Editorial Commentary

Encouraging prospects with sugemalimab in relapsed or refractory extranodal natural killer/T-cell lymphoma

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Extranodal natural killer/T-cell lymphoma (ENKTL) is one aggressive subtype of non-Hodgkin lymphomas that emerges from natural killer cells or cytotoxic T cells. Asparaginase (Asp)-inclusive protocols have significantly improved the prognosis of ENKTL patients, regardless of early-stage and advanced disease. Despite the improvement in overall survival (OS) rates, the five-year relapse rate remains at ~50%. The outcome for relapsed/refractory (R/R) patients remains dismal, exhibiting a median OS of less than 6 months (1). There is currently no universally recognized standard therapy for patients with R/R ENKTL, and the optimal treatment regimen has yet to be determined. Considering the limited efficacy of most chemotherapy-based therapies and the paucity of treatment options in this context, clinical trials that investigate novel therapies are prioritized as the primary approach for patients in this category.

High PD-L1 expression in ENKTL cells has shed light on immune obstruction of the PD-1/PD-L1 axis as a potential therapeutic approach for ENKTL. In a retrospective study led by Kwong's team, pembrolizumab demonstrated a 100% objective response rate (ORR) in seven R/R ENKTL patients who had previously shown resistance to Asp-based treatment and allogeneic stem cell transplantation. Among them, five patients achieved complete response (CR) (2) (*Table 1*). Another study involving seven R/R ENKTL patients treated with pembrolizumab reported responses in four patients, with two achieving CR after four cycles (3) (*Table 1*). Additionally, low-dose nivolumab, another anti-PD-1 antibody, was effective in all three R/R ENKTL patients, with one patient maintaining CR after nine treatment cycles (4). In a prospective phase II study evaluating sintilimab, an anti-PD-1 monoclonal antibody, in 28 patients with R/R ENKTL, an ORR of 75.0% and a CR rate of 21.4% were observed. After a median follow-up period of 30.4 months, it was found that the median OS had not been reached, and the estimated 2-year OS rate was 78.6%. Of note, only 25% of cases experienced serious adverse events, and no patient succumbed to treatment-related toxicity. Therefore, these results demonstrate that sintilimab is a safe and effective therapeutic approach for R/R ENKTCL (5) (*Table 1*). A phase II study conducted in Korea assessed avelumab, an anti-PD-L1 monoclonal antibody, in 21 R/R ENKTL patients, demonstrating a survival advantage with an ORR of 38% and a CR rate of 24% (6) (*Table 1*). Despite variability in ORR, possibly due to small sample sizes and patient heterogeneity, these findings indicate that PD-1/PD-L1 blockade could be an effective and safe approach to treating R/R ENKTL.

In a phase 2 trial (GEMSTONE-201) published in the *Journal of Clinical Oncology*, Huang *et al.* investigated the effectiveness of an anti-PD-L1 antibody sugemalimab as a therapeutic intervention for R/R ENKTL patients (7) (*Table 1*). The trial included 80 patients from 16 Chinese centers and compared sugemalimab (administered intravenously every 3 weeks at a dosage of 1,200 mg) to a placebo, with a maximum treatment duration of 24 months

Table 1 Clinical trials of anti-PD-1/PD-L1 monotherapy in NK/T cell lymphoma

Treatment	Study	Patients	Lines	No. of case	Efficacy	AEs	Ref.
Pembrolizumab (PD-1 antibody)	Retrospective, single-arm, multicenter study	R/R NK/T, stage IV (85.7%)	Median prior lines of therapy, 2 (range, 1–5)	7	ORR/CRR: 100% (7/7)/71.4% (5/7)	No irAEs	(2)
Pembrolizumab (PD-1 antibody)	Retrospective, single-arm, monocentric study	R/R NK/T, stage III–IV (42.9%)	Median prior lines of therapy, 4 (range, 3–10)	7	ORR/CRR: 57.1% (4/7)/28.6% (2/7); DOR/PFS/OS: 4.1/4.8/5 months	Grade 3 irAEs: pneumonitis, 2 (28.6%), thrombocytopenia, 1 (14.3%)	(3)
Nivolumab (PD-1 antibody)	Case report	R/R NK/T, stage IV (66.7%)	Second line	3	ORR/CRR: 66.7% (2/3)/66.7% (2/3)	CRS/TLS, 1 (33.3%)	(4)
Sintilimab (PD-1 antibody)	ORIENT-4 prospective, single-arm, multicenter, phase II study	R/R NK/T, stage IV (67.9%)	≥3, 53.6% (15/28)	28	ORR/CRR: 75.0% (21/28)/21.4% (6/28); median DOR, 4.1 months; median OS, not reached; 2-year OS rate, 78.6%	Grade 3 irAEs, ketoacidosis, 1 (3.6%)	(5)
Avelumab (PD-L1 antibody)	AVENT prospective, single-arm, monocentric, phase II study	R/R NK/T, stage IV (81%)	≥2, 67% (14/21)	21	ORR/CRR: 38% (8/21)/24% (5/21); median PFS, 2.7 months; median OS, not reached (because of subsequent salvage treatments)	Grade 3 AEs: neutropenia, 2 (10%); thrombocytopenia, 1 (5%); fatigue, 1 (5%); infusion-related reaction, 1 (5%); sore throat, 1 (5%)	(6)
Sugemalimab (PD-L1 antibody)	GEMSTONE-201 prospective, single-arm, multicenter, phase II study	R/R NK/T, stage IV (67.5%)	≥3, 21.3% (17/80)	80	IRRC-assessed ORR/CRR, 44.9% (35/78)/35.9% (28/78); median DOR, not reached	Grade 3/4: treatment-related AEs, 13 (16.3%); treatment-related serious AEs, 6 (7.5%)	(7)

AE, adverse event; R/R, relapsed/refractory; ORR, overall response rate; CRR, complete response rate; irAEs, immune-related adverse events; DOR, duration of response; PFS, progression-free survival; OS, overall survival; CRS, cytokine release syndrome; TLS, tumor lysis syndrome; IRRC, independent radiology review committee.

or until disease progression, death, or withdrawal from the study. The results, evaluated by an independent radiologic review committee, revealed an ORR of 44.9% (95% CI: 33.6–56.6%), with CR rate of 35.9% and partial response (PR) rate of 9%. The 12-month duration of response rate was 82.5% (95% CI: 62.0–92.6%). In terms of OS, the survival rates at 6-, 12-, and 18-month were 79.2% (95% CI: 68.3–86.7%), 67.5% (95% CI: 55.4–77.0%), and 57.9% (95% CI: 44.9–68.9%), respectively. The median OS was not reached (95% CI: 14.0 months to not reached) (7). These results of sugemalimab provide further evidence of the high efficacy of PD-1/PD-L1 inhibitors in R/R ENKTL.

To date, this investigation represents the most impressive clinical trial evaluating the efficacy and safety of an immune checkpoint inhibitor in R/R ENKTL. The high level of agreement between the independent review committee and investigator assessment validates the reliability of the data, the credibility of the treatment's efficacy, and the expertise of the investigators. These findings hold significant implications for future clinical research and treatment decisions for patients. Regarding safety, most treatment-emergent adverse events observed were grade 1–2 severity, with grade 3 events reported in 40.0% of patients. Overall, the treatment was well-tolerated, consistent with the expected safety profile for this particular class of drugs.

However, the current study does have certain limitations. Firstly, it was a single-arm study that lacked a direct control group. Due to the potentially low incidence rate of the disease, historical controls from a single center were utilized. Additionally, the analysis of PD-L1 expression on tumor cells and its correlation with the efficacy of PD-1/PD-L1 inhibitors was not conducted. Although prior reports have shown no correlation between PD-L1 expression on lymphoma cells and the response to

PD-1/PD-L1 inhibitors (8), two prospective studies have identified a correlation between elevated PD-L1 expression levels and improved immunotherapy response (6,9). Therefore, further investigation into the predictive value of PD-L1 expression levels for clinical response is warranted, with a larger patient cohort and more comprehensive exploration of biomarker expression.

The treatment landscape for NK/T-cell lymphoma can be further navigated through ongoing clinical trials exploring innovative therapies or rational combinations of different treatment modalities. NK/T-cell lymphoma cells express CD30 and CD38, which have been investigated as therapeutic targets (10-13). In addition, chidamide, an orally administered inhibitor of histone deacetylases (HDACi), has shown promise with an ORR of 38% (CR: 16%) in R/R ENKTL (14,15). Hence, future research should explore the combination of PD-1/PD-L1 inhibitors with anti-CD30 or anti-CD38 antibodies, as well as their combination with HDACi. A planned randomized phase III study (NCT05700448) aims to evaluate the efficacy and safety profile of sugemalimab in combination with the P-GemOx regimen compared to the P-GemOx regimen alone in R/R ENKTL patients. Given the radiosensitivity of NK/T-cell lymphoma, investigating the combination of PD-1/PD-L1 immune checkpoint blockade and radiotherapy, particularly in R/R status and stage I/II cases, could be a valuable approach to explore due to the potential synergistic effect observed in solid tumors with the abscopal response. Furthermore, administration of allogeneic Epstein-Barr virus (EBV)-specific T-cells from donors has demonstrated improved survival in individuals at high risk of relapse compared to historical cohorts (16). Additionally, chimeric antigen receptor (CAR) T-cell therapy has received approval for the treatment of patients with R/R large B-cell lymphoma who have undergone multiple prior systemic therapies. An ongoing trial is evaluating the efficacy and safety of anti-CD7 CAR-T cell therapy in CD7-positive T-cell lymphoma, including ENKTL (NCT04004637). Exploring higher CR rates through combination treatments or innovative approaches may ultimately lead to a higher cure rate in NK/T-cell lymphoma.

A recent study conducted by Xiong *et al.* utilized transcriptomics-based methodologies to classify NK/T-cell lymphomas into three distinct subtypes: tumor-suppressor/immune-modulator (TSIM), MGA-BRDT (MB), and HDAC9-EP300-ARID1A (HEA) (17). This classification system not only provides valuable prognostic information for patients but also has the potential to identify individuals who may derive greater benefits from specific treatments. This advancement in subtyping holds the potential to contribute to personalized medicine by guiding treatment decisions and improving patient outcomes.

In summary, the results from the phase II trial utilizing sugemalimab demonstrated its strong efficacy in R/R ENKTL patients. The emergence of PD-1/PD-L1 blockade represents a significant breakthrough in the treatment of this disease. However, further research is required to identify optimal combination therapies and subgroups of patients who may experience enhanced benefits from such specific treatments. By exploring these areas, we can continue to improve outcomes for individuals with ENKTL and advance the treatment paradigm for this aggressive lymphoma subtype.

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Footnote

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