Venetoclax in combination with chemotherapy as treatment for pediatric advanced hematologic malignancies: A narrow therapeutic window of promise and peril

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Abstract

Background: V **e**netoclax is frequently used as salvage treatment in pediatric, adolescent, and young adult (AYA) patients with advanced hematologic malignancies. However, more robust data are needed from real-world studies to guide the safe and appropriate use of venetoclax in this population. **Procedure:** We retrospectively reviewed the medical records of all patients diagnosed with hematologic malignancies less than 30 years of age treated with venetoclax outside of clinical trials at the University of California San Francisco (UCSF) Benioff Children's Hospitals from 2016 to 2022. **Results:** We identified 13 patients (AML *, n= 8*, B-ALL, *n= 3*, MDS, *n= 2)* aged 4 months to 27 years. A median of 3 prior lines of therapy were given (range 0 to 5). All patients received venetoclax in combination with either a hypomethylating agent or conventional chemotherapy. Three (23%) patients achieved a complete remission (CR); 2 (15%) achieved a partial remission (PR); 3 (23%) had stable disease (SD), and 5 (42%) had progressive disease. Median survival and time to progression from venetoclax initiation was 9 months (range 2.5 to 52 months), and 3 months (range 2 weeks to 7.5 months), respectively. Five patients (38%) developed life-threatening infections while receiving venetoclax, including bacteremia due to atypical organisms, invasive pulmonary infections with Aspergillus, cytomegalovirus (CMV) viremia, skin infections, encephalitis with bacterial brain abscesses. **Conclusions:** Venetoclax in combination with hypomethylating agents or cytotoxic chemotherapy was effective in a subset of pediatric/AYA patients with advanced hematologic malignancies, but was frequently associated with severe atypical infections, particularly in combination with cytotoxic chemotherapy.

Introduction

Therapeutic options for pediatric, adolescent and young adult (AYA) patients with relapsed/refractory acute myeloid leukemia (AML) are limited, and outcomes remain dismal; two-year relapse-free rates for these patients, even with current chemotherapeutic regimens and hematopoietic stem cell transplant (HSCT), are only 25%-30%.[1-3] Relapsed/refractory acute lymphoblastic leukemia (ALL) has also remained challenging to treat in children and AYA, with survival rates lagging significantly behind those observed at initial diagnosis. Although there have been improvements in outcomes over the past several decades, only 50% of children and AYA with first relapse of ALL experience long term survival, and outcomes are even worse with second or later relapses.[4] Novel therapeutic strategies are thus needed to improve outcomes in pediatric/AYA patients with relapsed/refractory (advanced) hematologic malignancies.

Venetoclax, a potent, highly selective, orally available inhibitor of the anti-apoptotic protein B-cell lymphoma-2 (BCL-2), has emerged as one such promising agent. Venetoclax in combination with low-dose cytarabine or hypomethylating agents is Food and Drug Administration-approved for adults with newly diagnosed chronic lymphocytic leukemia and AML, based on results supporting its safety and efficacy in

elderly adults deemed unfit for cytotoxic chemotherapy.[5-7] Several studies also suggest these combinations may be effective salvage regimens for adults with relapsed or refractory AML, even in heavily pre-treated populations.[8-10]

Venetoclax is currently the subject of several ongoing phase I/II clinical trials evaluating its safety and efficacy in pediatric/AYA patients with relapsed or refractory AML (NCT03194932) and in other malignancies (NCT03236857). A phase I dose-escalation study of venetoclax in combination with cytarabine with or without idarubicin in pediatric patients with relapsed/ refractory AML or ambiguous lineage leukemia supported the safety and efficacy of venetoclax and conventional chemotherapy in this population.[11]Another phase I dose escalation study demonstrated venetoclax with chemotherapy and low-dose navitoclax, a BCL-X_L/BCL-2 inhibitor, is a safe and promising combination in pediatric and adult patients with advanced ALL and lymphoblastic lymphoma.[12]

Aside from these early-phase trials, the published literature to date concerning venetoclax in pediatric/AYA patients with hematologic malignancies consists of a few single-institution reports that support the safety and efficacy of venetoclax in combination with cytotoxic chemotherapy in pediatric patients with ALL[13] and AML[14] and in combination therapy with azacitidine in pediatric patients with MDS or AML unfit for standard chemotherapy.[15]

While these reports are encouraging, more robust data are needed to guide clinicians in the safe and efficacious use of venetoclax combination therapy across a range of pediatric hematologic malignancies. We therefore retrospectively reviewed our institutional experience of venetoclax use in pediatric/AYA patients at the University of California San Francisco (UCSF) Benioff Children's Hospitals and report on 13 pediatric and AYA patients with hematologic malignancies who received venetoclax combination therapy outside of a clinical trial between 2016 and 2022. We report on exceptional responders and previously unreported toxicities.

Methods

After IRB approval, a retrospective chart review identified patients diagnosed with acute leukemia or MDS at age 30 years or younger who received venetoclax combination therapy at UCSF Benioff Children's Hospitals. Eligible diagnoses included AML, MDS, and ALL. Patients who were treated on a clinical trial were excluded from this study.

Complete remission (CR) was defined as disappearance of all clinical and/or radiologic evidence of disease, plus absolute neutrophil count (ANC) [?]1.0 $\times$ 10^3/L, platelet count [?]100 x 10^3/L, and bone marrow differential with <5% blasts by morphology or flow cytometry of bone marrow. Partial response (PR) was defined as no peripheral blasts or peripheral blood absolute blast count decreased by [?] 50% from baseline, bone marrow with 5 – 25% blasts and at least a 50% decrease in bone marrow blast percent from baseline, and no evidence of extramedullary disease. Progressive disease (PD) was defined as > 50% increase in absolute peripheral or bone marrow blasts by morphology or flow cytometry. Stable disease (SD) was defined as the conditions under which criteria for CR, PR, or PD were not met.

Minimal residual disease (MRD) was defined as multiparameter flow cytometry of bone marrow with less than 0.01% blasts. Venetoclax toxicities were graded per the Common Terminology Criteria for Adverse Events version 5.0. Overall survival (OS) defined as the time in months from the start of venetoclax therapy to death, and progression-free survival (PFS) was defined as the time from the start of venetoclax administration until disease progression or relapse. Patients alive without relapse or progression were censored at their date of last follow-up. Kaplan–Meier curves of OS and PFS were generated.

Next-Generation Sequencing

Next generation sequencing was available for 11 patients (14 samples). An institutional DNA sequencing panel assaying 479 cancer-related genes was used.[16] Genomic DNA was extracted from peripheral blood and tumor tissue microdissected from fresh frozen paraffin embedded blocks, as previously described. [16]Capture-based next-generation sequencing (NGS) was performed at the UCSF Clinical Cancer Genomics Laboratory,

using an assay targeting the coding regions of these genes, *TERT* promoter, select introns from 40 genes (for detection of gene fusions and other structural variants), and intergenic regions at regular intervals along each chromosome (for chromosomal copy number assessment), altogether with a total sequencing footprint of 2.8 Mb Sequencing libraries were prepared from genomic DNA with target enrichment performed by hybrid capture using a custom oligonucleotide library. Sequencing was performed on an Illumina HiSEquation 2500. Duplicate sequencing reads were removed computationally to allow for accurate allele frequency determination and copy number estimates. The analysis was based on the human reference sequence UCSC build hg19 (NCBI build 37). Single nucleotide variants and small insertions/deletions (indels) were visualized and verified using Integrated Genome Viewer.

Results

Patient and Disease Characteristics

Thirteen patients were identified, 8 (62%) with AML, 3 (23%) with B-ALL, and 2 (15%) with MDS. The median age upon initiation of venetoclax was 14 years (range: 4 months to 27 years). Six (46%) patients were male. Three patients had a history of a prior malignancy: one patient with T-ALL, one with AML, and one with neuroblastoma. The median number of lines of therapy was 3 (range 0 to 5). Five (38%) patients had received a hematopoietic stem cell transplant prior to receiving venetoclax therapy. Two patients had a defined predisposition to developing malignancy: one patient had Schwachman-Diamond Syndrome (SDS) who developed AML, and one had a germline *GATA2* mutation who developed MDS. Patient and disease characteristics are summarized in

Table 1.

Treatment and Response

All patients received venetoclax in combination with either a hypomethylating agent or conventional chemotherapy. Median follow-up time was 8 months from venetoclax initiation (range 2 to 52 months). Treatment regimens and responses for each patient are summarized in**Table 2 and in Figure 1.** The standard adult AML dosing of 400 mg daily (or adult equivalent weight-based dosing), with a bioequivalent dose for patients receiving a concurrent CYP3A4 inhibitor, was given.[17,18] Three of 8 patients with AML received venetoclax in combination with decitabine (20 mg/m^{2}daily for 5 days). In two of these three cases, the patient was a poor candidate for conventional chemotherapy due to morbidities from prior therapy; in one case, the patient with SDS and newly-diagnosed AML was deemed ineligible for standard chemotherapy due to the risk of toxicity.[19] The remaining 5 patients with AML received venetoclax in combination with cytarabine (1000 mg/m^2/dose every 12 hours for 8 total doses). One patient with an intracranial myeloid sarcoma received venetoclax and cytarabine with concomitant focal radiation therapy. Both patients with MDS received venetoclax in combination with a hypomethylating agent (decitabine in one case and azacitidine in the other).

Two of the three patients with relapsed B-ALL received venetoclax in combination with vincristine, dexamethasone, and PEG-asparaginase. One patient with relapsed B-ALL received venetoclax in combination with fludarabine, high-dose cytarabine, and G-CSF (FLAG).

The median number of cycles of venetoclax combination therapy patients received was 1 (range <1 to 3). The most common reason for discontinuation of venetoclax was disease progression in 6 patients (46%), and in 2 cases it was discontinued due to infections.

Three (23%) patients achieved a CR; 2 (15%) achieved a PR; 3 (23%) had stable disease, and 5 (42%) had PD. Of the 3 patients who achieved a CR, two had a diagnosis of relapsed B-ALL, and one had a diagnosis of SDS-associated AML. Two of these patients became MRD negative after one cycle of venetoclax combination therapy. All three patients who achieved a CR remain alive with no evidence of disease with a median follow-up time of 48 months.

Nine patients (69%) experienced disease progression following venetoclax therapy. Median survival was 9

months from venetoclax initiation (range 2.5 to 52 months), and median time to progression was 3 months (range 2 weeks to 7.5 months). (**Fig. 2).**

Toxicities

All patients experienced hematologic toxicity with grade 3-4 thrombocytopenia, anemia, and neutropenia. Non-hematologic Grade 3-4 adverse events (AEs) attributed to venetoclax are summarized in**Table 3** . Five patients (38%) developed grade 3 or higher infections while receiving venetoclax. Four patients (23%) developed bacteremia due to uncommon organisms (Vignettes 1-2), one of whom developed four distinct episodes of bacteremia in addition to multiple other infectious complications (Vignette 2). Patient 13 developed Grade 4 encephalitis with multiple rim-enhancing brain lesions thought to be bacterial abscesses (Vignette 3). Two patients developed invasive pulmonary infections with Aspergillus. Two patients developed grade 3 skin infections. Patient 6, an infant, developed grade 3 nausea, which prompted discontinuation of venetoclax. No deaths occurred within 30 days of the start of venetoclax combination therapy, and no grade 5 AEs were reported as associated with venetoclax. No clinically significant tumor lysis syndrome was seen.

To demonstrate the wide spectrum of hematologic malignancies treated with venetoclax and the range of infectious complications that arose in our experience, we share the following vignettes.

Vignettes

Vignette 1: Patient 5

A 14-year-old male with SDS presented with fever, pancytopenia, and peripheral blasts. Bone marrow biopsy confirmed a diagnosis of AML with 17% blasts, normal cytogenetics, and FISH. Targeted DNA panel sequencing revealed a somatic pathogenic mutation in IDH1 and a partial tandem duplication of KMT2A. Bone marrow examination showed a CR by morphology and negative MRD by flow cytometry after one cycle of venetoclax and decitabine. His first cycle was complicated by several episodes of febrile neutropenia and one episode of Rothia mucilaginosa bacteremia. He received a second cycle of venetoclax and decitabine and maintained his negative MRD status prior to receiving a matched unrelated donor HSCT. The patient has remained disease-free after 52 months of follow-up.

Vignette 2: Patient 10

A 19-year-old male with second relapsed AML, with initial relapse in the bone marrow and myeloid sarcoma in the cerebellar vermis requiring a total of 5 lines of therapy including allogeneic HSCT, presented with a second relapse isolated to the central nervous system (CNS) as suprasellar myeloid sarcoma two years after initial diagnosis. He received 2 cycles of venetoclax in combination with cytarabine in addition to focal radiation to a total of 24Gy. Despite bacterial and fungal prophylaxis with levofloxacin and micafungin, respectively, his course was complicated by multiple infections, including pulmonary infection with Aspergillus, Gram negative rod sepsis secondary to Klebsiella, additional distinct episodes of bacteremia secondary to Morganella, Staphylococcus epidermidis, and Actinomyces bacteremia, cytomegalovirus (CMV) viremia, a pilonidal abscess, and incidentally discovered appendicitis. Venetoclax was discontinued due to ongoing infections and was not restarted even after resolution of the infections due to persistent pancytopenia with severe thrombocytopenia. The patient developed concern for progressive CNS disease with a new lesion in the right medulla 7 months after initiation of venetoclax therapy, though subsequent imaging improved without intervention, raising the possibility of radiation necrosis or infection. He remains alive with unclear disease recurrence 9 months following initiation of venetoclax.

Vignette 3: Patient 12

A 15-year-old with iAMP21-B-ALL presented with early medullary relapse during cycle 6 of maintenance therapy with bone marrow evaluation demonstrating 94% blasts by flow cytometry. She commenced reinduction with venetoclax in combination with vincristine, PEG-asparaginase, and dexamethasone. She experienced multiple infectious complications during treatment with this regimen, including recurrent and prolonged Enterococcus faecalis bacteremia, invasive Aspergillus pneumonia, and rim-enhancing brain lesions

suspicious for bacterial brain abscesses, for which she was treated with a prolonged course of antibiotics. Bone marrow examination after one cycle showed a CR by morphology and MRD of 0.26% by flow cytometry. The patient achieved MRD negativity after receiving inotuzumab and subsequently underwent matched sibling HSCT.

Discussion

We report on our real-world experience using venetoclax in pediatric and AYA patients with hematologic malignancies. Our experience builds on emerging data demonstrating the efficacy of venetoclax across a range of diagnoses and underscores the risk of life-threatening infections that may be associated with venetoclax-based regimens in this population.

To date, published reports have concluded venetoclax is well-tolerated in combination with a variety of cytotoxic agents in pediatric/AYA patients with hematologic malignancies.[11-14] Our experience calls attention to the severity and range of atypical infections patients experienced during treatment with venetoclax. Five patients (38%) experienced at least one opportunistic infection, including bacteremia caused by multiple uncommon organisms, invasive pulmonary fungal disease, CMV viremia, and Grade 4 encephalitis with bacterial brain abscesses in one case. (Table 3, Vignettes 1-3). Infections occurred in an equal proportion of patients who received venetoclax combined with a hypomethylating agent and with cytotoxic chemotherapy, but they were generally more severe and prolonged with the latter combination. All patients who experienced serious infections notably received prophylactic antibiotics and antifungals at the start of venetoclax treatment with dose adjustments for concomitant azole use.[18]

Oncology providers should therefore be aware of the potential risk of life-threatening infections associated with venetoclax, particularly in combination with cytotoxic chemotherapy, and should consider dose modifications where appropriate as well as supportive therapies, including growth factor and infection prophylaxis. These interventions should also be investigated in a clinical trial setting.

Our experience also adds to the growing evidence[11,13-15] that venetoclax may be effective in combination with multiple regimens across a range of hematologic malignancies, even in the relapsed/refractory setting. We found a subset of responders, even among those who received multiple lines of prior therapy. Three patients achieved a CR: one patient with SDS-associated AML who received venetoclax and decitabine and achieved a CR after 1 cycle, and two patients with relapsed B-ALL who received venetoclax with a 3-drug induction chemotherapy backbone (vincristine, dexamethasone, and PEG-asparaginase) each achieved a CR after receiving one cycle of therapy. Both patients with B-ALL were subsequently treated with bispecific T-cell engagers as bridging therapy to HSCT. Two patients who had received 3 or more prior lines of chemotherapy achieved a PR: one patient with treatment related-AML who received venetoclax and decitabine and one patient with refractory AML who received venetoclax with cytarabine; neither patient had significant venetoclax-related toxicities.

Our experience is also in agreement with prior studies suggesting patients unfit for conventional chemotherapy may benefit from venetoclax in combination with a hypomethylating agent.[6,14] This combination was generally well-tolerated, and in two cases of patients with refractory AML, it afforded excellent quality of life in the palliative setting.

Venetoclax was not effective in our two cases of infant AML, both with GLIS fusions, which are associated with a highly refractory phenotype across pediatric AML subtypes. [20,21] Alternative therapies remain desperately needed in this population.

The ability to draw conclusions about specific subgroups of patients from this experience is limited by the small sample size and heterogeneous group of patients, disease biologies, and treatment regimens. Our cohort was predominantly comprised of patients with relapsed and refractory disease, 70% of whom had received 3 or more prior lines of therapy; thus, our findings may not be generalizable to other populations, including those receiving upfront therapy for newly diagnosed hematologic malignancies. Nevertheless, our experience highlights the potential promise and risks associated with venetoclax across a diverse set of

pediatric and AYA patients with hematologic malignancies, providing real-world evidence complementary to randomized clinical trial data for guiding decision-making in routine clinical practice. Our findings suggest incorporation of venetoclax into a variety of anti-leukemia regimens may be effective in a subset of pediatric and AYA patients with relapsed/refractory AML, ALL, and MDS, but this strategy may be associated with an increased risk of life-threatening infections. Future studies should focus on identifying subgroups of patients most likely to benefit from venetoclax and on mitigating previously underrecognized infectious complications.

Conflicts of Interest Statement

The authors do not have any conflicts of interests to declare.

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Legends

Tables

TABLE 1: Patient and disease characteristics

TABLE 2: Treatment and outcomes

TABLE 3: Non-hematologic adverse events

Figures

1. Swimmer plot showing the clinical course of each patient over time. Each bar represents one patient treated with venetoclax, color-coded based on diagnosis (AML, pink; B-ALL, green; MDS, blue). Dates of severe infection, hematopoietic stem cell transplantation (HSCT), disease progression, or death are depicted by symbols. Therapy combined with venetoclax are shown on the left with a white box (hypomethylating agent, HMA) or black box (chemotherapy). Response to therapy is depicted in the second column to the left: circles are filled (complete response, CR), partially filled (partial response, PR), empty (stable disease, SD), or contain an "X" (PD, progressive disease)

2. One-year overall and progression-free survival for 13 patients treated with venetoclax combination therapy

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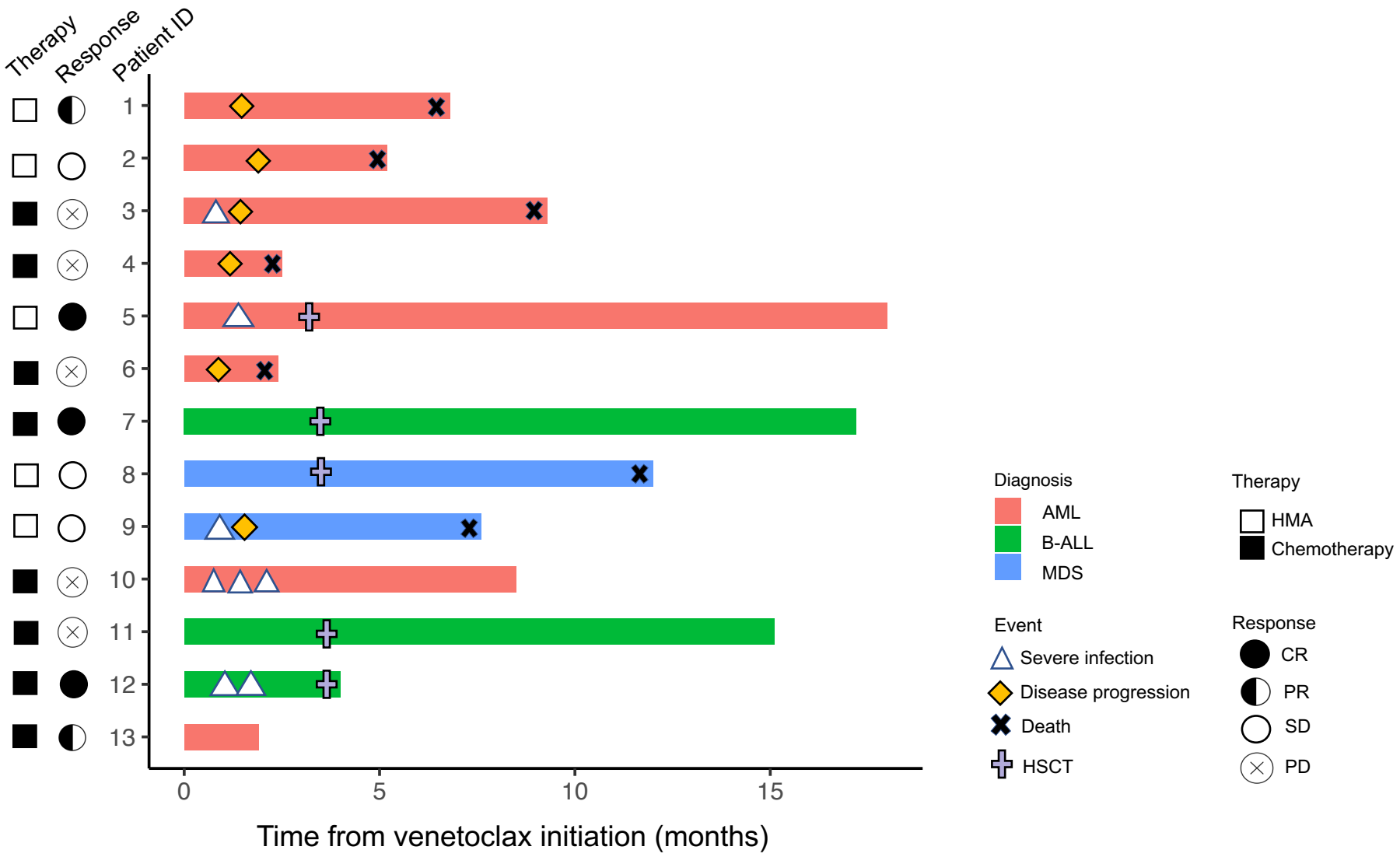
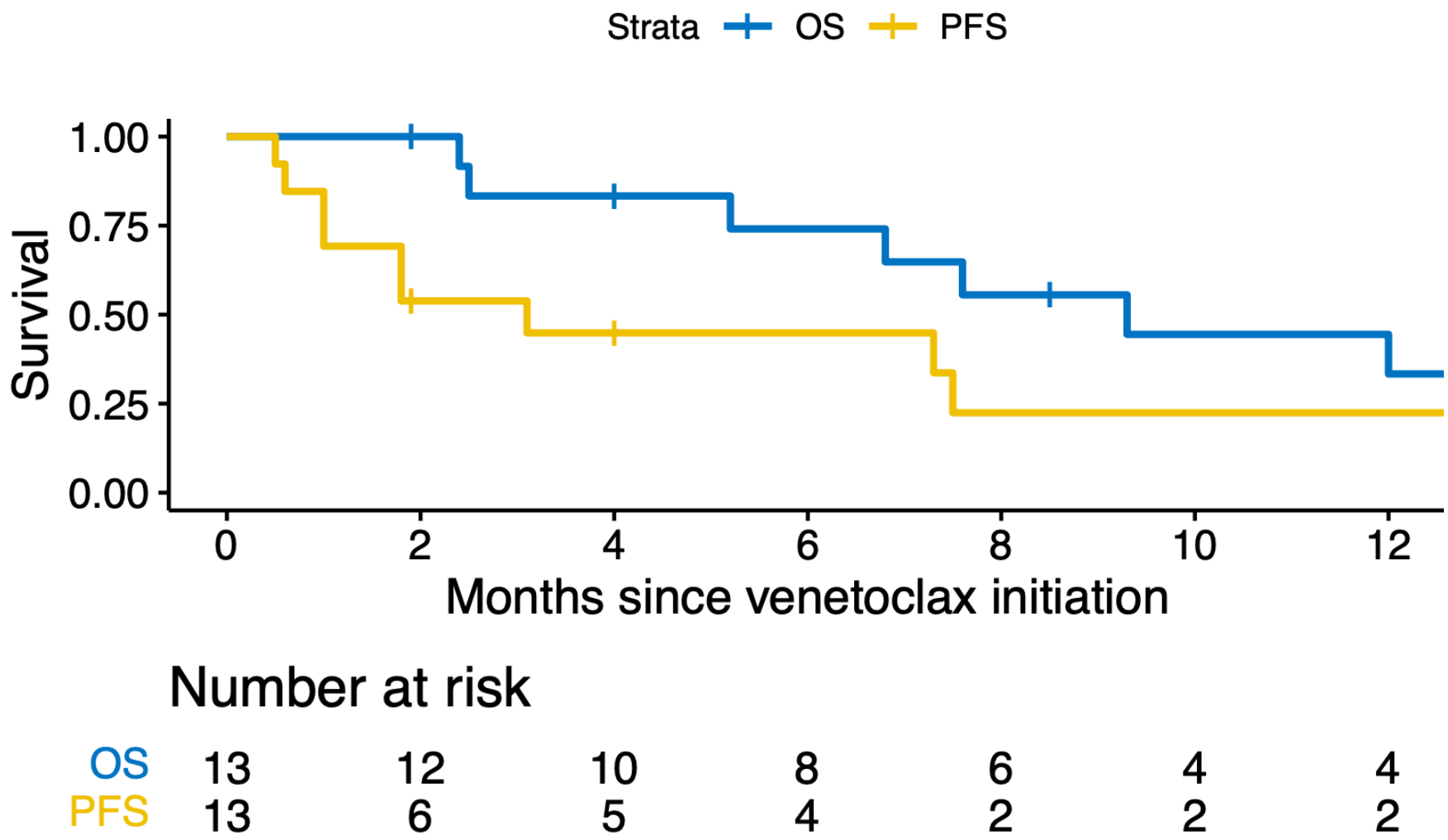

Therapy
Response
Patient ID
1
2
3
4
5
6
7
8
9
10
11
12
13
0
5
10
15
Time from venetoclax initiation (months)
Diagnosis
AML
B-ALL
MDS
Therapy
HMA
Chemotherapy
Event
Severe infection
Disease progression
Death
HSCT
Response
CR
PR
SD
PD


Strata
OS
PFS
1.00
0.75
0.50
0.25
0.00
Survival
0
2
4
6
8
10
12
Months since venetoclax initiation
Number at risk
OS 13 12 10 8 6 4 4
PFS 13 6 5 4 2 2 2