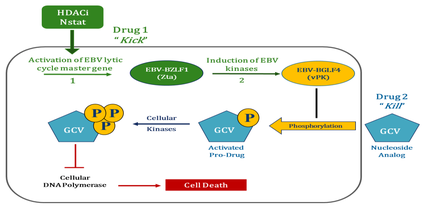
A GLOBAL PHASE 2 TRIAL OF NANATINOSTAT IN COMBINATION WITH VALGANCICLOVIR IN PATIENTS WITH EBV-POSITIVE (EBV+) RELAPSED/REFRACTORY PERIPHERAL T CELL LYMPHOMAS (NAVAL-1)

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INTRODUCTION

- Epstein-Barr virus-positive (EBV⁺) lymphomas are a heterogeneous group of malignancies that harbor latent EBV within the lymphoma cells, and are associated with variable clinical features, treatments, and prognoses.
- Outcomes in EBV⁺ lymphoma patients are typically inferior compared to EBV-negative (EBV⁻) lymphomas of the same subtype.[1]
- The all-oral combination of nanatinostat (Nstat), a potent Class-I HDACi, and valganciclovir (VGCV), is a novel mechanism to kill EBV⁺ tumor cells through inducing the expression of the lytic BGLF4 protein kinase to activate the nucleoside analog GCV via phosphorylation, resulting in termination of DNA replication and apoptosis (Fig 1).[2]



- The combination of Nstat plus VGCV was well-tolerated and showed promising preliminary activity in a Phase 1b/2 study of patients with relapsed/refractory (R/R) EBV⁺ lymphoma (n=55) (NCT03397706), with an overall response rate (ORR) of 40% and a complete response rate (CRR) of 19% in efficacy-evaluable patients.[3]
  - In patients with percutaneous T-cell lymphoma (PTCL, n=13), including 8 angioimmunoblastic (AITL) and 5 PTCL-not otherwise specified (NOS): 8 were evaluable and had an ORR/CR of 50%/38% and a duration of response (DOR) of 17.3 months.[4]

MATERIALS & METHODS

Stage 1 (n=10)*	Stage 2 (n=11)	Potential Stage 2 Expansion
EBV⁺ PTCL • Combination Nstat + VGCV therapy arm completed enrollment of Stages 1 and 2		
EBV⁺ PTCL • Nstat monotherapy arm closed after 10 patients	Expand lymphoma subtype(s) from Stage 1 meeting ORR threshold of 2/10 responses	Further expansion of promising lymphoma subtype(s) with additional patients may support registration
EBV⁺ DLBCL EBV⁺ PTLD Other EBV⁺ Lymphomas		

*Stage 1 PTCL patients were randomized 1:1 between Nstat alone or Nstat + VGCV; monotherapy patients who had stable disease (SD) at week 6 or anytime at progression had to option of crossing over to combination treatment.

- **Key Eligibility:**
  - R/R EBV⁺ (by EBER-ISH) PTCL NOS or AITL with ≥ 1 prior therapies
  - No available therapies in the opinion of the Investigator and or eligible for stem cell transplantation (SCT) or CAR-T therapy
  - Measurable disease per Cheson 2007
  - ECOG performance status 0 – 2
  - Adequate bone marrow, liver, and renal function
- **Dose Regimen**: Nstat 20mg orally once daily, days 1-4 per week with VGCV 900 mg orally once daily
- **Primary Endpoint**: ORR by independent central review
- **Data Cutoff:** 28 JUNE 2024

RESULTS

Demographics

Characteristic	Patients Enrolled in N-stat + VGCV Combination Stages 1 + 2 (N = 21)
Median age (y), [range]	**69.0 [47-85]**
Male / Female	**13 / 8**
ECOG performance status, Unknown / 0 / 1 / 2	**4 / 15 / 2**
Ethnicity	
• WHITE	13 (61.9%)
• ASIAN	4 (19.0%)
• BLACK OR AFRICAN AMERICAN	2 (9.5%)
• NOT REPORTED / UNKNOWN	2 (9.5%)
PTCL subtype	
• AITL	17 (81.0%)
• PTCL-NOS	4 (19.0%)
Prior lines of therapy	
• 1	10 (47.6%)
• 2	8 (38.1%)
• ≥3	3 (14.3%)
Median number of prior therapies [range]	**2 [1-4]**
Stage	
• Unknown	2 (9.5%)
• I-II	4 (19.0%)
• III-IV	15 (71.4%)

Safety

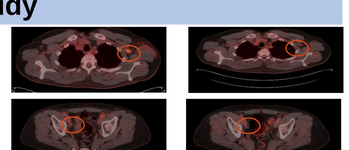
Most Frequently Occurring Treatment-Emergent Adverse Events by Severity Grade and Preferred Term

Preferred Term[1]	Stages 1 + 2 Nstat + VGCV (N=21)	
	All[2]	G3+G4
Fatigue	4 (19.0%)	0
Nausea	4 (19.0%)	0
Decreased appetite	3 (14.3%)	0
Diarrhea	3 (14.3%)	1 (4.8%)
Platelet count decreased	3 (14.3%)	1 (4.8%)

[1]Adverse events were coded to preferred terms using MedDRA, version 26.0; [2]One patient had G5 pancytopenia and sepsis

Case Study

- 52-year-old male with R/R EBV⁺ AITL (axillary, retroperitoneal, inguinal, and pelvic lymphadenopathy).
- Previously treated with CHEOP followed by Autologous SCT
- Treated with Nstat + VGCV x 5 months (partial response) then proceeded to Allogeneic SCT



Images courtesy of Dr. Brian Greenwell, Medical University of South Carolina

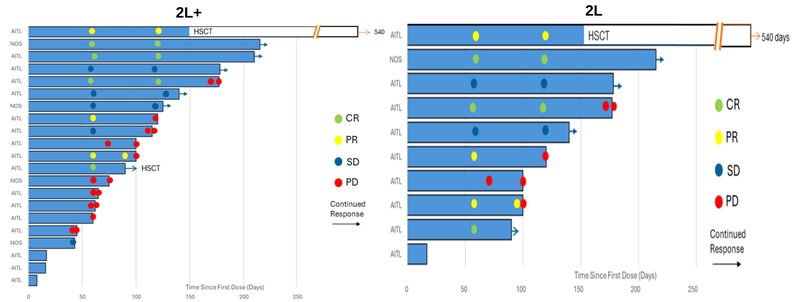
Efficacy

Stage 1 and Stage 2 Responses by Analysis Population

Analysis Population	ORR	CRR	CBR[1]
Intent-to-Treat (All Lines)[2]	7/21 (33%)	4/21 (19%)	10/21 (48%)
2L Intent-to-Treat[2]	6/10 (60%)	3/10 (30%)	8/10 (80%)
Efficacy-Evaluable (All Lines)[2,3]	7/17 (41%)	4/17 (24%)	10/17 (59%)
2L Efficacy-Evaluable[2,3]	6/9 (67%)	3/9 (33%)	8/9 (89%)

[1]Clinical benefit rate; includes 2 SDs in patients with 2L PTCL at Week 16 and 1 SD in patient with 3L PTCL at Week 16; [2]Investigator assessed; [3]Eligible patients who had at least 1 post-baseline radiographic assessment

Stages 1+2 EBV+ PTCL Patient Responses While on N-stat + VGCV (2nd line+ and 2nd line)



Median Duration of Response not yet reached with 7 patients still on study treatment or post-HSCT

Median Duration of Response not yet reached with 5 patients still on study treatment or post-HSCT

CONCLUSIONS

- Nstat+VGCV is emerging as a promising, generally well-tolerated treatment for patients with R/R EBV⁺ PTCL, particularly in the second-line treatment setting.
- Most common treatment-related adverse events have been hematological and gastrointestinal in nature, primarily mild to moderate in severity, and generally manageable or reversible.
- Enrollment in the PTCL expansion cohort is ongoing.

REFERENCES

1. Ding, et al. Acta Haematol 2016; 135 (1) : 21–28.
2. Haverkos BM et al. Blood 2021;138 (suppl 1): 623.
3. Haverkos BM, et al. Blood Adv (2023) 7 (20): 6339–6350.
4. Pereira et al, Hematol Transfus Cell Ther 2023: 45 (2) S344-S345.