addition of isolated human immune cells (PBMCs) significantly enhanced [NJ]-372-mediated EGFR and cMet downregulation, and dose-dependent tumor cell killing. Through depletion or enrichment of specific immune cell types, we demonstrated that monocytes and/or macrophages are necessary and sufficient for [NJ]-372 Fc interaction-mediated EGFR/cMet downmodulation and that macrophages are required for in vivo efficacy. Finally, through imaging studies tracking labeled [NJ]-372, we visualized monocyte/macrophage-mediated trogocytosis. Collectively, these data demonstrate a novel Fc-dependent mechanism of action of [NJ]-372 and support the continued clinical development in patients with aberrant EGFR and cMet signaling.

B04 Activity of Larotrectinib in Tropomyosin Receptor Kinase Fusion Lung Cancer


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Background: Tropomyosin receptor kinase (TRK) fusions involving neurotrophic receptor tyrosine kinase (NTRK)1, NTRK2, and NTRK3 genes occur in a range of tumor types. Larotrectinib, the first FDA-approved highly selective TRK inhibitor, has demonstrated an overall response rate (ORR) of 75% by independent central review across a broad spectrum of tumors that harbor NTRK gene fusions (Drilon et al., NEJM 2018;378:731–9). Here we report updated data on the lung cancer patients who have been treated with larotrectinib.

Methods: Patients with non-small cell lung cancer (NSCLC) from two clinical trials (NCT02122913 and NCT02576431) with TRK fusion cancer were included in this analysis. Larotrectinib (100 mg, twice daily) was administered on a continuous 28-day schedule until withdrawal, unacceptable toxicity, or disease progression. Here we report responses assessed by investigator (INV) per RECIST v1.1. Results: As of February 19, 2019, 12 patients with metastatic lung adenocarcinoma were enrolled. Median age was 49 years (range 25–76). Nine patients had fusions involving NTRK1 and diverse fusion partners: TPM3 (n=2), SQSTM1 (n=1), IRF2BP2 (n=2), TPR (n=1), CD74 (n=1), and EPS15 (n=2). Three patients had fusions involving NTRK3 (fusion partner: SQSTM1 [n=2] and ETV6 [n=1]). Eleven patients had prior systemic therapy (six patients had three or more prior therapies) with best responses on last prior treatment due to disease progression and one discontinued due to disease progression in non-target lesion. Larotrectinib was well tolerated, with treatment-related adverse events being predominantly grade 1–2. Conclusions: Larotrectinib is highly active in patients with advanced lung cancer harboring NTRK gene fusions, including those with central nervous system metastases, with a favorable safety profile. These results support the use of larotrectinib in TRK fusion lung cancer.

B05 Identifying SCLC Vulnerabilities Using Phenotypic Chemical Screens

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Small-cell lung carcinoma (SCLC) is an aggressive neuroendocrine cancer in which few actionable mutations have been uncovered in the last 30 years. With the goal of identifying chemically tractable proteins essential for SCLC viability, our lab has performed a phenotypic high-throughput small-molecule screen (HTS) in collaboration with the UTSW HTS Core Facility using a library of 200,000 drug-like compounds. We used a SCLC cancer cell line derived from a p53; Rb1 genetically engineered mouse model that recapitulates cardinal features of the human disease. By counter-screening against a panel of murine cancer cell lines (NSCLC, papillary thyroid cancer, and rhabdomyosarcoma), we identified 51 SCLC-selective toxins exhibiting at least 5-fold selectivity for SCLC cancer cells compared to the panel of non-SCLC cell lines. We hypothesized that identifying the target of these molecules will allow the discovery of important vulnerabilities for SCLC. To uncover the mechanism of action of these 51 SCLC-selective toxins, we are using two orthogonal approaches. One strategy uses forward genetics to identify compound resistant alleles that impair compound-target interaction. We recently demonstrated that engineering mismatch repair (MMR) deficiency into murine SCLC cancer cells (using CRISPR/Cas9 to silence Msh2) led to hypermutation and enabled the acquisition of compound resistant alleles for three anti-cancer compounds with known mechanisms of action. We used these cells to identify compound resistant alleles that co-occur in multiple resistant clones that emerge following selections in cell culture of these anticancer compounds. We are also using medicinal chemistry as another approach to elucidate the mechanism of action of the SCLC-selective toxins. In collaboration with the De Brabander lab, three from the 51 SCLC-selective toxins were chosen for suitability for medicinal chemistry efforts due to their high selectivity (over 10-fold). We are performing structure-activity relationship studies to optimize potency and selectivity as well as target-ID studies. We also developed analogs harboring cross-linkable moieties with the goal of being able to efficiently enrich candidate proteins that can be identified by mass spectrometry.

B06 Time-Resolved RNA-Seq Identifies Transient Gene Expression Changes Following Initial Chemotherapy Challenge in Small-Cell Lung Cancer


Small-cell lung cancer (SCLC) comprises about 15% of all lung cancer and exhibits a remarkably aggressive clinical course, with early metastasis, rapid development of chemoresistance, and an overall survival of 6%. While standard-of-care combination chemotherapy with platinum-based agents and etoposide elicits dramatic responses following initial treatment, chemoresistant disease develops rapidly and contributes to the poor mortality rate in this disease. Transcriptional changes and underlying epigenetic changes have increasingly been recognized in the development of chemoresistance across different cancer types and in response to a variety of neoplastic agents. Indeed, a notable study in SCLC identified a role of the enhancer of
Central nervous system (CNS) metastasis, such as brain metastasis and leptomeningeal carcinomatosis (LMC), occurs in 20–40% of all patients with cancer. Anaplastic lymphoma kinase (ALK) is a clinically validated drug target, and ALK rearrangements are found in approximately 3–5% of non-small cell lung cancer (NSCLC). ALK tyrosine kinase inhibitor (TKI) shows dramatic clinical efficacy in ALK-rearranged NSCLC patients, and the second-generation ALK-TKI alectinib is effective against CNS metastasis of ALK-rearranged NSCLC. However, the patients with ALK-rearrangement acquire resistance to alectinib over time and develop recurrent LMC metastasis. This study aimed to clarify the mechanism of resistance to alectinib in LMC and seek a novel therapeutic strategy. Alectinib-resistant cell line (A925L/AR) was established by continuous treatment with alectinib in the LMC mouse model inoculated with the alectinib-sensitive human lung cancer cell line, A925LPE3, which harbors the EML4-ALK gene fusion. The tumor model inoculated with the alectinib-sensitive human lung cancer cell line, A925LPE3, which harbors the EML4-ALK gene fusion. The tumor model inoculated with the alectinib-sensitive human lung cancer cell line, A925LPE3, which harbors the EML4-ALK gene fusion.

Introduction: Despite significant therapeutic advances, clinical outcome remains poor in most patients (pts) with NSCLC, due at least in part to their genotype. STK11 is a master kinase that controls cellular metabolism, while c-MYC is an oncogene altered in many cancers promoting proliferation. Preclinical data (PMID:24793789) suggest that c-MYC amplification in the setting of STK11 loss can lead to unchecked growth of cancer cells. We anecdotally observed rapid progression, primary treatment refractoriness, and dramatic clinical decline in several pts with metastatic NSCLC (mNSCLC) with concurrent STK11 loss and c-MYC amplification. Hence, we investigated the incidence and the prognostic impact of these biomarkers in mNSCLC. Methods: This study was performed through the Precision Medicine Exchange Consortium (PMEC), a consortium of 10 US academic medical centers that share clinically annotated genomic data under a central IRB-approved protocol. The PMEC database (PMEC-DB) was queried for NSCLC pts with either STK11 loss (cohort A), c-MYC amplification (cohort B), or both (cohort C). Comprehensive genomic profiling (CGP) was performed on tumor tissue utilizing the Foundation One 315 gene assay. Demographic and disease characteristics were analyzed. Survival curves were estimated using the Kaplan-Meier method. Results: Among the 1,952 pts with NSCLC in the PMEC-DB, 396 pts met the inclusion criteria with 246 (62%), 103 (26%), and 47 (11.8%) pts in cohorts A, B, and C, respectively. Median TMB for the entire study set was 8.7, there was no statistically significant difference between the 3 cohorts (p = 0.12). KRAS mutations were detected more frequently in cohort A compared to cohorts B and C (58 % vs. 18% vs 38%; p<0.0001). Clinical outcome data were available in 99 (25%) pts and were distributed among cohorts A, B, and C, in similar proportion to the overall study set with 60, 24, and 15 pts, respectively. Cohort C was associated with a nonadenocarcinoma histology compared to cohorts A and B (53.3%, 16.7%, and 33.3%, respectively, p=0.011). Non-adenocarcinoma subtypes in Cohort C were NSCLC NOS 33.3%, squamous 6.7%, and large cell neuroendocrine 13.3%. There was no difference in median overall survival (mOS) between cohorts A, B, and C (10 months, 17 months, and 11 months respectively, p =0.68).