A phase II 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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Patient Eligibility

Full eligibility criteria according to the protocol are listed below.

<u>Inclusion Criteria</u>

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.

<u>Exclusion Criteria</u>

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

1   Hu S, Xu-Monette ZY, Tzankov A, et al. MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program. *Blood* 2013; **121:** 4021–31.

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 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.
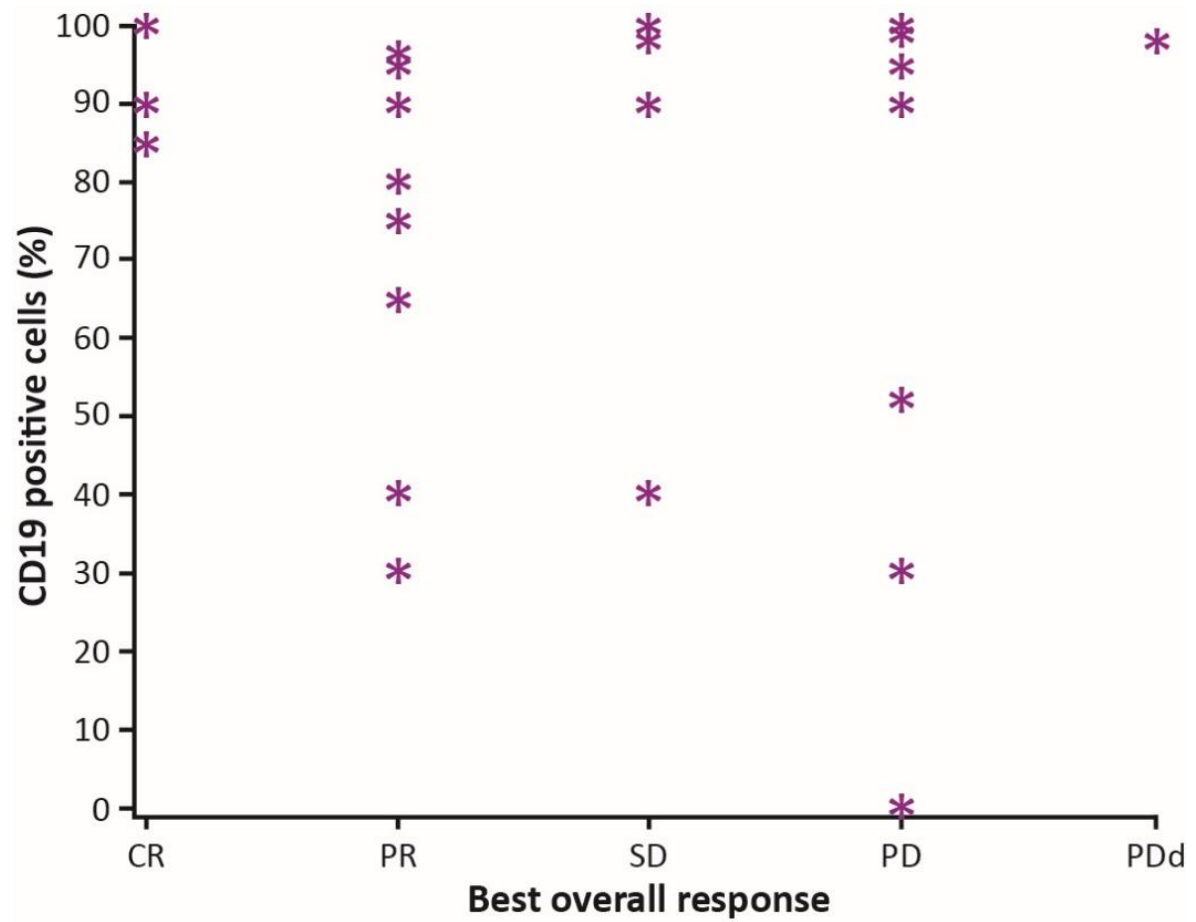
Supplementary table.

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