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. 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. The current study aimed to identify immune related signatures that associate with clinical response and/or the development of irAE.

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 radio- logical 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).

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MODELING THE EFFICACY OF NY-ESO-1 TCR T CELLS (LETETRESGENE AUTOLEUCEL; GSK3377794) 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 [lete-cel]; GSK3377794) 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 lete-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 lete-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 lete-cel infusion, the concentrations of IFNγ, 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, max)</th>
<th>Mean (std. dev.) peak persistence (median(range)(DNA))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>High</td>
<td>40%</td>
<td>Fluorodeoxyglucose: 30 mg/m² IV Days −5 to −1</td>
<td>6/12 (50%)</td>
<td>4.05 (0.451, 14.4)</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>50%</td>
<td>Fluorodeoxyglucose: 30 mg/m² IV Days −5 to −1</td>
<td>3/3 (100%)</td>
<td>2.81 (1.40, 3.01)</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>High</td>
<td>50%</td>
<td>Fluorodeoxyglucose: 30 mg/m² IV Days −5 to −1</td>
<td>4/5 (80%)</td>
<td>2.92 (0.32, 7.65)</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>50%</td>
<td>Fluorodeoxyglucose: 30 mg/m² IV Days −5 to −1</td>
<td>2/5 (40%)</td>
<td>1.10 (1.55, 2.50)</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>High</td>
<td>50%</td>
<td>Fluorodeoxyglucose: 30 mg/m² IV Days −5 to −1</td>
<td>4/3 (67%)</td>
<td>2.91 (0.32, 7.65)</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>50%</td>
<td>Fluorodeoxyglucose: 30 mg/m² IV Days −5 to −1</td>
<td>2/3 (67%)</td>
<td>2.91 (0.32, 7.65)</td>
</tr>
</tbody>
</table>

Conclusions Exposure–response analysis of study 208466 reveals that efficacy appears to be driven by weight-normalized...
cell dose and LDR via Pmax. Biomarker correlation analysis indicates that LDR impacts the level of IL-15 pre-infusion, which correlates with response directly. IFNγ, IL-6, and IL-2RA levels appear to be promising pharmacodynamic markers. Optimizing dose and LDR may offer opportunities to maximize antitumor efficacy.

Acknowledgements This study (208466) was funded by GlaxoSmithKline (GSK).

Trial Registration Clinicaltrials.gov NCT01343043

Ethics Approval This study was approved by the appropriate institutional review boards and independent ethics committees.

Background NY-ESO-1–specific T cells (letetresgene autoleucel [lete-cel]; GSK3377794) are autologous T cells transduced with a self-inactivating lentiviral vector to express an engineered NY-ESO-1–specific TCR that recognizes HLA-A*02–presented peptides derived from NY-ESO-1, a cancer/testis antigen (LETETRESGENE AUTOLEUCEL; GSK3377794) IN PATIENTS WITH ADVANCED SYNOVIAL SARCOMA (SS) NY-ESO-1 expression and lymphodepletion regimen in Cohorts 1–4, efficacy, and peak persistence in responders and nonresponders; mITT population

Methods Patients with unresectable, metastatic, or recurrent SS who were intolerant/nonresponsive to standard first-line chemotherapy enrolled in 4 cohorts based on NY-ESO-1 tumor expression were lymphodepleted and received lete-cel infusion (table 1). Primary endpoint was investigator-assessed overall response rate (ORR) per RECIST v1.1; secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. Transduced cell persistence was measured by qPCR of transgene vector copies in DNA extracted from PBMCs. Study was not designed/powered to compare cohorts.

Results Overall, 50 patients enrolled; 45 received lete-cel infusion (modified intent-to-treat population). Demographics were similar between cohorts. Median time in study was 480/278/605/643 days in Cohorts 1/2/3/4, respectively. At study completion, ORR ranged from 20%–50% between cohorts, with 1 complete (lasting 34 weeks) and 14 partial responses (table 1). In Cohorts 1/2/3/4, respectively, median DoR was 31.0/8.6/24.3/9.9/19.9 months; Cohort 4 median OS was immature. Across cohorts, Grade ≥3 adverse events (AEs) in ≥40% of patients were mostly hematologic in nature; Grade ≥3 serious AEs (SAEs) were most frequently febrile neutropenia, dyspnea, and neutropenia (table 2). AEs of special interest included cytokine release syndrome in 44% of patients (n=20; maximum Grade 1/2/3/4 in 9/7/3/1 patients, respectively; 5 patients had SAEs [Grade ≥3 in 2 patients]; all AEs/SAEs resolved); Guillain-Barré syndrome in 2 patients (Grade 3 SAEs; resolved with sequelae); and multilineage cytopenias in 96% of patients (n=43; maximum Grade 5 in 1 patient, Grade 3/4 in others). Peak persistence of transduced cells was generally higher in responders vs non-responders (table 1); time to peak persistence was similar between these groups (median 8 days). No patients tested positive for replication-competent lentivirus.

Conclusions In patients with advanced SS who need effective treatment, lete-cel had a manageable safety profile; responses occurred in all cohorts, but patients with high NY-ESO-1 expression and more intensive lymphodepletion regimen received greatest benefit.

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