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Editorial: Beyond chemotherapy and immunotherapy in thoracic malignancies: Overcoming resistance by tackling new molecular pathways

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Editorial on the Research Topic

Beyond chemotherapy and immunotherapy in thoracic malignancies: Overcoming resistance by tackling new molecular pathways

Chemotherapy and immunotherapy, administered sequentially or concurrently, represent the current standard of care for most patients with advanced non-small-cell lung cancer (NSCLC) and other thoracic malignancies (1). However, even when administered as a combination in first-line treatment of NSCLC, chemoimmunotherapy confers a median progression-free survival (PFS) of approximately 8-10 months and a median overall survival that falls below two years in both squamous and nonsquamous histologies (2–6). Immune checkpoint inhibitors (ICIs) administered as monotherapy in selected patients with high programmed-death ligand 1 (PD-L1) expression achieve better outcomes that, nevertheless, confer long-term responses only in a minority of patients (7–9).

Patients with advanced NSCLC who progress after chemoimmunotherapy, given either concurrently or sequentially, currently have limited treatment options. Second-line chemotherapy with docetaxel, administered alone or in combination with anti-angiogenic agents (ramucirumab, nindetanib), offers modest clinical outcomes (10, 11). ICIs given as monotherapy have been proven superior to docetaxel in patients progressing after first-line chemotherapy (12–15). Recent advances in elucidating the molecular biology of the disease have led to the identification of molecular pathways that could be exploited therapeutically in an effort to improve outcomes by overcoming resistance to immunotherapy and chemotherapy (1). The patterns of resistance to immunotherapy

have been extensively studied and may involve primary or secondary resistance as well as intrinsic and extrinsic mechanisms encompassing diverse molecular pathways (16). Consequently, potential strategies to overcome acquired resistance may include, among others:

-Combinations of immune checkpoint-modifying agents that either inhibit suppression of immune cells (antagonists) or activate the immune system (agonists). Examples include the synergistic activity of PD-(L) 1 inhibitors with anti-CTLA4 or anti-TIGIT monoclonal antibodies, as well as the combination with agonists of immune activation, such as OX-40 monoclonal antibodies (17)

- Combinations of ICIs with molecular targeted agents, such as tyrosine kinase inhibitors, that interfere with diverse molecular pathways, including cellular proliferation, apoptosis regulation, inflammation, DNA repair, epigenetic modification and angiogenesis. Metabolic pathways that are often associated with immune regulation involve the mitogen-activated protein kinase (MAPK), the phosphatidyl-inositol -3-kinase (PI3K) and the signaling transducer and activator of transcription (STAT) molecular pathways (18)

- Biotechnological advances have enabled the clinical development of novel molecules with unique properties, such as antibody-drug conjugates and bi-specific antibodies, that may act as "engagers" of the immune system to cancer cells, triggering thus the anti-tumor activity of the immune system against neoantigens (19, 20)

- Finally, the role of the tumor microenvironment and the identification of potential biomarkers of activity/resistance to novel treatment strategies is currently a field of active investigation to enhance anti-tumor immunity by studying the interaction of the tumor cells with the stroma and the surrounding host niche (21)

In the current Research Topic of *Frontiers*, we present eight (8) high-quality articles that evaluate the strategies above to tackle resistance to chemo-immunotherapy. Bie et al. comprehensively reviewed anti-PD-1/PD-L1 immunotherapy-related mechanisms, drug resistance-related mechanisms, and therapeutic efficacy-related predictive biomarkers. Zhang et al. studied the Effect of the Extracellular Superoxide Dismutase (SOD3) Gene in Lung Cancer, revealing its prognostic value, while Wu et al described a novel gene, *SPTBN2*, which is highly expressed in lung adenocarcinoma, positively correlates with poor prognosis, and can promote the proliferation, migration, and invasion of lung adenocarcinoma cells. Yuan et al. evaluated the DNA epigenetic methylation modification pattern of patients with lung adenocarcinoma, which could enhance our understanding of the features of tumor microenvironment characterization and may promote more favorable immunotherapy strategies for these patients. In a pivotal phase I/II study, Kim et al. showed the feasibility and preliminary signs of efficacy of the combination of Dasatinib and Osimertinib in TKI-naïve patients with advanced EGFR-mutant NSCLC, suggesting a synergistic effect for EGFR and SRC inhibition in this setting. In an exploratory study, Schneider et al. tested various Acute Phase Proteins as Early Predictors for Immunotherapy Response in Advanced NSCLC. They concluded that higher pre-therapeutic levels of haptoglobin and ceruloplasmin are independent predictors of a worse PFS. Suo et al. studied the effect of prior ant-angiogenic agents on the efficacy of anlotinib in patients with NSCLC and concluded that it might negatively affect the PFS. Finally, Frisone et al. summarized the definitions of resistance to immunotherapy and examined its underlying mechanisms and potential corresponding treatment strategies by focusing on recently published clinical trials and trials that are expected to deliver results soon.

Discovering ways and strategies to overcome resistance to immunotherapy, chemotherapy and targeted agents is a constantly evolving research field. In this ever-lasting scientific endeavor, the only road to successful outcomes passes through sound scientific ratiional, robust pre-clinical experimentation and well-designed and executed clinical trials. The algorithmic use of potent biomarkers, including liquid biopsies, will likely assist in identifying the subgroups of patients who will benefit the most from each experimental strategy. The collective goal of these strategies will be to implement individualized treatment approaches after chemotherapy and immunotherapy failure, based on the unique biological characteristics and mechanisms of primary or acquired resistance for each one of our patients. This personalized approach paves the way for precision oncology, which is the optimal strategy to improve the lives of our patients.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

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