CLINICAL STUDY REPORT

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 *Niv*olumab to G*e*mcitabine, Ox*a*liplatin plus Rit*u*ximab in case of B-cell lymphoma

NIVEAU/DSHNHL 2015-1

EudraCT number:	2016-002272-27
NCT number:	NCT03366272
Trial protocol code:	NIVEAU/DSHNHL 2015-1
Name of the IMP:	Nivolumab
Phase of development:	Phase III
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.
Study dates:	First patient first visit: 16 Jan 2018 Last patient last visit: 15 Jan 2025
Sponsor:	Saarland University Campus 66123 Saarbrücken, Germany
Coordinating Investigator:	Prof. Dr. Gerhard Held Internal Medicine I Saarland University Medical School 66421 Homburg/Saar, Germany
Version of the report	1.0
Date of the report:	January, 15th 2026

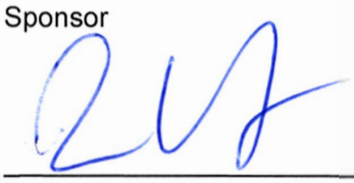
Signatures

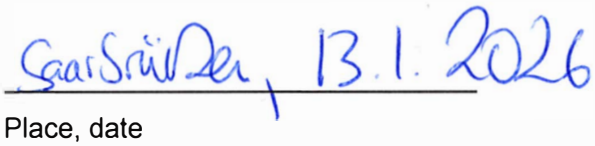
The undersigned authors agree to the contents of this clinical study report by their signatures. The reported clinical trial was conducted according to the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and applicable laws.

Coordinating Investigator (CI)

Prof. Dr. Gerhard Held	Homburg, 14.01.2026
	Place, date

Sponsor





Prof. Dr. Robert Ernst	Saarbrücken, 13.1.2026
	Place, date

1 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.	
Coordinating Investigator (Germany)	Prof. Dr. med. G. Held Internal Medicine I Saarland University Medical School 66421 Homburg/Saar, Germany Tel.:+49 (6841) 16-15014, Fax: +49 (6841) 16-15015 E-Mail: gerhard.held@uks.eu	
Coordinating Investigator (Austria)	Prof. Dr. Ulrich Jäger Univ.-Klinik Innere Medizin I Medizinische Universität Wien Währinger Gürtel 18-20 1090 Wien, Austria	

	Tel.: +43 1 40400/44090, Fax: +43 1 40400/40300 E-Mail: ulrich.jaeger@meduniwien.ac.at
Coordinating Investigator (Belgium)	Prof. Dr. M. Andre Dept. of Hematology CHU Mont-Godinne Avenue G. Therasse, 1 5530 Yvoir, Belgium Tel.: +32 81423864, Fax: +32 81 42 38 32 E-Mail: marc.andre@uclouvain.be
Coordinating Investigator (France)	Prof. Dr. R. Houot Dept. of Hematology Hôpital Pontchaillou 2 rue Henri Le Guilloux 35033 Rennes cedex, France Tel.: +33 2 99 28 98 73, Fax: +33 2 99 28 41 61 E-Mail: roch.houot@chu-rennes.fr
Coordinating Investigator (Israel)	Dr. A. Avigdor Division of Hematology and Bone-Marrow Transplantation Chaim Sheba Medical Center Tel Hashomer 5265601 Ramat Gan, Israel Tel.: + 972-52-6667154, Fax: +972-3-5307117 E-Mail: abraham.avigdor@sheba.health.gov.il
Coordinating Investigator (The Netherlands)	Dr. S. Tonino Dept. of Hematology Academic Medical Center Meibergdreef 9 1105 AZ Amsterdam, Netherlands Tel.: +31 20 5665785, Fax: + 31 20 6919743 E-Mail: s.h.tonino@amc.nl
Coordinating Investigator (Poland)	Anna Dąbrowska-Iwanicka, MD, PhD Dept. of Lymphoid Malignancies Maria Sklodowska-Curie Memorial Institute and Oncology Centre ul. Roentgena 5 02-781 Warszawa, Poland Tel.: +48 22 546 26 18 E-Mail: anna.dabrowska-iwanicka@coi.pl
Coordinating Investigator (Portugal)	Dr. M. Gomes da Silva Dept. of Hematology Instituto Português Oncologia Rua Professor Lima Basto 1099-023 Lisboa, Portugal Tel.: + 351 217229867, Fax: + 351 217229867 E-Mail: mgsilva@ipolisboa.min-saude.pt

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

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3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACRIN	American College of Radiology Imaging Network
ADR	adverse drug reaction
AE	adverse event
ALK	anaplastic lymphomkinase
ALL	acute lymphocytic leukemia
ALT	alanine-aminotransferase
AMG	Arzneimittelgesetz (german drug law)
ASR	annual safety report
AST	aspartate-aminotransferase
AUC	area under the curve
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BSA	body surface area
CCS	Canadian cardiac society
CD	cluster of differentiation
Cf	confer
CI	confidence interval
CL	clearance
CLL	chronic lymphocytic leukemia
CMV	cytomegalie virus
CNS	central nervous system
CPMP	Committee for Proprietary Medicinal Products
CR	complete remission
CRu	complete remission unconfirmed
CRF	case report form
CSF	cerebro-spinal fluid
CSP	clinical study protocol
CSR	clinical study report
CT	computer tomography
CTC	common toxicity criteria
CTC-AE	common toxicity criteria for adverse events
CTV	clinical target volume
CTX	chemotherapy
CV	Curriculum Vitae
d	day
DFG	Deutsche Forschungsgemeinschaft
DICOM	digital imaging and communications in medicine
DLBCL	diffuse large B-cell lymphoma
DMSC	data monitoring and safety committee
DSHNHL	Deutsche Studiengruppe hochmaligne Non-Hodgkin-Lymphome (german high-grade non-Hodgkin Lymphoma study group)
ECAT	emission computer assisted tomography
EBV	Epstein Barr virus
EC	ethics committee
ECG	electrocardiography

ECOG	toxicity and response criteria of the eastern cooperative oncology group
EF	ejection fraction
EFS	event free survival
e. g.	for example
ENT	ear-nose-throat
ESR	erythrocyte sedimention rate
EudraCT	European Database for Clinical Trials
FACS	fluorescence activated cell sorter
FAS	full analysis set
FDA	(US) Food and Drug Administration
FDG-PET	18F-fluorodeoxyglucose (FDG) positron emission tomography
Fe V1	forced expiratory volume in 1 second
FL	follicular lymphoma
FS	fractional shorting
γ-GT	gamma glutamyl transferase
GCP	good clinical practice
GCP-V	GCP-Verordnung (ordinance)
G-CSF	granulocyte-colony stimulating factor
GELA	Groupe d'études des lymphomes de l'adulte (French Lymphoma Study Group)
Gy	gray
HD-MTX	high dose methotrexat
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HR	hazard ratio
HSV	herpes simplex virus
ICH	international conference on harmonisation
ICRU	International Commission on Radiation Units and Measurements
i. e.	that is (id est)
IHP	International Harmonization Project
IMISE	Institut für medizinische Informatik, Statistik und Epidemiologie
IMP	investigational medicinal product
IMPD	investigational medicinal product dossier
IMRT	intensity-modulated radiation therapy
IPI	international prognostic index
ISF	investigator site file
ITT	intention-to-treat
i. v.	intravenous
KI	Konfidenzintervall
KML	Kompetenznetz Maligne Lymphome
LDH	Lactatdehydrogenase
LKP	Leiter der klinischen Prüfung / Coordinating investigator
MALT	mucosa-associated lymphoid tissue
MedDRA	Medicinal Dictionary for Regulatory Activities
MRT	magnetic resonance tomography

MTV	Metabolic tumor volume
MTX	methotrexate
MV	megavolt
NCI	National Cancer Institute (US National Institute of Health)
NCR	no carbon required
NCRI	National Cancer Research Institute (UK)
NHL	Non-Hodgkin lymphoma
NOS	not otherwise specified
NPV	negative predictive value
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
OS	overall survival
PACS	picture archiving and communication system
PCNSL	primary CNS lymphoma
PD	disease progression / progressive disease
PEI	Paul-Ehrlich-Institut
FDG-PET	positron emission tomography
PFS	progression free survival
PK	pharmacokinetic
p. o.	per os, orally
PP	per-protocol
PPS	per protocol set
PPV	positive predictive value
PR	partial responses
PRO	progression
PT	prephase treatment
PTV	planning target volume
R	rituximab
RE	restaging
RTX	radiotherapy
SAE	serious adverse event
SAP	statistical analyses plan
SAR	serious adverse reaction
SAS	safety analysis set
s. c.	subcutaneously
SCLC	small cell lung carcinoma
SD	stable disease
SGOT	serum glutamate oxalacetate transaminase
SGPT	serum glutamate pyruvate transaminase
SOP	standard operating procedures
SPD	sum of the products of the diameters
SUR	standardized uptake ratio
SUSAR	suspected unexpected serious adverse (drug) reaction
SUV	standardized uptake value
TLG	Total lesion glycolysis

TLG_{SUR}	SUR-derived TLG
TMA	tissue microarray
TMF	trial master file
UNV	upper limit of normal value
WHO	world health organisation
YR	year

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5 LIST OF TABLES

6 ETHICS

a) Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The clinical study protocol (CSP) and any amendments as well as the informed consent forms (ICF) and any other relevant documents were reviewed and approved by each study site's IEC before the start of the study. A list of all IECs/IRBs consulted can be found in Appendix 17.1.3.

b) Ethical Conduct of the Study

Performance, evaluation, and documentation of this study were specified in the CSP to ensure that the sponsor and investigator abide to the International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, the principles set out in the Declaration of Helsinki and applicable local law(s) and regulation(s). Strict adherence to all specifications described in the CSP was required, i.e., the investigator was not allowed to modify or change the procedures described in the CSP. Deviations from the protocol had to be documented and explained by the investigator and/or sponsor.

Documented approval from the competent IEC was obtained for the participating centers before start of the study. All investigators and other staff involved in the study were informed that the competent federal authorities and authorized representatives of the sponsor have the right to review study documentation and the study subjects' medical records at any time.

c) Patient Information and Consent

The patient information sheet, ICF and all other documents handed out to the trial subject were reviewed and approved by the IEC before their use. All written information handed out to the trial subjects were revised whenever new information relevant to the subject´s consent became available.

Trial subjects were not enrolled into the study unless they had voluntarily consented to take part in the trial, after having been informed verbally and in writing in comprehensible language of the nature, scope and possible consequences of the study by the investigator. The subjects also agreed that representatives of the sponsor (e.g. monitors or auditors) or the competent supervisory or federal authorities might be given access to the data recorded within the framework of the clinical trial. The trial subject was informed of the potential benefits and possible side effects of the investigational medicinal products (IMP) applied in this study.

Before entering the study, the ICF was read by and explained to all subjects. Each subject had ample time and opportunity to ask questions and was informed about the right to withdraw his/her consent at any time without giving reasons and without jeopardizing his/her further medical care.

The ICF was signed by the trial subjects and also signed and dated by the investigator. The originally signed ICF is archived in the investigator site file (ISF). Each subject received a copy of the written information sheet, confirmation of insurance inclusive conditions, and the signed ICF.

A copy of the patient information sheets and informed consent forms are provided in Appendix 17.1.3.

7 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The study was performed under the organization of Saarland University which acted as sponsor.

Prof. Dr. med. Gerhard Held (Internal Medicine I, Saarland University Medical School, Homburg/Saar, Germany) was appointed as Leiter der klinischen Prüfung (CI) according to German Drug Law.

Prof. Dr. med. Gerhard Held was also responsible for the medical coordination including medical advises and publications.

Only qualified investigators were selected to take part in the study. At each center, the principal investigator was responsible for the study. A list of participating centers and investigators is presented in attachment 5. Page 2 of this clinical study report (CSR) contains the signature of

the CI and the Sponsor representative, indicating that this CSR accurately describes the conduct and results of this study.
Key study personnel involved in the conduct of this study (amendment 7) is listed in Table 1.
All laboratory analyses were done by the local labs.
Statistical analyses were performed by ZKS/IMSE Leipzig according to an approved statistical analysis plan (SAP).

Table 1: Study administrative structure

Sponsor according to German Drug Law (AMG)	Prof. Dr. R. Ernst Vice-President for Research and Outreach Saarland University Campus 66123 Saarbrücken Tel.: +49 (681) 302-3864 E-mail: vp-forschung@uni-saarland.de
Coordinating Investigator (LKP according to German Drug law)	Prof. Dr. med. G. Held Internal Medicine I Saarland University Medical School D-66421 Homburg/Saar Tel.: +49 (6841) 16-15014 Fax: +49 (6841) 16-15015 E-Mail: gerhard.held@uks.eu
Scientific Study Coordination	Prof. Dr. med L.Thurner Internal Medicine I Saarland University Medical School D-66421 Homburg/Saar Tel.: +49 (6841) 16-15014 (or -15016), Fax: 16-15015 E-Mai: lorenz.thurner@uks.eu
Clinical Consultant	Dr. med. V. Poeschel Internal Medicine I Saarland University Medical School D-66421 Homburg/Saar Tel.: +49 (6841) 16-15014 (or -15016), Fax: 16-15015 E-Mail: dshnhl@uks.eu
Central Study Office	Dr. med. V. Pöschel, D. Ehlert, J. Ehlert Internal Medicine I Saarland University Medical School D-66421 Homburg/Saar Tel.: +49 (6841) 16-15014 (or -15232) Fax: +49 (6841) 16-15015 E-Mail: dshnhl@uks.eu
Biometry	Prof. Dr. M. Löffler, Dr. habil. M. Ziepert, Dr. B. Altmann IMISE, University of Leipzig, Härtelstr. 16-18 D-04107 Leipzig Tel.: +49 (341) 97-16100 Fax: +49 (341) 97-16109 E-Mail: marita.ziepert@imise.uni-leipzig.de

Data Management	N. Abo-Hasna, J. Haury, S. Maurer, E. Noe Internal Medicine I Saarland University Medical School D-66421 Homburg/Saar Tel.: +49 (6841) 16-1501 (or -15385,-1537, -15016, 15370) Fax: +49-(6841) 16-15015 E-Mail: dshnhl@uks.eu
Drug Safety	M. Dörschmann; H. Bogatsch, T. Haage IMISE, University of Leipzig, Härtelstr. 16-18 D-04107 Leipzig Tel.: +49 (341) 97-16129 Fax: +49 (341) 97-16278 E-Mail: pharmacovigilance@imise.uni-leipzig.de
Monitoring Germany	KCR CRO GmbH, Am Kupfergraben 4-4A, D-10117 Berlin Tel.: +49 30 206 07 975 E-Mail: info@kcrcro.com
Monitoring France & Belgium / Europe Supervising (except Germany)	LYSARC, Centre Hospitalier Lyon-Sud Secteur Sainte Eugénie - Pavillon 6D-F FR 69495 PIERRE-BÉNITE Cedex Tel.: +33 (0)4 27 01 27 12 Fax: +33 (0) 4 72 66 93 71 E-Mail: niveau@lysarc.org
Monitoring Austria	AGMT, Arbeitsgemeinschaft Medikamentöse Tumortherapie Gemeinnützige GmbH Gentzgasse 60/20 A 1180 Vienna
Monitoring Czech Republic	Czech Lymphoma Study Group/Kooperativní lymfomová skupina, U nemocnice 499/2, Nové Město, CZ 128 00 Praha 2
Monitoring Israel	NovaTrials CRO Ltd. 3 Golda-Meir St. IL 7403648 Ness-Ziona
Monitoring The Netherlands	HOVON, The Haemato Oncology Foundation for Adults in the Netherlands, P.O. Box 2040 NL 3000 CA Rotterdam
Monitoring Poland	Quantum Satis Sp. z o. o. Białostocka 24/41 PL 03-741 Warsaw
Monitoring Portugal	W4Research Lda Avenida Fontes Pereira de Melo, Nº 31, 7ºB PT 1050-117 Lisboa

Reference Pathology	Prof. Dr. med. A. Rosenwald Institute of Pathology University of Würzburg Josef-Schneider-Str. 2 D-97080 Würzburg Tel.: +49 (931) 31-81199 Fax: +49 (931) 31-81224 E-Mail: Rosenwald@mail.uni-wuerzburg.de
Funding	Bristol-Myers Squibb 777 Scudders Mill Road, Plainsboro, NJ 08536, USA
Brand name holder	Bristol-Myers Squibb Company PO Box 4000 Princeton, NJ 08543-4000, USA Tel.: +1-800-332-2056 E-Mai: medwiss.info@bms.com
Labeling & Distribution	KLIFO A/S Clinical Trial Supporz Smedeland 36 2600 Glostrup, Denmark Business registration no. 18 19 61 31 Tel.: +45 44 222 900 Fax: +45 39 20 90 45 www.klifo.com
Data Safety Monitoring Committee	Prof. Dr. med. Christian Gisselbrecht (Hematologist), Paris, France Prof. Dr. med. Pier Luigi Zinzani (Hematologist), Bologna, Italy Prof. Dr. rer. nat. Stefan Wagenpfeil (Statistician), Homburg/Saar, Germany

8 INTRODUCTION

Background information, rationale for the study and risk-benefit assessment are described in the CSP (see Appendix 16.1.1 or the latest version of the CSP).

9 STUDY OBJECTIVES AND ENDPOINTS

9.1 Primary objectives

To test whether 1-year PFS can be improved by Nivolumab plus (R)-GemOx followed by Nivolumab as consolidation instead of (R)-GemOx alone in patients with progressed or relapsed aggressive B-NHL not eligible for neither autologous nor allogeneic stem cell transplantation

9.2 Secondary objectives

- To determine whether survival can be increased by adding Nivolumab to standard (R)-GemOx.
- To determine whether outcome can be improved by adding Nivolumab to standard (R)-GemOx.
- To determine toxicity and protocol adherence of standard (R)-GemOx with or without Nivolumab.
- To evaluate quality of life of patients with relapsed or refractory aggressive Non-Hodgkin's Lymphoma treated with (R)-GemOx with or without Nivolumab.
- To determine outcome according biological parameters.

9.3 End points

9.3.1 Primary end point

The primary end point is 1-year progression free survival (PFS) of patients with B cell lymphoma. PFS is defined by the time between the day of randomisation until one of the following events occurs, whichever comes first:

- Disease progression (PD)
- Relapse
- Death due to any cause.

After first relapse or progression more than 90% of PFS-defining events occur early within a period of one year when rituximab was applied in first-line therapy.[1-3] In peripheral T-cell lymphoma a similar situation emerged[4]. Therefore 1-year PFS represents an appropriate endpoint in this trial.

An analysis was performed for the T-cell cohort, which included 78 patients only. The sample size is not powered to detect a significant difference in 1-year PFS. Therefore, progression free survival (PFS) was analysed in an additional manner. PFS of salvage therapy is mostly shorter compared to antecedent in relapsed lymphoma.[5,6] The time to progression ratio, which compares the PFS of two consecutives lines of treatment within the same patient, is becoming used in early phase trials to detect drug benefit.[7-12] If the treatment is inactive, PFS at 2nd line (PFS2) is expected to be shorter than PFS at 1st line (PFS1), whereas a PFS2/PFS1 ratio > 1 might reflect treatment benefit. Therefore, also the absolute PFS times and PFS2/PFS1 ratio of each patient will be calculated. The analysis will be positive if more patients have a PFS2/PFS1 ratio > 1 in the experimental compared to the standard arm, demonstrating promising efficacy to warrant further investigation. However, this will be done in a separate, independent study.

9.3.2 Secondary endpoints for efficacy

Secondary end points for efficacy are CR rate, PR rate, ORR, rate of primary progressions, relapse rate, event-free survival (EFS), and overall survival (OS).Response assessment will be done according The Lugano Classification of 2014.[13]
CR rate: Number of complete remissions divided by the number of patients.
PR rate: Number of partial remissions divided by the number of patients.
ORR: Number of complete and partial remissions divided by the number of patients.
Duration of response: Time from documentation of tumor response to disease progression or relapse.
Progression rate: Number of progressions during therapy or within two months after last cycle of chemotherapy divided by the number of patients.
Relapse rate: Number of relapses divided by the number of patients with complete or partial remission.
Event-free survival: Time between day of randomisation until one of the following events occurs, whichever comes first:

- disease progression (PD)
- start of additional unplanned anti-tumor treatment
- relapse
- death due to any cause.

Patients who have not experienced an event at the time of analysis will be censored at the most recent date of disease assessment.
Overall survival: Time between randomisation and death due to any cause; for patients who are alive this is the time between randomisation and the date when the patient was last known to be alive.

9.3.3 Secondary endpoints for toxicity

Secondary end points for safety are:

- adverse events (AE) (cf. 13.1);
- serious adverse events (SAE) (cf. 13.2);
- rate of treatment-related deaths (defined as the number of deaths during therapy or up to 2 months after the end of therapy divided by the number of patients who started study treatment);
- long-term sequelae and second malignancies

9.3.4 Secondary endpoints for protocol adherence

Secondary endpoints for protocol adherence are:

- number of chemotherapy cycles
- duration of chemotherapy cycles
- cumulative dose and relative dose of gemcitabine and oxaliplatin
- cumulative dose and relative dose of the monoclonal antibody nivolumab
- cumulative dose and relative dose of the monoclonal antibody rituximab.

9.3.5 Secondary endpoint for quality of life

Secondary endpoint for quality of life is evaluation of generic health-related quality of life as assessed by the EQ-5D-5L.

9.3.6 Secondary endpoints for outcome according to biology

Treatment effect of nivolumab regarding survival endpoints will also be evaluated according to biological parameters (PD-1 and PD-L1 expression, gene expression profile, alterations on chromosome 9p24.1).

10 INVESTIGATIONAL PLAN

The study was conducted according to the 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 V07.0-F / Date 10th of July 2023
- Version V08.0-F / Date 14th of August 2024
- SAP Version V1.2 / Date 18th of March 2024

Overall Study Design and Plan-Description

- This was a prospective, phase III, open-label, randomised, multicentre treatment-optimisation study with two parallel histology cohorts (B-cell and T-cell), each preceded by a cohort-specific safety run-in. In the B-cell cohort, patients with aggressive B-cell non-Hodgkin lymphoma in first relapse/progression and not eligible for autologous or allogeneic stem-cell transplantation were randomised 1:1 to (R)-GemOx with or without nivolumab; in the experimental arm, (R)-GemOx (8 cycles q2w) was followed by nivolumab consolidation of 36 weeks, resulting in a duration of treatment of 52 weeks in total.
- In the B-cell cohort the primary objective was to demonstrate an improvement in the 1-year progression-free survival (PFS) rate from 27% to 42% (corresponding to a hazard ratio of 0.66); the confirmatory comparison used a two-sided α of 5% and 80% power.
- Randomisation in the B-cell cohort was stratified by IPI (0–2 vs 3–5) and duration of first response (≤12 vs >12 months). The planned sample size was up to 388 patients in total (B-cell cohort n=310 allowing for ~5% loss to follow-up; T-cell cohort up to n=78).
- The T-cell cohort was analysed separately using the same endpoint definitions but was not powered for a confirmatory primary objective.
- It was pre-planned to perform a safety analysis, when both 10 patients with B-cell lymphoma as well as 5 patients with T-cell lymphoma have been included. In case the intended number of patients both B-cell as well as T-cell lymphoma would have not been recruited, a safety analysis would have been performed after inclusion of either 15 patients with B-cell or 7 patients with T-cell lymphoma at the latest. It was planned to perform the analysis after the last patient received the interim restaging after four cycles of (R)-GemOx and which would include safety data of an evaluation period of at least eight weeks of treatment in all patients, except those, who experience progressive disease before.
- Additionally, a safety analysis after the randomisation of thirty patients with Nivolumab was planned. A detailed description of AEs/SAEs, hematotoxicity, dose of (R)-GEMOX, dose of Nivolumab, duration of therapy and therapy-associated deaths was planned to, be performed for both treatment arms (with and without Nivolumab).
- Furthermore, an interim analysis of efficacy was pre-specified in the protocol. For PFS, the primary endpoint of the study, a formal criterion for early discontinuation was defined

using the alpha spending function (O' Brien-Fleming) to obtain the possibility to stop the trial earlier in case the experimental treatment arm with Nivolumab would be as superior as expected. The interim analysis of efficacy was planned to be performed including the first 180 patients from the B-cell cohort with completed documentation up to at least 1 follow up investigation per patient.

- A summary of the study design is given in Figure 1**.**
- For treatments please refer to Section 10.3
- For detailed description of the planned analyses please refer to chapter 14, Protocol Version V08.0-F / Date 14th of August 2024.

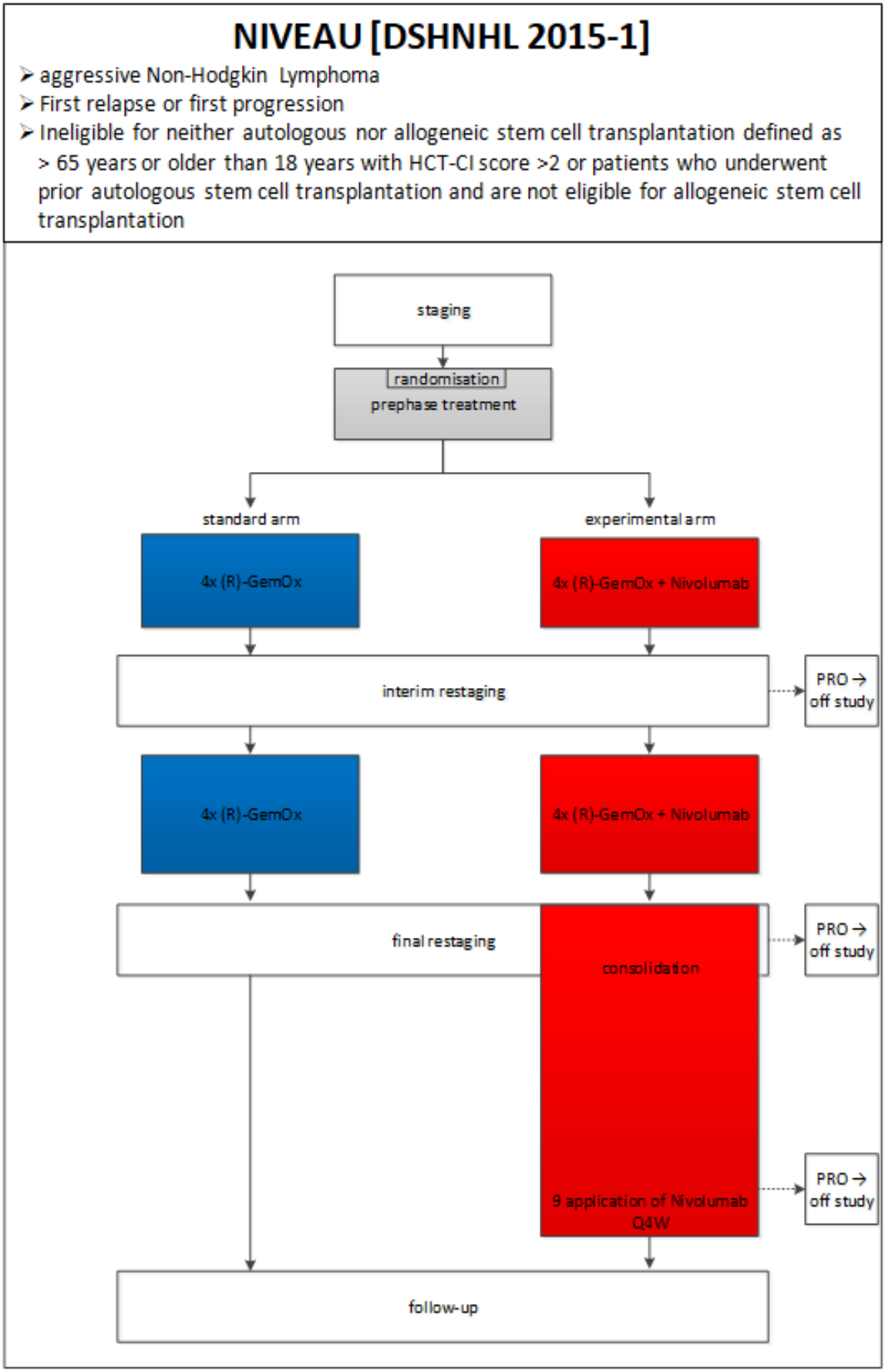


Figure 1: Trial Design

10.1 Discussion of Study Design, including the Choice of Control Groups

This phase III trial was a prospective, multicentre, randomised, open-label treatment optimisation study with two parallel histology cohorts (B-cell and T-cell), each preceded by a cohort-specific safety run-in to confirm the feasibility and safety of combining nivolumab with GemOx in the target population. The control treatment was an active standard-of-care salvage regimen: GemOx; in the B-cell cohort rituximab was added to reflect CD20-directed practice ((R)-GemOx), whereas in the T-cell cohort rituximab was not used. This choice provides a pragmatic comparator aligned with routine care for elderly or transplant-ineligible patients and allows a policy-relevant estimate of treatment effect.
The experimental strategy added nivolumab to (R)-GemOx during induction and continued nivolumab as consolidation, based on the biological rationale for PD-1 blockade in a setting with early event accumulation, aiming to reduce early progression and stabilise responses. An open-label conduct was methodologically appropriate because infusion schedules and supportive-care requirements differ substantially between arms; blinding would have required complex sham procedures with risk of operational bias. Potential assessment bias was mitigated through pre-specified response criteria, fixed assessment schedules, and a primary time-to-event endpoint.
Randomisation in the B-cell cohort was stratified by IPI (0-2 vs 3-5) and duration of first response (≤12 vs >;12 months) to balance prognostic risk and improve precision. The primary endpoint was 1-year PFS, chosen because most PFS-defining events after first relapse/progression occur within one year. The confirmatory test targeted an improvement of the 1-year PFS rate from 27% to 42% (hazard ratio ≈0.66) at a two-sided α of 0.05 and 80% power; an O'Brien-Fleming alpha-spending interim efficacy analysis was pre-specified after the first 180 B-cell patients with adequate follow-up. The T-cell cohort followed the same endpoint definitions and analytic methods, was analysed separately, and was not powered for a confirmatory primary objective. Overall, the design isolates the incremental effect of nivolumab on a widely used GemOx backbone while maintaining external validity for the intended real-world population.

10.2 Selection of Study Population

All patients with first relapse or progression of an aggressive non-Hodgkin lymphoma were eligible if they were ≥65 years of age, or >18 years with a Hematopoietic Cell Transplantation–Comorbidity Index (HCT-CI) >;2, or otherwise deemed ineligible for autologous or allogeneic stem-cell transplantation. Eligibility was irrespective of sex and disease stage; there was no upper age limit.
Enrolment was organised in two histology cohorts (B-cell and T-cell). Central/reference pathology confirmation and measurable disease at baseline were required;

10.2.1 Inclusion criteria

Subjects had to fulfill all of the following criteria to be included in this trial:

1. Age: all patient >65 years of age or > 18 years if not eligible for neither autologous nor allogeneic stem cell transplantation

2. Ineligibility for neither autologous nor allogeneic stem cell transplantation as defined as:

>65 years of age or

older than 18 years if HCT-CI score > 2 (cf. Appendix 24.2) or

patients who underwent prior autologous stem cell transplantation and are not eligible for allogeneic stem cell transplantation

3. Risk group: All risk groups (IPI 0 to 5)

4. Histology: Diagnosis of aggressive Non-Hodgkin's lymphoma, based on an excisional biopsy of a lymph node or on an appropriate sample of a lymph node or of an extranodal involvement at initial diagnosis or relapse or progression. The entities treated in the study were based on the WHO 2017 classification.

B-NHL:

- Follicular lymphoma grade IIIb
- DLBCL, not otherwise specified (NOS)T-cell/histiocyte-rich large B-cell lymphoma
- primary cutaneous DLBCL, leg type
- EBV-positive DLBCL, NOS
- DLBCL associated with chronic inflammation
- primary mediastinal (thymic) large B-cell lymphoma
- intravascular large B-cell lymphoma
- ALK-positive large B-cell lymphoma
- plasmablastic lymphoma
- primary effusion lymphoma
- HHV8+ DLBCL, NOS
- high-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements
- high-grade B-cell lymphoma, NOS
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

T-NHL:

- Aggressive NK cell leukemia
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK-positive
- Anaplastic large cell lymphoma, ALK-negative
- Peripheral T-cell lymphoma with TFH phenotype
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma

5. Performance status: Performance status ECOG 0 – 2. Alsopatients with performance status 0 –2 were eligible when assessed after prephase treatment. The performance status of each patient should have been assessed before the initiation and after the end of prephase treatment which, as experience has shown, can result in a significant improvement of the patient's performance status. The pre-treatment performance status which can range from ECOG 0 to ECOG 4 must have been documented in the Staging CRF; the performance status after the prephase treatment must have been documented in the respective Prephase Treatment CRF. A definition of the performance status is provided in Appendix 24.3 of the clinical trial protocol.

6. Previous therapy: Patients must have had only one prior chemotherapy regimen including an anthracycline. The last cytotoxic drug must be given at least four weeks prior randomization. Rituximab must have been part of the first-line regimen in case of B-cell lymphoma (except for primary CD20- negative lymphoma). Patients may have received prior radiation therapy as part of their first-line therapy.

7. Men who were sexually active with women of childbearing potential (WOCBP) must have used any contraceptive method with a failure rate of less than 1% per year.

Men who were sexually active with women of childbearing potential (WOCBP) must not have fathered a child during and up to 6 months after GemOx and up to 12 months after Rituximab and/or Nivolumab. They were advised to do cryoconservation of sperm prior to treatment.

Women who were not of childbearing potential ie, who were postmenopausal or surgically sterile as well as azoospermic men did not require contraception. A WOCBP was defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause was defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have had a documented serum follicle stimulating hormone (FSH) level higher than 40 mIU/mL.

8. Written informed consent of the patient

9. Contract of participation signed by the study centre and sponsor

10.2.2 Exclusion criteria

Subjects were excluded from the study if they displayed any of the following criteria:

1. Already initiated lymphoma therapy (except for the prephase treatment cf. 8.6.1 of the clinical trial protocol)
2. Serious accompanying disorder or impaired organ function (except when due to lymphoma involvement), in particular:

heart: angina pectoris CCS >2, cardiac failure e.g. NYHA >2
liver: total bilirubin >1.5 times the upper reference limit (except subjects with Gilbert Syndrome, who can have had total bilirubin <51 µmol/l), aspartate transaminase (AST) or alanine transaminase (ALT) >3 x institutional upper reference limit
kidney: creatinine clearance < 30 ml/min

3. WBC < 2.5 G/l, Neutrophils <2 G/l, Platelets <100G/l (did not apply if cytopenia was caused by lymphoma)

4. Prolongation of QTc interval > 450 ms, demonstrated in one electrocardiogram (done as triplicate). This did not apply for patients with a block of the right and/or left bundle branch.
5. Family history for Long QT-syndrome
6. Patients with an active, known or suspected autoimmune disease. Subjects were permitted to enroll if they had vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger
7. There must also have been no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration (except for treatment of lymphoma).
8. Chronic active hepatitis B or C as defined either HBs Ag positive or HBc Ac positive with detectable viral DNA or hepatitis C virus ribonucleic acid positive.
9. HIV-infection
10. Patients with a severe immunodeficiency
11. Previous therapy with Nivolumab, Gemcitabine or Oxaliplatin.
12. Patients with a “currently active” second malignancy other than non-melanoma skin cancer. Patients were not considered to have a “currently active” malignancy if they had completed therapy since 6 months and were considered by their physician to be less than 30% risk of relapse within one year.
13. CNS involvement of lymphoma (intracerebral, meningeal, intraspinal intradural) or primary CNS lymphoma
14. Persistent neuropathy grade >2 (NCI CTC-AE v4.03) (unless due to lymphoma involvement)
15. Pregnancy or breast-feeding women
16. Women of childbearing potential (WOCBP). A WOCBP was defined as any female who had experienced menarche and who had not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who was not postmenopausal. Menopause was defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have had a documented serum follicle stimulating hormone (FSH) level higher than 40 mIU/mL.
17. Active serious infections not controlled by oral and/or intravenous antibiotics or antifungal medication
18. Any medical condition which in the opinion of the investigator placed the subject at an unacceptably high risk for toxicities
19. Lymphomas other than those listed in the inclusion criteria notably indolent lymphoma, Mantle cell lymphoma, Burkitt lymphoma, adult T-cell leukemia/lymphoma.

20. Persons not able to understand the impact, nature, risks and consequences of the trial (including language barrier)
21. Persons not agreeing to the transmission of their pseudonymous data
22. Persons depending on sponsor or investigator
23. Persons from highly protected groups
24. Allergies and Adverse Drug Reaction History to study drug components
25. Participation in another clinical trial with drug intervention within 4 weeks prior to start of the first cycle and during the study. However, participation in a clinical trial of firstline therapy of lymphoma was allowed.

10.2.3 Removal of Patients from Therapy or Assessment

The eligibility criteria were chosen to ensure enrolment of elderly or transplant-ineligible patients with aggressive non-Hodgkin lymphoma in first relapse or progression, which was the indication investigated in this trial. Trial subjects had to be mentally capable of providing informed consent and clinically fit to receive study treatment; impairment of fitness attributable to lymphoma itself was not, per se, an exclusion criterion, provided overall eligibility was met. The intention was not to create an artificial study population but to mirror the real-life population of elderly patients with relapsed or progressed lymphoma. Thus, the inclusion and exclusion criteria enabled investigators to enrol each patient qualifying for this indication.
Reasons for early termination of trial participation for individual patients included:

- Decision of the treating physician
- Patient decision (including withdrawal of informed consent)
- Contact broken off by the patient (loss to follow-up)
- Disease progression
- Unacceptable toxicity meeting protocol-defined discontinuation criteria
- Pregnancy
- Initiation of non-protocol anti-tumour therapy
- Death

If a patient did not meet the inclusion and exclusion criteria, the patient was not to be included in the study. In general, violation of eligibility criteria was not a reason per se for early withdrawal. If, after randomisation, it became apparent that the patient had not been eligible at the time of randomisation, this had to be reported to the Central Study Office and, as applicable, to the responsible investigator. The sponsor or delegate discussed with the investigator whether further treatment within the study was justified or whether another treatment was indicated. Documentation of the patient's clinical data continued. The patient remained in the intention-to-treat analysis and recruitment was not affected (i.e., no replacement).
The reason for early termination of therapy had to be documented in the source data and on the respective eCRF. Patients with early termination of therapy were to be further documented (remission status; survival with and without lymphoma). A restaging at the time of early discontinuation was to be performed. In case of withdrawal of informed consent, the patient was informed that consent cannot be withdrawn for mandatory safety reporting (SAEs).

10.3 **Treatments**

10.3.1 Treatments administered

Prephase treatment represented a standard procedure and was NOT regarded to be a study specific procedure. However, prephase treatment was highly recommended, because it prevents tumor lysis syndrome in patients with extensive tumors, improves the performance status and to reduces the toxicity of the first chemotherapy cycle. In previous DSHNHL trials treatment related mortality after the first cycle was reduced significantly after introduction of prephase treatment.
Adequate hydration of patients should have been ensured and patients should have been given allopurinol prior to the start of prephase treatment in order to avoid tumor lysis syndrome.

Prephase treatment
All patients received a prephase treatment in the form of an approximately 7-day course of prednisone or prednisolone.

Prednisone or prednisolone	100 mg/d	p.o.	day* -6 to day 0

- *day 1 =day 1 of first (R)-GemOx cycle.

Prephase treatment was mandatory, but could be shortened in patients with low tumour load and excellent performance status or when progression of lymphoma was clinically evident under prephase treatment.

Administration of Nivolumab
Nivolumab was administered intravenously over approximately 60 minutes during induction together with (R)-GemOx and subsequently as consolidation therapy. At the beginning of the study, nivolumab dosing was body weight–adapted; later, a fixed dose regimen was implemented. During induction, nivolumab was administered at a fixed dose of 240 mg every 2 weeks (±2 days). In cycle 1, the timing depended on histology: in B-cell lymphomas, nivolumab was given on day −4 to −1, strictly before the first rituximab infusion; in CD20-negative T-cell lymphomas, nivolumab was administered on day 0. The second dose was given on day 15, followed by q2w dosing thereafter.
Consolidation began after completion of cycle 8. At the beginning of the study, consolidation nivolumab was administered every 2 weeks (q2w); later in the study, the consolidation schedule was changed to 480 mg every 4 weeks (q4w). Under the q4w schedule, the first consolidation dose (ninth overall administration) was given 2 weeks after the start of cycle 8. In total, up to 17 nivolumab administrations were planned over approximately one year or until disease progression, whichever occurred first. Continuation beyond progression was permitted only in rare, well-justified cases and only after prior discussion with the sponsor's representative. Premedication was not recommended in cycle 1; patients were carefully monitored for infusion-related reactions.
Minimum intervals between nivolumab doses were ≥12 days during induction and ≥21 days during consolidation. If nivolumab had already been given for a new chemotherapy cycle and chemotherapy was subsequently postponed, the next nivolumab dose was to be shifted to align with the subsequent chemotherapy cycle.
Before each dose, laboratory assessments were performed to detect immune-related adverse events: complete blood count, CRP, LDH, creatinine, ALT/AST, alkaline phosphatase and/or γ-GT, total bilirubin, and amylase and/or lipase. TSH (with reflex to free T3/free T4 if abnormal) was assessed at staging, interim restaging, final restaging, and approximately every 8 weeks during consolidation.
Dose reductions or escalations were not permitted. Doses could be delayed, interrupted, or permanently discontinued as needed. Reasons for delay included, inter alia, febrile neutropenia or neutrophils <0.5 G/L for >1 week despite G-CSF, any non-cutaneous grade 2 drug-related adverse event (with exceptions), selected grade 3 laboratory abnormalities, grade 3 skin reactions, or other medically relevant events at the investigator's discretion. In case of delay, weekly re-evaluation was performed. Treatment could be resumed once adverse events

had resolved to grade ≤1 or baseline (with protocol-defined exceptions, e.g., stable endocrinopathies on replacement therapy). Interruptions >6 weeks generally required permanent discontinuation unless otherwise specified in the protocol.

Administration of Rituximab
Rituximab was given intravenously at a dose of 375 mg/m^2 i.v. but only for patients with B-cell lymphoma. In the first cycle rituximab must have been given after the application of nivolumab in patients randomized to the experimental arm. The rituximab dose should not have been capped for patients with a BSA>2m^2**.**
Overall 8 administrations rituximab have been given concomitant to GemOx chemotherapy.
The rituximab schedule allowed for a deviation of ± 5 days after the first cycle of R-GemOx. Due to the sustained rituximab serum levels, such variations should not have affected efficacy or tolerability, and the preferred exact day of administration could be determined for reasons of feasibility, logistics and patient's convenience.
In the rare instances in which rituximab may have already been administered for the new cycle, but postponement of chemotherapy became necessary for unforeseen reasons, the next dose of rituximab should have been postponed accordingly, i.e. be given only within the temporal context of the following chemotherapy cycle.

G-CSF
In order to ensure that the next chemotherapy cycle could be initiated and to reduce the time of neutropenia which is associated with an increased risk of severe infections, patients should have received growth factor support. We strongly recommended peg-filgrastim on day 4, because peg-filgrastim given on day 4 was significantly better with respect to ameliorating the leukocyte nadir and shortening the time of leukocytopenia compared to peg-filgrastim day 2 or filgrastim and lenograstim.

Chemotherapy
- GemOx-regimen:

Gemcitabine	1000 mg/m^2	IV	day 1
Oxaliplatin	100 mg/m^2	IV	day 1

Recycle: GemOx on day 15,

No dose capping for patients with a BSA>2m^2.

10.3.2 Identity of Investigational Product(s)

OPDIVO™: Nivolumab
Bristol-Myers Squibb provided Nivolumab as an investigational agent. Nivolumab is not yet licensed by the EMA for the treatment of lymphomas, but OPDIVO® (nivolumab) is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

Drug Substance
Nivolumab is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains.

Table 2: Description of drug substance

Description:	Nivolumab is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2

	identical light chains. It is a programmed death receptor-1 (PD-1) blocking antibody that is expressed in a recombinant Chinese Hamster Ovary (CHO) cell line.
Chemical Name:	human immunoglobulin G4 (IgG4) monoclonal antibody
Generic Name:	Nivolumab
Molecular Formula:	$C_{6362}H_{9862}N_{1712}O_{1995}S_{42}$
Molecular Weight	146 kDa

All drugs used in this study are commercially available and approved for the treatment of aggressive non-Hodgkin lymphoma. Labelling and packaging of the IMP were performed in accordance with §42 AMG and §5 GCP-V. Nivolumab was ordered by the study sites via the central study office in Homburg and shipped to the respective hospital pharmacies by the distributor KLIFO A/S, Lautrupbjerg 4, 2750 Ballerup, Denmark.

10.3.3 Method of Assigning Patients to Treatment Groups

All patients who, after completion of staging, met all inclusion criteria and none of the exclusion criteria were centrally randomised. Randomisation was implemented in a database-supported electronic system using a minimisation procedure to ensure balance between treatment arms and across prespecified strata; the algorithm also accounted for potential imbalances introduced by the preceding safety run-in phases.

Separate randomisation lists were maintained for the B-cell and T-cell cohorts. Allocation was 1:1:

- B-cell cohort: (R)-GemOx vs (R)-GemOx + Nivolumab
- T-cell cohort: GemOx vs GemOx + Nivolumab

Stratification:

- B-cell cohort: International Prognostic Index (IPI 0-2 vs 3-5) and duration of first response (≤12 vs >12 months)
- T-cell cohort: identical strata (IPI 0-2 vs 3-5; duration of first response ≤12 vs >12 months)

Patients found post-randomisation to be ineligible at baseline remained in the intention-to-treat population; data collection continued and no replacement of patients occurred.

10.3.4 Selection of Doses in the Study

Dose levels and schedules were predefined by the protocol and not individually titrated. Until protocol version V05.0-F, Nivolumab was dosed at 3 mg/kg IV every 2 weeks. From V06.0-F onward, flat dosing was adopted to maintain exposure while simplifying administration: 240 mg IV q2w during induction and 480 mg IV q4w during consolidation. GemOx doses were fixed (gemcitabine 1000 mg/m² and oxaliplatin 100 mg/m² on day 1, q14d). In the B-cell cohort, rituximab 375 mg/m² was administered per schedule. Nivolumab dose reductions were not permitted (see protocol Version V08.0-F / Date 14th of August 2024 for delay/interruption criteria).

10.3.5 Selection and timing of dose for each patient

Minimum inter-dose intervals were ≥12 days (induction) and ≥21 days (consolidation). If chemotherapy for a new cycle was postponed after a Nivolumab dose had already been administered, the next Nivolumab dose was shifted to align with the subsequent chemotherapy cycle. Chemotherapy was scheduled q14d (GemOx: gemcitabine 1000 mg/m² day 1; oxaliplatin 100 mg/m² day 1). In the B-cell cohort, rituximab 375 mg/m² was administered on day 0 in cycle 1 and on day 1 in cycles 2–8. Start of each subsequent cycle required protocol-specified recovery; if day-15 criteria were unmet, the cycle was delayed and dose reductions applied to gemcitabine/oxaliplatin for delays of 8–14 days (75%) or >14 days (50%). Nivolumab dose reductions/escalations were not permitted; only delays, interruptions, or discontinuation per protocol.

The following figures give a detailed overview of the different therapy schemes for the patient cohorts:

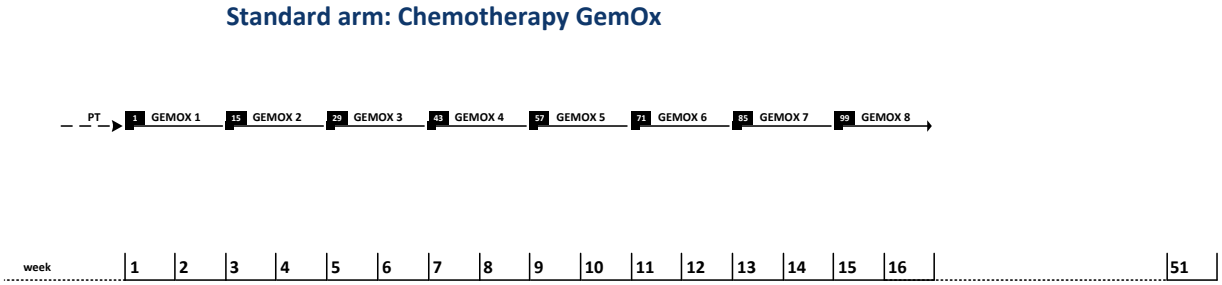


Figure 2: Overview therapy –Standard arm: GemOx chemotherapy for T-cell lymphoma

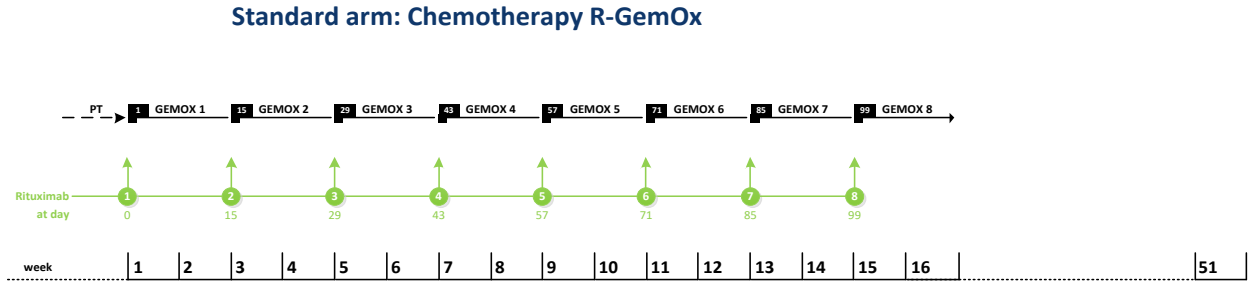


Figure 3: Overview therapy – Standard arm: R-GemOx chemotherapy for B-cell lymphoma

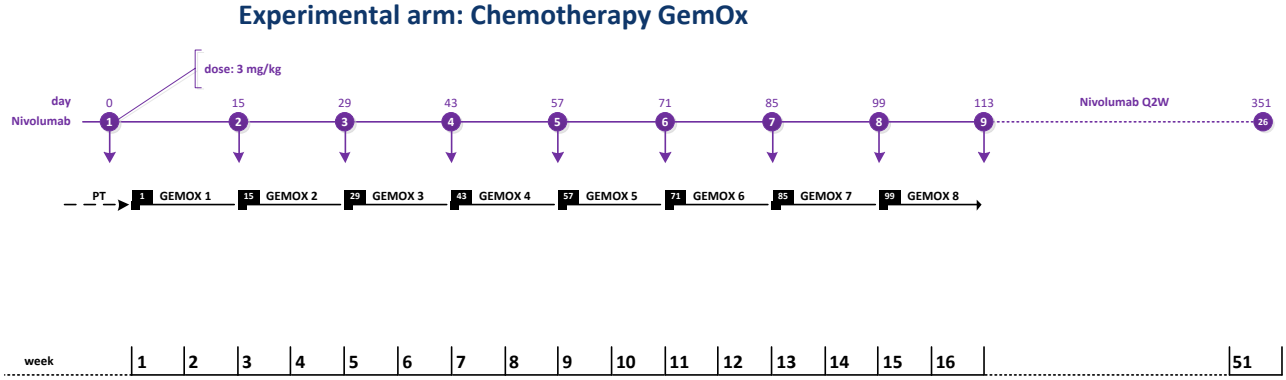


Figure 4: Overview therapy – Experimental arm: GemOx chemotherapy for T-cell lymphoma before protocol Version V06.0-F

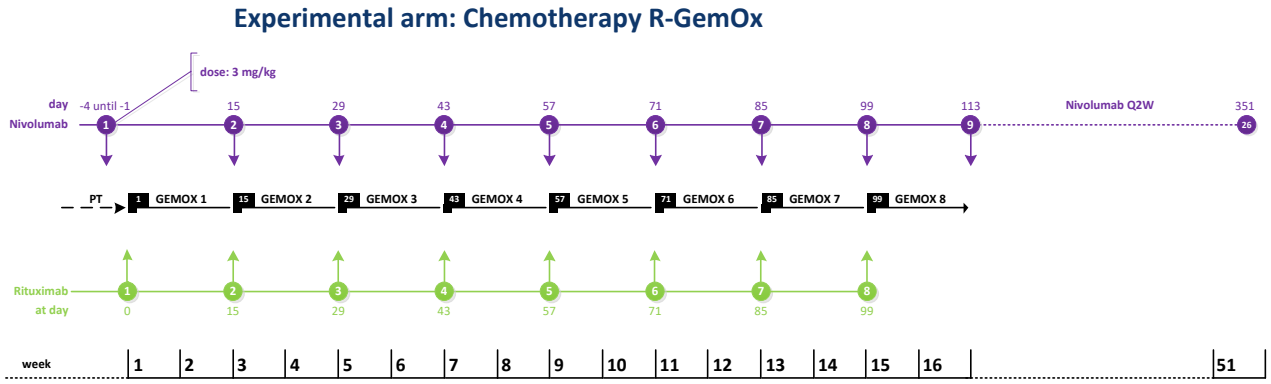


Figure 5: Overview therapy – Experimental arm: R-GemOx chemotherapy for B-cell lymphoma before protocol Version V06.0-F

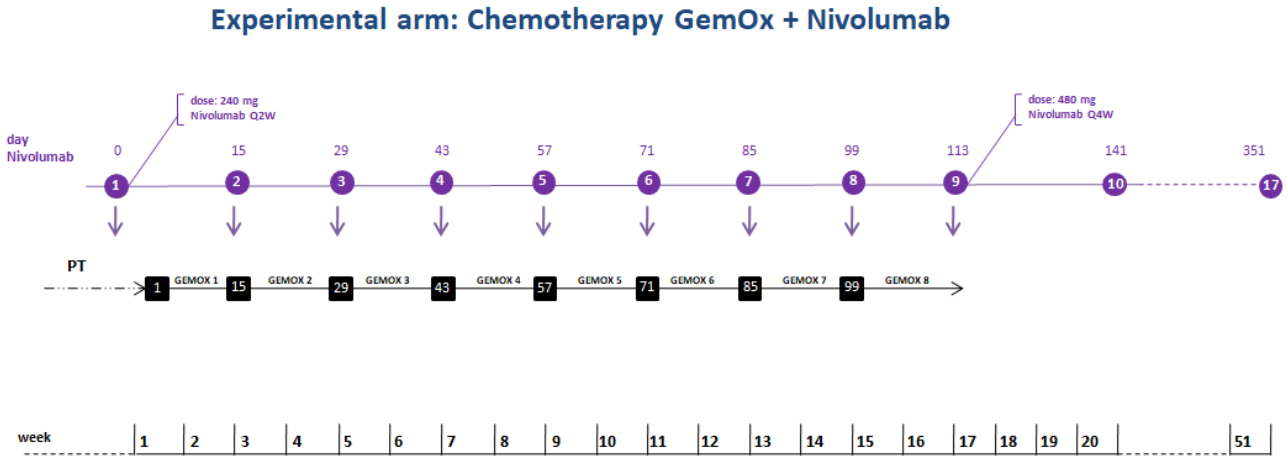


Figure 6: Overview therapy – Experimental arm: (R)-GemOx chemotherapy for T-cell lymphoma since protocol Version V06.0-F

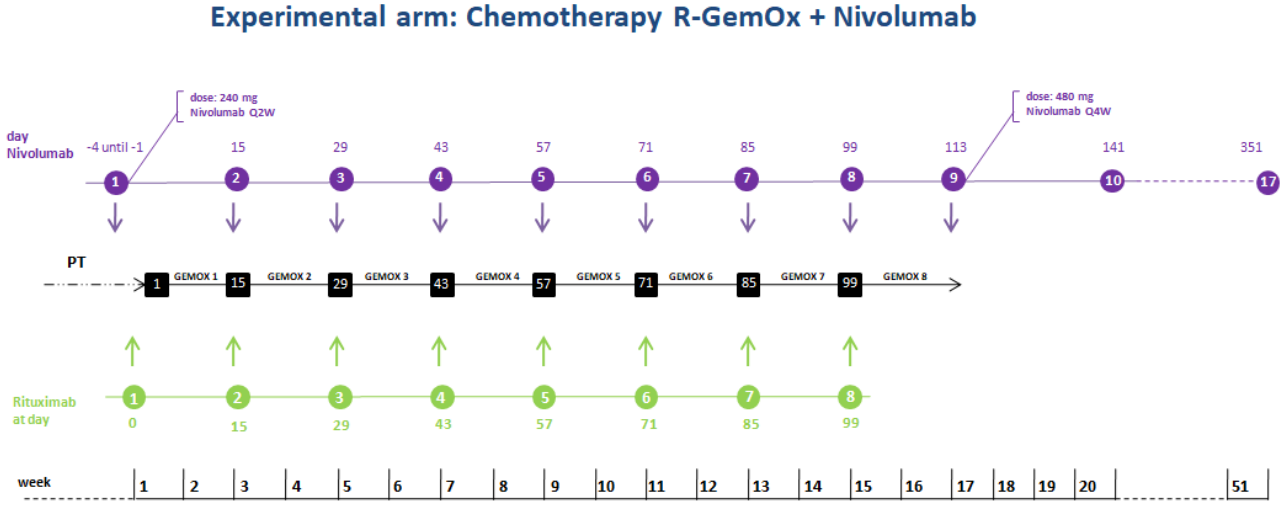


Figure 7: Overview therapy – Experimental arm: R-GemOx chemotherapy for B-cell lymphoma since protocol Version V06.0-F

10.3.6 Blinding

Not applicable, open-label study.

10.3.7 Prior and concomitant therapy

No systemic lymphoma therapy initiated after first relapse/progression was permitted, except for the protocol-recommended prephase. Eligibility required exactly one prior line of chemotherapy including an anthracycline; the last cytotoxic agent had to be given ≥4 weeks before randomisation. For B-cell lymphoma, rituximab had to be part of first-line therapy unless the tumour was primarily CD20-negative. Prior radiotherapy given as part of first-line treatment was allowed. Concomitant/supportive medication was permitted as per protocol and local standards. The protocol recommended prophylaxis and supportive care including: cotrimoxazole (PJP), aciclovir (HSV/VZV), antibacterial prophylaxis (e.g. ciprofloxacin) according to neutropenia risk, antifungal prophylaxis (e.g. oral amphotericin B), antiemetics at the investigator's discretion, uric-acid–lowering prophylaxis with allopurinol, meticulous oral hygiene with chlorhexidine and amphotericin B mouth rinses (particularly in patients with dentures), and hydrocortisone substitution after tapering prephase prednisone in patients with clinically relevant fatigue/adrenal insufficiency until the next cycle. For patients with resolved HBV infection (anti-HBc positive), pre-emptive entecavir 0.5 mg once daily for at least two years after the end of rituximab and monthly monitoring of ALT/AST and HBV-DNA for at least two years after the last rituximab dose were recommended. Growth-factor support (e.g. G-CSF) and other supportive measures were allowed per protocol; additional antitumour agents outside the study were not permitted.
For detailed information, please refer to chapter 8.8 of the CSP version 08.0-F, dated 14th of August 2024.

10.3.8 Treatment Compliance

Nivolumab was supplied by Bristol-Myers Squibb, packaged and labelled in accordance with ICH-GCP and applicable national regulations, and shipped to the Clinical Trial Unit (KLIFO), which coordinated distribution to the participating trial sites. Receipt, storage, dispensing, returns/destruction and accountability were documented by authorised personnel. IMP reconciliation was performed during monitoring and at study close-out.
Rituximab (B-cell cohort only), gemcitabine, oxaliplatin and prednisone/prednisolone were commercial products prescribed, prepared and administered per local standards; lot numbers were traceable in pharmacy records.
Treatment compliance was assessed based on eCRF data, including administered dose, date and time of administration, delays, interruptions or discontinuation with reason, and missed doses.
For nivolumab, the reference windows were as follows: during induction, nivolumab was initially administered every 2 weeks (q2w ±2 days) with a minimum inter-dose interval of ≥12 days. In a later phase of the study, nivolumab was administered during consolidation every 4 weeks (q4w) with a minimum inter-dose interval of ≥21 days. Dose reductions of nivolumab were not permitted; treatment delays, interruptions, or discontinuation followed prespecified protocol criteria. In general, interruptions exceeding 6 weeks required permanent discontinuation.
For GemOx chemotherapy (± rituximab), cycle start dates, postponements, and protocol-defined dose adjustments were documented. In case of treatment delays of 8–14 days, gemcitabine and oxaliplatin doses were reduced to 75%; delays exceeding 14 days required dose reduction to 50%.

10.4 **Efficacy and Safety Variables**

10.4.1 Efficacy and Safety Measurements Assessed and Flowchart

Specific time points for evaluation of efficacy variables and safety measures are given in the study flowcharts (Table *3*).
All parameters evaluated in this study as well as the methods to measure them, were standard variables / methods in clinical practice. They are widely used and generally recognized as reliable, accurate and relevant.

Table 3: Visit schedule and study-related measures
Standard arm: Schedule of assessments and recommended procedures

	screening prior to any therapy	pre-phase therapy	(R)-GemOx chemotherapy									final re-staging	follow-up
							interim re-staging						
			cycle 1	cycle 2	cycle 3	cycle 4	approx. 14 days after start of cycle 4	cycle 5	cycle 6	cycle 7	cycle 8	approx. 6-8 weeks after last CTX or ASAP if relapse/progression	1, 2,3,4,5, 6, 9, 12, 15,18,21, 24, 30, 36, 42,48, 54, 60 months[1] after final restaging
Prephase therapy		X											
GemOx			**d1**	**d15**	**d29**	**d43**		**d57**	**d71**	**d85**	**d99**		
Rituximab [2]			d0	d15	d29	d43		d57	d71	d85	d99		
Patient's history	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical examination	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Performance status	X[4a]	X[4b]	X[4c]	X[4c]	X[4c]	X[4c]	X	X[4c]	X[4c]	X[4c]	X[4c]	X	X
electrocardiogram	X[5a, 5b]		X[5b]	X[5b]	X[5b]	X[5b]		X[5b]	X[5b]	X[5b]	X[5b]		
CTC evaluation of side effects		X	X	X	X	X		X	X	X	X		X
Laboratory analysis	X[6a]		X[6b]	X[6b]	X[6b]	X[6b]	X[6c]	X[6b]	X[6b]	X[6b]	X[6b]	X[6c]	X[6c]
Thyreoid function test	X[7]						X[7]					X[7]	X[7]
Pregnancy test	X[8]												
CT neck/thorax/abdomen[9]	X						X					X[10]	X[11]
FDG-PET	X[12]											X[10,13]	
Bone marrow biopsy	X											X[14]	
5Q-5D-5L questionnaire	X												X[15]
Response assessment [16]	X						X					X	
Imaging exams uploading	X											X	

1 = or possibly longer
2 = only in patients with B-cell lymphoma
3 = including vital signs (blood pressure, heart rate, temperature)
4a= before prephase therapy 4b = at the end of prephase treatment 4c = minimum value during chemotherapy;
5a = to be taken in triplicate
5b= including QTc calculated by the formula of Fridericia
6a= haematogram with differential blood cell count; potassium, calcium, magnesium, LDH; ALT and/or AST; alkaline phosphatase and/or γ-GT; bilirubin; creatinine; amylase; lipase; TSH (reflex to free T3 and free T4 if abnormal TSH result); HIV-, HBV- and HCV serology;
6b = haematogram; potassium, calcium, CRP; LDH; creatinine; ALT and/or AST; alkaline phosphatase and/or γ-GT; total bilirubin, amylase, lipase. magnesium (only when QTc > 450 ms),

6c = haematogram; CRP; LDH; creatinine; ALT and/or AST; alkaline phosphatase and/or γ-GT; total bilirubin, amylase, lipase.
7 = TSH (reflex to free T3 and free T4 if abnormal TSH result)
8 = in women under 62 years of age (cf.**8.7.**).
9 = neck/thorax/abdomen: MRI also accepted, neck: ultrasound also accepted
10= final restaging is highly recommended to be performed as FDG-PET/(full-dose) CT procedure with FDG-PET and diagnostic CT acquisition as a single procedure.
11= highly recommended to perform CT scans at the third and sixth follow-up examination
12= FDG-PET highly recommended. The procedure is highly recommended to be performed as FDG-PET/[full-dose] CT procedure with FDG-PET and diagnostic CT acquisition as a single procedure
13= FDG-PET mandatory
14= if initially involved, not done or unspecified;
15 =only 3, 6, 9 and 12 months after final restaging, respectively.
16 = According to Lugano Classification. At interim staging, CT based response is evaluated.

Table 4: Visit schedule and study-related measures

Experimental arm: Schedule of assessments and recommended procedures (until protocol version 5.0)

	screening prior to any therapy	pre-phase therapy	(R)-GemOx chemotherapy									final re-staging	consolidation	follow-up
							interim re-staging							
			cycle 1	cycle 2	cycle 3	cycle 4	approx. 14 days after start of cycle 4	cycle 5	cycle 6	cycle 7	cycle 8	approx. 6-8 weeks after last CTX or ASAP if relapse/progression	cycle 9 - 26	1, 2, 3, 4, 5, 6, 9, 12, 15,18,21, 24, 30, 36, 42,48, 54, 60 months[1] after final restaging.
Prephase therapy		X												
GemOx			**d1**	**d15**	**d29**	**d43**		**d57**	**d71**	**d85**	**d99**			
Nivolumab		d-4[17]	d0[18]	d15	d29	d43		d57	d71	d85	d99		every 2 wks	
Rituximab [2]			d0	d15	d29	d43		d57	d71	d85	d99			
Patient's history	X	X	X	X	X	X	X	X	X	X	X	X	every 2 wks	X
Clinical examination	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	every 2 wks[3]	X[3]
Performance status	X[4a]	X[4b]	X[4c]	X[4c]	X[4c]	X[4c]	X	X[4c]	X[4c]	X[4c]	X[4c]	X	every 2 wks	X
elctrocardiogram	X[5a, 5b]		X[5b]	X[5b]	X[5b]	X[5b]		X[5b]	X[5b]	X[5b]	X[5b]			
CTC evaluation of side effects		X	X	X	X	X		X	X	X	X		every 2 wks	X
Laboratory analysis	X[6a]		X[6b]	X[6b]	X[6b]	X[6b]	X[6c]	X[6b]	X[6b]	X[6b]	X[6b]	X[6b]	every 2 wks[6c]	X[6c]
Thyreoid function test	X[7]						X[7]					X[7]	every 6 wks[7]	X[7]
Pregnancy test	X[8]													
CT neck/thorax/abdomen[9]	X						X					X[10]		X[11]
FDG-PET	X[12]											X[10,13]		
Bone marrow biopsy	X											X[14]		
5Q-5D-5L questionnaire	X													X[15]
Response assessment [16]							X					X		
Imaging exams uploading	X											X		

1 = or possibly longer
2 = only in patients with B-cell lymphoma
3 = including vital signs (blood pressure, heart rate, temperature)
4a= before prephase therapy 4b = at the end of prephase treatment 4c = minimum value during chemotherapy;
5a = to be taken in triplicate
5b= including QTc calculated by the formula of Fridericia

6a= haematogram with differential blood cell count; potassium, calcium, magnesium, LDH; ALT and/or AST; alkaline phosphatase and/or γ-GT; bilirubin; creatinine; amylase; lipase; TSH (reflex to free T3 and free T4 if abnormal TSH result); HIV-, HBV- and HCV serology;
6b = haematogram; potassium, calcium, CRP; LDH; creatinine; ALT and/or AST; alkaline phosphatase and/or γ-GT; total bilirubin, amylase, lipase. magnesium (only when QTc > 450 ms),
6c = haematogram; CRP; LDH; creatinine; ALT and/or AST; alkaline phosphatase and/or γ-GT; total bilirubin, amylase, lipase.
7 = TSH (reflex to free T3 and free T4 if abnormal TSH result)
8 = in women under 62 years of age (cf.**8.7**).
9 = neck/thorax/abdomen: MRI also accepted, neck: ultrasound also accepted
10= final restaging is highly recommended to be performed as FDG-PET/(full-dose) CT procedure with FDG-PET and diagnostic CT acquisition as a single procedure.
11= highly recommended to perform CT scans at the third and sixth follow-up examination
12= FDG-PET highly recommended. The procedure is highly recommended to be performed as FDG-PET/[full-dose] CT procedure with FDG-PET and diagnostic CT acquisition as a single procedure
13= FDG-PET mandatory
14= if initially involved, not done or unspecified;
15 = only 3, 6, 9 and 12 months after final restaging, respectively.
16 = According to Lugano Classification. At interim staging, CT based response is evaluated.
17 = can be given within day-4 and day-1 in B-cell lymphoma
18 = only in CD20-negative lymphoma

Table 5: Visit schedule and study-related measures
Experimental arm: Schedule of assessments and recommended procedures (from protocol version 5.0)

	screening prior to any therapy	pre-phase therapy	(R)-GemOx chemotherapy									final re-staging	consolidation	follow-up
							interim re-staging							
			cycle 1	cycle 2	cycle 3	cycle 4	approx. 14 days after start of cycle 4	cycle 5	cycle 6	cycle 7	cycle 8	approx. 6-8 weeks after last CTX or ASAP if relapse/progression	cycle 9 - 17	1, 2, 3, 4, 5, 6, 9, 12, 15,18,21, 24, 30, 36, 42,48, 54, 60 months[1] after final restaging.
Prephase therapy		X												
GemOx			**d1**	**d15**	**d29**	**d43**		**d57**	**d71**	**d85**	**d99**			
Nivolumab		d-4[17]	d0[18]	d15	d29	d43		d57	d71	d85	d99		every 4 wks[19]	
Rituximab [2]			d0	d15	d29	d43		d57	d71	d85	d99			
Patient's history	X	X	X	X	X	X	X	X	X	X	X	X	every 4 wks	X
Clinical examination	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	every 4 wks[3]	X[3]
Performance status	X[4a]	X[4b]	X[4c]	X[4c]	X[4c]	X[4c]	X	X[4c]	X[4c]	X[4c]	X[4c]	X	every 4 wks	X
elctrocardiogram	X[5a, 5b]		X[5b]	X[5b]	X[5b]	X[5b]		X[5b]	X[5b]	X[5b]	X[5b]			
CTC evaluation of side effects		X	X	X	X	X		X	X	X	X		every 4 wks	X
Laboratory analysis	X[6a]		X[6b]	X[6b]	X[6b]	X[6b]	X[6c]	X[6b]	X[6b]	X[6b]	X[6b]	X[6b]	every 4 wks[6c]	X[6c]
Thyreoid function test	X[7]						X[7]					X[7]	every 8wks[7]	X[7]
Pregnancy test	X[8]													
CT neck/thorax/abdomen[9]	X						X					X[10]		X[11]
FDG-PET	X[12]											X[10,13]		
Bone marrow biopsy	X											X[14]		
EQ-5D-5L questionnaire	X													X[15]
Response assessment [16]							X					X		
Imaging exams uploading	X											X		

1 = or possibly longer
2 = only in patients with B-cell lymphoma

3 = including vital signs (blood pressure, heart rate, temperature)
4a= before prephase therapy 4b = at the end of prephase treatment 4c = minimum value during chemotherapy;
5a = to be taken in triplicate
5b= including QTc calculated by the formula of Fridericia
6a= haematogram with differential blood cell count; potassium, calcium, magnesium, LDH; ALT and/or AST; alkaline phosphatase and/or γ-GT; bilirubin; creatinine; amylase and/or lipase; TSH (reflex to free T3 and free T4 if abnormal TSH result); HIV-, HBV- and HCV serology;
6b = haematogram; potassium, calcium, CRP; LDH; creatinine; ALT and/or AST; alkaline phosphatase and/or γ-GT; total bilirubin, amylase and/or lipase, magnesium (only when QTc > 450 ms),
6c = haematogram; CRP; LDH; creatinine; ALT and/or AST; alkaline phosphatase and/or γ-GT; total bilirubin, amylase and/or lipase.
7 = TSH (reflex to free T3 and free T4 if abnormal TSH result)
8 = in women under 62 years of age
9 = neck/thorax/abdomen: MRI also accepted, neck: ultrasound also accepted
10= final restaging is highly recommended to be performed as FDG-PET/(full-dose) CT procedure with FDG-PET and diagnostic CT acquisition as a single procedure.
11= highly recommended to perform CT scans at the third and sixth follow-up examination
12= FDG-PET highly recommended. The procedure is highly recommended to be performed as FDG-PET/[full-dose] CT procedure with FDG-PET and diagnostic CT acquisition as a single procedure
13= FDG-PET mandatory
14= if initially involved, not done or unspecified;
15 = should be assessed , irrespective of response 3, 6, 9 and 12 months after final restaging, or, if applicable, after early termination.
16 = According to Lugano Classification. At interim staging, CT based response is evaluated.
17 =can be given within day-4 and day-1 in B-cell lymphoma
18 =only in CD20-negative lymphoma
19=Please note that the first dose during nivolumab consolidation (i.e. the 9th nivolumab administration) will be given 2 weeks after start of cycle 8 Nivolumab-(R)-GemOx

10.4.2 Appropriateness of measurements

The timepoints of staging, restaging and follow-up were orientated according to clinical routine. Further examinations before each cycle were also part of clinical routine. For these reasons measurements were appropriately addressed in the clinical trial.

10.4.3 Primary Efficacy Variable (s)

PFS was defined by the time between the day of randomisation until one of the following events occurs, whichever comes first:

- Disease progression (PD)
- Relapse after achieving CR
- Progression after PR, stable disease (SD) or unknown
- Death due to any cause.

Patients who have not experienced an event at the time of analysis were censored at the most recent date of disease assessment.

10.4.4 Drug concentration measurements

No drug concentration measurements have been performed.

10.5 **Data Quality Assurance**

Participating trial centres were obliged to document each patient's disease course and treatment completely and accurately. Data capture was performed in the study-specific secuTrial eCRF in accordance with the Data Entry Guidelines. Entry could be delegated to trained site staff; however, the investigator/deputy reviewed and released all eCRF entries. All eCRF data had to be consistent with the corresponding source documents; direct entry of source data into the eCRF did not occur.
At the Central Study Office in Homburg, eCRFs were reviewed on an ongoing basis for completeness, accuracy, and plausibility. In addition, all documentation forms underwent medical review by the study physician at the Central Study Office, with particular attention to protocol deviations, the occurrence of adverse events (AEs), the occurrence of serious adverse events (SAEs, including SAE reports transmitted by fax), and the medical plausibility of the data.
This central review was complemented by on-site monitoring in accordance with the monitoring plan and monitoring manual. Monitors visited sites at regular intervals to assess trial progress, verify adherence to the protocol, discuss issues (including AEs/SAEs), check complete and accurate eCRF maintenance, validate eCRF entries against source documents (source data verification), and review the handling of investigational medicinal products. The scope and procedures of monitoring activities were described in detail in the monitoring manual, which also specified the minimum requirements using dedicated forms. After each visit, the monitor issued a monitoring report documenting trial progress and any findings (e.g., refusal of inspection).
In line with ICH-GCP and applicable data-protection requirements, investigators granted monitors, the sponsor or its designees, and competent authorities direct access to relevant source data/documents, while monitors were bound to maintain medical confidentiality.

10.6 **Statistical Methods Planned in the Protocol and Determination of Sample Size**

10.6.1 Statistical and analytical plans

The analyses followed the final SAP and the biostatistical specifications of the protocol. Primary analyses were performed in the Full Analysis Set (ITT principle); Per-Protocol (PPS) and Safety Analysis Set (SAS) were planned as supportive. Time-to-event endpoints (PFS/EFS/OS) were analysed using Kaplan–Meier methods, log-rank tests, and Cox proportional hazards models; response rates were summarised with 95% confidence intervals according to Clopper–Pearson.

The following statistical software and coding was used:

- IBM SPSS Statistics 29.0 for tabulations and tests.
- KM-Win for graphical support of Kaplan–Meier curves (B-cell final analysis: V1.53; T-cell analysis: V1.5.3) and R 3.4.2 (Sep 2017); for the B-cell final analysis, R 4.4.0 (patched, May 2024) was additionally used for cumulative incidence curves.
- 95% confidence intervals for rates (Clopper–Pearson) calculated with PASS 22.0.8 (B-cell cohort) or PASS 22.0.3 (T-cell cohort).
- AE/SAE coding according to MedDRA 28.0 (B-cell final analysis) or MedDRA 26.1 (T-cell analysis).

Data quality and monitoring
All secuTrial eCRF data were centrally reviewed in Homburg for completeness, accuracy, and plausibility; medical review considered protocol deviations, AEs/SAEs, and the medical plausibility of the data. On-site monitoring was performed in accordance with the monitoring plan/manual with regular onsite visits and source data verification.

An Independent Data Safety Monitoring Committee (DSMC) oversaw safety, efficacy signals, and trial integrity and reviewed in particular:

- data from the safety run-in phases,
- the safety analysis during randomisation,
- the interim efficacy analysis,
- the annual safety reports,
- the final analysis.

DSMC Members were: Prof. Dr. Gisselbrecht (Paris, France), Prof. Dr. Wagenpfeil (Homburg, Germany; until 15 Jun 2021), and Prof. Dr. P. L. Zinzani (Bologna, Italy).

10.6.2 Determination of sample size

The sample size for the NIVEAU trial was pre-specified in the Clinical Study Protocol (for further information please refer to CSP, version 10.0-F, dated 08 Apr 2024) and detailed in the Statistical Analysis Plan (SAP, version 3.0, dated 20 Jun 2024). Separate planning was performed for the B-cell and T-cell cohorts, reflecting their different objectives and statistical frameworks.
The B-cell cohort was the primary confirmatory cohort). In this cohort the primary objective was to demonstrate an improvement in 1-year progression-free survival (PFS) from **27%** in the control arm ((R)-GemOx) to **42%** in the experimental arm ((R)-GemOx + nivolumab), corresponding to a **hazard ratio (HR) of 0.66**.

The following assumptions were used for the power calculation:

- Two-sided alpha: 5%
- Statistical power: 80%
- Primary analysis: Kaplan–Meier comparison (log-rank test)
- Event-driven analysis with 1-year PFS as main endpoint
- One interim analysis using an O'Brien–Fleming α-spending function, performed after the first **180** randomised B-cell patients had reached 1-year follow-up.

Based on these assumptions, **292 patients** (146 per arm) were required. Allowing for approximately 5% loss to follow-up/missing primary endpoint, the target recruitment was increased to **310 B-cell patients**.

For the T-cell cohort, no confirmatory hypothesis testing was planned. The cohort was **not powered for statistical significance**, due to:

- lower incidence of peripheral T-cell lymphomas,
- expected slower recruitment,
- higher biological heterogeneity**.**

The planned sample size was up to **78 patients** to provide **descriptive estimates** of PFS, OS, ORR and safety. Efficacy analyses for the T-cell cohort were therefore **exploratory**, following the SAP.

Sample size calculations were performed according to the methodology outlined in:

- CSP v08.0-F Date 14th of August 2024
- SAP V1.2 / Date 18th of March 2024

Supporting tools included:

- PASS (versions 22.0.x) for rate confidence intervals
- Internal simulations based on historical DSHNHL datasets (first-relapse aggressive B-cell lymphoma)

The sample size determination ensured:

- adequate statistical power for the B-cell cohort,
- feasibility of recruitment,
- and descriptive but clinically meaningful analyses for the T-cell cohort.

The following statistical hypotheses were made regarding the:

- B-cell cohort (primary, confirmatory; endpoint: PFS)
  H0: There is no difference in PFS between (R)-GemOx and (R)-GemOx + nivolumab (HR = 1).
  H1: There is a difference in PFS (two-sided; expected superiority of the experimental arm with target HR ≈ 0.66; corresponding to 1-year PFS 27% vs 42%).
- T-cell cohort (exploratory)
  No confirmatory hypothesis was prespecified; efficacy is analysed descriptively according to the SAP

10.6.3 Changes in the Conduct of the Study or Planned Analyses

During the trial, 7 amendments have been submitted and approved.

The major changes were:

- Dose adaption from protocol version 6: Patients received eight 2-week cycles Nivolumab (240mg) plus (R)-GemOx followed by 9 4-week applications of Nivolumab (480mg) instead of eight 2-week cycles Nivolumab (3mg/kg) plus (R)-GemOx followed by 18 2-week applications of Nivolumab (3mg/kg)
- Recruitment ended prematurely at 31st March 2023 after 270 patients with B-cell lymphoma and 78 patients with T-cell lymphoma were included
  - 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

- As the last patient was included on 30th March 2023, follow-up for all patients within the trial ended on 15th January 2025

10.6.4 Primary Endpoint

The primary endpoint was 1-year progression-free survival (PFS) in the B-cell cohort. PFS was analysed on the Full Analysis Set (ITT principle). Kaplan–Meier methods were used to estimate survival functions, with 1-year PFS rates and 95% confidence intervals reported; medians with 95% CIs were provided when estimable. The primary between-arm comparison ((R)-GemOx vs (R)-GemOx + nivolumab) used a two-sided log-rank test (α=0.05). Hazard ratios with 95% CIs were obtained from Cox models adjusted for the prespecified minimisation/stratification factors (e.g., time to treatment failure ≤12 vs >12 months, IPI 0–2 vs 3–5); additional prognostic covariates (e.g., individual IPI items, age group, sex, bulky disease) were explored in supportive models. Given extended follow-up, additional PFS rates (e.g., 2- and 5-year) were summarised. Sensitivity analyses included the Per-Protocol Set and models reflecting protocol-version dosing (pre-V06.0-F weight-based vs post-V06.0-F flat-dosing) as well as the handling of intercurrent events as specified in the SAP. The T-cell cohort was analysed in parallel using the same methods but descriptively (no confirmatory hypothesis testing).

10.6.5 Secondary Endpoints

Time-to-event endpoints-event-free survival (EFS) and overall survival (OS) were analysed analogously to PFS (KM estimates, log-rank tests for the B-cell cohort, Cox models with 95% CIs; descriptive in the T-cell cohort). Response endpoints included complete response (CR), partial response (PR) and overall response rate (ORR = CR+PR) after eight cycles of (R)-GemOx; binomial 95% CIs were calculated (Clopper–Pearson). Duration of response was analysed by Kaplan–Meier methods. Additional prespecified rates were summarised with 95% CIs: primary progression during therapy or within two months after the last chemotherapy cycle, relapse rate, and rate of treatment-related deaths; long-term sequelae and second malignancies were tabulated. Protocol adherence and treatment compliance were reported as per protocol/SAP. Health-related quality of life (EQ-5D-5L index and VAS) was assessed at protocol-defined timepoints; changes from baseline and between-arm contrasts were summarised descriptively (exploratory models applied where appropriate). Correlative/translational analyses (e.g., outcomes by PD-L1/PD-1 expression, cell of origin, 9p24.1 alterations) were preplanned and evaluated descriptively using logistic regression/Cox models where applicable. Unless otherwise specified in the SAP, secondary endpoint p-values were considered exploratory without formal multiplicity control. Safety (AEs/SAEs) was summarised by MedDRA System Organ Class and Preferred Term, maximum CTCAE grade, seriousness, relatedness, onset timing, and events leading to dose delay, interruption or discontinuation; immune-related AESIs were reported per SAP.

10.6.6 Final Analysis

The final analysis was performed after all patients had completed study treatment and protocol-defined follow-up, all source data had been received, all data queries resolved, and the database was locked. The data cut-off for efficacy and safety was 15 January 2025. The scope and timing of the final analyses were prespecified in the CSP (v08.0-F, 14 Aug 2024) and the SAP (v3.0, 20 Jun 2024).

10.6.7 Subgroup Analysis

The main efficacy analysis was predefined to be performed in the full analysis set (FAS). In addition, as specified in the statistical analysis plan, if a difference of more than 10% between

the FAS and the per-protocol set (PPS) was observed, efficacy endpoints including EFS, PFS, and OS were also analyzed in the PPS as a sensitivity analysis.
Subgroup analyses for EFS, PFS and OS regarding IPI factors, IPI score (0-2 vs. 3-5), reference pathology, sex, age groups, type of treatment failure (primary progression or relapse), duration of first response (time to treatment failure ≤ 12 or > 12 months), PDL-1 and PD-1 expression, cell of origin and 9p24.1 alterations are planned.
In case of small sample size, some of the subgroups will not be presented. Additionally, analyses were performed including the per protocol sets.

10.6.8 Sensitivity Analysis

Sensitivity analyses regarding patients treated per protocol and outcome of patients with COVID-19 have been performed and will be presented subsequently.

10.6.9 Interim Analyses

During the conduct of the study, several pre-specified interim analyses were performed. These included an initial safety run-in phase, a safety analysis after treatment of the first 12 patients in the T-cell cohort receiving nivolumab (previously reported by Houot et al.), and a protocol-defined interim analysis after enrolment of approximately 170 patients in the B-cell cohort.
All interim analyses were conducted at the respective time points as specified in the protocol. The results of these analyses are not reiterated in this report.

11 STUDY PATIENTS

11.1 Disposition of Patients

A total of 366 patients were registered; 18 registered patients were not randomised. Overall, 348 patients were randomised at 76 study sites across eight countries (Germany, Austria, Belgium, France, Israel, Poland, Portugal, The Netherlands). One patient withdrew informed consent before start of study treatment.

Analysis populations

- Full Analysis Set (FAS, ITT principle): B-cell cohort n=270 (R-GemOx n=135; R-GemOx + nivolumab n=135); T-cell cohort n=77 (GemOx n=36; GemOx + nivolumab n=41). One randomised T-cell patient was excluded from FAS due to withdrawal of informed consent.
- Safety Analysis Set (SAS): all patients who received at least one dose of study treatment; identical to FAS except for the patient who withdrew prior to first dose.
- Per-Protocol Set (PPS): defined a priori (major eligibility deviations, absence of post-baseline assessment, relevant protocol violations); PPS summaries are provided in the efficacy section.

Treatment exposure
All randomised B-cell patients started protocol therapy. In the T-cell cohort, one patient withdrew consent before first dose; all others started assigned treatment. Patients could discontinue treatment early for predefined reasons (disease progression, unacceptable toxicity per protocol criteria, withdrawal of consent, death, pregnancy, initiation of non-protocol anti-tumour therapy); all reasons were captured in the eCRF and are summarised in the treatment discontinuation tables.

Country and site participation
The 348 randomised patients were enrolled across 76 centres in eight countries (Germany, Austria, Belgium, France, Israel, Poland, Portugal, The Netherlands). Site-level enrolment and country contributions are listed in Appendix 17.1.5 Investigator List and Enrolment by Site).

Follow-up status at data cut-off

Disposition and analysis sets are reported at the protocol-defined final cut-off (15 January 2025). (Note: theT-cell sub-cohort final analysis was performed per protocol on 23 January 2025; disposition numbers above reflect the same underlying randomised set.)

11.2 Protocol Deviations

Protocol deviations were recorded prospectively in the eCRF, source-verified during monitoring, and centrally classified (major/minor) per CSP/SAP. Patients with eligibility violations remained in the FAS under the ITT principle; pre-specified major deviations were excluded from the PPS. A complete listing is archived in the TMF (CSP v08.0-F Date 14th of August 2024; SAP V1.2 / Date 18th of March 2024).

B-cell cohort (FAS n=267)

- Violation of inclusion/exclusion criteria: 13 patients
- No reference pathology diagnosis as per protocol: 20 patients (including 2 overlapping with the above 13)
- Major deviation “treatment mismatch”: 2 patients (randomised to R-GemOx+nivolumab but treated with R-GemOx)
- No study treatment received (SAS exclusion): 3 cases (death before start; withdrawal of informed consent on day of randomisation; change of treatment due to intercurrent disease)
- Analysis sets: PPS n=234 (R-GemOx 118; R-GemOx+nivolumab 116)

T-cell cohort (FAS n=77; GemOx 36 / GemOx+nivolumab 41)

- Violation of inclusion/exclusion criteria: 4 patients
- No reference pathology diagnosis as per protocol: 12 patients
- No study treatment received: 1 case (withdrawal of informed consent at day 0)
- Analysis sets: PPS n=61 (GemOx 29; GemOx+nivolumab 32)

Impact on analysis

All affected patients were analysed in the FAS. For the PPS, exclusions were applied only for pre-specified major deviations per SAP (e.g., eligibility not met, missing baseline disease assessment, no post-baseline tumour assessment, repeated IMP dosing outside windows, prohibited concomitant anti-tumour therapy, treatment mismatch). Handling was as defined in the CSP/SAP.

The granular per-patient breakdown of eligibility violations (inclusion vs exclusion criteria) is presented in Table 6 (B-cell cohort) and Table 7 (T-cell cohort); complete listings are filed in the TMF.

Table 6: Violation of inclusion/exclusion criteria, FAS, B-cell (n=267)

Violation inclusion/exclusion criteria	R-GemOx (n=7)	R-GemOx + Niv (n=6)	Total (n=13)
Inclusion criteria 4: diagnosis of aggressive Non-Hodgkin's lymphoma	0	1	1
Inclusion criteria 6: only one prior chemotherapy regimen with anthracycline and Rituximab (if B-cell)	1	3	4
Exclusion criteria 1: already initiated lymphoma therapy	1	0	1
Exclusion criteria 2: serious accompanying disorder	1	0	1
Exclusion criteria 3: cytopenia	1	0	1
Exclusion criteria 4 (amend.): prolongation of QTc interval >450 ms	1	0	1
Exclusion criteria 6: autoimmune disease	2	1	3
Exclusion criteria 10 (amend.): severe immunodeficiency	0	1	1

Table 7: Violation of inclusion/exclusion criteria, FAS, T-cell (n=77)

	GemOx (n=36)	GemOx + Niv (n=41)	Total (n=77)
Violation inclusion/exclusion criteria	0	4	4
1. Patient > 65 years of age or older than 18 years if HCT-CI score > 2.		2	
11. Previous therapy with Nivolumab, Gemcitabine or Oxaliplatin.		1	
16. Women of childbearing potential (WOCBP).		1	

12 EFFICACY EVALUATION

12.1 Data Sets Analysed

The Full Analysis Set (FAS) comprised all randomized patients who received at least one dose of study treatment (prephase and/or [R]-GemOx ± nivolumab) and were analysed according to the randomized treatment arm (modified intention-to-treat). Patients who never started any study treatment were excluded from the FAS. The Per-Protocol Set (PPS) comprises all FAS patients without pre-specified major protocol deviations (incl. eligibility violations based on reference pathology, exclusion-criterion breaches, and major treatment deviations). The Safety Analysis

Set (SAS) included all patients who received at least one dose of study treatment. In this trial, the FAS and the SAS were identical in both cohorts.

B-cell cohort:

- Patients without any study treatment: n=3 (death before start, WIC at day of randomization, change of treatment due to intercurrent disease).
- FAS/SAS: n=267 (R-GemOx n=134; R-GemOx + nivolumab n=133).
- Patients in FAS with violation of inclusion/exclusion criteria: n=13.
- Patients in FAS without reference pathology diagnosis per protocol: n=20 (two overlap with the 13 above).
- Patients in FAS with major deviation “treatment mismatch” (randomized to R-GemOx + nivolumab, treated with R-GemOx): n=2.

T-cell cohort:

- Patients without any study treatment: n=1 (WIC at baseline).
- FAS/SAS: n=77 (GemOx n=36; GemOx + nivolumab n=41).
- Patients with violation of inclusion/exclusion criteria: n=4.
- Patients without reference pathology diagnosis per protocol: n=12.

All randomized patients who received any study treatment were in SAS; all patients eligible for FAS were evaluated by randomized arm (ITT). PPS excluded pre-specified major deviations per SAP; reasons were captured in the eCRF and listings.

12.2 Demographic and Other Baseline Characteristics

Up to the data cut-off (15 Jan 2025), 348 patients were randomized in the NIVEAU trial (B-cell cohort: 270; T-cell cohort: 78). Demographic and baseline characteristics for the B-cell cohort are summarized in Tables 8 to 15; corresponding summaries for the T-cell cohort are provided in Tables 16 to 22.

Table 8: Demographics I, FAS, B-cell cohort (n=267)

	R-GemOx (n=134)	R-GemOx + Niv (n=133)	p-value	Total (n=267)
Male Female	68 (51%) 66 (49%)	74 (56%) 59 (44%)	0.423	142 (53%) 125 (47%)
Age, median (range)	76 (65, 89)	76 (44, 86)	0.502	76 (44, 89)
Age > 60 years	134 (100%)	130 (98%)	0.122	264 (99%)
Age > 70 years	114 (85%)	108 (81%)	0.398	222 (83%)
Age > 75 years	72 (54%)	67 (50%)	0.583	139 (52%)
LDH > UNV	86 (64%)	80 (60%)	0.497	166 (62%)
ECOG > 1	25 (19%)	19 (14%)	0.336	44 (16%)
Stage III/ IV	89 (66%)	97 (73%)	0.247	186 (70%)
Extralymphatic involvement	90 (67%)	98 (74%)	0.243	188 (70%)
Extralymphatic involvement > 1	45 (34%)	64 (48%)	0.016	109 (41%)
IPI 0 1 2 3 4 5	0 (0%) 15 (11%) 38 (28%) 44 (33%) 29 (22%) 8 (6%)	0 (0%) 25 (19%) 23 (17%) 32 (24%) 42 (32%) 11 (8%)	0.027	0 (0%) 40 (15%) 61 (23%) 76 (28%) 71 (27%) 19 (7%)
IPI 0-2 3-5	53 (40%) 81 (60%)	48 (36%) 85 (64%)	0.560	101 (38%) 166 (62%)

Table 9: Demographics II, FAS, B-cell cohort (n=267)

	R-GemOx (n=134)	R-GemOx + Niv (n=133)	p-value	Total (n=267)
B symptoms*	25 (19%)	21 (16%)	0.534	46 (18%)
BM involvement	8 (6%)	22 (17%)	0.006	30 (11%)
Primary progression no yes	 88 (66%) 46 (34%)	 91 (68%) 42 (32%)	0.633	 179 (67%) 88 (33%)
Duration of first response ≤ 12 months > 12 months	 78 (58%) 56 (42%)	 74 (56%) 59 (44%)	0.672	 152 (57%) 115 (43%)

Table 10: Reference pathology I, FAS, B-cell cohort (n=267)

	R-GemOx (n=134)	R-GemOx + Niv (n=133)	Total (n=267)
With reference pathology (technical sufficient material)	131 (98%)	130 (98%)	261 (98%)
Without reference pathology (technical insufficient material or not reviewed)	3 (2%)	3 (2%)	6 (2%)

Table 11: Reference pathology II, FAS, B-cell cohort (n=267)

Diagnosis	R-GemOx (n=131)	R-GemOx + Niv (n=130)	Total (n=261)
B-cell according NIVEAU protocol			
Follicular lymphoma grade 3b	3 (2%)	3 (2%)	6 (2%)
DLBCL, not otherwise specified (NOS)	87 (66%)	99 (76%)	186 (71%)
DLBCL, centroblastic	8 (6%)	9 (7%)	17 (7%)
DLBCL, immunoblastic	1 (1%)	0 (0%)	1 (0.4%)
DLBCL, anaplastic	0 (0%)	1 (1%)	1 (0.4%)
T-cell/histiocyte-rich large B-cell lymphoma	2 (2%)	1 (1%)	3 (1%)
Primary cutaneous DLBCL, leg type	3 (2%)	1 (1%)	4 (2%)
EBV-positive DLBCL, NOS	4 (3%)	0 (0%)	4 (2%)
Intravascular large B-cell lymphoma	0 (0%)	1 (1%)	1 (0.4%)
Plasmablastic lymphoma	1 (1%)	0 (0%)	1 (0.4%)
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements	11 (8%)	4 (3%)	15 (6%)
High-grade B-cell lymphoma, NOS	1 (1%)	2 (2%)	3 (1%)
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma	1 (1%)	0 (0%)	1 (0.4%)
Aggressive B-cell lymphoma, further subtyping technically not possible	2 (2%)	2 (2%)	4 (2%)
not according to NIVEAU protocol	7 (5%)	7 (5%)	14 (5%)

Table 12: Reference pathology III, FAS, B-cell cohort (n=267)

Diagnosis not according to NIVEAU protocol	R-GemOx (n=131)	R-GemOx + Niv (n=130)	Total (n=261)
Other lymphoma	3 (2%)	1 (1%)	4 (2%)
Angioimmunoblastic T-cell lymphoma	1 (1%)	0 (0%)	1 (0.4%)
Low grade NHL	3 (2%)	5 (4%)	8 (3%)
No lymphoma	0 (0%)	1 (1%)	1 (0.4%)

Table 13: Reference pathology IV, FAS, B-cell cohort (n=267)

Diagnosis not according to NIVEAU protocol – further specification	R-GemOx (n=131)	R-GemOx + Niv (n=130)
Other lymphoma	• B lymphoma, small B cell + some large B cells transformation? • Inclassable • Mantle cell	• Burkitt
No lymphoma	--	• Tumoral necrosis

Table 14: Demographics, FAS, T-cell cohort (n=77)

	GemOx (n=36)	GemOx + Niv (n=41)	p-value	Total (n=77)
Male Female	18 (50%) 18 (50%)	25 (61%) 16 (39%)	0.333	43 (56%) 34 (44%)
Age, median (range)	73 (60, 83)	74 (53, 84)	0.678	73 (53, 84)
Age > 60 years	34 (94%)	39 (95%)	1.000	73 (95%)
Age > 70 years	26 (72%)	25 (61%)	0.298	51 (66%)
Age > 75 years	14 (39%)	19 (46%)	0.510	33 (43%)
LDH > UNV	26 (72%)	19 (46%)	0.021	45 (58%)
ECOG > 1	4 (11%)	10 (24%)	0.132	14 (18%)
Stage III/ IV	31 (86%)	36 (88%)	1.000	67 (87%)
Extralymphatic involvement	24 (67%)	29 (71%)	0.701	53 (69%)
Extralymphatic involvement > 1	12 (33%)	16 (39%)	0.604	28 (36%)
IPI 0 1 2 3 4 5	1 (3%) 3 (8%) 7 (19%) 12 (33%) 11 (31%) 2 (6%)	0 (0%) 3 (7%) 9 (22%) 18 (44%) 10 (24%) 1 (2%)	0.818	1 (1%) 6 (8%) 16 (21%) 30 (39%) 21 (27%) 3 (4%)
IPI 0-2 3-5	11 (31%) 25 (69%)	12 (29%) 29 (71%)	0.902	23 (30%) 54 (70%)
B symptoms	8 (22%)	12 (29%)	0.482	20 (26%)
BM involvement	15 (42%)	15 (37%)	0.648	30 (39%)
Primary progression no yes	 21 (58%) 15 (42%)	 30 (73%) 11 (27%)	0.170	 51 (66%) 26 (34%)
Duration of first response ≤ 12 months > 12 months	 25 (69%) 11 (31%)	 28 (68%) 13 (32%)	0.913	 53 (69%) 24 (31%)

Table 15: Reference pathology I, FAS, T-cell cohort (n=77)

	GemOx (n=36)	GemOx + Niv (n=41)	Total (n=77)
With reference pathology (technical sufficient material)	36 (100%)	40 (98%)	76 (99%)
Without reference pathology (technical insufficient material or not reviewed)	0 (0%)	1 (2%)	1 (1%)

Table 16: Reference pathology II, FAS, T-cell cohort (n=77)

Diagnosis	GemOx (n=36)	GemOx + Niv (n=40)	Total (n=76)
T-cell according NIVEAU protocol			
Enteropathy-associated T-cell lymphoma	0 (0%)	2 (5%)	2 (3%)
Peripheral T-cell lymphoma, NOS	6 (17%)	5 (13%)	11 (14%)
Angioimmunoblastic T-cell lymphoma	19 (53%)	20 (50%)	39 (51%)
Anaplastic large cell lymphoma, ALK-negative	0 (0%)	2 (5%)	2 (3%)
Peripheral T-cell lymphoma with TFH phenotype	4 (11%)	2 (5%)	6 (8%)
Monomorphic epitheliotropic intestinal T-cell lymphoma	0 (0%)	3 (8%)	3 (4%)
Aggressive T-cell lymphoma, further subtyping technically not possible	0 (0%)	2 (5%)	2 (3%)
Other lymphoma	7 (19%)	4 (10%)	11 (14%)

Table 17:Reference pathology III, FAS, T-cell cohort (n=77)

	GemOx (n=7)	GemOx + Niv (n=4)
Other lymphoma	- 3 x Extranodal NK/T-cell lymphoma, nasal type - PTCL, unclassifiable - EBV-positive DLBCL, NOS - nodular sclerosis Hodgkin Lymphoma - Transformed MF (mycosis fungoides)	- DLBCL + anapl. large cell ALK-neative - PTCL, unclassifiable due to insufficient material - transformed MF /CD30+ (mycosis fungoides) - unclassifiable lymphoma

12.3 **Measurements of Treatment Compliance**

12.3.1 Definitions and analysis rules

Treatment compliance was evaluated for each study medication using:

1. duration (time from first to last application; patients with fewer than two applications were excluded from duration/dose analyses)

2. absolute cumulative dose, and

3. relative dose versus protocol-planned totals.

For the B-cell analysis, these rules were explicitly stated on the final-analysis slides (inclusion ≥2 administrations; exclusion from absolute/relative dose summaries if body weight/BSA was missing; CD20-negative disease excluded from rituximab summaries; censoring at early discontinuation due to insufficient response or off-protocol histology). For the T-cell analysis, the same definitions were applied (duration definition, exclusion if weight/BSA was missing, censoring at early discontinuation).
Cycle/timing windows followed the protocol: chemotherapy was scheduled q14d; nivolumab was administered q2w (±2 days) during induction and q4w during consolidation. At study start, nivolumab dosing was body weight–adapted (3 mg/kg). From protocol version V06.0-F onward, flat dosing was implemented (240 mg q2w during induction and 480 mg q4w during consolidation). Planned durations and target totals were shown on the B-cell slides (e.g., rituximab 8 administrations ≈ 98–99 days; nivolumab induction 8 administrations ≈ 100 days).

12.3.2 Chemotherapy (GemOx) and Rituximab (B-cell cohort)

12.3.2.1 *Number of given GemOx cycles*

Across both arms, the distribution of actually administered GemOx cycles was skewed towards higher cycle counts. Most patients received multiple cycles in line with the planned 8-cycle induction; only a small subset discontinued after ≤2 cycles. The arm-wise distributions were comparable, without evidence of a systematic shift in cycle numbers between **R-GemOx** and **R-GemOx + Nivolumab.** A detailed summary of cycle distribution is provided in Table 18.

Table 18: Number of given GemOx cycles, FAS, B-cell cohort (n=267)

Number of given GemOx cycles	R-GemOx (n=134)	R-GemOx + Niv (n=133)	Total (n=267)
0	1* (1%)	3## (2%)	4 (1%)
1	10 (7%)	9 (7%)	19 (7%)
2	16 (12%)	10 (8%)	26 (10%)
3	10 (7%)	8 (6%)	18 (7%)
4	15 (11%)	16 (12%)	31 (12%)
5	7 (5%)	8 (6%)	15 (6%)
6	11 (8%)	5 (4%)	16 (6%)
7	4 (3%)	14 (11%)	18 (7%)
8	60 (45%)	60 (45%)	120 (45%)

12.3.2.2 *Course of GemOx therapy*

Arm-wise course tables documented whether GemOx was completed regularly or ended prematurely/irregularly, together with reasons for early discontinuation. In **both arms, 60 patients (45%)** completed GemOx **regularly**. Premature/irregular endings were mainly attributed to **progressive disease (PD)** and **excessive toxicity**; less frequent reasons included **intercurrent disease**, **patient decision to stop treatment**, and **other** causes. The joint “course × number-of-cycles” cross-tabulations (parts I/II) showed that early endings clustered at lower

cycle counts, while regular courses aligned with the administration of all planned cycles. Overall, the pattern and reasons for discontinuation were broadly similar between **R-GemOx** and **R-GemOx + Nivolumab.** A detailed summarisation of treatment course and cycle distribution is provided in Table 19 and Table 20.

Table 19: Course of therapy and given cycles GemOx I, FAS, B-cell cohort (n=267)

R-GemOx (n=134) Course of GemOx therapy	Number of given GemOx cycles								
	0	1	2	3	4	5	6	7	8
Regular									60 (45%)
Non-regular/ premature end of therapy									
Insufficient response (PD)	0 (0%)	7 (5%)	9 (7%)	8 (6%)	13 (10%)	4 (3%)	5 (4%)	2 (1%)	
Excessive toxicity	1* (1%)	1 (1%)	5 (4%)	2 (1%)	2 (1%)	3 (2%)	5 (4%)	2 (1%)	
Patient decision to terminate treatment	0 (0%)	1 (1%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	
Other	0 (0%)	1** (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

Table 20: Course of therapy and given cycles GemOx II, FAS, B-cell cohort (n=267)

R-GemOx + Niv (n=133) Course of GemOx therapy	Number of given GemOx cycles								
	0	1	2	3	4	5	6	7	8
Regular									60 (45%)
Non-regular/ premature end of therapy									
Insufficient response (PD)	2*/** (2%)	3 (2%)	6 (5%)	5 (4%)	14 (11%)	4 (3%)	4 (3%)	4 (3%)	
Excessive toxicity	1** (1%)	3 (2%)	3 (2%)	3 (2%)	1 (1%)	3 (2%)	1 (1%)	8 (6%)	
Histology outside of protocol definition	0 (0%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Intercurrent disease	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	
Patient decision to terminate treatment	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1*** (1%)	

12.3.2.3 *Duration (cycles/drugs)*

GemOx cycle duration (B-cell FAS): Distribution of cycle lengths; a small number of patients had cycles >32 days.
Total duration of gemcitabine/oxaliplatin: Medians per arm were close to plan for 8 applications (reference ≈98 days); observed medians were approximately 108/109 days for gemcitabine and 109/103 days for oxaliplatin in the two arms.
The duration of GemOx therapy, including cycle intervals and total administration times of rituximab, gemcitabine, and oxaliplatin, is documented in the graphical summaries provided in Figure 8 to Figure 11.

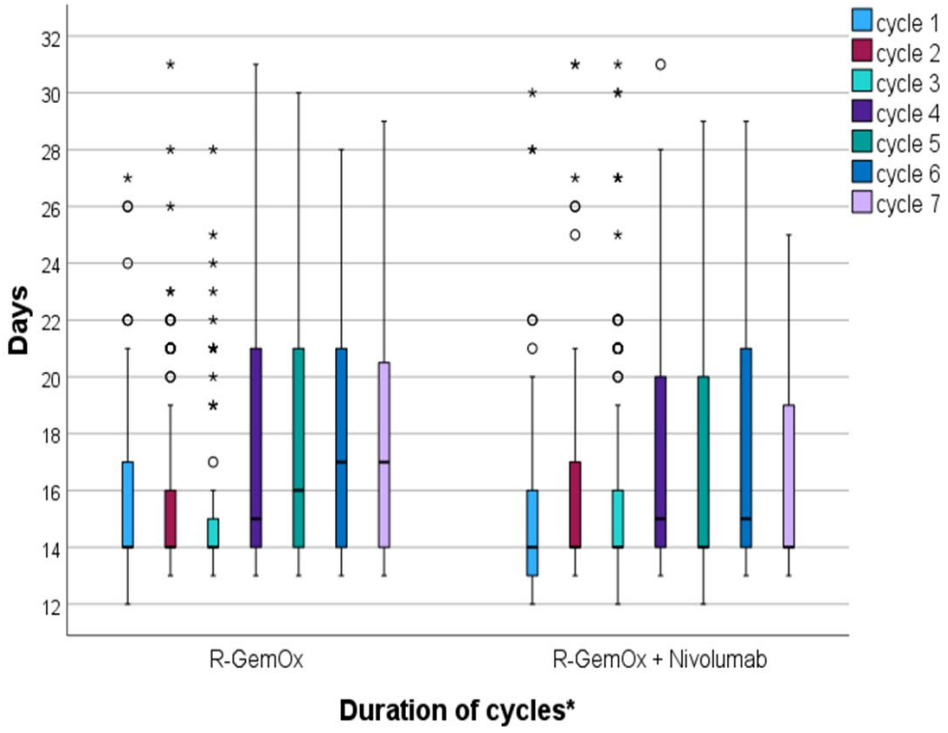


Figure 8: Duration of GemOx cycles, FAS, B-cell cohort (n=267) cycle-interval distribution;

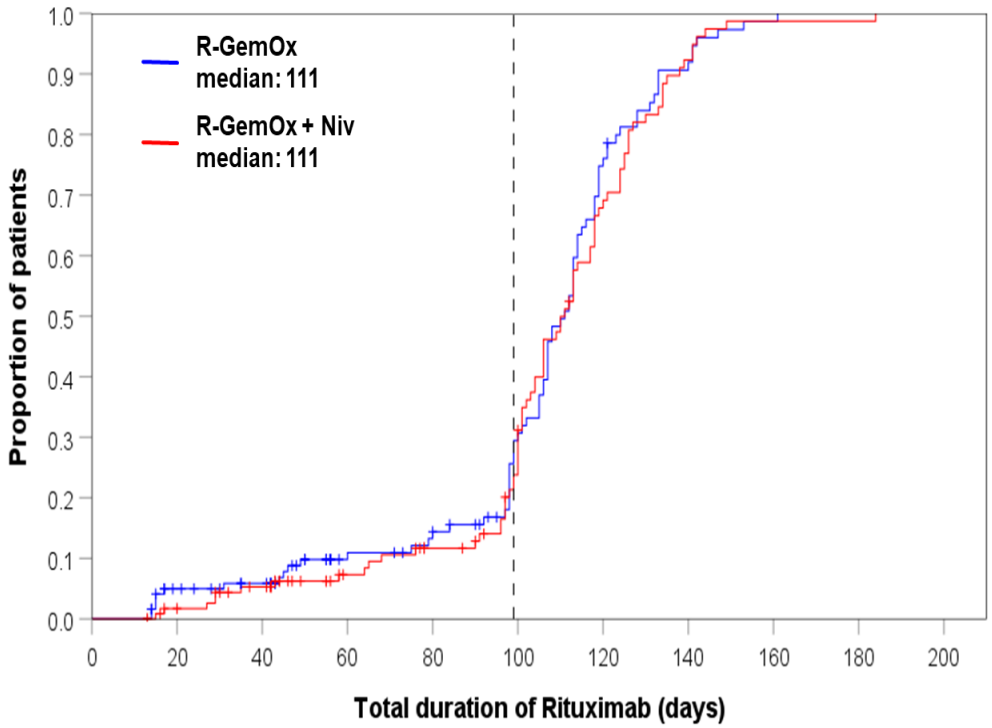


Figure 9: Total duration of Rituximab, FAS, B-cell cohort (n=267)

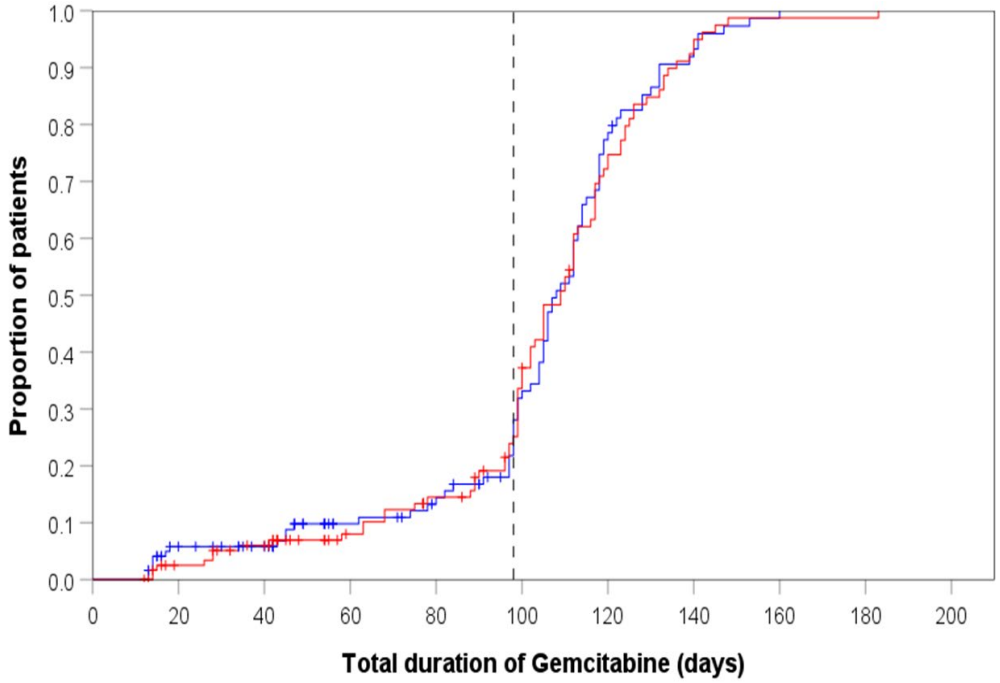


Figure 10: Total duration of Gemcitabine, FAS, B-cell cohort (n=267)-

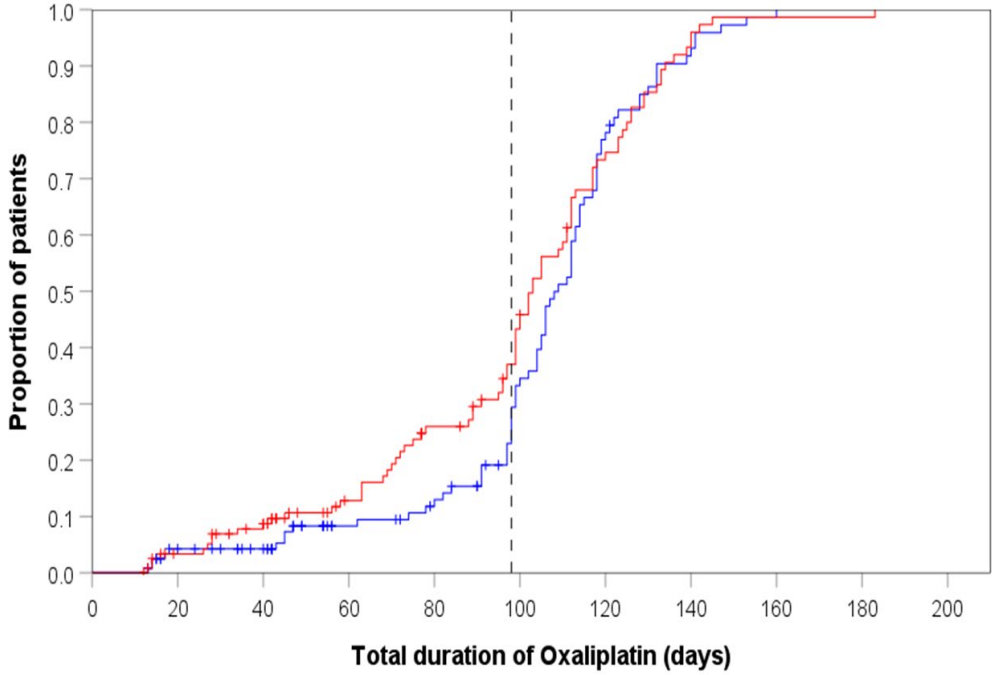


Figure 11: Total duration of Oxaliplatin, FAS, B-cell cohort (n=267)

12.3.2.4 *Absolute/relative cumulative dose*

For Rituximab, the protocol-planned cumulative dose was 3000 mg/m². Observed cumulative doses were on target in both arms; the median relative dose was approximately 1.00 in each arm, indicating high adherence to the planned antibody schedule.
For Gemcitabine and Oxaliplatin, absolute and relative cumulative doses were likewise close to protocol-planned totals across arms, with only small, clinically non-relevant differences. Per pre-specified analysis rules, patients without reliable weight/BSA data were excluded from relative-dose calculations; in cases of early treatment discontinuation (e.g., insufficient response, progression, toxicity), dosing was censored at the date of last administration. Overall, the data support predominantly on-plan delivery of GemOx chemotherapy.

Absolute and relative cumulative doses of rituximab, gemcitabine, and oxaliplatin were evaluated according to protocol-specified rules. The graphical summaries of all cumulative-dose analyses are presented in Figure 12 to Figure 17.

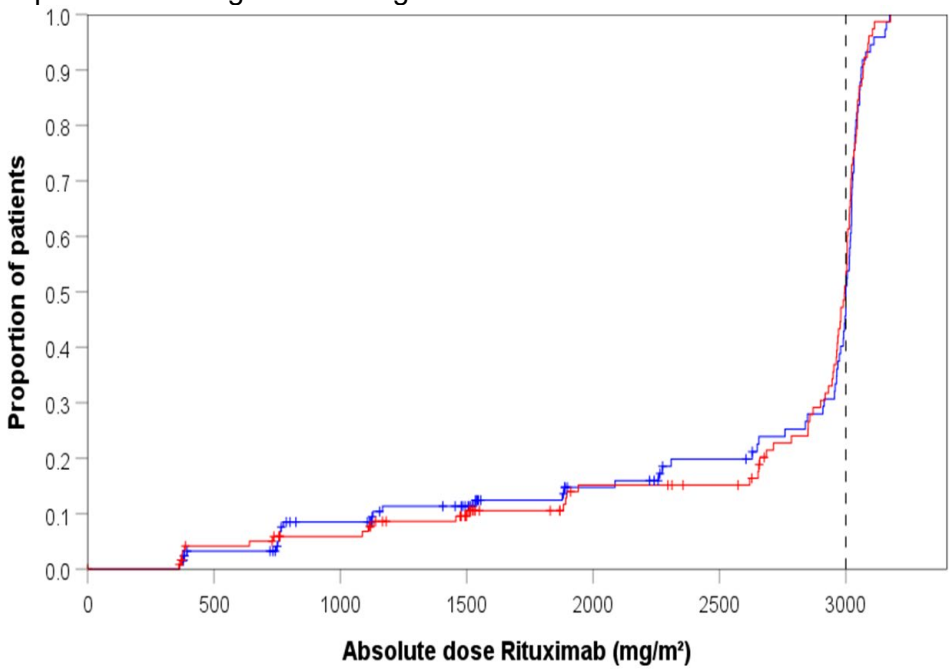


Figure 12: Absolute dose of Rituximab, FAS, B-cell cohort (n=267)

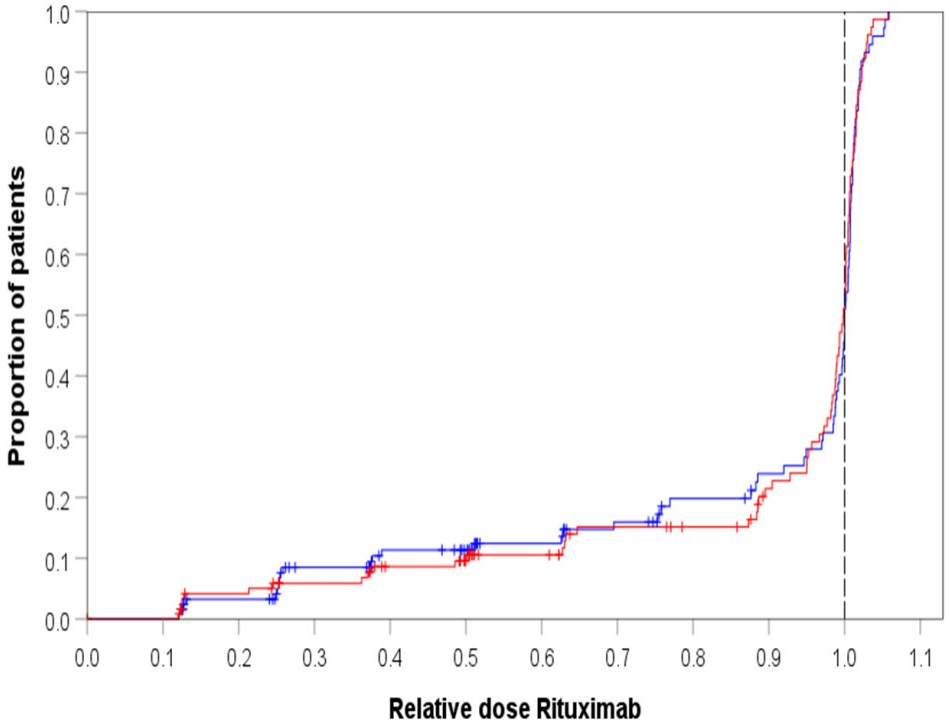


Figure 13: Relative dose of Rituximab, FAS, B-cell cohort (n=267)

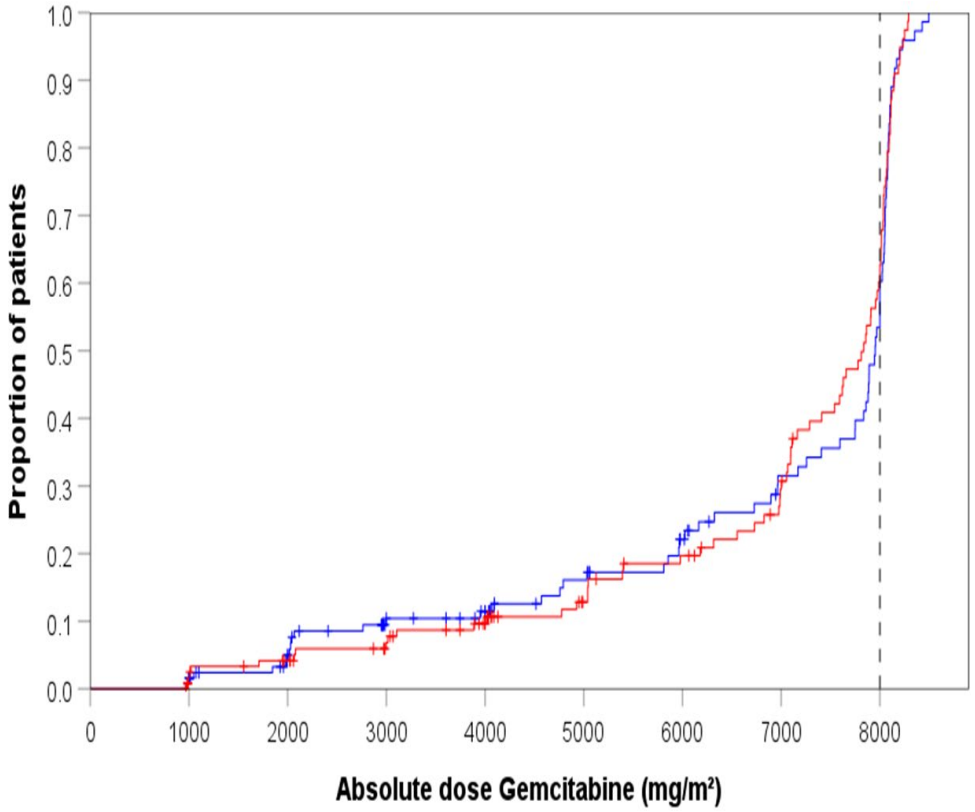


Figure 14: Absolute dose of Gemcitabine, FAS, B-cell cohort (n=267)

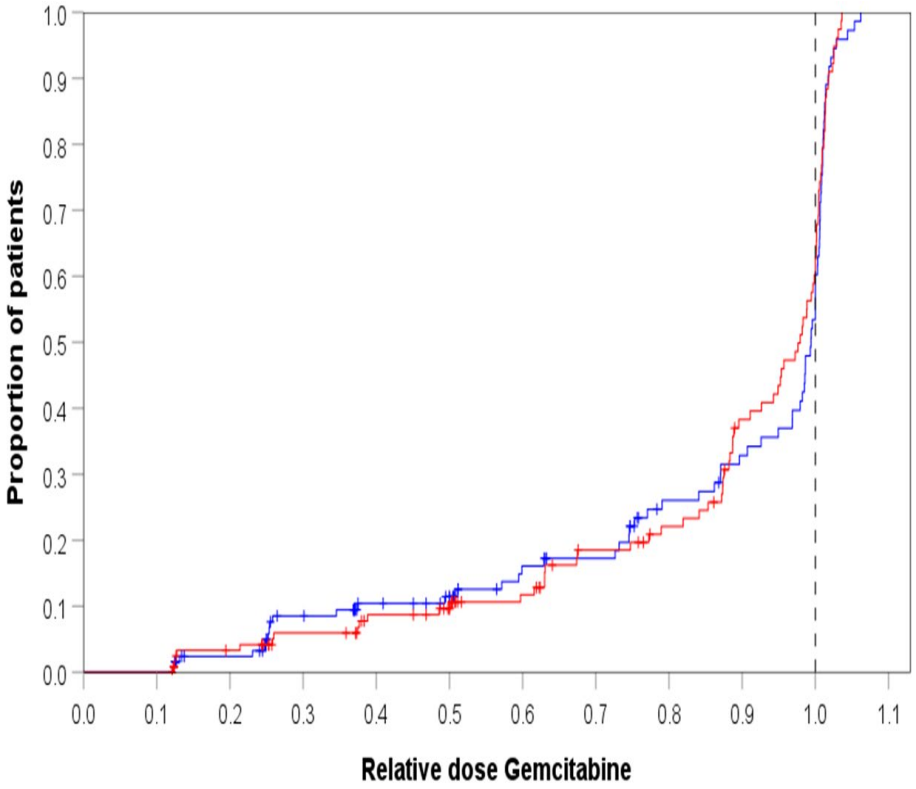


Figure 15: Relative dose of Gemcitabine, FAS, B-cell cohort (n=267

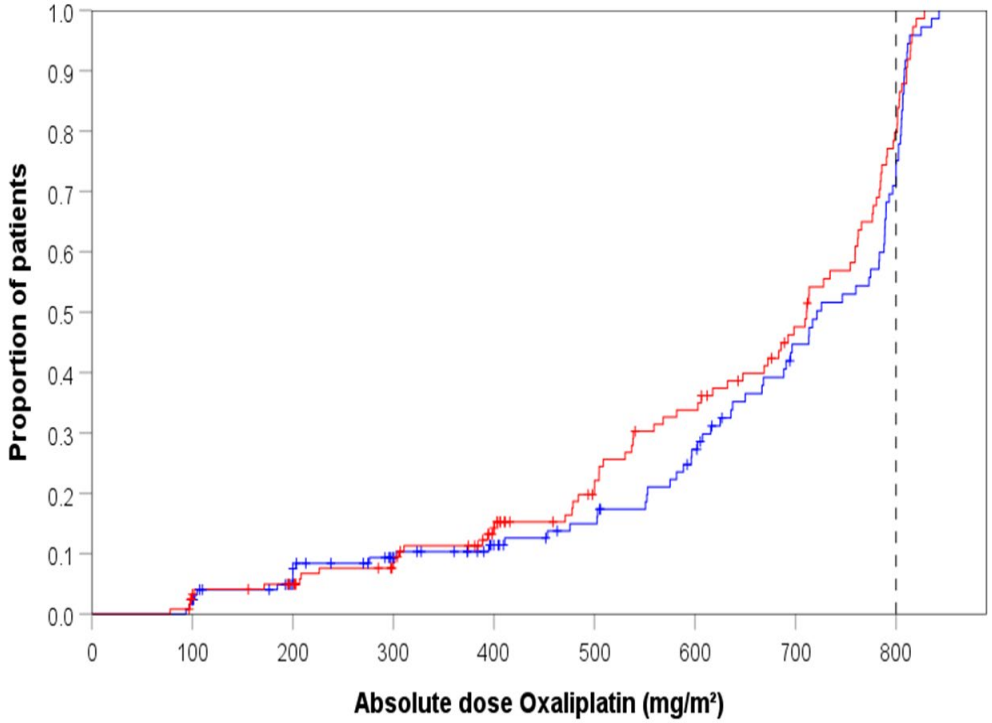


Figure 16: Absolute dose of Oxaliplatin, FAS, B-cell cohort (n= 267)

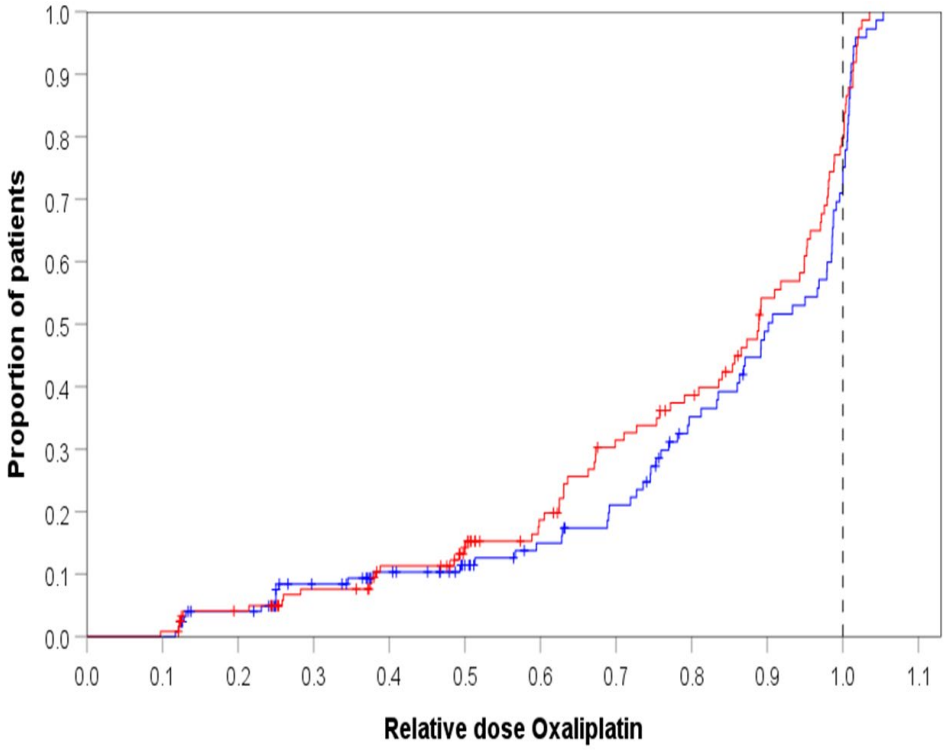


Figure 17: Relative dose of Oxaliplatin, FAS, B-cell cohort (n= 267)

12.3.3 Chemotherapy (GemOx) in the T-cell cohort

12.3.3.1 *Number of given GemOx cycles*

The distribution of administered GemOx cycles in the T-cell cohort is summarised in Table 28. Most patients received multiple GemOx cycles according to the planned induction schedule. Arm-wise distributions were generally comparable.

Table 21: Number of given GemOx cycles, FAS, T-cell cohort (n=77)

Number of given GemOx cycles	GemOx (n=36)	GemOx + Niv (n=41)	Total (n=77)
1	6 (17%)	6 (15%)	12 (16%)
2	5 (14%)	6 (15%)	11 (14%)
3	4 (11%)	3 (7%)	7 (9%)
4	7 (19%)	6 (15%)	13 (17%)
5	0 (0%)	3 (7%)	3 (4%)
6	1 (3%)	3 (7%)	4 (5%)
7	3 (8%)	1 (2%)	4 (5%)
8	10 (28%)	13 (32%)	23 (30%)

12.3.3.2 *Course of GemOx therapy*

The course of GemOx treatment in the T-cell cohort is summarised in Table 29 and Table 30. Arm-wise course tables classified treatment as **regularly completed** vs **premature/irregular end**, with reasons captured for early discontinuation. In both arms, the predominant reasons for premature end were **progressive disease (PD)** and **excessive toxicity**; less frequent categories were **intercurrent disease**, **patient decision to stop treatment**, and **other**. Cross-tabulations of **course × number of cycles** showed that early endings clustered at lower cycle counts, whereas regular courses aligned with administration of all planned cycles. Overall patterns and reasons were comparable between **GemOx** and **GemOx + Nivolumab.**

Table 22: Course of therapy and given cycles GemOx, FAS, T-cell cohort (n=77)

GemOx (n=36) Course of GemOx therapy	Number of given GemOx cycles							
	1	2	3	4	5	6	7	8
Regular								10 (28%)
Non-regular/ premature end of therapy								
Insufficient response (PD)	5 (14%)	5 (14%)	3 (8%)	6 (17%)	0 (0%)	1 (3%)	1 (3%)	
Excessive toxicity	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	2 (6%)	
Patient decision to terminate treatment	1 (3%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

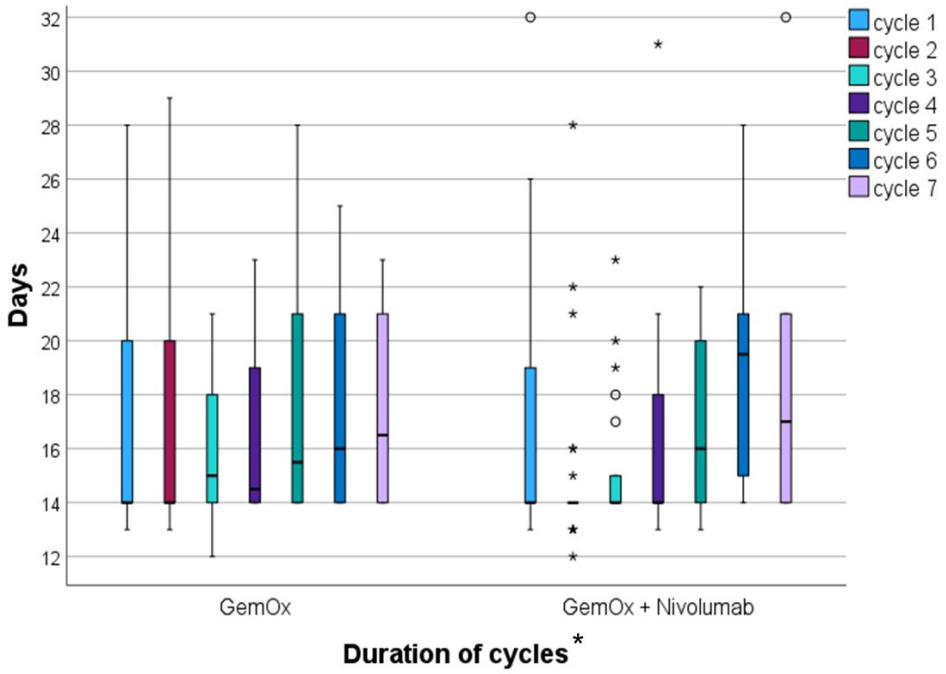
Table 23: Course of therapy and given cycles GemOx, FAS, T-cell cohort (n=77)

GemOx + Niv (n=41) Course of GemOx therapy	Number of given GemOx cycles							
	1	2	3	4	5	6	7	8
Regular								13 (32%)
Non-regular/ premature end of therapy								
Insufficient response (PD)	0 (0%)	4 (10%)	2 (5%)	3 (7%)	2 (5%)	2 (5%)	0 (0%)	
Excessive toxicity	6 (15%)	2 (5%)	1 (2%)	3 (7%)	0 (0%)	1 (2%)	1 (2%)	
Patient decision to terminate treatment	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	

12.3.3.3 *Duration and dose*

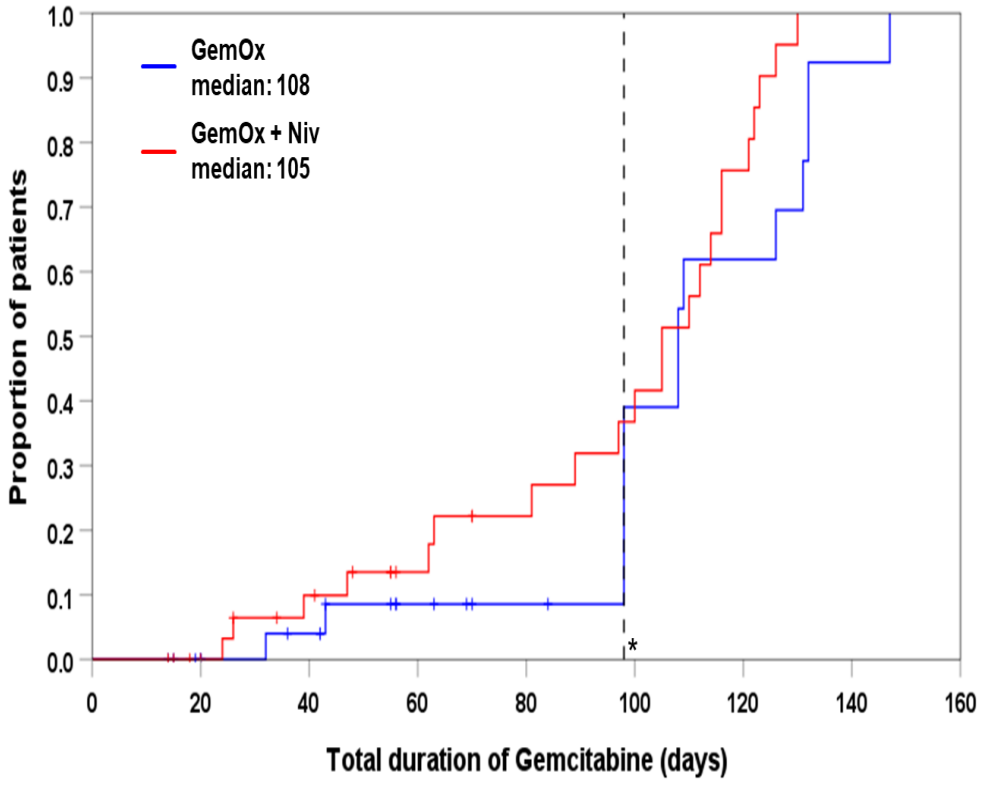
In the T-cell cohort (FAS), total treatment durations and absolute/relative cumulative doses of gemcitabine and oxaliplatin were summarized analogously to the B-cell cohort; patients with missing weight/body surface area were excluded from relative-dose calculations.
Cycle durations adhered to the planned 14-day schedule in both arms. Median cycle length was approximately 14–16 days with no systematic arm-level differences (GemOx vs. GemOx + nivolumab). Moderate extensions (≈18–21 days) and occasional outliers (>28–30 days) occurred in both arms, typically associated with toxicity, infections, or scheduling reasons. The planned total treatment duration for the 8-cycle GemOx induction (~112 days) was nearly achieved across treatment arms.

Absolute cumulative doses of gemcitabine and oxaliplatin were close to protocol targets. Relative dose intensity generally ranged ~0.90–1.00. Patients with missing weight/BSA were excluded from relative-dose analyses per pre-specified rules.
Impact of nivolumab:
No evidence of delayed chemotherapy, reduced absolute dose, or diminished dose intensity was observed in the nivolumab arm. Overall, GemOx feasibility and dose density were maintained with the addition of nivolumab.
Figures 18-24 display the cycle intervals, total treatment duration, and the absolute and relative cumulative doses of gemcitabine and oxaliplatin in the T-cell cohort.



*4 (1/3) patients with duration > 32 days

Figure 18: Duration of GemOx cycles, FAS, T-cell cohort (n=77)



*planned duration for 8 applications: 98 days

Figure 19: Total duration of Gemcitabine, FAS, T-cell cohort (n=77)

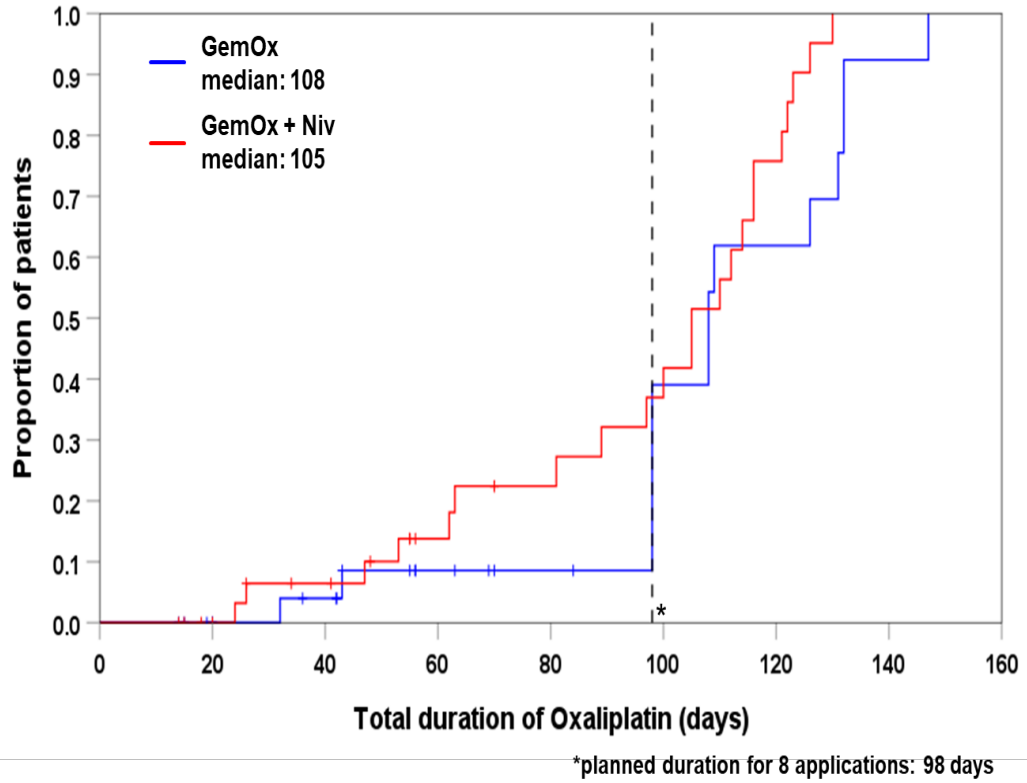


Figure 20: Total duration of Oxaliplatin, FAS, T-cell cohort (n=77)

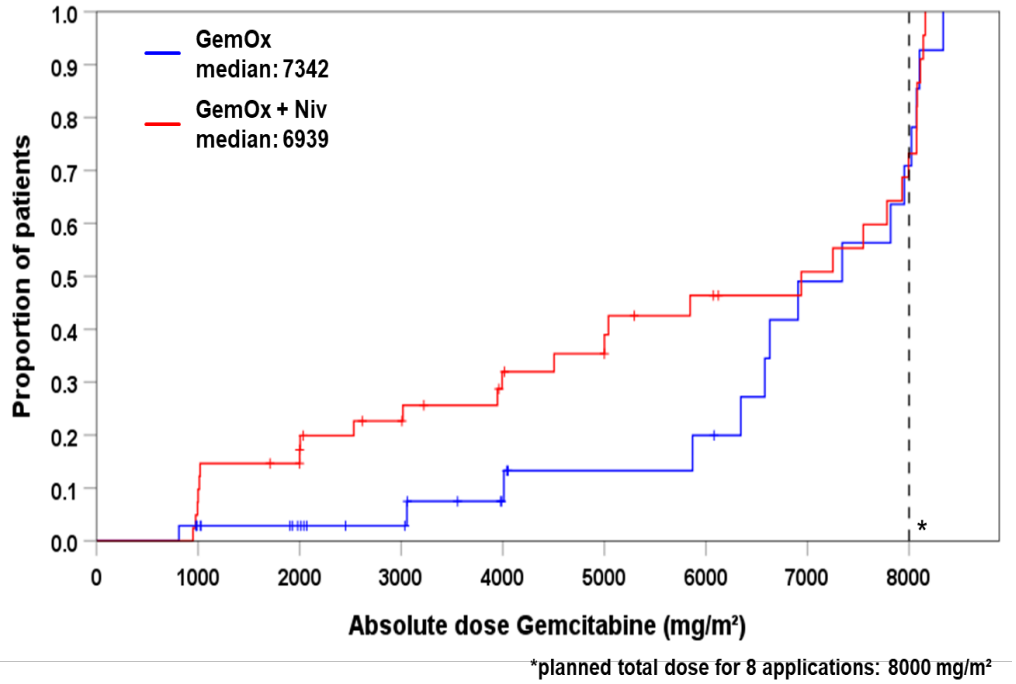


Figure 21: Absolute dose of Gemcitabine, FAS, T-cell cohort (n=77)

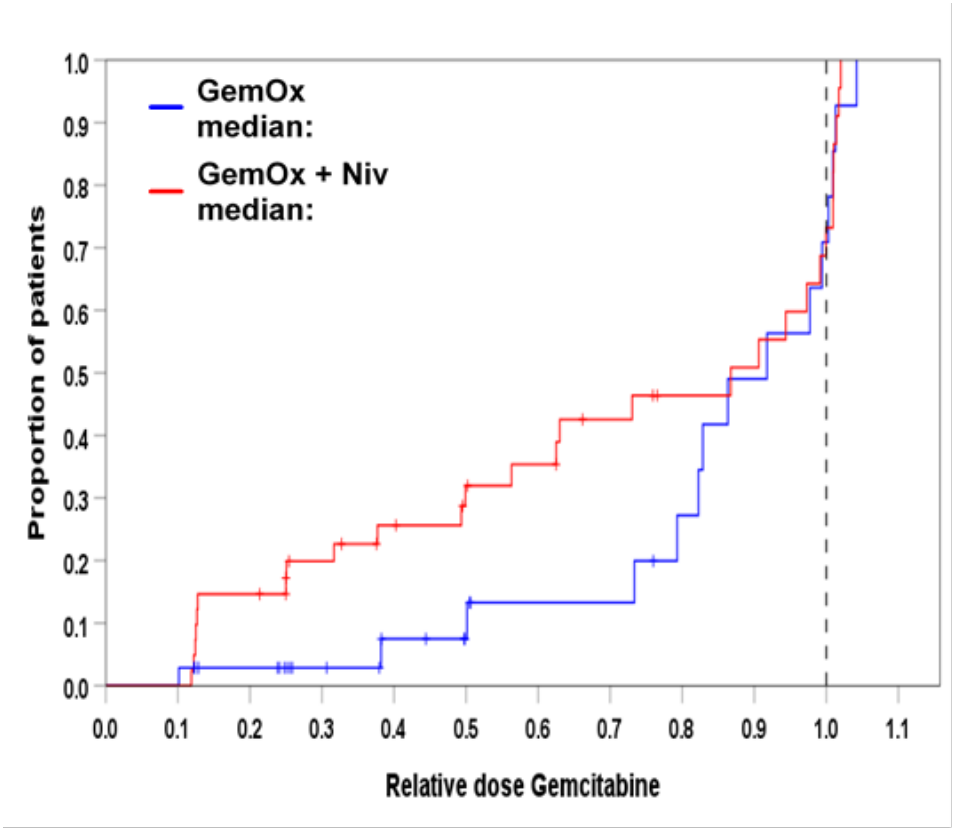


Figure 22: Relative dose of Gemcitabine, FAS, T-cell cohort (n=77)

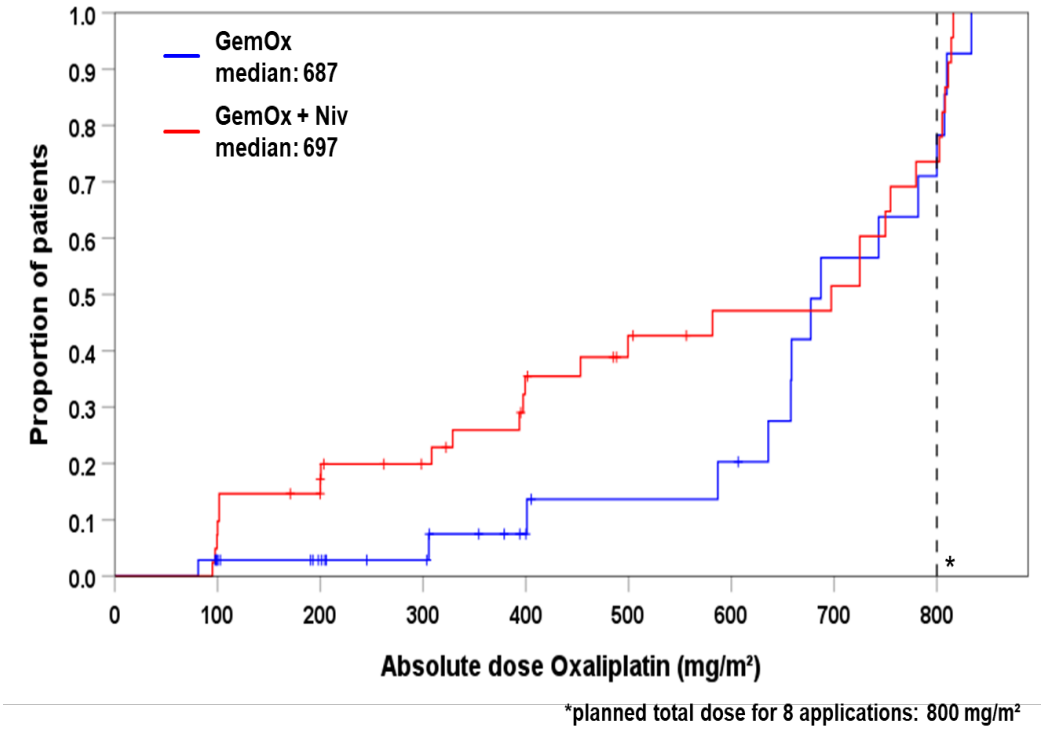


Figure 23: Absolute dose of Oxaliplatin, FAS, T-cell cohort (n=77)

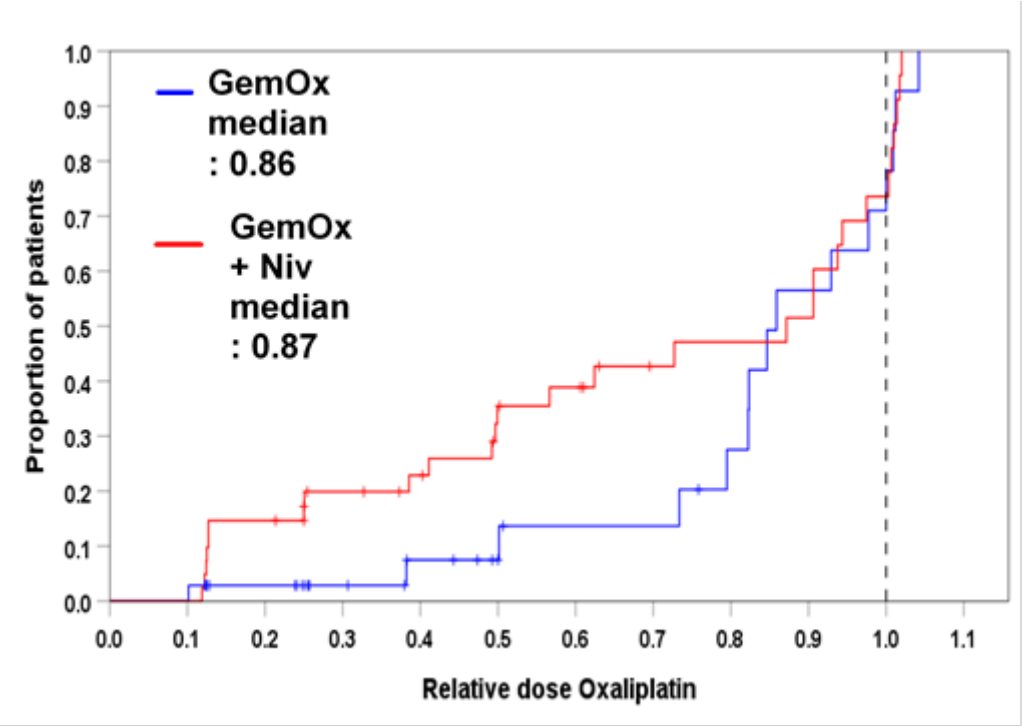


Figure 24: Relative dose of Oxaliplatin, FAS, T-cell cohort (n=77)

12.3.4 Nivolumab during GemOx (Induction) (FAS, B-cell cohort)

Across the nivolumab arm (FAS, n=133), less than half of the B-cell patients received the planned eight nivolumab administrations during the GemOx induction. 59% of the patients received fewer administrations, predominantly due to insufficient response, excessive toxicity, investigator/patient decision to discontinue, intercurrent illness, or other protocol-conforming reasons. Cycle-wise distributions are shown in the accompanying bar chart.
The distribution of administered nivolumab doses and the detailed treatment-course patterns during induction are fully presented in Tables 24–26.

Table 24: Number of given Nivolumab applications during R-GemOx, FAS, B-cell cohort (n=133)

Number of given Nivolumab applications	R-GemOx + Niv (n=133)
0	2 (2%)
1	13 (10%)
2	9 (7%)
3	8 (6%)
4	19 (14%)
5	8 (6%)
6	5 (4%)
7	14 (11%)
8	55 (41%)

The treatment-course summary indicates that the 41% of patients followed a regular schedule through induction. Irregular courses or premature discontinuations occurred mainly in the context of disease-related progression/insufficient response, immune- or chemo-related toxicity, or non-disease intercurrent events. Handling of these cases followed CSP/SAP rules (dose delays allowed within protocol windows; no nivolumab dose reductions; discontinuation if interruption

exceeded protocol thresholds). Reasons for discontinuation and the number of GemOx cycles completed at the time of stop are displayed in the course tables.

Table 25: Course of Nivolumab therapy during R-GemOx, FAS, B-cell cohort (n=133)

Course of Nivolumab therapy during GemOx	**R-GemOx + Niv (n=133)**
Regular	55 (41%)
Non-regular/ premature end of therapy	
Insufficient response (PD)	41 (31%)
Excessive toxicity	27 (20%)
Histology outside of protocol definition	2 (2%)
Intercurrent disease	1 (1%)
Patient decision to terminate treatment	3 (2%)
Other	4 (3%)

Table 26: Course of Nivolumab therapy during R-GemOx, FAS, B-cell cohort (n=133)

R-GemOx + Niv (n=133) Course of Nivolumab therapy during GemOx	Number of given Nivolumab applications								
	0	1	2	3	4	5	6	7	8
Regular									55 (41%)
Non-regular/ premature end of therapy									
Insufficient response (PD)	0 (0%)	6 (5%)	5 (4%)	5 (4%)	15 (11%)	3 (2%)	3 (2%)	4 (3%)	
Excessive toxicity	0 (0%)	4 (3%)	3 (2%)	3 (2%)	3 (2%)	3 (2%)	2 (2%)	9 (7%)	
Histology outside of protocol definition	0 (0%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Intercurrent disease	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Patient decision to terminate treatment	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	
Other	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)	

Definition of groups (per protocol amendments):
NO FLAT DOSE — randomised until 20-Jun-2020: weight-based dosing (historical; 3 mg/kg q2w during induction). n=47
SWITCH TO FLAT DOSE — randomised 21-Jun-2020 to 20-Jun-2021: started weight-based, then switched to flat dosing after amendment activation. n=44

FLAT DOSE ONLY — randomised from 21-Jun-2021: flat dosing throughout induction (240 mg q2w). n=42
Analysis rules: duration = time from first to last nivolumab dose during 8×GemOx (patients with ≥2 doses included); absolute cumulative dose = sum of administered mg (flat) or mg/kg (weight-based); relative dose = absolute dose / protocol-planned total for the patient's scheme; early discontinuations were censored for cumulative-dose summaries per SAP.
Results (FAS, B-cell cohort):
Planned duration for 8 administrations ≈ 100 days; observed medians by group were close to plan with similar dispersion across groups.
Absolute cumulative dose:
Flat-dose groups (SWITCH period post-switch; FLAT ONLY): median ≈ 1,920 mg over induction.
No-flat (weight-based): median ≈ 24 mg/kg over induction.
Relative dose (protocol adherence): high across all groups; median ≈ 1.00 for flat-dose patients and ≈ 0.99 for no-flat, indicating near-complete delivery of planned exposure.
Delays/interruptions: occasional off-schedule administrations occurred in all groups (toxicity, infections, logistics) without systematic differences between schemes; chemotherapy timing (GemOx q14d) was not adversely impacted by nivolumab scheme.
The duration and cumulative/relative nivolumab doses across all three dosing groups are fully illustrated in Figures 25–28.

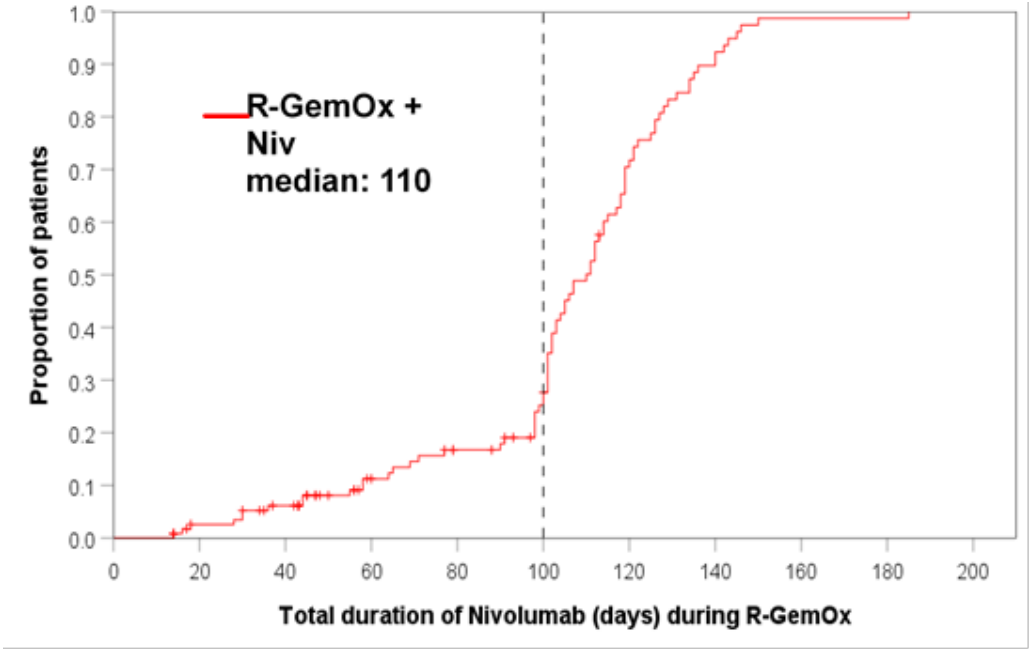


Figure 25: Total duration of Nivolumab during 8xGemOx, FAS, B-cell cohort (n=133)

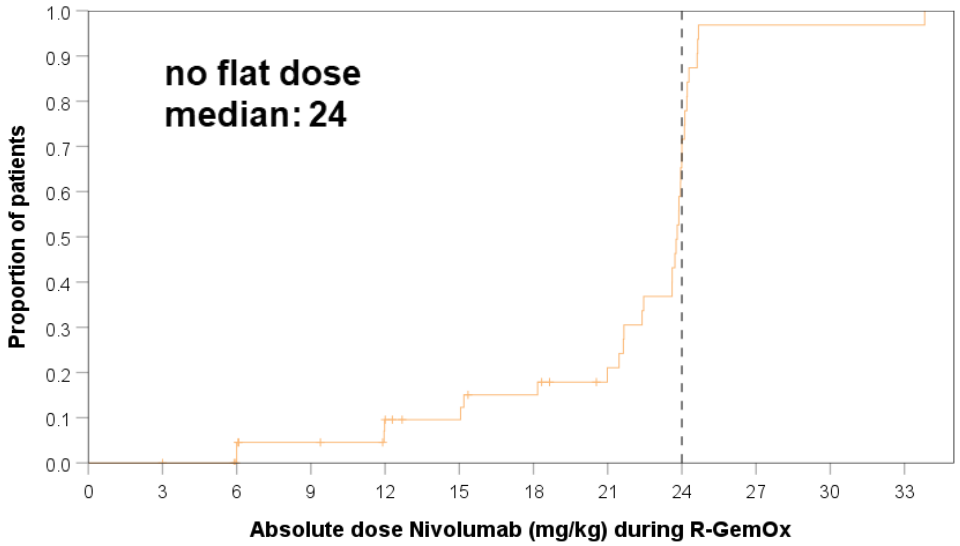


Figure 26: Absolute dose of Nivolumab per body weight, FAS, B-cell cohort (n=133)

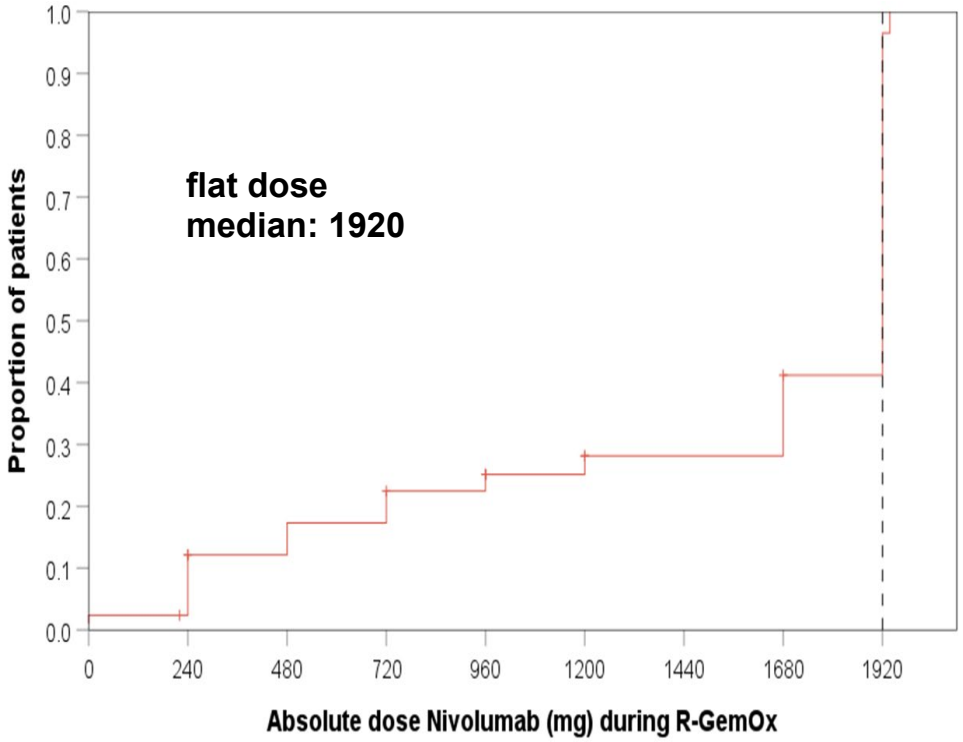


Figure 27: Absolute dose of Nivolumab flat dose, FAS, B-cell cohort (n=133)

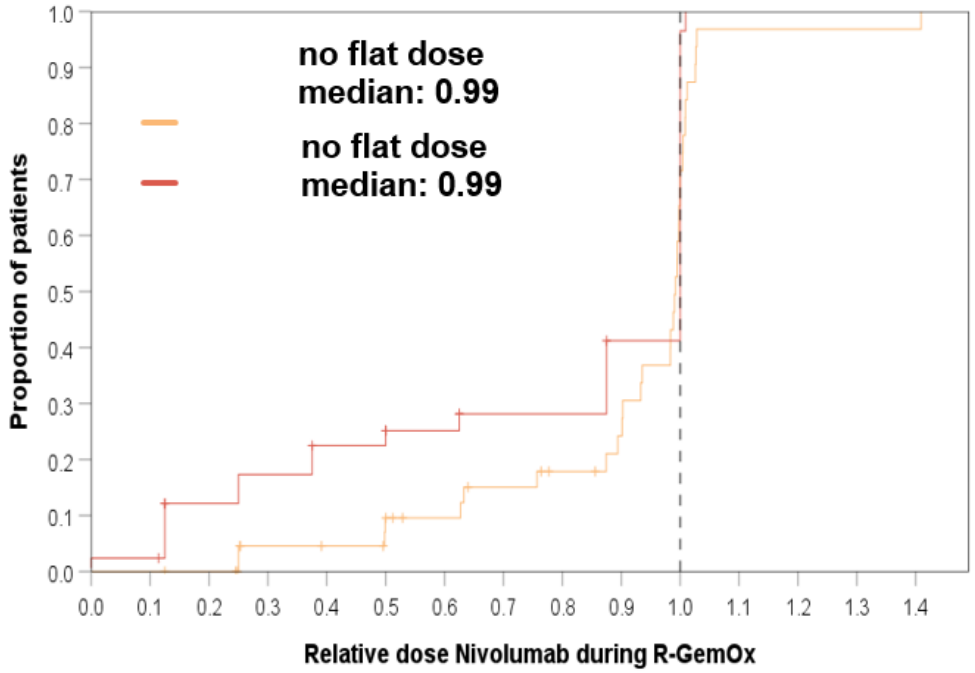


Figure 28: Relative dose of Nivolumab, FAS, B-cell cohort (n=133)

T-cell cohort

Only 29% of the patients received all 8 planned nivolumab administrations during GemOx. 59% of the patiens received ≤ 4 cycles. Premature discontinuations were mainly due to insufficient response/progression or toxicity; isolated cases were related to intercurrent illness or patient/physician decision. Dosing was predominantly on-schedule within protocol windows (q2w ±2 days); occasional off-schedule administrations or short interruptions occurred across individuals (typically AE, infection, logistics) without a systematic pattern. Chemotherapy timing (GemOx q14d) was not consistently impacted by nivolumab. The distribution of nivolumab administrations and the treatment-course patterns during induction are fully summarised in Tables 27-29.

Table 27: Number of given Nivolumab applications during GemOx, FAS, T-cell cohort (n=41):

Number of given Nivolumab applications	GemOx + Niv (n=41)
1	9 (22%)
2	6 (15%)
3	4 (10%)
4	5 (12%)
5	2 (5%)
6	2 (5%)
7	1 (2%)
8	12 (29%)

Table 28: Course of Nivolumab therapy during GemOx, FAS, T-cell cohort (n=41)

Course of Nivolumab therapy during GemOx	GemOx + Niv (n=41)
Regular	12 (29%)
Non-regular/ premature end of therapy	
Insufficient response (PD)	11 (27%)
Excessive toxicity	17 (41%)
Patient decision to terminate treatment	1 (2%)

Table 29: Course of Nivolumab therapy during GemOx, FAS, T-cell cohort (n=41)

GemOx + Niv (n=41) Course of Nivolumab therapy during GemOx	Number of given Nivolumab applications							
	1	2	3	4	5	6	7	8
Regular								12 (29%)
Non-regular/ premature end of therapy								
Insufficient response (PD)	0 (0%)	3 (7%)	2 (5%)	3 (7%)	1 (2%)	2 (5%)	0 (0%)	
Excessive toxicity	9 (22%)	3 (7%)	2 (5%)	1 (2%)	1 (2%)	0 (0%)	1 (2%)	
Patient decision to terminate treatment	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	

Total induction duration and nivolumab dose (absolute and relative) were summarised. For dose summaries, patients who received at least one flat dose during induction (n=10) were **excluded from the absolute-dose analysis** but **remained included in the relative-dose analysis**. Distribution of flat-dose exposure: flat dosing (240 mg) in all induction administrations (n=7); flat

dosing except cycle 1 (n=1); except cycles 1–2 (n=1); except cycles 1–4 (n=1). These results are fully illustrated in Figures 29-31.

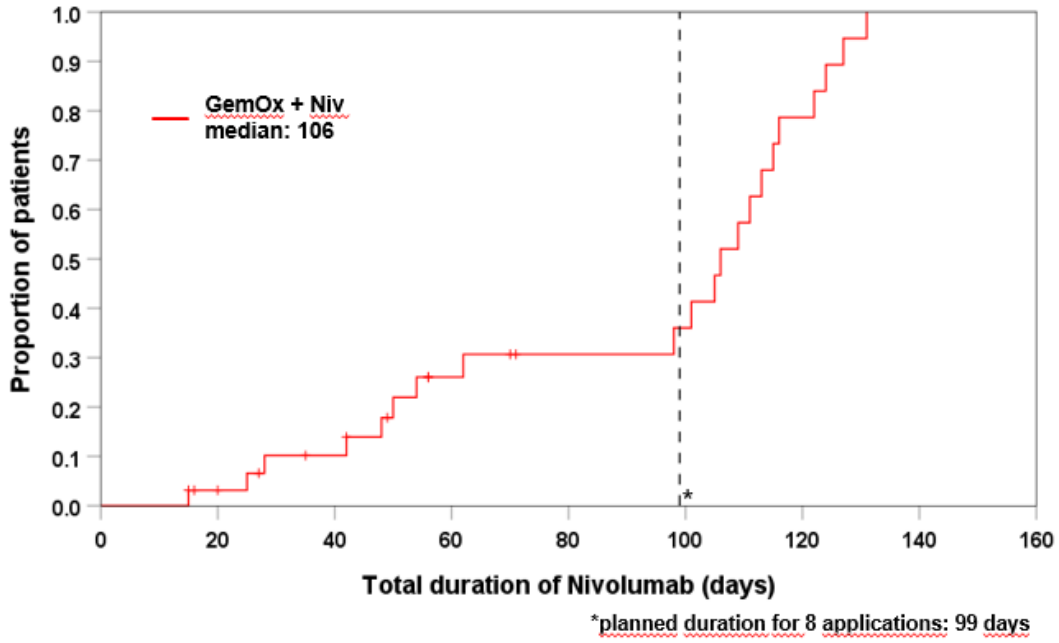


Figure 29: Total duration of Nivolumab during 8xGemOx, FAS, T-cell cohort (n=41)

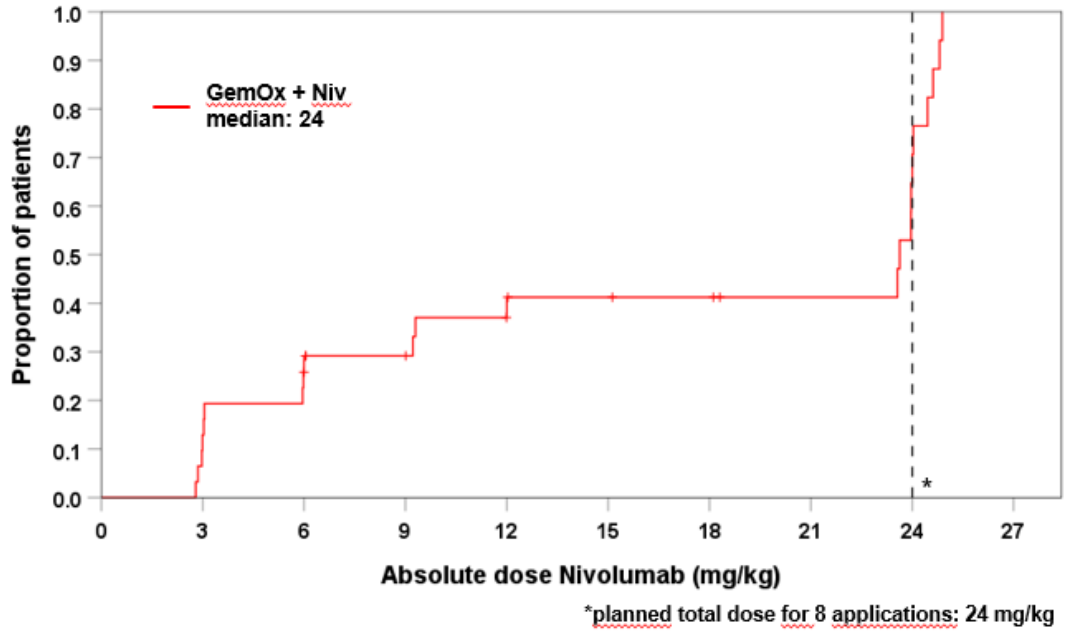


Figure 30: Absolute dose of Nivolumab, FAS, T-cell cohort (n=41)

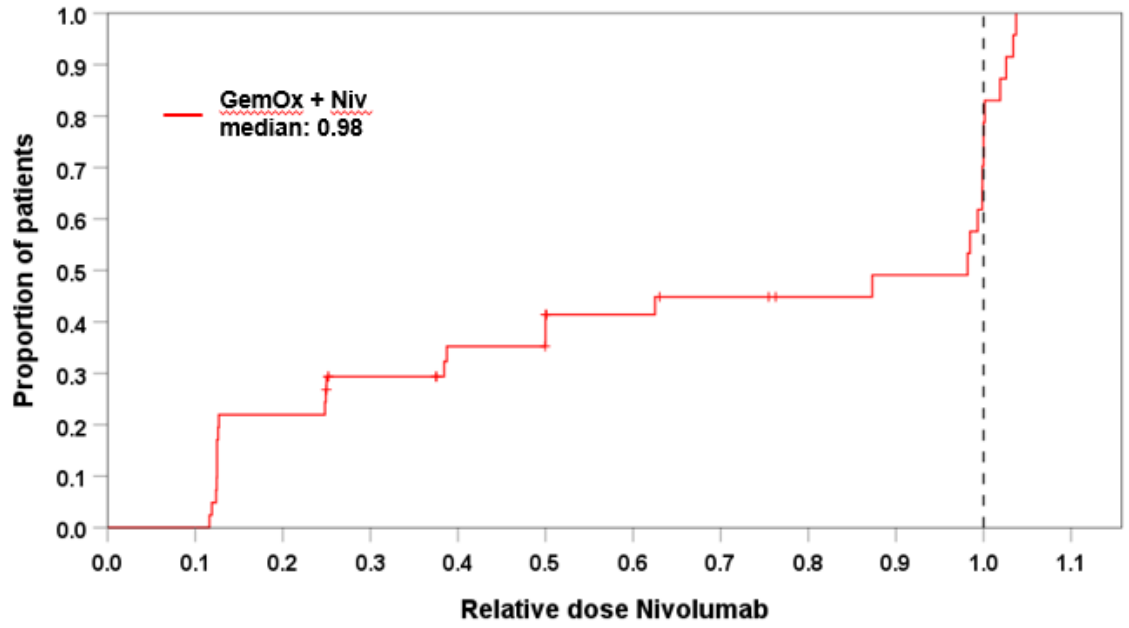


Figure 31: Relative dose of Nivolumab, FAS, T-cell cohort (n=41)

12.3.5 Nivolumab consolidation

B-cell cohort

Consolidation therapy was initiated in 57 of 133 patients (42.9%) in the nivolumab arm. A subset had received fewer than eight nivolumab applications during the 8×GemOx induction; additional patients did not enter consolidation due to insufficient response or PD-1–related hepatotoxicity.

For comparability across dosing schemes, nivolumab administrations were harmonized across dosing regimens. Each 480-mg q4w administration was counted as two applications, corresponding to a protocol-planned total of 9 q4w applications or 18 q2w applications. At study start, nivolumab was administered using a body weight–adapted dosing regimen (3 mg/kg q2w), which was considered equivalent to q2w flat dosing for the purpose of application counting.

The distribution of administered consolidation applications is shown in Table 30, demonstrating that many patients received fewer than the planned number, mainly due to progression, toxicity, intercurrent illness, or patient decision. A smaller subset completed consolidation as scheduled.

Table 30: Number of given Nivolumab applications during consolidation, FAS, B-cell cohort (n=57)

Number of given Nivolumab applications*	R-GemOx + Niv (n=57)
1	2 (4%)
2	7 (12%)
3	4 (7%)
4	5 (9%)
5	1 (2%)
6	6 (11%)
7	1 (2%)
8	1 (2%)
9	1 (2%)
10	5 (9%)
12	1 (2%)
14	3 (5%)
15	2 (4%)
16	6 (11%)
17	2 (4%)
18	10 (18%)

The treatment-course overview, including the frequency and reasons for premature discontinuation, is presented in Tables 31–32. Only 18% of patients received the complete course of Nivolumab consolidation. The most common reasons for early termination were progressive disease and toxicity; less frequent were contraindications, intercurrent events, and other investigator-documented reasons. Occasional off-schedule administrations occurred without any systematic pattern.

Table 31: Course of Nivolumab consolidation, FAS, B-cell cohort (n=57)

Course of Nivolumab therapy during consolidation	R-GemOx + Niv (n=57)
Regular	10 (18%)
Non-regular/ premature end of therapy	
Insufficient response (PD)	34 (60%)
Excessive toxicity	10 (18%)
Other	3 (5%)

Table 32: Course of Nivolumab consolidation, FAS, B-cell cohort (n=57)

R-GemOx + Niv (n=57)	Total number of applications during consolidation after R-GemOx*															
Course of Nivolumab therapy during consolidation	1	2	3	4	5	6	7	8	9	10	12	14	15	16	17	18
Regular																10 (18%)
Non-regular/ premature end of therapy																
Insufficient response (PD)	2 (4%)	6 (11%)	4 (7%)	4 (7%)	1 (2%)	5 (9%)	1 (2%)	1 (2%)	1 (2%)	5 (9%)	1 (2%)	0 (0%)	2 (4%)	1 (2%)	0 (0%)	
Excessive toxicity	0 (0%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (5%)	0 (0%)	4 (7%)	0 (0%)	
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	2 (4%)	

Q4-weekly dosing (q4w) were counted as 2 applications to be comparable with the q2-weekly (q2w) dosing schedule.
Total consolidation duration closely matched the protocol-defined windows (q4w or historic q2w equivalents) among patients without early discontinuation, while shortened durations reflected premature stop in the respective subgroup. Duration and cumulative-dose metrics for consolidation and for total nivolumab exposure are summarized in Figures 32–40.

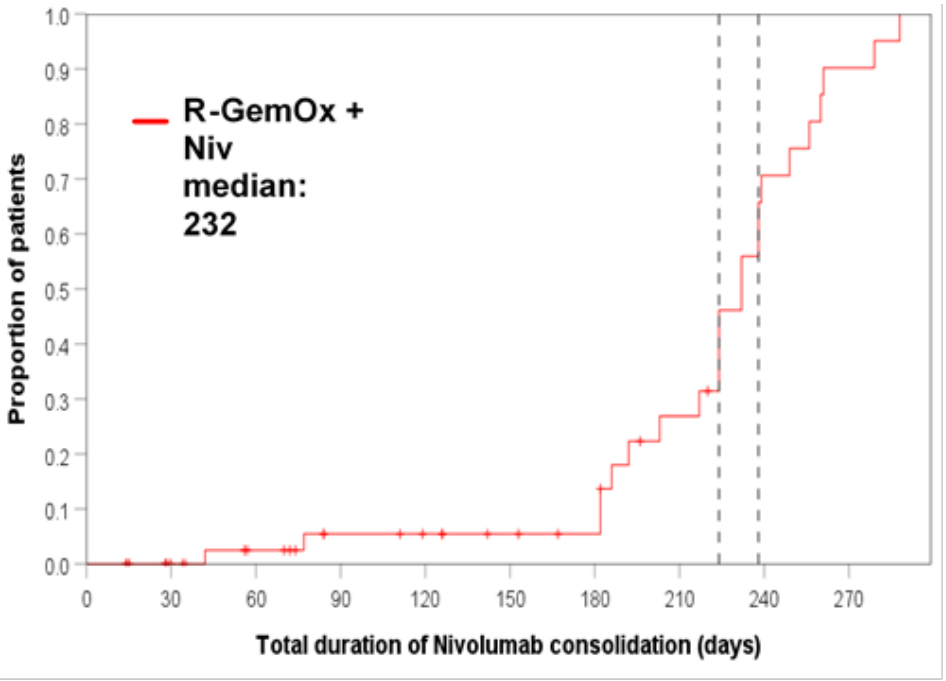


Figure 32: Total duration of Nivolumab consolidation, FAS, B-cell cohort (n=57)

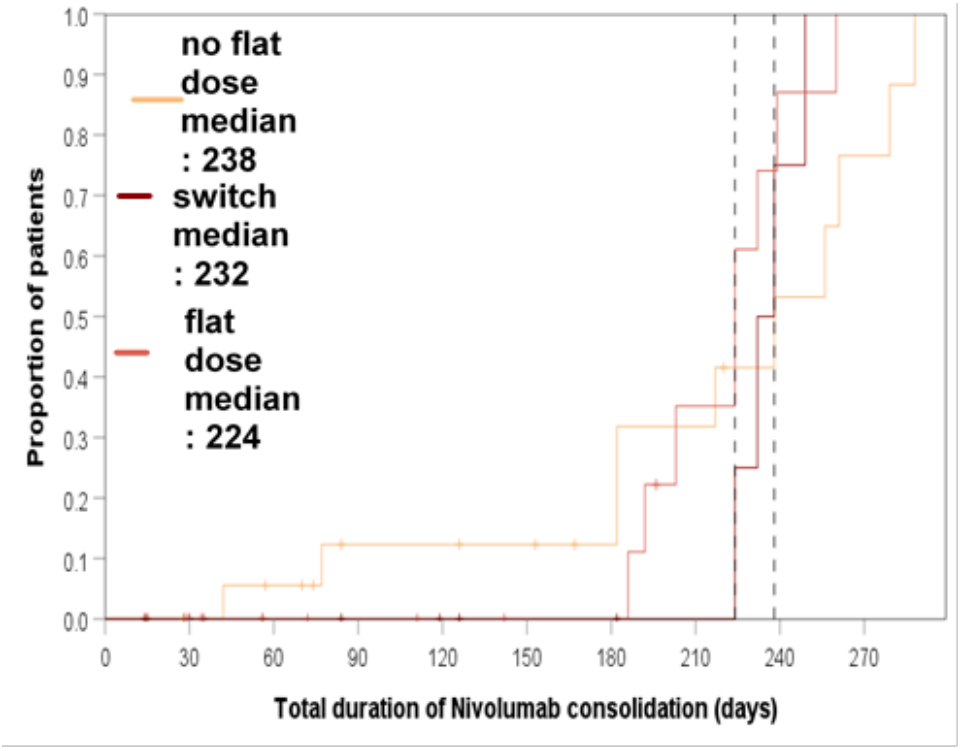


Figure 33: Total duration of Nivolumab consolidation, FAS, B-cell cohort (n=57)

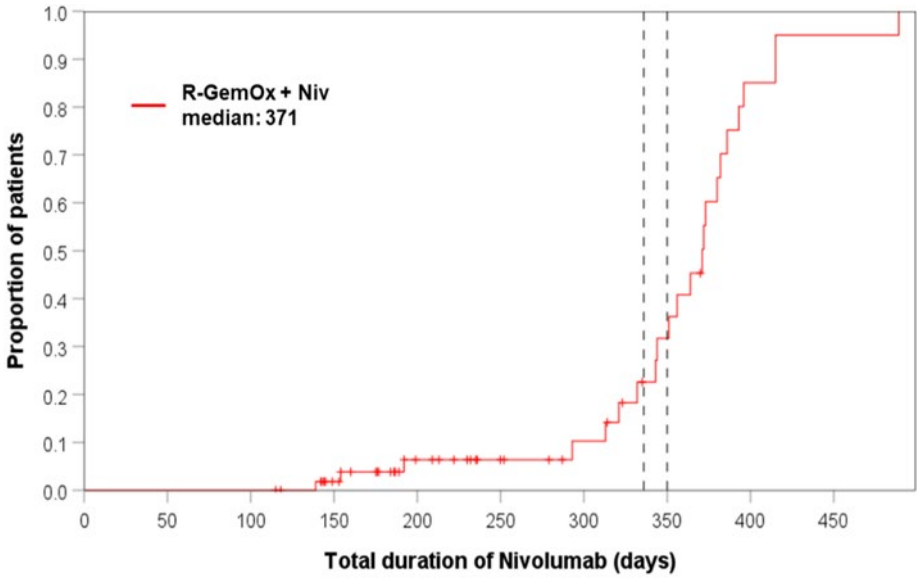


Figure 34: Total duration of Nivolumab, FAS, B-cell cohort (n=133)

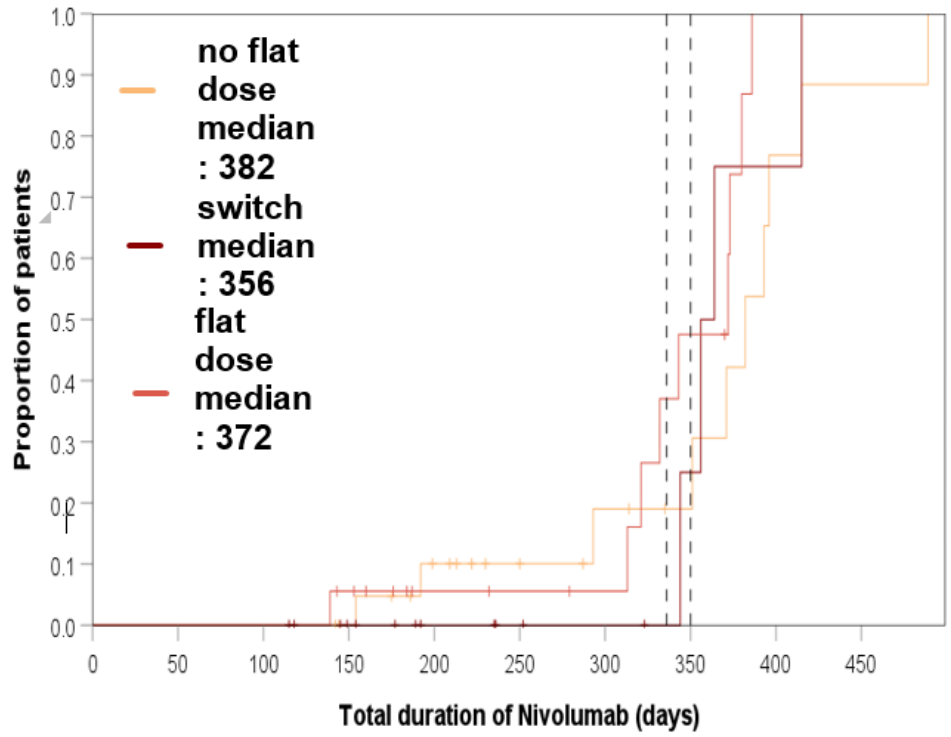
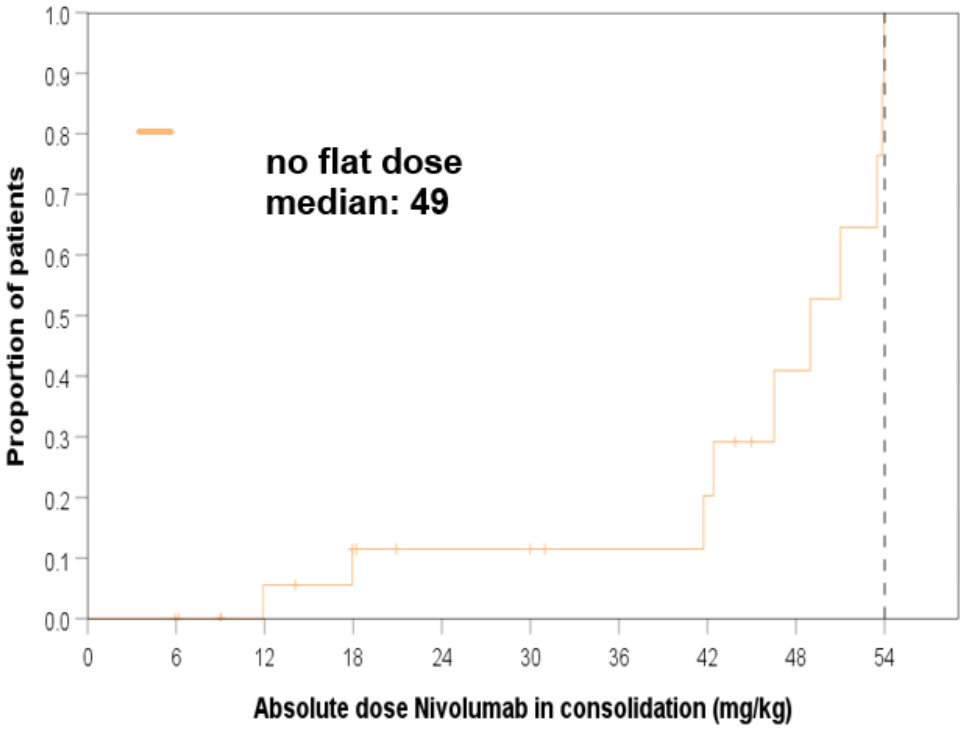
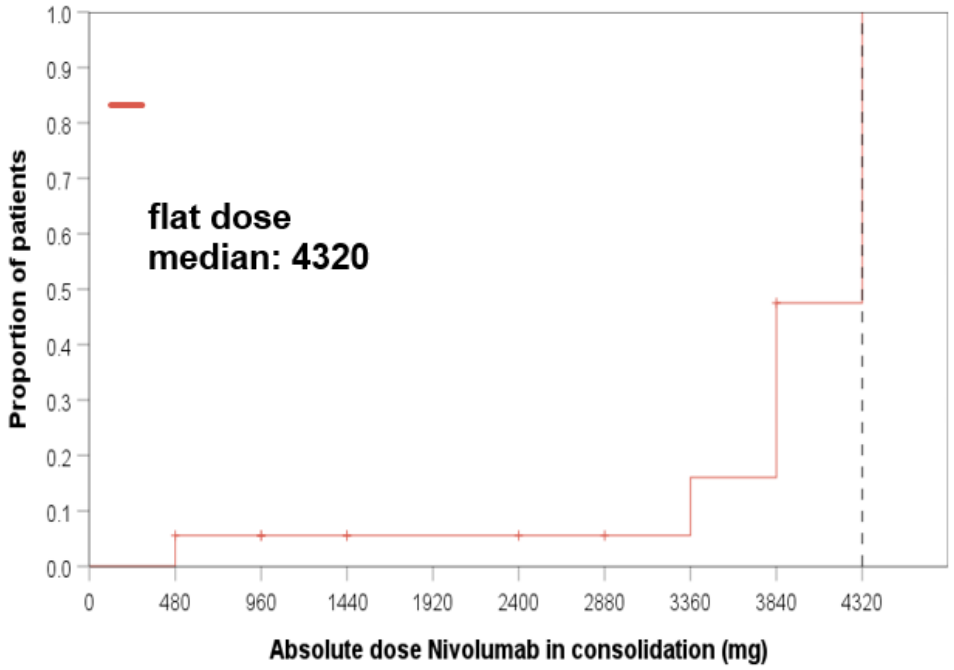


Figure 35: Total duration of Nivolumab, FAS, B-cell cohort (n=133)



***planned total dose for 18 applications: 54 mg/kg**

Figure 36: Absolute dose of Nivolumab per body weight in consolidation, FAS, B-cell cohort (n=57)



***planned total dose for 9 applications: 4320 mg**

Figure 37: Absolute dose of Nivolumab flat dose in consolidation, FAS, B-cell cohort (n=57)

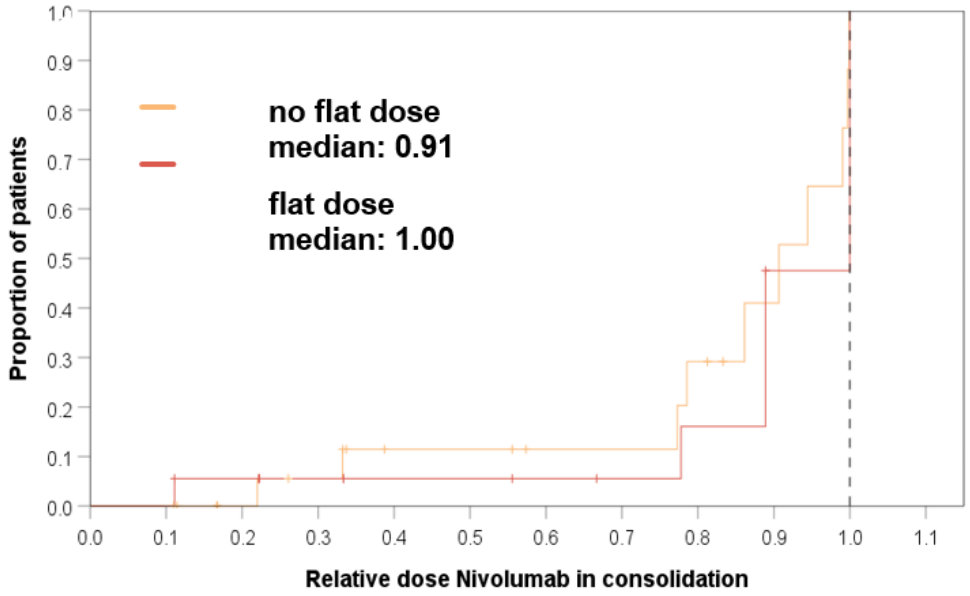
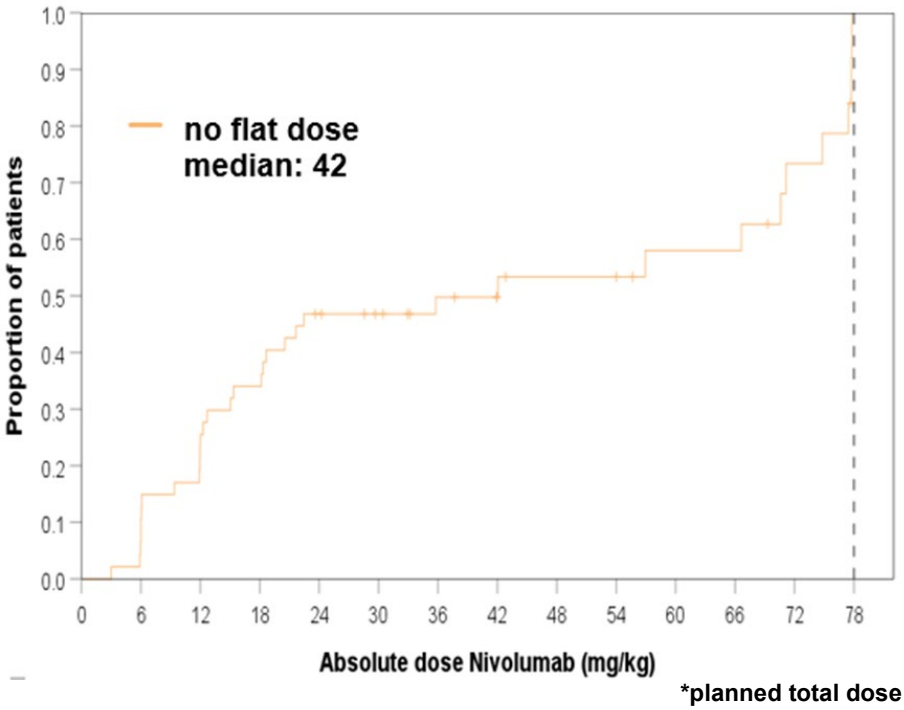
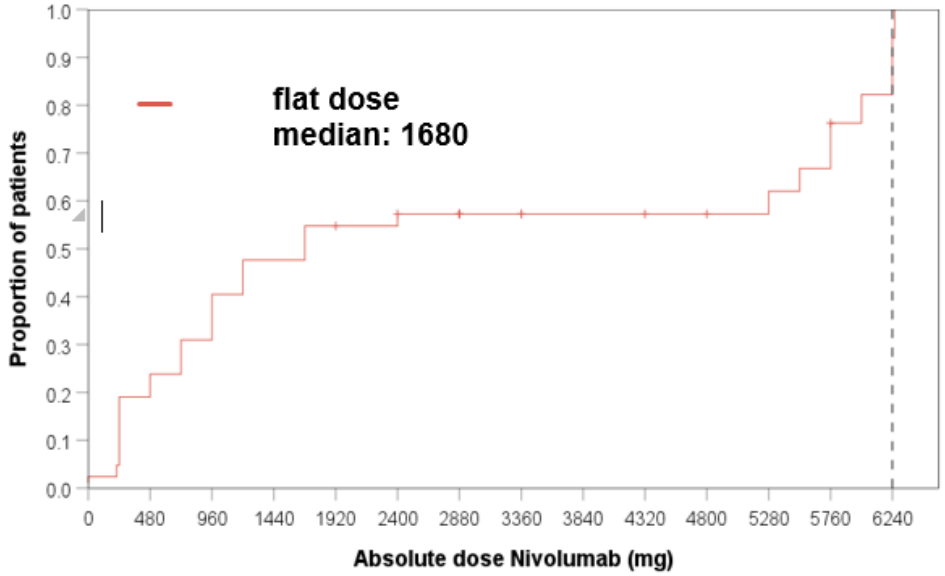


Figure 38: Relative dose of Nivolumab in consolidation, FAS, B-cell cohort (n=5)



***planned total dose for 26 applications: 78 mg/kg**

Figure 39: Absolute dose of Nivolumab per body weight, FAS, B-cell cohort (n=133)



***planned total dose for 18 applications: 6240 mg**

Figure 40: Absolute dose of Nivolumab flat dose, FAS, B-cell cohort (n=133)

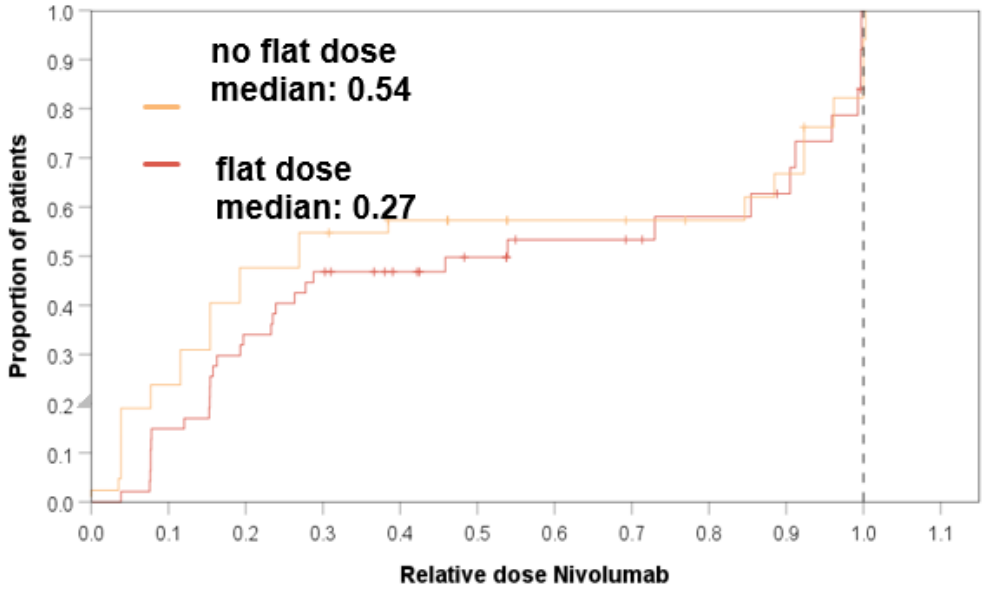


Figure 41: Relative dose of Nivolumab, FAS, B-cell cohort (n=133)

T-cell cohort

In the T-cell cohort (FAS), 12 patients received Nivolumab consolidation according to the protocol-defined intervals (q4w or historical q2w equivalents). Administration patterns were largely regular; occasional scheduling shifts occurred within the permitted windows. No systematic delays or recurrent deviations were observed, indicating that consolidation therapy was delivered as planned in the majority of patients.

The treatment-course overview of consolidation is provided in Table 33, documenting regular continuation versus premature end. 8/12 patients ended Nivolumab consolidation prematurely, six of them due to progressive disease.

Table 33: Course of Nivolumab consolidation, FAS, T-cell cohort (n=12)

Course of Nivolumab consolidation	GemOx + Niv (n=12)	Number of received Nivolumab apllications (480 mg flat dose were counted as 2 applications for comparability)
Regular	4 (33%)	18
Non-regular/ premature end of therapy		
Insufficient response (PD)	6 (50%)	2, 2, 7, 10, 14, 14
Excessive toxicity	1* (8%)	2
Patient decision to terminate treatment	1 (8%)	15

The administered absolute and relative Nivolumab doses were within protocol-defined targets for nearly all patients. Relative dose intensity remained high across the cohort, with no dose reductions required and only minimal schedule adjustments. Most patients received the nominal dose per consolidation cycle, reflecting near-complete dosing of the consolidation regimen. Dose summaries are shown in Table 34.

Table 34: Absolute/relative dose of Nivolumab during consolidation, FAS, T-cell cohort (n=12)

Nivolumab consolidation (n=12)
2 „cycles“: 2 applications 3 mg/kg
2 „cycles“: 2 applications 3 mg/kg
2 „cycles“: 2 applications 240 mg flat dose
7 „cycles“: 7 applications 3 mg/kg
10 „cycles“: 10 applications 3 mg/kg
14 „cycles“: 14 applications 3 mg/kg
14 „cycles“: 7 applications 480 mg flat dose
15 „cycles“: 1 application 3 mg/kg + 7 applications 480 mg flat dose
Regular: 18 applications 3 mg/kg
Regular: 18 applications 3 mg/kg
Regular: 18 applications 3 mg/kg
Regular: 9 applications 480 mg flat dose

Total consolidation duration displayed a narrow distribution around the expected protocol windows in patients who completed consolidation. Minor variations mainly reflected individual scheduling adjustments within acceptable limits. No systematic deviations or arm-specific patterns were detected. The distribution of total consolidation duration and total Nivolumab exposure is illustrated in Figures 42–43.

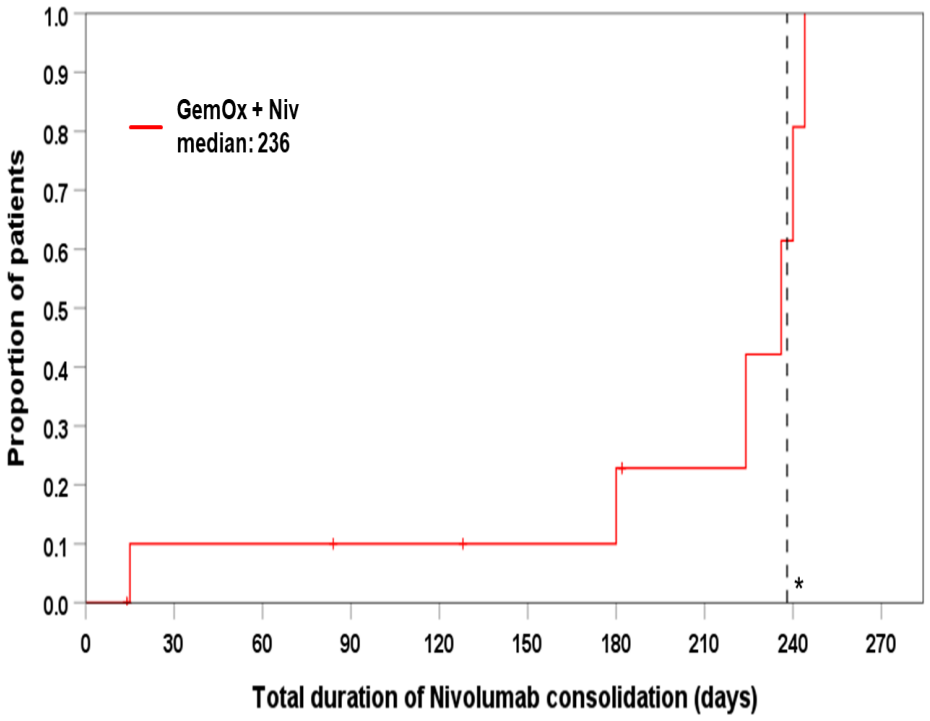


Figure 42: Total duration of Nivolumab consolidation, FAS, T-cell cohort (n=12)

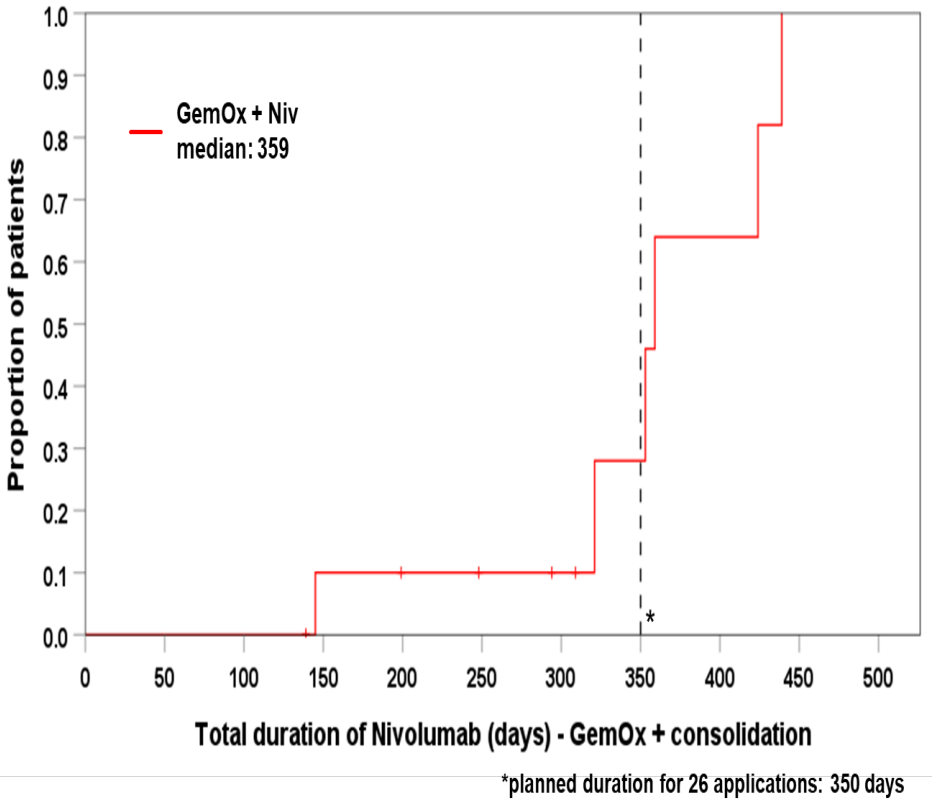


Figure 43: Total duration of Nivolumab, FAS, T-cell cohort (n=12)

12.3.6 Deviations impacting compliance

Premature treatment ends (insufficient response, toxicity, progression, etc.) and off-schedule administrations are documented on the course/premature-end slides for each cohort. Handling

followed CSP/SAP (e.g., censoring early stops in cumulative-dose summaries; classification as major/minor deviation; effect on PPS set membership).

12.4 Efficacy Results and Tabulations of Individual Patient Data

12.4.1 Analysis of Efficacy

Efficacy analyses were performed according to the statistical methodology prespecified in the Clinical Study Protocol (CSP) and Statistical Analysis Plan (SAP). All primary and secondary endpoints were evaluated in the Full Analysis Set (FAS), defined as all randomized patients who received at least one administration of study treatment and had at least one post-baseline disease assessment. Sensitivity analyses were performed in the Per Protocol Set (PPS), which excluded patients with major protocol deviations that could affect efficacy evaluation.
Analysis populations

- Full Analysis Set (FAS):

The Full Analysis Set comprised all randomized patients who received at least one dose of study treatment and were analysed according to the randomized treatment arm (modified ITT). Patients without any post-baseline tumour assessment were included in the FAS and were classified as non-responders in ORR analyses

- Per Protocol Set (PPS):

Patients without major protocol deviations relevant to efficacy, including but not limited to incorrect eligibility, missing baseline assessments, incorrect treatment, or insufficient exposure. PPS was used for sensitivity analyses of the primary endpoint.

- Safety Set:

The Safety Set included all patients who received at least one administration of any protocol-specified treatment (nivolumab as investigational medicinal product, and background therapy with GemOx ± rituximab, depending on cohort). This population was used for all safety analyses.

- General analytical principles:

All time-to-event endpoints (PFS, OS, EFS, DoR) were analyzed using Kaplan–Meier methodology. Median survival times and 95% confidence intervals were estimated using the Brookmeyer–Crowley method.
Between-arm comparisons were conducted using stratified log-rank tests according to SAP-prespecified stratification factors (primary refractory vs relapse, IPI category, age group).
Hazard ratios and 95% confidence intervals were estimated using stratified Cox proportional hazards models.
Binary endpoints (ORR, CR, PR, BOR) were summarized using proportions, exact two-sided 95% confidence intervals (Clopper–Pearson), and between-arm comparisons via the Cochran–Mantel–Haenszel (CMH) test.
No imputation of missing data was performed. Patients with missing post-baseline tumor assessments were counted as non-responders in ORR analyses.
Censoring rules for time-to-event analyses

- PFS:
  Patients without progression or death were censored at the date of last tumor assessment. Patients receiving subsequent anticancer therapy before documented progression were censored at the last progression-free assessment before new therapy.

- DoR:
  Measured only in responders (CR or PR). Censored at last tumor assessment for patients without progression, death, or start of next therapy.
- OS:
  Patients alive at data cutoff were censored at the last known date alive.
- EFS:
  Events included progression, death, or start of new anticancer treatment. Patients without events were censored at last assessment.

Subgroup analyses:
Prespecified subgroup analyses (PFS, ORR, OS) included:
age group, primary refractory vs relapsed disease, IPI category, LDH level, extranodal involvement, ECOG performance status, presence of B-symptoms, bone marrow involvement, and dosing subgroup (no-flat, switch, flat-dose).
Estimates were presented using forest plots, with hazard ratios and 95% confidence intervals.
Multiplicities
No adjustments for multiplicity were performed for secondary endpoints; these analyses are descriptive in nature.
Software
All statistical analyses were performed using IBM SPSS Statistics, R, and KM-Win, as prespecified in the SAP.

12.4.2 Progression-Free Survival (Primary Endpoint)

Progression-free survival (PFS) was analysed according to the SAP-defined methodology. PFS was defined as the time from randomisation to the first occurrence of disease progression or death from any cause. Patients without an event were censored at the date of their last tumour assessment. No imputation of missing or incomplete data was performed.

B-cell cohort
In the B-cell cohort, 1- year PFS was 27% *(95 KI: 15%; 29%) after R-GemOx and 23% (95% KI; 16%; 30%) after R-GemOx + Nivolumab. The Kaplan–Meier curves of both treatment arms showed no clinically meaningful or sustained separation throughout follow-up (Figure 43). The overall curve shapes and early event dynamics were comparable, with no consistent differences in the timing of progression or death. The censoring pattern appeared balanced across arms, with no indication of differential loss to follow-up.
The distribution of PFS events is summarised in Table 35**.**
Multivariable Cox regression adjusted for prespecified prognostic factors—including IPI-based risk components, sex, duration of prior response, and type of treatment failure—did not identify the treatment arm as an independent predictor of PFS, but duration of response<= 12 months and IPI 3-5 (Table 36).
Exploratory subgroup analyses based on Kaplan–Meier curves did not identify any subgroup with a consistent advantage for the nivolumab-containing regimen. Observed effects were heterogeneous and exploratory (Figure 44-52).

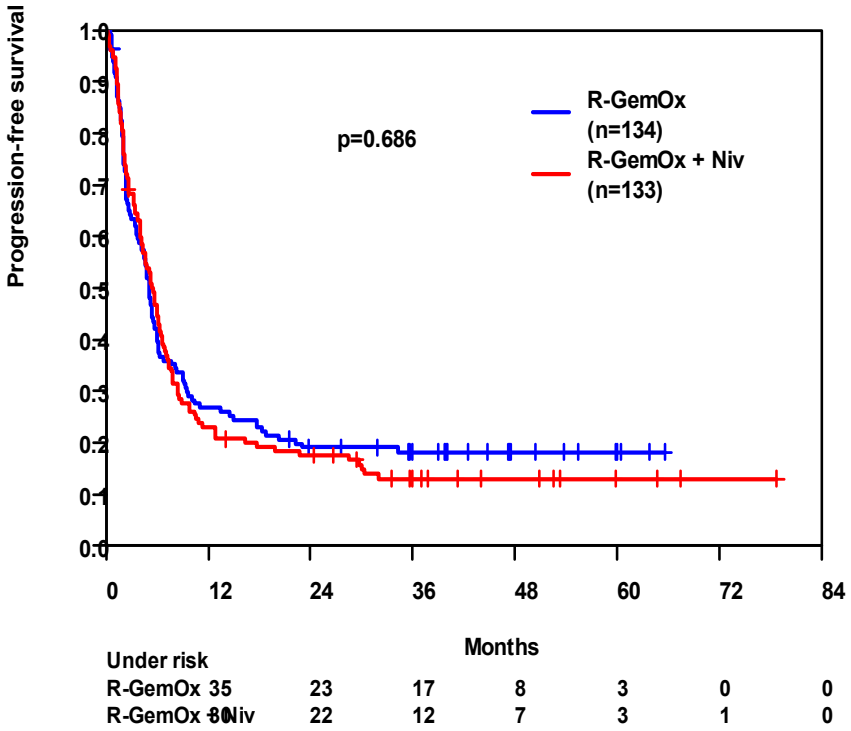


Figure 44: Progression-free survival, FAS, B-cell cohort (n=267)

Table 35: PFS event, FAS, B-cell cohort (n=267)

Events for PFS	R-GemOx (n=134)	R-GemOx + Niv (n=133)	Total (n=267)
Censored:			
CR/PR/SD/unknown and no progression/relapse, no death	27 (20%)	20 (15%)	47 (18%)
With event:			
Progression	85 (63%)	77 (58%)	162 (61%)
Relapse as earliest event	12 (9%)	16 (12%)	28 (10%)
Death as earliest event	10 (7%)	20 (15%)	30 (11%)

Table 36: Multivariate analysis, PFS – adjusted for strata, FAS, B-cell cohort (n=267)

Factor	HR	p-value	95% CI
8xGemOx + Niv vs. 8xGemOx	0.7	0.139	(0.4; 1.1)
Duration of first response <=12 vs. > 12 months	1.8	0.039	(1.0; 3.0)
IPI score 3-5 vs. 0-2	2.0	0.014	(1.1; 3.4)

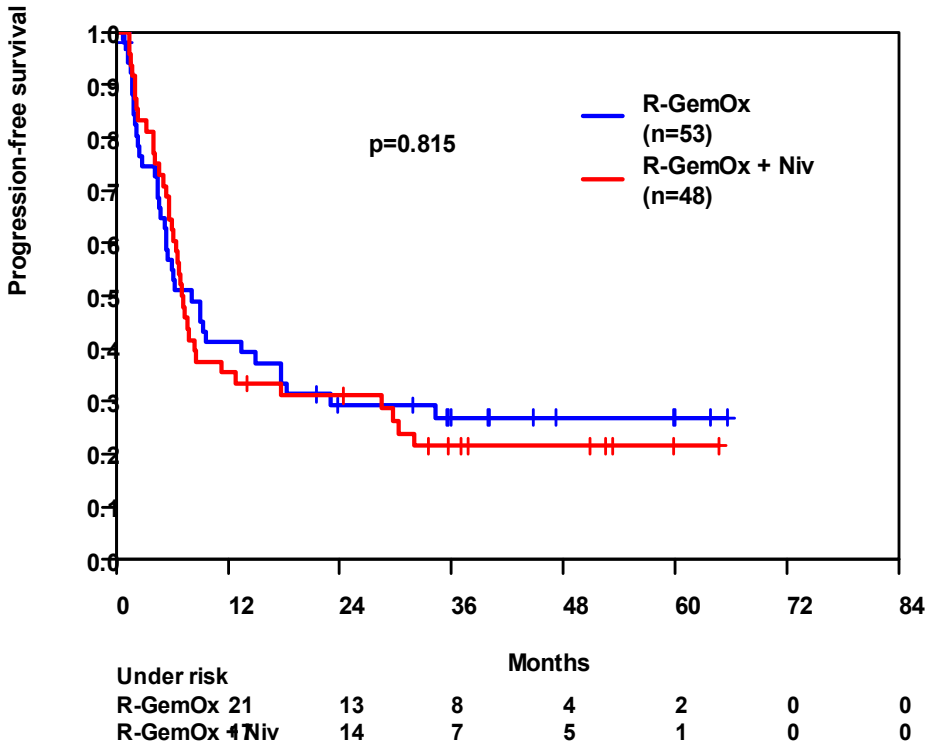


Figure 45: Progression-free survival, FAS, B-cell cohort, IPI 0-2 (n=101)

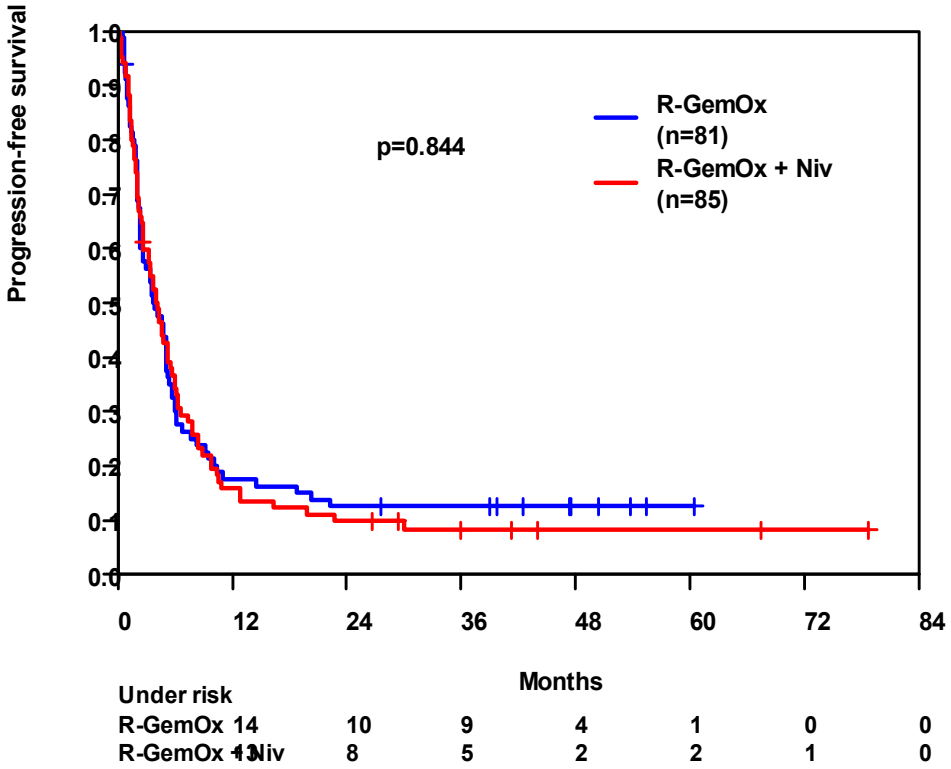


Figure 46: Progression-free survival, FAS, B-cell cohort, IPI 3-5 (n=166)

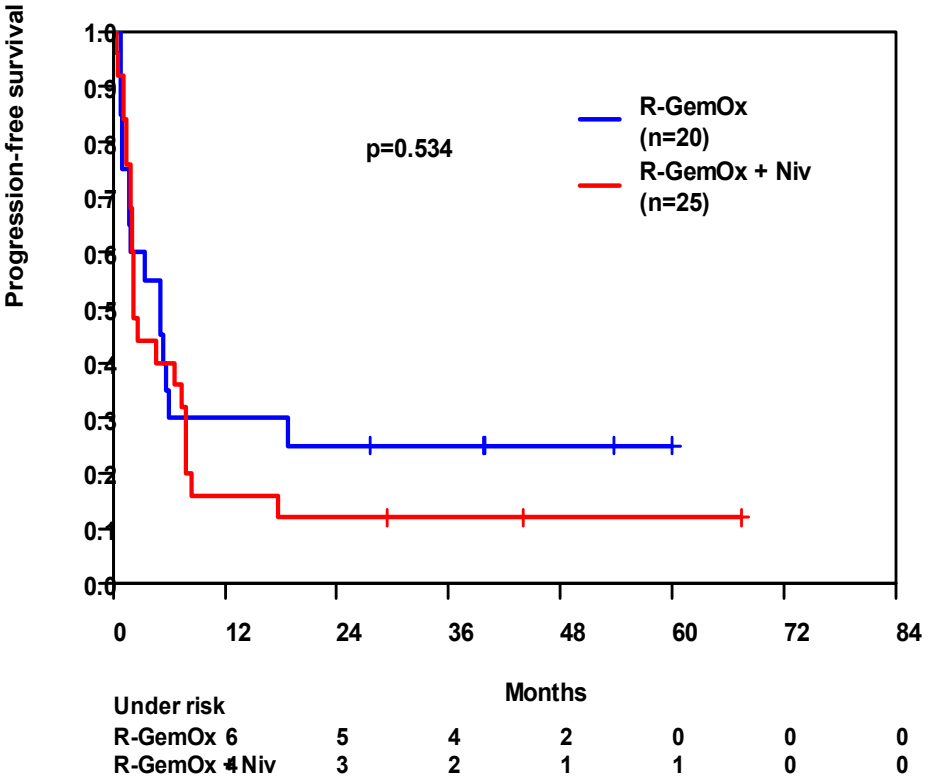


Figure 47: Progression-free survival, FAS, B-cell cohort, Age ≤ 70 (n=45)

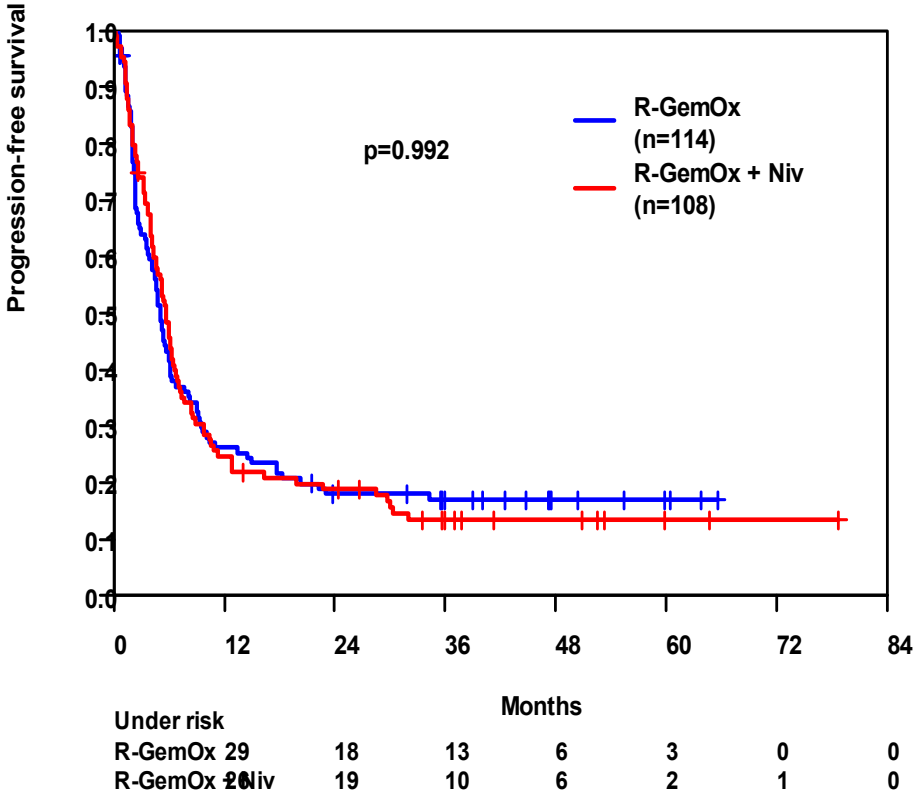


Figure 48: Progression-free survival, FAS, B-cell cohort, Age > 70 (n=222)

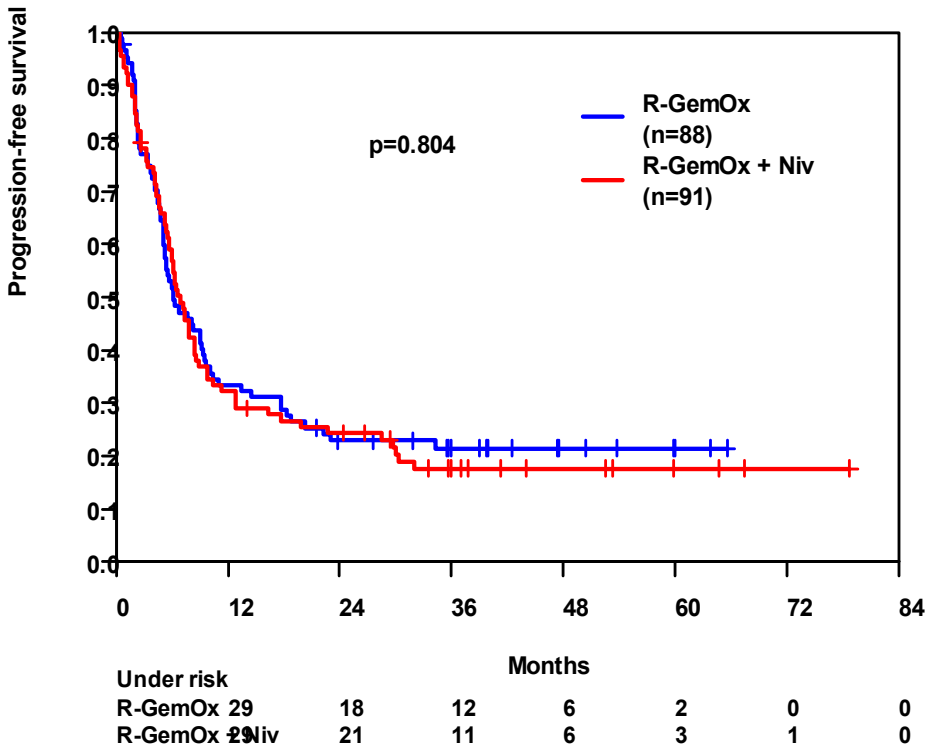


Figure 49: Progression-free survival, FAS, B-cell cohort, Failure: Relapse (n=179)

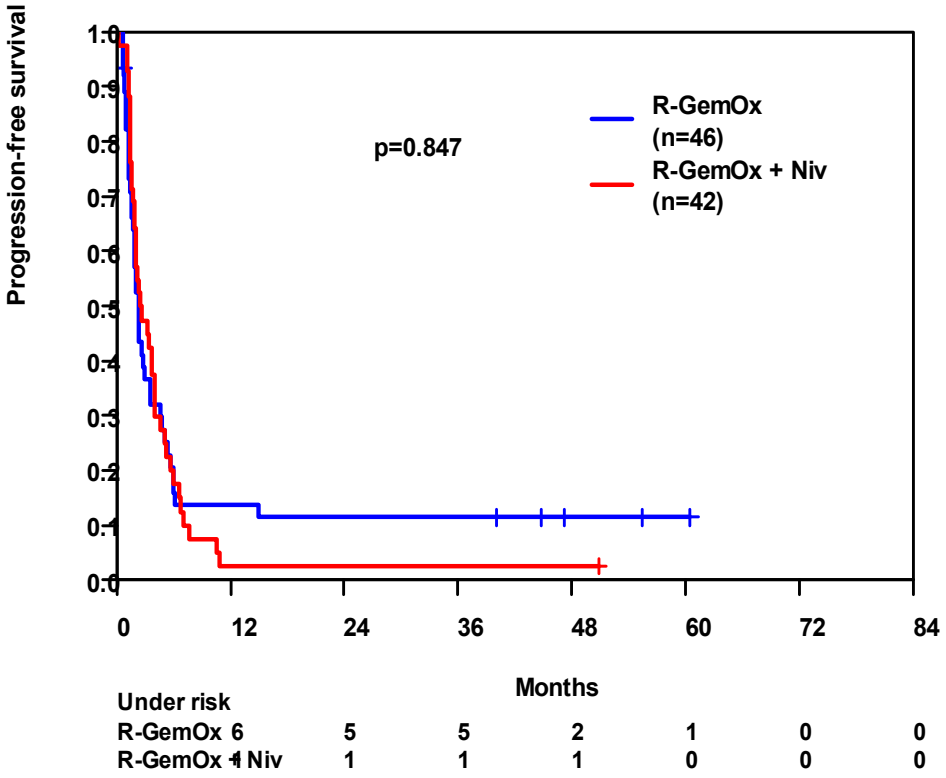


Figure 50: Progression-free survival, FAS, B-cell cohort, Failure: Primary progression (n=88)

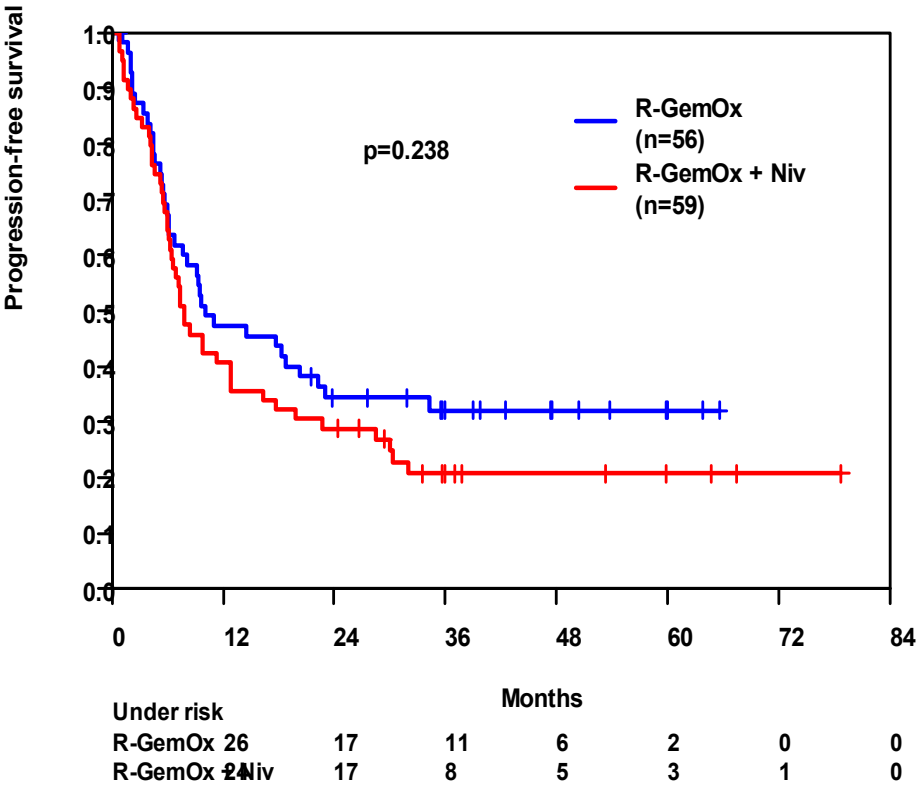


Figure 51: Progression-free survival, FAS, B-cell cohort, Duration of first response > 12 months (n=115)

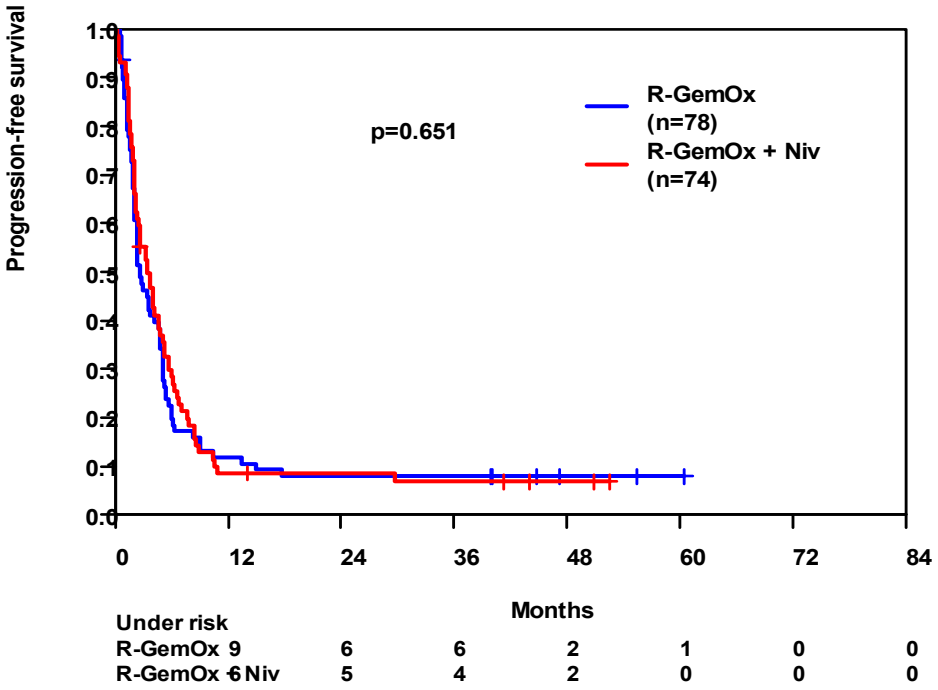


Figure 52: Progression-free survival, FAS, B-cell cohort, Duration of first response ≤ 12 months (n=152)

In the T-cell cohort, 1- year PFS was 9% (95% KI: 0% - 18%) after GemOx and 17% (95% KI: 6% - 29%) after GemOx + Nivolumab. The Kaplan–Meier curves demonstrated early events in both treatment arms, consistent with the dismal prognosis of relapsed/refractory PTCL (Figure 53). No prolonged or clinically meaningful separation was observed during follow-up. Early PFS events occurred in both treatment arms but were driven by different underlying reasons, including early disease progression as well as treatment-related toxicity.

PFS event distribution is presented in Table 37**.**
Multivariable Cox regression analyses did not indicate a treatment effect on PFS but duration of response<= 12 montahs and IPI 3-5 (Table 45). Exploratory subgroup analyses based on Kaplan–Meier curves did not identify any subgroup with a consistent advantage for the nivolumab-containing regimen. Observed effects were heterogeneous and exploratory. Figure 54-61

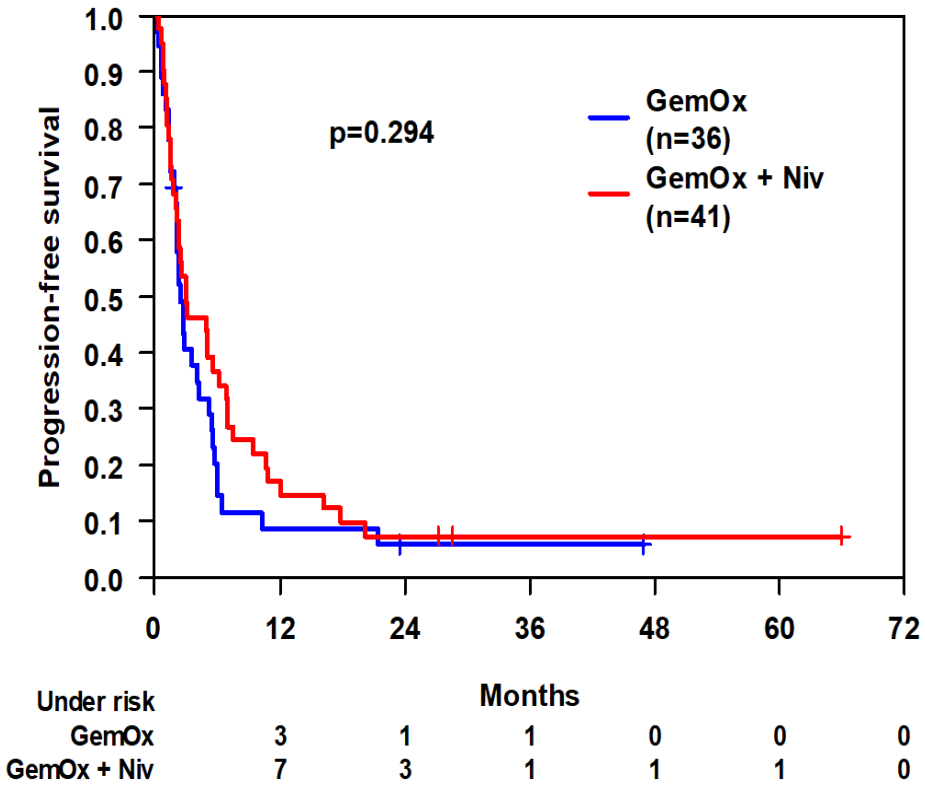


Figure 53: Progression-free survival, FAS, T-cell cohort (n=77)

Table 37: PFS event, FAS, T-cell cohort (n=77)

Events for PFS	GemOx (n=36)	GemOx + Niv (n=41)	Total (n=77)
Censored:			
CR/PR/SD/unknown and no progression/relapse, no death	3 (8%)	3 (7%)	6 (8%)
With event:			
Progression	29 (81%)	24 (59%)	53 (69%)
Relapse as earliest event	0 (0%)	3 (7%)	3 (4%)
Death as earliest event	4 (11%)	11 (27%)	15 (19%)

Table 38: Multivariate analysis, PFS – adjusted for strata, FAS, T-cell cohort (n=77)

Factor	HR	p-value	95% CI
8xGemOx + Niv vs. 8xGemOx	0.7	0.139	(0.4; 1.1)
Duration of first response <=12 vs. > 12 months	1.8	0.039	(1.0; 3.0)
IPI score 3-5 vs. 0-2	2.0	0.014	(1.1; 3.4)

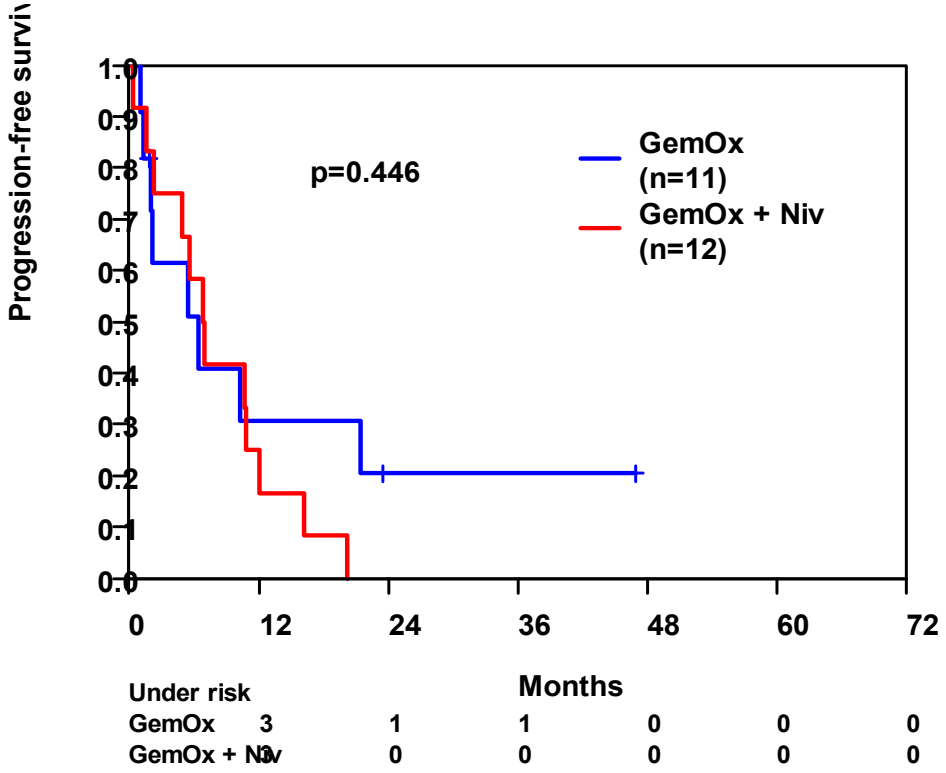


Figure 54: Progression-free survival, FAS, T-cell cohort, IPI 0-2 (n=23)

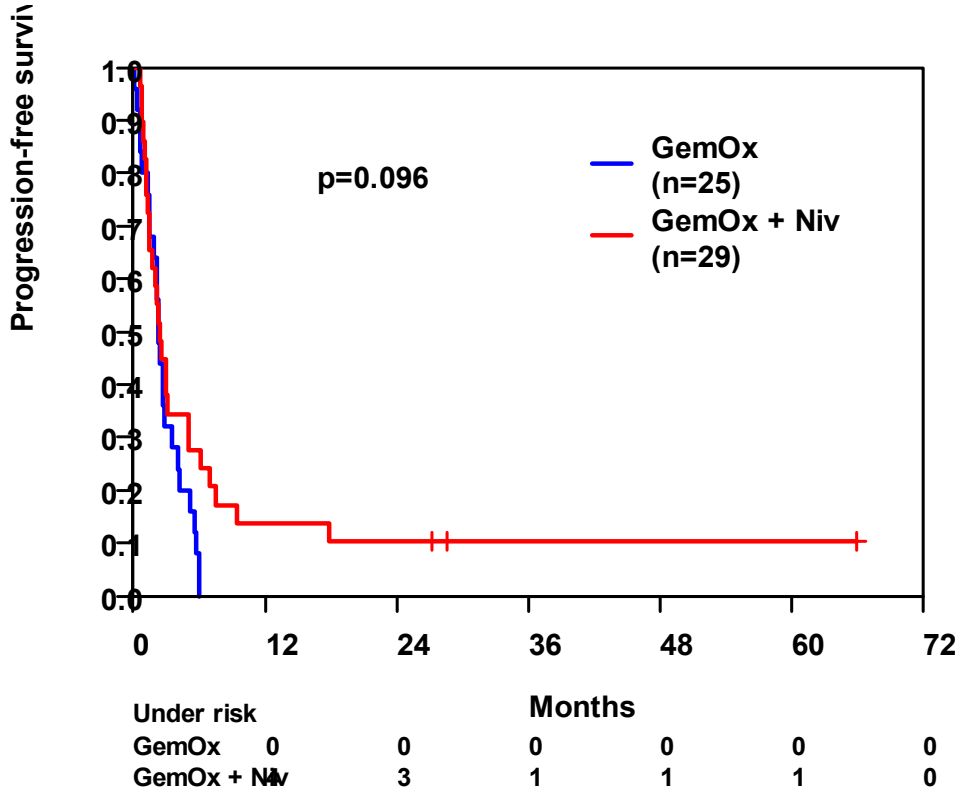


Figure 55: Progression-free survival, FAS, T-cell cohort, IPI 3-5 (n=54)

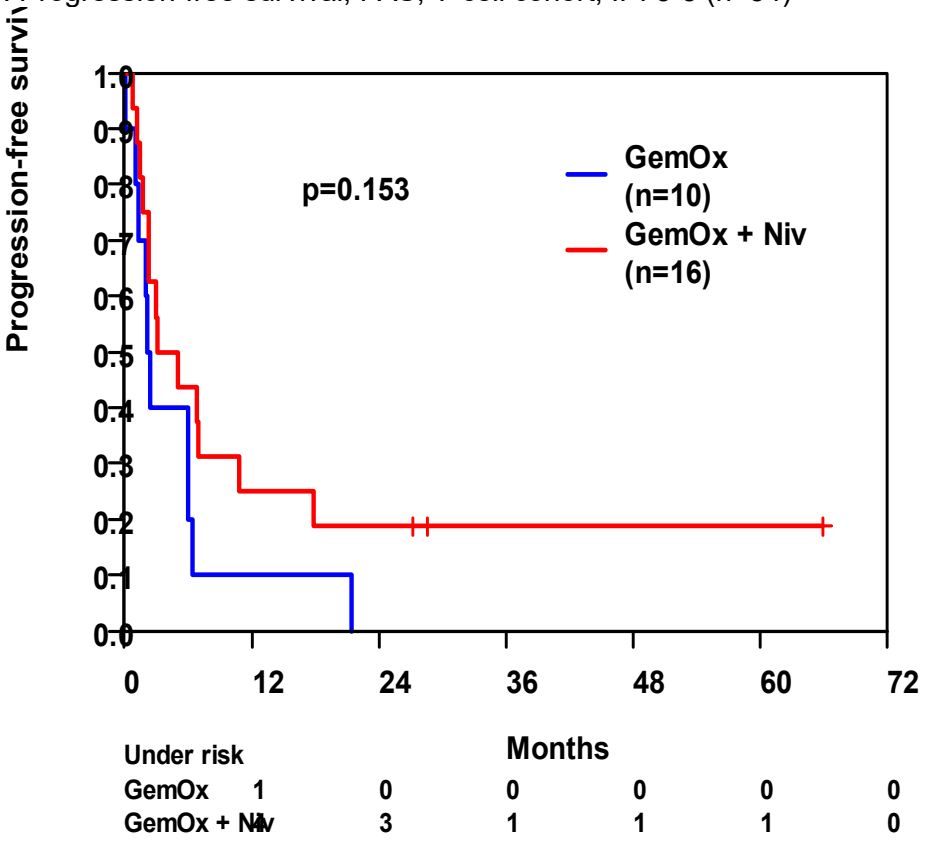


Figure 56: Progression-free survival, FAS, T-cell cohort, Age ≤ 70 (n=26)

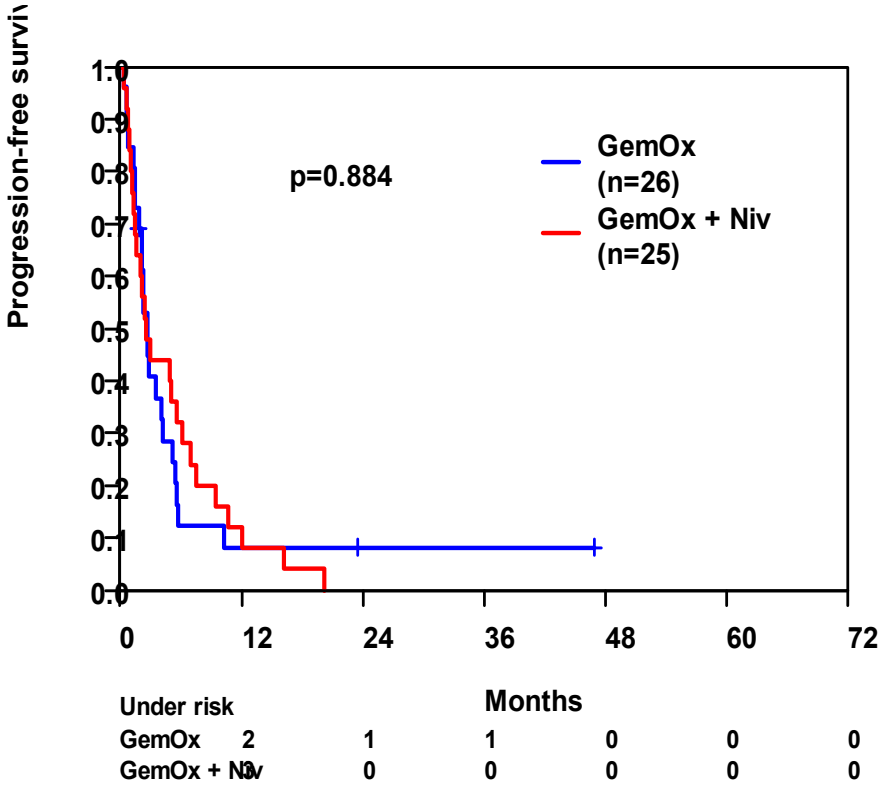


Figure 57: Progression-free survival, FAS, T-cell cohort, Age > 70 (n=51)

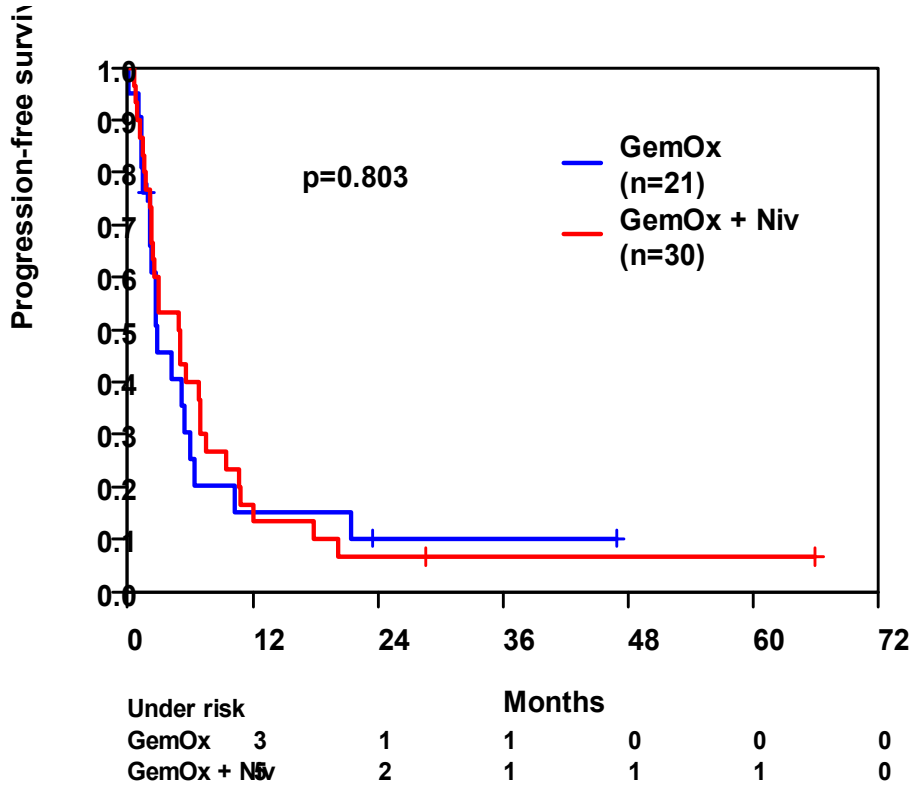


Figure 58: Progression-free survival, FAS, T-cell cohort, Failure: Relapse (n=51)

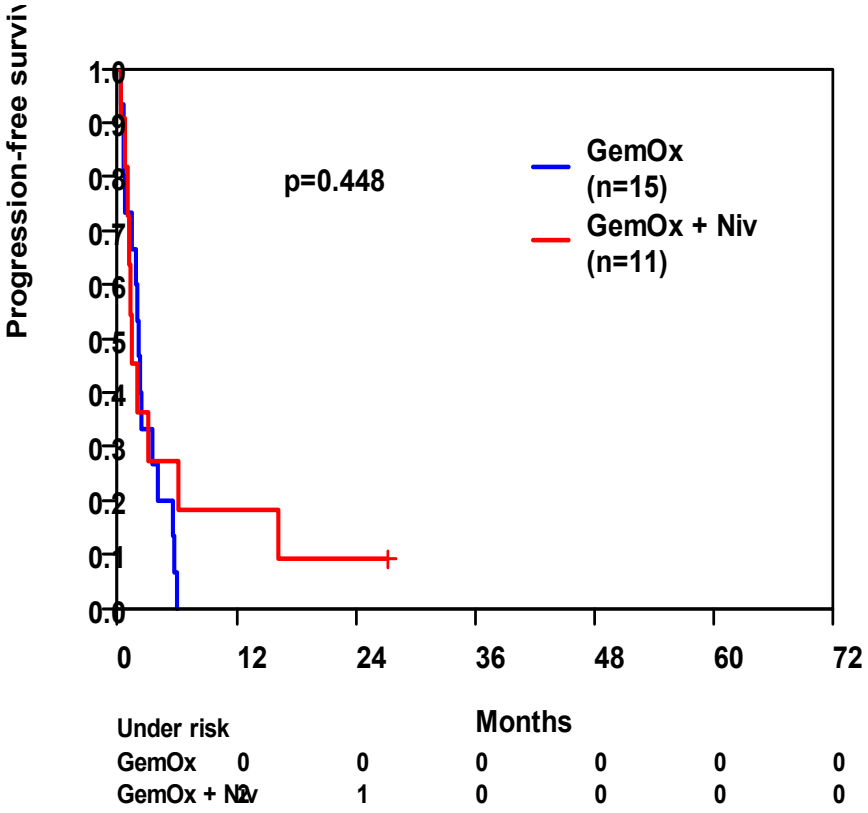


Figure 59:Progression-free survival, FAS, T-cell cohort, Failure: Primary progression (n=26)

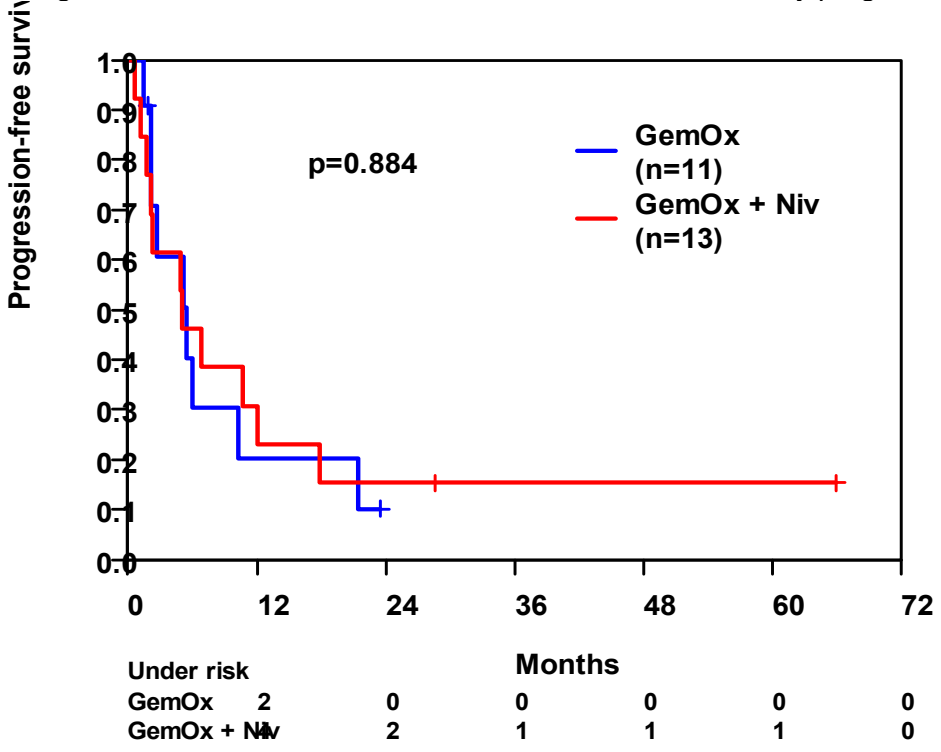


Figure 60: Progression-free survival, FAS, T-cell cohort, Duration of first response > 12months (n=24)

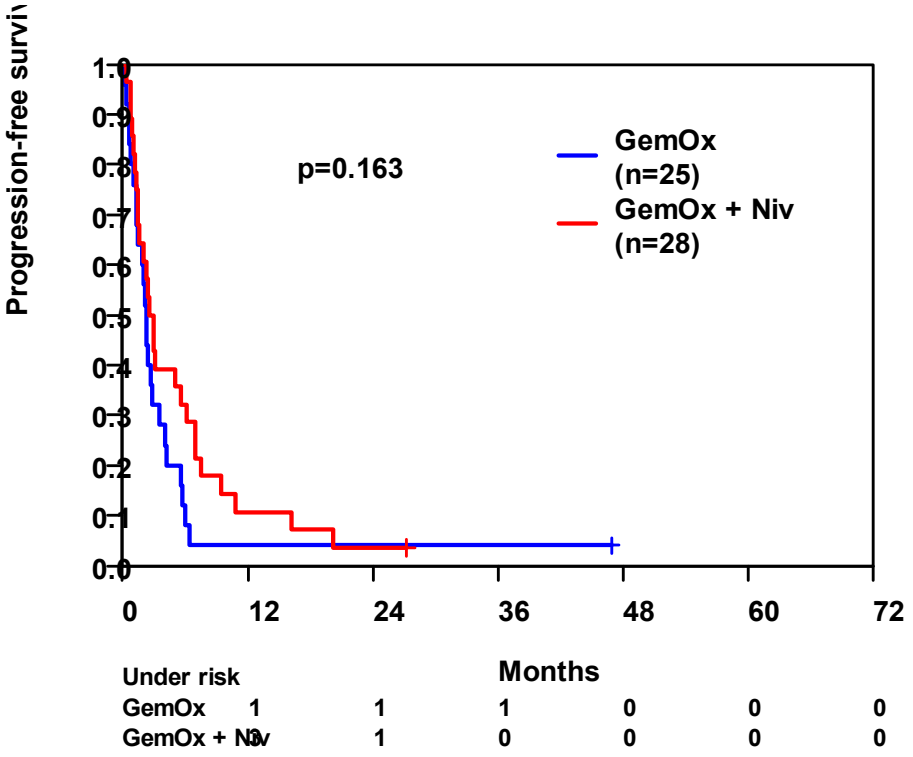


Figure 61: Progression-free survival, FAS, T-cell cohort, Duration of first response ≤ 12 months (n=53)

12.4.3 Analysis PFS1/PFS2 ratio

The ratio of PFS during study treatment to PFS following first-line therapy was analyzed descriptively in the T-cell cohort. PFS of first diagnosis was defined as the time from the start date of first-line treatment to the first documented disease assessment. Missing dates were imputed according to predefined rules. Due to differences in baseline characteristics and treatment context, PFS of first diagnosis is not comparable between treatment arms.

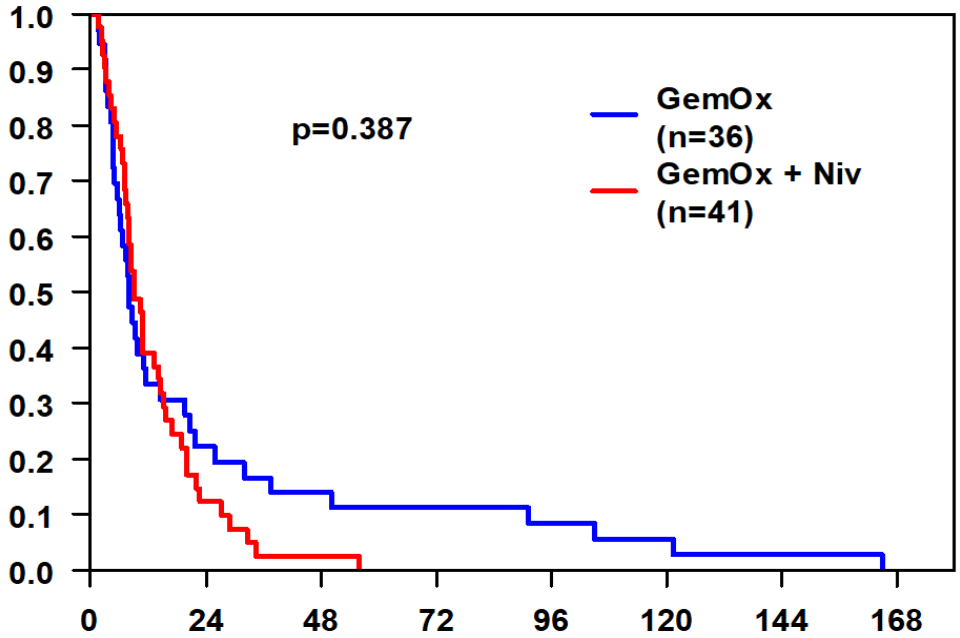


Figure 62: PFS of first line treatment (FLT), FAS, T-cell cohort (n=77)

Table 39: Ratio of PFS versus PFS of first diagnosis, FAS, T-cell cohort (n=77)

Ratio of PFS versus PFS of first diagnosis	GemOx (n=36)		GemOx + Niv (n=41)	
	n (%)	Cumulative %	n (%)	Cumulative %
> 0 & ≤ 0.2	15 (42%)	42	12 (29%)	29
> 0.2 & ≤ 0.4	8 (22%)	64	11 (27%)	56
> 0.4 & ≤ 0.6	3 (8%)	72	1 (2%)	59
> 0.6 & ≤ 0.8	4 (11%)	83	6 (15%)	73
> 0.8 & ≤ 1.0	2 (6%)	89	4 (10%)	83
> 1.0 & ≤ 1.3	2 (6%)	94	2 (5%)	88
> 1.3	2 (6%)	100	5 (12%)	100
Range (min, max)	(0.01, 7.55)		(0.02, 5.24)	

Table 40: Patients without PFS event, FAS, T-cell cohort (n=6)

Study treatment	Reference pathology diagnosis	PFS of first diagnosis (months)	PFS (month)	Ratio of PFS versus PFS of first diagnosis
8xGemOx	Angioimmunoblastic T-cell lymphoma	6	47	7.55
3xGemOx (WIC)	Angioimmunoblastic T-cell lymphoma	20	2	0.09
8xGemOx	Peripheral T-cell lymphoma, NOS	165	24	0.14
8xGemOx + Niv + consolidation (n=18)	Material technically insufficient, diagnosis not possible	20	66	3.27
7xGemOx + Niv (Ex. tox.)	Peripheral T-cell lymphoma, NOS	33	29	0.87
8xGemOx + Niv + consolidation (n=18)	Angioimmunoblastic T-cell lymphoma	5	27	5.24

Table 41: Patients with ratio of PFS versus PFS of first diagnosis > 1, FAS, T-cell cohort (n=11)

Study treatment (GemOx)	Reference pathology diagnosis	PFS of first diagnosis (months)	PFS (month)	PFS event	Ratio of PFS versus PFS of first diagnosis
8xGemOx	Angioimmunoblastic T-cell lymphoma	5	6	PD	1.20
8xGemOx	Transformed MF (Mycosis fungoides)	5	6	PD	1.21
7xGemOx (PD)	Extranodal NK/T-cell lymphoma, nasal type	1	3	PD	2.33
8xGemOx	Angioimmunoblastic T-cell lymphoma	6	47	censored	7.55

Table 42: Patients with ratio of PFS versus PFS of first diagnosis > 1, FAS, T-cell (n=11)

Study treatment (GemOx + Niv)	Reference pathology diagnosis	PFS of first diagnosis (months)	PFS (month)	PFS event	Ratio of PFS versus PFS of first diagnosis
6xGemOx + Niv (PD)	PTCL, unclassifiable due to insufficient material	3	3	PD	1.02
8xGemOx + Niv + consolidation (n=14) (PD)	Transformed MF /CD30+ (Mycosis fungoides)	10	11	PD	1.05
8xGemOx + Niv + consolidation (n=18)	Angioimmunoblastic T-cell lymphoma	7	16	PD	2.37
6xGemOx (Ex. tox.) + 8xNiv + consolidation (n=18)	Angioimmunoblastic T-cell lymphoma	8	20	PD	2.50
8xGemOx + Niv + consolidation (n=18)	Material technically insufficient, diagnosis not possible	20	66	censored	3.27
8xGemOx + 5xNiv (Ex. tox.)	Angioimmunoblastic T-cell lymphoma	2	6	Death (unknown)	3.94
8xGemOx + Niv + consolidation (n=18)	Angioimmunoblastic T-cell lymphoma	5	27	censored	5.24

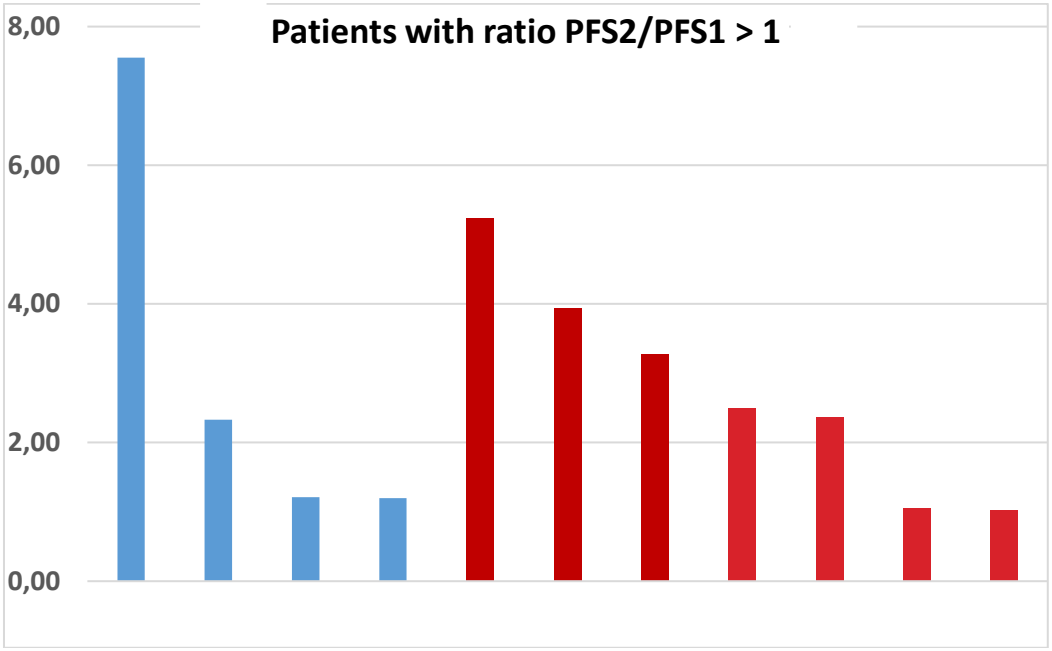


Figure 63: Patients with ratio PFS2/PFS1 > 1

Note: 6 patients without progression/death at data cut-off (GemOx n=3, GemOx + Nivolumab n=3)

*** Censored, no progression/death at data cut-off**

12.4.4 Response Rate

Tumor response was assessed according to the Lugano Classification (2014) as specified in the NIVEAU study protocol.

Complete Response (CR)

Complete response was defined as the complete disappearance of all clinical and radiological evidence of disease according to the Lugano criteria.

Partial Response (PR)

Partial response was defined as a reduction of at least 50% in the sum of the product of diameters of measurable lesions compared with baseline, without the appearance of new lesions or evidence of disease progression.

Overall Response Rate (ORR)

The overall response rate was defined as the proportion of patients achieving either a complete response or a partial response.

Stable Disease (SD)

Stable disease was defined as disease that did not meet the criteria for complete response, partial response, or progressive disease.

Progressive Disease (PD)

Progressive disease was defined as the appearance of new lesions or a significant increase in existing lesions consistent with disease progression according to the Lugano criteria.

Not Evaluable (NE)

Patients were classified as not evaluable if response assessment could not be performed due to missing or incomplete data.

Duration of Response (DoR)

The duration of response (DoR) was defined as the time from the date of first documented complete response (CR) or partial response (PR) until the date of disease progression, relapse, or death from any cause, whichever occurred first. Patients without a documented event at the time of analysis were censored at the date of the last adequate tumor assessment.

B-cell cohort

Response rates were evaluated in the **Full Analysis Set (FAS)** of the B-cell cohort and are summarized separately for the randomized treatment arms. Tumor response was assessed according to the Lugano Classification (2014) as defined in the study protocol.

Overall response rates, including complete and partial responses, were observed in both treatment groups. The distribution of response categories comprised complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE). Response outcomes are presented for all treated patients, irrespective of subsequent therapies.

Complete response rates were observed in both treatment arms, with additional analyses distinguishing between treated and untreated complete responses. Partial response rates were likewise documented and are reported separately. The overall response rate (ORR), defined as the proportion of patients achieving CR or PR, reflects the combined response activity of the respective treatment regimens.

Primary progression, defined as progressive disease as best response, was observed in a subset of patients. Treatment-related mortality and relapse after achieving complete response were additionally assessed and are summarized descriptively.

Response rates and related outcomes are provided in the corresponding tables 43-53, stratified by treatment arm, to allow a detailed evaluation of response patterns within the B-cell cohort.

Table 43: Response, FAS, B-cell cohort (n=267)

Response	R-GemOx (n=134)	R-GemOx + Niv (n=133)	Total (n=267)
Untreated CR	27 (20%)	27 (20%)	54 (20%)
CR and additional treatment	2 (1%)	2 (2%)	4 (1%)
Untreated PR	17 (13%)	15 (11%)	32 (12%)
PR and additional treatment	3 (2%)	1 (1%)	4 (1%)
Untreated SD	2 (1%)	11 (8%)	13 (5%)
SD and additional treatment	1 (1%)	1 (1%)	2 (1%)
PD	71 (53%)	60* (45%)	131 (49)
Untreated unknown	3 (2%)	0 (0%)	3 (1%)
Unknown and additional treatment	1 (1%)	2 (2%)	3 (1%)
Death (treatment related)	5 (4%)	10 (8%)	15 (6%)
Death (lymphoma ass.)	2 (1%)	4 (3%)	6 (2%)

Table 44: CR rates, FAS, B-cell cohort (n=267)

Therapy arm	CR rate	95% CI
R-GemOx (n=134)	29/134 (22%)	(15%; 30%)
R-GemOx + Niv (n=133)	29/133 (22%)	(15%; 30%)
Total (n=267)	58/267 (22%)	(17%; 27%)

Table 45: Untreated CR rates, FAS, B-cell cohort (n=267)

Therapy arm	untreated CR rate	95% CI
R-GemOx (n=134)	27/134 (20%)	(14%; 28%)
R-GemOx + Niv (n=133)	27/133 (20%)	(14%; 28%)
Total (n=267)	54/267 (20%)	(16%; 26%)

Table 46: PR rates, FAS, B-cell cohort (n=267)

Therapy arm	PR rate	95% CI
R-GemOx (n=134)	20/134 (15%)	(9%; 22%)
R-GemOx + Niv (n=133)	16/133 (12%)	(7%; 19%)
Total (n=267)	36/267 (13%)	(10%; 18%)

Table 47: Untreated PR rates, FAS, B-cell cohort (n=267)

Therapy arm	untreated PR rate	95% CI
R-GemOx (n=134)	17/134 (13%)	(8%; 20%)
R-GemOx + Niv (n=133)	15/133 (11%)	(6%; 18%)
Total (n=267)	32/267 (12%)	(8%; 16%)

Table 48: ORR rates, FAS, B-cell cohort (n=267)

Therapy arm	OR rate	95% CI
R-GemOx (n=134)	49/134 (37%)	(28%; 45%)
R-GemOx + Niv (n=133)	45/133 (34%)	(26%; 43%)
Total (n=267)	94/267 (35%)	(29%; 41%)

Table 49: Untreated ORR rates, FAS, B-cell cohort (n=267)

Therapy arm	untreated OR rate	95% CI
R-GemOx (n=134)	44/134 (33%)	(25%; 41%)
R-GemOx + Niv (n=133)	42/133 (32%)	(24%; 40%)
Total (n=267)	86/267 (32%)	(27%; 38%)

Table 50: Primary progression rates, FAS, B-cell cohort (n=267)

Therapy arm	PD rate	95% CI
R-GemOx (n=134)	71/134 (53%)	(44%; 62%)
R-GemOx + Niv (n=133)	60/133 (45%)	(36%; 54%)
Total (n=267)	131/267 (49%)	(43%; 55%)

Table 51: Treatment related mortality rates, FAS, B-cell cohort (n=267):

Therapy arm	TRM rate	95% CI
R-GemOx (n=134)	5/134 (4%)	(1%; 8%)
R-GemOx + Niv (n=133)	10/133 (8%)	(4%; 13%)
Total (n=267)	15/267 (6%)	(3%; 9%)

Table 52: Relapse after CR rates, FAS, B-cell cohort (n=267)

Therapy arm	Relapse after CR rate	95% CI
R-GemOx (n=134)	12/29 (41%)	(24%; 61%)
R-GemOx + Niv (n=133)	16/29 (55%)	(36%; 74%)
Total (n=267)	28/58 (48%)	(35%; 62%)

Table 53: Relapse after untreated CR rates, FAS, B-cell cohort (n=267)

Therapy arm	Relapse after untreated CR rate	95% CI
R-GemOx (n=134)	10/27 (37%)	(19%; 58%)
R-GemOx + Niv (n=133)	14/27 (52%)	(32%; 71%)
Total (n=267)	24/54 (44%)	(31%; 59%)

T-cell cohort

Response rates were evaluated in the **Full Analysis Set (FAS)** of the T-cell cohort and are summarized separately for the randomized treatment arms. Tumor response was assessed according to the Lugano Classification (2014) as defined in the study protocol.

The distribution of response categories included complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE). Response outcomes were assessed descriptively and are presented for all treated patients.

Complete responses were observed in both treatment arms. In addition, untreated complete responses were analyzed separately. Partial responses and untreated partial responses were likewise documented and are reported descriptively. The overall response rate (ORR), defined as the proportion of patients achieving either CR or PR, was evaluated for each treatment group.

Primary progression, defined as progressive disease as best response, was observed in a subset of patients. Furthermore, treatment-related mortality and relapse after achieving complete response, including relapse after untreated complete response, were assessed and summarized descriptively.

Detailed response outcomes for the T-cell cohort are provided in the corresponding tables 54-64.

Table 54: Response, FAS, T-cell cohort (n=77)

Response	GemOx (n=36)	GemOx + Niv (n=41)	Total (n=77)
Untreated CR	1 (3%)	5 (12%)	6 (8%)
CR and additional treatment	0 (0%)	0 (0%)	0 (0%)
Untreated PR	4 (11%)	8 (20%)	12 (16%)
PR and additional treatment	0 (0%)	1* (2%)	1 (1%)
Untreated SD	0 (0%)	1 (2%)	1 (1%)
SD and additional treatment	0 (0%)	1* (2%)	1 (1%)
PD	26 (72%)	15 (37%)	41 (53%)
Untreated unknown	1 (3%)	0 (0%)	1 (1%)
Unknown and additional treatment	0 (0%)	0 (0%)	0 (0%)
Death (treatment related)	3 (8%)	10 (24%)	13 (17%)
Death (lymphoma ass.)	1 (3%)	0 (0%)	1 (1%)

Table 55: CR rates, FAS, T-cell cohort (n=77)

Therapy arm	CR rate	95% CI
GemOx (n=36)	1/36 (3%)	(0%; 15%)
GemOx + Niv (n=41)	5/41 (12%)	(4%; 26%)
Total (n=77)	6/77 (8%)	(3%; 16%)

Table 56: Untreated CR rates, FAS, T-cell cohort (n=77)

Therapy arm	untreated CR rate	95% CI
GemOx (n=36)	1/36 (3%)	(0%; 15%)
GemOx + Niv (n=41)	5/41 (12%)	(4%; 26%)
Total (n=77)	6/77 (8%)	(3%; 16%)

Table 57: PR rates, FAS, T-cell cohort (n=77)

Therapy arm	PR rate	95% CI
GemOx (n=36)	4/36 (11%)	(3%; 26%)
GemOx + Niv (n=41)	9/41 (22%)	(11%; 38%)
Total (n=77)	13/77 (17%)	(9%; 27%)

Table 58: Untreated PR rates, FAS, T-cell cohort (n=77)

Therapy arm	untreated PR rate	95% CI
GemOx (n=36)	4/36 (11%)	(3%; 26%)
GemOx + Niv (n=41)	8/41 (20%)	(9%; 35%)
Total (n=77)	12/77 (16%)	(8%; 26%)

Table 59: ORR rates, FAS, T-cell cohort (n=77)

Therapy arm	OR rate	95% CI
GemOx (n=36)	5/36 (14%)	(5%; 29%)
GemOx + Niv (n=41)	14/41 (34%)	(20%; 51%)
Total (n=77)	19/77 (25%)	(16%; 36%)

Table 60: treated ORR rates, FAS, T-cell cohort (n=77)

Therapy arm	untreated OR rate	95% CI
GemOx (n=36)	5/36 (14%)	(5%; 29%)
GemOx + Niv (n=41)	13/41 (32%)	(18%; 48%)
Total (n=77)	18/77 (23%)	(15%; 34%)

Table 61: Primary progression rates, FAS, T-cell cohort (n=77)

Therapy arm	PD rate	95% CI
GemOx (n=36)	26/36 (72%)	(55%; 86%)
GemOx + Niv (n=41)	15/41 (37%)	(22%; 53%)
Total (n=77)	41/77 (53%)	(42%; 65%)

Table 62: Treatment related mortality rates, FAS, T-cell cohort (n=77)

Therapy arm	TRM rate	95% CI
GemOx (n=36)	3/36 (8%)	(2%; 22%)
GemOx + Niv (n=41)	10/41 (24%)	(12%; 40%)
Total (n=77)	13/77 (17%)	(9%; 27%)

Table 63: Relapse after CR rates, FAS, T-cell cohort (n=77)

Therapy arm	Relapse after CR rate	95% CI
GemOx (n=36)	0/1 (0%)	(0%; 98%)
GemOx + Niv (n=41)	3/5 (60%)	(15%; 95%)
Total (n=77)	3/6 (50%)	(12%; 88%)

Table 64: Relapse after untreated CR rates, FAS, T-cell cohort (n=77)

Therapy arm	Relapse after untreated CR rate	95% CI
GemOx (n=36)	0/1 (0%)	(0%; 98%)
GemOx + Niv (n=41)	3/5 (60%)	(15%; 95%)
Total (n=77)	3/6 (50%)	(12%; 88%)

12.4.5 Overall Survival (OS)

Overall survival (OS) was defined as the time from randomization to death from any cause, in accordance with the Statistical Analysis Plan (SAP). Patients alive at the data cutoff were censored at the date they were last known to be alive. No imputation of missing data was performed.

B-cell cohort

In the B-cell cohort, 1 year OS after R-GemOx was 51% (95% KI: 43% - 60%) and 58 % (95% KI: 49% - 66%) after R-GemOx+Nivolumab. The Kaplan–Meier curves of the two treatment arms (Figure 64) showed **no clinically relevant or sustained separation** throughout follow-up. The curve shapes and the timing of death events were comparable between arms, and the censoring distribution was balanced, with no indication of differential follow-up.

The distribution of deaths is summarised in Table 67 **(Cause of death, FAS)** and Table 68 **(Deaths within 2 months)**. These tables represent the OS event set for the B-cell cohort. The

PPS sensitivity analysis is presented in Table 65 with the corresponding survival curve in Figure 64.
Univariate (Table 67) and multivariate Cox regression analyses (Table 68) adjusted for predefined prognostic factors including IPI components, duration of prior response, type of treatment failure, and ECOG performance status—did **not identify the treatment arm as an independent predictor of OS but duration of reponse <=12 months and IPI 3-5**. Exploratory subgroup analyses showed no consistent advantage for the nivolumab-containing regimen.

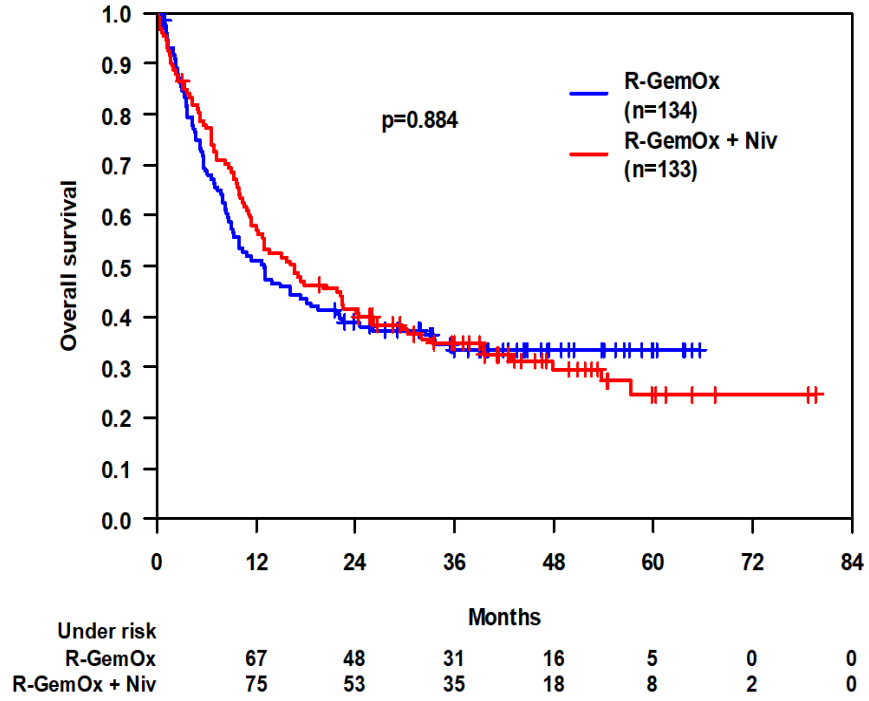


Figure 64: Overall survival, FAS, B-cell cohort (n=267)

Table 65: Cause of death, FAS, B-cell cohort (n=267)

Death	R-GemOx (n=134)	R-GemOx + Niv (n=133)	Total (n=267)
Number of deaths	**86 (64%)**	**90 (68%)**	**176 (66%)**
Lymphoma associated death	75 (87%)	65 (72%)	140 (80%)
Therapy related death due to NIVEAU therapy	6 (7%)	12 (13%)	18 (10%)
Therapy related death due to Salvage therapy	0 (0%)	2 (2%)	2 (1%)
Secondary neoplasia	0 (0%)	3 (3%)	3 (2%)
Other cause of death	4 (5%)	6 (7%)	10 (6%)
Unknown cause of death	1 (1%)	2 (2%)	3 (2%)

Table 66: Cause of death within 2 months after randomization, FAS, B-cell cohort (n=267)

Death within 2 months after randomization	R-GemOx (n=134)	R-GemOx + Niv (n=133)	Total (n=267)
Number of deaths	**9 (7%)**	**14 (11%)**	**23 (9%)**
Lymphoma associated death	7 (78%)	6 (43%)	13 (57%)
Therapy related death due to NIVEAU therapy	2 (22%)	7 (50%)	9 (39%)
Other cause of death	0 (0%)	1 (7%)	1 (4%)

Table 67: Univariate analysis, OS, FAS, B-cell cohort (n=267)

Factor	HR	p-value	95% CI
8xR-GemOx + Niv vs. 8xR-GemOx	1.0	0.884	(0.7; 1.3)

Table 68: Multivariate analysis, OS – adjusted for strata, FAS, B-cell cohort (n=267)

Factor	HR	p-value	95% CI
8xR-GemOx + Niv vs. 8xR-GemOx	1.0	0.742	(0.7; 1.3)
Duration of first response <=12 vs. > 12 months	2.7	<0.001	(2.0; 3.7)
IPI score 3-5 vs. 0-2	1.9	<0.001	(1.4; 2.6)

T-cell cohort

In the T-cell cohort, 1-year OS was 36% (95% KI: 20% - 52%) after GemOx and 42% (95% KI: 26% - 57%) after GemOx plus nivolumab. Early death events occurred frequently in both arms, Kaplan–Meier curves were largely overlapping, with no evidence of a sustained OS benefit with no evidence of improved OS in the nivolumab arm.

OS events are summarised in Table 69 (Cause of death, FAS) and Table 70 (Deaths within 2 months). Remarkably, there was a difference in causes of deaths. There were more lymphoma-associated deaths in the standard arm, 24 (83%) after GemOx compared to 20 (61%) after GemOx + nivolumab, respectively. Conversely, there were more therapy-related deaths in the experimental arm, 3 (8%) after GemOx compared to 10 (24%) after GemOx + nivolumab, respectively. 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. Response outcomes are described separately in the Response Rates section (see Tables 43-53). Overall survival was similar between treatment arms. A PPS

sensitivity analysis is provided in Table 69, with the corresponding Kaplan–Meier curve in Figure 65

Univariate (Table 71) and multivariate (Table 72) Cox regression analyses did not demonstrate a treatment effect. A higher International Prognostic Index (IPI) score was identified as an adverse prognostic factor for survival outcomes. Exploratory subgroup analyses did not identify any predefined patient subgroup with a consistent survival advantage. A trend towards inferior outcomes was observed in patients with a shorter duration of first response (≤12 months); however, this association did not reach statistical significance. Interpretation of these findings is limited by the small sample size.

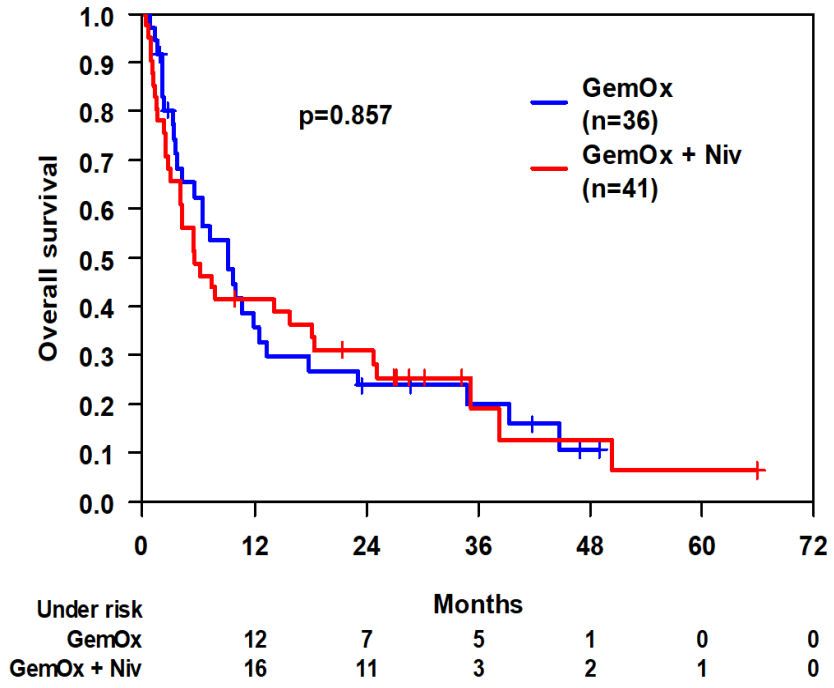


Figure 65: Overall survival, FAS, T-cell cohort (n=77)

Table 69: Cause of death, FAS, T-cell cohort (n=77)

Death	GemOx (n=36)	GemOx + Niv (n=41)	Total (n=77)
Number of deaths	**29 (81%)**	**33 (80%)**	**62 (81%)**
Lymphoma associated death	24 (83%)	20 (61%)	44 (71%)
Therapy related death due to NIVEAU therapy	3 (8%)	10 (24%)	13 (17%)
Therapy related death due to Salvage therapy	1 (3%)	1 (3%)	2 (3%)
Other cause of death	1 (3%)	1 (3%)	2 (3%)
Unknown cause of death	0 (0%)	1 (3%)	1 (2%)

Table 70: Cause of death within 2 months after randomization, FAS, T-cell cohort (n=77)

Death within 2 months after randomization	GemOx (n=36)	GemOx + Niv (n=41)	Total (n=77)
Number of deaths	**3 (8%)**	**9 (22%)**	**12 (16%)**
Lymphoma associated death	2 (67%)	3 (33%)	5 (42%)
Therapy related death due to NIVEAU therapy	1 (33%)	6 (67%)	7 (58%)

Table 71: Univariate analysis, OS, FAS, T-cell cohort (n=77)

Factor	HR	p-value	95% CI
8xGemOx + Niv vs. 8xGemOx	1.0	0.857	(0.6; 1.7)

Table 72: Multivariate analysis, OS – adjusted for strata, FAS, T-cell cohort (n=77)

Factor	HR	p-value	95% CI
8xGemOx + Niv vs. 8xGemOx	1.1	0.697	(0.7; 1.8)
Duration of first response <=12 vs. > 12 months	1.7	0.064	(1.0; 3.2)
IPI score 3-5 vs. 0-2	1.9	0.031	(1.1; 3.5)

12.4.6 Quality of Life (QoL, EQ-5D-5L)

Quality of life assessments (EQ-5D-5L) were prespecified in the protocol. However results are not available yet and will be presented subsequently.

12.4.7 Biomarker Analyses (PD-L1, PD-1, COO, 9p24.1)

Biomarker analyses (PD-L1 expression, PD-1 expression, cell-of-origin classification, or 9p24.1 alterations) were prespecified in the protocol. However results are not available yet and will be presented subsequently.

12.4.8 Statistical / Analytical Issues

All efficacy analyses were conducted according to the procedures defined in the Statistical Analysis Plan (SAP, Version 1.2). No deviations from the prespecified statistical methodology were implemented during the final evaluation. Analyses were primarily based on the Full Analysis Set (FAS), with supportive sensitivity analyses performed in the Per-Protocol Set (PPS) where applicable.
Time-to-event endpoints (PFS, OS, EFS, DoR) were analysed using Kaplan–Meier methodology. Median survival times and confidence intervals were estimated using the Brookmeyer–Crowley method. Stratified Cox proportional-hazards regression models were used for adjusted analyses, applying the stratification factors defined in the SAP (primary refractory vs. relapsed disease, IPI category, and age group). Proportional-hazards assumptions were assessed based on model diagnostics; no major violations were detected.
Binary endpoints (ORR, CR, PR, BOR) were analysed using exact two-sided 95% confidence intervals (Clopper–Pearson). Between-group comparisons were conducted using the Cochran–Mantel–Haenszel (CMH) test stratified by predefined factors. Missing post-baseline disease assessments were not imputed and were classified as non-response in accordance with the conservative analysis rules prespecified in the SAP.
For the T-cell cohort, the small cohort size (n=77; nivolumab arm n=41) limited the precision of survival estimates and the interpretability of subgroup analyses. As prespecified, these analyses are descriptive, and no adjustments for multiplicity were performed for secondary endpoints. The SAP did not prespecify modelling of treatment–covariate interactions, and no statistically meaningful interaction signals were observed in exploratory testing.
Sensitivity analyses were limited by sample size and the number of evaluable events. PPS analyses were consistent with FAS findings, with no indication of differential bias introduced by protocol deviations. An interim analysis of efficacy was performed after 180 of the planned 310 patients with B-cell lymphoma had been enrolled and was reviewed by the Data Safety Monitoring Committee (DSMC). No statistically relevant differences between treatment arms were identified, and there was no reason for premature termination of the study due to

superiority of one treatment arm. The interim analysis did not result in any modification of the final efficacy analysis.
All analyses were conducted using validated statistical software (R, IBM SPSS Statistics, and KM-Win), as prespecified.

12.4.9 Individual Patient Data Tabulations

All listings will be generated in accordance with the Statistical Analysis Plan and included in Appendix 16.4 **u**pon completion.

12.4.10 Dose/Concentration vs. Response

No pharmacokinetic (PK) or serum concentration data were collected in the NIVEAU study. Consequently, no exposure–response, dose–response, or concentration–response analyses were performed. All efficacy assessments were based solely on clinical response evaluations and time-to-event endpoints as defined in the protocol and SAP

12.4.11 Drug-drug and drug-disease interactions

No signs for drug-drug and drug-disease interactions were found.

12.4.12 Patient Profiles

Detailed patient profiles, including individual treatment courses, tumor assessments, censoring time points, and event histories, will be provided in the Appendix 16.2. These listings will allow verification of all aggregated efficacy outcomes reported in this section.

12.4.13 Efficacy Conclusion

Conclusions for efficacy are discussed for the V-cell and T-cell cohort separately.
B-cell cohort: 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 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.
T-cell cohort: 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 of first response assessment. 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. Thus, further studies of PD-1 antibodies warrant an effective control of toxicity.

13 SAFETY EVALUATION

13.1 **Analysis Set**

The Safety Analysis Set (SAS) comprised all patients who received at least one dose of any study treatment, including GemOx (± rituximab) and nivolumab where applicable. Safety analyses were conducted separately for the B-cell and T-cell cohorts and according to the randomized treatment arm. The SAS was similar in composition to the Full Analysis Set (FAS).

13.2 **Safety Endpoints**

Safety endpoints were evaluated descriptively according to the Statistical Analysis Plan (SAP). No inferential hypothesis testing was planned.
Assessed endpoints:

- Incidence of treatment-emergent adverse events (TEAEs)
- Grade ≥3 TEAEs
- Serious adverse events (SAEs)
- Treatment-related AEs
- AEs leading to dose reduction, delay, or discontinuation
- Immune-related adverse events (irAEs)
- Fatal adverse events (Grade 5)
- Laboratory abnormalities (hematology, chemistry)
- Vital signs and other clinically relevant safety observations

All safety analyses were performed in the SAS.

13.2.1 Primary Safety Endpoint

The primary safety assessment included the incidence, severity (CTCAE v5.0), seriousness, and causality of all TEAEs, SAEs, irAEs, and fatal AEs.
All events were assessed in the SAS.

13.2.2 Secondary Safety Endpoints

Secondary endpoints included the descriptive evaluation of:

- TEAE distribution by SOC and preferred term
- SAEs by SOC and PT
- Treatment-related AEs
- AEs causing treatment modification (delay, reduction, discontinuation)
- irAEs associated with PD-1 blockade
- Laboratory abnormalities
- Vital sign changes

13.3 **Extent of Exposure**

Exposure to study treatment was summarised descriptively based on the Safety Analysis Set (SAS), which includes all patients who received at least one dose of GemOx (± rituximab) and/or nivolumab. Treatment exposure was reviewed separately for the B-cell and T-cell cohorts and is documented in the corresponding graphical summaries provided in Section 12.
For the **B-cell cohort**, exposure included:

- number of GemOx induction cycles administered,
- number and timing of nivolumab administrations during induction (q2w),
- number of nivolumab administrations during consolidation: at the beginning of the study, consolidation nivolumab was administered every 2 weeks (q2w); later in the study, the consolidation schedule was changed to 480 mg every 4 weeks (q4w).
- total treatment duration for chemotherapy and immunotherapy,
- absolute and relative cumulative doses of gemcitabine, oxaliplatin, rituximab, and nivolumab,
- treatment interruptions or delays attributed to toxicity, infections, or logistical factors.

For the T-cell cohort, exposure is summarised analogously and includes:

- number and timing of GemOx cycles,
- nivolumab exposure during induction (absolute and relative dose),
- nivolumab exposure during consolidation (administered q2w at study start; later changed to 480 mg q4w) overall treatment duration and cumulative administered doses.

Across both cohorts, most patients received treatment in accordance with protocol-specified schedules. Deviations from planned dosing intervals were generally consistent with expected clinical circumstances and were not indicative of systematic issues.

13.4 Adverse Events and Serious Adverse Events

13.4.1 Adverse Events (AEs)

Analyses are presented separately for the B-cell and T-cell cohorts and stratified by treatment phase (GemOx ± nivolumab induction; nivolumab consolidation).

Summary of Adverse Events

Across both cohorts, hematologic toxicities were the most frequent CTCAE Grade 3–5 events during induction with GemOx ± nivolumab. Non-hematologic toxicities occurred infrequently. Nivolumab consolidation showed a favorable safety profile in both cohorts, with very few Grade ≥3 events and no unexpected immune-related toxicities (irAEs).

The T-cell cohort demonstrated a higher frequency of immunologically driven adverse events, particularly hepatobiliary and immune-mediated SOC categories, whereas the B-cell cohort exhibited a more pronounced chemotherapy-driven toxicity profile, especially thrombocytopenia and leukopenia.

Isolated Grade 5 AEs occurred in both cohorts but without clustering or any indication of treatment-related safety signals.

13.4.2 Display of adverse events

Displays of adverse events are maintained together with the clinical database at the Institute for Medical Informatics, Statistics and Epidemiology (IMISE), University of Leipzig, Germany. All AE tables and figures are included in Appendix 16.4.

Grade 3-5 adverse events for each treatment phase and cohort are summarised in the following tables and figures:

B-cell cohort — Induction (R-GemOx ± Nivolumab): Table 73–76
B-cell cohort — Nivolumab consolidation: Table 77-80
T-cell cohort — Induction (GemOx ± Nivolumab): Table 66–69
T-cell cohort — Nivolumab consolidation: Table 81-84
(All referenced tables and figures are provided in Appendix 16.4.)

Table 73: Adverse events grade 3-5 during R-GemOx ± Niv I, FAS, B-cell cohort (n=267)

Event	Number of cycles with CTC grade 3-5 / number of documented cycles		
	R-GemOx (n=749)	R-GemOx + Niv (n=775)	Total (n=1524)
Nausea	8/748 (1%)	10/773 (1%)	18/1521 (1%)
Anemia	44/748 (6%)	56/773 (7%)	100/1521 (7%)
Platelet count decreased	109/748 (15%)	97/773 (13%)	206/1521 (14%)
White blood cell decreased	47/748 (6%)	56/772 (7%)	103/1520 (7%)
Vomitting	4/748 (0.5%)	5/775 (1%)	9/1523 (1%)
Diarrhea	10/749 (1%)	7/774 (1%)	17/1523 (1%)
Constipation	1/748 (0.1%)	0/774 (0%)	1/1522 (0.1%)
Mucositis oral	0/748 (0%)	1/774 (0.1%)	1/1522 (0.1%)
Peripheral sensory neutropathy	8/748 (1%)	15/774 (2%)	23/1522 (2%)

Table 74: Adverse events grade 3-5 during R-GemOx ± Niv II, FAS, B-cell cohort (n=267)

Event	Number of cycles with CTC grade 3-5 / number of documented cycles		
	R-GemOx (n=749)	R-GemOx + Niv (n=775)	Total (n=1524)
Infection*	26/748 (3%)	40/775 (5%)	66/1523 (4%)
Fatigue	19/747 (3%)	5/774 (1%)	24/1521 (2%)
Pruritus	0/748 (0%)	3/774 (0.4%)	3/1522 (0.2%)
Rash	0/747 (0%)	2/774 (0.3%)	2/1521 (0.1%)
Lipase increased	67/663 (10%)	93/701 (13%)	160/1364 (12%)
Arthralgia	1/748 (0.1%)	4/774 (0.5%)	5/1522 (0.3%)
Amylase increased	9/587 (2%)	21/632 (3%)	30/1219 (2%)
Hyperglycemia	4/707 (1%)	2/707 (0.3)	6/1414 (0.4%)
Cough	0/747 (0%)	1/772 (0.1%)	1/1519 (0.1%)

Table 75: Adverse events grade 3-5 during R-GemOx ± Niv III, FAS, B-cell cohort (n=267)

Event	% of patients with CTC grade 3-5		
	R-GemOx (n=134)	R-GemOx + Niv (n=133)	Total (n=267)
Nausea	7/133 (5%)	8/133 (6%)	15/266 (6%)
Anemia	27/133 (20%)	28/133 (21%)	55/266 (21%)
Platelet count decreased	54/133 (41%)	49/133 (37%)	103/266 (39%)
White blood cell decreased	24/133 (18%)	31/133 (23%)	55/266 (21%)
Vomitting	4/133 (3%)	5/133 (4%)	9/266 (3%)
Diarrhea	8/134 (6%)	7/133 (5%)	15/267 (6%)
Constipation	1/133 (1%)	0/133 (0%)	1/266 (0.4%)
Mucositis oral	0/133 (0%)	1/133 (1%)	1/266 (0.4%)
Peripheral sensory neutropathy	6/133 (5%)	6/133 (5%)	12/266 (5%)

Table 76: Adverse events grade 3-5 during R-GemOx ± Niv IV, FAS, B-cell cohort (n=267)

Event	% of patients with CTC grade 3-5		
	R-GemOx (n=134)	R-GemOx + Niv (n=133)	Total (n=267)
Infection*	23/133 (17%)	30/133 (23%)	53/266 (20%)
Fatigue	10/132 (8%)	5/133 (4%)	15/265 (6%)
Pruritus	0/133 (0%)	2/133 (2%)	2/266 (1%)
Rash	0/133 (0%)	1/133 (1%)	1/266 (0.4%)
Lipase increased	27/129 (21%)	28/125 (22%)	55/254 (22%)
Arthralgia	1/133 (1%)	2/133 (2%)	3/266 (1%)
Amylase increased	5/118 (4%)	10/122 (8%)	15/240 (6%)
Hyperglycemia	3/130 (2%)	2/131 (2%)	5/261 (2%)
Cough	0/133 (0%)	1/133 (1%)	1/266 (0.4%)

Table 77: Adverse events grade 3-5 during Nivolumab consolidation I, FAS, B-cell cohort (n=57)

Event	Number of cycles with CTC grade 3-5 / number of documented cycles		
	14 days (n=277)	28 days (n=140)	Total (n=417)
Nausea	0/276 (0%)	0/140 (0%)	0/416 (0%)
Anemia	2/276 (1%)	0/140 (0%)	2/416 (0.5%)
White blood cell decreased	9/276 (3%)	1/140 (1%)	10/416 (2%)
Lymphocyte count decreased	26/274 (9%)	8/140 (6%)	34/414 (8%)
Neutrophilic count decreased	11/273 (4%)	1/140 (1%)	12/413 (3%)
Diarrhea	0/276 (0%)	0/140 (0%)	0/416 (0%)
Fatigue	0/275 (0%)	0/140 (0%)	0/415 (0%)
Pruritus	0/275 (0%)	0/140 (0%)	0/415 (0%)
Rash	0/276 (0%)	0/140 (0%)	0/416 (0%)

Table 78: Adverse events grade 3-5 during Nivolumab consolidation II, FAS, B-cell cohort (n=57)

Event	Number of cycles with CTC grade 3-5 / number of documented cycles		
	14 days (n=277)	28 days (n=140)	Total (n=417)
Infection	2/276 (1%)	0/140 (0%)	2/416 (0.5%)
Lipase increased	2/252 (1%)	6/124 (5%)	8/376 (2%)
Arthralgia	0/276 (0%)	0/140 (0%)	0/416 (0%)
Amylase increased	0/237 (0%)	0/127 (0%)	0/364 (0%)
Hyperglycemia	2/195 (1%)	0/137 (0%)	2/332 (1%)
Cough	0/275 (0%)	0/140 (0%)	0/415 (0%)

Table 79: Adverse events grade 3-5 during Nivolumab consolidation III, FAS, B-cell cohort (n=57)

Event	% of patients with CTC grade 3-5
	R-GemOx + Niv (n=57)
Nausea	0/57 (0%)
Anemia	2/57 (4%)
White blood cell decreased	6/57 (11%)
Lymphocyte count decreased	10/57 (18%)
Neutrophilic count decreased	5/57 (9%)
Diarrhea	0/57 (0%)
Fatigue	0/57 (0%)
Pruritus	0/57 (0%)
Rash	0/57 (0%)

Table 80: Adverse events grade 3-5 during Nivolumab consolidation IV, FAS, B-cell cohort (n=57)

Event	% of patients with CTC grade 3-5
	R-GemOx + Niv (n=57)
Infection	2/57 (4%)
Lipase increased	4/56 (7%)
Arthralgia	0/57 (0%)
Amylase increased	0/56 (0%)
Hyperglycemia	1/51 (2%)
Cough	0/57 (0%)

Table 81: Adverse events grade 3-5 during GemOx ± Niv I, FAS, T-cell cohort (n=77)

Event	Number of cycles with CTC grade 3-5 / number of documented cycles		
	GemOx (n=163)	GemOx + Niv (n=197)	Total (n=360)
Nausea	0/162 (0%)	1/197 (0.5%)	1/359 (0.3%)
Anemia	9/163 (6%)	43/197 (22%)	52/360 (14%)
Platelet count decreased	40/163 (25%)	68/197 (35%)	108/360 (30%)
White blood cell decreased	4/163 (2%)	30/197 (15%)	34/360 (9%)
Vomitting	0/162 (0%)	1/197 (0.5%)	1/359 (0.3%)
Diarrhea	0/162 (0%)	2/197 (1%)	2/359 (1%)
Constipation	0/162 (0%)	0/197 (0%)	0/359 (0%)
Mucositis oral	0/162 (0%)	2/197 (1%)	2/359 (1%)
Peripheral sensory neutropathy	0/162 (0%)	1/197 (0.5%)	1/359 (0.3%)

Table 82: Adverse events grade 3-5 during GemOx ± Niv II, FAS, T-cell cohort (n=77)

Event	Number of cycles with CTC grade 3-5 / number of documented cycles		
	GemOx (n=163)	GemOx + Niv (n=197)	Total (n=360)
Infection	8/163 (5%)	19/197** (10%)	27/360 (8%)
Fatigue	3/162 (2%)	13/197 (7%)	16/359 (4%)
Pruritus	0/162 (0%)	0/197 (0%)	0/359 (0%)
Rash	0/162(0%)	3/197* (2%)	3/359 (1%)
Lipase increased	10/151 (7%)	22/188 (12%)	32/339 (9%)
Arthralgia	0/162 (0%)	0/197 (0%)	0/359 (0%)
Amylase increased	6/124 (5%)	1/155 (1%)	7/279 (3%)
Hyperglycemia	0/152 (0%)	1/178 (1%)	1/330 (0.3%)
Cough	0/162 (0%)	0/197 (0%)	0/359 (0%)

Table 83: Adverse events grade 3-5 during GemOx ± Niv III, FAS, T-cell cohort (n=77)

Event	% of patients with CTC grade 3-5		
	GemOx (n=36)	GemOx + Niv (n=41)	Total (n=77)
Nausea	0/36 (0%)	1/41 (2%)	1/77 (1%)
Anemia	7/36 (19%)	18/41 (44%)	25/77 (32%)
Platelet count decreased	20/36 (56%)	25/41 (61%)	45/77 (58%)
White blood cell decreased	2/36 (6%)	12/41 (29%)	14/77 (18%)
Vomitting	0/36 (0%)	1/41 (2%)	1/77 (1%)
Diarrhea	0/36 (0%)	2/41 (5%)	2/77 (3%)
Constipation	0/36 (0%)	0/41 (0%)	0/77 (0%)
Mucositis oral	0/36 (0%)	2/41 (5%)	2/77 (3%)
Peripheral sensory neutropathy	0/36 (0%)	1/41 (2%)	1/77 (1%)

Table 84: Adverse events grade 3-5 during GemOx ± Niv IV, FAS, T-cell cohort (n=77)

Event	% of patients with CTC grade 3-5		
	GemOx (n=36)	GemOx + Niv (n=41)	Total (n=77)
Infection	5/36 (14%)	14/41** (34%)	19/77 (25%)
Fatigue	3/36 (8%)	9/41 (22%)	12/77 (16%)
Pruritus	0/36 (0%)	0/41 (0%)	0/77 (0%)
Rash	0/36 (0%)	2/41* (5%)	2/77 (3%)
Lipase increased	4/35 (11%)	12/40 (30%)	16/75 (21%)
Arthralgia	0/36 (0%)	0/41 (0%)	0/77 (0%)
Amylase increased	2/33 (6%)	1/37 (3%)	3/70 (4%)
Hyperglycemia	0/36 (0%)	1/40 (2%)	1/76 (1%)
Cough	0/36 (0%)	0/41 (0%)	0/77 (0%)

Table 85: Adverse events grade 3-5 during Nivolumab consolidation I, FAS, T-cell cohort (n=12)

Event	Number of cycles with CTC grade 3-5 / number of documented cycles
	GemOx + Niv (n=115)
Nausea	8/115 (7%)
Anemia	4/115 (3%)
White blood cell decreased	0/115 (0%)
Lymphocyte count decreased	3/115 (3%)
Neutrophilic count decreased	1/115 (1%)
Diarrhea	0/115 (0%)
Fatigue	0/115 (0%)
Pruritus	0/115 (0%)
Rash	0/115 (0%)

Table 86: Adverse events grade 3-5 during Nivolumab consolidation II, FAS, T-cell cohort (n=12)

Event	Number of cycles with CTC grade 3-5 / number of documented cycles
	GemOx + Niv (n=115)
Infection	0/115 (0%)
Lipase increased	0/102 (0%)
Arthralgia	0/115 (0%)
Amylase increased	0/80 (0%)
Hyperglycemia	0/91 (0%)
Cough	0/115 (0%)

Table 87: Adverse events grade 3-5 during Nivolumab consolidation III, FAS,

Event	% of patients with CTC grade 3-5
	GemOx + Niv (n=12)
Nausea	1/12 (8%)
Anemia	1/12 (8%)
White blood cell decreased	0/12 (0%)
Lymphocyte count decreased	1/12 (8%)
Neutrophilic count decreased	1/12 (8%)
Diarrhea	0/12 (0%)
Fatigue	0/12 (0%)
Pruritus	0/12 (0%)
Rash	0/12 (0%)

Table 88: Adverse events grade 3-5 during Nivolumab consolidation I, FAS, T-cell cohort(n=12)

Event	% of patients with CTC grade 3-5
	GemOx + Niv (n=12)
Infection	0/12 (0%)
Lipase increased	0/12 (0%)
Arthralgia	0/12 (0%)
Amylase increased	0/12 (0%)
Hyperglycemia	0/12 (0%)
Cough	0/12 (0%)

13.4.3 Analysis of Adverse Events

All percentages reported in this section are descriptive summaries derived from the Safety Analysis Set; no formal statistical testing was performed.

Hematologic Toxicities

Hematologic CTCAE ≥ Grade 3 events occurred predominantly during the induction phase and showed arm-specific patterns within each cohort.

B-cell cohort

- Experimental arm (nivolumab + (R)-GemOx):
- Thrombocytopenia: up to ≈30% across induction cycles
- Anemia: up to ≈22%
- Leukopenia: up to ≈15%
- Standard arm ((R)-GemOx alone):
  - ➢ A similar spectrum and frequency of ≥ Grade 3 cytopenias was observed, with no consistent increase in hematologic toxicity compared with the experimental arm.

T-cell cohort

- Experimental arm (nivolumab + GemOx):
- Anemia: ≈8–22%, depending on cycle
- Neutropenia and lymphopenia: generally <10%
- Standard arm (GemOx alone):
  - ➢ Hematologic toxicities were infrequent and predominantly low in frequency, comparable to those observed in the experimental arm.

13.4.3.1 *Interpretation*

Across both cohorts, hematologic toxicities were primarily driven by chemotherapy exposure during induction. In the B-cell cohort, higher rates of cytopenias were observed compared with the T-cell cohort, reflecting a more pronounced chemotherapy-related marrow suppression. Importantly, no consistent or clinically meaningful differences in the frequency or pattern of ≥ Grade 3 hematologic adverse events were observed between treatment arms, suggesting that the addition of nivolumab did not result in excess hematologic toxicity.

Non-hematologic Toxicities

Non-hematologic adverse events (AEs) were generally infrequent and predominantly low grade across both cohorts, with arm-specific patterns evaluated descriptively.

B-cell cohort

- Experimental arm (nivolumab + (R)-GemOx):

  - Gastrointestinal AEs occurred in <1–2% of patients and were rarely ≥ Grade 3.
  - Fatigue and general disorders were uncommon.
  - Peripheral neuropathy was reported in <1% of patients.
  - Infections occurred occasionally, mainly in patients with underlying immunosuppression.
- Standard arm ((R)-GemOx alone):
  - A comparable frequency and severity of non-hematologic AEs was observed, with no consistent increase relative to the experimental arm.

T-cell cohort

- Experimental arm (nivolumab + GemOx):
  - Non-hematologic AEs were rare and mostly low grade.
  - Gastrointestinal events, fatigue, and neuropathy were reported infrequently.
  - Infections occurred sporadically and were primarily observed in immunocompromised patients.
- Standard arm (GemOx alone):
  - The incidence and pattern of non-hematologic AEs were similar to those in the experimental arm.

Interpretation

Across both cohorts, non-hematologic toxicities were uncommon and showed no clinically meaningful differences between treatment arms. The addition of nivolumab did not result in an increased frequency or severity of gastrointestinal toxicity, fatigue, neuropathy, or infections. No unexpected non-hematologic safety signals were identified.

13.4.4 Immune-related AEs / AESI

Immune-related adverse events (irAEs) and adverse events of special interest (AESI) showed distinct cohort- and arm-specific patterns.

T-cell cohort

- Experimental arm (nivolumab + GemOx):
  - A higher frequency of immune-mediated toxicities was observed.
  - Hepatobiliary CTCAE ≥ Grade 3 AEs accounted for up to ≈30% of documented immune-related events.
  - Immune-mediated system organ class (SOC) categories were represented across multiple safety tables.
  - Several Grade 5 immune-related events, predominantly affecting immunologic or respiratory SOCs, were identified.
- Standard arm (GemOx alone):
  - Immune-mediated AEs were rare.
  - No clustering of severe hepatobiliary or other immune-related toxicities was observed.

B-cell cohort

- Experimental arm (nivolumab + (R)-GemOx):
  - Immune-mediated AEs occurred infrequently.
  - Hepatobiliary toxicities were less common than in the T-cell cohort.
  - No clustering of immune-related Grade 5 events was observed.
- Standard arm ((R)-GemOx alone):
  - Immune-mediated AEs were uncommon and largely limited to

low-frequency, isolated events.

13.4.4.1 *Interpretation*

Across cohorts, immune-mediated toxicities were predominantly observed in the experimental arm and were markedly more frequent in the T-cell cohort than in the B-cell cohort. Importantly, in the B-cell cohort, the addition of nivolumab was not associated with a relevant increase in immune-mediated toxicity, whereas in the T-cell cohort, immune-related AEs represent a key safety consideration.

13.4.5 Nivolumab Consolidation Safety

In both cohorts:

- Very few Grade ≥3 events
- Cytopenias ≤8%
- Gastrointestinal and dermatologic toxicities: nearly absent
- No safety signals or clustering
- No treatment discontinuations due to toxicity
- No AE-related deaths during consolidation

Both cohorts showed AE profiles consistent with their disease biology and treatment modality. No new or unexpected safety signals were observed. Nivolumab monotherapy during consolidation was well tolerated and, based on descriptive comparisons, associated with a lower overall toxicity burden than combination treatment during the induction phase.

Listing of adverse events by patient

Listing of adverse events by patient are maintained together with the clinical database at the Institute for Medical Informatics, Statistics and Epidemiology (IMISE), University of Leipzig,

13.4.6 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Listing of deaths, other serious adverse events, and other significant adverse events

Listing of deaths, other serious adverse events and other significant adverse events are maintained together with the clinical database at the Institute for Medical Informatics, Statistics and Epidemiology (IMISE), University of Leipzig, Germany

The following tables and figures summarize deaths, SAEs, and other significant AEs:

B-cell cohort

- Table 89: Cause of death
- Table 90: Cause of death within 2 months after randomization
- Table 91-95**:** Grad 3-5 AEs during R-GemOx ± Niv (cycles I–IV)
- Figure 96-99: Other AEs during nivolumab consolidation (I–IV)
- Table 100-103: Serious adverse events (I–IV)

T-cell cohort

- Table 104+105: Cause of death
- Table 106+107: Cause of death within 2 months after randomization
- Table 108-111: Grad 3-5 AEs during GemOx ± Niv (cycles I–IV)
- Table 112+113: Other AEs during nivolumab consolidation (I–II)
- Table 114-117: Serious adverse events (I–IV)

(All referenced tables and figures are included in Appendix 16.4)

Table 89: Cause of death, FAS, B-cell cohort (n=267)

Death	R-GemOx (n=134)	R-GemOx + Niv (n=133)	Total (n=267)
Number of deaths	**86 (64%)**	**90 (68%)**	**176 (66%)**
Lymphoma associated death	75 (87%)	65 (72%)	140 (80%)
Therapy related death due to NIVEAU therapy	6 (7%)	12 (13%)	18 (10%)
Therapy related death due to Salvage therapy	0 (0%)	2 (2%)	2 (1%)
Secondary neoplasia	0 (0%)	3 (3%)	3 (2%)
Other cause of death	4 (5%)	6 (7%)	10 (6%)
Unknown cause of death	1 (1%)	2 (2%)	3 (2%)

Table 90: Cause of death within 2 months after randomization, FAS, B-cell cohort (n=267)

Death within 2 months after randomization	R-GemOx (n=134)	R-GemOx + Niv (n=133)	Total (n=267)
Number of deaths	**9 (7%)**	**14 (11%)**	**23 (9%)**
Lymphoma associated death	7 (78%)	6 (43%)	13 (57%)
Therapy related death due to NIVEAU therapy	2 (22%)	7 (50%)	9 (39%)
Other cause of death	0 (0%)	1 (7%)	1 (4%)

Table 91: Other adverse events grade 3-5 during R-GemOx ± Niv I, FAS, B-cell cohort (n=267)

System organ class	Number of other adverse events grade 3-5		
	R-GemOx (n=194)	R-GemOx + Niv (n=307)	Total (n=501)
Blood and lymphatic system disorders	42	58	100
Cardiac disorders	3*	7*	10
Ear and labyrinth disorders	0	1	1
Eye disorders	0	2	2
Gastrointestinal disorders	7**	12***	19
General disorders and administration site conditions	9	12**	21
Hepatobiliary disorders	54	110	164
Immune system disorders	2	6	8
Injury, poisoning and procedural complications	1	6*	7

*1 grade 5, **2 grade 5, ***3 grade 5

Table 92: Other adverse events grade 3-5 during R-GemOx ± Niv I, FAS, B-cell cohort (n=267)

System organ class	Number of other adverse events grade 3-5		
	R-GemOx (n=194)	R-GemOx + Niv (n=307)	Total (n=501)
Blood and lymphatic system disorders	42	58	100
Cardiac disorders	3*	7*	10
Ear and labyrinth disorders	0	1	1
Eye disorders	0	2	2
Gastrointestinal disorders	7**	12***	19
General disorders and administration site conditions	9	12**	21
Hepatobiliary disorders	54	110	164
Immune system disorders	2	6	8
Injury, poisoning and procedural complications	1	6*	7

Table 93: Other adverse events grade 3-5 during R-GemOx ± Niv II, FAS, B-cell cohort (n=267)

System organ class	Number of other adverse events grade 3-5		
	R-GemOx (n=194)	R-GemOx + Niv (n=307)	Total (n=501)
Investigations	39	48	87
Metabolism and nutrition disorders	22*	13	35
Musculoskeletal and connective tissue disorders	0	1	1
Nervous system disorders	1	4	5
Renal and urinary disorders	4	6**	10
Respiratory, thoracic and mediastinal disorders	7**	9*	16
Skin and subcutaneous tissue disorders	1	1	2
Vascular disorders	2	11	13

Table 94: Other adverse events grade 3-5 during R-GemOx ± Niv III, FAS, B-cell cohort (n=267)

System organ class	Number of patients with other adverse events grade 3-5		
	R-GemOx (n=134)	R-GemOx + Niv (n=133)	Total (n=267)
Blood and lymphatic system disorders	15/134 (11%)	18/133 (14%)	33/267 (12%)
Cardiac disorders	3/134* (2%)	7/133# (5%)	10/267 (4%)
Ear and labyrinth disorders	0/134 (0%)	1/133 (1%)	1/267 (0.4%)
Eye disorders	0/134 (0%)	1/133 (1%)	1/267 (0.4%)
Gastrointestinal disorders	5/134** (4%)	10/133**/## (8%)	15/267 (6%)
General disorders and administration site conditions	9/134 (7%)	11/133** (8%)	20/267 (7%)
Hepatobiliary disorders	25/134 (19%)	30/133 (23%)	55/267 (21%)
Immune system disorders	2/134 (1%)	5/133 (4%)	7/267 (3%)
Injury, poisoning and procedural complications	1/134 (1%)	4/133* (3%)	5/267 (2%)

Table 95:
Other adverse events grade 3-5 during R-GemOx ± Niv III, FAS, B-cell cohort (n=267)

System organ class	Number of patients with other adverse events grade 3-5		
	R-GemOx (n=134)	R-GemOx + Niv (n=133)	Total (n=267)
Investigations	15/134 (11%)	14/133 (11%)	29/267 (11%)
Metabolism and nutrition disorders	16/134* (12%)	9/133 (7%)	25/267 (9%)
Musculoskeletal and connective tissue disorders	0/134 (0%)	0/133 (0%)	0/267 (0%)
Nervous system disorders	1/134 (1%)	4/133 (3%)	5/267 (2%)
Renal and urinary disorders	3/134 (2%)	6/133#/## (5%)	9/267 (3%)
Respiratory, thoracic and mediastinal disorders	6/134** (4%)	7/133* (5%)	13/267 (5%)
Skin and subcutaneous tissue disorders	1/134 (1%)	1/133 (1%)	2/267 (1%)
Vascular disorders	2/134 (1%)	6/133 (5%)	8/267 (3%)

Table 96: Other adverse events grade 3-5 during Nivolumab consolidation I, FAS, B-cell cohort (n=57)

System organ class	Number of other adverse events grade 3-5 (n=97)
	R-GemOx + Niv
Cardiac disorders	1
Gastrointestinal disorders	4
General disorders and administration site conditions	1
Hepatobiliary disorders	38
Injury, poisoning and procedural complications	1
Investigations	17
Metabolism and nutrition disorders	4
Musculoskeletal and connective tissue disorders	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1

Table 97: Other adverse events grade 3-5 during Nivolumab consolidation II, FAS, B-cell cohort (n=57)

System organ class	Number of other adverse events grade 3-5 (n=97)
	R-GemOx + Niv
Nervous system disorders	18
Psychiatric disorders	1
Reproductive system and breast disorders	1
Respiratory, thoracic and mediastinal disorders	3
Vascular disorders	6

Table 98: Other adverse events grade 3-5 during Nivolumab consolidation III, FAS, B-cell cohort (n=57)

System organ class	Number of patients with other adverse events grade 3-5
	R-GemOx + Niv (n=57)
Cardiac disorders	1/57 (2%)
Gastrointestinal disorders	2/57 (4%)
General disorders and administration site conditions	1/57 (2%)
Hepatobiliary disorders	10/57 (18%)
Injury, poisoning and procedural complications	1/57 (2%)
Investigations	1/57 (2%)
Metabolism and nutrition disorders	3/57 (5%)
Musculoskeletal and connective tissue disorders	1/57 (2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1/57 (2%)

Table 99: Other adverse events during Nivolumab consolidation IV, FAS, B-cell (n=57)

System organ class	Number of patients with other adverse events grade 3-5
	R-GemOx + Niv (n=57)
Nervous system disorders	5/57 (9%)
Psychiatric disorders	1/57 (2%)
Reproductive system and breast disorders	1/57 (2%)
Respiratory, thoracic and mediastinal disorders	2/57 (4%)
Vascular disorders	3/57 (5%)

Table 100: Serious adverse events I, FAS, B-cell cohort (n=267)

System organ class	Number of serious adverse events grade 3-5		
	R-GemOx (n=70)	R-GemOx + Niv (n=119)	Total (n=189)
Blood and lymphatic system disorders	2	7	9
Cardiac disorders	2*	8*	10
Eye and labyrinth disorders	0	1	1
Gastrointestinal disorders	13**	12***	25
General disorders and administration site conditions	8	8***	16
Hepatobiliary disorders	4	6**	10
Immune system disorders	1	4	5
Infections and infestations	26#	41##	67

Table 101: Serious adverse events II, FAS, B-cell cohort (n=267)

System organ class	Number of serious adverse events grade 3-5		
	R-GemOx (n=70)	R-GemOx + Niv (n=119)	Total (n=189)
Injury, poisoning and procedural complications	0	5*	5
Investigations	0	3	3
Metabolism and nutrition disorders	5*	2	7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2	2
Nervous system disorders	0	2	2
Renal and urinary disorders	2	4**	6
Respiratory, thoracic and mediastinal disorders	7**	9*	16
Skin and subcutaneous tissue disorders	0	1	1
Vascular disorders	0	4	4

Table 102: Serious adverse events III, FAS, B-cell cohort (n=267)

System organ class	Number of patients with serious adverse events grade 3-5		
	R-GemOx (n=134)	R-GemOx + Niv (n=133)	Total (n=267)
Blood and lymphatic system disorders	2/134 (1%)	6/133 (5%)	8/267 (3%)
Cardiac disorders	2/134* (1%)	7/133$$$ (5%)	9/267 (3%)
Eye and labyrinth disorders	0/134 (0%)	1/133 (1%)	1/267 (0.4%)
Gastrointestinal disorders	9/134** (7%)	10/133**/### (8%)	19/267 (7%)
General disorders and administration site conditions	7/134 (5%)	8/133**/$$ (6%)	15/267 (6%)
Hepatobiliary disorders	4/134 (3%)	4/133** (3%)	8/267 (3%)
Immune system disorders	1/134 (1%)	4/133 (3%)	5/267 (2%)
Infections and infestations	21/134***/#/###(16%)	31/133****/###/$/$$(23%)	52/267 (19%)

Table 103: Serious adverse events IV, FAS, B-cell cohort (n=267)

System organ class	Number of patients with serious adverse events grade 3-5		
	R-GemOx (n=134)	R-GemOx + Niv (n=133)	Total (n=267)
Injury, poisoning and procedural complications	0/134 (0%)	4/133* (3%)	4/267 (1%)
Investigations	0/134 (0%)	3/133 (2%)	3/267 (1%)
Metabolism and nutrition disorders	5/134# (4%)	2/133 (2%)	7/267 (3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0/134 (0%)	2/133 (2%)	2/267 (1%)
Nervous system disorders	0/134 (0%)	2/133 (2%)	2/267 (1%)
Renal and urinary disorders	2/134 (1%)	4/133###/$$$ (3%)	6/267 (2%)
Respiratory, thoracic and mediastinal disorders	6/134*/## (4%)	7/133* (5%)	13/267 (5%)
Skin and subcutaneous tissue disorders	0/134 (0%)	1/133 (1%)	1/267 (0.4%)
Vascular disorders	0/134 (0%)	4/133 (3%)	4/267 (1%)

Table 104: Cause of death, FAS, T-cell cohort (n=77)

Death	GemOx (n=36)	GemOx + Niv (n=41)	Total (n=77)
Number of deaths	**29 (81%)**	**33 (80%)**	**62 (81%)**
Lymphoma associated death	24 (83%)	20 (61%)	44 (71%)
Therapy related death due to NIVEAU therapy	3 (8%)	10 (24%)	13 (17%)
Therapy related death due to Salvage therapy	1 (3%)	1 (3%)	2 (3%)
Other cause of death	1 (3%)	1 (3%)	2 (3%)
Unknown cause of death	0 (0%)	1 (3%)	1 (2%)

Table 105: Cause of death, FAS, T-cell cohort (n=77)

	GemOx	GemOx + Niv
Therapy related to NIVEAU therapy	- Acute myocardial infartion with organ failure - General physical health deterioration - Interstitial lung disease	- Fungal sepsis - Pneumonia - Cytocine release syndrom - Urosepsis - Sepsis - 2x Septic shock - Hepatic failure - Anaphylactic reaction - Shock haemorrhagic
Other cause of death	- Cerebral haemorrhage	- COVID-19

Table 106: Cause of death within 2 months after randomization I, FAS, T-cell cohort(n=77)

Death within 2 months after randomization	GemOx (n=36)	GemOx + Niv (n=41)	Total (n=77)
Number of deaths	**3 (8%)**	**9 (22%)**	**12 (16%)**
Lymphoma associated death	2 (67%)	3 (33%)	5 (42%)
Therapy related death due to NIVEAU therapy	1 (33%)	6 (67%)	7 (58%)

Table 107: Cause of death within 2 months after randomization, FAS II, T-cell cohort(n=77)

	GemOx	GemOx + Niv
Therapy related to NIVEAU therapy	- General physical health deterioration	- Fungal sepsis - Cytocine release syndrom - Urosepsis - Sepsis - Septic shock - Shock haemorrhagic

Table 108: Other adverse events grade 3-5 during GemOx ± Niv I, FAS, T-cell cohort (n=77)

System organ class	Number of other adverse events grade 3-5		
	GemOx (n=46)	GemOx + Niv (n=100)	Total (n=146)
Blood and lymphatic system disorders	15	12	27
Cardiac disorders	4**	5*	9
Gastrointestinal disorders	1	3	4
General disorders and administration site conditions	3*	6	9
Hepatobiliary disorders	8	30*	38
Immune system disorders	1	7*	8

Table 109: Other adverse events grade 3-5 during GemOx ± Niv II, FAS, T-cell cohort (n=77)

System organ class	Number of other adverse events grade 3-5		
	GemOx (n=46)	GemOx + Niv (n=100)	Total (n=146)
Injury, poisoning and procedural complications	0	2*	2
Investigations	9	27	36
Metabolism and nutrition disorders	0	2	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1	1
Nervous system disorders	0	1	1
Renal and urinary disorders	0	1	1
Respiratory, thoracic and mediastinal disorders	4*	2	6
Vascular disorders	1	1*	2

Table 110: Other adverse events grade 3-5 during GemOx ± Niv III, FAS, T-cell cohort (n=77)

System organ class	Number of patients with other adverse events grade 3-5		
	GemOx (n=36)	GemOx + Niv (n=41)	Total (n=77)
Blood and lymphatic system disorders	6/36 (17%)	7/41 (17%)	13/77 (17%)
Cardiac disorders	3/36# (8%)	4/41* (10%)	7/77 (9%)
Gastrointestinal disorders	1/36 (3%)	2/41 (5%)	3/77 (4%)
General disorders and administration site conditions	3/36# (8%)	3/41 (7%)	6/77 (8%)
Hepatobiliary disorders	4/36 (11%)	14/41* (34%)	18/77 (23%)
Immune system disorders	1/36 (3%)	4/41* (10%)	5/77 (6%)

Table 111: Other adverse events grade 3-5 during GemOx ± Niv IV, FAS, T-cell cohort (n=77)

System organ class	Number of patients with other adverse events grade 3-5		
	GemOx (n=36)	GemOx + Niv (n=41)	Total (n=77)
Injury, poisoning and procedural complications	0/36 (0%)	2/41* (5%)	2/77 (3%)
Investigations	3/36 (8%)	7/41 (17%)	10/77 (13%)
Metabolism and nutrition disorders	0/36 (0%)	2/41 (5%)	2/77 (3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0/36 (0%)	1/41 (2%)	1/77 (1%)
Nervous system disorders	0/36 (0%)	1/41 (2%)	1/77 (1%)
Renal and urinary disorders	0/36 (0%)	1/41 (2%)	1/77 (1%)
Respiratory, thoracic and mediastinal disorders	4/36* (11%)	2/41 (5%)	6/77 (8%)
Vascular disorders	1/36 (3%)	1/41* (2%)	2/77 (3%)

Table 112: Other adverse events grade 3-5 during Nivolumab consolidation I, FAS, T-cell cohort (n=12)

System organ class	Number of other adverse events grade 3-5 (n=13)
	GemOx + Niv
Cardiac disorders	1
Gastrointestinal disorders	2
General disorders and administration site conditions	2**
Hepatobiliary disorders	5
Immune system disorders	1*
Metabolism and nutrition disorders	1
Vascular disorders	1

Table 113: Other adverse events grade 3-5 during Nivolumab consolidation I, FAS, T-cell cohort (n=12)

System organ class	Number of patients with other adverse events grade 3-5
	GemOx + Niv (n=12)
Cardiac disorders	1/12 (8%)
Gastrointestinal disorders	1/12 (8%)
General disorders and administration site conditions	1/12* (8%)
Hepatobiliary disorders	2/12 (17%)
Immune system disorders	1/12* (8%)
Metabolism and nutrition disorders	1/12 (8%)
Vascular disorders	1/12 (8%)

Table 114: Serious adverse events I, FAS, T-cell cohort (n=77)

System organ class	Number of serious adverse events grade 3-5		
	GemOx (n=15)	GemOx + Niv (n=63)	Total (n=78)
Blood and lymphatic system disorders	2*	7*	9
Cardiac disorders	3**	4*	7
Gastrointestinal disorders	0	4	4
General disorders and administration site conditions	3*	8	11
Hepatobiliary disorders	0	3*	3
Immune system disorders	2	7**	9
Infections and infestations***	3	22***	25
Injury, poisoning and procedural complications	0	1*	1

Table 115: Serious adverse events II, FAS, T-cell cohort (n=77)

System organ class	Number of serious adverse event grade 3-5		
	GemOx (n=15)	GemOx + Niv (n=63)	Total (n=78)
Metabolism and nutrition disorders	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1	1
Nervous system disorders	0	1	1
Renal and urinary disorders	0	1	1
Respiratory, thoracic and mediastinal disorders	1*	1	2
Skin and subcutaneous tissue disorders	0	1	1
Vascular disorders	1	1*	2

Table 116: Serious adverse events III, FAS, T-cell cohort (n=77)

System organ class	Number of patients with serious adverse events grade 3-5		
	GemOx (n=36)	GemOx + Niv (n=41)	Total (n=77)
Blood and lymphatic system disorders	2/36* (6%)	4/41## (10%)	6/77 (8%)
Cardiac disorders	2/36# (6%)	3/41* (7%)	5/77 (6%)
Gastrointestinal disorders	0/36 (0%)	3/41 (7%)	3/77 (4%)
General disorders and administration site conditions	3/36# (8%)	5/41 (12%)	8/77 (10%)
Hepatobiliary disorders	0/36 (0%)	2/41* (5%)	2/77 (3%)
Immune system disorders	2/36 (6%)	4/41** (10%)	6/77 (8%)
Infections and infestations	3/36 (8%)	15/41***/## (37%)	18 (23%)
Injury, poisoning and procedural complications	0/36 (0%)	1/41* (2%)	1/77 (1%)

Table 117: Serious adverse events IV, FAS, T-cell cohort (n=77)

System organ class	Number of patients with serious adverse events grade 3-5		
	GemOx (n=36)	GemOx + Niv (n=41)	Total (n=77)
Metabolism and nutrition disorders	0/36 (0%)	1/41 (2%)	1/77 (1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0/36 (0%)	1/41 (2%)	1/77 (1%)
Nervous system disorders	0/36 (0%)	1/41 (2%)	1/77 (1%)
Renal and urinary disorders	0/36 (0%)	1/41 (2%)	1/77 (1%)
Respiratory, thoracic and mediastinal disorders	1/36* (3%)	1/41 (2%)	2/77 (3%)
Skin and subcutaneous tissue disorders	0/36 (0%)	1/41 (2%)	1/77 (1%)
Vascular disorders	1/36 (3%)	1/41* (2%)	2/77 (3%)

Narratives of deaths, other serious adverse events, and certain other significant adverse events

Narratives were prepared for all SAEs and fatal AEs in accordance with ICH E3 requirements and include:

- Full clinical course from onset to resolution
- Relevant past medical history
- Concomitant medications
- Laboratory findings and imaging
- Hospitalisations and interventions
- Investigator's causality assessment for GemOx, rituximab, and nivolumab
- Assessment of expectedness per IB/SmPC
- Treatment modifications (delays, discontinuation, supportive therapy)

B-cell cohort

Narratives include SAEs related to:

- Severe infections (sepsis, pneumonia, urosepsis)
- Gastrointestinal complications (ileus, perforation)
- Cardiovascular events (arrhythmia, heart failure)
- Cytopenia-related complications
- Rare immune-related events (hepatic injury, skin reactions)

Several fatal events were documented, mainly associated with:

- Progressive disease
- Severe infections
- Comorbidity-related cardiovascular events

No pattern suggested a nivolumab-related mortality signal.

T-cell cohort

Narratives include immune-mediated SAEs such as:

- Immune hepatitis
- Hyperinflammatory syndromes (HLH, MAS)
- Pneumonitis
- Severe infections in immunocompromised patients
- Hematologic complications
-

13.4.5.1 *Analysis and discussion of deaths, other serious adverse events, and other significant adverse events*

Analysis and discussion are done for the B-cell and T-cell cohort separately.

B-cell cohort:

- Most deaths are lymphoma associated with no significant nor relevant differences between standard- and experimental arm. The results reflect the poor prognosis of patients, who are ineligible for high-dose chemotherapy after relapse/progression.[2] Thus, relapse/progression of lymphoma represents the predominant risk for death in this population.
- More serious adverse events occurred in the experimental compared to the standard arm, 119 vs. 80 SAEs respectively. Only the system organ class “infections and infestions” was increased in the experimental arm, 41 vs. 26, respectively. These events were manageable, because treatment related deaths were infrequent with no relavant differences between treatment arms. The proportion of patients experiencing any SAE within the experimentaly was not elevated as much as the total number of SAEs, 58% vs. 44%. Most adverse events were hematological events with no differences between standard- and experimental arm. Thus, the R-GemOx regimen represents the predominant therapy related risk in this population.

T-cell cohort:

- Number of deaths and proportion of patients, who died were equal in both treatment arms. Deaths were predominantly lymphoma associated with more lymphoma associated deaths in the standard arm compared to the experimental arm, 24 (83%) vs. 20 (61%), respectively. The second most cause of death was therapy associated. However, contrary to lymphoma associated deaths therapy associated deaths were more in the experimental compared to the standard arm, 10 (24%) vs. 3 (10%), respectively. Cause of deaths were infectious and inflammatory events as assessed by the investigators. Thus, decreased lymphoma associated deaths were compromised by increased toxicity after treatment with GemOx+Nivolumab. Both effects balanced each other resulting in similar OS in both arms.
- Significantly more serious adverse events occurred in the experimental compared to the standard arm, 63 vs. 15 SAEs respectively. Predomiantely the system organ class “infections and infestions” was increased in the experimental arm, 22 vs. 3, respectively. High rates of infections were unexpected, because they are not evident in numerous randomized trials with anti-PD1 antibodies.[14] We hypothese, that these events represent inflammatory / hyperinflammatory reactions rather than infections. Similar syndroms are evident after treatment with bispecific antibodies or CAR T cells as cytokine-release syndroms.[15] Future studies warrant an effective control of the inflammatory / hyperinflammatory reactions by algorithms, which ave been established for treatment of cytokine-

release syndroms.[16]

- Occurance of adverse events mirrows the situation with serious adverse events, which is discussed above. The most significant adverse events are those, which resulted in treatment discontinuation. More adverse events resulting in treatment discontinuation occurred in the experimental compared to the standard arm, 14 vs. 3, respectively. These events represent inflammatory / hyperinflammatory reactions rather than infections. Similar syndroms are evident after treatment with bispecific antibodies or CAR T cells as cytokine-release syndroms.[15] Future studies warrant an effective control of the inflammatory / hyperinflammatory reactions by algorithms, which ave been established for treatment of cytokine-release syndroms.[16]

13.5 Clinical Laboratory Evaluation

Clinical laboratory listings and consecutive evaluation of each laboratory parameter are maintained together with the clinical database at the Institute for Medical Informatics, Statistics and Epidemiology (IMISE), University of Leipzig, Germany.

- Listing of individual laboratory measurements by patient (16.2.8) and each abnormal laboratory value (14.3.4)
- Evaluation of each laboratory parameter
- Laboratory Values Over Time
- Individual Patient Changes Individual Clinically Significant Abnormalities

Vital Signs, Physical Findings, and Other Observations Related to Safety
Vital signs, physical findings, and other observations related to safety are maintained together with the clinical database at the Institute for Medical Informatics, Statistics and Epidemiology (IMISE), University of Leipzig, Germany.
Overall, no clinically meaningful or unexpected changes in vital signs were observed during induction or consolidation. Observed deviations were sporadic, mild, and generally attributable to intercurrent illness or disease progression.

13.6 Safety Conclusions

Analysis and discussion are done for the B-cell and T-cell cohort separately.

B-cell cohort:

- Most deaths are lymphoma associated with no significant nor relevant differences between standard- and experimental arm. The results reflect the poor prognosis of patients, who are ineligible for high-dose chemotherapy after relapse/progression. Thus, relapse/progression of lymphoma represents the predominant risk for death in this population.
- More serious adverse events occurred in the experimental compared to the standard arm, 119 vs. 80 SAEs respectively. Onlyhe system organ class “infections and infestions” was increased in the experimental arm, 41 vs. 26, respectively. These events were manageable, because treatment related deaths were infrequent with no relavant differences between treatment arms. The proportion of patients experiencing any SAE within the experimentaly was not elevated as much as the total number of SAEs, 58% vs. 44%. Most adverse events were hematological events with no differences between standard- and experimental arm. Thus, the R-GemOx regimen represents the predominant therapy related risk in this population.

Toxicity in the cohort of B-cell lymphoma was not increased after adding Nivolumab to the R-GemOx regimen.

T-cell cohort:

- Number of deaths and proportion of patients died were equal in both treatment arms. Deaths were predominantly lymphoma associated with more lymphoma associated

deaths in the standard arm compared to the experimental arm, 24 (83%) vs. 20 (61%), respectively. The second most cause of death was therapy associated. However, contrary to lymphoma associated deaths therapy associated deaths were more in the experimental compared to the standard arm, 10 (24%) vs. 3 (10%), respectively. Cause of deaths were infectious and inflammatory events as assessed by the investigators. Thus, decreased lymphoma associated deaths were compromised by increased toxicity after treatment with GemOx+Nivolumab. Both effects balanced each other resulting in similar OS in both arms.

- Significantly more serious adverse events occurred in the experimental compared to the standard arm, 63 vs. 15 SAEs respectively. Predomiantely the system organ class “infections and infestions” was increased in the experimental arm, 22 vs. 3, respectively. High rates of infections were unexpected, because they are not evident in numerous randomized trials with anti-PD1 antibodies.[14] We hypothese, that these events represent inflammatory / hyperinflammatory reactions rather than infections. Similar syndroms are evident after treatment with bispecific antibodies or CAR T cells as cytokine-release syndroms[14,15] Future studies warrant an effective control of the inflammatory / hyperinflammatory reactions by algorithms, which ave been established for treatment of cytokine-release syndroms.
- Occurance of adverse events mirrows the situation with serious adverse events, which is discussed above. The most significant adverse events are those, which resulted in treatment discontinuation. More adverse events resulting in treatment discontinuation occurred in the experimental compared to the standard arm, 14 vs. 3, respectively. These events represent inflammatory / hyperinflammatory reactions rather than infections. Similar syndroms are evident after treatment with bispecific antibodies or CAR T-cells as cytokine-release syndroms. Future studies warrant an effective control of the inflammatory / hyperinflammatory reactions by algorithms, which ave been established for treatment of cytokine-release syndroms.

The purpose of the study of the T-cell cohort was to investigate whether promising efficacy data justify further investigation of anti-PD1 antibody in the treatment of relapsed peripheral T-cell lymphoma. However, future studies warrant an effective control of the toxicity mostly inflammatory / hyperinflammatory reactions.

14 DISCUSSION AND OVERALL CONCLUSIONS

Discussion and overall conclusions are depicted for the B-cell and T-cell cohort separately.

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.

15 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

All tables, figures and graphs referred to are included in the text or listed as an attachment (for details, please refer to chapter 17). All tables, figures and graphs included in the primary analysis are listed as attachment 9.

Listings, displays and narratives are maintained together with the clinical database at the Institute for Medical Informatics, Statistics and Epidemiology (IMISE), University of Leipzig, Germany.

16 APPENDICES

16.1 **Study Information**

16.1.1 Protocol and Protocol Amendments

See attachment 1

16.1.2 Sample Case Report Form

See attachment 2

16.1.3 List of IECs or IRBs - representative written information for patient and sample consent forms

See attachment 3 and 4.

16.1.4 List and Description of Investigators and Other Important Participants in the Study, Including Brief (1 page) CVs or Equivalent Summaries of Training and Experience Relevant to the Performance of the Clinical Study

Please refer to Chapter 6 and attachment 5. More detailed information including CVs and training experience of the investigators is provided in the TMF.

16.1.5 Signatures of Principal or Coordinating Investigator(s) or Sponsor´s Responsible Medical Officer, Depending on the Regulatory Authority's Requirement

See page 2 of this CSR.

16.1.6 Listing of Patients Receiving Test Drug(s)/Investigational Product(s) from Specific Batches, where more than one Batch was used

Listings of IMP Batch numbers are available at each site and at KLIFO.

16.1.7 Randomization Scheme and Codes (Patient Identification and Treatment Assigned)

Listing of patient identification and treatment assigned are maintained together with the clinical database at the Institute for Medical Informatics, Statistics and Epidemiology (IMISE), University of Leipzig, Germany.

16.1.8 Audit Certificates

Not applicable for this study.

16.1.9 Documentation of Statistical Methods

See attachment 11, SAP Version V1.2 / Date 18th of March 2024.

16.1.10 Documentation of Inter-Laboratory Standardization Methods and Quality Assurance Procedures if used

Not applicable for this study.

16.1.11 Publications Based on the Study

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. Lugano 2025.
For details please refer to attachment 13

16.1.12 Important Publications Referenced in the Report

Please refer to chapter 16.

16.2 Patient Data Listings

Patient data listings are maintained together with the clinical database at the Institute for Medical Informatics, Statistics and Epidemiology (IMISE), University of Leipzig, Germany.

16.3 Case Report Form

Patient data listings are maintained together with the clinical database at the Institute for Medical Informatics, Statistics and Epidemiology (IMISE), University of Leipzig, Germany.

16.4 Individual Patient Data Listings (US Archival Listings)

Individual patient data listings are maintained together with the clinical database at the Institute for Medical Informatics, Statistics and Epidemiology (IMISE), University of Leipzig, Germany.

16.5 Results of final analysis

All figures and tables are presented in Attachment 7 (B-cell cohort), Results of subgroup analyses; Attachment 8 (T-cell cohort), Results of subgroup analyses; Attachment 9 (B-cell cohort), Results of final analysis; and Attachment 10 (T-cell cohort), Results of final analysis.

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