University of Colorado Cancer Center

Nanatinostat and Valganciclovir in Relapsed/Refractory Epstein-Barr Virus-Positive (EBV^{+}) Lymphomas: Final Results from the Phase 1b/2 VT3996-201 Study

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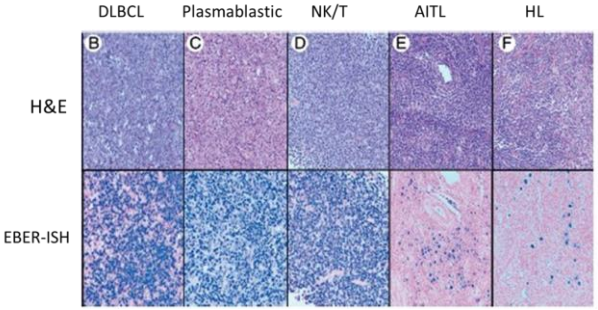
EBV-associated lymphomas:

Incidence and significance

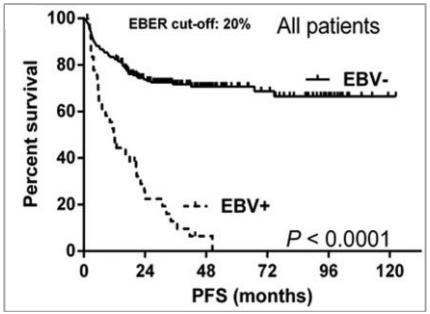
EBV positivity is detectable by in situ hybridization for EBV encoded RNA (EBER-ISH) in B cell, T cell, and NK cell lymphomas, and Hodgkin Lymphoma



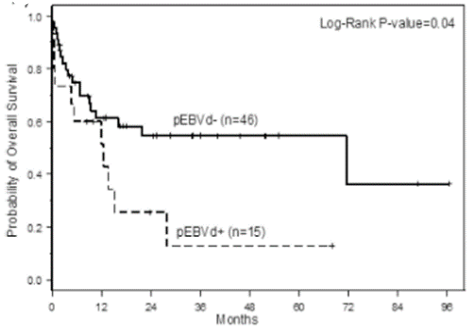
EBV positivity, per lymphoma subtype:

- DLBCL[4] 5-10%
- PTCL, NOS[2] 25-58%
- AITL[4] 70-80%
- ENKTL 100%
- PTLD[4] 60-80%
- Hodgkin's (cHL)[4] 20-30%
- Follicular[5] ~3%

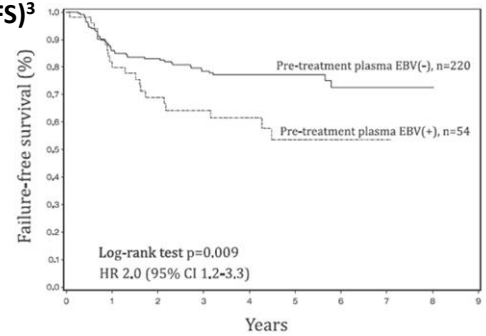
DLBCL (PFS)[1]



PTCL (OS)[2]



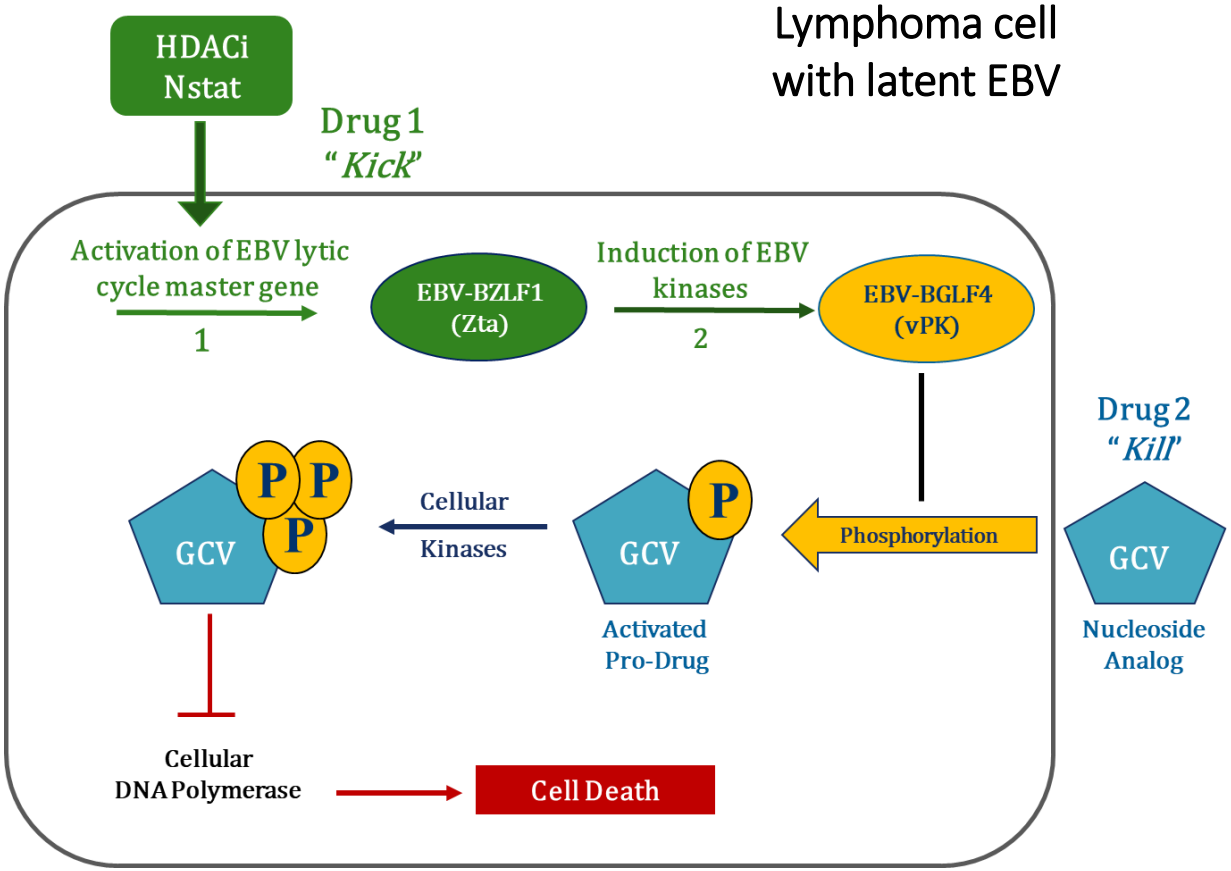
cHL (FFS)[3]



[1]Lu TX et al. Sci Rep. 2015;5:1-14
[2]Haverkos BM, et al. Int J Cancer. 2017; 140:1899-1906; Dupuis J et al. Blood. 2006;108:4163–9
[3]Kanakry JA, et al. Blood 2013;121:3547-53
[4]Swerdlow SH et al. (2017) WHO classification of Tumours of the Haematopoietic and Lymphoid Tissues
[5]Mackrides N et al. Am J Hematol. 2019.

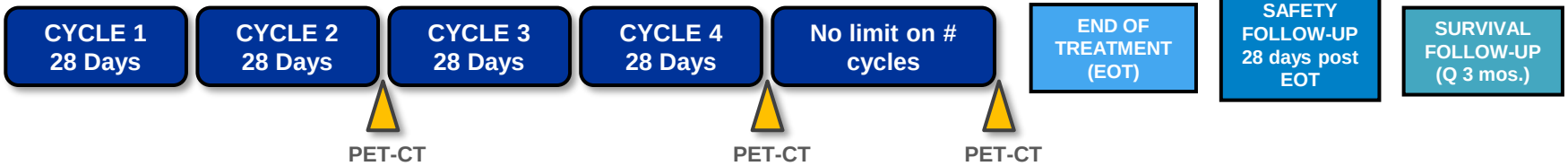
The “kick and kill” approach for EBV-associated lymphomas

Sensitizing EBV+ tumors to the cytotoxic effects of ganciclovir (GCV)



VT3996-201 phase 1b/2 study in R/R EBV^{+} lymphoma

- Open-label Phase 1b/2 study of nanatinostat (Nstat) plus valganciclovir (VGCV) in the US & Brazil
- Dose-ranging Phase 1b (N=25) - **RP2D:** Nstat 20 mg daily, 4 days/week + VGCV 900 mg daily (oral administration)
- Phase 2 expansion at the RP2D: N=30
- Eligibility:
  - R/R EBV^{+} lymphoma (by local pathology), any histology, ≥1 prior therapies with no curative options per Investigator
  - Hgb 8.0 g/dL, ANC ≥1 x 10^9/L, platelets ≥ 50 x 10^9/L, GFR >60 ml/min
  - ECOG 0-2; no CNS disease; HIV+ eligible in Phase 1, not Phase 2
- Response assessment: PET-CT (Lugano 2014) every 2 cycles until PD or withdrawal



- End-points: Safety, overall response rate (ORR), duration of response (DOR)
  - Other: PK, change in plasma EBV DNA (pEBVd)

Patient demographics

	All (n=55)	Phase 1b (n=25)	Phase 2 (n=30)
Median age (y), (range)	60 (19-84)	58 (19-84)	67 (23-81)
Male/Female	35/20	17/8	18/12
ECOG performance status, no. (%)			
• 0-1	48 (87%)	23 (92%)	25 (83%)
• 2	7 (13%)	2 (8%)	5 (17%)
No. of previous lines of antineoplastic therapy – no. (%)			
• 1	13 (24%)	5 (20%)	8 (27%)
• 2	19 (35%)	9 (36%)	10 (33%)
• ≥3	23 (42%)	11 (44%)	12 (40%)
Median no. prior therapies (range)	2 (1-11)	2 (1-11)	2 (1-6)
Brentuximab	14 (26%)	8 (32%)	6 (20%)
ASCT/alloSCT	12 (22%)	7 (28%)	5 (17%)
Checkpoint inhibitor	9 (16%)	5 (20%)	4 (13%)
HDAC inhibitor	6 (11%)	4 (16%)	2 (7%)
EBV CTL	5 (9%)	2 (8%)	3 (10%)
Refractory to last therapy (n,%)	41 (75%)	17 (68%)	24 (80%)
Exhausted all therapies per Investigator	53 (96%)	24 (96%)	29 (97%)

EBV^{+} lymphoma subtype

Diagnosis	Enrolled (n)
B-NHL	**10 (18%)**
DLBCL	7
Other B Cell	3
T/NK-NHL	**21 (38%)**
ENKTL	9
PTCL-NOS	5
AITL	6
CTCL	1
Immunodeficiency-associated LPD	**13 (24%)**
PTLD	4
Other [SLE (2), CVID (1), PI (1)]	4
HIV-associated [PBL (2), DLBCL (2), HL (1)]	5
Hodgkin (cHL)	**11 (20%)**
Total	**55**

Data cutoff date: 10.28.21

Grade 3/4 treatment-emergent AEs in ≥3 patients (5%)

	Phase 1b (n=25)			Phase 2 (n=30)		
	All	G3	G4	All	G3	G4
Thrombocytopenia	13 (52%)	5 (20%)	3 (12%)	7 (23%)	1 (3%)	2 (7%)
Neutropenia	10 (40%)	4 (16%)	5 (20%)	9 (30%)	3 (10%)	4 (13%)
Anemia	9 (36%)	4 (16%)	-	8 (27%)	6 (20%)	1 (3%)
Lymphopenia	6 (24%)	2 (8%)	3 (12%)	4 (13%)	2 (7%)	1 (3%)
Leukopenia	5 (20%)	1 (4%)	2 (8%)	5 (17%)	1 (3%)	1 (3%)
Acute kidney injury	4 (16%)	2 (8%)	1 (4%)	2 (7%)	-	1 (3%)
GI hemorrhage	2 (8%)	2 (8%)	-	2 (7%)	2 (7%)	-
Febrile neutropenia	1 (4%)	1 (4%)	-	3 (10%)	2 (7%)	1 (3%)

- Oral regimen was generally well-tolerated
- Most common TEAEs overall were:
  - Nausea (38%)
  - Thrombocytopenia (36%)
  - Neutropenia (34%)
  - Anemia, constipation (both 31%)
  - Creatinine elevation, diarrhea, fatigue (all 26%)
  - Decreased appetite (22%)
- Serious adverse events (SAEs) occurred in 16 patients (29%); 8 in phase 2. Treatment-related SAEs occurring in ≥2 patients were febrile neutropenia, acute kidney injury and pneumonia (all n=2)
- No study drug related deaths occurred in the treatment period

Clinical responses in evaluable patients (n=43)

Median time to response: 1.8 months (range: 33-162 days)

	All patients (n=43)	DLBCL (n=6)	Other B-NHL (n=2)	ENKTL (n=8)	PTCL-NOS/AITL (n=6)	CTCL (n=1)	HIV-L (n=4)	IA-LPD (n=6)	Hodgkin (cHL) (n=10)
Response									
ORR	**17 (40%)**	**4 (67%)**	**-**	**5 (63%)**	**4 (67%)**	-	**-**	**3 (50%)**	**1 (10%)**
CR	**8 (19%)**	**2 (33%)**	**-**	**1 (13%)**	**3 (50%)**	-	**-**	**2 (33%)**	-
PR	9 (21%)	2	-	4	1	-	-	1	1
SD	7 (16%)	1	-	-	1	-		-	5
PD	19 (44%)	1	2	3	1	1	4	3	4
Clinical benefit rate	24 (56%)	5 (83%)		5 (63%)	5 (83%)			3 (50%)	6 (60%)

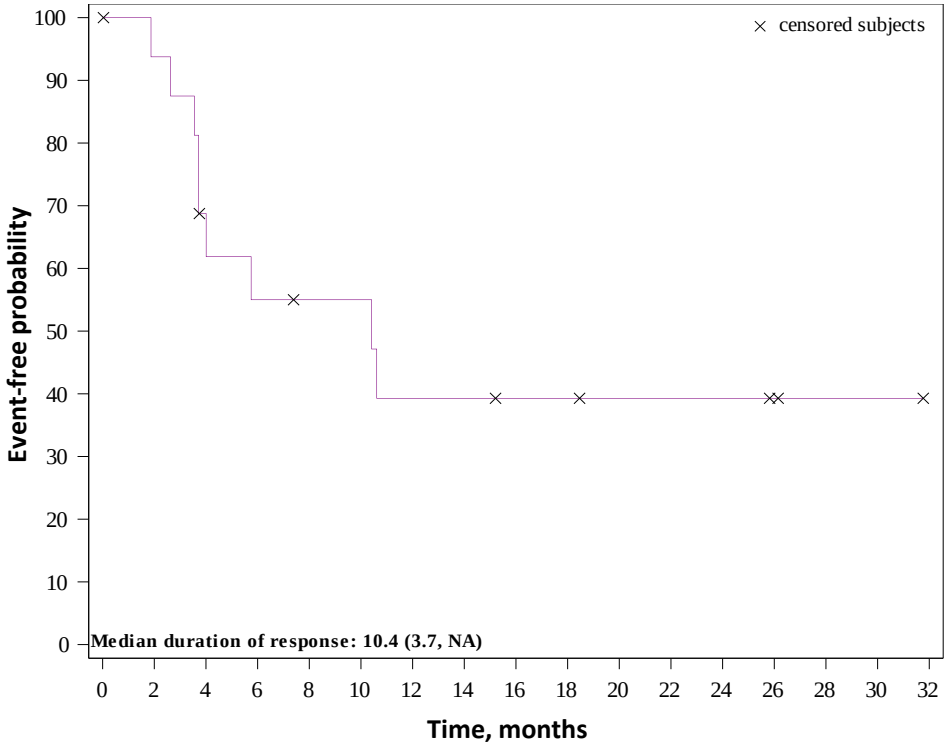
*Evaluable patients: EBER-ISH+ with ≥1 post-treatment response assessment

Prior therapies & responses in T/NK-NHL (N=15)

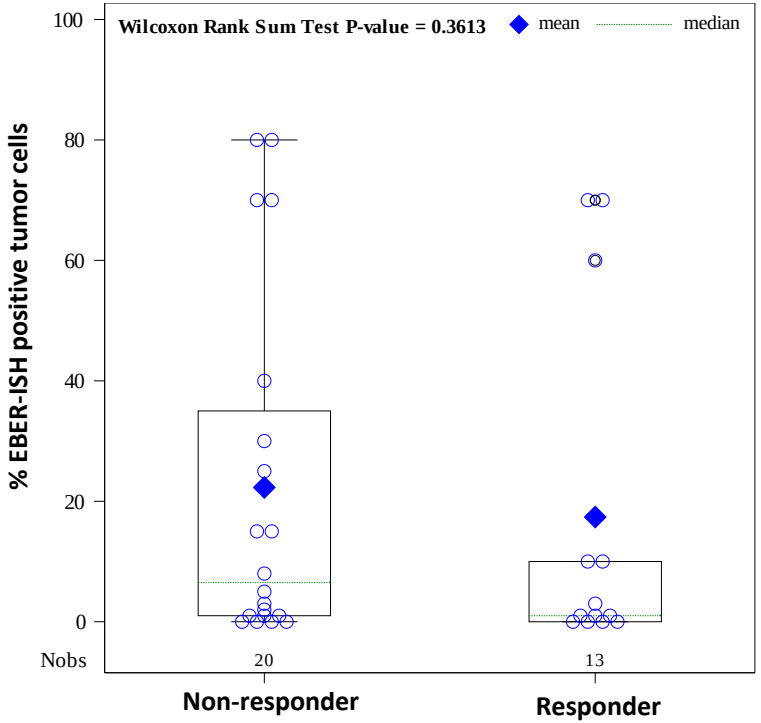
Age, sex	Subtype	Prior therapies	Refractory to last therapy	Response	Response duration
37, F	ENKTL	SMILE + XRT, ASCT	Y	PR	28 m (ongoing)
48, M	ENKTL	SMILE, SMILE, cisplatin + XRT	Y	PR	3.5 m (allo-SCT)
47, F	ENKTL	CHOP, mSMILE + IFRT, mSMILE, HDT-ASCT, EBV CTLs, pembrolizumab	Y	PR	9.2 m (ongoing)
60, F	ENKTL	IMEP, GDP, nivolumab + EBV CTLs	Y	CR	3.7 m
44, M	ENKTL	SMILE, ASCT, pembrolizumab	Y	PR	2.7 m
76, F	ENKTL	GemOx + XRT, pembrolizumab	Y	PD	--
69, F	ENKTL	P-GemOx	Y	PD	--
47, F	ENKTL	SMILE	Y	PD	--
66, M	AITL	CHOP	Y	CR	16.6 m (ongoing)
63, M*	AITL	CHOP, ICE	Y	CR	31.8 m
58, M	PTCL-NOS	CHOEP, romidepsin, ASCT, romidepsin	Y	PR	10.6 m
74, F	PTCL-NOS	CHOP	Y	CR	5.8 m (ASCT)
78, M	AITL	CHOP, BEAM/ASCT, prednisone	Y	SD	--
43, M	CTCL	alloSCT, Resimmune, Targretin, vorinostat	Y	PD	--
71, F	PTCL-NOS	R-CHOP, brentuximab, ICE	Y	PD	--

*remains in CR 20.7 m after stopping study drug

Median duration of response (n=17)
10.4 months

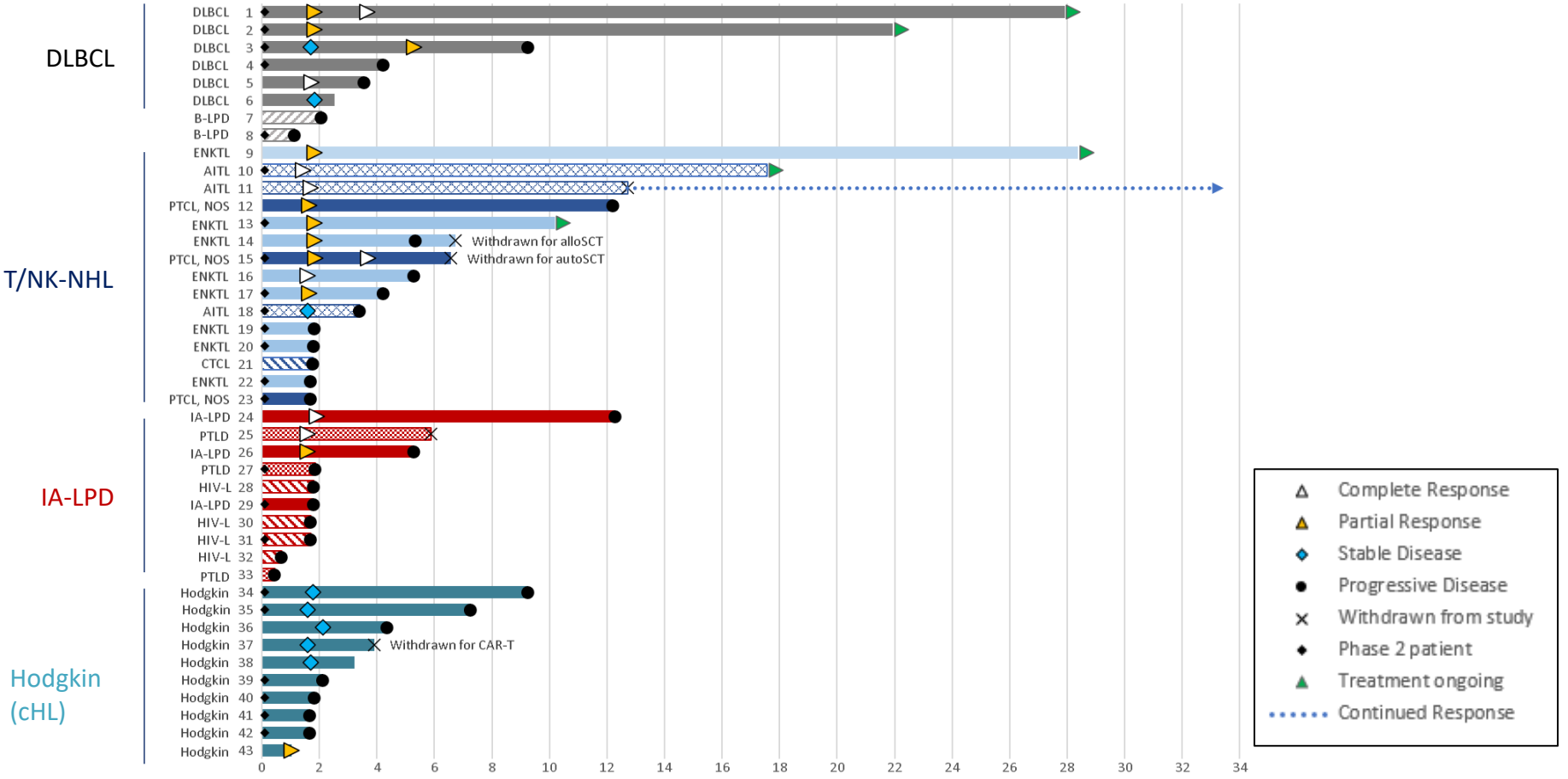


EBER-ISH positivity and response
(by central Lab - Neogenomics)



In 33 evaluable patients, no significant difference between the responders and non-responders in baseline EBER positivity was observed.

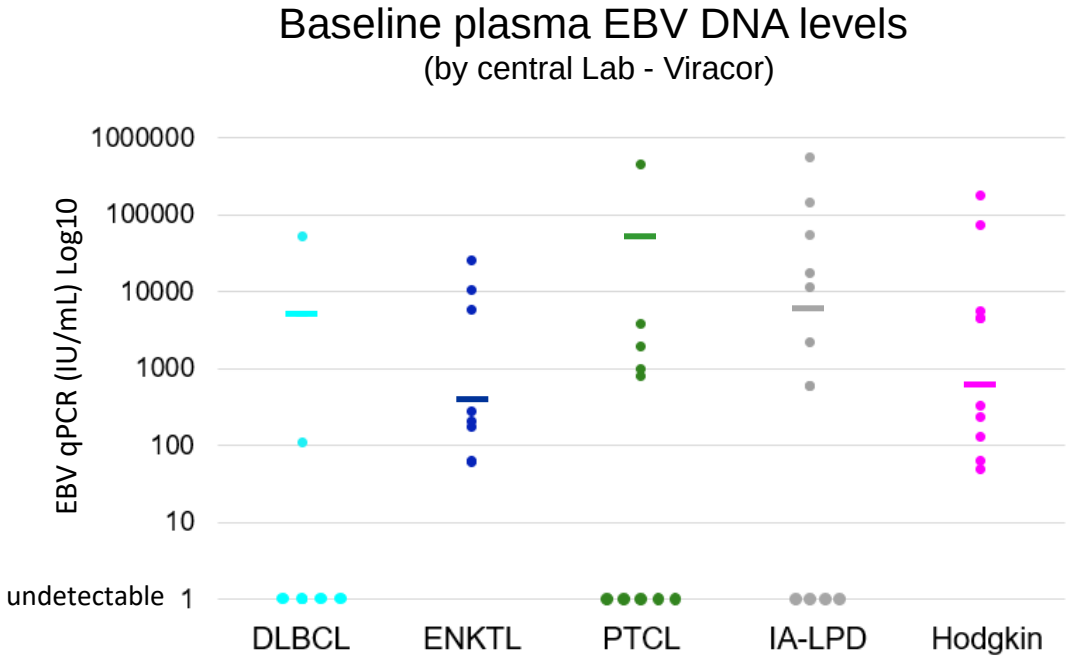
Response duration for all patients by lymphoma subtype



Baseline plasma EBV DNA (pEBVd) levels by lymphoma subtype[1]

- Baseline pEBVd measurement was available in 54/55 patients
- pEBVd was detected in 39 patients at study start (72%); not detectable in 15 (28%)
- Median pEBVd (detectable): 2200 IU/mL (range 49 - 575,000 IU/mL)

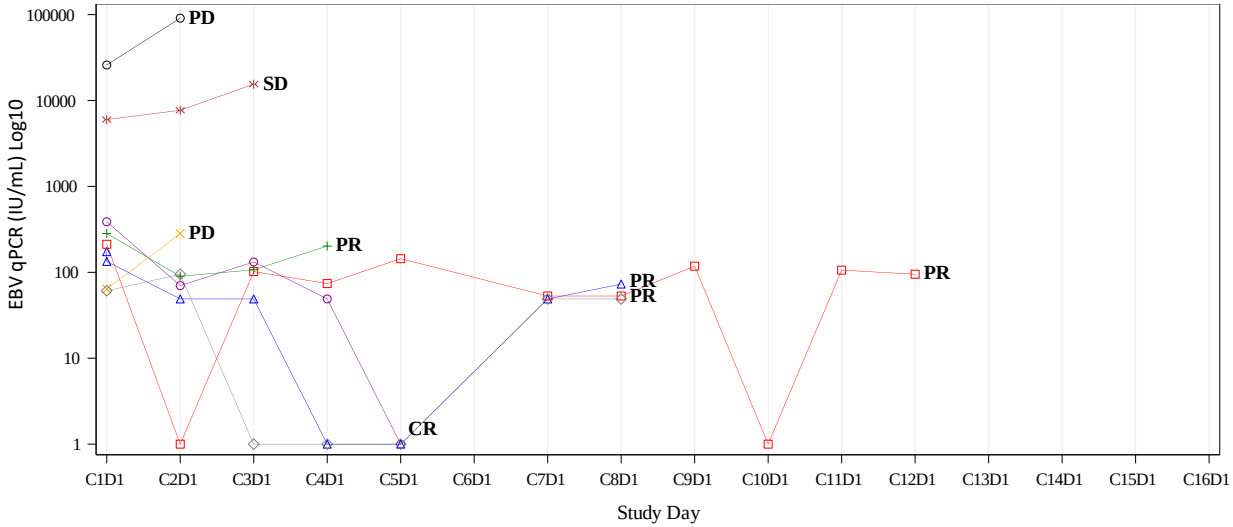
	Detectable plasma EBV DNA at baseline
DLBCL	3/7 (43%)
ENKTL	9/9 (100%)
PTCL	6/11 (55%)
IA-LPD	8/13 (62%)
Hodgkin	11/11 (100%)



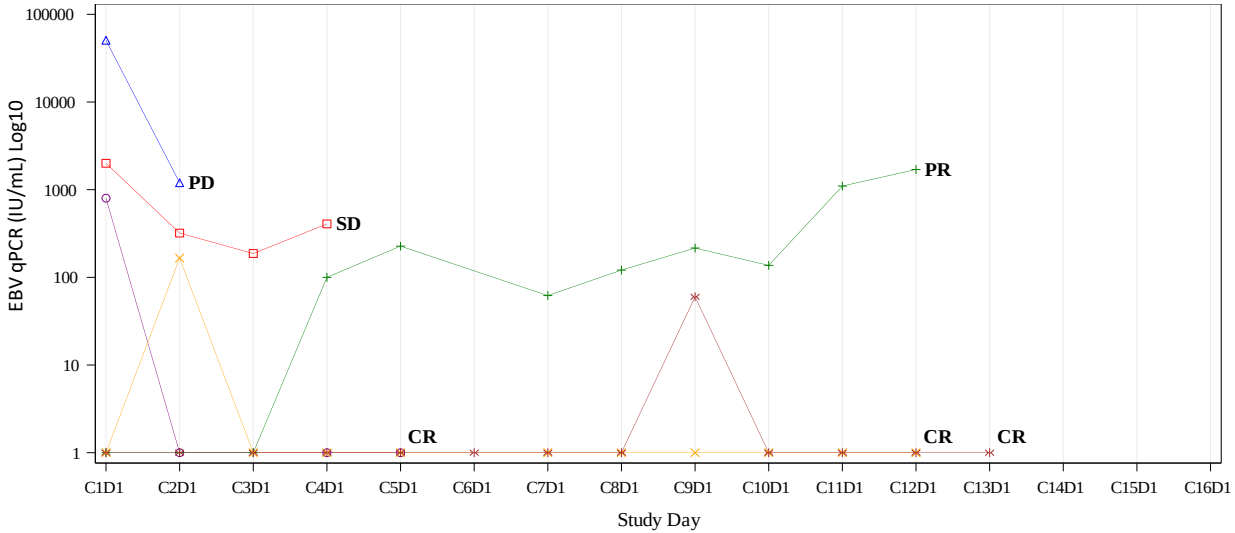
[1]All patients enrolled had EBV-positive lymphoma by EBER-ISH on tumor tissues as determined by each pathology laboratory

T/NK-NHL:
Plasma EBV DNA levels

ENKTL (n=8)

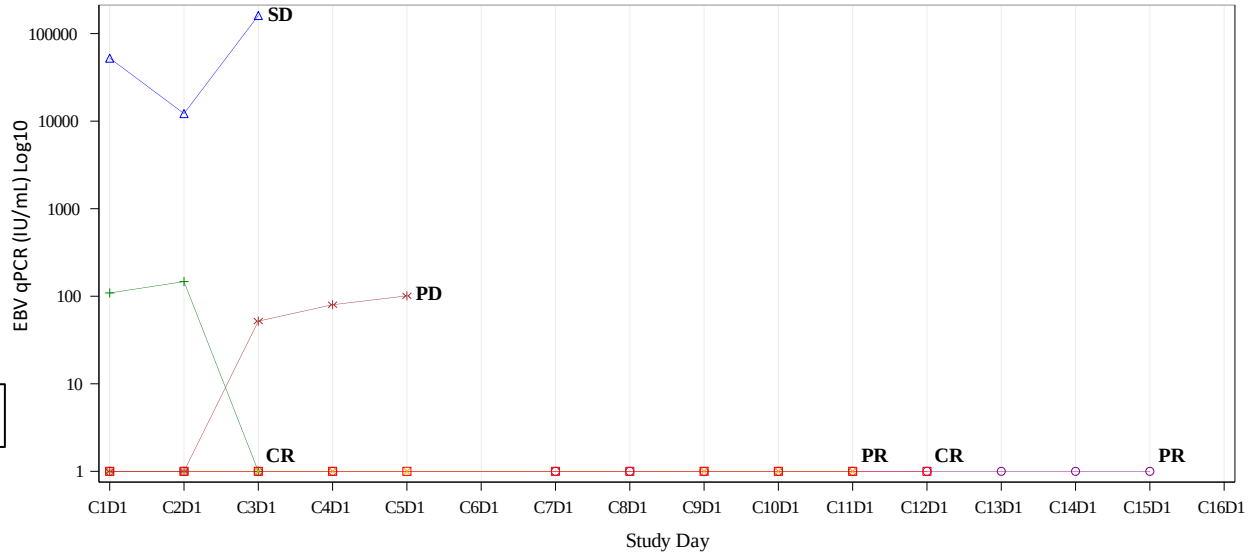


PTCL-NOS & AITL (n=6)

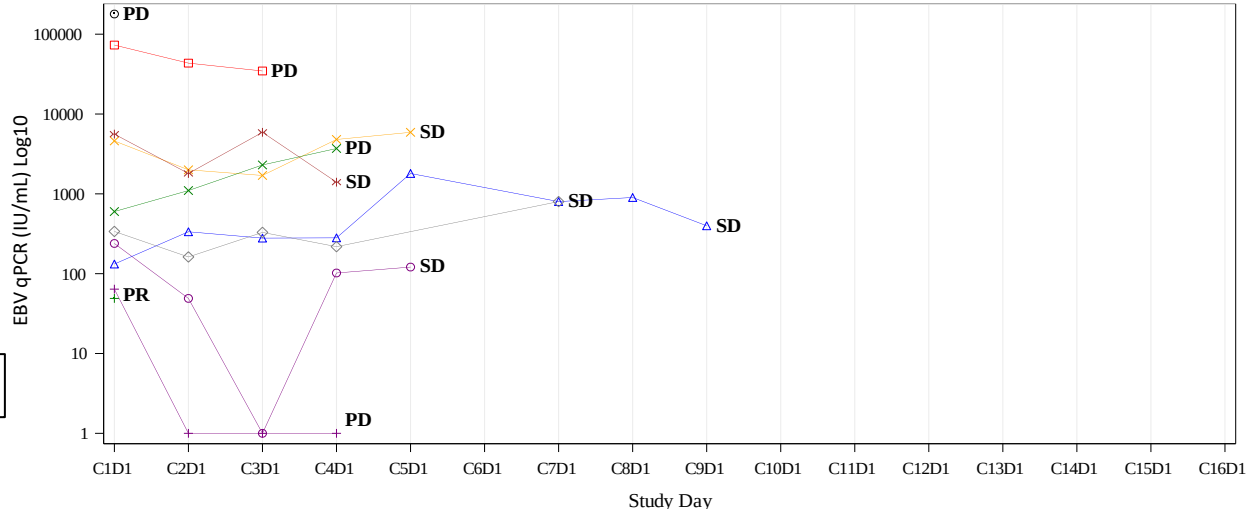


DLBCL and Hodgkin:
Plasma EBV DNA levels

DLBCL (n=6)



Hodgkin (n=10)



Conclusions

- Nanatinostat + VGCV is a novel EBV-targeting therapy with clear anti-tumor rationale in EBV-positive lymphomas
- Final results of the Phase Ib/II show that Nstat + VGCV is a well tolerated combination, with reversible low grade toxicities
- Lymphoma subtypes of different lineage respond to Nstat + VGCV, irrespective of patient's immune status and degree of EBER-ISH positivity. Complete responses in DLBCL, T and NK-cell lymphomas, and IA-LPD, with a median duration of response of 10.4 months
- Plasma EBV DNA levels were detected at baseline in 72% of patients and higher levels at baseline and during therapy were more often found in non responders, identifying a potential predictor of response
- Nanatinostat + VGCV offers a safe and active oral therapy for patients with EBV-positive lymphomas that is feasible in resource-limited and infrastructure-poor communities.
- **A global multicenter phase 2 basket study (NAVAL-1) is currently enrolling patients with R/R EBV+ lymphoma (NCT05011058)**

Acknowledgements

Investigators

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Patients and Families

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