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A Phase 2 multicenter study of the anti-CD19 antibody drug conjugate coltuximab ravtansine (SAR3419) in patients with relapsed or refractory diffuse large B-cell lymphoma previously treated with rituximab-based immunotherapy

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Abstract

This phase 2, single-arm, multicenter study examined the efficacy and safety of coltuximab ravtansine (an anti-CD19 antibody drug conjugate) in 61 patients with histologically documented (*de novo* or transformed) relapsed or refractory diffuse large B-cell lymphoma who had previously received rituximab containing immuno-chemotherapy. Patients had received a median of 2.0 (range 0–9) prior treatment regimens for diffuse large B-cell lymphoma and almost half (45.9%) had bulky disease (≥1 lesion >5 cm) at trial entry. Patients received coltuximab ravtansine (55 mg/m^2) in 4 weekly and 4 biweekly administrations until disease progression or unacceptable toxicity. 41 patients were eligible for inclusion in the per-protocol population. The primary endpoint, overall response rate (International Working Group criteria) in the per-protocol population, was 18/41 (43.9% [90% confidence interval 30.6-57.9%]). Median duration of response, progression-free survival and overall survival (all treated patients) were 4.7 (range 0.0–8.8) months, 4.4 (90% confidence interval 3.02-5.78) months, and 9.2 (90% confidence interval 6.57-12.09) months, respectively. Common non-hematologic adverse events included asthenia/fatigue (30%), nausea (23%), and diarrhea (20%). Grade 3-4 adverse events were reported in 23 patients (38%), the most frequent being hepatotoxicity (3%) and abdominal pain (3%). Eye disorders occurred in 15 patients (25%); all were grade 1-2 and none required a dose modification. Coltuximab ravtansine monotherapy was well tolerated and resulted in moderate clinical responses in pretreated patients with relapsed/refractory diffuse large B-cell lymphoma.

ClinicalTrials.gov trial identifier: NCT01472887

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequent form of non-Hodgkin lymphoma, representing approximately 30–58% of cases.[1] The majority of cases of DLBCL occur *de novo*, although some develop from indolent lymphoma.[2] DLBCL is subclassified as germinal center B-cell-like (GCB) or activated B-cell-like (ABC) subtypes based on gene expression profiling. The ABC subtype has a worse prognosis than the GCB subtype.[3] In addition, concurrent deregulation of *MYC* and *BCL2* has been associated with poor outcomes,[4,5] however the prognostic significance of these rearrangements remains controversial.[6-8]

Standard first-line therapy for DLBCL is cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone, combined with rituximab (R-CHOP). Five-year overall survival (OS) in patients treated with this regimen is over 70%.[9,10] Dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab (DA-EPOCH-R), showed promise as an alternative first line regimen to R-CHOP in a phase 2 study, [11] but failed to demonstrate superior event-free or overall survival (OS) in a phase 3 trial, which directly compared the two regimens[12]. The majority of patients in the phase 3 study had good prognostic features, and therefore it is possible that DA-EPOCH-R may provide an advantage in patients with an adverse prognosis (such as *MYC/BCL2* double-hit lymphoma) or rare subtypes (such as primary mediastinal lymphoma). However, the phase 3 study was not designed to answer this question, and R-CHOP remains the standard of care for the majority of unselected patients with DLBCL.[12-15] Salvage treatment with autologous stem cell transplantation (ASCT) is the most effective approach at first relapse. However, it can only be offered to young, fit patients, and long-term survival is only 40%.[16] There are limited treatment options with unsatisfying results for patients relapsing after, or ineligible for, ASCT.[17] New therapeutic strategies are essential for these patients.

Coltuximab ravtansine (SAR3419) is an anti-CD19 monoclonal antibody conjugated to a potent cytotoxic maytansinoid, DM4, *via* an optimized, hindered, disulfide bond. The antibody selectively binds to the CD19 antigen present on the majority of B cells, resulting in internalization of the receptor–drug complex and intracellular release of DM4. DM4 is a potent inhibitor of tubulin polymerization and microtubule assembly, functioning by similar mechanisms to vincristine and vindesine.[18,19]

Coltuximab ravtansine has been evaluated in patients with relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma. A first-in-human phase 1 study examined several dose levels in 3-weekly administrations. At the maximum tolerated dose (160 mg/m^2) few clinical responses and high levels of treatment-related ocular toxicity were observed.[20] A further phase 1, dose-escalation study examined once-weekly dosing and a modified schedule consisting of four weekly doses followed by four doses given once every 2 weeks. Both schedules showed anti-lymphoma activity in approximately 30% of patients with either indolent or aggressive disease. The maximum tolerated dose was 55 mg/m^2, and the modified dosing schedule was found to limit drug accumulation, reduce toxicity, and improve response rates.[19]

To confirm the clinical benefit observed in the phase 1 setting in a population with aggressive lymphoma, we conducted a phase 2, open-label, multicenter study evaluating coltuximab ravtansine monotherapy in transplant-ineligible patients with CD19-positive, R/R DLBCL.

Methods

Study design

In this phase 2, open-label, single-arm study patients received four weekly doses of intravenous (iv) coltuximab ravtansine 55 mg/m^2, followed by a 1-week rest period, then biweekly doses until disease progression (PD), unacceptable toxicity, or discontinuation of treatment. One cycle was 4

weeks, except for cycle 1 (5 weeks). At the investigator's discretion, patients received premedication consisting of iv diphenhydramine 50 mg and oral acetaminophen 650 mg 30-45 minutes before each infusion. Dose reductions were permitted (see supplementary materials).

Patients

Adult patients with *de novo* or transformed histologically confirmed DLBCL and >30% of cells expressing CD19 (local assessment) were enrolled. Patients had relapsed (progression ≥6 months after completion of last line of therapy) or refractory (progression during, or within 6 months of, a prior therapy) disease and had previously received standard chemotherapy (including rituximab). Patients with primary refractory disease (refractory to first line therapy) were ineligible. However some primary refractory patients were wrongly enrolled (see results). Full inclusion and exclusion criteria are included in the supplementary material.

All patients provided written informed consent. The protocol and subsequent amendments were approved by independent ethics committees and/or institutional review boards at each center. The study was conducted according to the Declaration of Helsinki.

Outcomes

The primary endpoint was overall response rate (ORR; proportion of patients achieving a partial response [PR] or complete response [CR] [International Working Group criteria[21]]). Secondary endpoints included duration of response (DOR; time from first PR or CR until PD or death), progression-free survival (PFS; time from first study treatment until PD or death), OS (time from first study treatment until death), and safety. Assessment of biomarkers was an exploratory endpoint.

Assessments

Assessment of clinical response involved physical examination, bone marrow biopsy, and computerized tomography (CT) every 12 weeks until PD or treatment discontinuation. Positron-

emission tomography (PET) was done at baseline and, if positive, repeated to confirm a CR. Patients with a negative CT but positive PET were classified as PR.

Adverse events (AEs) were classified using National Cancer Institute Common Terminology Criteria for Adverse Events (v4.03). Pre-specified AEs of special interest were eye disorders, neuropathy, and infusion-related reactions (all drug hypersensitivity reactions and treatment-related AEs occurring on the day of infusion).

Details of biomarker assessments are included in the supplementary materials.

Statistical analysis

The predicted beneficial ORR was ≥40%. Assuming 44 patients evaluable for response, the study had 90% power to reject the null hypothesis of an ORR of 20% with a one-sided α=0.05. An ORR of <20% was considered clinically uninteresting based on available observations from coltuximab ravtansine and new agents in relapsed/refractory non-Hodgkin lymphoma and/or DLBCL, for which activity ranged between 15% and 30% in Phase 2 studies.[22-28] The primary endpoint (ORR), was assessed in the per-protocol (PP) population (all treated patients who had an evaluable response assessment during or at the end of treatment or who died due to PD before response assessment, without any important protocol deviations affecting efficacy at study entry). ORR was also assessed in the biomarker-evaluable population (all patients with results of biomarker analysis from a fresh or archival sample). DOR and PFS were assessed in the PP population, and OS and safety were assessed in all treated patients (safety population).

Statistical analysis of biomarkers are detailed in the supplementary materials.

Results

Overall, 61 patients were enrolled (20 January 2012 to 23 July 2013) and received ≥1 dose of study drug (safety population). Twenty patients were excluded from the PP population (Figure 1), of whom

16 were wrongly enrolled in the study due to misclassification of their prior treatment history. Of these 16 patients, primary refractory disease was the sole important deviation at study entry in 14. The primary endpoint (ORR) was analyzed separately in this subgroup.

Baseline characteristics of the safety population are summarized in Table 1. Most patients (50/61 patients; 82.0%) presented with DLBCL at initial diagnosis. Of those patients with transformed lymphoma (n=11), seven were initially diagnosed with follicular lymphoma and nine had received prior anticancer therapy for non-DLBCL lymphoma (six patients received ≥1 prior anti-CD20-containing regimen). Almost half of the patients (45.9%) had bulky disease (defined as longest diameter of the lesion >5 cm for at least one location). Patients had received a median of 2.0 (range 0-9) prior treatment regimens for DLBCL, with 18 patients (29.5%) having received ≥3 prior regimens.

Patients received a median of 3 (range 1-10) cycles of therapy (median duration of treatment 13.3 [range 5-41] weeks). Thirty-nine of 61 treated patients (63.9%) received ≥3 treatment cycles, including 16 patients who received ≥6 cycles. Overall, 56 patients discontinued treatment due to: PD (n=47), AEs (n=6), or investigator's decision (n=3). At the time of analysis (6 May 2014), five patients were continuing on therapy.

The ORR (primary endpoint), analyzed in the PP population (n=41), was 43.9% (18/41; 90% CI 30.6-57.9%); therefore, the null hypothesis was rejected (P<0.0001). Among the 18 responders, 6 achieved CR (PET negative) and 12 achieved PR (PET positive [n=8] or not examined [n=4]) (Table 2). Seven patients (7/41; 17.1%) had stable disease, and the remaining patients (16/41; 39.0%) had progressive disease. Higher response rates were observed among patients with relapsed DLBCL (14/26; 53.8%, 90% CI 36.2-70.8%) compared with patients refractory to their last regimen (4/15; 26.7%, 90% CI 9.7-51.1%). A higher ORR (56.3%) was also observed in patients who received only 1 prior therapeutic regimen (n=16). At the time of analysis, six patients with relapsed disease were still responding to therapy (three CRs and three PRs).

ORR was also assessed in 14 patients with primary refractory disease (sole important deviation affecting efficacy) who were excluded from the PP population. Among these patients, the ORR was 21.4% (3/14; 90% CI 6.1-46.6%), with the majority having PD (9/14; 64.3%) and only one patient achieving CR.

Figure 2 shows the DOR in individual patients in the PP population according to initial responses. The median DOR was 4.7 (range 0-8.8) months. Of 18 patients who responded to coltuximab ravtansine treatment (PR or better), four achieved a DOR of >6 months (one of four patients with refractory disease and three of fourteen patients with relapsed disease). At the time of analysis, 34/41 patients (82.9%) in the PP population had experienced PD and the median PFS was 4.4 (90% CI 3.02-5.78) months. Forty-one of the 61 patients in the safety population had died at the analysis cut-off date. Estimated median OS was 9.2 (90% CI 6.57-12.09) months (Figure 3).

CD19 was locally assessed in all patients (n=41) during enrollment, and centrally assessed in 37/41 PP patients (90.2%) during biomarker analysis. Overall, 35 patients had ≥30% CD19-positive cells (range 30-100%). Variable levels of expression were recorded, with 11, 16, and 8 samples having a mean intensity of 1+, 2+, and 3+, respectively. The median H-score (see supplementary methods) was 162 (range 0-270). There was no relationship between levels of expression of CD19 and response; some patients with high CD19 expression had PD as their best response whereas some patients with lower expression experienced a PR (Supplementary Figure 1). Two patients with absent CD19 staining had progressive disease. For each measure of CD19 expression, the receiver-operating characteristic curve AUC values varied between 0.42 and 0.65, indicating that none of the CD19 expression measures showed good predictive accuracy for distinguishing between responders and non-responders (Supplementary Table 1). No significant optimal cut-off point for CD19 expression was identified. In addition, there was no apparent correlation between cell of origin classification or *MYC*/*BCL2* expression and response rate (data not shown).

All 61 patients in the safety population (Table 3) experienced ≥1 AE, including 33/61 patients (54%) who experienced ≥1 treatment-related AE. Grade 3-4 AEs were reported in 23/61 patients (38%), the most frequent being hepatotoxicity (2/61, 3%) and abdominal pain (2/61, 3%). Serious AEs (SAEs) were reported in 24/61 patients (39%). Six SAEs (occurring in 3 patients) were considered related to treatment: hepatotoxicity (n=2), pneumonia, abdominal pain, nausea, and grade 5 febrile neutropenia (n=1).

The most common grade 3-4 hematologic laboratory abnormalities were neutropenia (25%), lymphopenia (21%), and leucopenia (15%) (Table 3). Grade 3-4 non-hematologic laboratory abnormalities were rare, with elevated levels of aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase, and creatinine each occurring in 2 patients. Grade 3-4 febrile neutropenia was also observed in one patient, but did not require growth factor administration.

Eye disorders occurred in 15 patients (25%); all were grade 1-2 and none required a dose modification. Nineteen extracorneal eye disorders were observed in 13 patients (21.3%), with the first occurrence during cycle 1 (6 patients), cycle 2 (n=2), cycle 3 (n=3), cycle 7 (n=1), and cycle 9 (n=1). Fourteen of these events had resolved at the time of data cut-off, with a median recovery time of 12.5d (range 1-47). One patient experienced a corneal event (grade 2 keratitis during cycle 4), which resolved within 9d. A further two patients experienced dry eyes, occurring during cycle 1 and resolving after 13d and 17d, respectively. Neuropathy was observed in 7 patients (11%). Five patients (8%) reported peripheral neuropathy (PN) occurring during cycle 1 (n=3) or cycle 2 (n=2), including one case of grade 3 PN (unrelated to study treatment) in a patient with a history of the condition. Dose modifications were not required in any of the patients with PN, although none of these events had resolved at the time of analysis. A further two patients presented with events compatible with optic neuropathy (grade 1); this diagnosis was not confirmed, but could not be confidently excluded. Neither of these patients required a dose modification and both events resolved within a median of 9d (range 4-14). Overall, infusion-related reactions occurred in 10

patients (16%), and were most commonly gastrointestinal in nature (nausea 10%, vomiting 3%). Drug hypersensitivity was observed in one patient.

Dose modifications (dose omission, interruption, or cycle delay) due to AEs were required in 17 patients (28%), including 9 patients (15%) who experienced a grade 3-4 AE. Nine patients (15%) had ≥1 cycles delayed by >3d, and 9 patients (15%) had one dose omitted. One patient (2%) required a dose interruption due to grade 1 hypotension, which was considered to be unrelated to treatment.

Of eight patients (13%) who experienced AEs leading to death, seven were due to PD. The other patient who died developed febrile neutropenia 34d after the last dose of coltuximab ravtansine while receiving further anticancer therapy (gemcitabine–cisplatin); the investigator could not exclude the possibility that the event was due to a delayed effect of coltuximab ravtansine treatment.

Discussion

The results of this phase 2 trial indicate that treatment with coltuximab ravtansine as monotherapy is associated with moderate clinical responses in a proportion of DLBCL patients previously treated with rituximab-based chemotherapy, and has a favorable toxicity profile.

The responses described here are numerically higher than those reported in a phase 2 study of coltuximab ravtansine in combination with rituximab (ORR 44% [90% CI 30.6–57.9%] *versus* 31% [80% CI 22.0–41.6%], respectively).[29] However, patients enrolled in the combination study were limited to 3 cycles of treatment, whereas in the current study patients continued on therapy until disease progression or discontinuation due to an adverse event or investigator's decision. Additionally, the patients in the combination therapy study could be described as a more refractory population (60% of patients had primary refractory disease), whereas the primary analysis population for the current study excluded patients with primary refractory disease. It should be noted that some patients with primary refractory disease were wrongly included in this study due to

a misclassification of their prior treatment history. The response rates described here are in line with other antibody–drug conjugates, when tested as monotherapy (44–56%)[30,31] or in combination with rituximab (29–54%).[32,33] Interestingly, the anti-CD30 antibody–drug conjugate brentuximab vedotin achieved an ORR of 44% among patients with R/R DLBCL, most of whom were refractory to their first (76%) and last (82%) line of therapy.[30] The response rates were also similar to anti-CD19 monoclonal antibodies, such as MEDI-551, MOR208, and blinatumomab, currently in phase 2 development for DLBCL.[34-36] In comparison, in a recent multicenter, randomized study of the aza-anthracenedione pixantrone in patients with aggressive B-cell lymphoma (DLBCL, transformed indolent lymphoma, or follicular lymphoma)[37], the ORR was 26% (CR, 15%), with a median PFS of 5.7 months (95% CI 2.4–6.5).

The response rates among patients refractory to their first or last line of therapy were numerically lower than those observed among the relapsed patients included in the study (21.4% and 26.7% *versus* 53.8%, respectively). However, given the limited numbers of patients in each group it is difficult to draw firm conclusions.

Biomarker analysis revealed no apparent correlation between cell of origin classification or *MYC*/*BCL2* expression and clinical response. In addition, none of the CD19 expression measures analyzed showed good predictive accuracy for distinguishing responders and non-responders, and no significant optimal cut-off point for CD19 expression could be identified. This lack of correlation between CD19 expression and efficacy is counterintuitive, but may represent an effect of coltuximab ravtansine on the tumor microenvironment that is important for lymphoma cell growth and survival.[38] Additional *ad hoc* analyses would be required to investigate this further. Interestingly, preclinical studies have also demonstrated that low levels of CD22 or CD79B expression on target cells does not reduce the antitumor activities of pinatuzumab vedotin or polatuzumab vedotin, respectively.[39] Similar findings have also been reported in a brentuximab vedotin phase 2 study in DLBCL, in which responses were not dependent on CD30 expression.[30]

Overall, coltuximab ravtansine exhibited a favorable safety profile, with the majority of the most common AEs reported at grade 1-2. The most frequent grade 3-4 AEs were hematologic or gastrointestinal in nature. No study-onset occurrences of grade 3-4 PN or ocular toxicity were observed, and grade 1-2 toxicities were reversible and manageable. In addition the majority of these events occurred during cycles 1-2 suggesting that they may result from the more intensive dosing of coltuximab ravtansine during the first cycle of the study, rather than drug accumulation. Indeed Ribrag et al.[19] demonstrated a reduced incidence of ocular toxicities and PN with the optimized schedule used here *versus* a weekly dosing schedule. Dose modifications were required in 28% of patients due to AEs, approximately half of which were grade 3-4. No dose reductions were required during the study. SAEs considered related to study treatment were uncommon.

In conclusion, the results of this phase 2 study indicate that the optimized dosing regimen of coltuximab ravtansine may have some efficacy in patients with relapsed or refractory DLBCL, previously treated with rituximab.

Contributors

MT, LS, LH, SS, CO, and AMG were responsible for the study design. Data on this study was collected by JR. The study data was interpreted by all the authors and analyzed by LS, LH, SS, and CO. MT and AMG drafted the manuscript and GV, MJSD, DBY, CP, MC, AL, FTA, PGM, AJ. AMB, KS, MJT, JR, AG, MDN, LS, LH, SS, and CO all critically reviewed the manuscript. All authors gave final approval of the version to be published.

Declaration of interests

MT reports grants and personal fees from Roche, Celgene, Janssen, and Amgen, outside this work. JAR reports grants from Sanofi and Takeda, and personal fees from Takeda (speaker engagements and advisory boards), Cell Medica (advisory board), Novartis (advisory board), and Seattle Genetics (speaker engagements), outside this work. FTA reports personal fees for advisory boards, unrelated to this work, from Boehringer Ingelheim, Novartis Oncology, and Gilead. LS reports personal fees from Lincoln (contractor for Sanofi), during the conduct of this study. LH is an employee of Sanofi. CO is an employee and a stockholder of Sanofi. GV, MJSD, DBY, CP, MC, AL, PGM, AJ, AMB, KS, MJT, AG, MDN, SS, and AMG declare no competing interests.

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Table 1. Baseline characteristics (safety population; n=61)

Variable	Value, n (%)
Median age (range), years	69 (30–88)
Age group, years	
<65	17 (27.9%)
65–75	26 (42.6%)
≥75	18 (29.5%)
Sex	
Male	31 (50.8%)
Female	30 (49.2%)
Histology (investigator determined)	
De novo DLBCL	50 (82.0%)
Transformed DLBCL	11 (18.0%)
Cell of origin classification*	
ABC	16 (43.2%)
GCB	17 (45.9%)
Unclassified	4 (10.8%)
ECOG performance status†	
0	27 (45.0%)
1	26 (43.3%)
2	7 (11.7%)
Ann Arbor stage	
I	4 (6.6%)
II	11 (18.0%)
III	15 (24.6%)
IV	31 (50.8%)
International prognostic index score	
Low	12 (19.7%)
Low intermediate	11 (18.0%)
High intermediate	25 (41.0%)
High	13 (21.3%)
Lactate dehydrogenase >ULN†	41 (68.3%)
Extranodal involvement	36 (59.0%)
Bulky disease‡	28 (45.9%)
Prior transplant for DLBCL	12 (19.7%)
Disease status at study entry§	
Primary refractory	16 (26.7%)

Refractory to last regimen	16 (26.7%)
Relapsed	28 (46.7%)
Number of prior regimens for DLBCL	
0	1 (1.6%)
1	25 (41.0%)
2	17 (27.9%)
3	9 (14.8%)
>3	9 (14.8%)
Prior regimen for non-DLBCL lymphoma[¶]	9 (81.8%)

Data are n (%) unless otherwise stated.

ABC: activated B-cell-like; DLBCL: diffuse large B-cell lymphoma; ECOG: European Cooperative Oncology Group; GCB: germinal center B-cell-like; ULN: upper limit of normal.

*n=37. [†]n=60. [‡]Longest diameter of lesion >5 cm for at least 1 location. [§]n=60 (1 patient had received no prior regimen for DLBCL). [¶]n=11 (patients with transformed DLBCL).

Table 2. Summary of best response to treatment by subgroup based on International Working Group criteria

Response, n (%)	All (n=41)	Refractory to last regimen (n=15)	Relapsed (n=26)	Primary refractory (n=14)
ORR	18 (43.9%)	4 (26.7%)	14 (53.8%)	3 (21.4%)
90% CI*	30.6–57.9	9.7–51.1	36.2–70.8	6.1–46.6
CR	6 (14.6%)	1 (6.7%)	5 (19.2%)	1 (7.1%)
PR	12 (29.3%)	3 (20.0%)	9 (34.6%)	2 (14.3%)
SD	7 (17.1%)	3 (20.0%)	4 (15.4%)	2 (14.3%)
PD	16 (39.0%)	8 (53.3%)	8 (30.8%)	9 (64.3%)

CI: confidence interval; CR: complete response; ORR: overall response rate; PD: progressive disease; PR: partial response; SD: stable disease

Table 3. AEs occurring in ≥10% of patients (safety population; n=61)

AE, n (%)	All grades	Grade 3–4	Grade 5
Any AE	61 (100%)	23 (38%)	8 (13%)
Serious AEs	24 (39%)	14 (23%)	8 (13%)
AE leading to dose modification*	17 (28%)	9 (15%)	–
AE leading to discontinuation	4 (7%)	0	–
Non-hematologic AEs			
Asthenia/fatigue	18 (30%)	1 (2%)	0
Nausea	14 (23%)	1 (2%)	0
Diarrhea	12 (20%)	0	0
Cough	11 (18%)	0	0
Vomiting	8 (13%)	0	0
Decreased appetite	8 (13%)	0	0
Disease progression	8 (13%)	3 (5%)	5 (8%)
Back pain	7 (11%)	1 (2%)	0
Abdominal pain	7 (11%)	2 (3%)	0
Dyspnea	6 (10%)	1 (2%)	0
Constipation	6 (10%)	0	0
Peripheral edema	6 (10%)	0	0
Laboratory abnormalities			
Hematologic AEs†			
Anemia	53 (87%)	4 (7%)	–
Lymphopenia	41 (67%)	13 (21%)	–
Leukopenia	39 (64%)	9 (15%)	–
Thrombocytopenia	35 (57%)	6 (10%)	–
Neutropenia	32 (52%)	15 (25%)	–
Hepatic and renal abnormalities			
AST	37 (61%)	2 (3%)	–
Alkaline phosphatase‡	26 (45%)	2 (3%)	–
ALT	27 (44%)	2 (3%)	–
Creatinine	19 (31%)	2 (3%)	–
Bilirubin	9 (15%)	1 (2%)	–

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

*Including dose omission, interruption, and cycle delays. †Laboratory evaluations. ‡n=58.

Figure legends

Figure 1: Inclusion of patients in the per protocol (PP) efficacy analysis

Patients were recruited at 28 sites in the USA, Belgium, Czech Republic, Israel, Italy, Poland, Spain, Turkey and UK. The per protocol (PP) population consisted of all treated patients who had an evaluable response assessment during or at the end of the treatment protocol or who died due to PD before response assessment, without any important protocol deviations affecting efficacy at study entry. CT: computed tomography; DLBCL: diffuse large B-cell lymphoma. *Some patients met multiple exclusion criteria. [†]14 patients had primary refractory disease as their only protocol deviation.

Figure 2: Duration of response by individual patient in the PP population

Patients with a duration of response of 0.03 months were censored to the first documentation of the response, in the absence of another evaluable assessment before the cut-off date. CR: complete response; DLBCL: diffuse large B-cell lymphoma; PP: per protocol; PR: partial response.

Figure 3: Kaplan–Meier curve of progression-free survival (PP population) and overall survival (safety population)

OS: overall survival; PFS: progression-free survival.

Assessed for eligibility (n=79)

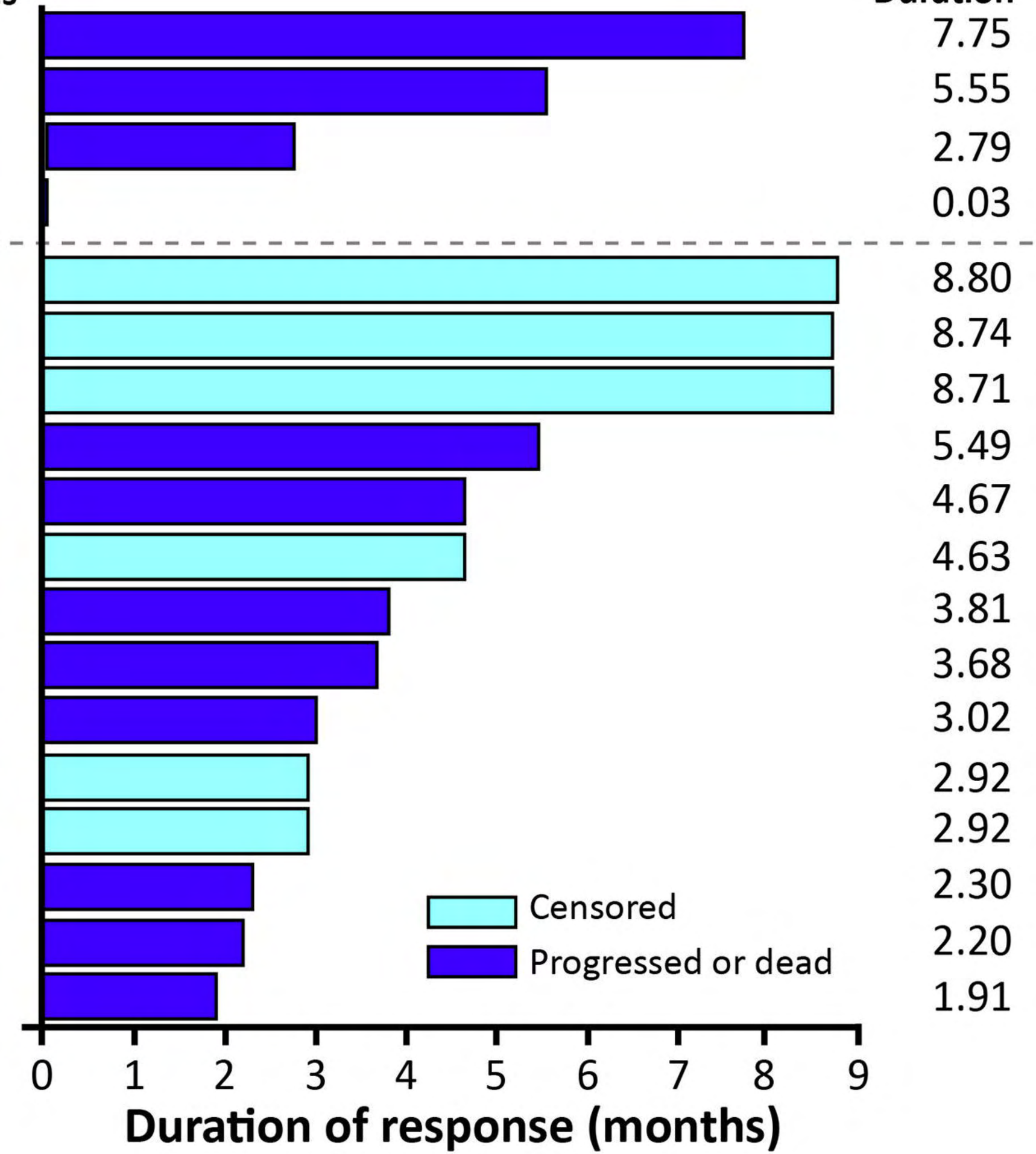
Excluded (n=18)
- Not meeting eligibility criteria (n=18)

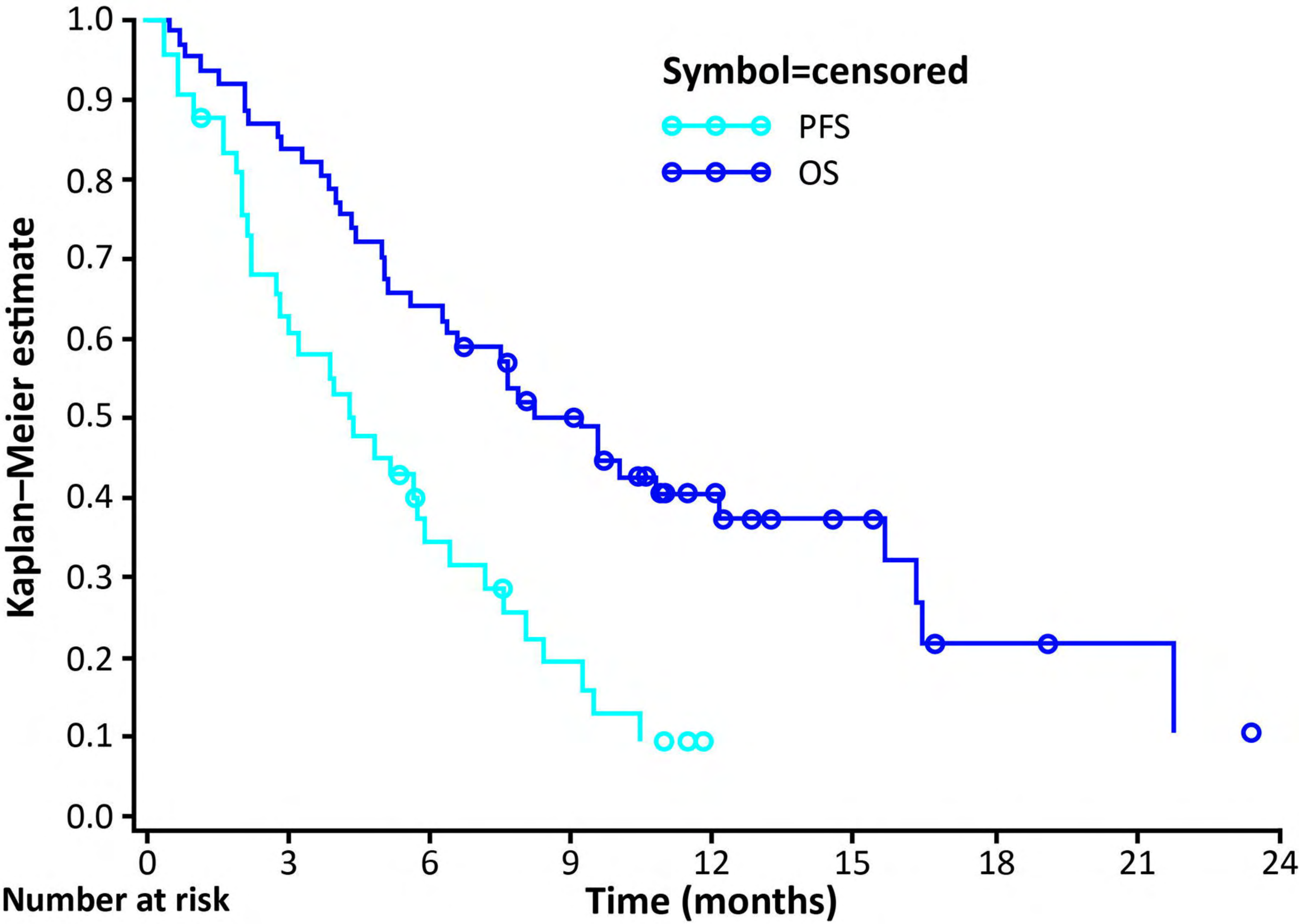
Treated (n=61)

- Excluded from efficacy analysis (n=20)*
  - No measurable lesion by CT (n=2)
  - No prior anti-CD20 therapy (n=1)
  - No relapsed DLBCL or not refractory after two lines (n=6)
  - Primary refractory (n=16)†
  - No evaluable response assessment (n=4)

Per-protocol (PP) population
- Included in efficacy analysis (n=41)

DLBCL status	Best response	No. of cycles	Duration
Refractory	PR	10	7.75
	PR	10	5.55
	PR	9	2.79
	CR	1	0.03
Relapsed	CR	14	8.80
	CR	12	8.74
	CR	12	8.71
	CR	8	5.49
	CR	6	4.67
	PR	11	4.63
	PR	6	3.81
	PR	6	3.68
	PR	6	3.02
	PR	7	2.92
	PR	9	2.92
	PR	7	2.30
	PR	4	2.20
	PR	5	1.91





Number at risk

Progression	41	25	12	6	0	0	0
Death	61	51	39	28	15	8	3

Supplementary methods

Patient Eligibility

Full eligibility criteria according to the protocol are listed below.

Inclusion Criteria

1. Histological diagnosis of DLBCL (de novo or transformed) expressing CD19 by immunohistochemistry or flow cytometry analysis (> 30% positivity), based on recent (less than 6 months) or new biopsy.
2. At least 1 prior specific therapeutic regimen, one of which should have included rituximab (patients previously eligible for transplantation: the salvage treatment followed by intensification and ASCT will be considered one regimen).
3. Either relapsed disease after standard 1st line therapy for aggressive lymphoma - not eligible for high dose chemotherapy with stem cell support, or relapsed or refractory disease after two lines of therapy one of which could have included ASCT. Relapsed disease is defined as progression after a disease free interval of at least 6 months after completion of last therapy. Refractory is defined as progression of disease during prior therapy or within 6 months from its completion.
4. Available paraffin-embedded tissue should have been collected no longer than 6 months prior to first administration of coltuximab ravtansine. Cryo-preserved tissue could not be used. If archival material were not available, a Fine Needle Aspiration (FNA) was obtained. Archival diagnosis biopsy may be used retrospectively as a complementary material for biomarkers analysis. If necessary, a specific informed consent was signed.
5. Signed written informed consent.

Exclusion Criteria

Patients who met all the inclusion criteria were screened for the following exclusion features:

1. Primary refractory disease

2. Primary mediastinal DLBCL.
3. Prior chemotherapy or radiotherapy within 4 weeks or radioimmunotherapy within 12 weeks prior to first administration of SAR3419. Earlier treatment was permitted if necessitated by the patient's medical condition (ie, rapidly progressive disease) following discussion with the sponsor.
4. Toxicities related to prior treatments not having recovered or improved to grade 1 (except for alopecia).
5. Age <18 years.
6. Performance score (ECOG) 3 or 4.
7. Evidence of cerebral or meningeal involvement by lymphoma.
8. Patients without bidimensionally measurable disease by CT scan (defined as presence of at least one tumor mass measuring >1.5 x 1.5 cm).
9. Prior allogeneic bone marrow transplantation.
10. Prior therapy with anti-CD19 monoclonal antibodies.
11. Systemic steroids at doses higher than the equivalent dose of 20 mg/day of prednisone within 2 weeks prior to first administration of SAR3419.
12. Known anaphylaxis to study proteins.
13. Corneal abnormalities at study entry requiring local treatment, recent history of eye surgery, history of keratitis or optic neuropathy.
14. Absolute neutrophil count <1000/µL (no hematologic growth factors in the 4 weeks before obtaining this result), or platelet count <75,000/µL. No hematologic limitation in case of bone marrow involvement by tumor.
15. Abnormal liver and kidney function as evidenced by: ASAT or ALAT > 3 x Upper Normal Limit (UNL), Total bilirubin > 1.5 x UNL unless Gilbert's disease, Serum Creatinine 1.5 x UNL and if creatinine > UNL and creatinine clearance < 50 mL/min.
16. Known HIV positivity.

17. Active HBV (HBsAg, HBeAg and viral DNA positive, with absence of anti-HBe antibody) or HCV infection (presence of circulating anti-HCV antibodies); non-active disease that may flare up following the treatment (carriers for HBsAg with presence of HBc antibodies).
18. Any serious active disease or co-morbid condition which in the opinion of the principle investigator will interfere with the safety or the compliance with the study.
19. Second malignancy other than basal cell or squamous cell carcinoma of the skin or in situ carcinoma of the cervix or the breast, unless the tumor was treated with curative intent at least 5 years prior to first administration of coltuximab ravtansine.
20. Unable to comply with scheduled visits or procedures.
21. Pregnant or breast-feeding women.
22. Patients with reproductive potential (female and male) who do not agree to use an accepted effective method of contraception during the study treatment period and for at least 3 months following completion of study treatment.

Dose modifications

Dose reduction to 40 mg/m^2 was permitted in patients who developed grade ≥3 non-hematologic toxicity but who had achieved clinical benefit (investigator's assessment), or if ≥2 toxicity-related dose delays occurred from cycle 2 onwards. If ≥2 dose delays occurred during cycle 1, or if further dose reductions were required from cycle 2 onwards, the patient was permanently withdrawn.

Ophthalmic assessments

Examination consisted of assessment of ocular/visual signs and symptoms, slit lamp examination and measurement of visual acuity. Schirmer's test was performed if needed. Patients with any ocular/visual symptom (i.e. blurred vision, photophobia) during treatment had these assessments repeated at the time of occurrence of the toxicity and then once weekly until resolution.

Biomarker assessments

Tumor biomarkers were evaluated in formalin-fixed, paraffin-embedded (FFPE) tumor tissue collected ≤6 months prior to enrolment or from freshly collected biopsies or fine-needle aspirates. CD19 was measured at each study site using immunohistochemistry (IHC) or flow cytometry, then reassessed by central review using IHC. CD19 expression was assessed through several measures: % of cells with positive staining at any intensity; average intensity (0 [no staining], 1+ [weak], 2+ [moderate], or 3+ [strong]); % of positive cells at each intensity; and H-score ([% of positive cells at intensity 1+] $\times$ 1 + [% of positive cells at intensity 2+] $\times$ 2 + [% of positive cells at intensity 3+] $\times$ 3).

MYC and *BCL2* expression were evaluated in FFPE samples using central IHC. Patients with ≥40% *MYC*-positive cells and ≥70% *BCL2*-positive cells were classified as *MYC*/*BCL2*-positive.[1] Cell of origin was determined using quantitative nuclease protection assay (qNPA) or, if qNPA results were missing, by IHC with classification according to the Choi algorithm.[2]

Statistical analysis

The predictive accuracy of CD19 as a biomarker for clinical response (ORR) was assessed using sensitivity and specificity measures. The sensitivity and specificity for each candidate value of each measure of CD19 expression (using central assessment) were calculated, and a plot of sensitivity versus 1-specificity as the threshold varies (receiver operating characteristics [ROC] curve) was plotted. The area under the curve (AUC) of the ROC curve was taken as a measure of predictive accuracy of the tested biomarker and was interpreted as the probability that a randomly selected responder would have a larger value of the biomarker compared to a randomly selected non-responder (a biomarker is non-informative when AUC is 0 and most informative when AUC is 1). An optimal threshold was then determined to define an enrichment signature that minimized the Fisher's exact test p-value for the difference in ORR between patients above and below the threshold. A target test profile for each candidate enrichment signature was defined based on three

criteria: minimum prevalence for biomarker positivity; minimum negative predictive value (proportion of non-responders in the biomarker negative group); and minimum absolute improvement in ORR in the biomarker positive group relative to the PP population.

References

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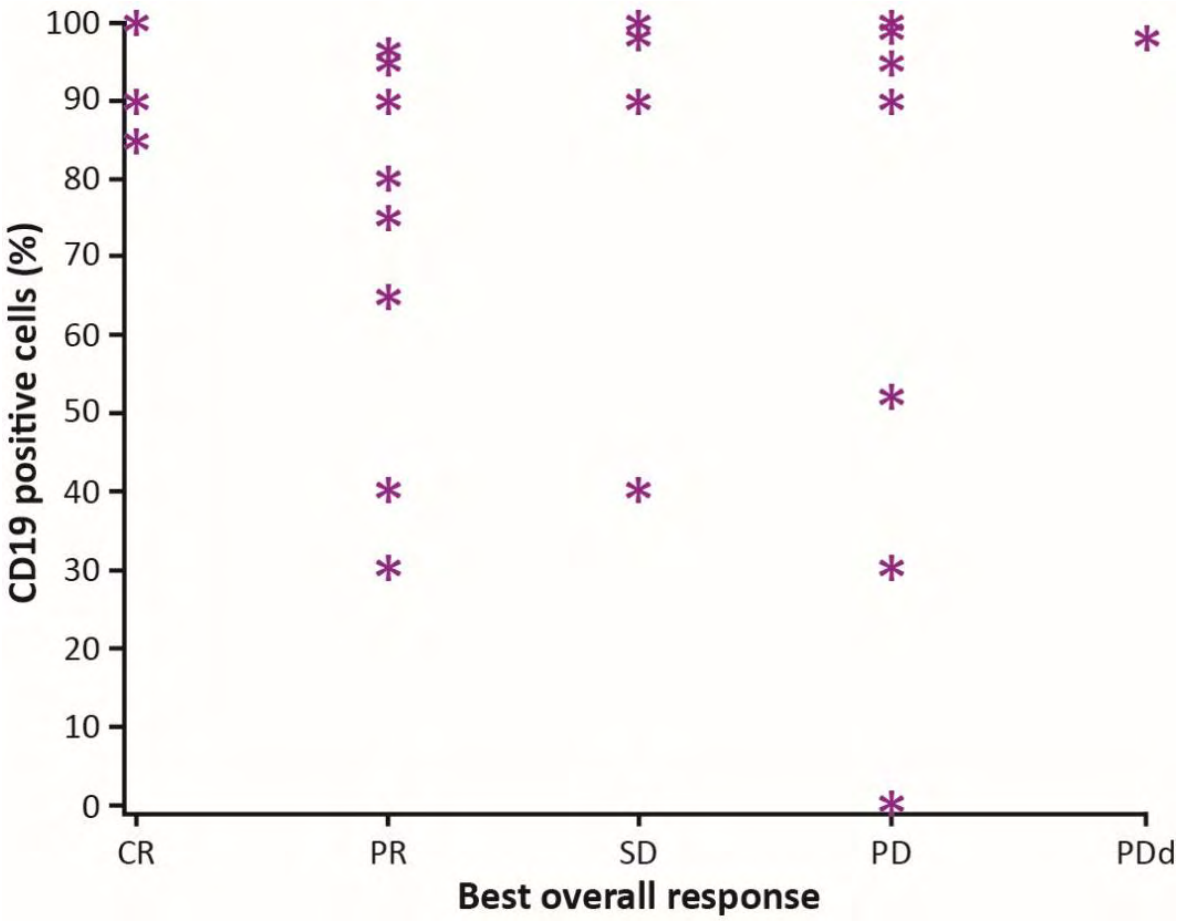
2 Choi WW, Weisenburger DD, Greiner TC, et al. A new immunostain algorithm classifies diffuse large B-cell lymphoma into molecular subtypes with high accuracy. *Clin Cancer Res* 2009; **15:** 5494–502.

Supplementary figure

Supplementary Figure 1. Responses by percentage of CD19-expressing cells at all intensity levels

CR: complete response; PD: progressive disease; PDd: death from progressive disease before response assessments were conducted; PR: partial response; SD: stable disease.



Supplementary table.

Supplementary Table 1. Predictive accuracy of CD19 expression levels as a biomarker for clinical response

CD19 Population	AUC (90% CI)
Average intensity	0.6 (0.45–0.75)
Percent positive cells	0.42 (0.26–0.58)
Percent positive cells at intensity 1+	0.56 (0.4–0.72)
Percent positive cells at intensity 2+	0.53 (0.37–0.69)
Percent positive cells at intensity 3+	0.65 (0.49–0.81)
H-score	0.57 (0.41–0.73)

AUC, area under the curve