# Yescarta® (axicabtagene ciloleucel)
# Cessation of Prior Bispecific Antibody Therapy in ZUMA-1 and ZUMA-7

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## Summary


ZUMA-1 and ZUMA-7

The following information taken from the ZUMA-1 and ZUMA-7 study protocols provides suggested washout periods prior to the scheduled date of leukapheresis.

- In the ZUMA-1 study, at least two weeks or five half-lives, whichever is shorter, must have elapsed between any systemic therapy, including chemotherapy, and the scheduled date of enrollment/leukapheresis.[1,2]
- In the ZUMA-7 study, at least two weeks or five half-lives, whichever is shorter, must have elapsed since any prior systemic cancer therapy at the time the patient provides consent.[3,4]

There are no Kite studies evaluating cessation of bispecific antibodies (BsAbs) as bridging therapy prior to lymphodepleting therapy and Yescarta infusion.

Real-World Data

- A retrospective analysis by Crochet, et al. evaluated efficacy and safety outcomes in patients with refractory/relapsed large B-cell lymphoma (LBCL) with CD-19 targeting chimeric antigen receptor (CAR) T-cells after prior BsAbs exposure. There were 47 patients studied and 22 of the patients (47%) received Yescarta after BsAbs therapy, including glofitamab, mosunetuzumab, odronextamab, plamotamab, and epcoritamab. The median time from the last dose of BsAbs therapy to leukapheresis was 51 days (range, 13-512 days).

# Study Background

### *ZUMA-1 Study Design[1,2]*

ZUMA-1 (NCT02348216) was the pivotal, phase 2 open-label, multicenter, single-arm study that assessed the safety and efficacy of Yescarta for the treatment of patients with refractory, aggressive B-cell non-Hodgkin lymphoma (NHL). Key eligibility criteria included adult patients with refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL), or transformed follicular lymphoma (TFL) to DLBCL. In the study, patients must have had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1 and adequate hematologic (absolute lymphocyte count [ALC] ≥100/µL, absolute neutrophil count [ANC] ≥1000/µL, and a platelet count ≥75,000/µL), renal, hepatic, and cardiac function.

### *ZUMA-7 Study Design[3,4]*

ZUMA-7 (NCT03391466) was a randomized, open-label, multicenter, phase 3 study to assess the safety and efficacy of Yescarta versus standard care as second-line therapy in patients with relapsed or refractory LBCL after failure of conventional first-line therapy. Key eligibility criteria included adult patients with refractory or relapsed LBCL (including DLBCL not otherwise specified [NOS], high grade B-cell lymphoma [HGBCL] with or without MYC and B-cell lymphoma 2 [BCL2] and/or BCL6 rearrangement, DLBCL arising from follicular lymphoma [FL], and T-cell/histiocyte-rich large B-cell lymphoma), with intent to proceed to high-dose therapy with autologous stem cell transplant (HDT-ASCT). In the study, patients must have had an ECOG PS of 0-1 and adequate organ function, and had received prior anti-CD20 monoclonal antibody therapy and an anthracycline-containing chemotherapy regimen.

# Cessation of Prior Bispecific Antibody Therapy

### *Suggested Timing of Current or Previous Therapies Prior to Leukapheresis:*

There are no Kite studies evaluating the washout period of BsAbs as bridging therapy prior to lymphodepleting therapy and Yescarta infusion.

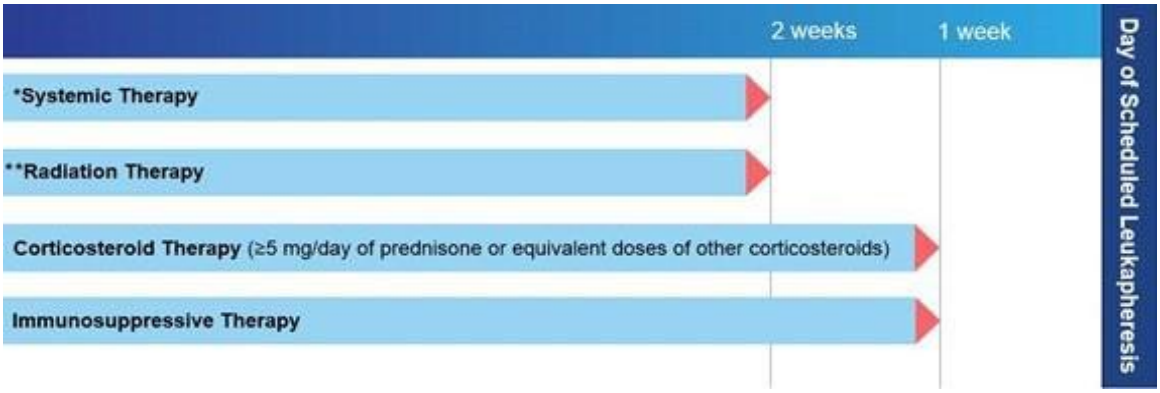
The following information taken from the ZUMA-1 and ZUMA-7 study protocols provides suggested washout periods prior to the scheduled date of leukapheresis.

- In the ZUMA-1 study, at least two weeks or five half-lives, whichever is shorter, must have elapsed between any systemic therapy, including chemotherapy, and the scheduled date of enrollment/leukapheresis.[2]
- In the ZUMA-7 study, at least two weeks or five half-lives, whichever is shorter, must have elapsed since any prior systemic cancer therapy at the time the patient provides consent.[4]

In ZUMA-1, toxicities due to prior therapy must have been stable and recovered to ≤Grade 1 (except for clinical non-significant toxicities such as alopecia) before proceeding to enrollment/leukapheresis.[2] The suggested timing on cessation of current or previous therapies prior to enrollment/leukapheresis in ZUMA-1 is further illustrated in Figures 1 and 2.

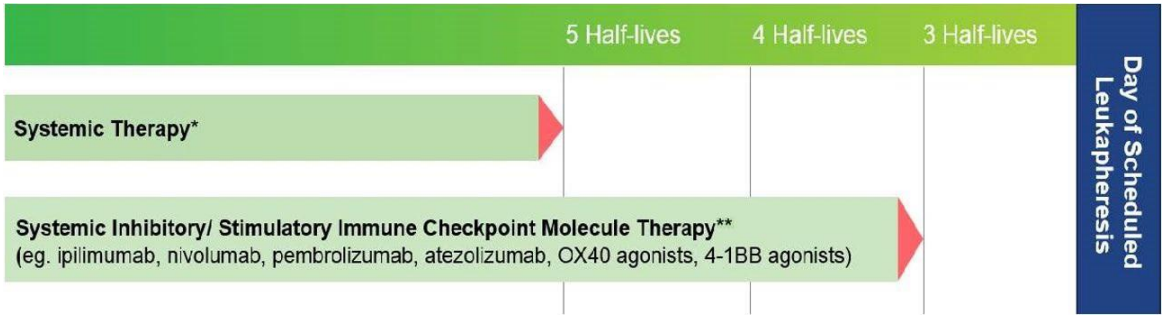
In the ZUMA-7 study, at least two weeks or five half-lives, whichever is shorter, must have elapsed since any prior systemic cancer therapy at the time the patient provides consent.[4]

**Figure 1. Cessation of Therapies Prior to Leukapheresis[1,2]**




*In ZUMA-1, at least two weeks or five half-lives, whichever is shorter, must have elapsed since any prior systemic therapy (except for systemic inhibitory/stimulatory immune checkpoint molecule therapy [see Figure 2 below])
**Prior radiation therapy was permitted in the ZUMA-1 study protocol as outlined in the inclusion criteria

**Figure 2. Cessation of Therapies Prior to Leukapheresis[1,2]**




*In ZUMA-1, at least two weeks or five half-lives, whichever is shorter, must have elapsed since any prior systemic therapy (see Figure 1 above)
**According to the ZUMA-1 study protocol

### *Suggested Timing of Bridging Therapy Prior to Lymphodepleting Therapy and Yescarta Infusion:*

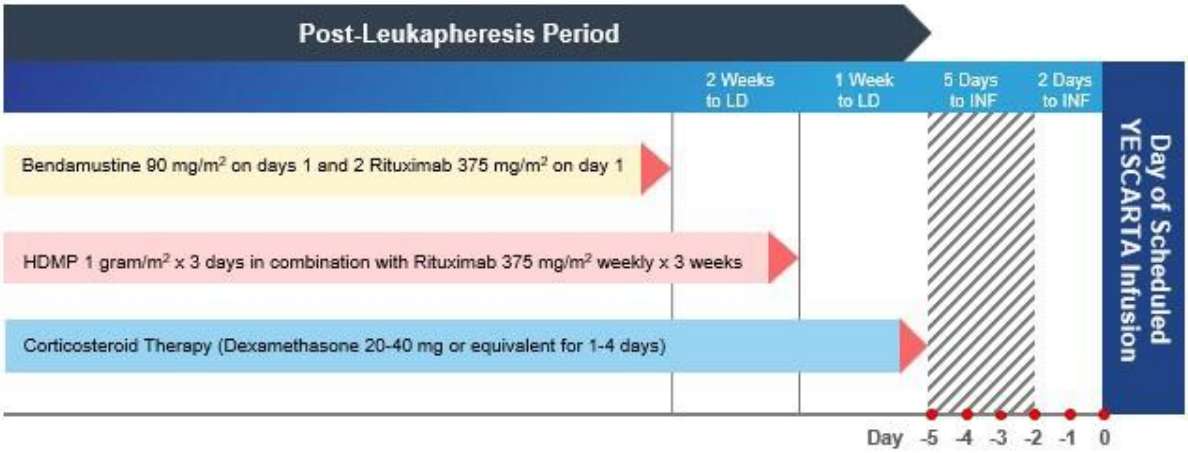
There are no Kite studies evaluating cessation of BsAbs as bridging therapy prior to lymphodepleting therapy and Yescarta infusion. The pivotal ZUMA-1 study (Cohorts 1+2) protocol did not allow for bridging therapy.[2]

The following information taken from the ZUMA-1 Cohorts 4+6, and ZUMA-7 study protocols provide suggested timing of bridging therapy prior to the scheduled start date of lymphodepleting chemotherapy and Yescarta infusion.

Bridging therapy was allowed in phase 2 safety management cohorts (Cohorts 4+6) of the ZUMA-1 study, as outlined in Figure 3 below.[5]

In ZUMA-7, bridging therapy was limited to corticosteroids and must have been administered after leukapheresis and completed at least five days prior to initiating Yescarta.[4] Bridging therapy was administered to 65 patients.[3]

**Figure 3. Cessation of Bridging Therapies in ZUMA-1 Safety Management Cohorts 4+6 Prior To Lymphodepleting Chemotherapy and Yescarta Infusion[5]**




= Lymphodepleting chemotherapy consisting of fludarabine 30 mg/m$^2$ and cyclophosphamide 500 mg/m$^2$ administered on Day -5, Day -4, and Day -3. HDMP = high-dose methylprednisolone; INF = infusion, LD = lymphodepletion

The use of bridging therapy after leukapheresis and before lymphodepleting chemotherapy is at the discretion of the treating physician. As stated in the USPI, while the patient awaits the product, additional chemotherapy (not the lymphodepletion) may be necessary and may increase the risk of adverse events during the pre-infusion period.[6]

# Real-World Data

## Crochet, et al.[7]

### *Study Design*

In a letter to the editor in *Blood,* Crochet, et al. evaluated efficacy and safety outcomes in a retrospective analysis of patients with refractory/relapsed LBCL with CD-19 targeting CAR T-cells after prior BsAbs exposure. The retrospective analysis looked at patients from 11 French and 4 Spanish centers between 2018 to January 2023. Patients who had been exposed to CD19/CD3 BsAbs were excluded from this analysis. Efficacy outcomes reported include overall response rate (ORR), complete response rate (CRR), overall survival (OS), median progression-free survival (PFS), and 6-month PFS. Safety outcomes reported include incidence of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

### *Results*

There were 47 patients identified in this retrospective analysis, and 22 patients (47%) received Yescarta. Of note, BsAbs therapy was the last regimen before CAR T therapy in 26 patients (55%). CD20/CD3 bispecific therapy was administered in 43 patients (91%) and included glofitamab (n=23), mosunetuzumab (n=8), odronextamab (n=6), plamotamab (n=3), and epcoritamab (n=3). Further baseline characteristics of the patients at the time of lymphodepleting chemotherapy are summarized in Table 1.

The median time from the last dose of BsAbs therapy to leukapheresis was 51 days (range, 13-512 days), whereas the median time from leukapheresis to CAR T infusion was 43 days

(34-103). Overall, the time from the last dose of BsAbs therapy to CAR T-cell infusion was 97 days (range, 47-572). The author concluded the washout period observed in their study seemed to provide sufficient BsAbs clearance to allow T-cell fitness recovery before leukapheresis considering that the half-life of BsAbs is relatively short (10-20 days).

**Table 1. Demographic and Clinical Characteristics of Patients at Time of Lymphodepleting Chemotherapy**

| Characteristics | Patients (N=47) |
|---|---|
| Age, median (range), years | 65 (31-82) |
| Male sex, no. (%) | 31 (66) |
| ECOG performance status >1, no. (%) | 4 (9) |
| Disease stage III or IV, no. (%) | 42 (89) |
| **Histology, no. (%)** | |
| DLBCL NOS | 38 (81) |
| TFL | 5 (11) |
| THRLBCL | 2 (4) |
| PMBL | 1 (2) |
| HGBCL | 1 (2) |
| No. of prior therapies, median (range)† | 3 (2-9) |
| **CAR T-cell therapy, no. (%)** | |
| Axi-cel | 22 (47) |
| Tisa-cel | 20 (42) |
| Liso-cel | 5 (11) |
| **BsAb Therapy, no. (%)‡** | |
| CD20/CD3 | 43 (91) |
| CD22/CD3 | 4 (9) |
| **Bridging therapy, no. (%)** | 42 (89) |
| Immunochemotherapy | 29 (62) |
| Targeted therapy | 9 (19) |
| Radiotherapy | 3 (6) |
| Not specified | 1 (2) |
| **Response to bridging, no. (%)∫** | |
| Responder (CR/PR) | 11 (28) |
| Nonresponder (SD/PD) | 28 (72) |

† Median number of prior lines of therapy before BsAbs was 2 (range, 1-6)
‡ CD20/CD3 bispecifics (n = 43/47) included glofitamab (n=23), epcoritamab (n=3), mosunetuzumab (n=8), odronextamab (n=6), and plamotamab (n=3).

∫ Evaluable response in 39 patients (3 patients with missing data)
Axi-cel=axicabtagene ciloleucel; BsAb=bispecific antibody; CAR=chimeric antigen receptor; CR=complete response; DLBCL=diffuse large B-cell lymphoma; ECOG=Eastern Cooperative Oncology Group; HGBCL=high-grade B-cell lymphoma; Liso-cel=lisocabtagene maruleucel; NOS=not otherwise specified; PD=progressive disease; PMBL=primary mediastinal B-cell lymphoma; PR=partial response; SD=stable disease; TFL=transformed follicular lymphoma; THRLBCL=T-cell histiocyte-rich large B-cell lymphoma; Tisa-cel=tisagenlecleucel.

The best ORR and CRR achieved with prior BsAbs treatment were 46% and 19%, respectively.[7,8] Median PFS was 3.1 months (95% confidence interval [CI] 2.7-4.4), and 6-month PFS was 21% (95% CI 11%-34%).

The best ORR and CRR achieved with CAR T treatment were 85% and 43%, respectively.[7,8] There was no significant difference between patients who had previously responded (partial response or complete response) or not (stable disease or progressive disease) to BsAbs treatment (86% [41%] vs 84% [44%]; *P*=1.0). Median PFS was 6.6 months (95% CI 2.6-not reached) with a median follow-up of 10.5 months.

The ORR (CR) of patients previously exposed to BsAbs within 50 days of leukapheresis was similar to patients who had a longer washout (82% [32%] vs 84% [52%]; *P*=0.36). The same comparable outcomes were observed for PFS and OS.

CRS after BsAbs therapy occurred in 27 patients (57%), mostly Grade 1-2 with only 1 Grade 3 event. There were no ICANS events. The incidence of any Grade CRS and ICANS after CAR therapy was 79% (Grade ≥3 in 6%) and 23% (Grade ≥3 in 2%), respectively. There were no differences in the rate of CRS after CAR T cells according to previous CRS occurrence with BsAbs (78% vs 79%; *P*=1.0).

# References


1. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377(26):2531-2544. DOI: 10.1056/NEJMoa1707447
2. [Protocol] Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377:2531-2544. DOI: 10.1056/NEJMoa1707447
3. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. *N Engl J Med*. 2022;386(7):640-654. DOI: 10.1056/NEJMoa2116133
4. [Protocol] Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. *N Engl J Med*. 2022;386(7):640-654. DOI: 10.1056/NEJMoa2116133
5. Data on File, Kite Pharma.
6. YESCARTA® (axicabtagene ciloleucel) [US Prescribing Information]. Santa Monica, CA: Kite Pharma, Inc.
7. Crochet G, Iacoboni G, Couturier A, et al. Efficacy of CAR T-cell therapy is not impaired by previous bispecific antibody treatment in large B-cell lymphoma. *Blood*. 2024;144(3):334-338. DOI: 10.1182/blood.2024024526
8. [Supplementary Material] Crochet G, Iacoboni G, Couturier A, et al. Efficacy of CAR T-cell therapy is not impaired by previous bispecific antibody treatment in large B-cell lymphoma. *Blood*. 2024;144(3):334-338. DOI: 10.1182/blood.2024024526

## Abbreviations

ALC=absolute lymphocyte count
ANC=absolute neutrophil count
Axi-cel=axicabtagene ciloleucel
BsAb=bispecific antibody
CAR=chimeric antigen receptor
CRR=complete response rate
CR=complete response
CRS=cytokine release syndrome
DLBCL=diffuse large B-cell lymphoma
ECOG=Eastern Cooperative Oncology Group
FL=follicular lymphoma
HDT-ASCT=high-dose therapy with autologous stem cell transplant
HGBCL=high-grade B-cell lymphoma
ICANS= immune effector cell-associated neurotoxicity syndrome
LBCL=large B-cell lymphoma
Liso-cel=lisocabtagene maruleucel
NHL=non-Hodgkin lymphoma
NOS=not otherwise specified
ORR=overall response rate
OS=overall survival
PD=progressive disease
PFS=progression-free survival
PMBL=primary mediastinal B-cell lymphoma
PMBCL=primary mediastinal large B-cell lymphoma
PR=partial response
SD=stable disease
TFL=transformed follicular lymphoma
THRLBCL=T-cell histiocyte-rich large B-cell lymphoma
Tisa-cel=tisagenlecleucel.

## Product Label

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