156P: A Phase 1b/2 Study of Nanatinostat (Nstat) Plus Valganciclovir (VGCV) in Advanced Epstein-Barr Virus Positive (EBV+) Solid Tumors and with Pembrolizumab (PEM) in Recurrent/Metastatic Nasopharyngeal Carcinoma (RM-NPC)

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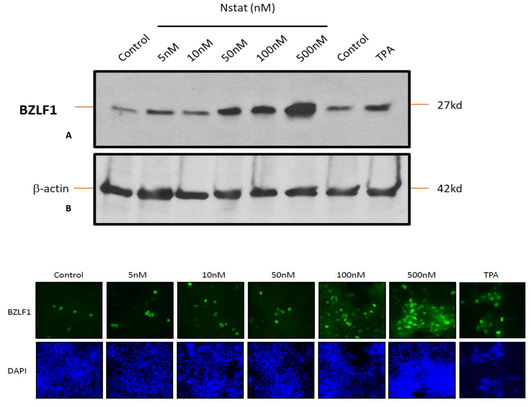
Background

- EBV is linked to the pathogenesis of NPC; high pre-treatment plasma EBV DNA (pEBVd) levels and slow clearance are associated with inferior outcomes.[a,b]
- EBV is predominantly latent in NPC; induction of the viral lytic phase by histone deacetylase inhibitors (HDACis) renders EBV+ tumor cells susceptible to the cytotoxic activity of ganciclovir (GCV).[c]
- Nanatinostat (Nstat) is a potent oral Class-I HDACi that induces the EBV lytic cycle in EBV+ NPC cells **(Figure 1)** and expression of the lytic BGLF4 protein kinase, activating GCV via phosphorylation. GCV-triphosphate becomes incorporated into cellular DNA, resulting in chain termination and apoptosis.[d]
- Targeting EBV with Nstat and valganciclovir (VGCV, the oral prodrug of GCV) in NPC represents a novel therapeutic approach.
- The RP2D of Nstat 20 mg 4 days/week plus VGCV 900 mg daily was well-tolerated and demonstrated clinical activity in a phase 1b/2 study in patients with R/R EBV+ lymphoma (n=55).[e]
- This phase 1b/2, open-label, multicenter study is evaluating the safety, pharmacokinetics (PK), and preliminary activity of the all-oral combination of Nstat + VGCV in patients with advanced EBV+ solid tumors.
- Additionally, the combination of pembrolizumab (PEM) together with Nstat + VGCV will be evaluated in RM-NPC patients.

Figure 1. Nstat induces the EBV lytic cycle in NPC cells



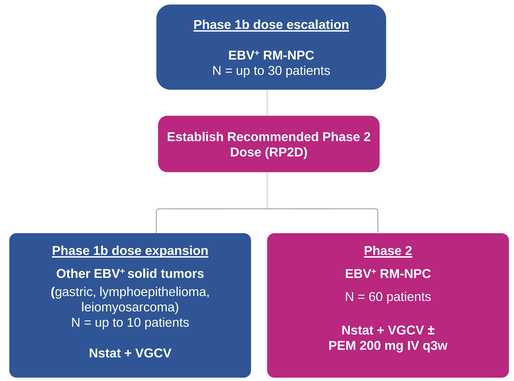
Activation of BZLF1, the master EBV lytic cycle switch protein by Nstat: A) Western blot B) Immunofluorescence. BZLF1 drives expression of lytic viral proteins including BGLF4, the viral protein kinase.

Methods

Key Eligibility Criteria

- **EBV+ RM-NPC:** 1 prior line of platinum-based chemotherapy (max. 3 prior lines of therapy) with no curative options.
- **Phase 1b dose expansion cohort:** Advanced/metastatic EBV+ non-NPC solid tumors with no available curative therapies.
- Measurable disease per RECIST v1.1.
- No anti-tumor cytotoxic drugs, biologic therapy, immunotherapy, or other investigational drugs within 4 weeks or >5 half-lives.
- No active CNS disease.

Figure 2. Study Design



- Dose level 1 (DL1) was the RP2D from the VT3996-201 study in patients with R/R EBV+ lymphoma.[e]
- Tumor evaluation (RECIST v1.1) is performed at week 8, every 6 weeks for 6 months, then every 12 weeks until disease progression.
- Plasma EBV DNA (pEBVd) titers were assessed monthly via real-time quantitative polymerase chain reaction (PCR).

Table 1: Phase 1b provisional dose levels (DLs)

Dose level	Nstat oral dose (days 1-4/wk)	VGCV oral dose	N
1	20 mg	900 mg daily	3
2	30 mg	900 mg daily	4
3	40 mg	900 mg daily	3
4	10 mg BID	900 mg BID x 21 d, then QD	-
5	20 mg / 10 mg split dose	900 mg BID x 21 d, then QD	-

Results

- Data is reported on 10 patients from DL1-3 in this analysis (cutoff date 14 Nov 22).
- The baseline characteristics of the patients are presented in **Table 2.**

Table 2. Patient Demographics

Characteristic	DL1-3 Patients (N=10)
Median age (y), (range)	49 (19-61)
Male / Female	9/1
ECOG performance status: 0 / 1	5/5
Ethnicity • Asian • White	 8 (80%) 2 (20%)
Prior lines of antineoplastic therapy in R/M setting – no. (%) • 1 • 2 • 3 Median no. prior therapies (range)	 1 (10%) 4 (40%) 5 (50%) 3 (1-3)
Therapies in R/M Setting – 1st Line: • Cisplatin/gemcitabine • Docetaxel +/- cisplatin Therapies in R/M Setting – 2nd Line: • Immune checkpoint inhibitor	 6 2 5
Baseline disease burden • TNM: IVA / IVB • Oligometastatic disease • Pulmonary metastasis • Hepatic metastasis	 3 (30%) / 7 (70%) 1 (10%) 4 (40%) 5 (50%)
Plasma EBV DNA titer[b] ≥10,000 IU/mL <10,000 IU/mL	 6 (60%) 4 (40%)

Safety

- The majority of treatment-related adverse events (TRAEs) were classified as mild-moderate **(Table 3)**; no DLTs were reported in the first 3 dose levels.
- One SAE was reported (cancer pain), unrelated to study drug.

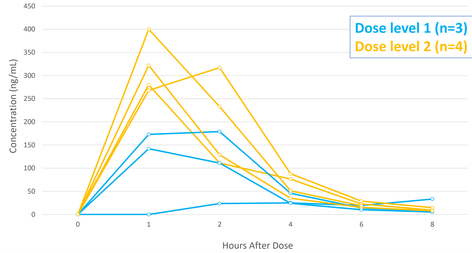
Table 3. Treatment-related adverse events in ≥2 patients

Adverse event	Dose level 1 (n=3)		Dose level 2 (n=4)		Dose level 3 (n=3)		Overall (N=10)	
	G1-2	G3-4	G1-2	G3-4	G1-2	G3-4	G1-2	G3-4
Fatigue	1		2			1	3	1
Nausea	1		2		1		4	
Creatinine increased	1		2				3	
Anemia	1		1				2	
Anorexia	1		1				2	
Lymphopenia			2				2	
Thrombocytopenia	1		1				2	
Rash			1		1		2	

Pharmacokinetics

- PK concentration-time curves for Nstat for DL1 and DL2 patients **(Figure 3)** indicated a dose-dependent increase in exposure. Exposure at 20mg was similar to that observed in a study of patients with relapsed/refractory EBV+ lymphomas.[e]

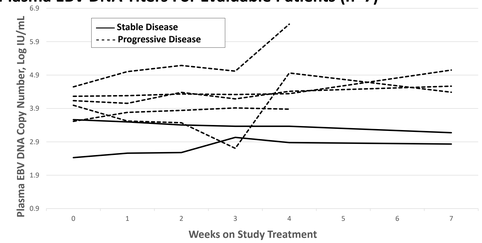
Figure 3. Nanatinostat plasma concentration-time curves for DL 1 and 2 patients (n=7)



Anti-tumor activity

- Of 7 patients evaluable as of data cutoff, 2 had stable disease (SD) and 5 had progressive disease (PD) as a best response.
- Plasma EBV DNA titers are shown in **Figure 4.**

Figure 4. Plasma EBV DNA Titers For Evaluable Patients (n=7)



Conclusions

The all-oral combination of Nstat + VGCV represents a novel approach for the treatment of advanced EBV+ NPC and is generally well-tolerated at doses exceeding the RP2D for R/R lymphoma. Most TRAEs were low-grade, gastrointestinal or constitutional in nature. Enrollment to dose level 4 (Nstat 10 mg BID, 4 days per week plus VGCV 900 mg BID x 21d, then daily) is anticipated to open this month, pending Safety Committee review.

References

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