

Updated Results of an Investigator-Initiated Phase II Study of Pembrolizumab and Romidepsin for Patients with Relapsed or Refractory T-Cell Lymphoma (TCL) With Survival Analysis

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Background

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous and aggressive group of non-Hodgkin lymphomas. For most subtypes, relapsed/refractory PTCL (r/r TCL) have a poor prognosis and newer therapies have not been approved since 2014, making it imperative to develop new, efficacious therapies for PTCLs.

Anti-cancer agents Romidepsin (HDAC inhibitor/HDACi) and Pembrolizumab (anti-PD-L1) have modest activity in PTCLs. Based on their mechanisms of action, we hypothesized that their combination may cause synergistic priming of the immune system leading to durable responses.

PD-L1 expression in nodal TCL is between 17%-50%. Single agent PD-1/PD-L1 inhibitors resulted in an Overall Response Rate (ORR) ~33%, median Overall Survival (mOS) of 10.6 months and median Duration of Response (mDoR) of 2.9 months. Histone deacetylase inhibitors (HDACi) have an ORR of around 30%, with Complete Response (CR) rate of around 15%.

HDACi are associated with increased PD-L1 expression and augmented responses to anti–PD-L1 therapy.

Hypothesis and Rationale

Hypothesis: TCLs have mutations in epigenetic modifier genes that may impair immunogenicity and promote immune escape

Rationale for PD-1 inhibitor + HDACi: combination of these two therapies may lead to synergistic tumor eradication.

Methods

Between February 2018-April 2022, 38 patients were enrolled in this study (6 phase I and 32 phase II patients). The study schedule was Pembrolizumab at 200 mg on day 1 and Romidepsin 14 mg/m2 on days 1 and 8, in a 21-day cycle. The maximum number of cycles was 35. Adverse events were monitored and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 guidelines. The primary endpoint for the phase II part is overall response (OR: CR+PR); the 6 patients enrolled in the phase I part were included in the response assessment. Secondary objectives included progression free survival (PFS) and overall survival (OS). Outcome assessment were performed utilizing Lugano Revised Response Criteria. Kaplan-Meier method was used to estimate PFS and OS.

Demographics for Phase 1 and II	TCL (n=38)
Age (median; range in years) <60 n (%) ≥60 n (%)	67 (32-82) 5 (13.2) 33 (86.8)
Gender, n (%)	Male: 22 (57.9) Female: 16 (42.1)
Race, n (%)	Caucasian: 24 (63.2) Black: 7 (18.4) Asian: 4(10.5) Other: 3 (7.9)
ECOG ≤2, n (%)	38 (100)
Histologic classification, n (%) Nodal TfH PTCL ALCL ALK+ ALK- BIA Cutaneous Extranodal	 29 (76.3) 12 13 1 2 1 4 (10.5) 5 (13.2)
Bone marrow involvement, n (%)	16 (42.1)
Elevated LDH, n (%)	**26 (68.4)**
Stage III/IV, n (%)	24 (63.2)
Disease status, n (%)	Relapse: 7 (18.4) Refractory: 31 (81.6)
Prior therapies CHOP/CHOP protocol CHOEP EPOCH BV with CHP or CHEP or Benda Others: ABVD, Cisplatin, DeVIC, Gemcitabine, SMILE	 10 10 3 8 7
Prior SCT, n (%)	9 (23.7)
IPI, n (%) 0 1 2 3 4	 1 (2.6) 5 (13.1) 10 (26.3) 15 (39.5) 7 (18.5%)
PD-L1 by IHC (IQR 0-30, max 95) <7.5 ≥7.5	n=32 16 (50) 16 (50)

Table 1 **Demographics and Characteristics**

The number of patients in the intention to treat population (ITT) for the primary endpoint of overall response (Table 1) was 38; the median age was 67 with a male predominance (57.9%). Majority of the patients (86.8%) were >60 years. LDH was elevated in 68.4% and 63.2% of patients had Stage III/IV disease. The median PD-L1 expression was 7.5% (IQR 0-30, max 95).

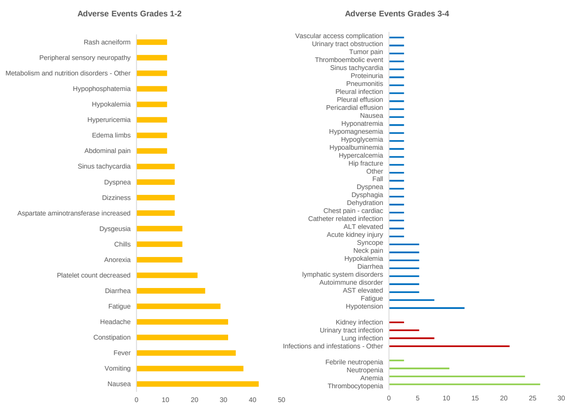


Table 2 **Safety - Adverse Events**

The most common ≥ grade 3 adverse events were infections (n=11) and thrombocytopenia (n=10). Three patients stopped therapy due to development of immune related adverse events (iRAEs) - Grade 1 cytokine storm (n=1), Grade 3 gastritis (n=1), Grade 4 colitis (n=1).

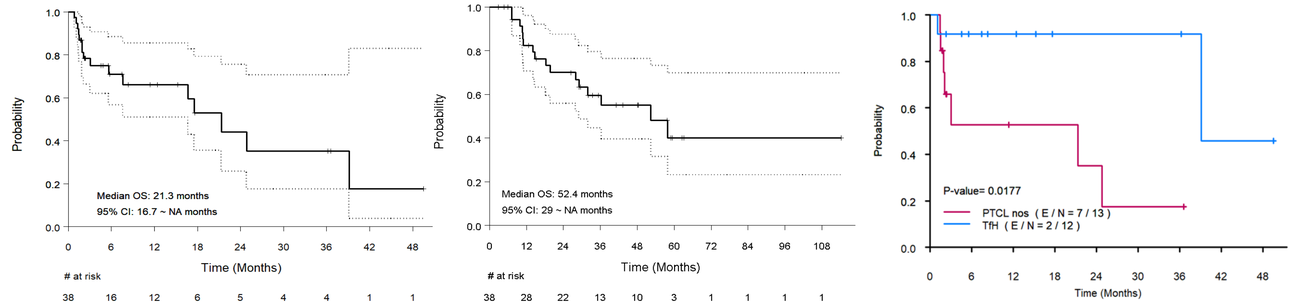


Figure 2 **Overall Survival (OS) on study (left), Overall Survival since Diagnosis (middle), Overall Survival by Diagnosis Subtype (right)**

The median Overall Survival (OS) on study was 21.3 months, with a median follow-up of 11.4 months (95% CI: 5.6 ~ 36.6 mos). The median Overall Survival since Diagnosis was 52.4 months, with a median follow-up 43.3 months (95% CI: 33.5 ~ 62.5 mos). The median overall survival was significantly different (p-value = 0.0177) in study subjects with PTCL-NOS (magenta) as compared to subjects with PTCL-TfH (blue). Subjects with PTCL-TfH had a higher probability of Survival in the study period.

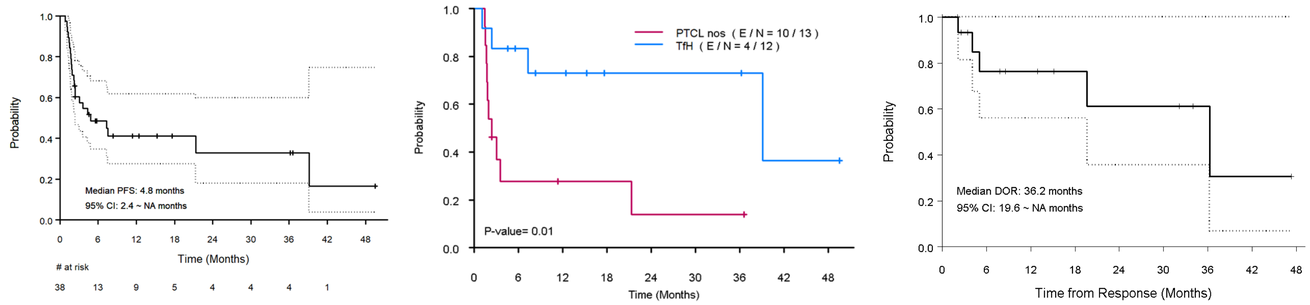


Figure 2 **Progression Free Survival (PFS) (left), Progression Free Survival (PFS) by Diagnosis (middle), Median Duration of Response (DOR) (right)**

The median PFS on study was 4.8 months (95% CI: 2.4 ~ N/A mos). The median PFS was significantly different (p-value = 0.01) in study subjects with PTCL-NOS (magenta) as compared to subjects with PTCL-TfH (blue). Subjects with PTCL-TfH had a higher probability of PFS during the study period. The median DOR was 36.2 months (95% CI: 19.6 ~ N/A mos).

Conclusions

•Romidepsin and pembrolizumab in combination leads to high response rates and prolonged remissions.

•The combination has promising PFS and OS in r/r TCL and supports further development of this approach
- TfH subtype have the best PFS and OS

•No association between PDL1 expression and response

•Future directions:
- correlatives
- larger phase II study is planned

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