POTENTIAL MECHANISMS OF RESISTANCE IDENTIFIED THROUGH ANALYSIS OF MULTIPLE BIOMARKERS IN IMMUNE HOT NON-RESPONDERS WITH NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH TISLELIZUMAB


http://dx.doi.org/10.1136/jitc-2020-SITC2020.0075

76 POTENTIAL MECHANISMS OF RESISTANCE IDENTIFIED THROUGH ANALYSIS OF MULTIPLE BIOMARKERS IN IMMUNE HOT NON-RESPONDERS WITH NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH TISLELIZUMAB

1Jayesh Desai*, 2Qing Zhou, 3Sanjeev Deva, 4Jun Zhao, 5Jie Wang, 6Wei Tan, 7Xiaoping Ma, 8Yun Zhang, 9Zhirong Shen, 10Xikun Wu, 11Shiangjiin Leaw, 12Juan Zhang, 13Yun Zhang, 14Zhirong Shen, 15Shiangjiin Leaw, 16Xikun Wu, 17Juan Zhang, 18Yun Zhang, 19Zhirong Shen, 20Shiangjiin Leaw, 21Xikun Wu, 22Juan Zhang, 23Yun Zhang, 24Zhirong Shen, 25Shiangjiin Leaw, 26Xikun Wu, 27Juan Zhang, 28Yun Zhang, 29Zhirong Shen, 30Shiangjiin Leaw, 31Xikun Wu, 32Juan Zhang, 33Yun Zhang, 34Zhirong Shen, 35Shiangjiin Leaw, 36Xikun Wu, 37Juan Zhang, 38Yun Zhang, 39Zhirong Shen, 40Shiangjiin Leaw.

Background Tislelizumab, an anti-PD-1 monoclonal antibody, has demonstrated clinical benefit for patients with NSCLC. The underlying response and resistance mechanisms to tisleli- zubum treatment remain unknown.

Methods Baseline tumor samples from 59 nonsquamous (NSQ) and 41 squamous (SQ) NSCLC patients treated with tislelizumab monotherapy (NCT02407990 and NCT04068519) were tested for gene mutations using large panel next generation sequencing and RNA expression using gene expression profiling (GEP). Precision Immuno-Oncology Panel, HTG Molecular Diagnostics). GEP analyses of NSQ and SQ NSCLC were per- formed separately due to different gene expression patterns.

Results The ORR, mPFS, and mOS in this pooled NSCLC cohort were 15.2% (95% CI: 9.0, 23.6), 4.1 months (95% CI: 2.20, 6.11), and 15.1 months (95% CI: 11.20, NE), respectively, with a median study follow-up of 15.3 months (95% CI: 14.06, 15.90). Non-responders (NRs) exhibited distinct tumor and immune gene signature profiles and could be clustered into two subgroups: NR1 and NR2. Compared with responders, NR1 had elevated cell cycle signatures in both NSQ (P=0.2) and SQ (P=0.03) cohorts, and a trend of decreased inflammatory gene signature profiles. However, NR2 showed comparable or even higher tumor inflammation (18-gene), and CD8+ T-cell signature scores in both NSQ and SQ cohorts and could be classified as immune hot. To explore the resistance mechanisms of immune hot NRs, differentially expressed gene analyses between immune hot NR2 and responders were performed. M2 macrophage and Treg signature scores were higher in NR2 in both NSQ (M2, P=0.05; Treg, P=0.03) and SQ (M2, P=0.05 [subgroup of NR2]; Treg, P=0.03) cohorts; significantly higher expression of immune regulatory genes included PIK3CD, CCR2, CD244, IRAK3, and MAP4K1 (P<0.05) in NSQ and PIK3CD, CCR2, CD40, CD163, and MMP12 (P<0.05) in SQ. Significantly higher epithelial–mesenchymal transition (EMT) and angiogenesis gene expression, including SNAI1, FAP, VEGF, and TEK (P<0.05) genes, were also observed in SQ NR2. Moreover, gene mutation analysis identified seven immune hot NR patients harboring either driver mutations (RET fusion, ROSI fusion, BRAF, and PIK3CA amp) or well-established resistance mutations (loss of function mutation in JAK2, STK11, and MDM2 amplification).

Conclusions Despite the presence of immune hot factors, a subgroup of tislelizumab NRs with NSCLC were identified. High levels of immune suppressive factors, such as M2 macro- phage and Treg signatures, angiogenesis, and EMT genes, as well as the existence of driver/resistance mutations, may indi- cate mechanisms of resistance of immune hot NRs, highlight- ing potential novel treatment targets.

Acknowledgements Editorial assistance was provided by Agnieszka Laskowska, PhD, and Elizabeth Hermans, PhD (OPEN Health Medical Communications, Chicago, IL), and funded by the study sponsor.

Trial Registration NCT02407990 and NCT04068519

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0076

77 ASSOCIATION BETWEEN PROGRAMMED DEATH-LIGAND 1 (PD-L1) EXPRESSION AND GENE SIGNATURES OF RESPONSE OR RESISTANCE TO TISLELIZUMAB MONOTHERAPY IN HEPATOCELLULAR CARCINOMA (HCC)

1Min-Mo Hou, 2Kun-Ming Rau, 3Yoon-Koo Kang, 4Jong-Seok Lee, 5Hong-Ming Pan, 6Ying Yuan, 7Cunying Yu, 8Yun Zhang, 9Xiaoping Ma, 10Xian Wu, 11Xin Li, 12Katie Wood, 13Chia-Jui Yen*. 1Chang Gung Memorial Hospital, Taoayn, Taiwan, Province of China; 2Kadusung Chang Gung Memorial Hospital, Kaohsuing, Taiwan, Province of China; 3Asian Medical Center, Seoul, Korea, Republic of; 4National University Bundang Hospital, Seonan-si, Korea, Republic of; 5Sir Run Run Shaw Hospital, Hangzhou, China; 6Second Affiliated Hospital Zhejiang, Hangzhou, China; 7BeiGene (Beijing) Co., Ltd., Beijing, China; 8BeiGene USA, Inc., San Mateo, CA, USA; 9National Cheng Kung University Hospital, Tainan City, Taiwan, Province of China.

Background PD-L1 inhibitors are treatment options for patients with HCC who have progressed after first-line
sorafenib treatment. Tislelizumab, an anti-PD-1 monoclonal antibody, has demonstrated single-agent antitumor activity in patients with advanced, previously treated HCC in two early phase studies (NCT02407990, NCT04068519). Association of biomarkers, including PD-L1 expression and gene expression profiles (GEP), with response and resistance to tislelizumab were explored.

Methods PD-L1 expression was evaluated on tumor cells (TC) using the VENTANA PD-L1 (SP263) assay in baseline tumor samples collected before or after sorafenib treatment. GEP were assessed using the 1392-gene HTG GEP EdgeSeq panel. Signature scores were calculated using the Gene Set Variation Analysis package with publicly available gene signatures (GS). Wilcoxon rank-sum test was used to analyze differential gene signatures (DEG); GS association with PFS and OS was evaluated using Cox proportional hazards models.

Results Single-agent tislelizumab demonstrated antitumor activity in advanced, previously treated HCC (ORR=13%; CB [PR +SD >6 months]=31%, median PFS=3.3 months; median OS=13.3 months). PD-L1+ (TC≥1% prevalence and GEP showed different patterns in samples collected before and after sorafenib exposure (figure 1). While non-exposed samples (n=16) were enriched for immune suppressive signatures, sorafenib-exposed samples (n=41) showed higher PD-L1+ prevalence (53.7% vs 25%; P=0.08) and immune-cell activation signatures along with co-inhibition molecules. In sorafenib-exposed samples, PD-L1 expression was positively correlated with CB (P=0.0027) and a trend of longer PFS (HR=0.56, 95% CI:0.28–1.13). ORR was higher in PD-L1+ than PD-L1− sorafenib-exposed samples (23.8% vs 0%; P=0.049). DEG analysis in sorafenib-exposed samples demonstrated that NK-mediated cytotoxicity GS was positively correlated with CB (P=0.03), as well as a trend of longer PFS (HR=0.43, 95% CI:0.17–1.06). Across the different analyses, no correlation with OS was observed. Patients considered non-responders (NRs) were found clustered into three distinct GEP subgroups (NR1, NR2, NR3). Compared with responders, NR1 had enhanced angiogenesis signatures (P=0.01), including TEK, KDR, HGF, and EGR1. Despite high inflamed tumor signatures, NR2 had increased expression of T-cell inhibition GS scores (P=0.01), including CD274, CTLA4, TIGIT, and CD96. The NR3 subgroup showed higher cell-cycle GS levels. Patients considered non-responders (NRs) were found clustered into three distinct GEP subgroups (NR1, NR2, NR3). Compared with responders, NR1 had enhanced angiogenesis signatures (P=0.01), including TEK, KDR, HGF, and EGR1. Despite high inflamed tumor signatures, NR2 had increased expression of T-cell inhibition GS scores (P=0.01), including CD274, CTLA4, TIGIT, and CD96. The NR3 subgroup showed higher cell-cycle GS levels. Patients considered non-responders (NRs) were found clustered into three distinct GEP subgroups (NR1, NR2, NR3). Compared with responders, NR1 had enhanced angiogenesis signatures (P=0.01), including TEK, KDR, HGF, and EGR1. Despite high inflamed tumor signatures, NR2 had increased expression of T-cell inhibition GS scores (P=0.01), including CD274, CTLA4, TIGIT, and CD96. The NR3 subgroup showed higher cell-cycle GS levels.