Background

T-cell therapy

Adoptive T-cell therapy aims to generate an antitumor T-cell immune response by infusing a cancer patient’s own T cells that have been extracted, engineered, and expanded to express a tumor-specific TCR. Emerging clinical data demonstrate that adoptive cellular therapy has the potential to be practice-changing in the management of relapsed/refractory MM.1,2 NY-ESO-1 T cells (GSK3377794) are autologous polyclonal T cells transduced by a self-inactivating lentiviral vector to express an affinity-enhanced TCR capable of recognizing NY-ESO-1 or LAGE-1a antitumorigenic peptides in complex with HLA-A*02 (Figure 1).1,2

Clinical experience with GSK3377794

In prior studies, encouraging clinical activity has been shown with GSK3377794 treatment in patients with synovial sarcoma, melanoma, anaplastic thyroid cell carcinoma, and in patients with MM receiving GSK3377794 after autologous stem cell transplant.1,4 NY-ESO-1 and LAGE-1a are immunogenic tumor-associated antigens frequently overexpressed in MM and are linked to poor clinical outcome.2,3 Multiple phase 1 and 2 trials are evaluating GSK3377794 in solid tumors. Pembrolizumab, a selective humanized IgG4 anti-PD-1 monoclonal antibody that blocks the interaction of PD-1 with PD-L1 and PD-L2, may synergize with immunomodulatory drugs to enhance tumor suppression. We hypothesized that combining GSK3377794 and pembrolizumab may result in a synergistic antitumor effect.

Combination therapy

Pembrolizumab, a selective humanized IgG4 anti-PD-1 monoclonal antibody that blocks the intersection of PD-1 with PD-L1 and PD-L2, may synergize with immunomodulatory drugs to enhance tumor suppression. We hypothesized that combining GSK3377794 and pembrolizumab may result in a synergistic antitumor effect.

Study objective

To evaluate safety and efficacy of GSK3377794 alone or in combination with pembrolizumab in patients with MM.

Figure 1. GSK3377794 mechanism of action.

Study design

This study (NCT03168438) is:

- Pilot study
- Open label
- Multicenter

- Treatment screening
- Treatment assignment
- Follow-up

Screening

- 50 patients assigned to either Arm 1 or Arm 2
- Considered for Arm 1 will be completed before screening/enrollment of patients to Arm 2

Treatment

- Arm 1: Pembrolizumab (single IV infusion of 200 or 300 mg)
- Arm 2: Pembrolizumab (300 mg IV Q2W) starting Week 3 or Week 6 (tableaux 1 and 3)

Follow-up

- EOT: LTFU up to 15 years ( Study: 2017)
- EOT: LTFU up to 10 years (Study: 2019)

Table 1

Patient flow

<table>
<thead>
<tr>
<th>PART 1</th>
<th>Eligibility screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening ICF</td>
<td>HLA-A<em>02:01, HLA-A</em>02:05, and/or HLA-A*02:06 blood testing</td>
</tr>
<tr>
<td>Study eligibility (IE)</td>
<td>NY-ESO-1/ LAGE-1a expression bone marrow testing</td>
</tr>
<tr>
<td>ICF for Parts 2 and 3</td>
<td>Leukapheresis/ manufacturing</td>
</tr>
<tr>
<td>Treatment assignment</td>
<td>Leukapheresis</td>
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<tr>
<td></td>
<td>Cell manufacturing</td>
</tr>
<tr>
<td></td>
<td>Bridging therapy (if clinically needed)</td>
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<tr>
<td></td>
<td>G-CSF (Day -4 if clinically needed)</td>
</tr>
<tr>
<td></td>
<td>Study treatment</td>
</tr>
</tbody>
</table>

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References


Acknowledgments

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Ethics approval statement

This study (NCT03168438) was conducted under approval by the appropriate institutional ethics committees.

Disclosures

AJ is an employee of GSK; ANH is an employee of and holds equity in GSK, Collegeville, PA, USA; AKB is an employee of Winship Cancer Institute, Emory University; MTS is an employee of and holds equity in Merck. SA, BPH, and JLK are employees of and hold equity in GSK; KB is an employee of and holds equity in Atara Biotherapeutics and holds equity in Merck; MM is an employee of and holds equity in GSK, Collegeville, PA, USA; and YW is an employee of and holds equity in Abbvie, North Chicago, IL, USA. This study (NCT03168438) is: Primary objective: assess safety and tolerability of GSK3377794 treatment (no pembrolizumab) endpoints include: Adverse events, including serious adverse events Laboratory assessments Cardiac assessment via electrocardiogram Secondary objective: assess antitumor activity of GSK3377794 treatment (no pembrolizumab) endpoints include: ORR TTR DoF (for patients who achieve ≥ PR) PFS

Study objectives and endpoints

Primary objective: assess safety and tolerability of GSK3377794 treatment (no pembrolizumab) endpoints include: Adverse events, including serious adverse events Laboratory assessments Cardiac assessment via electrocardiogram Secondary objective: assess antitumor activity of GSK3377794 treatment (no pembrolizumab) endpoints include: ORR TTR DoF (for patients who achieve ≥ PR) PFS

Current status

Enrollment began January 2017
In the study database as of November 4, 2019:

- 98 patients consented
- 43 (of 94) tested positive for HLA-A*02:01, HLA-A*02:05 ± HLA-A*02:06
- 15/26 tested positive for NY-ESO-1 ± LAGE-1a, illustrating high expression of this antigen in MM

To date, 4 patients were enrolled and assigned a treatment arm; 3 patients have been treated with GSK3377794, demonstrating feasibility of identifying and treating HLA-A*02/antigen-positive patients with relapsed/refractory MM.

Estimated completion date (final data collection date for the last enrolled patient) - April 2021

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