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Official Journal of the European Society for Medical Oncology

Volume 8, 2023 Supplement 1S5

Molecular Analysis for Precision Oncology Congress 2023

Paris, France
4-6 October 2023

ABSTRACT BOOK

Guest Editors:
Molecular Analysis for Precision Oncology Congress 2023 Scientific Committee

34P Functional diagnostics and ex-vivo screening of erlotinib and nintedanib in non-small cell lung carcinoma: Implications for multidrug resistance and personalized therapy

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Background: Multidrug resistance (MDR) hampers tyrosine kinase inhibitor (TKI) efficacy in non-small cell lung carcinoma (NSCLC). ABC transporters ABCB1, ABCC1, and ABCG2 trigger MDR by effluxing drugs from cancer cells. We studied erlotinib and nintedanib effects in patient-derived NSCLC cultures, MDR phenotype impact, and genetic alterations influencing drug response.

Methods: ABC transporter expression in 10 NSCLC patient-derived cell cultures was assessed after TKI treatment via immunofluorescence assay which enables discrimination between cancer and stromal cells. Erlotinib (1 μM − 4 μM) and nintedanib (2.5 μM − 20 μM) were used in clinically relevant concentrations. Whole exome sequencing was employed to analyze genetic alterations in NSCLC samples.

Results: Erlotinib selectively inhibited cancer cell growth (IC_{50}: 0.25 μM − 3.2 μM). It increased ABCC1 expression in 4/10 cultures and ABCB1/ABCG2 in 2/10 cultures. Erlotinib induced MDR markers expression at all concentrations. Nintedanib stimulated cancer cell growth at lower concentrations (<10 μM) and caused 90% cell death at higher concentrations (>15 μM), enriching the culture with cancer cells with high expression of ABCB1, ABCC1, and ABCG2. TKIs had no impact on MDR marker expression in stromal cells. Genetic alterations without clinical relevance for NSCLC were found in EGFR, ALK, ROS1, RET, and BRAF. L858R mutation in EGFR, indicated for erlotinib treatment, was detected in one patient, although all patients were responsive to erlotinib. Genetic alterations related to drug response were found in ABCB1 (7/10 patients) and ABCG2 (1/10 patients).

Conclusions: The employed functional diagnostics approach can effectively assess how erlotinib and nintedanib influence the MDR phenotype for individual patients. The ex-vivo screening system utilized in this study identifies the sensitivity of cancer and stromal cells and the correlation between response and their MDR profile, as well as the dependence of drug response on genetic alterations. This approach holds great promise for advancing personalized treatment strategies in NSCLC.

Legal entity responsible for the study: The authors.

Funding: Science Fund of the Republic of Serbia - TargetedResponse - 7739737.

Disclosure: All authors have declared no conflicts of interest.

https://doi.org/10.1016/j.esmoop.2023.101680

35P Enhancing efficacy of the MEK inhibitor trametinib in KRAS-mutated colorectal cancer cells

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Background: Metastatic colorectal cancer (mCRC) is the 2nd leading cause of cancer deaths in the US. >50% of patients with mCRC harbor mutations in KRAS or NRAS. Direct RAS targeting has failed to benefit patients with mCRC. Targeting MEK, a downstream mediator of RAS, failed to demonstrate efficacy in patients with mCRC. We hypothesize that identifying combination therapies using unbiased screening has the potential to improve the efficacy of MEK targeting in patients with KRAS mutated mCRC. The aims of this study were to perform unbiased high-throughput screening (HTS) using KRAS mutated CRC spheroids to identify drugs that, when combined with the MEK inhibitor trametinib, would enhance its efficacy.

Methods: We performed unbiased HTS using KRAS mutated CRC spheroids to investigate the synergistic effect of trametinib with agents from two distinct "clinically ready" compound library sets: 1) the NCI oncology set V, and 2) a custom compound set composed of FDA approved drugs or drugs in clinical trials. Using the Bliss model of synergy, paclitaxel was identified to be synergistic with trametinib. Effects of combining trametinib with paclitaxel were validated in vitro by cell growth assays and in vivo using KRAS mutated patient derived xenografts (PDXs).

Results: HTS studies showed that combining trametinib with paclitaxel was synergistic in CRC spheroids. This combination was validated in vitro by MTT and colony formation assays in multiple CRC cell lines. Analyses of Annexin V/PI staining by flow cytometry demonstrated that the drug combination increased cell death in multiple CRC cell lines when compared to single agents. Importantly, when compared to the monotherapies, combining trametinib with paclitaxel led to significant tumor growth inhibition in PDXs with KRAS G12D and G13D mutations, but not in a PDX with KRAS G12C mutation.

Conclusions: Our unbiased HTS and in vitro and in vivo validation studies demonstrated that combining trametinib with paclitaxel can enhance the efficacy of MEK inhibitors in KRAS mutated CRC cells and PDXs. Our in vivo studies using clinically achievable doses may serve as the basis for future clinical studies to determine the efficacy of this drug combination in patients with KRAS mutated mCRC.

Legal entity responsible for the study: L. Ellis.

Funding: Department of Defense (CA181043): Rajat Bhattacharya Department of Defense (CA140515): Lee M. Ellis The Ruben Distinguished Chair in Gastroenterology Cancer Research, MD Anderson Cancer Center.

Disclosure: All authors have declared no conflicts of interest.

https://doi.org/10.1016/j.esmoop.2023.101681

36P Comparison of pelitinib, tepotinib or docetaxel efficacy according to the copy number or gene alteration status of EGFR, MET, HRAS, KRAS and NRAS genes

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Background: In gastric cancer (GC), MET and EGFR amplification have been identified in about 2-24% and 27-64% of GC patients respectively. In this study, we characterized 286 carcinogenesis-related gene alteration and copy number variations (CNVs) in 4 human GC cell line and analyzed difference in the susceptibility of these cells to pelitinib, tepotinib or docetaxel.

Methods: Utilizing next-generation sequencing panel, we evaluated the 286 gene alteration and CNVs in 4 GC cells. Also, we assessed the antitumor activity of pelitinib, tepotinib and docetaxel in GC cell lines and xenograft model. The effect of pelitinib, tepotinib and docetaxel on cell viability (IC_{50}), apoptotic cell death, tumor volume and H&E staining were evaluated by MTS and flow cytometry. Antitumor efficacy was assessed in MKN45 xenograft mice.

Results: Compared to tepotinib, pelitinib inhibited the growth of GC cells with a gained EGFR (CNV > 3, without HRAS, KRAS and NRAS mutation) and amplified MET (CNV > 30) in a dose-dependent manner with a concomitant induction of cell death. In a murine xenograft model, tumor volumes were significantly reduced in the pelitinib, tepotinib or docetaxel-treated groups, when administered by daily oral gavage at a dose of 10, 10, 5 mg/kg/day respectively. Histologically, pelitinib, tepotinib or docetaxel induced more necrosis than in the control group.

Conclusions: We found that pelitinib has anti-tumor activity not only in EGFR gain GCs without mutated HRAS, KRAS and NRAS but also MET amplified GCs.

Legal entity responsible for the study: The authors.

Funding: This research was funded by the Korea Health Technology R&D Project (grant number HI22C1375) and the National Research and Development Program for Cancer Control (grant number HA17C0054), Ministry of Health and Welfare, and Hallym University Research Fund, which had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Disclosure: All authors have declared no conflicts of interest.

https://doi.org/10.1016/j.esmoop.2023.101682

37P NET-mediated radio-resistance in early-stage non-small cell lung cancer

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Background: Early-stage non-small cell lung cancer (NSCLC) has a 5-year survival rate of 63%. Current standards of care include surgery in the form of lobectomy or resection and stereotactic ablative radiotherapy (SABR). However, the current limitation of SABR is the moderate rates of reoccurrence in patients receiving treatment. We hypothesize that Neutrophil Extracellular Traps (NETs) may play a role in radio-resistance by decreasing T cell infiltration and activation in the tumor microenvironment.

Methods: The SABR-Bridge cohort is comprised of patients eligible for surgery that instead received neoadjuvant SABR followed by surgery 3-6 months later due to the SARS-COV-2 Pandemic. This cohort provides the unique ability to analyze changes in the microenvironment in non-responders after radiation. In addition, we use an orthotopic model of NSCLC with LLC1 cells injected into the left lung of wildtype or PAD4KO mice. Mice were then irradiated on day 7 and the tumor microenvironment