Tableaucelecleucel in Combination With Pembrolizumab in Platinum-pretreated, Recurrent/Metastatic Epstein-Barr Virus-Associated Nasopharyngeal Carcinoma

Lillian L. Siu, MD, FRCPC,1 Joshua M. Bauml, MD,2 Douglas Adkins, MD,3 A. Dimitrios Colevas, MD,4 Cesar A. Perez, MD,5 Jennifer H. Choe, MD, PhD,6 Yang Zhang, PhD,7 Willis H. Navarro, MD,7 Missak Haigentz Jr, MD,8 Guilherme Rabinowits, MD,9 David G. Pfeifer, MD10

1 Princess Margaret Cancer Centre, Toronto, Ontario, Canada; 2 Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; 3 Washington University School of Medicine, St. Louis, Missouri, USA; 4 Stanford Cancer Institute, Stanford, California, USA; 5 Sylvester Comprehensive Cancer Center, Miami, Florida, USA; 6 Duke University, Durham, North Carolina, USA; 7 Atara Biotherapeutics, South San Francisco, California, USA; 8 Memorial Sloan Kettering Cancer Center, New York, New York, USA

BACKGROUND

- Nasopharyngeal carcinoma (NPC) is an undifferentiated squamous cell carcinoma with a worldwide incidence of approximately 80,000 new cases per year
- Approximately 25% of patients with NPC develop recurrent or metastatic disease
- Despite improvements in first- and second-line treatments, metastatic NPC has a poor prognosis with a median overall survival (OS) of 21-29 months
- A majority of NPC are associated with Epstein-Barr virus (EBV), and the anti-PD-1 antibody pembrolizumab, demonstrated antitumor activity in a phase 1b study of patients with recurrent or metastatic NPC, with an objective response rate (ORR) of 29% and a median OS of 16.5 months
- Tableaucelecleucel (tab-cel) is an off-the-shelf, allogeneic EBV-targeted T cell immunotherapy selected from a library of T cells with the most appropriate HLA restriction to address the patient’s disease
- In a phase 2 study of patients with recurrent or metastatic EBV+ NPC, tableaucelecleucel immunotherapy had a favorable safety profile with an overall response rate of 21% and a 2-year OS rate of 84%

Tableaucelecleucel Mechanism of Action

- EBV-specific T cells selectively identify the EBV-encoding viruses displaying the same HLA restriction
- The EBV-specific T cell receptor recognizes the tumor cell in an HLA-restricted manner and becomes activated
- EBV-specific T cells are activated and proliferate to attack target cells
- In the absence of target antigen, proliferation of T cell stops and their levels are reduced

STUDY SCHEMA

1. Patients With Complete or Partial Response After 2 Treatment Cycles in Phase 2

- Phase 1b, multicenter, open-label, single-arm study in patients with platinum-pretreated, recurrent/metastatic EBV+ NPC
- Overall planned sample size: 40-60 patients
- Tableaucelecleucel will be selected for each patient from the library of available cell products based on matching ≥2 HLA alleles, at least one of which is a restricting HLA allele (HLA-DR, HLA-DQ, or HLA-DP), of the patient

Key Eligibility Criteria

- Availability of an appropriately HLA-matched and restricted tableucelcelucel
- Male or female ≥ 12 years of age
- Incurable, locally recurrent or metastatic EBV+ NPC
- Measurable disease according to RECIST 1.1
- Prior therapy with platinum-containing regimen
- Phase 1b: checkpoint inhibitor naive or refractory to an anti-PD-1 or anti-PD-1 monoclonal antibody
- Phase 2: checkpoint inhibitor naive
- Life expectancy ≥ 16 years
- Adequate organ function
- Written informed consent
- No anti-thymocyte globulin or similar anti-T cell antibody therapy
- ≥ 7 days prior to cycle 1

Planned Dose Table

<table>
<thead>
<tr>
<th>Phase</th>
<th>Number of Patients</th>
<th>Prior Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>12-24</td>
<td>Checkpoint inhibitor naive or PD-1/PD-L1 failures (ie, refractory to or relapsed after PD-1/PD-L1 treatment)</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>Checkpoint inhibitor naive</td>
</tr>
</tbody>
</table>

Planned Doses of Tableaucelecleucel and Pembrolizumab

<table>
<thead>
<tr>
<th>Phase</th>
<th>Tableaucelecleucel Dose</th>
<th>Pembrolizumab Adult Dose</th>
<th>Pembrolizumab Pediatric Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>1 x 10^6 cells/kg on days 1, 8, and 15</td>
<td>200 mg on day 1</td>
<td>2 mg/kg on day 1</td>
</tr>
<tr>
<td>2</td>
<td>1 x 10^6 cells/kg on days 1, 8, and 15</td>
<td>200 mg on day 1</td>
<td>2 mg/kg on day 1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase</th>
<th>Tableaucelecleucel Dose</th>
<th>Pembrolizumab Adult Dose</th>
<th>Pembrolizumab Pediatric Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 x 10^6 cells/kg on days 1, 8, and 15</td>
<td>200 mg on day 1</td>
<td>2 mg/kg on day 1</td>
</tr>
<tr>
<td>2</td>
<td>1 x 10^6 cells/kg on days 1, 8, and 15</td>
<td>200 mg on day 1</td>
<td>2 mg/kg on day 1</td>
</tr>
</tbody>
</table>

REFERENCES


ACKNOWLEDGMENTS AND DISCLOSURES

This study was funded by Atara Biotherapeutics (NCI/NCI642). Acknowledgments: The authors would like to thank Todd Shih, MD, PhD, for her contributions to the study. Writing support for this poster was funded by Atara Biotherapeutics and provided by Kathryn Boone, PhD.


DLT Definition

- Grade 4 nonhematologic toxicity or grade 4 hematologic toxicity lasting ≥ 7 days (except thrombocytopenia)
- Grade 3 nonhematologic AE, except for grade 3 fatigue for ≤ 3 days; grade 3 diarrhea, nausea, or vomiting without use of anti-emetics
- No withdrawal of an anti-diarrheal drug due to an uncontrolled event
- No withdrawal of corticosteroids or anti-inflammatory agents
- Grade 3/4 non-hematologic laboratory value if:
  - Clinically significant medical intervention required to treat the laboratory abnormality
  - Abnormality leads to hospitalization, persists for ≥ 1 week, or results in drug-induced liver injury
- Exceptions are clinically nonsignificant, treatable, or reversible laboratory abnormalities
- Grade 3/4 febrile neutropenia
- > 2 week delay in starting cycle 2 due to treatment-related toxicity
- Treatment-related toxicity resulting in discontinuation of treatment during cycle
- Missing ≥ 25% of pembrolizumab or tableaucelecleucel doses due to investigational product-related AEs during cycle

Grade 5 toxicity

Treatment Phase

- All patients (phase 1b/2) will receive two 21-day cycles of combination immunotherapy
- Based on response to treatment, patients may receive one additional consolidation cycle with the same tableaucelecleucel and pembrolizumab; tableaucelecleucel with the same or a different HLA restriction, if available (without pembrolizumab)
- A maximum of 4 treatment consolidation cycles and 1 HLA restriction switch, if available, will be permitted

Maintenance Phase

- Patients will receive tableaucelecleucel on day 1 and pembrolizumab on days 1, 15, 29, and every 64 days after maintenance cycles until disease progression, unacceptable toxicity, or a total of 35 pembrolizumab infusions

Follow-up

- Patients will be followed every 3 months until 12 months after the last dose of tableaucelecleucel or disease progression

Endpoints

Primary
- Phase 1b
  - Incidence of DLTs
  - Maximum tolerated dose or recommended phase 2 dose of tableaucelecleucel in combination with pembrolizumab
- Phase 2
  - ORR of tableaucelecleucel plus pembrolizumab
  - Safety of tableaucelecleucel plus pembrolizumab

Secondary
- Complete response (CR), duration of response, progression-free survival, and OS
- Immune response rate (IRR) and duration of immune response
- Exploratory
- Immune biomarkers to correlate with clinical outcomes

Statistical Analysis

- Estimated ORR for the combination immunotherapy is 24.5%
- Based on the exact binomial test at the 1-sided alpha = 0.025 significance level, a sample size of 36 subjects will provide 95% power to detect a true ORR of ≥ 25%. The null hypothesis is ORR ≤ 20%
- The point estimate of ORR and the corresponding 95% CI will be provided
- Efficacy and safety analyses will include all enrolled patients who receive ≥ 1 dose of any tableaucelecleucel
- Primary analysis of tumor response-based endpoints is based on tumor assessments following administration of ≥ 1 cycle of tableaucelecleucel or pembrolizumab
- Efficacy endpoints that are defined as proportions, including CR rate and IRR, will be summarized using two-sided exact binomial 95% confidence intervals
- Adverse events will be graded according to CTCAE version 5