Yescarta® (axicabtagene ciloleucel, axi-cel) Cessation of Prior Therapies in ZUMA-1 and ZUMA-7

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Summary

Cessation of Therapies Prior to Leukapheresis

Prior systemic therapy:

- In the ZUMA-1 study, at least two weeks or five half-lives, whichever is shorter, must have elapsed since any prior systemic therapy and enrollment/leukapheresis, except for systemic inhibitory/stimulatory immune checkpoint therapy.[1] At least three half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy and enrollment/leukapheresis (e.g., ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists).[1]
- 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.[2]

Prior radiation therapy:

- In ZUMA-1, at least two weeks must have elapsed prior to the scheduled date for enrollment/leukapheresis.[1]

Prior corticosteroid (≥5 mg/day of prednisone or equivalent) or immunosuppressive therapy:

- Must be avoided for seven days prior to enrollment/leukapheresis and five days prior to Yescarta administration.[1,2]

Cessation of Bridging Therapy Prior to Conditioning Chemotherapy and Yescarta Infusion

- In the pivotal ZUMA-1 study (Cohorts 1+2), bridging therapy was not allowed but was permitted in the ZUMA-1 safety management cohorts (Cohorts 4+6).[3]
- In the ZUMA-1 study (Cohorts 1+2), a new baseline positron emission tomography-computed tomography (PET-CT) was performed for patients who received bridging therapy between enrollment/leukapheresis and start of lymphodepleting chemotherapy.[3]

- In the ZUMA-7 study, bridging therapy was limited to corticosteroids and must be administered after leukapheresis and completed at least five days prior to initiating Yescarta.[2,4]

Cessation of Vaccines Prior to Conditioning Chemotherapy and Yescarta Infusion

Per the Yescarta US Prescribing Information (USPI), vaccination with live virus vaccines is not recommended for at least six weeks prior to the start of lymphodepleting chemotherapy, during Yescarta treatment, and until immune recovery following treatment with Yescarta.[7]

Prescribing Information[7]

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

- Adult patients with large B-cell lymphoma (LBCL) that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.
- Adult patients with relapsed or refractory LBCL after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), primary mediastinal large B-cell lymphoma (PMBCL), high grade B-cell lymphoma (HGBCL), and DLBCL arising from follicular lymphoma (FL).

Limitations of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

- Adult patients with relapsed or refractory FL after two or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Vaccination with live virus vaccines is not recommended for at least six weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA treatment, and until immune recovery following treatment with YESCARTA.

YESCARTA should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after YESCARTA infusion and treat appropriately. Administer prophylactic antimicrobials according to local guidelines.

Study Background

ZUMA-1 Study Design[1,5]

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).[1,5] Key eligibility criteria included adult patients with refractory DLBCL, PMBCL, or transformed follicular lymphoma (TFL) to DLBCL.[1] 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.[1] If patients showed signs and symptoms

of a serious active infection, they were not allowed to receive treatment until the infection resolved.[1]

ZUMA-7 Study Design[2,6]

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.[2,6] Key eligibility criteria included adult patients with refractory or relapsed LBCL (including DLBCL NOS, HGBCL with or without *MYC* and B-cell lymphoma 2 [*BCL2*] and/or *BCL6* rearrangement, DLBCL arising from 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. Patients must have had no evidence of infection prior to leukapheresis.[2]

Cessation of Prior Therapies

Suggested Timing of Current or Previous Therapies Prior to Leukapheresis:

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

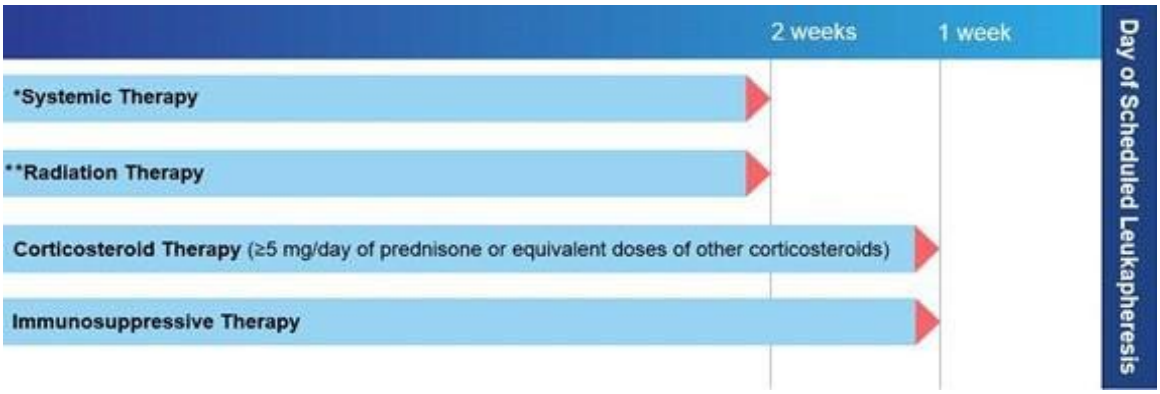
- **In the ZUMA-1 study, at least two weeks or five half-lives, whichever is shorter, must have elapsed between any systemic therapy, including chemotherapy, and the scheduled date of enrollment/leukapheresis.[1]**
    - Exception: at least three half-lives between any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy and the scheduled date of enrollment/leukapheresis (e.g., ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1 BB agonists).[1]
- **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.[2]**
- The ZUMA-1 study protocol also suggests providing at least two weeks between any prior radiation therapy to a target index lesion and the scheduled date of enrollment/leukapheresis; radiation to a non-target lesion was allowed up to the scheduled date of enrollment/leukapheresis.[1]
- In the ZUMA-1 and ZUMA-7 studies, at least one week between any prior corticosteroid therapy (at a pharmacologic dose) and the scheduled date of enrollment/leukapheresis and five days prior to Yescarta infusion.[1,2]
- In the ZUMA-1 and ZUMA-7 studies, at least one week between any immunosuppressive therapy and the scheduled date of enrollment/leukapheresis and five days prior to Yescarta infusion.[1,2]

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.[1]

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

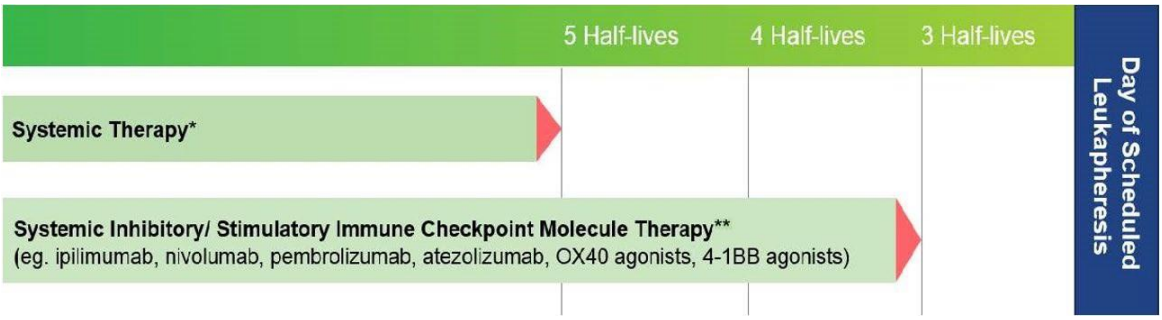
study, at least two weeks or five half-lives, whichever is shorter, must have elapsed since any prior systemic cancer therapy at the time the patient provides consent.[2]

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:

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

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.[7]

Since the pivotal ZUMA-1 study (Cohorts 1+2) protocol did not allow for bridging therapy, Kite does not have any data available regarding the use of bridging therapy from pivotal Cohorts 1+2 of this study.[7] However, bridging therapy was allowed in phase 2 safety management cohorts (Cohorts 4+6) of the ZUMA-1 study, as outlined in Table 1 below.

In ZUMA-7, bridging therapy was limited to corticosteroids (such as dexamethasone at a dose of 20-40 mg or equivalent, either PO or IV daily for 1 to 4 days) and must have been administered after leukapheresis and completed at least five days prior to initiating Yescarta.[2] Bridging therapy was administered to 65 patients.[6]

Table 1. Bridging Therapy Regimens Allowed in ZUMA-1 Safety Management Cohorts (Cohorts 4+6) of the ZUMA-1 Study[3]

Type of Therapy	Dosing and Frequency	Recommended Washout Period
Bendamustine + Rituximab	Bendamustine 90 mg/m^2 on Days 1 and 2; Rituximab 375 mg/m^2 on Day 1	Therapy must be completed at least 14 days prior to the start date of lymphodepleting chemotherapy
HDMP + Rituximab	HDMP 1 gram/m^2 x 3 days; Rituximab 375 mg/m^2 weekly x 3 weeks	Therapy must be completed at least seven days prior to start date of lymphodepleting chemotherapy
Corticosteroid Therapy*	Dexamethasone 20-40 mg or equivalent, either PO or IV daily for 1 to 4 days	Therapy must be completed at least five days prior to start date of Yescarta infusion

*Choice of corticosteroid and dosing can be adjusted for age/comorbidities or per clinical judgment

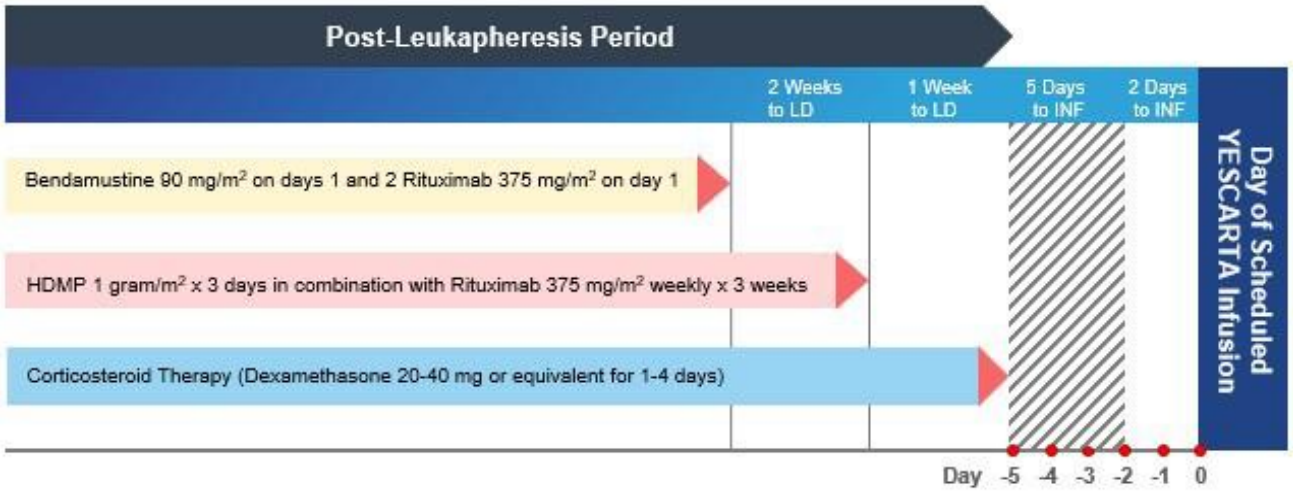
In the ZUMA-1 study and for select Kite clinical studies, after leukapheresis and before Yescarta infusion, radiation to a nontarget lesion was allowed.[1] The appropriate washout period between radiation therapy to a non-target lesion and the start of Yescarta infusion was at the discretion of the treating physician.

In the ZUMA-1 (Cohorts 4+6) study, when bridging therapy was given, chemistry panel and complete blood cell (CBC) counts with differential would be repeated prior to starting lymphodepleting chemotherapy to determine eligibility to proceed.[3]

Additionally, in the ZUMA-1 (Cohorts 4+6) study, a PET-CT scan would be performed to establish a new baseline.[3]

The suggested timing on cessation of bridging therapies in ZUMA-1 safety management cohorts is further illustrated in Figure 3.

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



= 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

References

1. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma [ZUMA-1 Redacted Protocol]. *N Engl J Med*. 2017;377:2531-2544. doi: 10.1056/NEJMoa1707447
2. Protocol for: 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
3. Data on File, Kite Pharma.
4. Supplement to: 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. 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
6. 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
7. YESCARTA® (axicabtagene ciloleucel) [US Prescribing Information]. Santa Monica, CA: Kite Pharma, Inc. 2023.

Abbreviations

ALC=absolute lymphocyte count
ANC=absolute neutrophil count
CBC=complete blood cell
DLBCL=diffuse large B-cell lymphoma
ECOG PS=Eastern Cooperative Oncology Group performance status
HDMP=high-dose methylprednisolone
HDT-ASCT=high-dose therapy with autologous stem cell transplant
HGBCL=high grade B-cell lymphoma
INF=infusion
IV=intravenous
LBCL=large B-cell lymphoma
LD=lymphodepletion
NHL=non-Hodgkin lymphoma
NOS=not otherwise specified
PET/CT=positron emission tomography/computed tomography
PMBCL=primary mediastinal large B-cell lymphoma
PO=oral
TFL=transformed follicular lymphoma
USPI= US Prescribing Information

Product Label

For the full indication, important safety information, and Boxed Warning(s), please refer to the YESCARTA® (axicabtagene ciloleucel) US Prescribing Information available at: https://www.gilead.com/-/media/files/pdfs/medicines/oncology/yescarta/yescarta-pi.pdf.

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