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 23%; 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:0.17–0.95) was observed. Patients considered non-responders (NRs) were found clustered into three distinct GEP subgroups (NR1, NR2, NR3). Compared with responders, NR1 had increased expression of T-cell inhibition GS, as well as response and PFS from tislelizumab in advanced HCC patients. Elevated angiogenesis, immune exhaustion, and cell-cycle GS levels may indicate resistance to single-agent PD-1 inhibitors and is suggestive of potential treatment strategies. Validation is warranted in future clinical trials (NCT03412773).

Acknowledgements This study was sponsored by BeiGene, Ltd. Writing and editorial assistance was provided by Regina Switzer, PhD, and Elizabeth Hermans, PhD (OPEN Health Medical Communications, Chicago, IL), and funded by the study sponsor.

Trial Registration NCT02407990, NCT04068519

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0077

Abstract 78 Table 1 T-cell and MHC I gene signatures associated with clinical efficacy of tislelizumab in patients with UC

Abstract 77 Figure 1 Median difference in gene signatures before and after sorafenib exposure
improvement in clinical efficacy (40% objective response rate [ORR]), 5.26 month median progression-free survival [PFS], and 15.2 month median OS) than other subgroups (table 1). In addition to immune-related genes in the microenvironment, DEG analysis also revealed that tumor-related genes were highly expressed in non-responders, such as intrinsic genes related to angiogenesis (VEGFA [P = 0.07], KDR [P = 0.07]), the mTOR pathway (MTOR [P = 0.015]), and DNA damage repair (REV3L [P = 0.007]). MTOR and REV3L were associated with shorter PFS (P = 0.02; P = 0.003) and OS (P = 0.03; P = 0.008), respectively.

Conclusions By using GEP, T-cell and MHC I GS were identified as potentially predictive biomarkers of response to tislelizumab monotherapy in PD-L1+ UC in this retrospective analysis. By combining these two GS scores, patients with optimal efficacy responses could be identified. Conversely, high expression of tumor intrinsic genes related to angiogenesis and the mTOR pathway may indicate resistance and suggest potential future drug combinations for these patients. Both findings warrant further validation in a phase 3 study (NCT03967977).

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

Trial Registration CTR20170071

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0078

Table 1: Tumor-immune signatures associated with clinical efficacy of tislelizumab in patients with ESCC

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number of Patients</th>
<th>TLR High (n=21)</th>
<th>TLR Low (n=22)</th>
<th>Single TLR Signature</th>
<th>Log2FoldChange (PFS)</th>
<th>Combined Signature</th>
<th>Log2FoldChange (OS)</th>
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</thead>
<tbody>
<tr>
<td>NR1</td>
<td>5</td>
<td>3.68</td>
<td>1.98</td>
<td>NR1</td>
<td>-1.13 (&lt;0.01)</td>
<td>NR1</td>
<td>-2.06 (&lt;0.01)</td>
</tr>
<tr>
<td>NR2</td>
<td>6</td>
<td>3.05</td>
<td>2.04</td>
<td>NR2</td>
<td>1.01 (0.12)</td>
<td>NR2</td>
<td>1.01 (0.12)</td>
</tr>
<tr>
<td>NR3</td>
<td>9</td>
<td>3.95</td>
<td>2.36</td>
<td>NR3</td>
<td>1.24 (0.08)</td>
<td>NR3</td>
<td>1.24 (0.08)</td>
</tr>
<tr>
<td>NR4</td>
<td>12</td>
<td>2.93</td>
<td>1.71</td>
<td>NR4</td>
<td>0.43 (0.75)</td>
<td>NR4</td>
<td>0.43 (0.75)</td>
</tr>
</tbody>
</table>

Abstract 79 Table 1: Tumor-immune signatures associated with clinical efficacy of tislelizumab in patients with ESCC

Background Tislelizumab, an anti-PD-1 monoclonal antibody, showed promising clinical outcomes for patients with ESCC. Here, the tumor and immune microenvironment is investigated using gene expression profiles (GEP) and gene signatures associated with clinical efficacy in patients with ESCC receiving tislelizumab either as monotherapy (NCT02407990, NCT04068519) or in combination with chemotherapy (5-fluorouracil plus cisplatin; NCT03469557) or in combination with chemotherapy (5-fluorouracil plus cisplatin; NCT03469557).

Methods Baseline tumor samples were subjected to GEP using a 1392-gene HTG EdgeSeq panel. Signature scores were calculated using the Gene Set Variation Analysis package with publicly available gene signatures. Differential gene signature (DEG) analysis was performed between responders and non-responders using the Wilcoxon rank-sum test. Associations between gene signatures and survival were evaluated using the Cox proportional hazards model.

Results In GEP-evaluable patients receiving monotherapy (n=43), DEG analysis showed toll-like receptor (TLR) signature scores, driven by TLR8, TLR6, TIRAP, and TLR4, were positively correlated with response and survival, while Treg scores, driven by FOXP3, EBI3, TNFRSF18, and BATF, showed a negative correlation. After combining TLR-high and Treg-low scores (as defined by median cutoff), the prediction of clinical efficacy was further improved (table 1). In addition to Treg scores, non-responders (NR) to tislelizumab monotherapy could be further clustered into four subgroups (NR1, NR2, NR3, and NR4), each exhibiting distinct resistance signatures. Despite a high level of immune infiltration, NR1 expressed a higher exhaustion signature (CD96, CTLA4, TIGIT, HAVCR2, etc.) versus responders (P = 0.01). Both NR2 and NR3 demonstrated a trend of enhanced cell-cycle signatures versus responders (P = 0.07 and P = 0.08, respectively), accompanied by a lower NK signature (KIR2DS4, KIR.panl, CD56) in NR2 and a lack of immune infiltration in NR3. In the NR4 subgroup, a trend toward higher TH17 (P < 0.01) and IL-17F signatures (Log2FC=0.56, P = 0.10) versus responders was observed. GEP-evaluable patients (n=12) receiving tislelizumab in combination with chemotherapy had an objective response rate of 58% (n=7), with a different gene signature pattern than those observed in patients receiving monotherapy. Responders to combination therapy showed higher DNA repair repair versus responders (P = 0.07), while angiogenesis signatures were significantly higher in NR vs responders (P = 0.01). Consistent with this, NR exhibited higher expression of VEGFC at a single gene level (Log2FC=2.46, P < 0.01).

Conclusions While higher TLR signaling was associated with clinical benefit of tislelizumab monotherapy, elevated Treg, exhaustion, cell cycle, and TH17 signatures may indicate resistance. Signatures predictive for combination therapy may vary. Both immune- and tumor-related features may be considered for validation in phase 3 studies (NCT03430843, NCT03783442).

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

Trial Registration NCT02407990, NCT04068519, NCT03469557

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0079

Abstract 80: Evaluation of the TruSight Oncology 500 Assay for routine clinical testing of Tumor Mutational Burden (TMB) and Clinical Utility for Predicting Response to Pembrolizumab

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Background Various biomarkers have been investigated for their ability to identify patients more likely to respond to pembrolizumab (as defined by median cutoff), the prediction of clinical efficacy was further improved (table 1). In addition to Treg scores, non-responders (NR) to tislelizumab monotherapy could be further clustered into four subgroups (NR1, NR2, NR3, and NR4), each exhibiting distinct resistance signatures. Despite a high level of immune infiltration, NR1 expressed a higher exhaustion signature (CD96, CTLA4, TIGIT, HAVCR2, etc.) versus responders (P = 0.01). Both NR2 and NR3 demonstrated a trend of enhanced cell-cycle signatures versus responders (P = 0.07 and P = 0.08, respectively), accompanied by a lower NK signature (KIR2DS4, KIR.panl, CD56) in NR2 and a lack of immune infiltration in NR3. In the NR4 subgroup, a trend toward higher TH17 (P < 0.01) and IL-17F signatures (Log2FC=0.56, P = 0.10) versus responders was observed. GEP-evaluable patients (n=12) receiving tislelizumab in combination with chemotherapy had an objective response rate of 58% (n=7), with a different gene signature pattern than those observed in patients receiving monotherapy. Responders to combination therapy showed higher DNA repair repair versus responders (P = 0.07), while angiogenesis signatures were significantly higher in NR vs responders (P = 0.01). Consistent with this, NR exhibited higher expression of VEGFC at a single gene level (Log2FC=2.46, P < 0.01).