be useful as a practical and informative surrogates for outcomes, suggesting number of EN sites involvement assessed by CT and PET-CT as feasible clinical surrogate for outcomes in this population. New biomarkers are essential to better stratify patients with PTCL. Still, in practice, it is also necessary to have ways to stratify these patients using clinical data, mainly in regions with low-income resources. These indicators reflect distinct biological characteristics that merit further molecular investigation, potentially enhancing tailored therapies. Registries are essential given the rarity and poor prognosis associated with these diseases as well as generate hypotheses.

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NANATINOSTAT WITH OR WITHOUT VALGANCICLOVIR IN PATIENTS WITH RELAPSED/REFRACTORY EBV-POSITIVE PERIPHERAL T-CELL LYMPHOMA (NAVAL-1 STAGE 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. Outcomes of EBV + Peripheral T-Cell Lymphoma (PTCL) patients are typically inferior to their EBV − counterpart, and thus represent an unmet medical need. Nanatinostat (Nstat) is a potent Class-I histone deacetylase inhibitor. With a novel mechanism of action, Nstat induces expression of the lytic BGLF4 protein kinase, which activates the nucleoside analog ganciclovir (GCV), derived from valganciclovir (VGCV) via phosphorylation. Incorporation of phosho-GCV into cellular DNA results in termination of DNA replication and apoptosis. **Materials and methods:** NAVAL-1 (NCR05011058) is an adaptive Phase 2, open-label, single-arm, two-stage, basket trial. In Stage 1 of the relapsed/refractory (R/R) EBV + PTCL cohort, 20 patients were randomized 1:1 to receive Nstat (20 mg orally once daily, 4 days/week) alone or in combination with VGCV (900 mg orally once daily, 7 days/week) and followed for efficacy and safety. Results: As of 28 June, 2024, the investigator-assessed overall response rate (ORR) by Cheson 2007 in the 10-patient Nstat+VGCV arm was 50% (with a duration of response that is maturing) with a complete response rate (CRR) of 20% in the intent-to-treat (ITT) population (ORR 71% and CRR 29% in the efficacy-evaluable population). One responding patient discontinued Nstat+VGCV to undergo allogeneic stem cell transplantation and remains lymphoma-free over 1 year. In the 10-patient Nstat monotherapy arm, the ORR and CRR were 10% and 0%, respectively, in the ITT population. Five patients without monotherapy response crossed over to combination therapy, including one who had a partial response and another with stable disease for 24+ weeks, both still ongoing. Most TRAEs have been hematological or gastrointestinal in nature and primarily Grade 1-2 in severity. Most Grade ≥3 TRAEs have been generally manageable or reversible except for one patient with Grade 5 TRAE of sepsis in the context of severe cytopenias. **Conclusion:** Combination Nstat+VGCV is a promising, generally well-tolerated treatment for patients with R/R EBV + PTCL that has shown improved efficacy over Nstat monotherapy in the challenging scenario of R/R PTCL.

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

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Introduction: Patients with Epstein-Barr virus-positive (EBV+) lymphoma are currently faced with challenging outcomes and represent an unmet medical need. Clinical outcomes in this population may be inferior to the EBV− counterpart in different lymphoma subtypes, including Peripheral T-Cell Lymphoma (PTCL). With a novel mechanism of action, nanatinostat (Nstat, a potent Class-I histone deacetylase inhibitor) induces expression of the lytic BGLF4 protein kinase, which activates the nucleoside analog ganciclovir (GCV), derived from valganciclovir (VGCV) via phosphorylation. Incorporation of phospho-GCV into cellular DNA results in termination of DNA synthesis causing apoptosis. **Materials and methods:** NAVAL-1 (NCR05011058) is an adaptive Phase 2, open-label, single-arm, two-stage, basket trial. Each lymphoma subtype cohort where ≥2 of 10 patients in Stage 1 responded to Nstat (20 mg orally once daily, 4 days/week) and VGCV (900 mg orally once daily, 7 days/week) continued to enroll 11 patients in Stage 2, for a total of 21 patients in each cohort. Efficacy and safety data from the 21-patient relapsed/refractory (R/R) EBV + PTCL cohort are presented herein. **Results:** As of 28 June, 2024, the investigator-assessed overall response rate (ORR), as assessed by Cheson 2007, in 21 patients treated with Nstat+VGCV was 33% (with a median duration of response that has not yet been reached) with a complete response rate (CRR) of 19% in the intent-to-treat population (ORR 41% and CRR 24% in the efficacy-evaluable population), including 2 patients who were able to proceed to allogeneic hematopoietic stem cell transplant. Patients receiving the combination in the second-line treatment setting had higher ORR (60%), with a CRR of 30% (efficacy-evaluable ORR 67% and CRR 33%). Most TRAEs have been hematological or gastrointestinal in nature and primarily Grade 1-2 in severity, and most Grade ≥3 TRAEs have been generally manageable or reversible except for one Grade 5 TRAE of sepsis in the context of severe cytopenias. Serious TRAEs have included influenza, pneumonia, upper respiratory tract infection, pancytopenia and sepsis (1 each). **Conclusion:** 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. Enrollment in the PTCL expansion is ongoing.

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UNVEILING THE PROGNOSTIC CHALLENGES OF NODAL PERIPHERAL T-CELL LYMPHOMAS: A MULTICENTER REAL-WORLD STUDY

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Introduction: Peripheral T-cell lymphomas (PTCL) are a rare group of malignancies derived from mature T-cells or natural killer cells, characterized by significant clinical-biological heterogeneity despite being grouped together. These entities have unique clinical, morphological, phenotypic, and molecular signatures. The predominantly nodal presentation group includes the histological variants ALK-positive anaplastic large cell lymphoma (ALK1+ ALCL), ALK-negative anaplastic large cell lymphoma (ALK1- ALCL), angioimmunoblastic T-cell lymphoma (AITL), and PTCL, not otherwise specified (PTCL-NOS). The central pillar of treatment for this subgroup of lymphomas is based on anthracycline-containing polychemotherapy regimens and upfront consolidation with autologous hematopoietic stem cell transplantation, although unfavorable outcomes such as primary refractory disease and early relapses are still common, except for the ALK1+ ALCL subgroup. **Methodology:** Hence, a multicenter, real-world, ambispective study was conducted, involving reference institutions in Brazil and two in the USA, to evaluate the main clinical-demographic characteristics associated with the outcomes of 179 patients diagnosed with nodal PTCL. **Results and discussion:** Individuals with nodal PTCL often presented at diagnosis with unfavorable clinical features, including a high frequency of advanced disease (stages III and IV), high tumor burden, poor performance status (ECOG ≥ 2 points), and frequent allocation in high-risk categories of the IPI and PIT prognostic indices. Patients with nodal PTCL included in this study globally exhibited low Complete Response rates, as well as shortened Overall Survival (OS) and Progression-Free Survival (PFS). In this cohort, we did not identify a robust survival benefit from the intensification of the CHOP regimen with the addition of etoposide (CHOEP protocol) or with BV-CHP. Age ≥ 60 years, ECOG ≥ 2, and lack of complete remission after primary therapy centered on CHOP-like chemotherapy were identified as independent prognostic factors associated with worse survival in this cohort represented by the four main histopathological subtypes of nodal PTCL. **Conclusion:** This analysis demonstrated a high frequency of unfavorable clinical features and poor OS and PFS outcomes in patients with nodal PTCL, regardless of the frontline chemotherapy regimen.

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REVEALING HIDDEN PATTERNS: HOW UNSUPERVISED MACHINE LEARNING AND MCA PREDICT SURVIVAL IN NODAL PERIPHERAL T-CELL LYMPHOMA PATIENTS

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