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Letter

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Prolonged Remissions After Nivolumab Plus Gemcitabine/Oxaliplatin in Relapsed/Refractory T-cell Lymphoma

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Peripheral T-cell lymphomas (PTCL) represent a heterogeneous group of aggressive lymphomas, which usually carry a poor prognosis. Malignant T cells may overexpress programmed death ligand 1 (PD-L1), which signals via programmed death-1 (PD-1) receptor, and provides an inhibitory signal on normal T-cells further suppressing antitumor immunity. They can also express PD1, which may act as a tumor suppressor on malignant T cells.¹ Thus, in principle, blocking the PD1/PDL1 synapse in PTCL may lead to either tumor regression or progression.² Nevertheless, PD1-blockade demonstrated antitumor activity in monotherapy in patients with relapsed/refractory (R/R) PTCL with an ORR around 33%.^{3,4}

The NIVEAU trial is an ongoing international, multicenter, randomized, open label, phase 3 study testing Nivolumab (Nivo)

in combination with Gemcitabine and Oxaliplatin (Gem-Ox) [± Rituximab] for patients with aggressive (B and T cells) non-Hodgkin lymphoma, in first relapse or progression, who are not eligible for high-dose chemotherapy (NCT03366272). Here, we performed a preliminary analysis of the experimental arm (Nivo-GemOx) of the PTCL cohort to assess the safety and efficacy of this regimen in this population.

Key eligibility criteria include the following: first relapse or progression of PTCL, ineligibility for high-dose therapy (defined as age > 65 years or older than 18 years if HCT-CI score > 2), only 1 prior chemotherapy regimen including an anthracycline. Patients in the experimental arm were planned to receive 8 cycles Nivolumab (3 mg/kg at day 0 of cycle 1 and day 1 of cycle 2–8) plus Gemcitabine (1000 mg/m² at day 1) and Oxaliplatin

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NIVEAU (NCT03366272)

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(100 mg/m² at day 1) in 2-week intervals followed by additional 18 infusions of Nivolumab (3 mg/kg) biweekly as consolidation over a period of 1 year or until progression. Response was evaluated after 4 and 8 cycles of Nivo-GemOx according to the Lugano classification,⁵ and every 3 months by CT-scan during consolidation therapy. Each progression/relapse of PTCL had to be reported as an SAE.

The analysis (data cutoff October 16, 2020) included 12 patients enrolled in the experimental arm (Supplementary Digital Content Table 1, <http://links.lww.com/HS/A216>): 4 (33%) PTCL NOS, 3 (25%) AITL, 1 (8%) nodal TFH-PTCL, 2 (17%) ALCL ALK-, 1 (8%) EATL, and 1 (8%) MEITL. Median age was 69.5 years (range, 53–80), 7 (58%) patients were male, 2 (17%) had received a prior autologous stem cell transplantation, and 5 (42%) were refractory to first line therapy. At enrollment, performance status was 0–1 in 9 (75%) pts and 2 in 3 (25%) pts, 11 (92%) had Ann Arbor stage III–IV, 2 (17%) had B-symptoms, 7 (58%) had more than 1 extranodal site and 4 (33%) had elevated LDH. PD1 and PD-L1 were expressed by the tumor cells in 6/10 (60%) and 2/11 (18%) patients, respectively (Table 1).

Patients have received a median of 6 (range, 1–8) cycles of GemOx and 8 (range, 1–26) infusions of nivolumab. Treatment was prematurely discontinued in 9 patients (7 during induction and 2 during consolidation), due to lymphoma progression (n = 6), toxicity (n = 2), or intercurrent disease (n = 1, yeast septicemia). There were 28 SAE in 11 patients, including 8 progressive diseases (Supplementary Digital Content Tables 2; <http://links.lww.com/HS/A216> and 3; <http://links.lww.com/HS/A216>).

Nine (75%) patients achieved an objective response (4 complete responses and 5 partial responses). Two patients experienced primary progression upon Nivo-GemOx (Table 1): patient 9 (MEITL, PD1-negative) and patient 12 (PTCL-NOS, strongly PD1-positive). In these 2 patients, tumor growth rate (TGR) assessed during the first cycle of Nivo-GemOx (experimental period) was more than 2-fold higher than TGR assessed during the prior line of therapy (reference period) (Supplementary Digital Content Figure 1; <http://links.lww.com/HS/A216>). Unfortunately, the reference period cannot be a wash-out period (off-therapy) in aggressive lymphoma. In this fast-growing disease, the reference period is the prior line of therapy, as only on-treatment CT-scans are available before initiation of the experimental salvage treatment regimen. Thus, the standard criteria for hyperprogression, which have been established in solid tumors, could not be strictly applied in our cohort of

patients.⁶ Nevertheless, patient 9 (MEITL, PD1-negative), which progressed after first-line therapy of 2 cycles of CHOEP and 2 cycles of high-dose Methotrexate experienced a second progression after the second cycle of GemOx. Patient 12 (PTCL-NOS, strongly PD1-positive), which progressed 1 month after 6 cycles of CHOP plus additive radiotherapy experienced a rapid second progression within its first cycle of study treatment, when again a partial remission lasting several months could be achieved after switching to third-line therapy. In this patient, nivolumab might have promoted lymphoma progression. However, shorter duration of remission in relapse represents a common phenomenon in lymphoma. Thus, establishing scientific criteria for hyperprogression are warranted. We did not find a clear correlation between PD1/PD-L1 expression on tumor cells and response to Nivo-GemOx. However, PD-L1 may also be expressed by bystander cells from the tumor microenvironment. This will be further explored in the final analysis of the clinical trial. Among the 9 responding patients, the median DOR was 14.9 months. Median PFS2 (time from randomization to second relapse/progression/death) was 6.9 months (95% CI, 0.3–13.5) versus 7.7 months (95% CI, 7.2–8.2) for PFS1 (time from diagnosis to first relapse/progression). Importantly, PFS2 was superior to PFS1 in 4 out of 10 patients (40%), and not informative in 2 pts: patient 10 who is still on therapy (ongoing PFS) and patient 8 who died prematurely of infection (Figure 1). Median OS was 24.8 months (95% CI, 1.6–47.9). After a median follow-up of 26.8 months, 7 patients have died, either from lymphoma (n = 5) or infection (n = 2, 1 COVID-19 infection and 1 yeast septicemia), and 5 remain alive.

These preliminary results show that nivolumab in combination with GemOx is well tolerated. Although some reports raised the concern that anti-PD1 therapy may promote tumor proliferation in T-cell lymphoma,^{1,7,8} other studies demonstrated that anti-PD1 had efficacy in these neoplasms.^{9–11} Interestingly, the combination of Nivolumab with GemOx lead to high response rates and prolonged remissions (compared to first-line treatment) in a subset of patients. Longer PFS after salvage therapy suggests that it is more effective than the previous line of therapy, a CHOP-based regimen in our study. The combination of anti-PD1 antibody with chemotherapy may indeed have additive or synergistic clinical activity. Chemotherapy, notably gemcitabine and oxaliplatin, can promote tumor immunity by inducing immunogenic cell death and by disrupting the immunosuppressive tumor microenvironment.¹² Additionally, anti-PD1 therapy may not only stimulate the antitumor immune response but also may sensitize to chemotherapy.^{13–15} In non-Hodgkin

Table 1.

PD1 and PD-L1 Expression in Individual Patients^a

Pt	Histology	PD1 Expression on Tumor Cells (%)	PD-L1 Expression on Tumor Cells (%)	Best Response by Investigator
1	Enteropathy-associated T-cell lymphoma (EATL)	0	0	PR
2	Peripheral T-cell lymphoma, NOS (PTCL-NOS)	5	0	CR
3	Anaplastic large cell lymphoma, ALK-negative (ALK-ALCL)	10	100	PR
4	Angioimmunoblastic T-cell lymphoma (AITL)	0	0	CR
5	Nodal peripheral T-cell lymphoma with TFH phenotype (TFH-PTCL)	0	0	PR
6	Peripheral T-cell lymphoma, NOS ^b	NA	NA	CR
7	Anaplastic large cell lymphoma, ALK-negative ^b	NA	50	PR
8	Angioimmunoblastic T-cell lymphoma	60	0	SD
9	Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)	0	0	PD
10	Peripheral T-cell lymphoma, NOS	5	0	CR
11	Angioimmunoblastic T-cell lymphoma	50	0	PR
12	Peripheral T-cell lymphoma, NOS	90	0	PD

^aPD-1/PD-L1 expression was assessed by IHC and centrally reviewed. Immunostains for PD1 and PD-L1 were performed using a Leica Bond automated immunostainer, with the following primary antibodies: PD1, clone NAT105 mouse monoclonal antibody, Abcam Ab52587; PD-L1, clone QR001 recombinant rabbit monoclonal antibody, Quartett.

^bAbsence or inadequate material for central pathology review.

NA = not assessable.

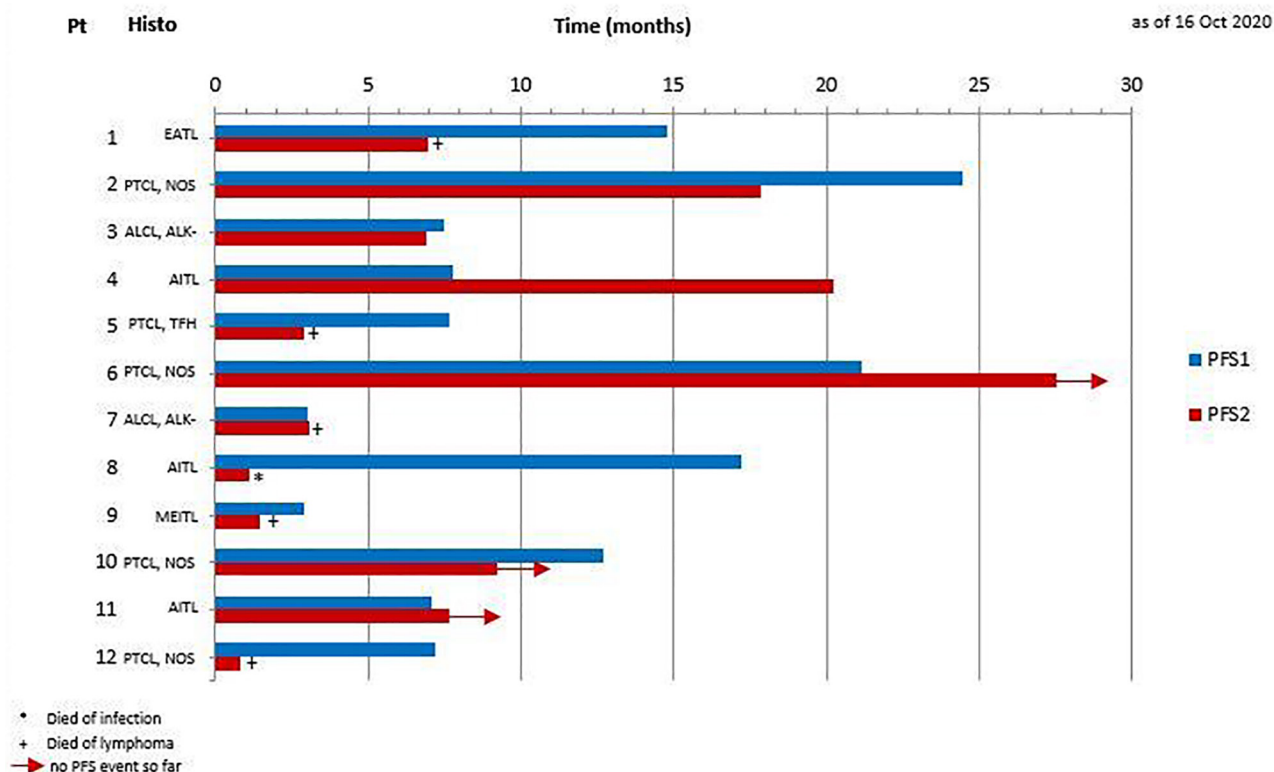


Figure 1. PFS1 vs PFS2 for individual patients. PFS1 is defined as the time from diagnosis to first relapse/progression. PFS2 is defined as the time from randomisation to second relapse/progression or death.

lymphoma, a retrospective study showed that the duration of response (DOR) to therapies given after checkpoint blockade therapy were longer than the DOR to treatment immediately prior to checkpoint blockade therapy, suggesting a potentiation effect of the immunotherapy.¹⁴ Cytostatic drugs like gemcitabine and oxaliplatin are disrupting DNA replication, which requires transition into cell cycle.^{16,17} One might speculate, that blocking the PD1 pathway results in increased T-cell receptor signaling and proliferation, rendering the cell more susceptible for chemotherapy.¹

Overall, these preliminary results show encouraging efficacy and safety profiles of the Nivo-GemOx regimen in R/R PTCL. These findings will have to be confirmed on a larger number of patients and by comparing this combination with the control arm (Gem-Ox) once the NIVEAU study will be completed. Translational research (including evaluation of tumor micro-environment, oncogenic TCR alterations, and *Pdcd1* genomic deletions) will also be performed to identify predictive markers of efficacy. The NIVEAU phase 3 trial is actively enrolling patients.

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