Immunotherapy and Targeted Therapy: New Data from ASCO 2026

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> The optimal integration of immunotherapy and targeted therapy remains a critical question in oncology, particularly for patients who do not respond to initial treatments. Recent presentations at ASCO 2026 highlight advancements in combination strategies for advanced gastric adenocarcinoma and EGFR-mutated NSCLC, alongside a novel machine learning framework for identifying immunotherapy drug targets.

KEY TAKEAWAYS

- The Pivot: Machine learning is now identifying novel immunotherapy targets, potentially bypassing resistance mechanisms.
- The Data: Tislelizumab plus chemotherapy demonstrated a median overall survival of 15.0 months versus 12.9 months with placebo plus chemotherapy in advanced gastric cancer.2
- The Action: Clinicians should consider combination strategies, particularly in advanced gastric cancer, and monitor for emerging targeted therapy options in NSCLC post-osimertinib progression.

Immunotherapy has transformed cancer treatment, yet a substantial proportion of patients do not achieve a clinical response. This necessitates the exploration of alternative strategies, including novel immuno-oncology targets and combination regimens, to overcome resistance to standard therapies.1,2,3 Despite significant advances with immune checkpoint inhibitors, primary and acquired resistance remains a major challenge, highlighting the need for a deeper understanding of tumor immunology and the development of predictive biomarkers and new therapeutic targets. The complexity of the tumor microenvironment and the diverse mechanisms of immune evasion contribute to this resistance, prompting research into multi-modal approaches.1,2,3

What the studies did

A multimodal graph neural network system, Mining Immunotherapy Drug tArgetS (MIDAS), was developed for immuno-oncology target discovery. MIDAS integrates gene interactions, multi-omic patient profiles, immune cell biology, antigen processing, disease associations, and phenotypic consequences of genetic perturbations.1 The system demonstrated generalizability to time-sliced data, outperforming existing baselines like OpenTargets, and accurately ranked approved targets above those in clinical development.1 MIDAS also identified immunotherapy-response-associated genes in unseen patients, indicating its ability to capture determinants of immunotherapy response.1 Interpretability analyses revealed MIDAS's reliance on autoimmunity, regulatory networks, and immuno-oncology pathways.1 Functional perturbation of oncostatin M-oncostatin M receptor signaling, a target proposed by MIDAS, in TRACERx melanoma-patient-derived explants, resulted in reduced dysfunctional CD8+ T

cells, which are associated with immunotherapy response, and decreased CCL4 levels.1 Oncostatin M and oncostatin M receptor expression correlated with altered T cell and macrophage profiles in bulk transcriptomic data from patient samples, consistent with a role in modulating the tumor microenvironment towards immunosuppressive, tumor-promoting phenotypes.1 The MIDAS framework leveraged a comprehensive dataset including genomic, transcriptomic, and proteomic data from various cancer types, alongside detailed immune cell characterization, to build a robust predictive model for target identification. This integration allowed for a holistic view of the biological processes underlying immunotherapy response and resistance.1

In advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma, a post-hoc analysis of the RATIONALE-305 study investigated tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment.2 This analysis included patients with or without peritoneal metastases.2 Gastric and GEJ adenocarcinoma represent a significant global health burden, often diagnosed at advanced stages with poor prognosis. Standard first-line treatment typically involves chemotherapy, but the addition of immune checkpoint inhibitors has shown promise. Tislelizumab is a humanized anti-PD-1 monoclonal antibody designed to minimize FcγR binding to macrophages, potentially enhancing its anti-tumor activity.2 The RATIONALE-305 study was a global, randomized, double-blind, placebo-controlled phase 3 trial evaluating the efficacy and safety of tislelizumab plus chemotherapy. The post-hoc analysis specifically aimed to understand the treatment effect in a broader patient population, including those with peritoneal metastases, a subgroup often associated with particularly aggressive disease and limited treatment options.2

For patients with EGFR-mutated advanced non-small cell lung cancer (NSCLC) who progressed on first-line osimertinib, the ORCHARD study evaluated the combination of osimertinib plus selumetinib in those with BRAF alterations.3 EGFR-mutated NSCLC is a distinct subtype, and while EGFR tyrosine kinase inhibitors (TKIs) like osimertinib are highly effective initially, resistance inevitably develops. BRAF alterations, though less common, can emerge as a mechanism of acquired resistance to EGFR TKIs. Selumetinib is a MEK inhibitor, and the rationale for this combination therapy is to target parallel or downstream signaling pathways that contribute to resistance, thereby overcoming the limitations of single-agent therapy. The ORCHARD study was designed as a multi-cohort, open-label, phase 1b/2 study, exploring various combination strategies for patients who had progressed on first-line osimertinib. This specific cohort focused on patients with identified BRAF alterations.3

Key Findings

The MIDAS framework presents a machine learning approach for analyzing multimodal data to discover immuno-oncology targets.1

In the RATIONALE-305 post-hoc analysis, tislelizumab plus chemotherapy demonstrated a median overall survival (OS) of 15.0 months (95% CI, 13.0-16.9) compared to 12.9 months (95% CI, 11.1-14.3) for placebo plus chemotherapy (HR, 0.77; 95% CI, 0.65-0.92; P=0.004).2 The objective response rate (ORR) was 46.3% (95% CI, 41.6-51.0) with tislelizumab plus chemotherapy versus 35.0% (95% CI, 30.5-39.7) with placebo plus chemotherapy.2 The median progression-free survival (PFS) was 6.9 months (95% CI, 6.1-7.9) versus 5.6 months (95% CI, 5.4-6.0) (HR, 0.70; 95% CI, 0.59-0.83; p<0.001).2 These results suggest that the addition of tislelizumab to chemotherapy provides a clinically meaningful survival benefit for patients with advanced gastric or GEJ adenocarcinoma, including those with peritoneal metastases, a population historically associated with poor outcomes.2

The ORCHARD study explored osimertinib plus selumetinib in EGFR-mutated advanced NSCLC patients with BRAF

alterations after progression on first-line osimertinib.3 Specific efficacy data for this combination in this subgroup were not detailed in the provided abstract, but the study design addresses a critical unmet need in resistance mechanisms to EGFR TKIs.3 The study aimed to evaluate the safety and preliminary efficacy of this targeted combination in a difficult-to-treat population, seeking to overcome acquired resistance.3

Limitations & Next Steps

The MIDAS study is a computational framework validated with patient-derived explants; further clinical validation in human trials is required to confirm the efficacy of targeting oncostatin M-oncostatin M receptor signaling.1 While the use of patient-derived explants provides a more physiologically relevant model than cell lines, it does not fully replicate the complex in vivo tumor microenvironment and systemic immune responses. Therefore, prospective clinical trials are essential to translate these computational findings into actionable therapeutic strategies.1 The RATIONALE-305 data on gastric/GEJ adenocarcinoma is a post-hoc analysis, which may be subject to selection bias and confounding, and prospective studies are needed to confirm these findings in specific subgroups, such as those with peritoneal metastases.2 While post-hoc analyses can generate hypotheses, their retrospective nature limits definitive conclusions regarding efficacy in specific subgroups. Future randomized controlled trials specifically designed to evaluate immunotherapy in patients with peritoneal metastases would provide stronger evidence.2 The ORCHARD study abstract did not provide specific outcome data, limiting the ability to assess the clinical utility of osimertinib plus selumetinib in the described patient population.3 The absence of detailed efficacy metrics, such as ORR, PFS, or OS, prevents a comprehensive evaluation of the clinical benefit of this combination therapy. Further publications detailing these outcomes are anticipated to fully understand the potential role of this regimen in managing resistance to EGFR TKIs.3

CLINICAL IMPLICATIONS

The integration of machine learning into drug discovery, as exemplified by the MIDAS framework, represents a significant shift in how novel immunotherapy targets are identified. While the functional perturbation of oncostatin M-oncostatin M receptor signaling in explants is promising, the leap from computational prediction and ex vivo validation to clinical efficacy in patients remains substantial. Clinicians should view such advancements as foundational research, requiring rigorous clinical trials before impacting practice. The precision offered by these computational tools, however, could streamline the drug development pipeline, potentially bringing more targeted immunotherapies to market faster.

For patients with advanced gastric or gastroesophageal junction adenocarcinoma, the RATIONALE-305 post-hoc analysis provides further evidence for the benefit of tislelizumab plus chemotherapy as a first-line option. A median overall survival advantage of 2.1 months, with a hazard ratio of 0.77, is clinically meaningful in this aggressive disease. This data supports the continued adoption of checkpoint inhibitors in combination with chemotherapy for this patient population, aligning with current trends in gastrointestinal oncology. However, the post-hoc nature means these results should be interpreted with appropriate caution, particularly when considering specific subgroups like those with peritoneal metastases.

The ORCHARD study's focus on EGFR-mutated NSCLC with BRAF alterations post-osimertinib progression highlights the ongoing challenge of acquired resistance to targeted therapies. The strategy of combining osimertinib with selumetinib, a MEK inhibitor, addresses a known resistance pathway. While specific efficacy data were not provided in the abstract, the premise of targeting parallel or downstream pathways to

> overcome resistance is a rational approach. This underscores the need for comprehensive genomic profiling at progression to guide subsequent treatment decisions, moving beyond single-agent strategies to more complex, tailored combinations.

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