Yescarta® (axicabtagene ciloleucel) CD19 Expression and Outcomes

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Summary

Background and Clinical Trial Screening

- CD19 is a transmembrane protein expressed only in the B cell lineage.[1]
  - A screening assay for determination of CD19 positivity was not required for eligibility in the ZUMA-1, ZUMA-5 or ZUMA-7 studies.[1-3]
  - Patients with low or undetectable CD19 antigen by immunohistochemical (IHC) analysis may respond to Yescarta, so study protocols did not exclude such patients.[1,2]

Clinical Trial Study Results

- While a limited number of patients were included in various subgroup analyses, similar response rates were observed in patients with CD19-negative disease at baseline compared to those with CD19-positive disease at baseline in ZUMA-1, ZUMA-5 and ZUMA-7.[2-5]
- Response results stratified by baseline CD19 H-score were also similar in ZUMA-1 and ZUMA-5.[2,4,5]
- In ZUMA-7, the reduced efficacy of Yescarta in the CD19 H-score low (≤median) subgroup may be dependent on low/suboptimal target expression and/or concurrent immunosuppressive environment.[3]

Real World Data

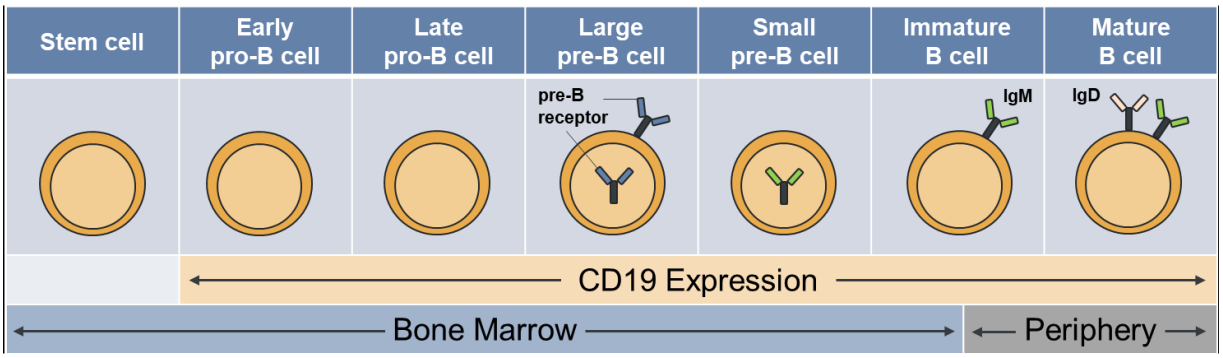
- There is currently little real-world data available on efficacy outcomes in patients stratified by CD19 status prior to axi-cel infusion.

CD19 Expression and Outcomes

Background

CD19 is a transmembrane protein expressed only in the B cell lineage.[1] It is expressed in B cells starting at the early pro-B cell stage until the final differentiation stage and is not expressed in pluripotent hematopoietic stem cells or most plasma cells (Figure 1).[1,6] The rationale for using anti-CD19 in chimeric antigen receptor (CAR) T cell therapy is because CD19 expression is maintained in B cell malignancies including all subtypes of B-cell non-Hodgkin lymphomas (NHL), chronic lymphocytic leukemia (CLL), and non-T cell acute lymphoblastic leukemia (ALL), but not in any normal tissue other than the B cell lineage.[1,7]

Figure 1. B Cell Maturation and CD19 Expression[7]



IgD=immunoglobulin D; IgG=immunoglobulin G; IgM=immunoglobulin M.
Adapted from Murphy KM, Weaver C, eds. Janeway's Immunobiology. 9th ed. Garland Science; 2017.

ZUMA-1 Study Design and Results

The ZUMA-1 study was a pivotal, phase 2 clinical trial (N=101) that evaluated the safety and efficacy of Yescarta in patients with refractory, aggressive non-Hodgkin lymphoma.[4] Study eligibility required histologic confirmation of diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), or transformed follicular lymphoma (TFL) at the central laboratory.[1]

Testing for CD19 Positivity

A screening assay for determination of CD19 positivity was not required for eligibility in the study.[1] CD19 status was determined by immunohistochemistry (IHC).[2] Various limitations have been identified when utilizing IHC analysis to determine CD19 expression, including less sensitivity to detect low levels of antigen expression, inaccuracy of assessed antigen positivity due to tumor sample degradation over time, and heterogenous tumor CD19 expression levels. Because patients with low or undetectable CD19 antigen by IHC may respond to Yescarta, the study protocol did not exclude such patients.[1,2]

Outcomes According to Baseline CD19 H-Score

A subgroup analysis was conducted in ZUMA-1 to evaluate any associations between the intensity and prevalence of baseline CD19 expression and efficacy, safety, and pharmacokinetic outcomes.[5] Although confirmation of CD19 positivity was not required for eligibility in ZUMA-1, baseline tumor tissue was collected from enrolled patients prior to treatment with Yescarta and retrospectively tested for CD19 expression.[1]

A CD19 H-score was calculated as a product of IHC staining intensity (scale 1-3) multiplied by the percentage of tumor cells at a given intensity (0-100%).[5] At baseline, 82 patients in the phase 2 portion were evaluated for CD19 expression and 74 patients (90%) were CD19 positive. Patients with a CD19 H-score of zero were considered CD19-negative by IHC. The median CD19 H-Score was 210 (range, 0-300). Prevalence and intensity of baseline CD19 expression levels were not associated with response, blood CAR T cell levels, or grade ≥3 cytokine release syndrome (CRS) or neurologic events (NE) as presented in Table 1.

Table 1. Response Rates, CAR T Cell Levels, and Adverse Events Across CD19 H-Score Subgroups[5]

	CD19 H-score 0 to <100 (n=19)	CD19 H-score 100 to <200 (n=16)	CD19 H-score 200 to 300 (n=47)
ORR, n (%)	16 (84)	14 (88)	39 (83)
CR, n (%)	11 (58)	10 (63)	25 (53)
Median peak CAR levels (range), cells/μL	50.6 (1.6-1226.4)	43.2 (1.5-190.4)	32.4 (0.8-1513.7)
Median CAR AUC (range), cells/μL days	566.3 (30.5-14329.3)	667.6 (5.1-1359.3)	448.4 (14.4-11506.6)
Grade ≥3 CRS, n (%)	2 (11)	4 (25)	5 (11)
Grade ≥3 Neurologic Events, n (%)	5 (26)	7 (44)	14 (30)

AUC=area under the curve; CAR=chimeric antigen receptor; CR=complete response; CRS=cytokine release syndrome; DLBCL=diffuse large B-cell lymphoma; ORR=objective response rate PMBCL=primary mediastinal B-cell lymphoma; TFL=transformed follicular lymphoma.

Outcomes According to Baseline CD19 Status

Similar response rates were observed in 8 patients with CD19-negative disease compared to those with CD19-positive disease at baseline (n=74), which suggests the potential limitations in CD19 detection rather than true CD19 negativity (Table 2).[4]

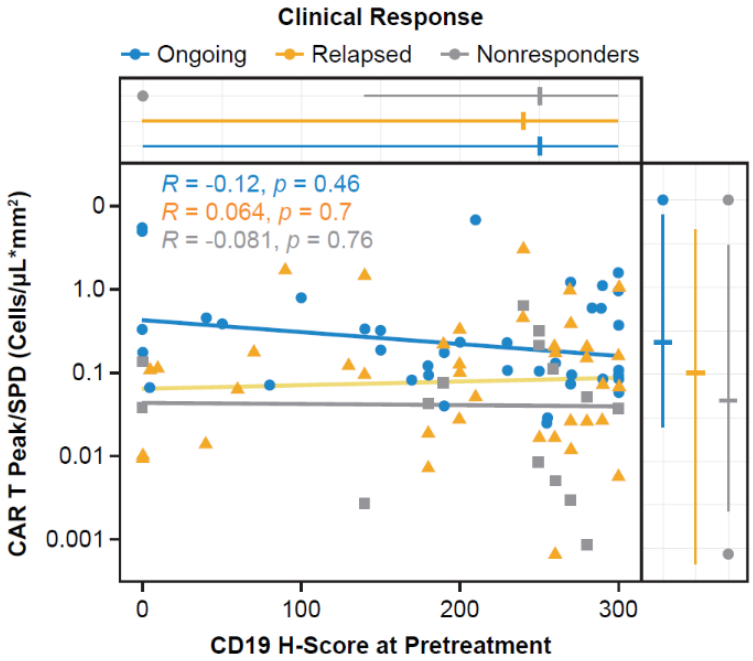
Table 2. Efficacy Outcomes According to CD19 Status[4]

CD19 Status, n/N (%)	Patients with DLBCL	Patients with PMBCL or TFL	All Patients	Objective Response Rate
Negative	7/63 (11)	1/19 (5)	8/82 (10)	75%
Positive	56/63 (89)	18/19 (95)	74/82 (90)	85%

DLBCL=diffuse large B-cell lymphoma; PMBCL=primary mediastinal B cell lymphoma; TFL=transformed follicular lymphoma.

A subsequent analysis of ZUMA-1 patients' tumor biopsies pretreatment (N=100) and post-relapse (N=20) was performed.[8] CD19 H-scores prior to Yescarta infusion were not significantly different across either best response or ongoing response groups (Figure 2).

Figure 2. Association between pretreatment CD19 H-score with engraftment index (CAR T Peak/SPD) and clinical response[8]



SPD=sum of product of perpendicular diameters

Long-term Outcomes

A long-term analysis of ZUMA-1 patients found that 30 out of 74 patients with CD19-positive disease at baseline had ongoing responses at 24 months (41%, 95% CI 0.29-0.53). Four out of 8 patients with CD19-negative disease at baseline had ongoing responses at 24 months (50%, 95% CI 0.16-0.84).[9]

ZUMA-5 Study Design and Results

The ZUMA-5 study was a phase 2, multicenter, single-arm study of Yescarta in patients with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL), including follicular lymphoma (FL) and marginal zone lymphoma (MZL).[10,11] A screening assay for determination of CD19 positivity was not required for eligibility in the study.

Retrospective Analysis of CD19 Expression

A retrospective analysis of CD19 tumor expression was conducted in the ZUMA-5 study. Of 104 FL patients with evaluable samples, 93 patients (89.4%) had CD19-positive disease and 11 patients (10.6%) had CD19-negative by IHC based on an H-score cutoff of >5 per central assessment.[2]

ORR was 92% (95% CI 83-97) for patients that were CD19-positive (n=83) and 100% (95% CI 66-100) for patients that were CD19-negative (n=9) at baseline. ORR was 92% (95% CI 80-98) for patients with a CD19 H-score ≤150 (n=48) and 93% (95% CI: 81-99) for patients with a CD19 H-score >150 at baseline.[2]

A limited number of patients were included in these analyses and results should be interpreted with caution.

ZUMA-7 Study Design and Results

The ZUMA-7 study is an international, multicenter, randomized, phase 3 trial comparing Yescarta with standard care as second-line treatment in patients with early relapsed (≤ 12 months) or refractory large B-cell lymphoma (LBCL).[12] CD19 staining was not required for participation in ZUMA-7, and testing was retrospectively conducted per central laboratory.[3]

Exploratory Analysis of CD19 Expression

As part of an exploratory analysis for ZUMA-7, CD19 protein expression was assessed by immunohistochemistry (H-score), and the numbers of patients included in the median CD19 H-score, were 170 in the Yescarta arm, 168 in the standard care arm, and 338 overall.[3] The median CD19 H-score for the 338 patients in ZUMA-7 was 150 (range, 0- 300). The median CD19 H-score for the 170 Yescarta patients and 168 standard care patients was 140 (range, 0-300) and 160 (range, 0-280), respectively.[3]

Yescarta showed improved EFS and remained superior to standard care irrespective of high (>median) or low (≤median) CD19 expression/H-score.[3] Additionally, patients deemed CD19 negative by immunohistochemistry (H-score <5) still presented substantial responses to Yescarta with 85% ORR versus 67% in the standard care arm.[3]

Information regarding EFS and CD19 protein expression from the Yescarta and standard care arms of ZUMA-7 can be found in Table 3. Associations between biomarkers and clinical outcomes were assessed using descriptive statistics (*P*<0.05 was considered significant).[3]

Table 3. EFS by CD19 Protein Expression[3]

Subgroup	No. of Patients	HR (95% CI)	*P*-value
High CD19 (Yescarta vs Standard Care)	Yescarta: 68 Standard Care: 77	0.283 (0.184-0.433)	<0.0001
Low CD19 (Yescarta vs Standard Care)	Yescarta: 81 Standard Care: 67	0.572 (0.390-0.840)	0.0044
Yescarta CD19 (High vs Low)	High: 68 Low:81	0.627 (0.407-0.966)	0.0341
Standard Care CD19 (High vs Low)	High: 77 Low: 67	1.254 (0.868-1.812)	0.2284

CI=confidence interval; EFS=event-free survival; HR=hazard ratio.

Furthermore, lower CD19 protein expression (H-score) overlapped with a more complex/immune-infiltrated tumor microenvironment, and the reduced efficacy of Yescarta in the CD19 H-score low (≤median) subgroup may be dependent on low/suboptimal target expression and/or concurrent immunosuppressive environment.[3]

Peak CAR T-cell expansion was comparable between patients with high (>median) and low (≤median) CD19 H-score (above vs below median CD19 H-score, *P*=0.6704). CD19 expression did not associate with Grade ≥3 CRD or NEs.[3]

Information from ZUMA-7 regarding safety outcomes for patients based on CD19 status, has not been presented and is not available.

Real-World Data

There is currently little real-world data available on efficacy outcomes stratified by CD19 status prior to Yescarta infusion.

The US Lymphoma CAR-T Cell Consortium is a group of 17 US centers certified for treatment of LBCL patients with commercial Yescarta.[13] A retrospective analysis of patients with known CD19 status from this dataset revealed 87.7% of patients had CD19-positive disease by IHC (92.6% by flow cytometry). However, outcomes stratified by CD19 status were not described in this study.

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Abbreviations

ALL=acute lymphoblastic leukemia
AUC=area under the curve
CAR=chimeric antigen receptor
CI=confidence interval
CLL= chronic lymphocytic leukemia
CR=complete response
CRS=cytokine release syndrome
DLBCL=diffuse large B-cell lymphoma
EFS=event-free survival
FL=follicular lymphoma
HR=hazard ratio
IgD=immunoglobulin D
IgG=immunoglobulin G
IgM=immunoglobulin M
IHC= immunohistochemical
iNHL=indolent non-Hodgkin lymphoma
MZL=marginal zone lymphoma
NE=neurologic event
NHL=non-Hodgkin lymphoma
ORR= objective response rate
PMBCL= primary mediastinal B-cell lymphoma
R/R=relapsed/refractory
SPD=sum of product of perpendicular diameters
TFL=transformed follicular lymphoma

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