SYNOPSIS

Date of Report	15 Jan 2026
Title of the study	Improvement of Outcome in Elderly Patients or Patients not eligible for high-dose chemotherapy with Aggressive Non-Hodgkin Lymphoma in first Relapse or Progression by adding Nivolumab to Gemcitabine, Oxaliplatin plus Rituximab in case of B-cell lymphoma.
EudraCT number	2016-002272-27
NCT number	NCT03366272
Sponsor	Vice President for Research and Technology Saarland University Post Office Box 151150 D-66041 Saarbrücken Tel.: +49 (681) 302-3643 Fax: +49 (681) 302-3001 E-Mail: vp-forschung@uni-saarland.de
Phase	III
Primary objective of the study	Improvement of 1-yr PFS by Nivolumab plus (R)-GemOx followed by Nivolumab consolidation instead of (R)-GemOx alone.
Treatment	Immunochemotherapy consists in eight cycles (R)-GemOx (Gemcitabine 1000 mg/m^2, d1, Oxaliplatin 100 mg/m^2, d1, Rituximab 375 mg/m^2 in case of B-cell lymphoma disease, repeated every 2 wks) **Standard arm:** eight cycles of (R)-GemOx. **Experimental arm:** eight cycles of Nivolumab (240 mg) plus (R)-GemOx in 2-wk intervals followed by additional 9 infusions of Nivolumab (480mg) in 4-wk intervals as consolidation or up to progression or unacceptable toxicity, whatever occurs first. Switching to flat-dosing 240 mg every 2 weeks (Q2W) and 480 mg given every 4 weeks (Q4W) should start immediately when protocol version 6.0 will be activated. All patients are treated in the experimental arm in the safety run-in phases
Study treatment (IMP)	Opdivo® Generic Name: Nivolumab

	Trade Name:	Opdivo®
	Mode(s) of action:	Inhibition of the interaction of PD-1 with its ligands, PD-L1 and PD-L2
	Manufacturer:	Bristol-Myers Squibb
	Dose:	until protocol V05.0-F, 3 mg/kg IV q2w; from V06.0-F, flat dosing (fixed dose, independent of body weight): 240 mg IV q2w during induction and 480 mg IV q4w during consolidation (first consolidation dose 2 weeks after start of cycle 8).
	Route of administration:	Intravenous (i.v.) injection
	Formulation:	Aqueous solution
Indication	Patients with first relapse or progression of aggressive Non-Hodgkin's Lymphoma who are not eligible neither for autologous nor allogeneic stem cell transplantation	
Diagnosis and main criteria for inclusion	Patients with first relapse or progression of aggressive Non-Hodgkin's Lymphoma who are not eligible for neither autologous nor allogeneic stem cell transplantation, defined as age >65 years or > 18 years old with HCT-CI score >2 or patients who underwent prior autologous stem cell transplantation and are not eligible for allogeneic stem cell transplantation.	
Study design	International, multicentre, randomized, open-label, treatment optimization study, preceded by safety run-in phases conducted for B-cell and T-cell lymphoma separately.	
Methodology	The study consisted of a treatment period with (immuno) chemotherapy combined with an immune therapy (depending on randomization) and a follow-up period for all study participants. During the study, efficacy and tolerability of the study medication were investigated.	
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Study centers and investigators (as of 01/2025)	See attachment 5
Study period	First patient first visit (FPFV): 12 Jan 2018 Last patient last visit (LPLV): 15 Jan 2025
Number of patients	A maximum of 388 patients were planned to be included. Of those 310 patients with B-cell lymphoma and a maximum of 78 patients with T-cell lymphoma. Analyzed: In the Full Analysis Set (FAS), 270 patients with B-cell lymphoma and 78 patients with T-cell lymphoma were included, resulting in a total of 348 patients analyzed. Due to low recruitment rate randomization was stopped on March, 31st, 2023. Therefore, the number of included patients is lower than initially intended.
Criteria for evaluation	**Primary endpoint:** Progression-free survival **Selected secondary endpoints:** Rate of complete remission (CR) Rate of partial remission (PR) Rate of complete and partial remissions (ORR) Duration of response Rate of progressions during therapy or within two months after last cycle of chemotherapy (PD) Relapse rate (RR) Event free survival (EFS) Overall survival (OS) Rate of treatment-related deaths Long-term sequelae and second malignancies Protocol adherence Quality of life (EQ-5D-5L) Biological parameters
Statistical methods	NIVEAU (B-cell cohort): International, multicentre, randomised, open-label phase III treatment-optimisation study comparing (R)-GemOx vs (R)-GemOx + nivolumab (induction + consolidation), powered to detect an improvement of 1-year PFS from 27% to 42% (hazard ratio 0.66), two-sided α=5%, power 80%. Required for analysis: 292 B-NHL patients (146/arm); allowing ~5% loss to follow-up → planned n=310. One O'Brien–Fleming α-spending interim at the first 180 B-cell patients. Primary endpoint: 1-year PFS; key secondary endpoints: EFS, OS, ORR.

	NIVEAU (T-cell cohort): Parallel randomised, open-label comparison (GemOx vs GemOx + nivolumab), analysed separately; up to 78 patients planned; efficacy endpoints as per protocol, descriptive for this cohort.
Substantial protocol changes	The study was conducted according to the Clinical Study Protocol (CSP) versions: Version V01.0-F /Date 30th of December, 2016 Version V02.0-F /Date 08th of March, 2017 Version V03.0-F /Date 11th of September,2017 Version V04.0-F /Date 02nd of October, 2018 Version V05.0-F /Date 21th of December, 2018 Version V06.0-F / Date 21th of December, 2020 Version V07.1-F / Date 10th of July 2023 Version V08.0-F / Date 14th of August 2024
Publications	Houot R, Poeschel V, Altmann B, et al. Nivolumab in Combination with Gemcitabine and Oxaliplatin (GemOx) in Relapse/Refractory T-Cell Lymphoma: Preliminary Results of the Experimental Arm of the Niveau Trial. Blood 2020; 136(Supplement 1): 33-4. Held G., Poeschel V., Altmann B., et al. Nivolumab in combination with Gemcitabine and Oxaliplatin (GemOx) in Relapse/Refractory T-cell Lymphoma: Preliminary results of the experimental arm of the NIVEAU trial. Oncol Res Treat 2021;44(suppl 4):I Houot R, Poeschel V, Altmann B, et al. Prolonged Remissions After Nivolumab Plus Gemcitabine/Oxaliplatin in Relapsed/Refractory T-cell Lymphoma. Hemasphere. 2022 Jan 10;6(2):e672. Held G, Haioun C, Houot R, et al. Analysis of a Safety Run-in Cohort from Niveau, a Phase 3 Study for Patients with Aggressive Non-Hodgkin Lymphoma in First Relapse or Progression Not Eligible for High-Dose Chemotherapy (HDT), Testing Nivolumab in Combination with Gemcitabine, Oxaliplatin (GemOx) Plus Rituximab (R) in Case of B-Cell Lymphoma. Blood 2019; 134(Supplement_1): 4085- Thurner L., Poeschel V., Haioun C., et al. Analysis of a safety run-in cohort from NIVEAU, a phase 3 study for patients with aggressive Non-Hodgkin lymphoma in first relapse or progression not eligible for High-Dose Chemotherapy (HDT) testing Nivolumab in combination with (R)-GemOx. Oncol Res Treat 2020;43(suppl 4):VIII Thurner L, Poeschel V, Altmann B, et al. Pre-Planned Interim Safety Analysis of the Niveau Trial, a Randomized Phase 3 Study for Patients with Aggressive Non-Hodgkin Lymphoma in First Relapse or Progression Not Eligible for High-Dose Chemotherapy (HDT), Testing Nivolumab in Combination with Gemcitabine,

	Oxaliplatin (GemOx) Plus Rituximab (R) in Case of B-Cell Lymphoma. Blood 2020; 136(Supplement 1): 32-. Held G, Altmann B, Kerkhoff A et al. R-GemOx Plus Nivolumab Vs R-GemOx As Second-Line Therapy for Large B-Cell Lymphoma in Transplant-Ineligible Patients: Interim Analysis of the Niveau Trial, an International, Randomized Phase 3 Study of the AGMT, GLA, HOVON, Lysa and PLRG. Blood (2023): 142 (Supplement 1): 43. Held G, Altmann B, de Leval L et al. Nivolumab + GemOx as second-line therapy for peripheral T cell lymphoma in transplant-ineligible patients: final analysis of a sub-cohort of the randomized NIVEAU trial. Hematological Oncology (2025): 43, Issue S3 . For details please refer to attachment 13.
Financing	Bristol-Myers Squibb 777 Scudders Mill Road, Plainsboro, NJ 08536, USA
Discussion and overall conclusions	**B-cell cohort:** Recruitment started on Jan. 12th 2018. An interim analysis of B-cell lymphoma was performed in 180 of the 310 planned patients with B-cell lymphoma. The results have been presented to the DSMC. The DSMC concluded that there is no statically relevant difference in toxicity. Furthermore, that there is no reason to terminate the trial prematurely for superiority of one arm. After a complex discussion involving the Data Safety Monitoring Committee, the Protocol Committee and the Working Parties of the Study Groups taking into account the lower recruitment rate since 07/2022 and competing therapies were available for this patient population in the meantime the recruitment ended prematurely at 31st March 2023. So far 270 patients with B-cell lymphoma were included. The last patient was included on 30th March 2023. The number of included patients allowed for a clear scientific conclusion concerning primary and secondary endpoints. No difference in 1-year PFS appeared, which represents the primary endpoint. Also, PFS depicted by the method of Kaplan-Meier over time was similar, both in the standard- as well as in the experimental arm. No differences in response rates were detected, PR, CR and ORR, respectively. OS was similar. Thus, Nivolumab when added to GemOx chemotherapy did not increased efficacy. The design of the study was appropriate to draw this conclusion. Most PFS-events occurred during the first year after inclusion. The primary endpoint 1-year PFS comprehensively reflects the course of patients, which have been included in the study. 1-year PFS was 29% in the standard arm, exactly as assumed in the sample size calculation of initial planning. Therefore, the study represents a clear negative study. An anti-PD1 has no role in the treatment in patients with relapsed/refractory B-cell lymphoma ineligible for highdose chemotherapy. Importantly, the prognosis in the standard arm was poor, demonstrating inferiority of R-GemOx regimen compared to newer treatment options like CAR T-cells or bispecific antibodies.[17,18]

	T-cell cohort: Recruitment started on Jan. 12th 2018 and stopped after inclusion of 78 patients as planned on Dec 31th 2021. A safety run-in phase was performed, which included 6 patients with T-cell lymphoma. Also a safety analysis was performed in the first 12 patients, who have been randomized in the experimental arm and received GemOx+Nivolumab.[19] A more complex situation appeared in the T cell cohort, First, only 78 patients were included. The sample size was not powered to detect a statistical difference in 1-year PFS, which was chosen as primary endpoint for the B-cell cohort. The aim was to obtain results, which suggest promising efficacy and warrant further investigation in a separate study. Therefore, progression free survival (PFS) was analysed in an additional manner. The analysis was supposed to be positive if more patients have a PFS2/PFS1 ratio > 1 in the experimental compared to the standard arm. No difference in 1-year PFS appeared, but more patients experienced a PFS2/PFS1 ratio >1. OS was similar. Nivolumab increased response rates of GemOx, PR, CR as well as ORR. Contrary, there are more therapy related deaths at the time point before first response assessment. Also, the amount of serious adverse events and adverse events were increased in the experimental arm. Thus, increased response rates were compromised by increased toxicity after treatment with GemOx+Nivolumab. Both effects balanced each other resulting in similar OS in both arms. Increased toxicity is caused by inflammatory / hyperinflammatory reactions rather than infections. Similar syndroms are evident after treatment with bispecific antibodies and CAR T-cells as cytokine-release syndroms.[14] Future studies warrant an effective control of the inflammatory / hyperinflammatory reactions by algorithms, which ave been established for treatment of cytokine-release syndroms. Importantly, the prognosis in the standard arm was very poor, demonstrating poor efficacy of the GemOx regimen for treatment of relapsed/refractory peripheral T-cell lymphoma. Further research is urgently needed to improve the poor prognosis in these patients. In this light, the results of our study are important, because increased response rates in the experimental arm allows for the hypothesis, that Nivolumab might increase efficacy.

Coordinating Investigator (CI)

Homburg, 14.01.2026

Prof. Dr. Gerhard Held

Place, date