single-agent PD-1 immune checkpoint blockade (ICB) will not respond to these treatments. Among those who do respond, long-term survival is possible but modestly prevalent. Many NSCLC patients now receive chemo-immunotherapy as front-line treatment, exhausting the inventory of the most active agents against the disease in the first-line setting. New strategies to improve response rates and salvage therapeutic benefit at the time of progression on PD-1 ICB monotherapy or PD-1 ICB containing regimens are imperative. Common-gamma-chain agonist cytokine immunotherapies have been in use in solid tumors as FDA-approved agents since 1992, yet their use remains restricted to specialty centers willing to offer inpatient administration of highly toxic doses of recombinant IL-2 in order to achieve rare clinical responses. IL-15, a member of the IL-2 common-gamma chain receptor family of cytokines, is a potent agonist for CD8+ T-cells and is the canonical growth factor for natural killer cells, yet it spares activation of the CD4+ compartment of T cells due to poor interaction with CD25. Here we present an updated experience of combining the IL-15-based superagonist N-803 with the PD-1 immune checkpoint blockade antibody nivolumab in patients with metastatic non-small cell lung cancer. Previously we have published the dose-finding experience and preliminary clinical results from the phase Ib portion (PMID 29628312) of this ongoing phase Ib/II trial. In addition to patients treated with the recommended phase II dose from the phase IB study, we also present the experience of alternate cytokine dosing schedules and the correlate work used to determine optimal administration. Uniquely important responders, including durable response after chemoimmunotherapy failure as well as potential biomarkers of response, will be discussed. This investigator-initiated clinical trial will conclude soon, but also discussed will be two follow-on industry-sponsored trials examining the combination in two NSCLC settings at a time of burgeoning interest in cytokine therapies.

A38 Gemcitabine Improves Suppressive Immune Microenvironment Induced by Long-Term Treatment with EGFR-TKIs: Implications for Combination Chemotherapy and Immunotherapy

X. Wu,1 J. Tang,1 X. Liu,1 Q. Ma,1 P. Shu,1 Q. Deng,1 K. Li,1 B. Zhang,1 Y. Wang2,3
1Department of Thoracic Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan/CN, 2Department of Oncology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing/CN, 3Department of Oncology, Sichuan Cancer Hospital, Chengdu, Sichuan/CN

Background: For patients harboring epidermal growth factor receptor (EGFR)-sensitive mutations, the use of EGFR tyrosine kinase inhibitors (EGFR-TKIs) has brought admirable survival. However, patients with EGFR tyrosine kinase inhibitors have mostly improved overall survival (OS) and progression-free survival (PFS) of non-small cell lung cancer (NSCLC) patients. The aims of this study were to determine whether gemcitabine or pemetrexed improves suppressive immune microenvironment by long-term treatment with EGFR-TKIs. Methods: We adopted long-term use of EGFR-TKI models to investigate the responses of immune microenvironment to gemcitabine and pemetrexed. We analyzed the serum levels of IL-1β, IL-6, and IL-10 after chemotherapy. Results: In our investigation, a significantly higher percentage of myeloid-derived suppressor cells (MDSCs) was detected in long-term erlotinib-treated mice. Compared with the pemetrexed for the long-term use of EGFR-TKI models, the level of MDSCs was consistently reduced, CD8+ T cells, CD4+ T cells, and dendritic cells were elevated. Analysis of inflammatory factors in serum showed that gemcitabine decreased the levels of L-1β, IL-6, and IL-10. Conclusion: These data suggested that gemcitabine could reverse MDSC-mediated immune suppression and modulate the tumor microenvironment, thereby improving the efficacy of immune-based therapies. The results indicated a combination therapy using chemotherapy and immunotherapy for patients with EGFR mutation or who acquired resistance to EGFR-TKIs. It was also suggested that the combination use of MDSC-scavenging drugs may enhance the efficacy of anti-PD-1 immunotherapy.
HUVEC cell proliferation was promoted instead of the JNK pathway and Akt-related pathway.

A40
Antioxidant, Anti-Inflammatory, and Antiapoptotic Potential of Curcumin in Benzo(a)pyrene (BaP)-Induced Lung Injury in Rats

S. Almatroodi, A. Rahmani
Qassim University, Buraydah, Qassim/SA

Benzo(a)pyrene (BaP) is a well-known pollutant that directly induces inflammatory microenvironment in the lung. It also enhances oxidative stress and apoptosis and interferes with several other molecular pathways including cell death, survival, and proliferation that disturb normal homeostasis of the lung. Curcumin (Cur) has potent anti-inflammatory, antioxidant activity that defends cells from oxidative stress and cell death. The objectives of the present study were to explore the protective effects of curcumin against long-term administration of BaP-induced disturbances in lungs of rats. Male rats were randomly divided into four groups: saline control, BaP only, BaP + Cur, and Cur only. Lung injury histopathology, electron microscopy, inflammatory cytokine release, antioxidant levels, apoptosis, and cell cycle were examined. Instillation of BaP significantly increased infiltration of inflammatory cells in alveolar space and inflammatory cytokine in blood. Histopathologic examination found BaP-induced pulmonary inflammatory changes were improved after administration of curcumin as evident by less infiltration of macrophages and neutrophils in alveolar space, less deposition of collagen, and edema. Furthermore, electron microscopy results also showed necrotic changes and broken cell membrane of Type II epithelial cell (T2E) of alveoli in BaP group, which was reduced after addition of curcumin treatment. In addition, we found BaP plus curcumin treatment effectively reduced inflammatory cytokines TNF-α and IL-6 in blood serum, but no significant changes were found in CRP levels. Moreover, the levels of tunnel staining and p53 expression were significantly increased by BaP, whereas these changes were noticeably modulated after curcumin treatment. BaP also interferes in normal cell cycle, which was markedly improved with curcumin treatment. Overall, these findings suggest that curcumin attenuates BaP-induced lung injury, probably through inhibiting inflammation, oxidative stress, and apoptosis in lung epithelial cells, and improving cell proliferation and antioxidants' level. Thus, curcumin may be an alternative therapy for improving the outcomes of benzo(a)pyrene-induced lung injury.

A41
EO1001: A First-in-Class Irreversible Pan-ErbB Inhibitor with Excellent Brain Penetration


Background: ErbB receptor tyrosine kinases EGFR (ErbB1), HER2 (ErbB2, neu), HER3 (ErbB3), and HER4 (ErbB4) are part of a complex network activating signaling pathways involved in cell growth and survival. Mutations causing errant ErbB activation are an oncogenic driver in many cancers including NSCLC. Inhibitors targeting ErbB mutations have transformed outcomes for patients; however, resistance to treatment develops rapidly. The various ErbB receptors have overlapping roles in oncogenesis and crosstalk between ErbB family members is associated with acquired resistance and metastases. For example, amplification of HER2 is a well-established mechanism of acquired resistance to EGFR-TKIs. The development of next-generation agents targeting multiple ErbB receptors has shown promise but has been limited by toxicity and poor brain penetration. Up to 80% of NSCLC patients will experience a brain lesion associated with their disease; treatment-resistant phenotypes metastasizing to the brain have become an important driver of morbidity and mortality and patients have limited therapeutic options. New agents are needed to address this important and growing unmet medical need. EO1001 is a first-in-class, oral, brain-penetrating, irreversible pan-ErbB inhibitor targeting ErbB1, ErbB2, and ErbB4 that is positioned for near-term entry into clinical development. Methods: In vitro testing: EO1001 exhibits excellent and balanced equipotent activity against all three important ErbB receptors including EGFR, HER2, and HER4 with low nM activity (0.4 to 7.4 nM), with high specificity vs. off-target receptors. In vivo studies: Following oral administration, EO1001 treatment resulted in a statistically significant improvement in outcomes compared to positive and negative controls in erbB-positive mouse orthotopic models including N87 (Her2+), H1975 (EGFR/T790M), GBM12 (EGFR+), GBM39 (EGFRvIII+). EO1001 rapidly enters the CNS at high concentrations relative to plasma and inhibits signaling downstream of mutant ErbB receptors in tumor tissue. Treatment with EO1001 was generally well tolerated with no gastrointestinal side effects observed at efficacious doses in mouse xenograft models. PK and Toxicity Results: Preclinical pharmacokinetic and toxicology studies have been completed. EO-1001 exhibits a half-life of 16-20 hours in rodent models. Toxicities typical of the ErbB inhibitor class, including gastrointestinal effects, weight loss, and decreased activity, were observed at higher dose groups in both rodent and non-rodent species. Extrapolation to human dosing suggests an attractive therapeutic window in comparison to other agents in the class. Conclusion and Next Steps: EO1001 has the potential to be a best-in-class CNS-penetrating pan-ErbB inhibitor amenable for use as a single agent and in combination regimens. First-in-man clinical testing with EO1001 is planned. Continued characterization of EO1001 activity against specific ErbB mutations will be undertaken in parallel.