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, 2 B. Zhang, 1 Y. Wang 1
1Department of Thoracic Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan/CN, 2Department of Oncology, Sichuan Cancer Hospital, 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 mutation cannot benefit from anti-PD-1/PD-L1 alone as second-line therapy, from the analysis of results of immunotherapy clinical trials. In fact, immunotherapy with programmed cell death 1 (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 correlative 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.

A39 Reactive Cutaneous Capillary Endothelial Proliferation Caused by Camrelizumab (SHR-1210) Through Activation of HIF-1α/VEGF Signaling Pathway

X. Wu, 1 X. Zhang, 2 P. Shu, 1 Q. Ma, 1 Y. Chen, 1 D. Li, 1 Y. Wang 1
1Department of Thoracic Oncology, Cancer Center, West China Hospital, Chengdu, Sichuan/CN, 2Department of Oncology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing/CN, 3Precision Medicine Center, Precision Medicine Key Laboratory of Sichuan Province, West China Hospital, Sichuan University, Chengdu, Sichuan/CN

Background: Monoclonal anti-programmed cell death 1 (PD-1) antibodies are effective cancer therapeutics, but camrelizumab (SHR-1210) caused reactive cutaneous capillary endothelial proliferation (RCEP) in patients. This symptom was not detected in the clinical trials of other PD-1/PD-L1 antibodies approved by the Food and Drug Administration (FDA). Therefore, it is of great significance to verify the phenomenon of camrelizumab (SHR-1210) to promote the proliferation of human blood vessels and to explore its possible mechanisms for the effective control of its side effects and the continuation of clinical trials. Methods: We chose the cells mainly involved in the blood vessels, umbilical vein endothelial cells (HUVEC), as experimental object. Cholceystokinin c-terminal octapeptide (CCK-8) assay was used to detect the proliferation of HUVEC cells. Transwell cell migration and invasion assay were used to detect the cell migration ability; apoptosis detection by terminal-deoxynucleotidyl transferase-mediated nick end labeling (TUNEL) assay was used to detect the apoptosis; ELISA was used to detect the expression of VEGF and bFGF in the cell supernatants; Western blot test was used to detect HIF-1α, p44/42 (ERK1/2), p-p44/42 (p-Erk1/2), p38, p-p38, JNK, p-JNK, Akt, and p-Akt. Results: The CCK-8 test suggested that 150 μg/ml and 200 μg/ml camrelizumab (SHR-1210) compared to the control group showed a significant increase in cell proliferation. We chose 150 μg/ml as the working concentration for follow-up experiments. Transwell cell migration and invasion assay suggested that the number of cell migration increased significantly in the camrelizumab (SHR-1210) treated group. The results of apoptosis detection by terminal-deoxynucleotidyl transferase-mediated nick end labeling (TUNEL) assay showed that there was no significant difference in the number of apoptotic cells and apoptosis index (AI) between the camrelizumab (SHR-1210) treated group and the control group. ELISA results showed that the concentration of VEGF in the supernatant of the camrelizumab (SHR-1210) treated group was significantly higher than that of the control group, but there was no significant difference in the concentration of bFGF. Western blot results indicated the expression of HIF-1α was significantly increased in the camrelizumab (SHR-1210) treated group, and the expression of p-p44/42 (p-Erk1/2) and p-p38 was significantly increased, while p-JNK and p-Akt were not significantly increased. Conclusion: Camrelizumab (SHR-1210) can promote proliferation and migration of HUVEC cells without inhibiting apoptosis. It can promote the expression of VEGF in HUVEC cells and promote the proliferation and migration of HUVEC cells through VEGF without promoting the expression of bFGF. By activating the HIF-1α/VEGF pathway and its upstream signal pathways ERK and p38MAPK,