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

Abstract # TPS6092

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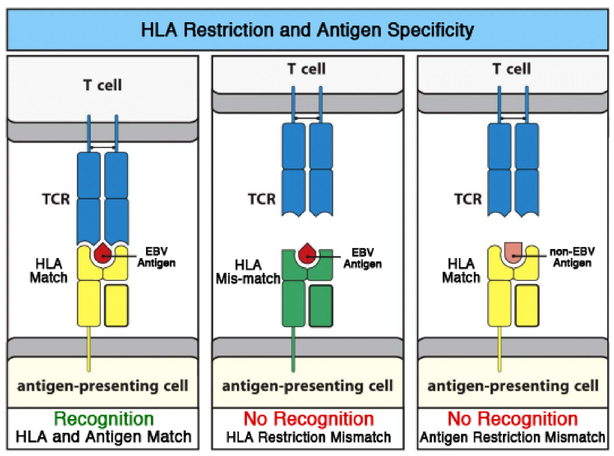
BACKGROUND

- 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[1]
- A majority of NPCs are associated with Epstein-Barr virus (EBV), and upregulation of programmed cell death-ligand 1 (PD-L1) expression upon EBV infection is thought to play a role in the pathogenesis of NPC
- The anti-PD1 antibody, pembrolizumab, demonstrated anti-tumor activity in a phase 1b study of patients with recurrent or metastatic NPC, with an objective response rate (ORR) of 26% and median OS of 16.5 months[2]
- Tabelecleucel (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, tabelecleucel immunotherapy had a favorable safety profile with an overall response rate of 21% and a 2-year OS rate of 84%[3]
- Given that tabelecleucel and pembrolizumab have shown promising results in the treatment of patients with recurrent or metastatic EBV+ NPC, we are conducting a phase 1b/2 study to evaluate the potential synergistic effect of combining both immunotherapies

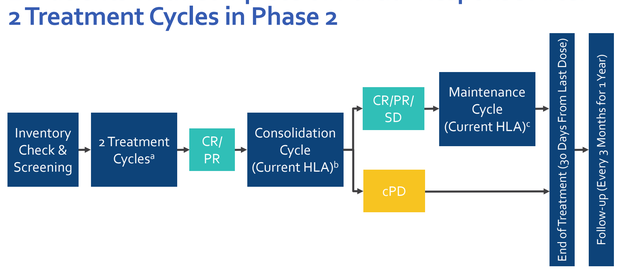
Tabelecleucel Mechanism of Action

- EBV-specific T cells selectively identify the EBV antigen-expressing cells 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 cells stops and their levels are reduced



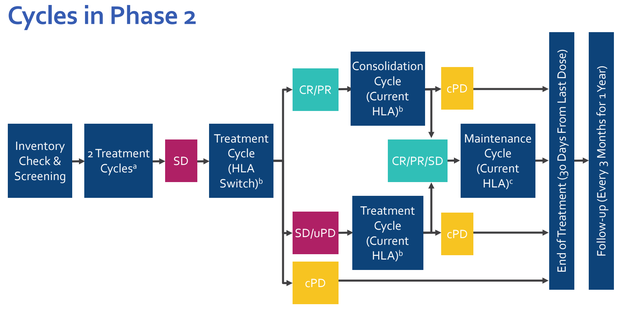
STUDY SCHEMA

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



[a]Tabelecleucel on days 1, 8, and 15; pembrolizumab on day 1 (21-day cycle). Assessment of response between day 16 and day 21 of 2nd cycle. [b]Tabelecleucel on days 1, 8, and 15; pembrolizumab on day 1 (21-day cycle). Assessment of response between day 16 and day 21 of cycle. [c]Tabelecleucel on day 1; pembrolizumab on days 1, 21, 42, and 63 (84-day cycle). Assessment of response between day 75 and day 79 of cycle.
cPD = confirmed progressive disease; CR = complete response; PR = partial response; SD = stable disease.

2. Patients With Stable Disease After 2 Treatment Cycles in Phase 2



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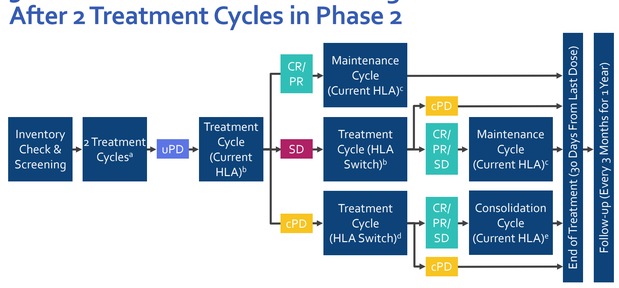
3. Patients With Unconfirmed Progressive Disease After 2 Treatment Cycles in Phase 2



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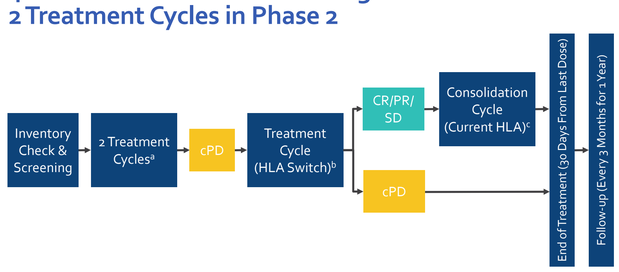

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STUDY DESIGN

- Phase 1b/2, multicenter, open-label, single-arm study in patients with platinum-pretreated, recurrent/metastatic EBV+ NPC
- Overall planned sample size: 48–60 patients
- Tabelecleucel will be selected for each patient from the library of available tabelecleucel based on matching ≥ 2 HLA alleles, at least one of which is a restricting HLA allele, ie, shared between the tabelecleucel source material (donor) and the patient

Key Eligibility Criteria

- Availability of an appropriately HLA-matched and restricted tabelecleucel
- 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 naïve or refractory to an anti-PD-1 or anti-PD-L1 monoclonal antibody
- Phase 2: checkpoint inhibitor naïve
- Life expectancy ≥ 4 months at screening
- Eastern Cooperative Oncology Group performance status of < 2 for patients aged > 16 years; Lansky score ≥ 70 for subjects aged 12 to 16 years
- Adequate organ function
- Written informed consent
- No anti-thymocyte globulin or similar anti-T cell antibody therapy ≤ 4 weeks prior day 1 of cycle 1

Planned Sample Size

Phase	Number of Patients	Prior Therapy
1b	12–24	• Checkpoint inhibitor naïve or PD-1/PD-L1 failures (ie, refractory to or relapsed after PD-1/PD-L1 treatment) • ≥ 6 of 12 patients must have disease that is refractory to an anti-PD-1 or anti-PD-L1 monoclonal antibody for each dose level explored
2	36	• Checkpoint inhibitor naïve

Planned Doses of Tabelecleucel and Pembrolizumab

	Tabelecleucel Dose	Pembrolizumab Adult Dose	Pembrolizumab Pediatric Dose
Dose level 1	2 x 10^6 cells/kg on days 1, 8, and 15	200 mg on day 1	2 mg/kg on day 1
Dose level 2[a]	1 x 10^6 cells/kg on days 1, 8, and 15	200 mg on day 1	2 mg/kg on day 1

[a]Dose de-escalation: If ≥ 2 of the initial 6 patients, or ≥ 4 of the initial 12 patients in phase 1b have a DLT in the first 21 days, an additional 12 patients will receive a reduced dose of tabelecleucel (1 x 10^6 cells/kg) in combination with pembrolizumab.

Phase 1b

- 12–24 patients will be treated with tabelecleucel in combination with pembrolizumab
- Tabelecleucel will be administered initially to 12 patients at 2 x 10^6 cells/kg IV on days 1, 8, and 15 of a 21-day cycle
- Adult and pediatric patients will also receive 200 mg and 2 mg/kg pembrolizumab IV, respectively, on day 1 of each 21-day cycle, ~1 hour before tabelecleucel

Phase 2

- A Safety Data Review Committee will review reported dose limiting toxicities (DLTs) and cumulative safety as soon as possible after the last patient enrolled in phase 1b completes cycle 1 to determine enrollment into phase 2
- 36 patients who are naïve to checkpoint inhibitors will be enrolled in phase 2 to examine the clinical benefits of the combination of tabelecleucel and pembrolizumab
- Dose de-escalation is not permitted in phase 2

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 or anti-diarrheals; grade 3 rash without use of corticosteroids or anti-inflammatory agents
- Grade 3/4 non-hematologic laboratory value if:
  - Clinically significant medical intervention required to treat the patient
  - 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 1
- Missing > 25% of pembrolizumab or tabelecleucel doses due to investigational product-related AEs during cycle 1
- 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 tabelecleucel HLA restriction or additional treatment cycles with tabelecleucel with the same or a different HLA restriction
- Patients with progressive disease may continue treatment with tabelecleucel with 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 tabelecleucel on day 1 and pembrolizumab on days 1, 21, 42, and 63 of 84-day 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 tabelecleucel or disease progression

Endpoints

Primary

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

Secondary

- Complete response (CR) rate, 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 ≥ 45%. Based on the exact binomial test at the 1-sided alpha = 0.025 significance level, a sample size of 36 subjects will provide 90% power to detect a true ORR of ≥ 45%. 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 tabelecleucel.
- Primary analysis of tumor response-based endpoints is based on tumor assessments following administration of up to 2 tabelecleucel HLA restrictions.
- 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.

REFERENCES

1. Zhang, et al. *Lancet.* 2016;388:1883-92.
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