Reinduction therapy with everolimus in combination with dexamethasone, high-dose cytarabine and cisplatinum in patients with relapsed or refractory classical Hodgkin lymphoma: an experimental phase I/II multicentre trial of the German Hodgkin Study Group (GHSG HD-R3i)

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Summary
Reinduction chemotherapy followed by high-dose chemotherapy and autologous stem cell transplant (HDCT + ASCT) is second-line standard of care for transplant-eligible patients with relapsed/refractory classical Hodgkin lymphoma (r/r cHL) but has a high failure rate. Because response to reinduction is predictive of the outcome after HDCT + ASCT, we aimed to improve the standard dexamethasone, high-dose cytarabine and cisplatinum (DHAP) reinduction regimen by addition of the oral mammalian target of rapamycin inhibitor everolimus (everDHAP). Transplant-eligible patients aged 18–60 years with histologically confirmed r/r cHL were included in this experimental phase I/II trial. Everolimus (10 mg/day, determined in phase-I-part) was administered on day 0–13 of each DHAP cycle. From July 2014 to March 2018, 50 patients were recruited to the phase II everDHAP group; two were not evaluable, three discontinued due to toxicity. Randomization to a placebo group stopped in October 2015 due to poor recruitment after nine patients. The primary end-point of computed tomography (CT)-based complete remission (CR) after two cycles of everDHAP was expected to be ≥40%. With a CT-based CR rate of 27% (n = 12/45) after two cycles of everDHAP the trial did not meet the primary end-point. Adding everolimus to DHAP is thus feasible; however, the everDHAP regimen failed to show an improved efficacy.

Keywords: everolimus, Hodgkin lymphoma, relapse, salvage, reinduction.
Introduction

Most patients suffering from Hodgkin lymphoma (HL) are cured with adequate risk-adapted first-line treatment; however, 10–30% of patients are primary refractory to first-line treatment or will subsequently relapse.1-8

The current standard-of-care treatment for transplant-eligible patients with relapsed/refractory classical HL (r/r cHL) is reinduction therapy, with e.g. two cycles of dexamethasone, high-dose cytarabine and cisplatinum (DHAP), followed by consolidating high-dose chemotherapy (HDCT), usually with high-dose carmustine (BCNU), etoposide, cytarabine and melphalan (BEAM), and subsequent autologous stem cell transplant (ASCT).9,10 However, even with consolidative approaches for high-risk patients11,12 long-term progression-free survival (PFS) is only approximately 50%.9,10,13

Owing to the lack of randomized phase III trials comparing different reinduction combinations there is no universally accepted standard salvage regimen. Due to high response rates and reasonable tolerability the DHAP regimen has become the standard approach within the German Hodgkin Study Group (GHSG) and other cooperative groups. The computed tomography (CT)-based overall response rate (ORR) with two cycles of time-intensified DHAP was 89% [21% CR, 68% partial remission (PR)] in a prospective phase II trial and more recent data have confirmed these results.14,15

Response to reinduction therapy is predictive of the final outcome after HDCT + ASCT with regards to PFS and overall survival (OS).11,16,17,18,19,20 Therefore, increasing the CR rate after DHAP reinduction is a reasonable strategy to improve cure rates after HDCT + ASCT. Combining the DHAP chemotherapy regimen with a more targeted agent was thus considered a promising approach.

The rationale to investigate inhibitors of mammalian target of rapamycin (mTOR) in HL derives from trials demonstrating activation of the phosphatidylinositol 3-kinase (PI3K) pathway in this malignancy and studies providing proof of concept regarding the clinical use of mTOR inhibitors in r/r HL.21-24 The small-molecule mTOR inhibitor everolimus previously demonstrated safety and efficacy in various malignancies25 and showed promising response rates in phase II trials in heavily pretreated HL patients with ORR of 47% and 46%.23,24 Multiple in vitro studies suggest a synergism of mTOR inhibitors when combined with dexamethasone and cisplatin and thus support their integration in the DHAP salvage regimen for the treatment of r/r cHL patients.26-30

The GHSG HD-R3i trial thus investigated the addition of oral everolimus to time-intensified (i.e. two-week cycles31) DHAP regarding feasibility and safety, as well as efficacy in terms of complete remission (CR) rates achieved prior to HDCT, with the goal of increasing cure rates in patients with r/r cHL. Here, we report the final results of the phase I and the phase II part of this trial.

Patients and methods

The prospective, randomized, placebo-controlled, multicentre phase I/II GHSG HD-R3i trial (NCT01453504) was conducted at 16 trial sites in Germany. The trial was designed by the GHSG steering committee and approved by the ethics committees of the participating centres (Data S1). It was carried out in accordance with the ethical principles of the Helsinki declaration and conducted in conformity with the International Conference on Harmonization guidelines for Good Clinical Practice. An independent data safety monitoring board regularly evaluated patient safety and efficacy data.

Patients aged 18–60 years with histologically confirmed r/r cHL in all clinical stages were eligible for study inclusion. Any previously administered first-line polychemotherapy regimen was permitted. In case of multiple relapse, any previously administered salvage therapy was permitted but no prior HDCT + ASCT. Other main inclusion criteria included a World Health Organization activity index32 of ≤2 and the absence of major organ dysfunction as specified in the
protocol. All patients provided written informed consent prior trial enrolment.

The HD-R3i trial was planned as a phase I/II trial. Primary objective of phase I was to identify a safe daily dose of oral everolimus for phase II of the trial, with the determined recommended phase II dose (RPTD) being the highest dose level at which <1/3 of patients experience a dose-limiting toxicity (DLT) when treated with two cycles of everolimus plus DHAP (everDHAP). Everolimus daily dose levels of 2.5, 5, 7.5 and 10 mg were tested in combination with DHAP in a modified 3 + 3 design. Administration of everolimus started one day before DHAP, allowing for an adequate loading of oral everolimus before chemotherapy, on day 0 of the first cycle, and continued for 14 days. Time-intensified DHAP was administered at standard doses [dexamethasone 40 mg (days 1–4), cisplatinum 100 mg/m² (day 1), high-dose cytarabine 2000 mg/m² (day 2)].14 Granulocyte colony-stimulating factor (G-CSF) was administered adjusted to body weight from day 4 onwards until peripheral blood stem cell (PBSC) harvest. The described scheme was repeated for the second cycle of everDHAP in the same manner starting on day 14 of the first cycle.

Primary end-point of phase I was the rate of patients experiencing DLTs during two cycles of the combination therapy with everDHAP. Pre-defined DLTs included unsuccessful stem cell mobilization (<2 × 10⁶ CD34⁺ cells/kg) and any non-haematological toxicity ≥ grade 3 with the exception of nausea/vomiting in the absence of appropriate anti-emetic therapy. Grade III/IV non-haematological toxicities known from DHAP counted as DLT from second occurrence in any patient onwards. Grade III/IV haematological toxicities counted as DLTs in case of prolonged time to recovery (neutropenia grade IV for more than 10 days or thrombocytopenia grade IV for more than five days). Secondary objectives of phase I were evaluation of feasibility and safety of everDHAP, secondary end-points thus included adverse events, tumour-related results of therapy or death, treatment administration and time to recovery after end of treatment.

In the phase II part of this trial patients were randomly assigned (1:1) to receive either two cycles of everDHAP or to receive two cycles of placebo plus DHAP (placDHAP) with four stratification factors [trial centre, age (<45 years vs ≥45 years), sex and history of either progressive disease or multiple relapse (yes versus no)]. During the randomized phase of the study patients and investigators were blinded for treatment allocation.

In the everDHAP group everolimus was administered at a dose of 10 mg/day (RPTD determined in phase I) on day 0–13 of the first cycle. In the placDHAP group, matching placebo was administered in the same schedule and manner. In both groups, time-intensified DHAP was administered as described above. If necessary, dose reduction according to prespecified dose adjustment guidelines was permitted. For the second cycle the described scheme was repeated starting on day 14 of the first cycle. Again, G-CSF was given from day 4 on. The planned duration of induction therapy was 28 days including PBSC harvest between cycle 1 and cycle 2. Restaging by 18FDG-positron-emission-tomography (PET)-CT was performed on day 21 of the second cycle provided that blood values had recovered (neutrophil granulocytes ≥ 1500/mm³, thrombocytes ≥ 75 000/mm³) and the patient had recovered from severe toxicities; performance of a PET scan was mandatory only for patients not achieving a CR in the CT scan.

Primary efficacy end-point of the phase II part of the trial was the rate of patients with CR or CR unconfirmed (CRu) according to the CT-based final restaging after two cycles of everDHAP. CR was defined as complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms. CRu included patients who fulfilled criteria for CR but also had a residual lymph node mass > 1.5 cm in greatest transverse diameter that had regressed by more than 75% in the sum of the products of the greatest diameter (SPD) and/or individual nodes that were previously confluent that had regressed by more than 75% in their SPD compared with the size of the original mass. Secondary efficacy end-points of the trial were PET-based CR rate³² after two cycles of induction therapy as well as PFS (time between date of completion of all initial staging examinations and date of first progression/relapse or death or, in cases of continuing response, date of the last documented follow-up) and OS (time between date of completion of all initial staging examinations and the date of death or date of the last documented follow-up). Time to recovery after the first and second cycle of induction therapy as well as duration of induction therapy were additional secondary end-points. Further secondary feasibility end-points included discontinuation rate and dose reduction rate of trial medication, rates of successful PBSC collection after first and/or second cycle of induction therapy as well as adverse events and quality of life.

Phase I data were analysed by exploratory analysis of safety and available clinical information such as efficacy and feasibility. The a priori defined criterion for proceeding with phase II was a maximum tolerable dose of at least 5 mg everolimus in combination with DHAP. In phase II, the primary efficacy end-point was tested with an exact single-stage phase II design. We aimed to show a superior CR rate with everDHAP as compared to historical data with DHAP (CR rate 21%).¹⁴,¹⁵ Based on the exact binomial distribution, we tested the null hypothesis H₀ ‘CR rate after everDHAP ≤ 21%’ whereby 21% denoted the benchmark for ineffectiveness. Assuming a true CR rate ≥40% after everDHAP, accepting a type I error probability α < 0.05 and aiming at a statistical power 1 − β ≥ 0.90, we planned to recruit n = 50 patients into the everDHAP group. Because data on PET-responses after DHAP were not available when the trial was planned CT-based CR rate was the primary end-point of the trial. However, to get reference data of tolerability and efficacy of everDHAP and contemporary DHAP.
therapy including PET response rates we planned to recruit the same number of patients into the placDHAP group. Patients treated with placDHAP are presented in a descriptive way only and not used for statistical comparison tests due to premature closure of the placDHAP arm in light of poor recruitment. Statistical analysis of secondary end-points was exploratory; all patients who had received at least one dose of study medication were included in the safety and feasibility analyses. PFS and OS were estimated using the Kaplan–Meier method and SAS version 9.4 (SAS Inc., Cary, NC, USA) was used for all statistical analyses.

Results
Between March 2012 and January 2014 a total of 14 patients with r/r cHL were recruited to phase I of the trial. All patients received at least one dose of everolimus. Median age was 33-5 years, six patients were female and eight were male. Stage III/IV disease was present in 11 patients. Two patients (both at the 7.5 mg level) had a premature treatment termination and did not receive the second cycle, one patient due to ototoxicity of grade I at investigator’s discretion and one patient due to neurotoxicity of grade III/IV. One patient (7.5 mg cohort) suffered from ototoxicity of grade III/IV between end of treatment and restaging. Both grade III/IV toxicities were pre-defined as known toxicities from the DHAP regimen and thus they were not considered dose-limiting at this first occurrence. No further non-haematological grade III/IV adverse events were reported. All patients but one experienced grade III/IV thrombocytopenia and leukopenia. No DLTs occurred and ever DHAP was shown to be safe and feasible up to a daily everolimus dose of 10 mg which was consequently defined as RPTD. CT-based ORR was 92% (11/12) with 50% CR/CRu (n = 6/12), 41.7% PR (n = 5/12) and 8.3% stable disease (n = 1/12) rate. One death occurred in a patient with pneumococcal sepsis one year after the end of study treatment.

Between July 2014 and March 2018, a total of 59 patients with r/r cHL were included in the phase II part of the trial (Fig 1). After randomization of 18 patients (nine patients into the experimental and nine patients into the placebo group) randomization was stopped in October 2015 due to poor recruitment. Thereafter, a further 41 patients were enrolled to receive everDHAP. Therefore, data of the placebo group are very limited and reported for completeness only. Of 50 patients recruited to the everDHAP group, two were not evaluable (one withdrawal of consent to participate, one revised diagnosis; both had not yet started treatment), resulting in 48 patients evaluable for secondary end-points. Three additional patients discontinued everDHAP due to toxicity and were not included in the efficacy analysis set as no per-protocol restaging after induction therapy was performed.

![Consort diagram of phase II](wileyonlinelibrary.com)
Characteristics of the 48 patients included in the ever-DHAP group are shown in Table I. Median age at the time of inclusion was 33 years, with 16 female (33%) and 32 male (67%) patients included. Five patients (11%) had B symptoms and 13 patients (27%) had Ann Arbor stage IV. At the time of enrolment, seven patients (15%) were refractory to previous treatment (defined as progressive disease during or within three months after the end of the previous treatment); 15 (32%) had an early relapse within 12 months from the last treatment and 25 (53%) had a late relapse more than 12 months after last treatment. Thirteen patients (29%) had a Josting risk score > 1 and 14 (30%) a RisPACT risk score > 1.1,34 Characteristics of the placDHAP group appear similar (Table I), but the small group size of nine patients is prohibiting any conclusion or comparison.

Primary end-point evaluation demonstrated a CT-based CR after two cycles of therapy in 27% ($n = 12/45$) of patients in the ever-DHAP group (Additional data, Table II). The observed CR rate of 27% [95% confidence interval (CI): 15–42] failed to meet the predefined efficacy end-point (CT-based CR rate $\geq$ 40%) and was not significantly superior to historical CR rates of 21% after two cycles of DHAP determined in the GHSG HDR2-trial15 ($P = 0.23$, exact one-sided binomial test) or descriptively observed in the placDHAP group (22%; $n = 2/9$).

Positron emission tomography-based restaging after two cycles of induction therapy demonstrated that approximately half of the PRs after ever-DHAP were PET-negative with a Deauville score $< 4$ resulting in a PET-based CR rate of 56% ($n = 22/39$, 95% CI = 41–71) with ever-DHAP (additional data, Table III). The PET-based CR rate in the placDHAP group was 25% ($n = 2/8$).

Table IV summarizes general feasibility parameters with ever-DHAP. During phase II, 9/44 patients (20%) needed dose reductions in the first and 13/42 patients (31%) in the second cycle. A delayed recovery $> 14$ days was observed in 2/44 (5%) and 6/38 (14%) patients in cycle 1 and 2 respectively. In cycle 1 and 2, 39/41 (95%) and 27/36 (75%) patients respectively, experienced common terminology criteria for adverse events (CTCAE) grade IV toxicity with ever-DHAP (Table V). Most of these toxicities were haematological with no grade IV non-haematological toxicities observed. Grade III non-haematological toxicities included nausea, mucositis, other gastrointestinal side effects and infections (see Table V for more details). PBSC collection was successful in 44 ever-DHAP patients (98%),

### Table I. Patient characteristics at time of enrolment.

| everDHAP ($n = 48$) | placDHAP ($n = 9$) |
|---------------------|--------------------|
| **Sex**             |                    |
| Female              | 16 (33)            | 2 (22)          |
| Male                | 32 (67)            | 7 (78)          |
| **Age (18–60 years)**|                    |
| <45 years           | 32 (67)            | 8 (89)          |
| $\geq$45 years      | 16 (33)            | 1 (11)          |
| **ECOG**            |                    |
| 0                   | 35 (75)            | 5 (56)          |
| 1–2                 | 12 (25)            | 4 (44)          |
| **B symptoms**      |                    |
| No                  | 42 (89)            | 9 (100)         |
| Yes                 | 5 (11)             | -               |
| **Number of relapses**|                  |
| 1                   | 47 (98)            | 9 (100)         |
| 2                   | 1 (2)              | -               |
| **Time to relapse** |                    |
| Progressive disease | 15 (32)            | 1 (11)          |
| Early relapse ($\leq$12 months) | 25 (53) | 5 (56) |
| Late relapse ($>$12 months) | -            | -               |
| **Ann Arbor stage** |                    |
| I                   | 6 (13)             | 1 (11)          |
| II                  | 18 (38)            | 4 (44)          |
| III                 | 11 (23)            | 1 (11)          |
| IV                  | 13 (27)            | 3 (33)          |

DHAP, dexamethasone, high-dose cytarabine and cisplatinum; ECOG, Eastern Cooperative Oncology Group; everDHAP, everolimus plus DHAP; placDHAP, placebo plus DHAP.

### Table II. CT-based tumour status after induction therapy.

| everDHAP | placDHAP# |
|----------|-----------|
| N        | %         | N        | %         |
| Early tumour response | | | |
| Complete remission | 12 | 27 | 2 | 22 |
| Partial remission  | 26 | 58 | 2 | 22 |
| No change         | 5  | 11  | 5  | 56  |
| Progressive disease | 2  | 4  | -  | -   |
| Total             | 45 | 100 | 9 | 100 |

CT, computed tomography; DHAP, dexamethasone, high-dose cytarabine and cisplatinum; everDHAP, everolimus plus DHAP; placDHAP, placebo plus DHAP.

#Purely descriptive; no confirmatory test.

### Table III. PET-based evaluation of tumour status after induction therapy.

| everDHAP | placDHAP# |
|----------|-----------|
| N        | %         | N        | %         |
| Early tumour response | | | |
| Complete remission | 22 | 56 | 2 | 25 |
| or PET-negative PET-positive | 17 | 44 | 6 | 75 |
| Total     | 39 | 100 | 8 | 100 |

DHAP, dexamethasone, high-dose cytarabine and cisplatinum; everDHAP, everolimus plus DHAP; placDHAP, placebo plus DHAP; PET, positron emission tomography.

#Purely descriptive; no confirmatory test.
Two patients were refractory to treatment with everDHAP (4%). With a median observation time (MOT) of 14 months for PFS, nine and two patients experienced a second and third relapse respectively, after treatment with everDHAP followed by HDCT + ASCT. A total of three deaths (MOT for OS 13 months) occurred, and all were attributed to toxicity of HDCT + ASCT.

Discussion

We report the results of the multicentre GHSG HD-R3i phase I/II trial that evaluated the addition of the mTOR inhibitor everolimus to the established DHAP salvage chemotherapy regimen with the aim of improving response to reinduction before HDCT + ASCT in patients with r/r cHL.

Two principal findings arise from our study: first, reinduction with combined oral mTOR inhibition with 10 mg everolimus/day and DHAP at standard doses is feasible and tolerable. Second, addition of everolimus to DHAP does not result in improved efficacy of the reinduction regimen in terms of CT-measured CR rates after two cycles of everDHAP.

Historical CR rates of DHAP are around 21%. The HD-R3i trial intended to reach a CT-based CR rate of ≥40% with everDHAP which would constitute a significant and clinically relevant improvement. With a CT-based CR rate of 27% after two cycles of DHAP plus everolimus, however, the trial failed to meet its primary end-point. Furthermore, Kaplan–Meier curves of PFS and OS of the everDHAP group indicated no relevant difference to current standard induction therapy in patients with r/r cHL.

Table IV. Feasibility of treatment.

|                        | Cycle 1 | Cycle 2 |
|------------------------|---------|---------|
|                        | everDHAP | placDHAP | everDHAP | placDHAP |
| n# %#                  | n# %#    | n# %#    | n# %#    | n# %#    |
| Dose reduction of ever/placebo | Yes | 9 20 | - | - | Yes | 13 31 | 2 25 | No | 35 80 | 8 100 | 29 69 | 6 75 |
| Delayed recovery >14 days | Yes | 2 5 | - | - | Yes | 6 14 | - | - | No | 42 95 | 8 100 | 38 86 | 9 100 |
| Max. toxicity (CTCAE) grade | 3 | 2 5 | - | - | 9 25 | 2 40 | 4 | 39 95 | 8 100 | 27 75 | 3 60 |
| Duration of apheresis (days) | 1 | 35 80 | 9 100 | 2 | 8 18 | - | - | >2 | 1 2 | - | - |
| Successful PBSC collection (>2 x 10^9 CD34+ cells/kg) | Yes | 44 98 | 8 100 | No | 1 2 | - | - |

CTCAE, common terminology criteria for adverse events; DHAP, dexamethasone, high-dose cytarabine and cisplatinum; everDHAP, everolimus plus DHAP; PBSC, peripheral blood stem cell; placDHAP, placebo plus DHAP.

*#n < 45 due to missing documentation or treatment discontinuation, percentages rely on available data.*

Table V. CTCAE toxicities.

|                        | Cycle 1 (N = 41#) | Cycle 2 (N = 36#) |
|------------------------|------------------|------------------|
|                        | Grade III | Grade IV | Grade III | Grade IV |
|                        | n | % | n | % | n | % | n | % |
| Anaemia                | 3 | 7 | 1 | 2 | 5 | 14 | - | - |
| Thrombopenia           | 4 | 10 | 33 | 80 | 6 | 17 | 25 | 69 |
| Leukopenia             | 4 | 10 | 31 | 76 | 6 | 17 | 14 | 39 |
| Nausea/vomiting        | 5 | 12 | - | - | 2 | 6 | - | - |
| Mucositis              | 3 | 7 | - | - | - | - | - | - |
| Gastrointestinal       | 2 | 5 | - | - | - | - | - | - |
| Heart                  | - | - | - | - | 1 | 3 | - | - |
| Infections             | 2 | 5 | - | - | 3 | 8 | - | - |
| Skin                   | 1 | 2 | - | - | - | - | - | - |

CTCAE, common terminology criteria for adverse events.

*#N < 45 due to missing documentation or treatment discontinuation, percentages rely on available data.*
and 70% respectively). Other regimens such as ifosfamide, carboplatin, etoposide (ICE) or ifosfamide, gemcitabine, etoposide and vinorelbine (IGEV) demonstrated higher CR rates of 26–29% (ORR 88–89%) and 54% (ORR 81%) respectively. It should be taken into account that the last-mentioned CR rates were assessed via PET scan. Today, the use of a PET scan in order to assess response to reinduction is considered standard of care. In our trial, PET-based restaging after two cycles of induction therapy demonstrated that approximately half of the PRs after everDHAP were PET-negative with a Deauville score < 4 resulting in a PET-based CR rate of 56% with everDHAP. This finding is in the range of PET-based CR rates described for the IGEV and ICE regimens.

For many years, clinical research has focussed on improving second-line therapy by treatment intensification including second salvage therapies, tandem HDCT + ASCT and consolidation. As still half of all patients fail to reach long-term remissions with any of those approaches and acute and long-term toxicity remain high due to the use of HDCT, the need for better therapeutic options for HL patients experiencing relapsed or refractory disease and for those ineligible for HDCT + ASCT remains unmet.

In our approach, we intended to improve response to an already established conventional reinduction regimen by the addition of the mTOR inhibitor everolimus. However, almost all patients in our trial experienced haematological toxicities of grade III and IV. In order to improve the currently established reinduction regimens without increasing bone marrow toxicity, newer substances with low haematological toxicity could be more suitable. New effective substances such as the antibody–drug conjugate brentuximab vedotin (BV) targeting CD30 as well as checkpoint inhibitors targeting PD-1 (programmed cell death protein 1) are now available for patients with r/r HL and demonstrate high response rates with good tolerability. There are several studies incorporating those substances in r/r cHL: Kersten and colleagues combined BV with DHAP and reported that 81% of patients achieved a
metabolic CR as measured by PET before continuing to HDCT and ASCT. The combination of BV with ICE in the same indication was investigated by Moskowitz already in 2015 and resulted in PET negativity in 76% of patients; after BV alone 13% (ORR 68%) and 27% of patients had a CR. BV in combination with the ICE regime was recently also investigated by Lynch and colleagues with a reported 74% CR (combination with the ICE regime was recently also investigated after two cycles, BV in combination with bendamustine or the ESHAP regime (etoposide, methylprednisolone, high-dose cytarabine, cisplatin) demonstrated similar efficacy results. The addition of the PD-1 inhibitor nivolumab to the ICE regimen resulted in CR in 96% of patients, while 77% (n = 22/26) achieved CR after nivolumab alone. Moskowitz and colleagues recently investigated the addition of the PD-1 inhibitor pembrolizumab to the gemcitabine, vinorelbine and doxorubicin (GVD) regimen and demonstrated good tolerability and high efficacy with CR rates of 93%.55

Addition of new substances to already established conventional chemotherapy regimens may induce higher CR rates prior to consolidation with HDCT + ASCT and might thereby improve PFS and OS. However, further intensifying genotoxic therapy, even if the implemented substances usually do not have significant haematological toxicity, will still presumably increase the general toxicity of the treatment strategy. On top of that, low-risk patients already responding well to established regimens receive an unnecessary treatment intensification (and consequently an unnecessary increase in toxicity). Thus, an increase in treatment intensity should be adjusted to the individual patients’ needs.11

Instead of adding targeted substances to the reinduction regimen such drugs could replace the conventional chemotherapeutic agents allowing for a reduction of treatment burden for well-responding patients and de-escalation of genotoxic interventions in low-risk patients. Herrera and colleagues demonstrated high response rates in two trials investigating reinduction treatment with BV alone and BV in combination with nivolumab with CR rates of 43% and 62% respectively. However, the relatively long treatment duration of three months for the induction part in their trial with BV and nivolumab may be regarded as a disadvantage of this approach. In addition, all therapeutic approaches that have been illuminated so far contain consolidative HDCT, which comprises major toxicities. However, probably not all patients with r/r cHL need HDCT + ASCT and approaches replacing HDCT, e.g. by the use of PD-1 inhibitors combined with established chemotherapeutic salvage regimens or PD-1 inhibitors + BV, appear promising.

Based on this hypothesis, the GHSG is currently initiating a phase II trial introducing PD-1 inhibitors in second-line therapy of r/r cHL with the aim to abandon highly toxic HDCT in well-responding patients. As PD-1 blockade alone is not likely to be sufficient as a curative concept, pembrolizumab will be combined with conventional ICE chemotherapy in a PET-adapted strategy. Similarly, inspired by their positive results investigating pembrolizumab plus GVD as reinduction combination, Moskowitz and colleagues are currently planning a high-dose-chemotherapy-free cohort within their trial, assuming that HDCT plus ASCT may be shifted to the third-line setting. Combined chemoimmunotherapy is currently being examined in several trials as some chemotherapeutic agents are known to evoke immune response against the tumour which facilitates curative chemotherapy and might play a crucial role for long-term remissions. Synergistic effects of chemotherapy with PD-1 inhibitors may thus facilitate an effective therapy with limited toxicity.

Altogether, our analysis of the GHSG HD-R3i trial demonstrated that the addition of everolimus to time-intensified DHAP is feasible but fails to show an improved efficacy in terms of CR rates prior HDCT. Moreover, PFS and OS also did not indicate any major advantage for the everDHAP combination. When comparing our results to other contemporary trials and therapeutic concepts, other targeted substances than mTOR inhibitors appear more promising for the treatment of r/r cHL.

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Author contributions
PB, AE, MF, BvT provided conception and design and administrative support; BB, SB, PJB, DAE, J-MH, AH, CK, SS, CS, MT, AV and VV provided study material or patients; HH, HM and AP carried out the statistical analysis; SG, HM and BvT drafted and revised the manuscript; All authors approved of the submitted and final version.

Conflicts of interest
AH: Celgene: other, travel expenses; Roche: other, travel expenses. AV: Amgen: consultancy, Roche: consultancy, honoraria; BMS: consultancy, honoraria; Gilead Kite: consultancy, honoraria; Novartis: consultancy, honoraria; Takeda: consultancy, AstraZeneca: honoraria. MST: Amgen: honoraria, membership on an entity’s Board of Directors or advisory committee, other, travel, research funding; F. Hoffmann-La Roche Ltd: membership on an entity’s Board of Directors or advisory committees, other, travel, research funding; Boehringer Ingelheim: research funding; Regeneron Pharmaceuticals, Inc.: honoraria, research funding. BB: Astellas;
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Supporting Information

Additional supporting information may be found online in
the Supporting Information section at the end of the article.

Data S1. Supplementary methods.

References

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