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Daratumumab combining with venetoclax, three-day multi-frequency decitabine, vincristine, dexamethasone (VDVD) as the salvage treatment of relapsed/refractory T-cell acute lymphoblastic leukemia

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Declarations:

Consent for publication:

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Author's contributions:

Kaiqi Liu and Xiaohui Suo designed the study. Mi Yingchang provided guidance on the plan and offered rationalization suggestions. Congcong Zhang collected the data, and wrote the manuscript. Congcong Zhang, Fang Zheng, Liyun Zhao, Ziyuan Nie, Yinling Li, Xiaohan Zhang, Kangxin Tuo, Chunmei Liu, Jiaru Xing, Jiaojie Song, Huichun Wang, Xiaohui Suo, Yingchang Mi, Kaiqi Liu were involved in patient management, patient follow-up and clinical data collection. Ziyuan Nie collated the data and analyzed it. Yingchang Mi and Kaiqi Liu revised the manuscript and provided valuable advice. All authors read and approved the final manuscript. ALL authors had full access to all the data and had final responsibility for the decision to submit for publication.

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Dear Editor

T-cell acute lymphoblastic leukemia (T-ALL) is a heterogeneous and aggressive hematologic malignancy. Over recent decades, progress of diagnostic techniques, chemotherapy, and allogeneic hematopoietic stem cell transplantation (Allo-HSCT) technology have significantly improved outcomes for newly diagnosed T-ALL. [1,2]. However, the therapeutic efficacy of conventional chemotherapy for refractory/relapsed (R/R) T-cell acute lymphoblastic leukemia (T-ALL) is still dismal and a clinical challenge [3,4].

Recent several years, with the application of small molecule targeted drugs (e.g., BCL-2 inhibitor Venetoclax, HDAC inhibitor Chidamide), CD38-antibody (Daratumumab) based therapies, and chimeric antigen receptor T-cell therapy (including CD7 CAR T-cell therapy and CD5 CAR T-cell therapy), the efficacy for relapsed/refractory T-ALL has been significantly improved [5-10]. However, the optimal treatment regimen remains under ongoing investigations. Our previous studies demonstrated that Venetoclax (VEN) combined with three-day multi-frequency decitabine (DEC3-VEN) exhibited superior therapeutic efficacy in elder patients with de novo acute myeloid leukemia (AML), achieving a composite complete remission (cCR; CR+CRi) rate of 86.7% and minimal residual disease (MRD) negativity rate of 75.8% [11]. Therefore, we designed VEN combined with three-day multi-frequency decitabine (DEC), vincristine (VCR), dexamethasone (DXM) (VDVD) and Daratumumab (Dara) (Dara-VDVD) as salvage therapy for R/R T-ALL. The study protocol was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013) and approved by the Health Human Research Ethics Committee of Handan Central Hospital, Handan, Hebei, China. Written informed consent was obtained from the patients' parents/guardians. In this study, we retrospectively evaluated the therapeutic efficacy of Dara-VDVD in 10 R/R T-ALL patients across six hospitals in China.

From August 2024 to October 2025, ten patients with R/R T-ALL were treated with Dara-VDVD in six hospitals in China after obtaining informed consent. Out of the ten patients, six were relapsed, four were refractory, the median number of previous lines of therapy was 2 (1-5). Based on the stage of differentiation, 4 out of 10 patients were diagnosed with Pro-T-ALL, 2 with Pre-T-ALL, 2 with ETP-ALL, and 2 with Cortical-T-ALL. None of the 10 patients presented with

central nervous system (CNS) involvement at the time of treatment. The median age was 56 (range, 19–76) years and three patients were female. Data of the ten patients were collected and analyzed (as shown in Table 1).

ALL patients were treated with Dara-VDVD. The regimen consisted of 11-day VEN (100mg on Day 1; 200mg on Day 2; and 400mg on Days 3–11), three-day course of DEC (20 mg/m2/q8h, Days 4–6, infusion over ≥2 hours), vincristine (2mg on Days 1 and 8), dexamethasone (10 mg/m2/d on Days 1–4 and 8–11), and Dara (administered as either a single 8mg/kg dose on Day 1 or two 8mg/kg doses on Days 1 and 8) (Figure 1). Three patients received single dose of Daratumumab (Dara), seven patients received two doses of Dara. Hydroxyurea or CTX and Pred (CTX 0.4 g/day, Pred 1mg/kg/day) were permitted for cytoreduction in patient with high white blood cell (WBC) until the WBC count was $\leq 25 \times 10^9$/L. If a triazole antifungal drug (posaconazole, voriconazole) was used, the dose of VEN was reduced to 100 mg daily. Hematopoietic growth factors (e.g., G-CSF, TPO) was permitted during the myelosuppressive phase.

After one cycle of treatment, 9 paitents achieved complete remission (CR), 1 patient no response (NR). The NR patient who had previously been treated with Dara and VEN, subsequently underwent salvage therapy with CD7 CART and achieved CR. Of the 9 CR patients, 5 (55.6%) were determined to be MRD-negative (flow cytometry).

During the induction treatment, the most common Grade 3-4 hematologic adverse events were agranulocytosis, anemia, and thrombocytopenia. The median time to WBC$\geqslant 1\times10^9$/L and PLT $\geqslant 30\times10^9$/L post-induction therapy was 16 (range: 9-21) and 11 (range: 8-15) days, respectively. The most frequent Grade 3-4 non-hematologic adverse event was infection, including upper respiratory infections and pneumonia. No cases of tumor lysis syndrome were observed, and no patient deaths occurred during this period.

Allo-HSCT were recommended for patients who achieved CR. Patients who could not proceed to allo-HSCT received consolidation treatment and intrathecal (IT) therapy for the Prevention of central nervous system leukemia (CNL). Up to January 30, 2026, with a median follow-up of 7

(3–12) months, three patients accepted allo-HSCT, one patient died due to post-transplantation infection, and two patients remain in complete remission. Among the non-transplant patients, three cases experienced recurrence and died due to disease progression. The survival status of all 10 patients is shown in Figure 2.

Treatment of R/R T-ALL remains a clinical challenge. The novel agents are being investigated as potential treatments of R/R T-ALL. Cao's study demonstrated that the combination of Venetoclax (VEN) and Azacitidine (AZA) in the treatment of R/R T-ALL achieved an overall response rate (ORR) of 76% with a complete remission (CR) rate of 68% [7]. Several other reports also demonstrated that the combination of VEN with chemotherapy improves treatment outcomes in R/R T-ALL [8,12,13]. T-ALL typically exhibits high expression of CD38. Therefore, Dara may be employed in the treatment of R/R T-ALL. In 2024, Bhatla demonstrated that Dara combined with chemotherapy significantly improved treatment outcomes of R/R T-ALL [6]. Feng et al. reported achieving a complete response (CR) through administration of the Dara-VA+HAA regimen in patients with relapsed/refractory T-ALL [14].

Our preliminary findings suggest that DEC3-VEN demonstrates significantly superior efficacy compared to the conventional VEN+AZA regimen in elderly patients with acute myeloid leukemia (AML) [11]. Therefore, we designed the Dara-VDVD regimen as salvage regimen of R/R T-ALL. The results demonstrated that 90% (9/10) of patients with R/R T-ALL achieved CR after one cycle of treatment. The sole non-responder was a patient who was exposed to Dara and VEN, and had experienced multiple relapses. This preliminary result is superior to those reported in previous studies by Guan W, Bhatla T, and Cao HY on R/R T-ALL with CR rate around 40-60% after one cycle of treatment [5,6,7]. Comparing with chimeric antigen receptor T-cell therapy [9,10], the regimen demonstrates more safety profiles, and challenges in the collection of normal T Cells for CART Therapy. To date, allo-HSCT remains the only curative approach for R/R T-ALL. Therefore, our regimen can serve as a bridge to transplantation. This combination demonstrated improved efficacy in T-ALL regardless of ETP-ALL or not, and suggests that induction therapy for newly diagnosed T-ALL could deviate from the conventional chemotherapy regimen used previously.

Considering the age of the patients in this group, the median age was 56 (range 19–76) years, with four patients aged over 60 years (including two patients older than 70 years). Our treatment protocol showed superior safety, none of patients died during the treatment.

This study has several limitations. First, the sample size was limited. Secondly, patients with refractory or relapsed T-ALL should undergo allogeneic stem cell transplantation as soon as possible upon achieving second remission. The transplantation rate in this cohort was relatively low, and patients who did not receive transplantation exhibited shorter survival durations. The remission periods of the 3 patients without transplantation who experienced recurrence were all less than 1 year. Third, as none of the 10 patients presented with CNS involvement at the time of treatment, we were unable to evaluate the efficacy of this regimen in CNL. For R/R T-ALL with CNL, we recommend combined IT and High-dose chemotherapy or CART therapy as a superior treatment option. Based on our previous research findings, clinical studies are being designed and developed to evaluate the application of Dara-VDVD as a salvage regimen for patients with relapsed/refractory and newly diagnosed T-ALL.

In conclusion, our preliminary results demonstrated that venetoclax combined with three-day multi-frequency Decitabine, Vincristine, Dexamethasone (VDVD) and Daratumumab (Dara)(Dara-VDVD) is an effective and well-tolerated salvage regimen for patients with R/R T-ALL. Further investigation will involve enrolling more patients to validate this finding.

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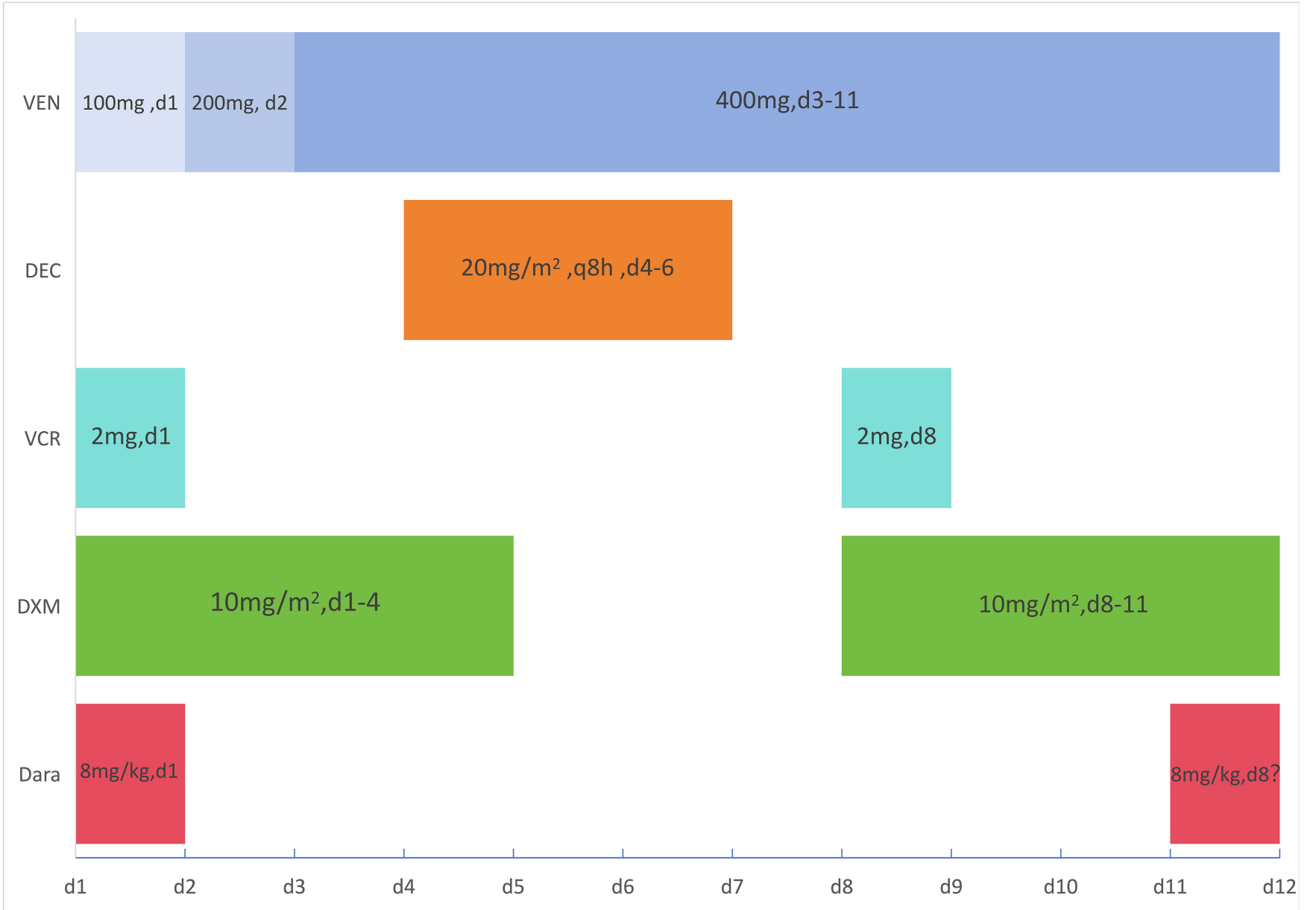
Table 1 Clinical characteristics at diagnosis of the 10 R/R T-ALL patients

No	Sex	Age (y)	Diagnosis (immunophenotype stage) Diagnosis	Relapse /Refractory	The median number of previous lines of therapy	Chromosome	Gene rearrangement	Mutation at diagnosed (NGS)	Dara dose, (mg)	Response	MRD (10^{-4})
1	F	62	Pre-T-ALL	Relapse	1	46, XX	Neg	NOTCH1 PAX5 FBXW7	8mg/kg d1,8	CR	Neg
2	M	41	Pro-T-ALL	Relapse	2	NA	MLL::ELL	FBXW7 ZNF292 SPEN3	8mg/kg d1	CR	0.19
3	F	52	Pro-T-ALL	Refractory	5	46, XX	Neg	Neg	8mg/kg d1,8	CR	Neg
4	F	72	Pro-T-ALL	Refractory	1	46, XX, +Mar	Neg	NA	8mg/kg d1	CR	Neg
5	M	76	Cortical-T-ALL	Relapse	2	NA	Neg	NA	8mg/kg d1	CR	0.14
6	M	37	Pro-T-ALL	Refractory	1	46, XY	Neg	IL-7R NOTCH1 WT1	8mg/kg d1,8	CR	0.29
7	M	19	ETP-ALL	Relapse	2	46, XY	Neg	RUNX1	8mg/kg d1,8	CR	Neg
8	M	60	ETP-ALL	Refractory	1	46, XY	P2RY8::CRLF2	FLIT3/ITD EZH2 SETD18 PHF6	8mg/kg d1,8	CR	Neg
9	M	56	Pre-T-ALL	Relapse	1	45,XY,der (8;20) (q10;q10)/46,xy	NA	NA	8mg/kg d1,8	CR	0.41
10	M	31	Cortical-T-ALL	Relapse	3	46, XY	Neg	NOTCH1 N-RAS FAT1	8mg/kg d1,8	NR	

Figure 1 Treatment schema of Dara-VDVD (Dara: daratumumab, VEN: venetoclax, DEC: decitabine, VCR: vincristine, DXM dexamethasone)

Figure 2 Swimmer plot of the 10 patients with R/R T-ALL


VEN
100mg ,d1
200mg, d2
400mg,d3-11
DEC
20mg/m² ,q8h ,d4-6
VCR
2mg,d1
2mg,d8
DXM
10mg/m²,d1-4
10mg/m²,d8-11
Dara
8mg/kg,d1
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d10
d11
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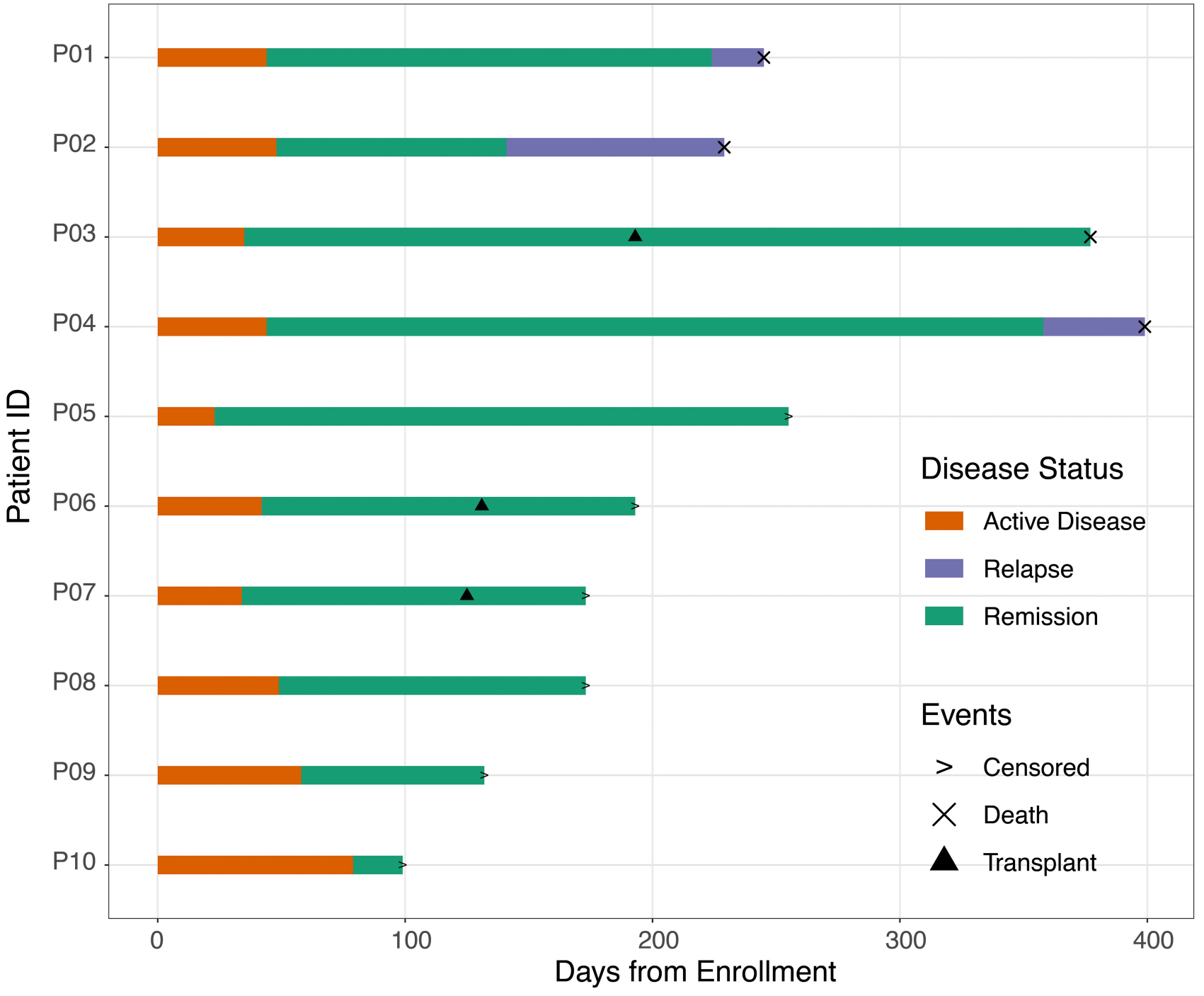
Patient ID
P01
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Days from Enrollment
Disease Status
Active Disease
Relapse
Remission
Events
Censored
Death
Transplant