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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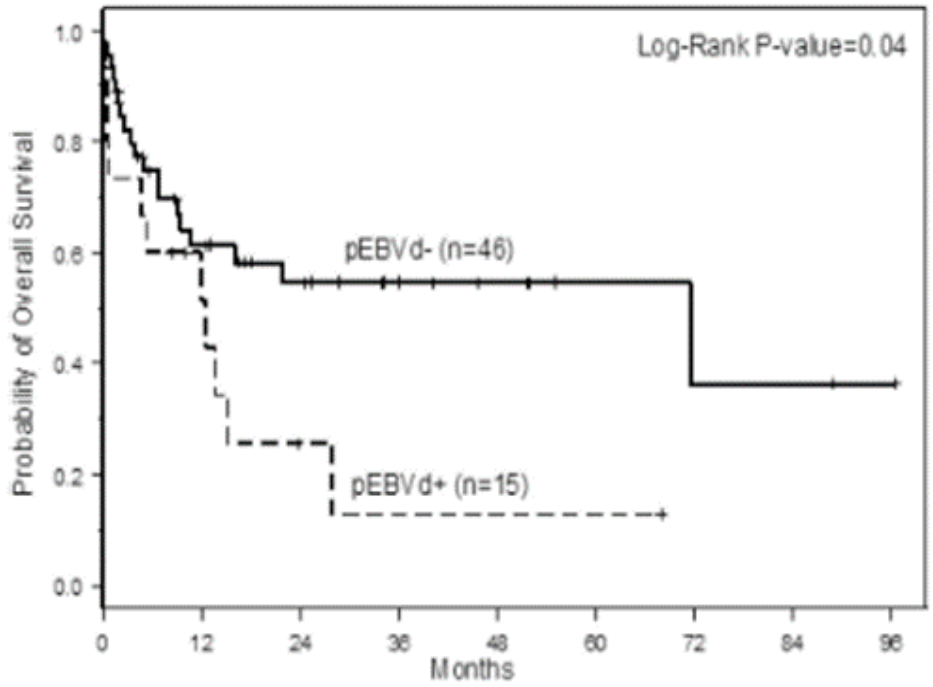
Epstein-Barr Virus (EBV): A High Global Cancer Priority

EBV+ malignancies account for ~2% of new cancer cases globally and associated with adverse survival outcomes

- ~90% of the adult population are infected w/ EBV
- Persists as a life-long latent infection, remaining dormant within cell nuclei
- Latency confers resistance to anti-viral therapies and facilitates evasion of immune detection
- Linked to a variety of cancers
  - >300,000 new cases/year of EBV+ lymphomas and solid tumors[2]
- Poor prognosis
- Responsible for ~180,000 cancer deaths/year[2]

Peripheral T-Cell Lymphoma[1] (Overall Survival)

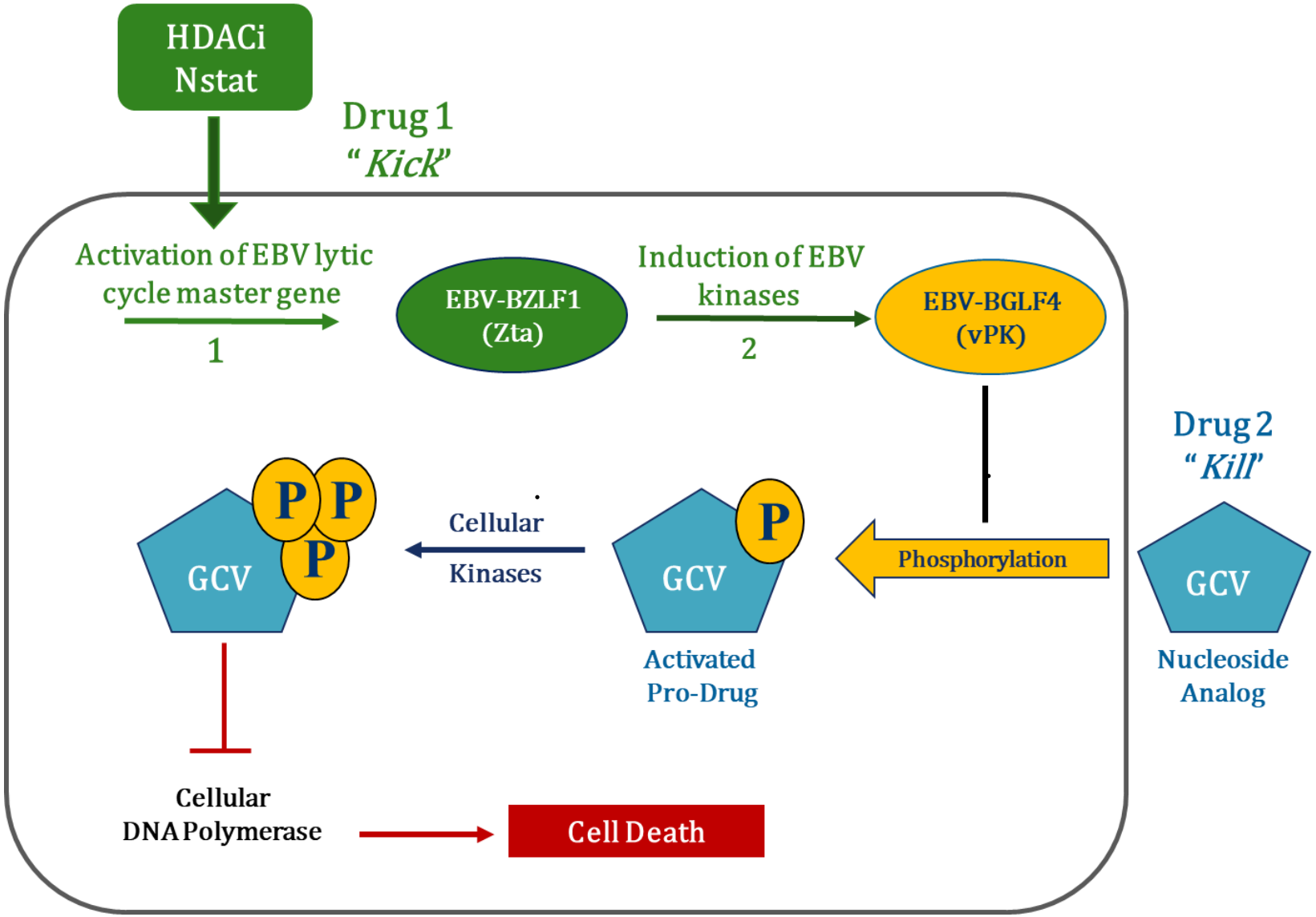


[1]Haverkos BM et al. Int J Cancer. 2017; 140:1899-1906; Dupuis J et al. Blood. 2006;108:4163–9 [2] Wu L, et al. Exp. Therapeutic Med. 15: 3687, 2018; Kahn G, et al. BMJ 10:1136, 2020.

The "*Kick and Kill*" approach for EBV-associated lymphomas

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

Lymphoma Cell with Latent EBV



Haverkos et al, Blood Adv 2023. 7 (20): 6339–6350

Study VT3996-201 (Phase 1b/2 Open Label Study) Showed Encouraging Anti-Tumor Activity in Relapsed/Refractory EBV+ Lymphoma[1]

- 55 patients enrolled across multiple EBV+ lymphoma subtypes
  - 13 with nodal PTCL (8 AITL, 5 PTCL-NOS)
    - 8 PTCL patients evaluable for efficacy[2]
- Eligibility:
  - R/R EBV lymphoma (by local pathology), any histology
  - ≥1 prior therapies with no curative options per Investigator
  - ECOG PS: 0-2

blood advances	**Study VT3996-201 R/R EBV+ PTCL Data[1] (n=13)**
	Evaluable Patients[3] (n=8)
Response	
ORR	**4 (50%)**
CR	**3 (38%)**
PR	1
SD	1
PD	3
Clinical Benefit Rate	5 (63%)
DOR	**17.3 months**

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; ORR=overall response rate

[1]Haverkos et al, Blood Adv 2023; 7 (20): 6339–6350; [2]Pereira et al, Hematol Transfus Cell Ther 2023; 45 (2) S344-S345, [2]Data presented at HEMO 2023, [3]Evaluable patients: EBER-ISH+ with ≥1 post-treatment response assessment

NAVAL-1 Trial Design: Pivotal Phase 2 Study in Patients with R/R EBV⁺ Lymphoma

Global study with an adaptive Simon 2-stage design

Patient population:

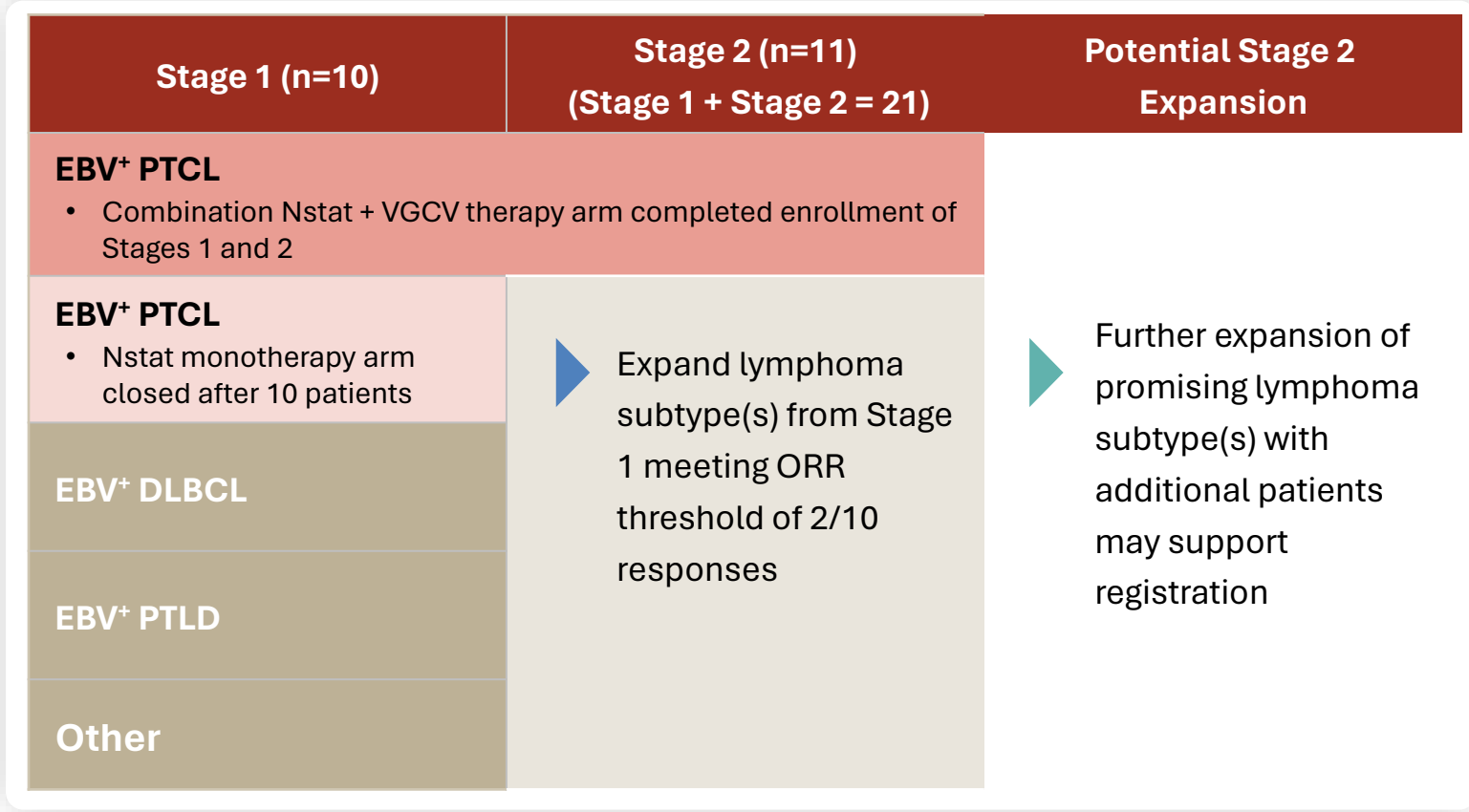
- R/R EBV⁺ lymphoma with **≥1** prior therapies and no curative options

PTCL cohort randomization:

- Patients randomized to either combination Nstat + VGCV therapy or Nstat monotherapy in Stage 1

Primary endpoint:

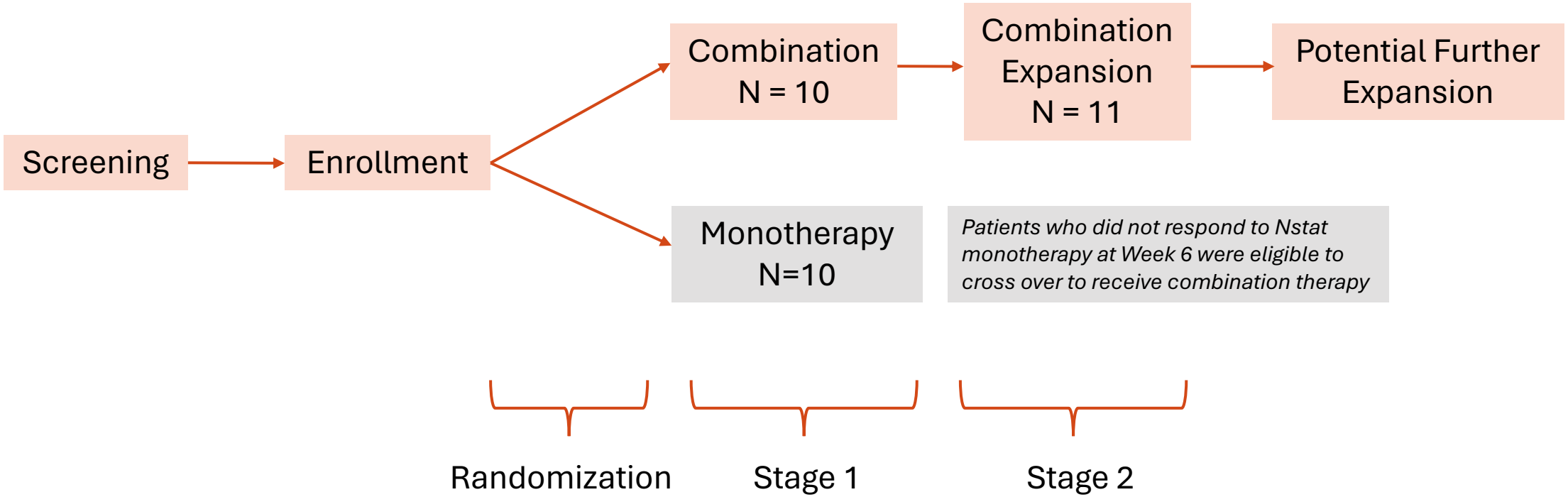
- Objective response rate (ORR) by independent central review
- Potential to further expand indications with promising anti-tumor activity after Stage 2



R/R: Relapsed or Refractory, PTCL: Peripheral T-cell lymphoma, DLBCL: Diffuse large B-cell lymphoma (DLBCL), PTLD: Post-transplant lymphoproliferative

NAVAL-1 R/R EBV+ PTCL Arm Study Design

Stage 1 Data (N=20) to be Shared Today



NAVAL-1 Trial: Stage 1 Demographics for Patients with R/R EBV+ PTCL

65% of patients with ≥2 prior lines of therapy; 75% with advanced disease

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Characteristic	Patients Enrolled in Stage 1 (N = 20*)
Median age (y), [range]	69 [47-78]
Male / Female	16 / 4
ECOG performance status, Unknown / 0 / 1 / 2	1 / 4 / 14 / 1
Ethnicity • WHITE • ASIAN • BLACK OR AFRICAN AMERICAN • NOT REPORTED	 10 (50%) 7 (35%) 2 (10%) 1 (5%)
Prior lines of therapy • 1 • 2 • ≥3 Median number of prior therapies [range]	 7 (35%) 7 (35%) 6 (30%) 2 [1-6]
Stage • Unknown • I-II • III-IV	 2 (10%) 3 (15%) 15 (75%)

*10 patients received combination Nstat + VGCV therapy and 10 patients received Nstat monotherapy

Combination Nstat + VGCV Therapy Provides Substantially Greater Anti-Tumor Response Than Nstat Monotherapy

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NAVAL-1 Stage 1 Responses by Treatment Subgroup and Analysis Population

Intent-to-Treat Population[1]

PTCL Treatment Subgroup	ORR	CRR
Nstat + VGCV, Stage 1 (n=10)	5/10 (50%)	2/10 (20%)
Nstat monotherapy, Stage 1 (n=10)	1/10 (10%)	0/10 (0%)

Efficacy-Evaluable Population[1, 2]

PTCL Treatment Subgroup	ORR	CRR
Nstat + VGCV, Stage 1 (n=7)	5/7 (71%)	2/7 (29%)
Nstat monotherapy, Stage 1 (n=8)	1/8 (13%)	0/8 (0%)

ORR, overall response rate; CRR, complete response rate

[1]Investigator assessed; [2]Eligible patients who had at least 1 post-baseline radiographic assessment

Consistent and Robust Anti-tumor Activity Demonstrated Across Clinical Trials of Nstat + VGCV

Study 201 (Phase 1b/2 study) vs NAVAL-1 trial: Comparison of evaluable patients

HEMO 2023	Study 201: Combination Nstat + VGCV Therapy[1] (n=13)
	Evaluable Patients (n=8)
Response	
ORR	**4 (50%)**
CR	**3 (38%)**
PR	1
SD	1
PD	3
Clinical Benefit Rate	5 (63%)
Data Cutoff	May 4, 2023

NAVAL-1 2024	Combination Nstat + VGCV Therapy (n=10)
	Evaluable Patients (n=7)
Response	
ORR	**5 (71%)**
CR	**2 (29%)**
PR	3
SD	0
PD	2
Clinical Benefit Rate	5 (71%)
Data Cutoff	Feb 7, 2024

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; ORR=overall response rate, Clinical Benefit Rate=CR+PR+SD

[1]Pereira et al, Hematol Transfus Cell Ther 2023

Combination Nstat + VGCV Therapy Resulted in 5x Greater Response Rate

Randomized comparison of combination Nstat + VGCV therapy to Nstat monotherapy (ITT population)

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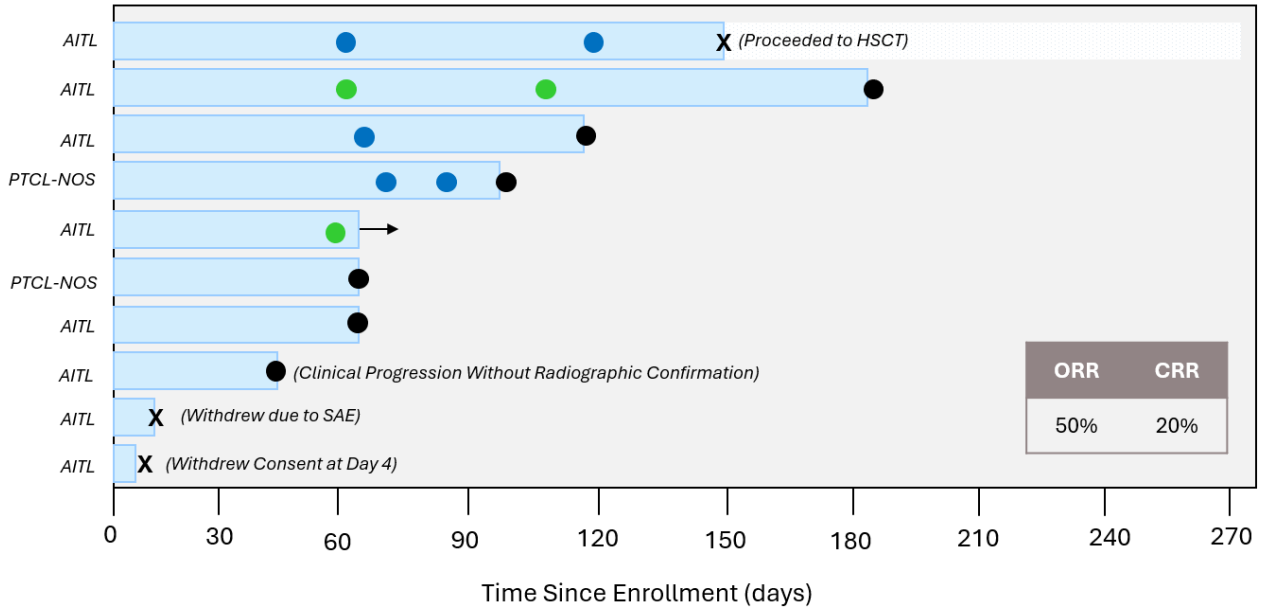
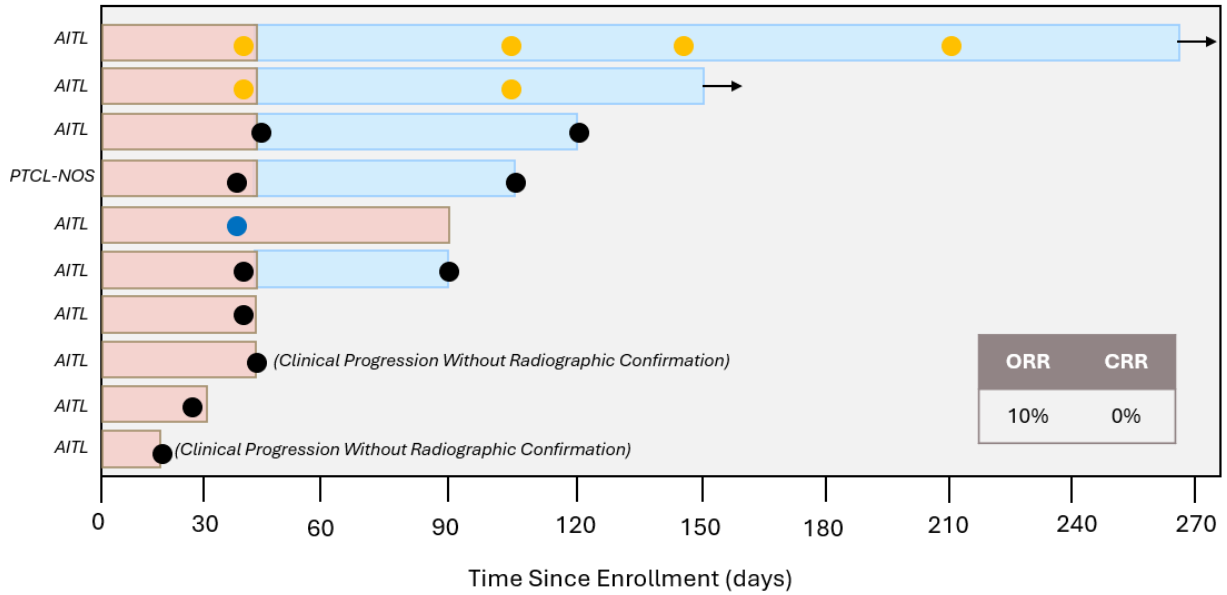
Combination Nstat + VGCV Therapy

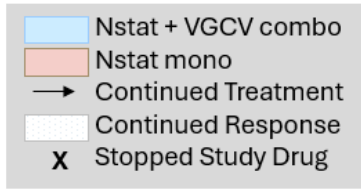
5/10 (50%) Responses

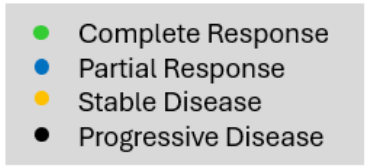


Nstat Monotherapy

1 PR/10 (10%) Response







Responder at 16 Weeks Proceeded to HSCT and Continues in Response

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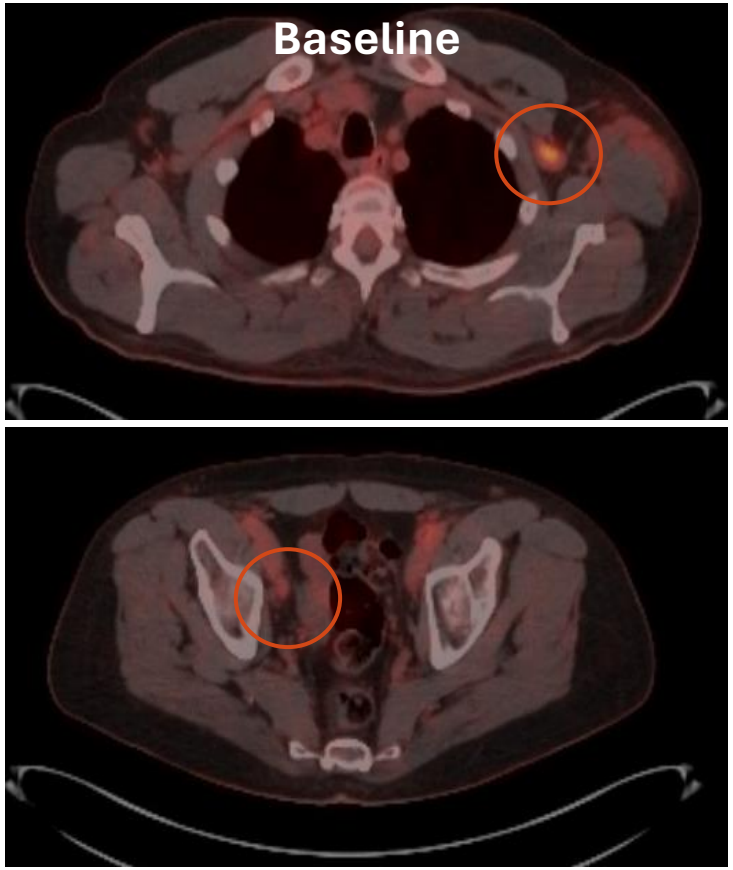
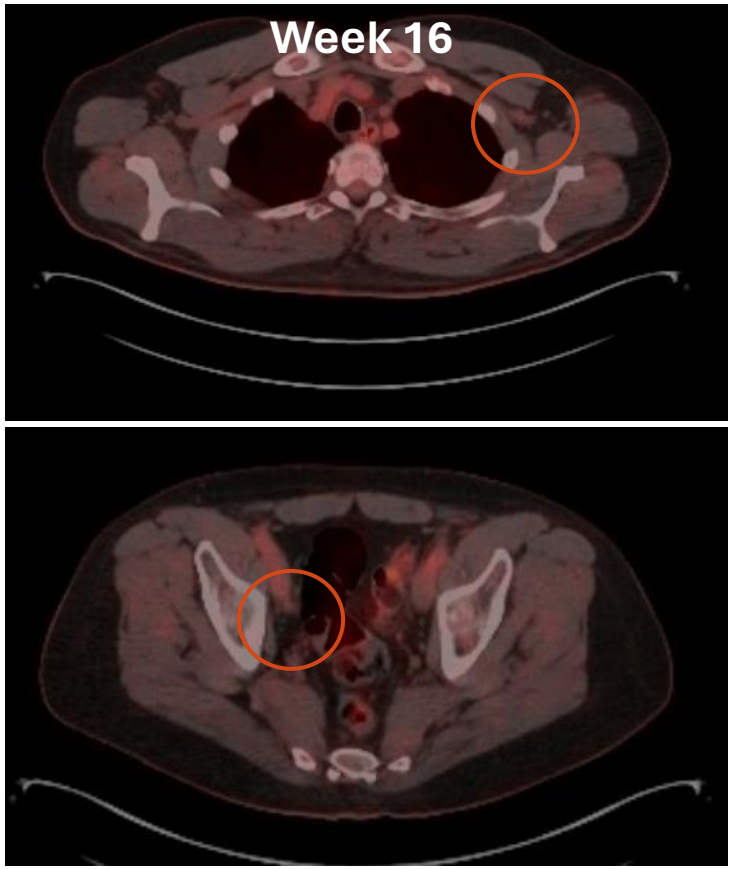
CT scans of confirmed PR

- 52-year-old male with R/R EBV^{+} AITL (axillary, retroperitoneal, inguinal, and pelvic lymphadenopathy)
- Previously treated with CHEOP followed by autologous stem cell transplant
- Treated with Nstat 20 mg days 1-4/week + VGCV 900 mg QD x 5 months then proceeded to allogeneic stem cell transplant
- Continues in response as of the most recent radiographic follow-up 260 days after the initial response on Nstat + VGCV





Courtesy of Dr. Brian Greenwell, Medical University of South Carolina

All-Oral Regimen of Combination Nstat + VGCV Therapy was Generally Well-Tolerated

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Most Frequently Occurring (≥10%) Treatment-Related Treatment-Emergent Adverse Events by Severity Grade and Preferred Term

Preferred Term[1]	Combination Nstat + VGCV Therapy (N=10)		Nstat Monotherapy (N=10)	
	All[2]	G3+G4	All	G3+G4
Platelet count decreased	2 (20.0%)	1 (10.0%)	1 (10.0%)	0
Anaemia	1 (10.0%)	0	5 (50.0%)	4 (40.0%)
Fatigue	1 (10.0%)	0	3 (30.0%)	0
Decreased appetite	1 (10.0%)	0	3 (30.0%)	0
Nausea	1 (10.0%)	0	2 (20.0%)	0
Diarrhoea	1 (10.0%)	1 (10.0%)	2 (20.0%)	0
Weight decreased	1 (10.0%)	0	0	0

[1]Adverse events were coded to preferred terms using MedDRA, version 26.0
[2]One combination Nstat + VGCV therapy patient had G5 pancytopenia and sepsis

Conclusions

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- Greater clinical efficacy of combination Nstat and VGCV therapy than Nstat monotherapy observed (together with the known absence of anticancer activity for VGCV alone) suggests that both drugs in the combination regimen are contributing to its anti-tumor activity as predicted by their mechanisms of action

- Most common treatment-related adverse events have been hematological and gastrointestinal in nature, primarily mild to moderate in severity, and generally manageable or reversible

- Combination Nstat and VGCV therapy is emerging as a promising, generally well-tolerated, convenient, all-oral treatment for patients with R/R EBV^{+} PTCL, having exceeded the Stage 1 efficacy threshold for expansion into Stage 2 of the NAVAL-1 trial

Thank You (谢谢)