Abstract 383358: A Phase 1b/2 Study of Nanatinostat and Valganciclovir in Patients with Advanced Epstein-Barr Virus Positive (EBV+) Solid Tumors and in Combination with Pembrolizumab in Patients with Recurrent/Metastatic Nasopharyngeal Carcinoma (RM-NPC)

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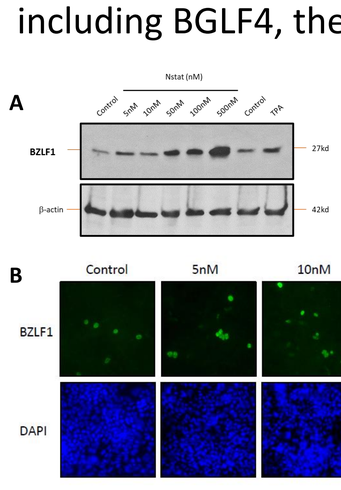
Background

- Epstein-Barr virus (EBV) is linked to the pathogenesis of NPC; first-line chemoradiation is commonly followed by recurrence and poor prognosis emphasizing the need for new treatment options. Targeting EBV in NPC represents a novel therapeutic approach.
- EBV is predominantly latent in NPC; preclinical studies demonstrated that induction of the viral lytic phase by histone deacetylase inhibitors (HDACi) renders EBV+ tumor cells susceptible to the cytotoxic activity of ganciclovir (GCV).[a]
- Nanatinostat (Nstat) is a potent Class-I HDACi that induces the expression of the lytic BGLF4 protein kinase in EBV+ tumor cells (Fig 1), which activates the nucleoside analog GCV via phosphorylation. Phosphorylated GCV becomes incorporated into cellular DNA causing chain termination and apoptosis.

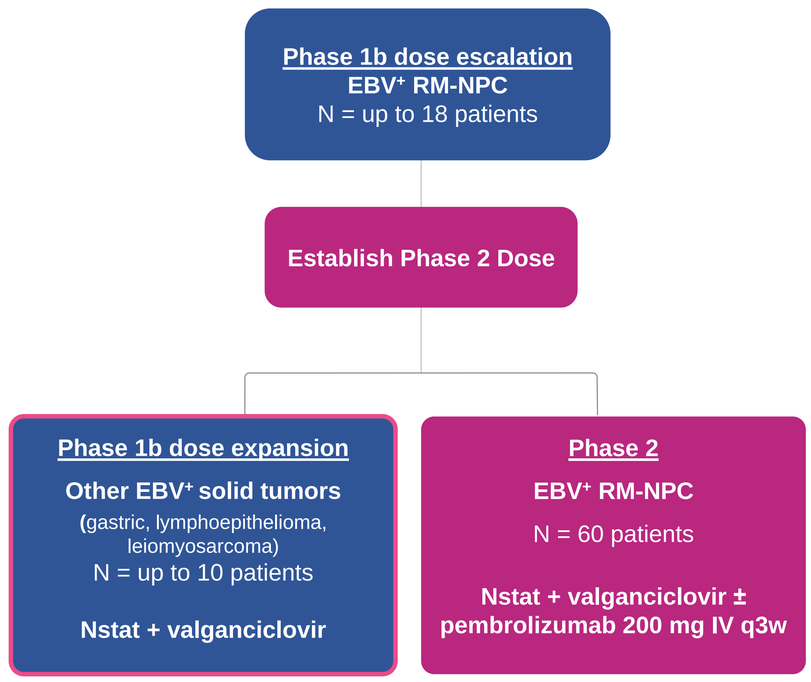
Figure 1. Nstat induces the EBV lytic cycle in NPC cells

- 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



- This phase 1b/2, open-label, multicenter study will evaluate the safety, pharmacokinetics (PK), and preliminary activity of the all-oral combination of Nstat + valganciclovir (VGCV) in patients with advanced EBV+ solid tumors. Additionally, the combination of pembrolizumab together with Nstat + VGCV will be evaluated in RM-NPC patients.

Study Design



- Starting dose for Cohort 1: Nstat 20 mg daily,
- 4 days/week + VGCV 900 mg daily (both oral).
- Tumor evaluation (per RECIST v1.1) will be performed at Week 8, every 6 weeks for 6 months, then every 12 weeks until disease progression.

Key Eligibility Criteria

INCLUSION CRITERIA

- Age ≥18
- EBV+ RM-NPC, 1 prior line of platinum-based chemotherapy (max. 3 prior lines of therapy) with no potentially 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
- ECOG performance status 0 or 1
- Adequate bone marrow, renal and liver function

EXCLUSION CRITERIA

- Anti-tumor treatment with cytotoxic drugs, biologic therapy, immunotherapy, or other investigational drugs within 4 weeks or >5 half-lives, whichever is shorter
- <14 days from prior local radiotherapy
- Active CNS disease
- Inability to take/absorb oral medication
- Active infection requiring systemic therapy

Endpoints

PRIMARY

Phase 1b:

- Incidence of dose limiting toxicities (DLTs)

Phase 2:

- Overall response rate

SECONDARY

- Incidence and severity of AEs
- Duration of response
- Disease control rate
- Progression free and overall survival
- PK

Current status

Phase 1b:

- First patient was dosed on 28 January 2022.
- Cohort 1 has been completed without any dose-limiting toxicity.
- Enrollment to dose level 2 (Nstat 30 mg daily, 4 days per week) is anticipated to begin in June 2022, pending Safety Monitoring Committee review.

References

[a]Hui KW, et al. Int J Cancer 2016:138

Acknowledgements

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