Early Response to First-Line Anti–PD-1 Treatment in Hodgkin Lymphoma: A PET-Based Analysis from the Prospective, Randomized Phase II NIVAHL Trial

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ABSTRACT

Purpose: A primary analysis of the ongoing NIVAHL trial demonstrated unexpectedly high interim complete response rates to nivolumab-based first-line treatment in early-stage unfavorable Hodgkin lymphoma. However, biomarkers such as metabolic tumor volume (MTV) or total lesion glycolysis (TLG) and their change under treatment (ΔMTV and ΔTLG), measured on PET, might provide additional relevant information for response assessment in this setting. Hence, the current analysis aimed to investigate early response to checkpoint inhibitor therapy beyond conventional criteria.

Patients and Methods: NIVAHL is a prospective, randomized phase II trial that recruited between April 2017 and October 2018. Patients in arms A and B were assessed for early treatment response after two courses of doxorubicin, vinblastine, and dacarbazine with two concomitant nivolumab infusions per cycle (2 × N-AVD) and 4 × nivolumab, respectively. In the current analysis, we included all 59 individuals with PET images available to the central review panel for quantitative analysis before April 30, 2019.

Results: At interim restaging, we determined a mean ΔMTV and ΔTLG of −99.8% each in arm A after 2 × N-AVD, compared with −91.4% and −91.9%, respectively, for treatment group B undergoing 4 × nivolumab. This high decrease in MTV and TLG was observed regardless of the initial lymphoma burden.

Conclusions: Our study showed that nivolumab-based first-line treatment leads to rapid, near-complete reduction of tumor metabolism in early-stage unfavorable Hodgkin lymphoma. Thus, PET-derived biomarkers might allow reduction or even omission of chemotherapy and radiotherapy. Furthermore, MTV and TLG could be also used to optimize immune checkpoint-targeting treatments in other cancers.

Introduction

Over recent decades, primary cure rates of Hodgkin lymphoma have been markedly increased through refinement of risk-adapted treatment concepts. In early-stage unfavorable disease, individuals receive four cycles of polychemotherapy, which is usually followed by 30 Gy irradiation (1, 2). Omission of radiotherapy appears feasible only in patients achieving complete remission (CR) status on PET who have undergone intensified systemic treatment without compromising progression-free survival (PFS; refs. 3–5). Hence, strategies to decrease potential acute and long-term toxicities while maintaining the excellent efficacy remain of immediate interest in Hodgkin lymphoma treatment (6–8).

Immune checkpoint inhibitors blocking programmed cell death protein 1 (PD-1) interaction with its ligands have shown remarkable response and PFS rates in patients with relapsed or refractory (R/R) Hodgkin lymphoma (9, 10). Consequently, the anti-PD-1 agents nivolumab and pembrolizumab were recently approved for this indication. The German Hodgkin Study Group examines first-line anti-PD-1–based Hodgkin lymphoma treatment in the ongoing investigator-initiated, randomized, multicenter phase II NIVAHL trial, which on primary analysis yielded an excellent PFS and an unexpectedly high interim CR rate of 51.0% after 4×nivolumab monotherapy (11).

Established criteria may not accurately reflect the early therapeutic effects of PD-1 blockade, particularly in treatment-naïve patients (12). This partially also applies to the modified therapy decision guidelines, which are largely directed at indefinite immune checkpoint blockade in metastatic or multiply relapsed disease (13, 14). However, some recently introduced PET parameters appear promising as additional

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Translational Relevance

While cure rates in Hodgkin lymphoma have been steadily improved over the last decades, decreasing acute and long-term toxicities of treatment still remains a challenge. The prospective, randomized phase II NIVAHL trial showed unexpectedly high complete remission rates to programmed cell death protein 1 (PD-1) blockade in treatment-naïve early-stage unfavorable disease. However, some *in vivo* biomarkers measured on PET might be valuable additional measures for early response assessment. At interim restaging, the vast majority of patients achieved complete or near-complete reduction of metabolic tumor volume (MTV) and total lesion glycolysis (TLG) after 4 × nivolumab either in combination with two courses of doxorubicin, vinblastine, and dacarbazine or as monotherapy. These PET parameters reflect the high efficacy of anti–PD-1–based treatment in Hodgkin lymphoma and may allow reduction or even omission of chemotherapy and radiotherapy. Moreover, MTV and TLG could also maximize benefits of immune checkpoint blockade in other malignancies.

measures of response in this treatment setting (15). The reliable identification of individuals who benefit considerably from immunotherapy could facilitate tailored approaches geared toward changes in lymphoma burden. We therefore evaluated the potential of metabolic tumor volume (MTV) and total lesion glycolysis (TLG) as biomarkers for early response assessment in treatment-naïve Hodgkin lymphoma patients undergoing anti-PD-1 therapy.

Patients and Methods

Analysis set and treatment groups

Between April 2017 and October 2018, 110 individuals with treatment-naïve, early-stage unfavorable classical Hodgkin lymphoma ages 18 to 60 years were prospectively enrolled in the NIVAHL trial at 35 German centers. While treatment group A underwent four courses of doxorubicin, vinblastine, and dacarbazine (AVD) plus two concomitant nivolumab infusions per cycle (N-AVD), arm B received sequential therapy, consisting of four nivolumab doses followed by 2 × N-AVD and 2× AVD. In both treatment groups, 30 Gy consolidative irradiation was administered at the end of systemic treatment. After 2 × N-AVD and 4 × nivolumab, respectively, patients in arm A and B were evaluated for response with PET/CT and contrast-enhanced CT of all initially involved sites. According to German guidelines as well as reimbursement standards at the time of study initiation, PET was not mandatory for staging and has hence not been conducted in each individual enrolled. All patients from the intention-to-treat population completed study therapy and are currently under follow-up. Detailed methods and a primary analysis reporting CR rates after completion of radiotherapy have recently been published (11). The current analysis set consisted of all 59 individuals who underwent PET at both baseline and interim response assessment, with images available to the central review panel for quantitative evaluation before April 30, 2019 (**Fig. 1**).

NIVAHL has been approved by the institutional ethics committee and adhered to the principles of the Declaration of Helsinki. In accordance with the Good Clinical Practice guidelines of the International Conference on Harmonization, patients provided written informed consent before inclusion.

Response assessment criteria

We obtained the following parameters from PET images to evaluate early treatment response in both treatment groups:

(i) MTV with a standardized uptake value (SUV) of 4.0 as fixed threshold
(ii) TLG calculated by multiplication of MTV and mean SUV

All patients were examined at baseline and first interim restaging for evaluation of the respective metabolic changes, recorded as ΔMTV and ΔTLG, using the PET/CT viewer in FIJI (ImageJ). Morphologic response was assessed on the basis of two-dimensional measurements for a maximum of six target lesions, from which the sum of the product

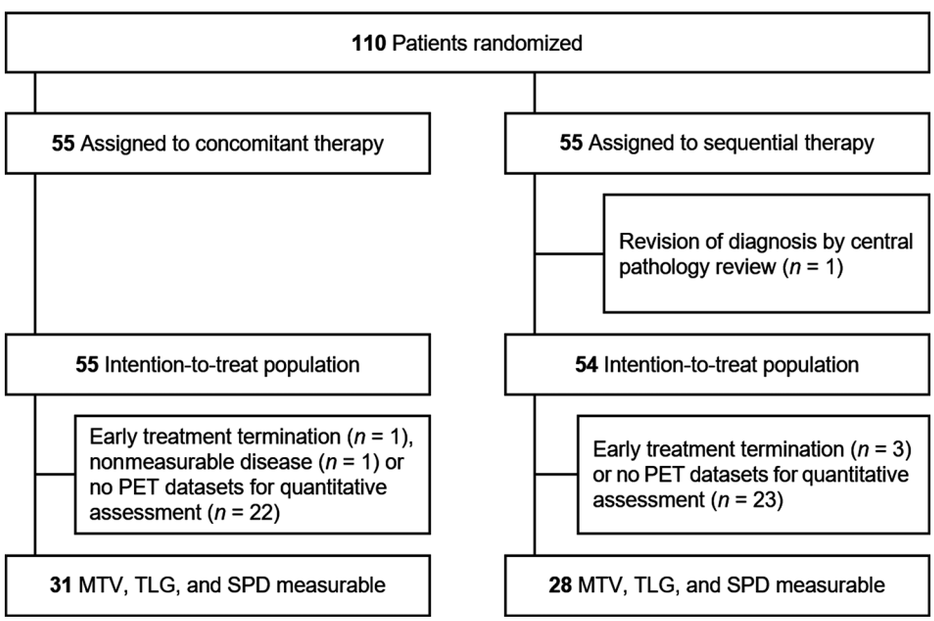

Figure 1.
Flow chart illustrating patient inclusion process of the current analysis.

of greatest diameters (SPD) and respective change under therapy (ΔSPD) were calculated, as proposed in the Lugano classification (16). All imaging was reviewed by the nuclear medicine experts of our central review panel who determined MTV, TLG, and SPD blinded for further patient outcome.

Statistical evaluation

For the measures obtained, we calculated means with SDs and created waterfall plots to visualize changes in tumor burden. Patient characteristics were evaluated using descriptive statistics and *P* values result from Fisher exact or Wilcoxon rank-sum test. All data analysis was performed with SAS software version 9.4 (SAS Institute).

Data sharing statement

The datasets generated and analyzed during this study are available from the corresponding authors on reasonable request.

Results

Patient characteristics

The 59 patients eligible had a median age of 27 years and 36 were female (61.0%). All presented with stage II disease, and involvement of three or more lymph node areas was identified as the most common risk factor (74.6%, $n = 44$). Except from a significantly higher proportion of individuals having stage II and bulky lymphoma, characteristics were similar to those of NIVAHL patients not suitable for the current analysis (**Table 1**).

Early response to treatment

Mean baseline MTV and TLG were 123.8 mL (SD, 133.4) and 886.4 g (SD, 1033.1), respectively, in arm A undergoing concomitant therapy, compared with 176.6 mL (SD, 140.9) and 1267.3 g (SD, 1148.7), respectively, for treatment group B, which was assigned to the sequential approach. At early interim response assessment, PET showed a marked reduction in tumor load, with an average ΔMTV and ΔTLG of −99.8% each (SD, 0.7 and 0.6, respectively) after 2 × N-AVD and −91.4% (SD, 27.2) and −91.9% (SD, 25.9), respectively, in patients who underwent 4 × nivolumab upfront (**Figs. 2** and **3**). Near-complete MTV reductions were observed in both treatment groups regardless of the initial lymphoma burden. A ΔMTV ≥90% was documented for 93.3% ($n = 28/30$) and 96.6% ($n = 28/29$) of patients with initial MTV above and below the median value of 112.9 mL, respectively. Following these first therapy courses, mean MTV and TLG were 0.4 mL (SD, 1.6) and 2.1 g (SD, 7.9), respectively, in arm A and 11.4 mL (SD, 35.8) and 68.3 g (SD, 214.0), respectively, for treatment group B.

On the basis of the Lugano criteria and taking a Deauville score ≥4 as PET-positive (16, 17), interim CR was attained in 77.4% ($n = 24$) and

Table 1. Baseline characteristics and demographics of patients eligible for the analysis compared with those not suitable.

	MTV, TLG, and SPD measurable ($n = 59$)	No complete assessment ($n = 50$)	*P*
Treatment group			
Concomitant (A)	31 (52.5)	24 (48.0)	0.70
Sequential (B)	28 (47.5)	26 (52.0)	
Age, years			
Median	27	26	0.69
Range	18–57	18–60	
Sex			
Female	36 (61.0)	29 (58.0)	0.85
Male	23 (39.0)	21 (42.0)	
ECOG performance status			
0	45 (76.3)	38 (76.0)	1.0
1	14 (23.7)	12 (24.0)	
Ann Arbor stage			
IA	0	4 (8.0)	0.014
IB	0	1 (2.0)	
IIA	43 (72.9)	39 (78.0)	
IIB	16 (27.1)	6 (12.0)	
Risk factors			
Involvement of three or more nodal areas	44 (74.6)	31 (62.0)	0.21
Bulky disease[a]	33/58 (56.9)	39 (78.0)	0.025
Elevated ESR[b]	30 (50.8)	22 (44.0)	0.56
Extranodal disease	10 (16.9)	4 (8.0)	0.25
Large mediastinal mass[c]	8 (13.6)	14 (28.0)	0.093
Histologic subtype			
Nodular sclerosis	36 (61.0)	33/49 (67.3)	0.92
Mixed cellularity	8 (13.6)	5/49 (10.2)	
Lymphocyte-rich	2 (3.4)	1/49 (2.0)	
Unspecified	13 (22.0)	10/49 (20.4)	

Note: Data are *n* (%) or *n/N* (%) unless specified otherwise.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESR, erythrocyte sedimentation rate.
[a]Presence of a lesion with ≥5 cm in longest diameter.
[b]≥50 mm/hour for patients without B symptoms and ≥30 mm/hour in case of B symptoms.
[c]≥1/3 of the maximal thoracic diameter as measured on chest radiography.

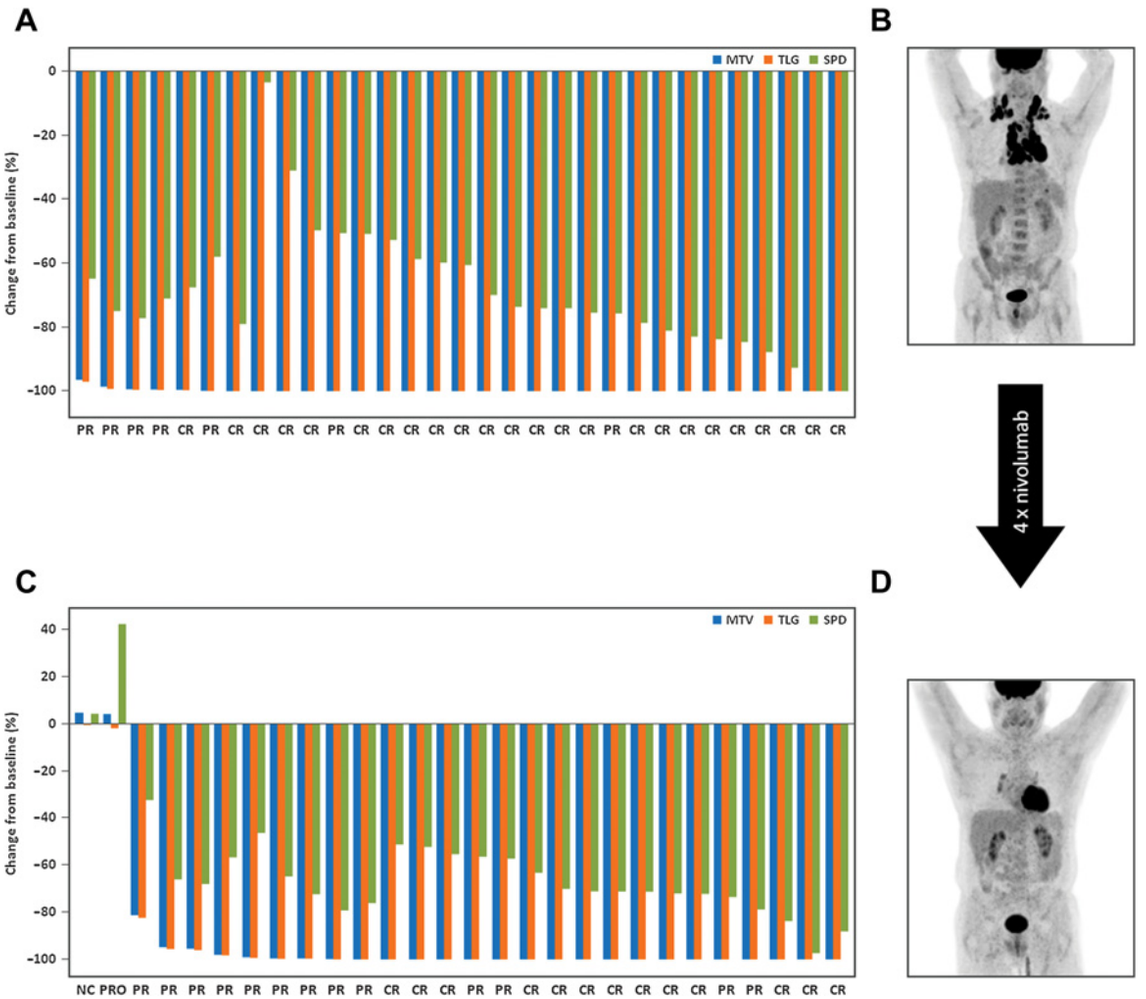

Figure 2.

Early effects of study treatment. Waterfall plots showing decrease in tumor burden at interim response assessment for the individuals from arm A receiving 2 × N-AVD (**A**), compared with those in arm B after 4 × nivolumab (**C**). Baseline and interim PET of a patient with marked decrease in supradiaphragmatic disease (**B**) and a small amount of residual tumor tissue after nivolumab monotherapy (**D**). NC, no change; PRO, progressive disease; PR, partial response.

46.4% (n = 13) of eligible patients undergoing 2 × N-AVD and 4 × nivolumab, respectively. Among individuals with baseline MTV above the median, however, a smaller proportion achieved Deauville scores <4 compared with those showing lower MTV at staging (39.9%, n = 18/30 vs. 86.2%, n = 4/29). Moreover, we documented a mean ΔSPD of −69.1% (SD, 19.6) and −60.7% (SD, 27.6), respectively, at early response assessment in treatment groups A and B.

Discussion

Our study examined response to anti-PD-1–based first-line therapy in Hodgkin lymphoma using PET-derived biomarkers. We observed early near-complete reductions of metabolic tumor burden in most individuals from both arms, despite a lower rate of early CR after sequential treatment. Whether the residual PET positivity in patients with partial remission (PR) but substantial MTV reduction reflects active lymphoma tissue or inflammation remains unclear due to the lack of rebiopsies at this time point. However, all but one primary progressive patient were in CR at last data cut-off after a median follow-up of 13 months. Hence, interim CR rates determined with established criteria may underestimate the individual benefits from PD-1 blockade in therapy-naïve Hodgkin lymphoma. Early results of another ongoing phase II trial assessing sequential first-line treatment with pembrolizumab and AVD showed a similar discrepancy between conventionally assessed response rates and metabolic tumor burden (18), highlighting the potential value of PET-derived biomarkers in addition to existing response criteria. While the modified therapy decision guidelines are helpful for indefinite immune checkpoint inhibition (13, 14), tailored first-line treatment could benefit from more continuous parameters such as ΔMTV. In this setting, achieving a PR by established criteria with substantial MTV reduction may be considered sufficient for deescalation.

Two small, retrospective single-center studies indicated the feasibility of using ΔMTV and ΔTLG in response assessment of R/R Hodgkin lymphoma patients undergoing anti-PD-1 monotherapy (19, 20). Interestingly, the MTV decrease was significantly greater for individuals achieving CR than in those with stable or progressive

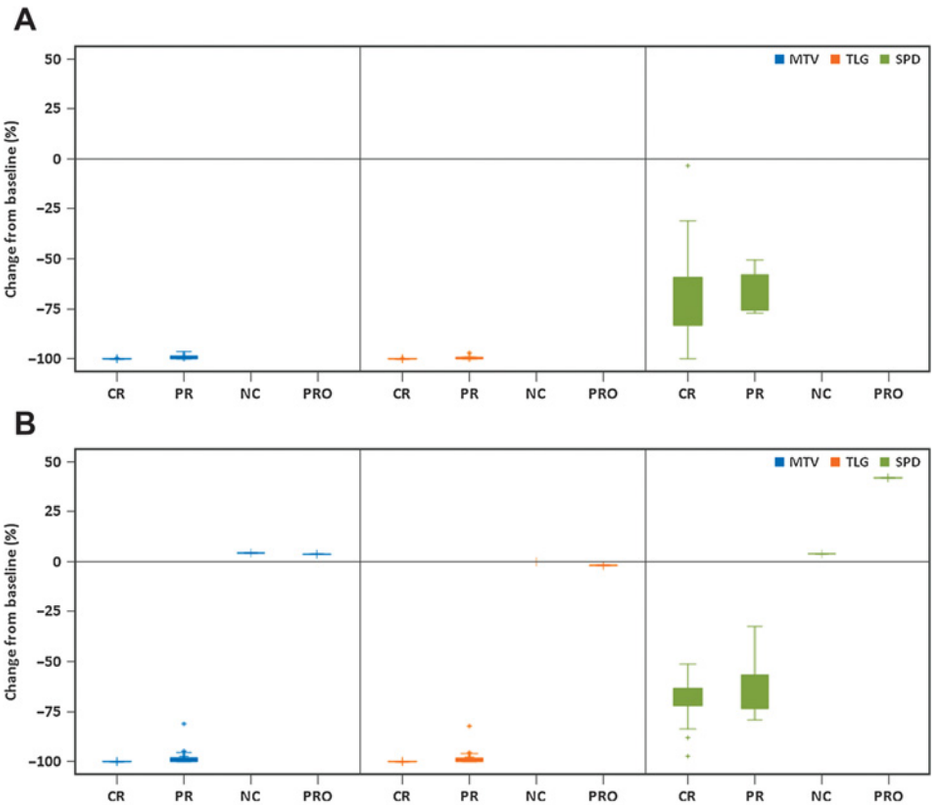

Figure 3.
Comparison of response assessment methods by interim remission status. Box plots demonstrating a wider spread of SPDs as compared with MTV and TLG for patients from arm A undergoing 2 × N-AVD (**A**) and those in treatment group B receiving 4 × nivolumab (**B**). NC, no change; PRO, progressive disease; PR, partial response.

disease. Our analysis showed a similar reduction of MTV and TLG in patients achieving interim PR or CR. Castello and colleagues additionally reported a positive correlation between ΔMTV and response at later time points. Hence, timely identification of individuals with high treatment sensitivity based on PET-derived biomarkers could be the key to tailored immunotherapy regimens.

In summary, we showed that ΔMTV and ΔTLG may be valid parameters for accurate quantification of response to PD-1 inhibitors. The rapid reduction in tumor metabolism after nivolumab alone indicates a relevant role of first-line anti-PD-1–based debulking therapy for Hodgkin lymphoma. Our analysis is limited by the short follow-up period and potential bias was introduced by a higher proportion of individuals with bulky and stage II disease in the current sample as compared with the total trial population. Future studies are therefore required to investigate whether PET-derived biomarkers can safely guide reduction or even omission of chemotherapy and radiotherapy in patients with Hodgkin lymphoma with substantial early MTV reduction.

Authors' Disclosures

U. Keller reports personal fees and other from Bristol Myers Squibb during the conduct of the study; personal fees and other from Roche, Janssen-Cilag, Takeda, Gilead, Amgen, and Celgene; and personal fees from Pentixapharm, Hexal, Pfizer, Astra-Zeneca outside the submitted work. J. Meissner reports other from Merck Sharp & Dohme, Bristol Myers Squibb, Takeda, Celgene, and Hexal outside the submitted work. K. Trautmann-Grill reports personal fees from Bristol Myers Squibb and personal fees and nonfinancial support from Takeda and Celgene outside the submitted work. M. Fuchs reports personal fees from Amgen, Takeda, and Celgene outside the submitted work. B. von Tresckow reports grants from Bristol Myers Squibb during the conduct of the study; personal fees from Amgen, Pfizer, Gilead, Roche, and Pentixafarm; and grants, personal fees, and nonfinancial support from Merck Sharp & Dohme, Takeda, and Novartis outside the submitted work. P. Borchmann reports personal fees from Bristol Myers Squibb during the conduct of the study. A. Engert reports grants and nonfinancial support from Bristol Myers Squibb during the conduct of the study and personal fees from Bristol Myers Squibb, Merck Sharp & Dohme, and Takeda outside the submitted work. P.J. Bröckelmann reports grants from Bristol Myers Squibb during the conduct of the study; grants, personal fees, and nonfinancial support from Bristol Myers Squibb and Takeda; and grants from Merck Sharp & Dohme and Affimed Therapeutics outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

C.-A. Voltin: Conceptualization, resources, data curation, software, formal analysis, investigation, methodology, writing-original draft. **J. Mettler:** Conceptualization, resources, data curation, software, formal analysis, investigation, methodology, writing-review and editing. **L. van Heek:** Resources, data curation, software, investigation, methodology, writing-review and editing. **H. Goergen:** Data curation, formal analysis, visualization, project administration, writing-review and editing. **H. Müller:** Data curation, formal analysis, visualization, writing-review and editing. **C. Baues:** Investigation, writing-review and editing. **U. Keller:** Investigation, writing-review and editing. **J. Meissner:** Investigation, writing-review and editing. **K. Trautmann-Grill:** Investigation, writing-review and editing. **A. Kerkhoff:** Investigation, writing-review and editing. **M. Fuchs:** Resources, investigation, project administration, writing-review and editing. **S. Sasse:** Investigation, writing-review and editing. **B. von Tresckow:** Investigation, writing-review and editing. **M. Dietlein:** Resources, investigation, writing-review and editing. **P. Borchmann:** Conceptualization, resources, investigation, writing-review and editing. **A. Engert:** Resources, supervision, funding acquisition, investigation, writing-review and editing. **C. Kobe:** Conceptualization, resources, data curation, software, formal analysis, supervision, validation, investigation, methodology, writing-review and editing. **P.J. Bröckelmann:** Conceptualization, resources, supervision, funding acquisition, investigation, methodology, writing-original draft, writing-review and editing.

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