Tecartus® (brexucabtagene autoleucel) Cessation of Prior Therapies for Adult B-ALL

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Summary

Cessation of Therapies Prior to Leukapheresis[1]

- Salvage systemic therapy (including chemotherapy, tyrosine kinase inhibitors [TKIs] for Philadelphia chromosome positive [Ph+] disease, and blinatumomab) for at least 1 week or 5 half-lives (whichever is shorter) prior to leukapheresis.
- Systemic inhibitory/stimulatory immune checkpoint therapy for at least 3 half-lives prior to leukapheresis.
- Alemtuzumab for at least 6 months prior to leukapheresis.
- Cladribine and clofarabine for at least 3 months prior to leukapheresis.
- PEG-asparaginase for at least 3 weeks prior to leukapheresis.
- Donor lymphocyte infusion for at least 4 weeks prior to leukapheresis.
- Treatment for graft-versus-host disease (GVHD) or immunosuppressive antibody for at least 4 weeks prior to leukapheresis.
- Prior corticosteroid (>5 mg/day of prednisone or equivalent) or immunosuppressive therapy for at least 7 days prior to leukapheresis and 5 days prior to Tecartus administration.[1]

Cessation of Bridging Therapy Prior to Conditioning Chemotherapy[1]

- Bridging therapy for at least 7 days or 5 half-lives (whichever is shorter) prior to initiating conditioning chemotherapy.

Cessation of Therapies Prior to Tecartus Infusion[1]

- TKIs for Ph+ ALL patients for at least 1 week prior to Tecartus infusion.[1]
- Prior corticosteroid (>5 mg/day of prednisone or equivalent) or immunosuppressive therapy for at least 5 days prior to Tecartus administration.[1]
- CSF prophylaxis for at least 7 days prior to Tecartus infusion.[1]

Background

ZUMA-3 Study Design

ZUMA-3 (NCT02348216) was a phase 1/2 open-label, multicenter, single-arm study that assessed the safety and efficacy of Tecartus for the treatment of adult patients with relapsed/refractory B-cell precursor lymphoblastic leukemia (B-ALL).[2,3] Key eligibility criteria included adult patients 18 years of age or older who had relapsed/refractory B-ALL with morphologic disease in the bone marrow (greater than 5% blasts) at study entry.[1]

Cessation of Prior Therapies

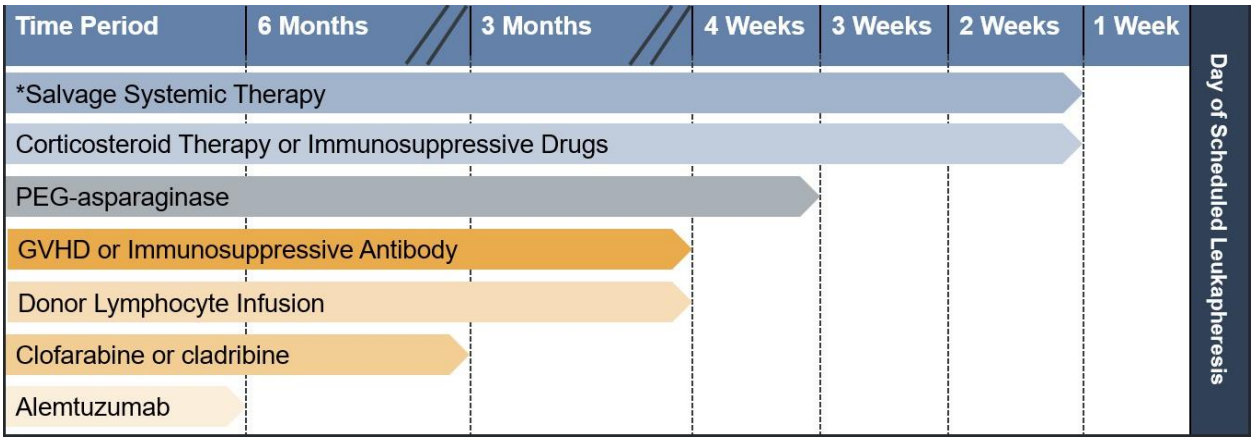
Suggested Timing of Therapies Prior to Leukapheresis[1]

The following information taken from the ZUMA-3 study protocol provides suggested washout periods prior to the scheduled date of leukapheresis.[1]

- Salvage systemic therapy (including chemotherapy, TKIs for Ph+ disease, and blinatumomab) at least 1 week or 5 half- lives (whichever is shorter) prior to leukapheresis.
- At least 3 half-lives between any prior systemic inhibitory/stimulatory immune checkpoint molecular therapy and the scheduled date of leukapheresis (e.g., ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists, etc.).
- Treatment with alemtuzumab at least 6 months prior to leukapheresis.
- Treatment with clofarabine or cladribine at least 3 months prior to leukapheresis.
- Treatment with PEG-asparaginase at least 3 weeks prior to leukapheresis.
- Donor lymphocyte infusion at least 4 weeks prior to leukapheresis.
- Treatment with any drug for GVHD (e.g., calcineurin inhibitors, methotrexate, mycophenolate, rapamycin, thalidomide, etc.) or any immunosuppressive antibody at least 4 weeks prior to leukapheresis (e.g., anti-CD20, anti-tumor necrosis factor, anti-interleukin 6 or anti-interleukin 6 receptor, etc.).
- At least 1 week between the scheduled date of leukapheresis and any prior corticosteroid therapy at pharmacologic dose (> 5 mg/day of prednisone or equivalent doses of other corticosteroids) or other immunosuppressive drugs.

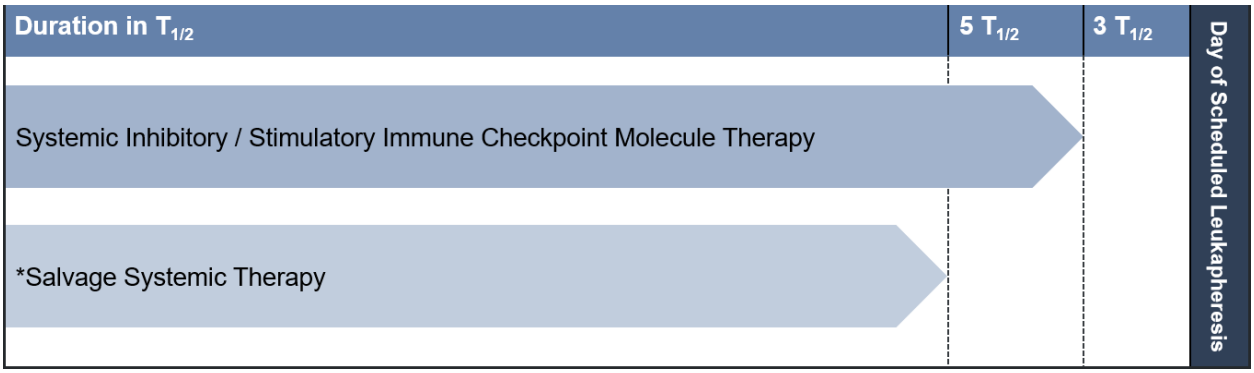
The suggested timing on cessation of therapies prior to leukapheresis is further illustrated in Figures 1 and 2.[1]

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



* At least 1 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy
[a] Figure not drawn to scale

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



*At least 1 weeks or 5 half-lives, whichever is shorter, must have elapsed since any prior systemic therapy (see Figure 1 above)

Suggested Timing of Bridging Therapy Prior to Lymphodepleting Chemotherapy[1]

The following information taken from the ZUMA-3 study protocol provides suggested washout periods prior to the scheduled start date of lymphodepleting chemotherapy.

The use of bridging therapy after leukapheresis and before lymphodepleting chemotherapy is at the discretion of the treating physician and was recommended particularly for patients with high disease burden at baseline (>25% leukemic blasts in the bone marrow [BM] or ≥1000 blasts/mm^3 in peripheral circulation by local review). Bridging therapy administered after leukapheresis should have been completed at least 7 days or 5 half-lives (whichever is shorter) prior to initiating conditioning chemotherapy.[1]

Various bridging therapy regimens were allowed in the ZUMA-3 study and are listed in Table 1.[1]

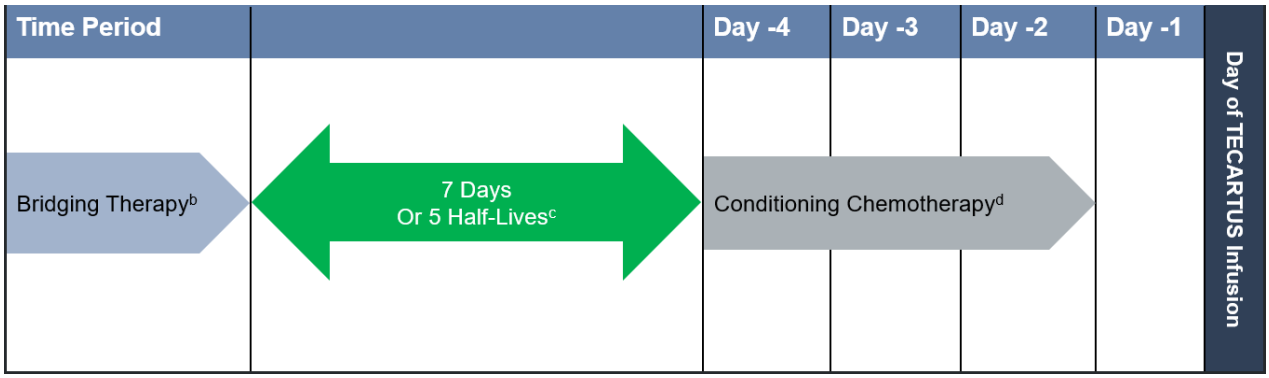
Table 1. Bridging Therapy Regimens Allowed in the ZUMA-3 Study[1,†]

Bridging Chemotherapy Regimens[1]	
Attenuated VAD	Vincristine non-liposomal (1-2 mg IV weekly) or liposomal (2.25 mg/m^2 IV weekly), and dexamethasone 20-40 mg IV or PO daily x 3-4 days per week. Optional doxorubicin 50 mg/m^2 IV x1 (first week only)
Mercaptopurine (6-MP)	50-75 mg/m^2/day by mouth (administer at bedtime on an empty stomach to improve absorption)
Hydroxyurea	Doses titrated between 15-50 mg/kg/day (rounded to the nearest 500 mg capsule and given as a single daily oral dose on a continuous basis)
DOMP	Dexamethasone 6 mg/m^2/day PO (or IV) divided BID days 1-5, vincristine 1·5 mg/m^2 (maximum dose 2 mg) IV on day 1, methotrexate 20 mg/m^2 PO weekly, 6-MP 50-75 mg/m^2/day PO daily
Attenuated FLAG/FLAG-IDA	Fludarabine 30 mg/m^2 IV days 1-2, cytarabine 2 g/m^2 IV days 1-2, G-CSF 5 µg/kg SC or IV starts on day 3 and can continue until day before the start of conditioning chemotherapy. With or without idarubicin 6 mg/m^2 IV days 1-2
Mini-hyper CVAD (courses A and/or B)	Course A: Cyclophosphamide 150 mg/m^2 every 12 h x 3 days, dexamethasone 20 mg/day IV or PO daily days 1-4 and 11-14, vincristine 2 mg IV x1. Course B: methotrexate 250 mg/m^2 IV over 24 hours on day 1, cytarabine 0.5 g/m^2 IV every 12 hours x 4 doses on days 2 and 3

[†]Use of a tyrosine kinase inhibitor (TKI) in combination with any of the above regimens was allowed for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia and Philadelphia chromosome-like acute lymphoblastic leukemia.
BID=twice daily; CVAD=cyclophosphamide, vincristine, doxorubicin, and dexamethasone; DOMP=dexamethasone, 6-mercaptopurine, methotrexate, and vincristine; FLAG=fludarabine, high-dose cytarabine, and G-CSF; G-CSF=granulocyte-colony stimulating factor; IDA=idarubicin; IV=intravenous; MP=6-mercaptopurine; PO=oral; SC=subcutaneous; TKI=tyrosine kinase inhibitor; VAD=vincristine, doxorubicin, and dexamethasone.

The suggested timing for cessation of bridging therapies is further illustrated in Figure 3.[1,2]

Figure 3. Cessation of Bridging Therapy Prior to Lymphodepleting Chemotherapy[1,2,a]



[a] Figure not drawn to scale
[b] Bridging therapy (if applicable) was allowed with (1) Attenuated VAD (2) Mercaptopurine (6-MP), (3) Hydroxyurea, (4) DOMP, (5) Attenuated FLAG/FLAG-IDA, (6) Mini-hyper CVAD (courses A or B)
[c] Bridging therapy (if applicable) must have been completed at least 7 days or 5 half-lives prior to the start of conditioning chemotherapy.
[d] Conditioning chemotherapy consisted of fludarabine 25 mg/m^2 and cyclophosphamide 900 mg/m^2 administered on Day -4, Day -3, and Day -2 prior to Tecartus infusion.

Suggested Timing of Therapies Prior to Tecartus Infusion[1]

The following information taken from the ZUMA-3 study protocol provides suggested timing of therapies prior to Tecartus infusion.

- At least 1 week between the scheduled date of Tecartus infusion and any prior corticosteroid therapy at pharmacologic dose (> 5 mg/day of prednisone or equivalent doses of other corticosteroids) or other immunosuppressive drugs.
- TKIs for Ph+ ALL patients at least 1 week prior to Tecartus infusion, including but not limited to imatinib, dasatinib, and ponatinib.

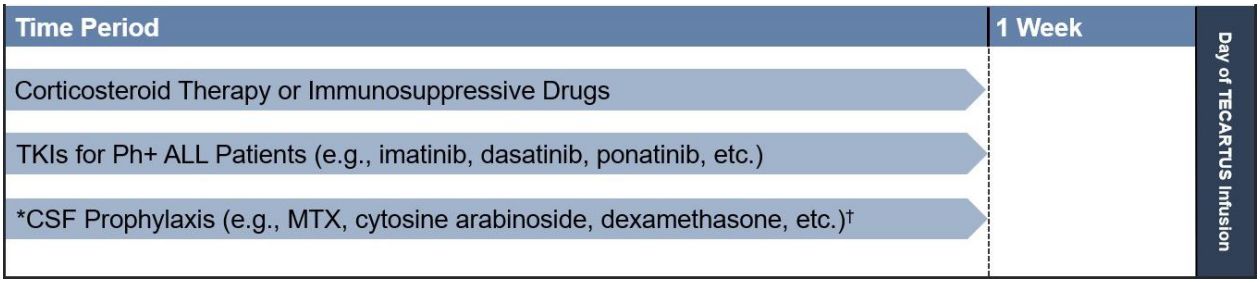
Suggest Timing of CSF Prophylaxis Prior to Tecartus Infusion[1]

All subjects in the ZUMA-3 study received CSF prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines (e.g., methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, or dexamethasone 4 mg or equivalent steroid dose).[1] CSF prophylaxis was administered at any time during screening (e.g., at the time of lumbar puncture at screening) through 7 days prior to Tecartus infusion.

Patients who were enrolled with CNS-2 disease at baseline received CSF prophylaxis after leukapheresis and at least 7 days prior to Tecartus infusion, unless otherwise approved. Multiple doses of CSF prophylaxis could have been given per investigator discretion in accordance with institutional guidelines, but at least 7 days must have passed between the last dose of CSF prophylaxis and Tecartus infusion.

The suggested timing for the cessation of therapies prior to Tecartus infusion is further illustrated in Figure 4.[1,2]

Figure 4. Cessation Therapies Prior to Tecartus Infusion[1,2]



*At least 7 days must pass between the last dose of CSF prophylaxis and Tecartus Infusion
†Examples of CSF prophylaxis regimens stated in the ZUMA-3 Study protocol.

References

1. [Supplementary Appendix] Shah BD, Ghobadi A, Oluwole OO, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. Lancet. 2021;S0140- 6736(21)01222-8. DOI: 10.1016/S0140-6736(21)01222-8
2. Shah BD, Ghobadi A, Oluwole OO, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. Lancet. 2021;S0140-6736(21)01222-8. DOI: 10.1016/S0140-6736(21)01222-8
3. Data on File, Kite Pharma.

Abbreviations

6-MP=mercaptopurine
BID=twice daily
B-ALL= B-cell precursor lymphoblastic leukemia
CVAD=cyclophosphamide, vincristine, doxorubicin, dexamethasone
DOMP=dexamethasone, 6-mercaptopurine, methotrexate, vincristine
FLAG=fludarabine, high-dose cytarabine, and G-CSF
G-CSF=granulocyte-colony stimulating factor
GVHD=graft-verus-host disease
IDA=idarubicin
IV=intravenous
MTX=methotrexate
PO=oral
SC=subcutaneous
TKI=tyrosine kinase inhibitor
VAD=vincristine, doxorubicin, dexamethasone

Product Label

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

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