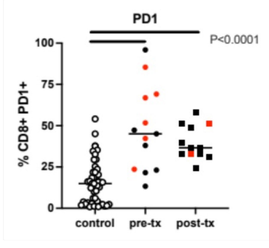
Phase 2 Study of Nivolumab in Epstein-Barr Virus (EBV)-Positive Lymphoproliferative Disorders (LPD) and EBV-Positive Non-Hodgkin Lymphomas (NHL)

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Background

- Programmed cell death protein-1 (PD-1) is a signaling molecule on the surface of T-cells that suppresses the cytotoxic effects of T-cells on tumor cells.
- Increased PD-1 expression on CD8+ T-cells compared to healthy controls has been shown in patients with LYG, which could be reversed with immunotherapy using interferon alpha-2b (*Melani et al Lancet Hematology 2023*).



- Elevated programmed death-ligand 1 (PD-L1) has been observed in other EBV-LPDs and NHLs as well as chronic viral infections, such as EBV.
- Hypothesis: Nivolumab (anti-PD-1 antibody) therapy may reverse T-cell exhaustion and result in anti-tumor responses in patients with LYG and other EBV-LPDs and NHLs, including those with systemic and/or CNS involvement.

Methods

- Key Inclusion Criteria:
  - Relapsed/refractory (R/R) and untreated EBV-LPD and B-cell NHL (R/R only)
  - Known immunodeficiency or autoimmune illness eligible if not on steroids or immunosuppression within 14 days of study
  - CNS involvement permitted if no seizures within 4 weeks of study
- Key Exclusion Criteria:
  - Prior immunotherapy (PD-1/PD-L1/PD-L2/CD137/CTLA-4 antibodies)
  - Solid organ transplant
  - HIV infection
- Nivolumab 480 mg IV every 4 weeks
  - 1 year duration (if CR); 2 years duration maximum (if <CR)
- Baseline CT, PET, MRI brain, flow of blood and CSF, BM, and optional tumor biopsy were performed.
- Restaging CT after cycles 3, 6, 13, 19, and EoT, and PET after cycles 1, 3 and EoT.
- Surveillance CT performed q3m for 1 y, q6m for yrs 2-5 then annually.

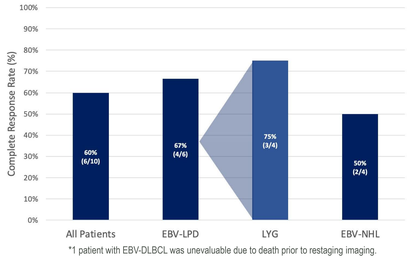
Results

Table 1: Baseline Characteristics

Characteristics	EBV-LPD cohort (N=6)	EBV-NHL cohort (N=5)	All Patients (N=11)
Age- median (range)	54 (47-67)	40 (20-51)	48 (20-67)
Male- no. (%)	4 (67)	4 (80)	8 (73)
Histology- no. (%)			
CAEBV*	1 (17)	--	1 (9)
EBV B-LPD	1 (17)	--	1 (9)
G1-2 LYG	4 (67)	--	4 (36)
G3 LYG	--	0 (0)	0 (0)
EBV-DLBCL NOS	--	5 (100)	5 (45)
ECOG ≥ 2- no. (%)	1 (17)	1 (20)	2 (18)
Stage III/IV- no. (%)	6 (100)	5 (100)	11 (100)
Elevated LDH- no. (%)	0 (0)	5 (100)	5 (45)
Extranodal sites ≥ 2- no. (%)	4(67)	3 (60)	7 (64)
Extranodal sites – no. (%)			
Lung	3 (50)	4 (80)	7 (64)
CNS	2 (33)	0 (0)	2 (18)
Other*	4 (67)	4 (80)	8 (73)
CD4 count- median (range)	401 (99-1304)	152 (112-255)	255 (99-1304)
CD8 count- median (range)	125 (22-1237)	49 (9-630)	86 (9-1237)
CD19 count- median (range)	61 (18-573)	0 (0-162)	50 (0-573)
NK count-median (range)	179 (68-447)	86 (7-264)	157 (7-447)
EBV VL- median (range)	1.28 (0-6.78)	0 (0-5.33)	0 (0-6.78)
IgG level-median (range)	1010 (707-1389)	568 (205-1856)	857 (205-1856)
IgA level-median (range)	117 (88-248)	122 (33-627)	122 (33-627)
IgM level-median (range)	40 (29-167)	25 (<5-70)	35 (<5-167)
Prior therapy- median (range)	1 (0-1)	2 (1-6)	1 (0-6)
Prior therapy- no. (%)			
None	3 (50)	0 (0)	3 (27)
Chemotherapy	3 (50)	5 (100)	8 (73)
Rituximab	3 (50)	4 (80)	7 (64)
Allo-HSCT	0 (0)	1 (20)	1 (9)
Refractory to last therapy- no. (%)**	1 (33)	3 (60)	4 (50)

*Other sites include: Muscle (N=5), skin (N=3), kidney (N=2), pharynx (N=2), bone (N=2), bone marrow (N=1), trachea (N=1), adrenal (N=1), liver (N=1), pancreas (N=1), peritoneal (N=1); **Treated patients only (N=8).

Figure 1: Complete Response Rate by Cohort



*1 patient with EBV-DLBCL was unevaluable due to death prior to restaging imaging.

Figure 2: Adverse Events

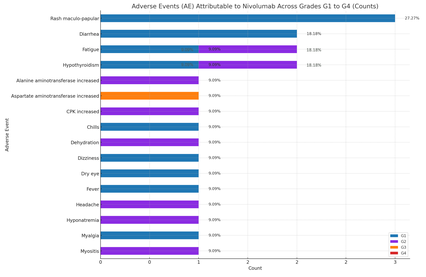
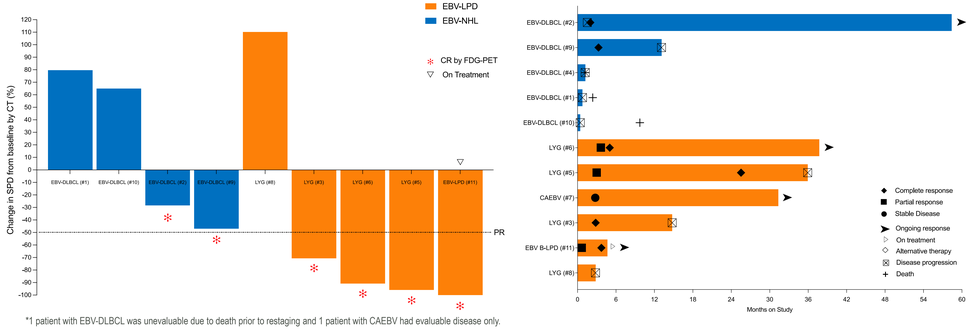
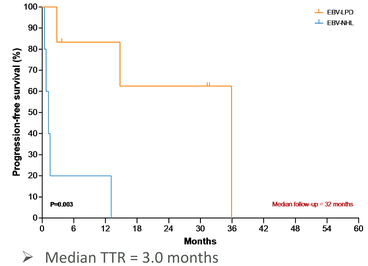


Figure 3: Tumor Reduction and Clinical Outcome



*1 patient with EBV-DLBCL was unevaluable due to death prior to restaging and 1 patient with CAEBV had evaluable disease only.

Figure 4: Progression-free Survival (PFS) by Cohort



- Median TTR = 3.0 months
- 50% (3/6) responses ongoing, from 3-56 months
- 2-year PFS 33%; 63% vs 0% in LPD vs NHL (P=0.003)
- 2-year OS 72%; 100% vs 40% in LPD vs NHL (P=0.04)

Conclusions

- Nivolumab is well tolerated in LYG and other EBV-LPDs and NHLs without unexpected toxicities
- Nivolumab is active in EBV-LPD and NHL and can result in durable CRs, including patients with EBV-LPD of the CNS
- Durable CRs were observed in both patient cohorts with ongoing remission in 50% of patients
- Study enrollment continues to better assess treatment activity and durability

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