other targets

Beyond HER2, CLDN18.2, and immunotherapy-based combinations, the later-line pipeline continues to expand. The TROP2-directed ADC SKB264 has shown encouraging activity and is now being evaluated in phase III trials. Targeted strategies against established oncogenic drivers, including MET amplification and KRAS alterations, are also advancing. Although FGFR2b-targeted monoclonal antibodies failed to improve outcomes in the first-line setting, FGFR2b-directed ADCs are now being explored as a potential alternative strategy. In addition, early-phase trials are investigating other novel surface antigens (e.g., CEACAM5, CDH17, B7-H3), tumor microenvironment modulators (e.g., DKK1), and synthetic lethal strategies targeting MTAP deletions. Mature clinical data from these ongoing investigations will be needed to define their clinical value.

FUTURE PERSPECTIVES

In summary, further progress in GC will depend not only on adding treatment options, but also on selecting patients, timing intensification or de-escalation, and sequencing therapies as resistance emerges. Static, single-marker frameworks are unlikely to answer these questions. Future biomarker strategies should combine conventional immunohistochemistry thresholds with spatial immune architecture, tertiary lymphoid structures, ctDNA dynamics, microbiome features and quantitative antigen assessment.[9,10]

In the perioperative setting, ctDNA-guided decision-making represents a practical opportunity for risk-adapted treatment. Prospective trials should test whether ctDNA clearance after neoadjuvant therapy can identify patients suitable for reduced adjuvant treatment and whether persistent ctDNA positivity should trigger intensification. In metastatic disease, modality-specific biomarkers will become increasingly important as ADCs, bispecific antibodies and cellular therapies move into earlier-line settings. CLDN18.2-directed treatment may require antigen-density and spatial-heterogeneity metrics, while HER2-directed ADCs may require quantitative HER2 assessment. Ultimately, drug development and biomarker qualification should proceed together, so that intensification, combination and sequencing strategies are guided by tumor biology rather than broad treatment categories.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used OpenAI Codex to assist with language editing and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

REFERENCES

1. Janjigian Y.Y., Al-Batran S.-E., Wainberg Z.A., et al. (2025). Perioperative durvalumab in gastric and gastroesophageal junction cancer. *N. Engl. J. Med.* **393**:217–230. DOI:10.1056/NEJMoa2503701
2. Shen L., Zhang X., Ji K., et al. (2026). Perioperative serplulimab with neoadjuvant chemotherapy versus perioperative chemotherapy in PD-L1-positive gastric cancer (ASTRUM-006): A randomised, double-blind, multicentre, phase 3 study. *Lancet* **407**:2542–2553. DOI:10.1016/S0140-6736(26)00974-8
3. Janjigian Y.Y., Kawazoe A., Bai Y., et al. (2023). Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: Interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial. *Lancet* **402**:2197–2208. DOI:10.1016/S0140-6736(23)02033-0
4. Teran E., Pazo R., Carita L., et al. (2026). Claudin 18.2 expression in gastroesophageal adenocarcinoma: biomarker overlap and association with clinical outcomes in a European cohort. *ESMO Open* **11**:106053. DOI:10.1016/j.esmoop.2025.106053.
5. Shitara K., Lordick F., Bang Y.-J., et al. (2023). Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): A multicentre, randomised, double-blind, phase 3 trial. *Lancet* **401**:1655–1668. DOI:10.1016/S0140-6736(23)00620-7.
6. Rha S.Y., Oh D.-Y., Yanez P., et al. (2023). Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): A multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol.* **24**:1181–1195. DOI:10.1016/S1470-2045(23)00515-6
7. Shitara K., Van Cutsem E., Gumus M., et al. (2025). Trastuzumab deruxtecan or ramucirumab plus paclitaxel in gastric cancer. *N. Engl. J. Med.* **393**:336–348. DOI:10.1056/NEJMoa2503119
8. Qi C., Liu C., Peng Z., et al. (2025). Claudin-18 isoform 2-specific CAR T-cell therapy (satri-cel) versus treatment of physician's choice for previously treated advanced gastric or gastro-oesophageal junction cancer (CT041-ST-01): A randomised, open-label, phase 2 trial. *Lancet* **405**:2049–2060. DOI:10.1016/S0140-6736(25)00860-8
9. Jia K., Chen Y., Dai D., et al. (2026). Impact of Helicobacter pylori infection on gut and intratumoral microbiome and its association with immunotherapy response in gastrointestinal cancer. *BMC Med.* **24**:79. DOI:10.1186/s12916-025-04575-0
10. Jia K., Chen Y., Xie Y., et al. (2023). Multidimensional immune profiling in Gastric Cancer Multiplex Immunohistochemistry Atlas from Peking University Cancer Hospital project informs PD-1/PD-L1 blockade efficacy. *Eur. J. Cancer* **189**:112931. DOI:10.1016/j.ejca.2023.05.019

AUTHOR CONTRIBUTIONS

Zhao Jin, Xi Jiao, Tong Xie, and Lin Shen contributed to the conceptualization, literature review, drafting, and revision of the manuscript. Lin Shen supervised the work and provided critical intellectual input. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

Lin Shen is an Editorial Board member of *The Innovation Oncology* and was blinded from reviewing or making final decisions on the manuscript. Peer review was handled independently of this member and their research group. The other authors report no conflict of interest.