Targeting Epstein-Barr virus-associated malignancies using "Kick and Kill"

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Epstein-Barr virus (EBV), a ubiquitous lymphotropic herpesvirus, is associated with a heterogenous group of clonal lymphoproliferations and lymphoid neoplasms, of different lineage and stage of maturation. The degree of association of these malignancies with EBV varies depending on tumor subtype and geographic location. Detection of EBV within the lymphoma lesion is often a marker for poor prognosis. To date, there are no FDA-approved therapies that specifically target latent EBV in tumors; current therapies are indifferent to the presence of the virus.

Here, we provide data describing a "kick and kill" approach that exploits the presence of EBV in tumor cells. The approach relies on inducing the expression of the lytic BGLF4 protein kinase, which activates ganciclovir (GCV) via phosphorylation to block DNA replication and trigger tumor cell apoptosis. The kick is provided by nanatinostat (NStat), a potent HDAC inhibitor that specifically targets HDACs 1, 2, and 3 at nanomolar concentrations.

Our pre-clinical data demonstrate that NStat induces expression of the EBV lytic cycle genes, including the viral protein kinase BGLF4. Treatment of the HH514-16 Burkitt lymphoma cell line with NStat and GCV inhibits both cellular and viral DNA replication resulting in significant cell death.

Clinically, results from a phase 1b/2 trial (NCT03397706) evaluating the all-oral combination of NStat and valganciclovir (VGCV), a prodrug of GCV, in patients with relapsed/refractory (R/R) EBV^+ lymphoma who received ≥1 prior therapies and had no curative options were recently reported [1].

Fifty-five patients were enrolled; 75% (41/55) were refractory to their last therapy, and 96% (53/55) had exhausted all standard therapies (per Investigator). In the 43 evaluable patients across all lymphoma subtypes, the overall response rate (ORR) was 40% (17/43), with complete responses (CR) in 19% (8/43). The highest overall response rates were observed in patients with EBV^+ diffuse large B-cell lymphoma, NOS (4/6; 67%), peripheral T-cell lymphoma, NOS (4/6; 67%), and extranodal NK/T cell lymphoma (5/8; 63%). The median duration of response for all responders was 10.4 months.

In summary, our preclinical data demonstrate that NStat is a potent HDACi and in combination with GCV is lethal to EBV^+ tumor cells. In patients, Nstat and VGCV were generally well-tolerated, with a manageable safety profile and show promising efficacy in R/R EBV^+ lymphomas, particularly in refractory T/NK-NHL, a group of aggressive lymphomas with dismal outcome. Further evaluation of this combination therapy for the treatment of recurrent EBV^+ lymphomas is ongoing in the phase 2 VT3996-202 trial (NAVAL-1; NCT05011058).

[1] Haverkos et al, 2021, Blood, 138 [Suppl 1]:623 ASH Annual Meeting