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Targeting DLL3 in Small-Cell Lung Cancer with Novel Modalities

J.T. Poirier New York University Langone Health, New York, NY/US

Delta-like ligand 3 (DLL3) is single-pass transmembrane Notch ligand that interacts with full-length, unprocessed NOTCH1 in the Golgi apparatus, inhibiting the pathway in cis. DLL3 is selectively overexpressed in the subtype of small-cell lung cancer (SCLC) driven by the transcription factor ASCL1 (SCLC-A) that accounts for 70% percent of diagnoses (95% CI [60–79]) (1). In one study immunoreactivity was observed in 1,040/1,363 (70.4%) of SCLC specimens, consistent with this incidence (2). Overexpression of DLL3 leads to low-level cell surface expression of the protein on the order of 10,000 proteins per cell while expression in normal tissues is restricted to intracellular compartments: the same study demonstrated only low to moderate cytoplasmic or nuclear immunoreactivity in normal adult tissues (3). High expression of DLL3 has also been reported in low-grade glioma (4,5), neuroendocrine prostate (6), and occasionally in other cancer types when neuroendocrine features are present (7,8). The exclusively selective expression of surface DLL3 on cancer cells presents an excellent target for a variety of therapeutic strategies. Rovalpituzumab tesirine (Rova-T; SC161D6.5) is an antibody-drug conjugate consisting of a monoclonal antibody targeting DLL3, a cathepsin-cleaving linker, and a pyrrolobenzodiazepine (PBD) warhead (4). The first-in-human clinical trial of Rova-T in recurrent SCLC demonstrated encouraging activity despite often severe side effects attributable to the PBD warhead (9); however, the phase 2 TRINITY study showed a disappointing 16% objective response rate while reporting a similar toxicity profile (NCT02674568). Subsequently, the phase 3 TAHOE study was halted due to shorter overall survival in the treatment arm. A phase 3 trial of Rova-T in the maintenance setting (MERU) was terminated at the interim analysis due to lack of survival benefit (NCT03033511). AbbVie has discontinued development of Rova-T. Other DLL3-targeting strategies under active investigation include the bispecific T-cell engager (BITE) AMG757 (NCT03319940) and a chimeric antigen receptor CAR-T AMG119 (NCT03392064). These agents have shown significant antitumor activity in preclinical models of SCLC; however, AMG119 required direct delivery of the engineered T cells for activity. AMG575 was therefore the more potent of the two molecules and may be better suited to overcome known barriers to CAR-T activity in solid tumors. Alternative strategies remain under exploration including the use of 89Zr-SC16, a PET radiotracer, for in vivo imaging and as a companion diagnostic to optimize the selection of patients for treatment with DLL3-directed therapeutic agents. 89Zr-labeled-SC16 antibody successfully delineated normal tissue from subcutaneous and orthotopic SCLC xenografts. Radiotracer accumulation in tumors was directly correlated with the degree of DLL3 expression and also correlated with response to SC16LD6.5 therapy in SCLC patient-derived xenograft models. On the basis of these preclinical results, an investigator-initiated first-in-human phase 1/2 clinical trial of 89Zr-SC16 was recently opened to determine the safety and feasibility of immunoPET imaging of DLL3 in patients with small-cell lung cancer. References: 1. Rudin CM et al. Molecular subtypes of small cell lung cancer: A synthesis of human and mouse model data. Nat Rev Cancer 2019;19:289-97, https://doi.org/10.1038/s41568-019-0133-9. 2. 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IA25
Adaptive Determinants of Metastatic Progression in Lung Adenocarcinoma

S. Adua, E. Wingrove, K. Patel, Z. Liu, D. Nguyen Yale School of Medicine, New Haven, CT/US

The central nervous system (CNS) is a major site of treatment refractory metastases from lung cancers, yet deciphering the mechanisms of brain relapse remains a challenge because of the complexity of the brain tumor microenvironment (TME) and the perceived pharmacologic limitations of systemic therapies. To define the molecular landscape of brain metastases in situ, we developed a bulk RNA sequencing-based approach (BMX-seq), which leverages the transcriptome of tumor xenografts and effectively distinguishes tumor cell and stromal gene expression with increased accuracy and sensitivity. BMX-seq analysis was also integrated with single-cell profiling of distinct metastasis cell populations. In models of metastatic non-small cell lung cancer, we demonstrate that tumor cells in the brain exhibit an enhanced capacity for resistance to targeted therapies, despite strong brain penetration of drug. Accordingly, BMX-seq reveals shifts in cytoskeletal signaling, metabolic stress, and neuronal-like lineage programs in tumor cells as they adapt to the TME and the reciprocal neuroinflammatory response of the stroma. Several transcriptional hallmarks of metastasis are identified that are specific to particular regions of the brain and confirmed in syngeneic models and patient biopsies. Finally, certain epigenetic alterations can be reversed, while others are features of selected tumor cell populations. Despite recent improvements in the pharmacologic properties of targeted therapies, drug resistance in the CNS still develops. Our results suggest that adaptive epigenetic responses to the brain TME not only promote malignant outgrowth but also precondition disseminated tumor cells for subsequent therapeutic responses.

IA26
Stage-Specific Roles of RB Constrain Tumor Progression, Lineage Fidelity, and Metastasis

D.M. Feldser University of Pennsylvania, Philadelphia, PA/US

Mutations in the Rb tumor suppressor pathway are a hallmark of cancer and a prevalent feature of lung adenocarcinoma. Additionally, recent clinical successes with cyclin-dependent kinase inhibitors have reinvigorated interest in reactivating the Retinoblastoma (Rb) pathway to treat lung adenocarcinoma and other tumor types. Remarkably, though, Rb’s role in suppressing lung adenocarcinoma remains unclear and whether Rb pathway...