IMMUNE CORRELATES OF CLINICAL RESPONSE TO AVELUMAB IN PATIENTS WITH ADVANCED THYMIC EPITHELIAL TUMORS

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Background Thymic epithelial tumors (TET), consisting of thymomas and thymic carcinomas, are PD-L1-expressing tumors characterized by varying degrees of lymphocytic infiltration and a predisposition towards the development of paraneoplastic autoimmunity. As part of a phase I study (NCT01772004), the anti-tumor activity of patients with relapsed, advanced TET to avelumab (anti-PD-L1), was demonstrated and was accompanied by a high frequency of immune related adverse events (irAE). The current study aimed to identify immune related signatures that associate with clinical response and/or the development of irAE.

Methods Eight patients with recurrent TET were treated with avelumab at doses of 10 mg/kg to 20 mg/kg every 2 weeks until disease progression or development of intolerable side effects. Peripheral blood mononuclear cells (PBMC) were obtained before and during therapy, and interrogated by multicolor flow cytometry to evaluate 123 immune subsets, as well as by T-cell receptor (TCR) sequencing to evaluate TCR diversity.

Results Four of 8 TET patients had partial responses and 3 had stable disease. All responders developed irAEs that resolved with immunosuppressive therapy, compared to only 1 of 4 non responders. Analyses of PBMC subsets prior to therapy showed that responders had higher absolute lymphocyte counts, and lower frequencies of B cells, Tregs, conventional dendritic cells (cDCs), and NK cells, compared to non-responders. There was also a trend towards a higher level of TCR diversity in those patients who subsequently had a radiological response and developed irAE.

Conclusions Immune profiling identified specific immune measures prior to therapy that differed between responders and non-responders, that may serve as predictive biomarkers to identify patients with relapsed TET most likely to benefit from avelumab and/or to develop irAE.

Trial Registration NCT01772004

Ethics Approval All patients provided written informed consent for participation in a clinical trial that was approved by the Institutional Review Board at the National Cancer Institute (NCT01772004).

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0296

MODELING THE EFFICACY OF NY-ESO-1 TCR T CELLS (LETETRESGENE AUTOLEUCEL; GSK377794) IN PATIENTS WITH SYNOVIAL SARCOMA: CORRELATIONS OF RESPONSE WITH TRANSDUCED CELL KINETICS AND BIOMARKERS

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Background NY-ESO-1–specific T cells (letetresgene autoleucel [letel-cel]; GSK377794) are autologous CD4+ and CD8+ T cells transduced to express a high-affinity T-cell receptor that recognizes NY-ESO-1 antigen in complex with HLA-A*02. NY-ESO-1 is a cancer testis antigen that is expressed in many cancers, including synovial sarcoma (SS). Study 208466 (NCT01343043) is a Phase I clinical trial that assessed the safety and efficacy of letel-cel in patients with advanced SS (presented in complementary abstract). This abstract presents correlations of transduced cell kinetics and biomarkers with response.

Methods Patients with unresectable, metastatic, or recurrent SS were enrolled to 4 cohorts based on NY-ESO-1 expression levels and received different lymphodepleting regimens (LDR) prior to letel-cel infusion (N=45) (table 1). Response was assessed per RECIST v1.1. Transduced cell kinetics (persistence) were measured by quantitative PCR of transgene vector copies in DNA extracted from peripheral blood mononuclear cells. Serum cytokines were measured by Meso Scale Discovery (MSD) immunoassay. Gene expression within tumor biopsies was evaluated by Nanostring. Post hoc analyses were evaluated in a hypothesis-driven manner using logistic and linear regression. Potential determinants of peak persistence and clinical response were tested using generalized linear models.

Results Higher peak persistence (Pmax) was associated (p=0.012) with response across cohorts. Higher weight-normalized cell dose (p=0.00421) and LDR (p=0.000910) were associated with Pmax according to the generalized linear model: Pmax ~ cell dose + LDR. These relationships allowed for accurate retrospective prediction of probability of response. Low LDR resulted in higher endogenous lymphocyte counts on the day of dosing, which trended with lack of response within and across cohorts. While the impact of fludarabine on IL-15 levels has been previously reported, data presented here show a novel, positive correlation between IL-15 levels pre-infusion and response (p=0.0332). Post letel-cel infusion, the concentrations of IFNy, IL-6, and IL-2RA within the first week were increased in responders vs non-responders. The peak expression of IL-2RA within the first week showed a linear correlation to Pmax. Analysis of tumor biopsies showed good correlation between NY-ESO-1 mRNA and protein expression.

Abstract 297 Table 1 NY-ESO-1 expression, lymphodepletion regimen, overall response rate, mean transduced cell dose, and mean peak persistence in Cohorts 1–4

<table>
<thead>
<tr>
<th>Cohort</th>
<th>NY-ESO-1 expression</th>
<th>Lymphodepletion regimen</th>
<th>Response rate (%)</th>
<th>Mean transduced cell dose in Millions (mean ± std. dev.)</th>
<th>Mean (int. rel.) peak persistence (median range (IQR))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>High</td>
<td>High</td>
<td>6/12 (50%)</td>
<td>4.05 (0.451, 14.4)</td>
<td>70,000 (5.560)</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td>High</td>
<td>0/12 (0%)</td>
<td>0.01 (0.00, 0.02)</td>
<td>0 (0.00, 0.00)</td>
</tr>
<tr>
<td>3</td>
<td>Low</td>
<td>Low</td>
<td>0/20 (0%)</td>
<td>0.01 (0.00, 0.02)</td>
<td>0 (0.00, 0.00)</td>
</tr>
</tbody>
</table>

Conclusions Exposure–response analysis of study 208466 reveals that efficacy appears to be driven by weight-normalized...