OPEN

How We Incorporate Venetoclax in Treatment Regimens for Acute Myeloid Leukemia

Abhishek Maiti, MBBS and Marina Y. Konopleva, MD, PhD

Abstract: Venetoclax has transformed the therapeutic landscape of acute myeloid leukemia (AML). Hypomethylating agents with venetoclax (HMA-VEN) have significantly improved outcomes and have become the standard therapy for older/unfit patients with newly diagnosed AML and are comparable to intensive chemotherapy in salvage setting. Venetoclax with intensive chemotherapy have shown high response rates in both frontline and salvage setting in younger patients, and triplet combinations with HMA-VEN and FLT3 inhibitors have shown encouraging results in *FLT3*^{mut} AML. While patients with *NPM1*^{mut}, *IDH1/2*^{mut} experience favorable outcomes, those with *TP53*^{mut} and secondary AML may experience minimal benefit from the addition of venetoclax. Despite improved outcomes, severe cytopenias and infectious complications are common with venetoclax-based regimens. Early response evaluation, dose reductions, venetoclax interruptions, use of growth factors, and prophylactic antimicrobials may minimize such myelosuppression and risk of infections. Outcomes after failure of frontline HMA-VEN are dismal, and novel approaches are needed to abrogate primary and acquired resistance.

Key Words: Acute myeloid leukemia, azacitidine, chemotherapy, decitabine, venetoclax

(*Cancer J* 2022;28: 2–13)

Acute myeloid leukemia (AML) is the most common acute leukemia in adults with a median age of 68 years at presentation.[1] Heterogeneous disease biology, comorbidities in older patients, and toxicities of standard therapies had long posed formidable challenges for treatment. Consequently, outcomes had been poor with treatment avoidance in the community, high early mortality, and poor long-term survival.[2,3] Lack of effective therapies and difficulty administering chemotherapy in older patients contributed to therapeutic nihilism, with up to 25% to 40% of newly diagnosed patients provided supportive care only.[4,5] Consequently, long-term cure rates for newly diagnosed AML in older patients have been low at 5% to 20%, with worse outcomes in high-risk subgroups.[6]

From the Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX.

Conflicts of Interest and Source of Funding: This work was supported in part by the MD Anderson Cancer Center Support Grant CA016672 from the National Cancer Institute. A.M. was supported in part by the American Society of Clinical Oncology Young Investigator Award. M.Y.K. was supported in part by the Research Project Grant Program (R01CA235622) from the National Institutes of Health. A.M. has received research funding from Celgene Corporation, Conquer Cancer Foundation. M.Y.K. has received grants from NIH, NCI, Abbvie, Genentech, Stemline Therapeutics, Forty-Seven, Eli Lilly, Cellectis, Calithera, Ablynx, and AstraZeneca; consulting/honorarium from AbbVie, Genentech, F. Hoffman La-Roche, Stemline Therapeutics, Amgen, Forty-Seven, Kisoji; clinical trial support from Ascentage; and has stocks/royalties in Reata Pharmaceutical.

Reprints: Marina Y. Konopleva, MD, PhD, Department of Leukemia, The University of Texas MD Anderson Cancer Center, 1400 Holcombe Blvd, Unit 428, Houston, TX 77030. E-mail: mkonople@mdanderson.org.

ISSN: 1528-9117

Hypomethylating agents (HMAs) or low-dose cytarabine (LDAC) had previously been the standard therapy for older or 'unfit' patients with newly diagnosed AML and offered complete remission (CR) or CR with incomplete hematologic recovery (CRi) rates of 1% to 30% and median overall survival (OS) of 4 to 10 months.[7–10] For patients 'fit' for intensive therapy or younger patients, the standard had been combination of cytarabine with anthracycline, which offered CR rates of 60% to 85% in patients younger than 60 years with median OS of 16 to 24 months and 40% to 60% in older patients with median OS of 9 to 12 months.[11–13] Addition of purine analogs were subsequently shown to improve outcomes in AML.[14,15] On the other hand, outcomes in relapsed or refractory (R/R) AML have been poor with CR/CRi rates of 4% to 16% and median OS of 2 to 7 months in younger patients with worse outcomes in 'unfit' or older population.[16,17]

Within this context of long-standing unmet need, development of venetoclax led to a paradigm shift in the therapeutic landscape of AML. Venetoclax is a selective and potent oral inhibitor of BCL-2, and binding of venetoclax to antiapoptotic protein BCL-2 leads to the displacement of BH3-only proapoptotic activators from BCL-2, which can then bind to proapoptotic effectors to initiate the intrinsic apoptotic cascade.[18,19] Venetoclax is active in several hematological malignancies either because of their dependency on BCL-2 or by lowering the apoptotic threshold and working synergistically with other agents. BCL-2 is highly expressed in AML including leukemia stem cells, and consequently, venetoclax has shown remarkable activity in combination with HMA or chemotherapy in older and younger patients. We herein review different approaches of incorporating venetoclax in the treatment regimens for AML and our approach toward optimizing efficacy and minimizing toxicities.

VENETOCLAX-BASED REGIMENS IN AML

Despite underwhelming results in the single-agent phase II trial in R/R AML, synergistic combinations have led to impressive rates and depth of response in newly diagnosed AML and prolongation of OS. Several venetoclax-based regimens have been evaluated in prospective clinical trials in frontline and salvage setting in younger and older patients with AML (Table 1, Fig. 1). In the following sections, we highlight outcomes in specific populations.

Newly Diagnosed AML

Venetoclax is currently approved by the US Food and Drug Administration for patients with comorbidities precluding intensive chemotherapy or those older than 75 years. For this population, venetoclax has been evaluated in combination with azacitidine for 7 days, decitabine for 5 days, and LDAC for 10 days.[21,23,28] Other lower-intensity regimens evaluated in unfit patients or those older than 60 years include venetoclax in combination with 10-day decitabine, or cladribine-LDAC alternating with azacitidine.[25,30] These regimens have shown low 30-day mortality 0% to 13%, CR/CRi rates of 41% to 94%, measurable residual disease (MRD) negativity rates of 27% to 77% in responders, and median OS of 8.4 to extending beyond 14.7 months

TABLE 1. Prospective Clinical Trials Evaluating Venetoclax-Based Regimens in AML

Agent(s)	Trial Phase	Prior Therapy	N	Age, y	Cytogenetic Risk per ELN	CR/CRi, %	CR, %	MRD-Neg, %	Median DOR/RFS/EFS, mo	Median OS/1-y OS	Reference
Single agent	II	None/HMA/IC/SCT	32	71 (19–84)	Nonfavorable	19	6	..	..	4.7	20
AZA 7 d	III	None	286	76 (49–91)	Nonfavorable	66	37	37	DOR 17.5	14.7	21,22
AZA 7 d	Ib/II	None	72	74 (65–86)	Nonfavorable	33–76	27	29	DOR 6.7-NR	8.8-NR	23,24
DEC 5 d	Ib/II	None	73	74 (64–86)	Nonfavorable	60–73	35	29	DOR 6.7-NR	14.2-NR	23,24
DEC 10 d*	II	None	85	72 (63–89)	Nonfavorable	81	61	63	DOR 9.7	12.4	25,26
DEC 10 d*	II	HMA/IC/SCT	83	66 (18–85)	Nonfavorable	41	23	51	DOR NR	6.8	25,27
LDAC	III	None/HMA	143	76 (36–93)	Any	48	27	6	DOR 8.1	8.4	28,29
Clad-LDAC/AZA	II	None	48	68 (57–84)	Nonfavorable	94	77	80	RFS NR	NR/70%	30
5 + 2 Ara-c Ida	II	None/HMA	51	72 (63–80)	Any	72	41	83	..	11.2	31
FLAG-Ida	II	None	29	45 (20–65)	Non-APL	90†	69	96	DOR NR	NR/94%	32
FLAG-Ida	II	HMA/IC/SCT	23	47 (22–66)	Non-APL	61†	48	79	DOR NR	NR/68%	32
CLIA	II	HMA	41	48 (18–64)	Non-APL	95	85	94	EFS NR	NR/90%	33
CPX-351	II	HMA/IC/VEN/SCT	18	51 (29–71)	Nonfavorable	37	6	14	RFS NR	6.4	34
Gilteritinib	Ib	Ven/FLT3i/HMA/IC/SCT	56	63 (21–85)	Non-APL	76§	18	..	..	10.5	35
Ivosidenib	Ib/II‡	None/HMA/IC/SCT	12	69 (44–84)	Nonfavorable	83†	50	40	DOR 7–13.0	NR/67–83%	36
Triplet regimens											
DEC10 quizartinib	II	None	5	69 (65–85)	Nonfavorable	100	100	80	..	14.5	37
DEC10 quizartinib	II	HMA/IC/FLT3i/SCT	23	50 (23–86)	Nonfavorable	65	13	36	..	7.5	37
AZA ivosidenib	Ib/II‡	None/HMA/IC/SCT	13	65 (56–76)	Nonfavorable	85	54	42	DOR NR	NR/50%	36
AZA pevonedistat	II	None/HMA	12	74 (61–79)	Nonfavorable	70	50	..	7.4	7.9	38

*Concomitant FLT3 inhibitors were allowed.

†Includes CRh with partial hematologic recovery.

‡Included myelodysplastic syndrome/myeloproliferative neoplasm with ≥10% blasts.

§Included patients with morphologic leukemia-free state.

APL indicates acute promyelocytic leukemia; AZA, azacitidine; Clad, cladribine; CLIA, cladribine, Ida, cytarabine; DEC, decitabine; DOR, CR/CRi duration of response; EFS, event-free survival, outcomes reported in months; FLAG-Ida, fludarabine, cytarabine, GCSF, idarubicin; FLT3i, FLT3 inhibitor; IC, intensive chemotherapy; MRD-Neg, MRD negativity among responding patients measured by flow cytometry or molecular techniques; NR, not reached; RFS, relapse-free survival; .., no data to report.

(Table 1). Retrospective comparison suggested that HMA-VEN-based lower-intensity approach may be better than intensive chemotherapy in older unfit as well as in fit patients with newly diagnosed AML (overall hazard ratio [HR] for death 0.48; 95% confidence interval [CI], 0.29–0.79; $P < 0.01$).[26] A trial evaluating azacitidine venetoclax in patients younger than 60 years with newly diagnosed AML is ongoing (NCT03573024). However, randomized trials are needed to definitively evaluate the benefit compared with intensive chemotherapy in younger/fit patients. A more intensive regimen evaluated in patients older than 60 years include 5 + 2 regimen of cytarabine with idarubicin (Ida).[31] In comparison, for younger patients with AML fit for intensive therapy, venetoclax with fludarabine, cytarabine (FLAG-Ida) or CLIA has shown very promising results with 30-day mortality of 0%, CR/CRi rates of 90% to 95%, negative MRD in 94% to 96% of responders, median OS not reached, and 1-year OS of 90% to 94%.[32,33] Evaluation of cytarabine and daunorubicin (7 + 3) with venetoclax in newly diagnosed patients younger than 60 years (NCT03709758) and 5-day oral decitabine with venetoclax in frontline and salvage setting for patients older than 60 years (NCT04746235) is ongoing.

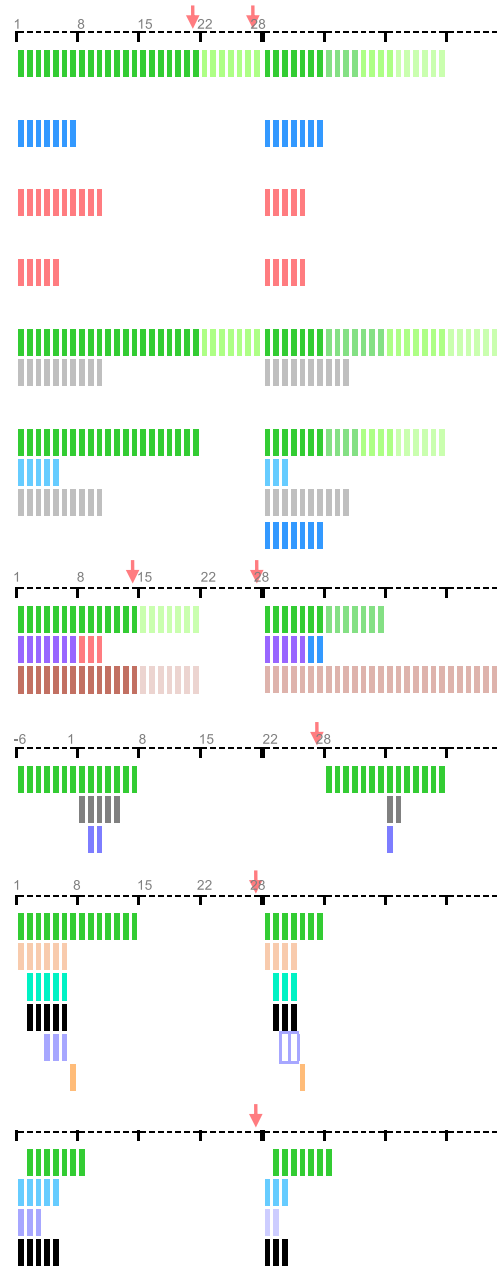
Relapsed or Refractory AML

Lower-intensity regimen evaluated in R/R AML include 10-day decitabine with venetoclax, which conferred 30-day mortality of 9%, CR/CRi rate of 42%, MRD negativity in 54% of responders, and median OS of 7.8 months with overall outcomes similar to or better than intensive chemotherapy (HR for death, 0.56; 95% CI, 0.37–0.86; $P = 0.008$).[25,27] Other retrospective studies have shown similar outcomes with CR/CRi rates of 43% to 50% and median OS of 3.0 to 7.8 months.[39] In comparison, for younger patients with R/R AML fit for intensive chemotherapy, FLAG-Ida with venetoclax is an attractive option, which showed 30-day mortality of 0%, composite CR (CRc) rate of 61%, negative MRD in 79% of responders with median OS not reached, and 1-year OS of 69%.[32] A registry-based study with FLA-Ida and venetoclax corroborated these results with CR/CRi rate of 69%, negative MRD in 22% of patients and 6-month OS of 76%.[40] Venetoclax with liposomal daunorubicin with cytarabine in salvage setting has shown 30-day mortality of 11% with CR/CRi rate of 37%, negative MRD in 18% of responders, and median OS of 10.5 months.[34] Evaluation of venetoclax with cladribine, cytarabine, granulocyte colony-stimulating factor (GCSF), and mitoxantrone in frontline and salvage setting (NCT04797767) and 10-day regimen of oral decitabine with venetoclax in salvage setting (NCT04975919) are planned.

Maintenance Therapy

The role of venetoclax-based regimens as maintenance therapy is unknown. Such regimens will need optimization to mitigate the risk of myelosuppression and infections, while preserving quality of life. The value of continuing HMA-VEN in frontline patients with MRD is unclear, given poor outcomes noted in a single-center trial with median OS of 5 to 10 months in MRD-positive nonfavorable risk AML patients treated with DEC10-VEN.[41] Retrospective data suggest that early allogeneic stem-cell transplantation

Regimen	Induction	Consolidation
VEN 400 mg/d	D1-21/28	D1-7 to 21
AZA-VEN		
Aza 75 mg/m^2/d	D1-7	D1-7
DEC10-VEN		
Dec 20 mg/m^2/d	D1-10	D1-5
DEC5-VEN		
Dec 20 mg/m^2/d	D1-5	D1-5
LDAC-VEN		
Ven 600 mg/d	D1-28	D1-28
LDAC 20 mg/m^2/d	D1-10	D1-10
Clad-LDAC a/w AZA - VEN		
Ven 400 mg/d	D1-21	D1-7 to 21
Clad 5 mg/m^2/d	D1-5	D1-3
LDAC 20 mg BID	D1-10	D1-10
Aza 75 mg/m^2/d		D1-7
HMA VEN FLT3i		
Ven 400 mg/d	D1-14	D1-7 to 21
DEC5-10 or AZA7	10/7 days	DEC5 / AZA7
FLT3 inhibitor	D1-14 DL 0	Daily DL (-1)
5+2 VEN		
Ven 600 mg/d	D -6 to 7	D (-6) to 7
Ara-c 100 mg/m^2/d cIV	D1-5	D1-2
Idarubicin 12 mg/m^2/d	D2-3	D1
FLAG-IDA VEN		
Ven 400 mg/d	D1-14	D1-7
Filgrastim 5 mcg/kg/d	D1-6	D1-4
Fludarabine 30 mg/m^2/d	D2-6	D2-4
Ara-c 1.5 g/m^2/d	D2-6	D2-4
Idarubicin 8/6* mg/m^2/d	D4-6*	D3-4
Pegfilgrastim 6 mg	D7	D5
CLIA VEN		
Ven 400 mg/d	D2-8	D2-8
Clad 5 mg/m^2/d	D1-5	D1-3
Idarubicin 10/8* mg/m^2/d	D1-3	D1-2
Ara-c 1.5/1 g/m^2/d	D1-5	D1-3



Comments

= bone marrow (BM) evaluation

Perform BM evaluation on C1D21 and hold VEN if blasts ≤5% or aplasia. For consolidation consider reducing VEN duration from 21 to 14 or 7 days in pts with myelosuppression

VEN dose of 50-70 mg with strong CYP3A4i or 300 mg with moderate CYP3A4i

Induction: up to 2 cy Consolidation: 2 cy of CLAD-LDAC alternating with 2 cy of AZA for up to total 18 cy

Induction: 14 days of venetoclax + FLT3i. BMBx on C1D14 and hold therapy if blasts ≤5%. Consolidation: FLT3i continuously at one dose level lower.

Induction: up to 1 cy Consolidation: up to 4 cy, Maintenance: VEN x14d x14d q28d x7cy

Induction: 1-2 cy Consolidation: up to 4-6 cy. *IDA dose is 6 mg/m^2/d on D4-5 for induction in R/R AML IDA is optional in up to 2 consolidation cy per physician discretion

Induction: 1-2 cy; Consolidation: up to 4-5 cy with IDA 8 mg/m^2 For pts ≥60 yrs, ara-c dose was 1.5 g/m^2 for induction and 0.75 g/m^2 for consolidation

FIGURE 1. Treatment schema of selected venetoclax-based regimens in AML. AZA indicates azacytidine; a/w, alternating with; Clad, cladribine; cy, cycle; D or d, day; DEC, decitabine; DL, dose level; i, inhibitor; IDA, idarubicin; LDAC, low-dose cytarabine; q, every; VEN, venetoclax.

(allo-SCT) may offer better OS compared with continuation of HMA-VEN after response, and single-agent venetoclax maintenance may be feasible post–allo-SCT.[42,43] Several trials are evaluating HMA-VEN as a maintenance strategy after induction chemotherapy (NCT04102020), after allo-SCT (NCT04161885), and as MRD-directed therapy after allo-SCT (NCT04809181).

OUTCOMES IN MUTATIONAL AND CLINICAL SUBGROUPS

In the frontline setting, HMA-VEN confers significantly better outcomes compared with HMA alone, or intensive chemotherapy, in patients with *NPM1*^{mut} and *IDH1/2*^{mut}.[21,26,44] In younger patients with R/R AML, HMA-VEN offers outcomes comparable to intensive chemotherapy across major mutational subgroups of *NPM1*, *IDH1/2*, *TP53*, *RUNX1*, *ASXL1*, *K/NRAS*.[27]

NPM1^{mut} AML

Among patients with favorable-risk *NPM1*^{mut} who are considered potentially curable, HMA-VEN is highly effective compared with HMA or intensive chemotherapy offering CR/CRi rates of 67% to 96% compared with 24% to 36% with HMA alone and 89% with intensive chemotherapy and significantly longer OS of 70% at 4 years with HMA-VEN, compared with median

OS of nearly 6 months with HMA in older patients and 1 to 6 years with intensive chemotherapy, depending on *FLT3* status.[21,26,44] In newly diagnosed patients with *NPM1*^{mut}, risk of death with HMA-VEN was reduced by 60% to 70% compared with intensive chemotherapy and by 30% compared with HMA alone.[21,26,44]

FLT3^{mut} AML

Among patients with *FLT3*^{mut} AML, HMA-VEN in frontline setting offers CR/CRi rate of 74% to 100% of patients with median OS of 11.5 months compared with azacitidine, which showed CR/CRi rate of 50% and median OS of 8.5 months.[45,46] Venetoclax demonstrates synergy with FLT3 inhibitors, and combination with gilteritinib in R/R *FLT3*^{mut} AML showed CRc rate of 86%, molecular MRD clearance in 69% of responders, and median OS of 10.5 months.[47,48] Triplet therapy with decitabine, venetoclax, and FLT3 inhibitors has shown promising outcomes and can potentially eliminate other clones not eradicated by venetoclax and FLT3 inhibitor. In the frontline setting, such triplet regimens have shown CRc rates of 92% to 100% with MRD-negative rates of 56% and 91% by flow cytometry and multiplex polymerase chain reaction, respectively, and 1-year OS of up to 80%.[49,50] Retrospective analysis showed such triplets confer remarkably better OS in frontline setting compared with intensive chemotherapy with FLT3 inhibitors with nearly 80% reduction in risk of death (HR, 0.21; 95% CI, 0.10–0.43).[26] In the salvage setting, such triplet regimens have shown CRc rates of 62% to 69% with MRD-negative rates of 55% to 63% and 44% to 100% by flow cytometry and multiplex polymerase chain reaction, respectively, and median OS of 6.8 to 7.2 months.[49,50] Longer follow-up is needed to understand optimal duration of each agent for such triplet regimens. Evaluation of additional triplets including azacitidine, venetoclax, and gilteritinib (NCT04140487) and "total oral therapy" with decitabine/cedazuridine, venetoclax, and gilteritinib (NCT05010122) are ongoing. While CLIA with venetoclax and FLT3 inhibitor has been prospectively evaluated in a small number of patients, more data are needed to evaluate safety of such intensive chemotherapy-based combinations.[33]

IDH1/2^{mut} AML

Patients with *IDH1/2*^{mut} AML have overall favorable outcomes with HMA-VEN. In the frontline setting, CR/CRi rate in *IDH1*^{mut} AML is 75% to 100%, with median OS not reached and 1-year OS of 72%, and CR/CRi in *IDH2*^{mut} AML is 75% to 86% with median OS of 29.6 months.[21,51,52] These outcomes were significantly better than intensive chemotherapy in the frontline setting, with nearly 90% reduction in risk of death (HR, 0.12; 95% CI, 0.06–0.25).[26] Outcomes are expectedly inferior in salvage setting, with CR/CRi rate in *IDH1*^{mut} AML of 33%, with median OS not reached and 1-year OS of 66%, and CR/CRi in *IDH2*^{mut} AML of 54%, with median OS of 14.7 months.[51] Consequently, mature results from triplet regimens with IDH1/2 inhibitors are eagerly awaited.

Early results from triplet combination with ivosidenib, venetoclax with or without azacitidine in newly diagnosed and R/R patients showed CR/CRi rates of 67% to 100%.[36] The 1-year OS in newly diagnosed AML was 100%, and that in R/R patients was 50%.[36] Patients with *IDH1/2* and *NPM1* comutation may have favorable outcomes with HMA-VEN in the frontline setting, whereas those with RAS pathway or *TP53* mutation have inferior outcomes.[52,53] Although up to 90% of patients with *IDH1/2*^{mut} responding to HMA-VEN achieve negative MRD by flow cytometry, rate of negative molecular MRD by *IDH1/2* next-generation sequencing was almost half at 52%.[52] Triplet therapy with HMA, venetoclax and IDH1/2 inhibitor may help augment mutation clearance and improve poor outcomes in patients with such concomitant signaling mutations.

TP53^{mut} AML

TP53 mutation confers resistance to venetoclax and patients with AML have poor outcomes with HMA-VEN regimens with median OS in frontline setting being 5 to 10 months, and in salvage setting being 5 months.[54–57] Venetoclax may not offer meaningful benefit over HMA alone with CR/CRi rate of 57% versus 41% and median OS of 5.2 versus 4.9 months, respectively.[56] Consequently, results of prospective trials combining azacitidine and venetoclax with magrolimab (NCT04435691), and another trial with azacitidine and magrolimab (NCT04778397) may help clarify the role of adding venetoclax for such patients.

Secondary AML

Secondary AML (sAML) including AML from prior antecedent hematological disorder and therapy-related AML (t-AML) are well recognized adverse risk subsets. Within this subgroup, treated sAML patients with prior therapy for antecedent hematological disorder has significantly worse outcomes compared with untreated patients.[58] Whereas the VIALE-C trial evaluated LDAC with venetoclax and DEC10-VEN trial including such patients, the VIALE-A trial evaluating azacitidine with venetoclax did not include treated sAML patients. Among patients newly diagnosed with t-AML, HMA-VEN in frontline setting offers CRc rates of 61% to 81% and median OS of 7.0 to 16.4 months.[25,59] Among patients with antecedent hematological disorder, venetoclax-based regimens in frontline setting offer a CRc rate of 43% to 66% with a median OS of 6.0 to 15.9 months.[25,59,60] In patients with antecedent hematological disorder progressing on HMA, addition of venetoclax may improve outcomes (unpublished data), and this approach is being evaluated in a multicenter trial (NCT04905810).

PRACTICAL ASPECTS OF MANAGING VENETOCLAX-BASED REGIMENS

Although outcomes in AML have improved vastly with venetoclax-based regimens, these regimens are not without toxicities. Febrile neutropenia occurs in 30% to 50% of patients, and grade 3/4 cytopenias occur in up to 45% of patients even with lower-intensity regimens.[21,29,32,61] With this new opportunity to treat older or frail patients who may have previously gone untreated, we need to be proactive to avoid adverse events with such regimens. In the following sections, we have summarized some practical aspects of managing venetoclax-based regimens and potential complications we follow at our institution to minimize such toxicities (Table 2).

Response Assessment and Treatment Discontinuation

We recommend early response assessment to determine scope for withholding venetoclax and targeted therapy to allow bone marrow (BM) recovery (Fig. 2). For lower-intensity regimens, we recommend BM evaluation at cycle 1 day 21 to assess for blast clearance. For intensive chemotherapy-based regimens as venetoclax is stopped early on day 7 or 14, we perform BM evaluation on cycle 1 day 28. For triplet therapy with venetoclax, FLT3 inhibitor, and HMA, we perform the first BM evaluation on cycle 1 day 14. In case of residual disease with BM blasts >5%, we continue venetoclax, and FLT3 inhibitor, for an additional week. For residual disease (>5% blasts) at the end of cycle 1 on day 28, we initiate subsequent cycle without delay. For patients achieving response by the end of cycle 1, we use GCSF to boost count recovery and minimize periods of neutropenia. We wait for count recovery up to CR criteria, i.e., absolute neutrophil count (ANC) >1 $\times$ 10^9/L and platelet count >100 $\times$ 10^9/L, or at the very least

TABLE 2. Recommendations to Optimize Venetoclax Use in AML

Clinical Issues	Recommendations
Dose ramp-up	• Ramp-up over 3 or 4 d for target dose of 400 or 600 mg, respectively. • e.g., 100 mg on D1, 200 mg on D2, 400 mg on D3; 600 mg on D4
Inpatient monitoring	• Newly diagnosed AML → admit until hematologic recovery or for first cycle • Relapsed/refractory AML → admit for duration of venetoclax ramp-up
Outpatient monitoring	• Consider outpatient follow-up 3 to 1 time per week
Minimizing risk of TLS	• Identify high risk patients → renal dysfunction, hyperuricemia, high lactate dehydrogenase, sensitive mutations *IDH1/2*, *NPM1* • Cytoreduction to WBC count <10 to 25 × 10^9/L prior to starting venetoclax • TLS prophylaxis prior to starting venetoclax and adequate hydration • TLS monitoring every 6–8 h until 24 h after reaching target dose • If significant biochemical, or clinical TLS → hold venetoclax until resolution
Premedications	• Antiemetic prophylaxis if used with HMA or intensive chemotherapy
Food and supplements	• Avoid grapefruit, starfruit, pomelo, Seville oranges, and St John's wort • Administer venetoclax 30 min after a meal with 1 cup of water
Washout	• 3-day washout for strong or moderate CYP3A4 inhibitor food or drug
Optimizing venetoclax dose	• Avoid CYP3A4 inhibitor during dose ramp-up • Ensure appropriate dose reduction with CYP3A4 or P-glycoprotein inhibitors
Renal impairment	• Avoid in glomerular filtration rate <30 mL/min due to lack of pharmacokinetic data
Liver dysfunction	• For severe liver dysfunction (Child-Pugh class C), reduce dose by 50%
Minimizing myelosuppression	
Cycle 1 venetoclax duration	• Perform BM evaluation between days 14 and 28 depending on regimen • If BM shows ≤5% blasts consider "venetoclax holiday" until complete (CR) or at least partial (CRh) hematologic recovery • If BM shows persistent AML, continue venetoclax or start next cycle without interruption, depending on timepoint
Venetoclax duration during consolidation or maintenance	• Reduce venetoclax duration instead of dose in cases of myelosuppression • If marrow blasts ≤5% and grade 4 neutropenia for >7 d or hematologic recovery takes >14 d following venetoclax interruption → reduce venetoclax in stepwise manner from 21 d to 14 d to 7 d per cycle • For neutropenic fever or severe infections → hold venetoclax until resolution
Dose reduction of concomitant therapy	• For older patients with marrow blasts ≤5% and marrow cellularity 15%–30% → reduce HMA or LDAC dose to 50% • If marrow cellularity <15%, reduce HMA dose to 33% • For younger patients with prolonged myelosuppression or severe infections, consider decreasing subsequent chemotherapy dose by 20%–33%
Growth factor use	• For patients achieving remission or hypocellular or aplastic BM on day 21 or day 14, administer daily GCSF until ANC >1.5 × 10^9/L • For consolidation or maintenance, consider prophylactic peg-filgrastim 1 d after last dose of HMA, LDAC, or chemotherapy • For neutropenic fever or severe infections → use GCSF until ANC recovery
Minimizing infections	• "Triple antimicrobial" prophylaxis for all patients • Antibiotic → fluoroquinolone or oral third-generation cephalosporin • Antifungal → posaconazole, isavuconazole, or voriconazole • Antiviral → valacyclovir or acyclovir • For elevated liver function tests due to azoles → change to echinocandin
Triplet therapy with FLT3 inhibitor	• Perform BM evaluation on day 14 to assess for response • If BM blasts ≤5% blasts, hold venetoclax and FLT3 inhibitor until partial or complete hematologic recovery • For subsequent cycles administer FLT3 inhibitor at 1 lower dose level continuously and reduce venetoclax to ≤14 d, depending on response, county recovery, BM cellularity, and infectious complications
Duration of therapy	• Continue therapy for at least 2 cycles with lower-intensity regimens - Discontinue therapy if no blast reduction or clinical benefit after 3–4 cycles of lower-intensity therapy, provided alternative options or clinical trials are available - In the absence of SCT, lower-intensity regimens may be continued indefinitely • For intensive therapy-based regimens, we recommend discontinuation if no response after 2 cycles of induction. - In responding patients, continue up to 6 total cycles of therapy, if tolerated, followed by maintenance therapy indefinitely • For patients achieving response with severe or recurrent infections or significant myelosuppression, consider de-escalation of therapy

Modified with permission from DiNardo and Wei.[62]

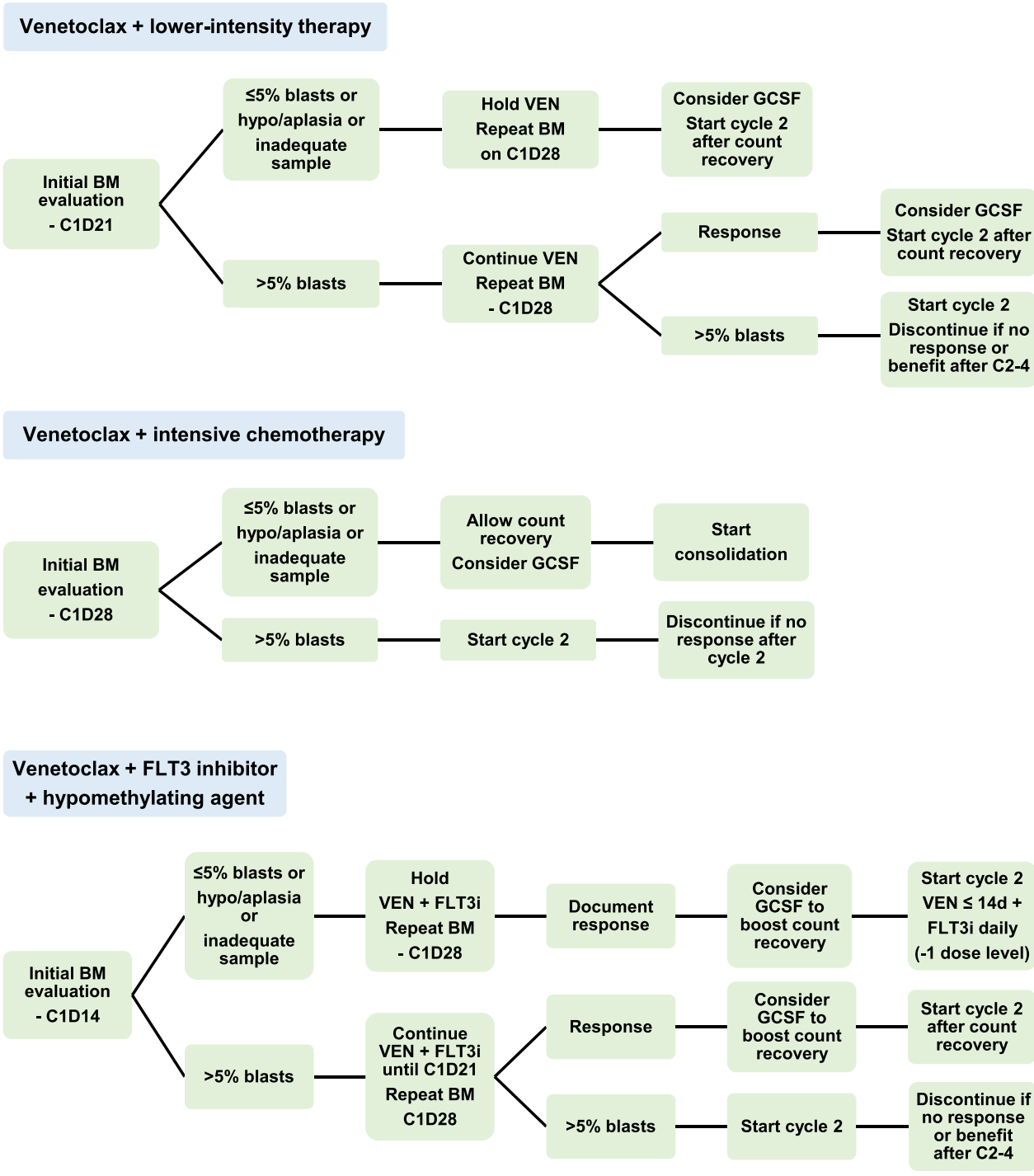


FIGURE 2. Timing of BM evaluations and treatment decision making for venetoclax-based regimens in AML. Count recovery implies peripheral blood counts to CR criteria, i.e., ANC >1 × 10^9/L and platelet count >100 × 10^9/L, or at least until CRh, i.e., ANC >0.5 × 10^9/L and platelet count >50 × 10^9/L. C indicates cycle; D, day; FLT3i, FLT3 inhibitor; VEN, venetoclax.

until CRh, i.e., CR with partial hematologic recovery with ANC >0.5 × 10^9/L and platelet count >50 × 10^9/L before starting the next cycle. After achievement of a response, we recommend repeating BM evaluation once after cycle 4 and once every 3 to 6 cycles subsequently, or earlier in cases of new or prolonged cytopenias. Such close monitoring may help early diagnosis of clonal evolution, or MRD or cytogenetic relapse, and guide therapeutic decision making.

For lower-intensity venetoclax-based regimens, the median time to first response is 1.2 to 1.5 months in the frontline setting and nearly 1.8 months in salvage setting.[25,61,62] For intensive chemotherapy-based regimens, the median time to first response is 0.9 to 1.2 months in frontline and salvage setting.[32] Consequently, we suggest treatment with at least 2 cycles for lower-intensity regimens and discontinue if no response or clinical benefit

by up to 3 to 4 cycles of therapy. For intensive chemotherapy-based regimens, we recommend up to 2 cycles of induction and discontinuation of treatment if no response after cycle 2.

Treatment After Response

For all eligible patients, we offer allo-SCT in first remission for those with European LeukemiaNet 2017 (ELN) nonfavorable-risk AML or those with persistently positive MRD followed by maintenance therapy indefinitely, preferably on a clinical. For patients not proceeding to allo-SCT, we continue lower-intensity venetoclax-based therapy, or sometimes de-escalate to modified maintenance therapy indefinitely, depending on prior history of hematologic recovery and complications. For patients treated with intensive chemotherapy-based regimen, we continue treatment for up to a maximum of 6 cycles of therapy followed by maintenance therapy indefinitely. However, in patients experiencing severe or recurrent infectious complications, or prolonged severe cytopenias, we minimize treatment exposure or consider early discontinuation in favor of either low-intensity maintenance with HMA or low-dose HMA with venetoclax, or single-agent venetoclax, or targeted therapy with FLT3 or IDH1/2 inhibitor, or even active surveillance. Optimal duration of venetoclax-based lower-intensity regimens is unknown, and some patients with favorable-risk disease and in deep remission may be candidates for treatment discontinuation and active surveillance.[53] However, prospective studies are needed to clarify the value of such elective treatment discontinuation.

Tumor Lysis Syndrome

Laboratory evidence of tumor lysis syndrome (TLS) has been reported in 1% to 6% of patients with lower-intensity venetoclax-based regimens and 0% to 6% of patients with chemotherapy-based regimens.[21,29,31–33,63–65] Incidence of clinical TLS has been lower with reported rates of 0% to 2.7%.[63,64] Such low incidence is likely the result of aggressive measures to ensure white blood cell (WBC) count less than 10×10^9 to 25×10^9/L prior to initiation of venetoclax ramp-up and routine TLS prophylaxis. We recommend identification of patients who may be at high risk of TLS. Some risk factors include baseline renal dysfunction with creatinine >1.4 mg/dL, uric acid >7.5 mg/dL, elevated lactate dehydrogenase, proliferative AML, high circulating blasts, and AML with mutations sensitive to venetoclax including *IDH1/2*, *NPM1*, and so on.

For such high-risk patients, we recommend cytoreduction to WBC count $<10 \times 10^9$/L using hydroxyurea and/or cytarabine 100 mg/m^2 IV daily or up to 2 g/m^2. We administer intravenous hydration prior to starting with close attention to fluid balance and avoiding volume overload and starting allopurinol within 72 hours prior to starting venetoclax or rasburicase if applicable. We recommend close monitoring for laboratory TLS starting within 4 hours prior to initiation and every 6 to 8 hours following venetoclax dose and after each ramp-up, until 24 hours after reaching target dose, or normalization of TLS chemistries, whichever is later. In case of significant biochemical or any clinical TLS, we recommend holding venetoclax until resolution, nephrology consultation, and monitoring in intermediate or intensive care unit with telemetry. For older or unfit patients we recommend inpatient admission for the first cycle or at least until hematologic recovery to minimize risk of early mortality.[65]

Minimizing Myelosuppression

Venetoclax-based regimens are associated with significant myelosuppression. Median time to ANC recovery to CRh threshold of 0.5×10^9/L ranged from 32 to 40 days with lower-intensity therapy and 27 to 37 days with intensive chemotherapy.[25,29,31–33] Absolute neutrophil count recovery may occur earlier by 5 to 6 days in newly diagnosed patients compared with R/R patients and by 2 to 7 days during consolidation compared with induction, depending on the regimen.[25,31,32] Absolute neutrophil count recovery to 0.5×10^9/L may take longer up to 44 to 47 days with "FLT3 inhibitor triplets."[49] Such prolonged myelosuppression significantly increases the risk of serious infectious complications and warrants proactive management to mitigate such risk. As discussed previously, early timing of response evaluation and providing "venetoclax holiday" are crucial to allow hematologic recovery. Below we have summarized some additional approaches to minimize such myelosuppression by optimizing venetoclax duration during induction and consolidation, reducing doses of chemotherapy and by liberal use of growth factors.

In addition to early stopping of venetoclax during induction in responding or aplastic patients, we recommend reduction of venetoclax duration instead of dose during consolidation in cases of delay in count recovery after induction. For patients with leukemia clearance and grade 4 neutropenia for more than a week, or hematologic recovery taking more than 2 weeks, we reduce venetoclax dose from 3 weeks to 2 weeks and even as low as 1 week. For patients in remission after triplet therapy with FLT3 inhibitors, venetoclax, and HMA, we continue FLT3 inhibitor daily at 1 dose level lower, for example, gilteritinib 80 mg daily instead of 120 mg, and venetoclax for 2 weeks or less during each cycle.[49] In addition, we reduce venetoclax duration to 10 days or fewer for patients with severe infectious complications.

We consider reducing dose of chemotherapy agents in cases of myelosuppression. For older patients with leukemia clearance and BM cellularity between 15% and 30%, we recommend 50% reduction of dose of HMA or LDAC.[62] If BM cellularity goes below 15%, we reduce HMA dose to 33%. For younger patients with higher expected cellularity, in cases of serious infectious complications or prolonged myelosuppression requiring more than 6 weeks for count recovery, we recommend reducing chemotherapy by 1

TABLE 3. Venetoclax Dosing With Azole Antifungals

Standard Dose	Moderate CYP3A4 or P-Gp Inhibitor, e.g., Isavuconazole	Strong CYP3A4 Inhibitor, e.g., Voriconazole, Posaconazole	Echinocandin
100 mg	50 mg	10 mg	No dose reduction needed
200 mg	100 mg	20 mg	
400 mg	≤200 mg	50–70 mg (50 mg with posaconazole)	
600 mg*	≤300 mg	50–70 mg	

*For venetoclax with LDAC or 5 + 2 regimen of cytarabine with Ida.

dose level or by 20% to 33% of planned doses.[66] For FLAG-Ida venetoclax regimen, we administer lower dose of Ida in salvage setting and do not administer Ida routinely during consolidation.[32] For younger patients who do not proceed to allo-SCT and have recurrent or serious infectious complications or prolonged myelosuppression, we may consider discontinuing intensive chemotherapy early and transitioning to low-intensity maintenance therapy, ideally on clinical trials.

We liberally use growth factors to reduce duration of neutropenia. For patients who achieve remission or hypocellular marrow

TABLE 4. Selected Clinical Trials Evaluating Venetoclax Combinations in AML

Agent	Backbone	Frontline	Salvage	Phase	Identifier
Chemotherapy					
Pegcrisantaspase			✓	1	NCT04666649
Antibody drug conjugate					
Tagraxofusp (anti-CD123 ADC)	Azacitidine	✓	✓	1	NCT03113643
IMGN632 (anti-CD33 ADC)	Azacitidine	✓	✓	1/2	NCT04086264
Lintuzumab-Ac225 (anti-CD33 ab)	Azacitidine		✓	1/2	NCT03932318
Lintuzumab-Ac225 (anti-CD33 ab)			✓	1/2	NCT03867682
Gemtuzumab ozogamicin			✓	1	NCT04070768
Immunotherapy					
ADI-PEG 20		✓		1	NCT05001828
Cusatuzumab (anti-CD70 ab)	Azacitidine	✓		1	NCT04150887
Sabatolimab (anti-TIM-3 antibody)	Azacitidine	✓		2	NCT04150029
Evorpacept (anti-CD47 ab)	Azacitidine	✓	✓	1/2	NCT04755244
Magrolimab (anti-CD47 ab)	Azacitidine	✓	✓	1/2	NCT04435691
DSP107 (SIRPα/4-1BBL ab)	Azacitidine	✓	✓	1	NCT04937166
ABBV-621 (TRAIL agonist)			✓	1	NCT03082209
Kinase inhibitors					
Gilteritinib	Oral decitabine	✓	✓	1/2	NCT05010122
Gilteritinib	Azacitidine		✓	1/2	NCT04140487
CA-4948 (IRAK4 inhibitor)	Azacitidine		✓	1/2	NCT04278768
IDH inhibitor	Oral decitabine		✓	1/2	NCT04774393
Quizartinib	Decitabine		✓	1/2	NCT03735875
Ponatinib	Decitabine		✓	2	NCT04188405
Trametinib	Azacitidine		✓	2	NCT04487106
Alvocidib (CDK9 inhibitor)			✓	2	NCT03969420
CYC065 (CDK2/9 inhibitor)			✓	1	NCT04017546
Dinaciclib (multi-CDK inhibitor)			✓	1	NCT03484520
Ruxolitinib			✓	1	NCT03874052
MCL-1 inhibitor					
AZD5991			✓	1/2	NCT03218683
S 64315			✓	1	NCT03672695
MDM2 inhibitor					
Milademetan	LDAC		✓	1/2	NCT03634228
Idasanutlin			✓	1/2	NCT04029688
HDM201			✓	1	NCT03940352
Miscellaneous agents					
Pitavastatin		✓		1	NCT04512105
Tamibarotene (RARα agonist)		✓		2	NCT04905407
Salsalate (nonsteroidal anti-inflammatory drug)	HMA	✓		2	NCT04146038
Uproleselan (E-selectin inhibitor)	Azacitidine	✓		1	NCT04964505
CC-90011 (LSD-1 inhibitor)		✓	✓	1	NCT04748848
OPB-11107 (STAT3 inhibitor)	Decitabine	✓	✓	1	NCT03063944
CC-90009 (CELMoD)	Azacitidine	✓	✓	1/2	NCT04336982
DS-1594b (menin inhibitor)	Azacitidine		✓	1/2	NCT04752163
Omacetaxine			✓	1/2	NCT04874194 NCT04926285
Selinexor (XPO1 inhibitor)			✓	1	NCT04898894 NCT03955783

TRAIL indicates tumor necrosis factor–related apoptosis-inducing ligand.

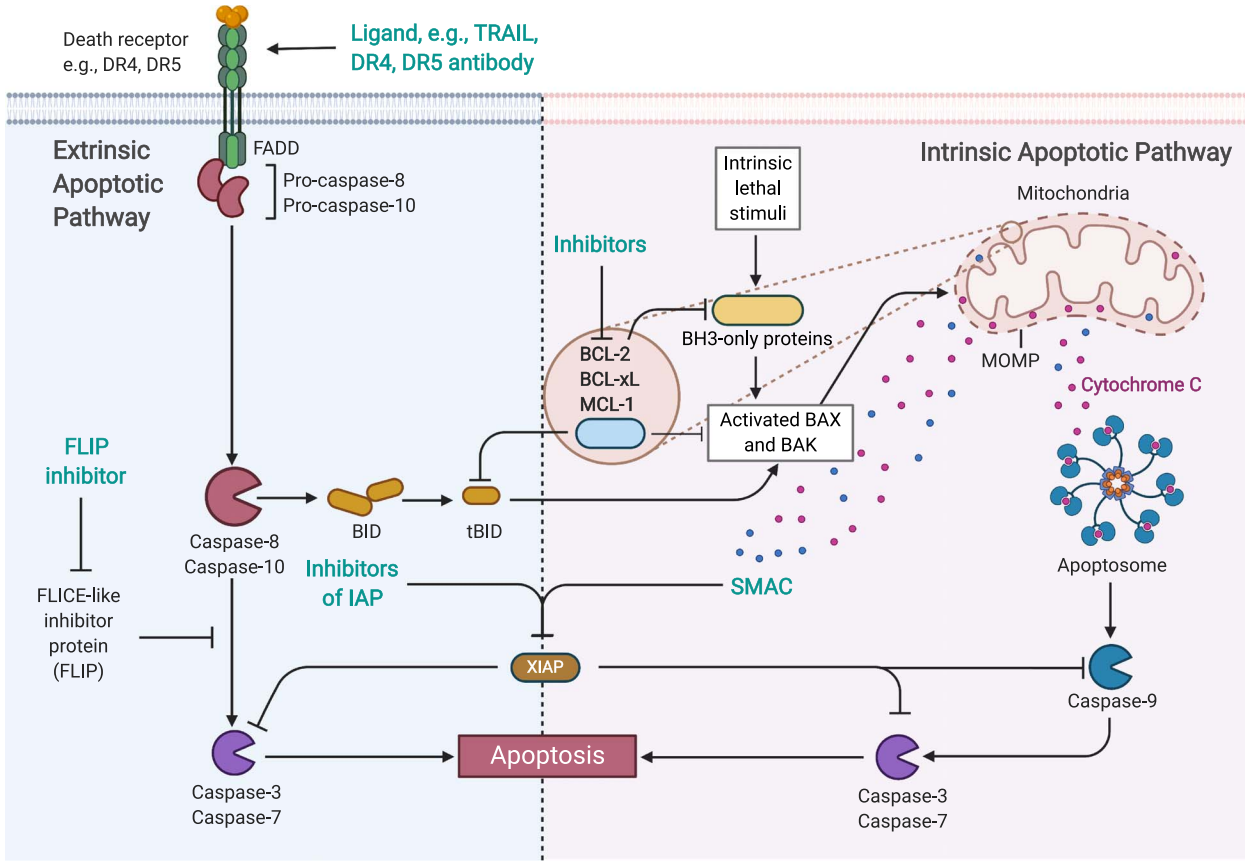


FIGURE 3. Future approaches to leverage the apoptotic pathway in AML. Reproduced with permission from Maiti et al.[74]

on cycle 1 day 21, or day 14 with FLT3 inhibitor triplet, we use daily filgrastim until ANC trends greater than 1.5×10^9/L. Similarly, we use daily filgrastim for patients presenting with infectious complications. For patients receiving consolidation or maintenance with history or delayed count recovery or infections, we consider adding peg-filgrastim after the last dose of HMA, LDAC, or chemotherapy. We attempt to avoid growth factors within 4 to 5 days of anticipated BM evaluation. We do not use thrombopoietin receptor agonists to accelerate platelet recovery.

Minimizing Infections

Risk of febrile neutropenia is upward of 30% to 40% with venetoclax-based lower-intensity therapies and 34% to 78% with intensive chemotherapy.[21,25,29,31,32,66] Consequently, we recommend prophylaxis with an antibiotic, antifungal, and antiviral for all patients receiving venetoclax-based regimens. Fluoroquinolones are preferred with oral third-generation cephalosporins, for example, cefpodoxime, being alternative agents for patients intolerant to fluoroquinolones.[67] Similarly, we recommend mold-active triazole antifungals prophylaxis due to significant reduction in death related to fungal infections.[68] Isavuconazole or posaconazole may have better tolerance than voriconazole in this regard.[69–71] It is critical to ensure appropriate venetoclax dose reduction with azole antifungals, for example, 50 mg of venetoclax with concomitant posaconazole (Table 3). We do not use fluconazole because of lack of mold coverage. Patients with significant elevation of liver function test attributed to azole antifungals may be switched to parenteral echinocandin with appropriate venetoclax dose correction. In addition, we recommend prophylaxis for herpes simplex virus and varicella zoster virus with acyclovir or valacyclovir. For patients presenting with neutropenic fever or infectious complications, we administer daily filgrastim and hold venetoclax until resolution of fevers and clinical improvement.

Existing guidelines from oncology and infectious disease societies are mostly based on evidence derived from patients with AML treated with intensive chemotherapy or SCT.[72,73] However, given the older age of the majority of patients with AML, significant myelosuppression, and frequent breakthrough infections, we believe that these recommendations are applicable to patients receiving venetoclax-based regimens. Our recommendations are further supported by the observation that despite the use of 'triple antimicrobial prophylaxis' in the DEC10-VEN trial in frontline and salvage setting, breakthrough infections with ANC $<1.0 \times 10^9$/L occurred in 46% of patients.[25] Isolated organisms included gram-negative bacteria in 49% of cases, gram-positive bacteria in 23% of cases, viruses in 15% of cases, fungi in 11% of cases, and nontubercular mycobacteria in 2% of cases (unpublished data).

FUTURE DIRECTIONS

Despite the transformative impact of venetoclax on the field of AML, 10% to 50% of newly diagnosed older patients may not respond to venetoclax-based lower-intensity regimens and 3% to 15% may not respond to venetoclax-based intensive or nonintensive chemotherapy regimens.[74] In addition, up to 40% of responding patients may experience relapse following response to HMA-VEN.[75] This population is enriched with patients having t-AML, sAML from antecedent hematological disorder, monocytic morphology, and ELN adverse-risk disease. Outcomes in such patients after failure of frontline HMA-VEN are dismal with CR/CRi rate of

13% and median OS of 2.4 months.[54,75,76] Consequently, novel approaches to abrogate primary and acquired resistance to venetoclax are urgently needed, and several such combinations are being evaluated in clinic (Table 4).

Combinatorial approaches targeting different facets of apoptotic machinery are attractive approaches to overcome resistance (Fig. 3). Such strategies include targeting other members of the intrinsic apoptotic pathway including MCL-1, BCL-xL; extrinsic apoptotic pathway including tumor necrosis factor–related apoptosis-inducing ligand, FLICE-like inhibitory protein (FLIP or CFLAR); and augmenting apoptosis by inhibiting p53 degradation via MDM2 inhibition, among others.[74] In addition, combining venetoclax with immunotherapeutic and cellular therapy approaches to leverage leukemia killing via cell intrinsic and extrinsic mechanisms warrants further investigation as well. Venetoclax has been shown to boost T-cell–mediated antileukemic effector function through augmenting reactive oxygen species production and has shown synergy with immune checkpoint blockade in preclinical studies.[77,78] Venetoclax is nontoxic to T cells and has been shown to improve chimeric antigen receptor T-cell efficacy and may presensitize leukemia to cellular therapies.[79,80]

CONCLUSIONS

Venetoclax-based combination strategies have improved outcomes for older and younger patients both in frontline and salvage setting. Emerging data have paved the way for further ways to optimize such regimens and venetoclax dosing to minimize toxicities while maintaining efficacy. Prevention and proactive management of myelosuppression along with "triple antimicrobial prophylaxis" can further reduce the risk of infectious complications inherent in patients with AML. This is particularly important as we enter the era of venetoclax-based "triplet regimens," which may increase risk of such myelosuppression. Future pragmatic trials are needed to optimize venetoclax dosing strategies and determine optimal chemotherapy backbone for younger and older patients. Novel combinatorial approaches are needed to abrogate primary and acquired resistance to prevent failure and improve outcomes with venetoclax.

REFERENCES

1. Surveillance, Epidemiology, and End Results. Acute myeloid leukemia—Cancer Stat Facts [Internet]. Cited January 1, 2018. Available at: https://seer.cancer.gov/statfacts/html/amyl.html.
2. Vasu S, Kohlschmidt J, Mrózek K, et al. Ten-year outcome of patients with acute myeloid leukemia not treated with allogeneic transplantation in first complete remission. *Blood Adv*. 2018;2:1645–1650.
3. Kantarjian H, Ravandi F, O'Brien S, et al. Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia. *Blood*. 2010;116:4422–4429.
4. Ma E, Bonthapally V, Chawla A, et al. An evaluation of treatment patterns and outcomes in elderly patients newly diagnosed with acute myeloid leukemia: a retrospective analysis of electronic medical records from US community oncology practices. *Clin Lymphoma Myeloma Leuk*. 2016;16:625–636.e3.
5. Bhatt VR, Shostrom V, Gundabolu K, et al. Utilization of initial chemotherapy for newly diagnosed acute myeloid leukemia in the United States. *Blood Adv*. 2018;2:1277–1282.
6. Sasaki K, Ravandi F, Kadia TM, et al. De novo acute myeloid leukemia: a population-based study of outcome in the United States based on the Surveillance, Epidemiology, and End Results (SEER) database, 1980 to 2017. *Cancer*. 2021;127:2049–2061.
7. Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *J Clin Oncol*. 2012;30:2670–2677.
8. Burnett AK, Milligan D, Prentice AG, et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-*trans* retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. *Cancer*. 2007;109:1114–1124.
9. Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood*. 2015;126:291–299.
10. Short NJ, Kantarjian HM, Loghavi S, et al. Treatment with a 5-day versus a 10-day schedule of decitabine in older patients with newly diagnosed acute myeloid leukaemia: a randomised phase 2 trial [Internet]. *Lancet Haematol*. 2018. Cited December 20, 2018. Available at: http://www.sciencedirect.com/science/article/pii/S2352302618301820. Accessed December 20, 2018.
11. Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. *N Engl J Med*. 2015;373:1136–1152.
12. Löwenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med*. 2009;361:1235–1248.
13. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med*. 2009;361:1249–1259.
14. Holowiecki J, Grosicki S, Robak T, et al. Addition of cladribine to daunorubicin and cytarabine increases complete remission rate after a single course of induction treatment in acute myeloid leukemia. Multicenter, phase III study. *Leukemia*. 2004;18:989–997.
15. Holowiecki J, Grosicki S, Giebel S, et al. Cladribine, but not fludarabine, added to daunorubicin and cytarabine during induction prolongs survival of patients with acute myeloid leukemia: a multicenter, randomized phase III study. *J Clin Oncol Off J Am Soc Clin Oncol*. 2012;30:2441–2448.
16. Ravandi F, Pierce S, Garcia-Manero G, et al. Salvage therapy outcomes in a historical cohort of patients with relapsed or refractory acute myeloid leukemia. *Clin Lymphoma Myeloma Leuk*. 2020;20:e871–e882.
17. Roboz GJ, Rosenblat T, Arellano M, et al. International randomized phase III study of elacytarabine versus investigator choice in patients with relapsed/refractory acute myeloid leukemia. *J Clin Oncol*. 2014;32:1919–1926.
18. Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. *Nat Med*. 2013;19:202–208.
19. Pan R, Hogdal LJ, Benito JM, et al. Selective BCL-2 inhibition by ABT-199 causes on-target cell death in acute myeloid leukemia. *Cancer Discov*. 2014;4:362–375.
20. Konopleva M, Pollyea DA, Potluri J, et al. Efficacy and biological correlates of response in a phase II study of venetoclax monotherapy in patients with acute myelogenous leukemia. *Cancer Discov [Internet]*. 2016;6:1106–1117. Cited July 29, 2018. Available at: http://cancerdiscovery.aacrjournals.org/content/early/2016/08/09/2159-8290.CD-16-0313.
21. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383:617–629.
22. Pratz K, Jonas BA, Pullarkat V, et al. Measurable residual disease response in acute myeloid leukemia treated with venetoclax and azacitidine. *J Clin Oncol*. 2021;39(suppl 15):7018.
23. DiNardo CD, Pratz KW, Letai A, et al. Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. *Lancet Oncol*. 2018;19:216–228.
24. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. *Blood*. 2019;133:7–17.
25. DiNardo CD, Maiti A, Rausch CR, et al. 10-Day decitabine with venetoclax for newly diagnosed intensive chemotherapy ineligible, and relapsed or refractory acute myeloid leukaemia: a single-centre, phase 2 trial. *Lancet Haematol*. 2020;7:e724–e736.
26. Maiti A, Qiao W, Sasaki K, et al. Venetoclax with decitabine vs intensive chemotherapy in acute myeloid leukemia: a propensity score matched analysis stratified by risk of treatment-related mortality. *Am J Hematol*. 2021;96:282–291.
27. Maiti A, DiNardo CD, Qiao W, et al. Ten-day decitabine with venetoclax versus intensive chemotherapy in relapsed or refractory acute myeloid leukemia: a propensity score–matched analysis. *Cancer*. 2021;127:4213–4220. doi:10.1002/cncr.33814.

28. Wei AH, Strickland SA Jr., Hou JZ, et al. Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: results from a phase Ib/II study. *J Clin Oncol*. 2019;37:1277–1284. JCO.18.01600.
29. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood*. 2020;135:2137–2145.
30. Kadia T. Phase II study of venetoclax added to cladribine + low dose AraC (LDAC) alternating with 5-azacytidine demonstrates high rates of minimal residual disease (MRD) negative complete remissions (CR) and excellent tolerability in older patients with newly diagnosed acute myeloid leukemia (AML) [Internet]. ASH; 2020. Cited August 21, 2021. Available at: https://ash.confex.com/ash/2020/webprogram/Paper142092.html.
31. Chua CC, Roberts AW, Reynolds J, et al. Chemotherapy and Venetoclax in Elderly Acute Myeloid Leukemia Trial (CAVEAT): a phase Ib dose-escalation study of venetoclax combined with modified intensive chemotherapy. *J Clin Oncol*. 2020;38:3506–3517.
32. DiNardo CD, Lachowiez CA, Takahashi K, et al. Venetoclax combined with FLAG-Ida induction and consolidation in newly diagnosed and relapsed or refractory acute myeloid leukemia. *J Clin Oncol*. 2021;39:2768–2778. JCO.20.03736.
33. Kadia TM, Reville PK, Borthakur G, et al. Venetoclax plus intensive chemotherapy with cladribine, idarubicin, and cytarabine in patients with newly diagnosed acute myeloid leukaemia or high-risk myelodysplastic syndrome: a cohort from a single-centre, single-arm, phase 2 trial. *Lancet Haematol*. 2021;8:e552–e561.
34. Kadia T. Phase II study of CPX-351 plus venetoclax in patients with acute myeloid leukemia (AML) [Internet]. ASH; 2020. Cited August 21, 2021. Available at: https://ash.confex.com/ash/2020/webprogram/Paper142074.html.
35. Altman JK, Daver NG, Maly J, et al. Efficacy and safety of venetoclax in combination with gilteritinib for relapsed/refractory FLT3-mutated acute myeloid leukemia: updated analyses of a phase 1B study. In: HemaSphere. Cited August 21, 2021. Available at: https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/324543/jessica.k.altman.efficacy.and.safety.of.venetoclax.in.combination.with.html.
36. Lachowiez CA, Borthakur G, Loghavi S, et al. A phase Ib/II study of ivosidenib with venetoclax +/− azacitidine in IDH1-mutated myeloid malignancies. *J Clin Oncol*. 2021;39(suppl 15):7012.
37. Yilmaz M, Muftuoglu M, Kantarjian HM, et al. Quizartinib (Quiz) with decitabine (DAC) and venetoclax (VEN) is highly active in patients (pts) with FLT3-ITD mutated acute myeloid leukemia (AML)–RAS/MAPK mutations continue to drive primary and secondary resistance. *Blood*. 2021;138(suppl 1):370.
38. Short N, Bose P, DiNardo C, et al. Preliminary results of a phase I/II study of azacitidine, venetoclax and pevonedistat in patients with secondary acute myeloid leukemia who are unfit for intensive chemotherapy [Internet]. *HemaSphere*. Cited August 21, 2021. Available at: https://library.ehaweb.org/eha/2020/eha25th/294475/nicholas.short.preliminary.results.of.a.phase.i.ii.study.of.azacitidine.html.
39. Bewersdorf JP, Giri S, Wang R, et al. Venetoclax as monotherapy and in combination with hypomethylating agents or low dose cytarabine in relapsed and treatment refractory acute myeloid leukemia: a systematic review and meta-analysis. *Haematologica*. 2020;105:2659–2663.
40. Shahswar R, Beutel G, Klement P, et al. FLA-Ida salvage chemotherapy combined with a seven-day course of venetoclax (FLAVIda) in patients with relapsed/refractory acute leukaemia. *Br J Haematol*. 2020;188:e11–e15.
41. Maiti A, DiNardo CD, Wang SA, et al. Prognostic value of measurable residual disease after venetoclax and decitabine in acute myeloid leukemia. *Blood Adv*. 2021;5:1876–1883.
42. Pollyea DA, Winters A, Jordan CT, et al. Allogeneic transplant improves AML outcomes compared to maintenance venetoclax and azacitidine following response to initial venetoclax and azacitidine therapy. *Blood*. 2020;136:24.
43. Kent A, Pollyea DA, Winters A, et al. Venetoclax is safe and tolerable as post-transplant maintenance therapy for AML patients at high risk for relapse. *Blood*. 2020;136:11–12.
44. Lachowiez CA, Loghavi S, Kadia TM, et al. Outcomes of older patients with NPM1-mutated AML: current treatments and the promise of venetoclax-based regimens. *Blood Adv*. 2020;4:1311–1320.
45. Aldoss I, Zhang J, Mei M, et al. Venetoclax and hypomethylating agents in FLT3-mutated acute myeloid leukemia [Internet]. *Am J Hematol*. 2020. Cited July 12, 2020. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/ajh.25929.
46. Konopleva M, Thirman M, Pratz KW, et al. Results of venetoclax and azacitidine combination in chemotherapy ineligible untreated patients with acute myeloid leukemia with FLT3 mutations. *Blood*. 2020;136:8–10.
47. Ma J, Zhao S, Qiao X, et al. Inhibition of Bcl-2 synergistically enhances the antileukemic activity of midostaurin and gilteritinib in preclinical models of FLT3-mutated acute myeloid leukemia. *Clin Cancer Res*. 2019;25:6815–6826.
48. Altman JK, Daver N, Maly J, et al. AML-162: efficacy and safety of venetoclax in combination with gilteritinib for relapsed/refractory FLT3-mutated acute myeloid leukemia: updated analyses of a phase 1b study. *Clin Lymphoma Myeloma Leuk*. 2021;21:S285.
49. Maiti A, DiNardo CD, Daver NG, et al. Triplet therapy with venetoclax, FLT3 inhibitor and decitabine for FLT3-mutated acute myeloid leukemia. *Blood Cancer J*. 2021;11:25.
50. Yilmaz M, Kantarjian HM, Muftuoglu M, et al. Quizartinib with decitabine and venetoclax (triplet) is highly active in patients with FLT3-ITD mutated acute myeloid leukemia (AML). *J Clin Oncol*. 2021;39(suppl 15):e19019.
51. Venugopal S, Maiti A, DiNardo CD, et al. Decitabine and venetoclax for IDH1/2-mutated acute myeloid leukemia. *Am J Hematol*. 2021;96:E154–E157.
52. Hammond D, Loghavi S, Konopleva M, et al. Response patterns and MRD by flow cytometry and NGS in patients with mutant-IDH acute myeloid leukemia treated with venetoclax in combination with hypomethylating agents. *Blood*. 2020;136:35–36.
53. Chua CC, Hammond D, Kent A, et al. AML-212: treatment free remission (TFR) after ceasing venetoclax-based therapy in responding patients with acute myeloid leukemia. *Clin Lymphoma Myeloma Leuk*. 2021;21:S291–S292.
54. Nechiporuk T, Kurtz SE, Nikolova O, et al. The TP53 apoptotic network is a primary mediator of resistance to BCL2 inhibition in AML cells. *Cancer Discov*. 2019;9:910–925. CD-19-0125.
55. DiNardo CD, Tiong IS, Quaglieri A, et al. Molecular patterns of response and treatment failure after frontline venetoclax combinations in older patients with AML. *Blood*. 2020;135:791–803.
56. Kim K, Maiti A, Loghavi S, et al. Outcomes of TP53-mutant acute myeloid leukemia with decitabine and venetoclax. *Cancer [Internet]*. 2021;127:3772–3781. Cited July 13, 2021. Available at: https://acsjournals.onlinelibrary.wiley.com/doi/abs/10.1002/cncr.33689.
57. Aldoss I, Zhang J, Pillai R, et al. Venetoclax and hypomethylating agents in TP53-mutated acute myeloid leukaemia. *Br J Haematol*. 2019;187:e45–e48.
58. Boddu P, Kantarjian HM, Garcia-Manero G, et al. Treated secondary acute myeloid leukemia: a distinct high-risk subset of AML with adverse prognosis. *Blood Adv*. 2017;1:1312–1323.
59. Pullarkat V, Pratz K, Dohner H, et al. Venetoclax and azacitidine combination in chemotherapy ineligible untreated patients with therapy-related myeloid neoplasms, antecedent myelodysplastic syndromes, or myelodysplastic/myeloproliferative neoplasms. *J Clin Oncol*. 2021;39(suppl 15):7011.
60. Masarova L, DiNardo CD, Bose P, et al. Single-center experience with venetoclax combinations in patients with newly diagnosed and relapsed AML evolving from MPNs. *Blood Adv*. 2021;5:2156–2164.
61. Jonas BA, Pollyea DA. How we use venetoclax with hypomethylating agents for the treatment of newly diagnosed patients with acute myeloid leukemia. *Leukemia*. 2019;33:2795–2804.
62. DiNardo CD, Wei AH. How I treat acute myeloid leukemia in the era of new drugs. *Blood*. 2020;135:85–96.
63. Diao S, Nichols ED, DiNardo C, et al. Incidence of tumor lysis syndrome in patients with acute myeloid leukemia undergoing low-intensity induction with venetoclax. *Am J Hematol*. 2021;96:E65–E68.
64. Amany Keruakous RS, Saleem R, Steven Asch A, Stephenson Cancer Center OC, University of Oklahoma Health Sciences Center OC. Venetoclax-induced tumor lysis syndrome in acute myeloid leukemia: real world experience. Cited May 14, 2020. Available at: https://meetinglibrary.asco.org/record/185366/abstract.
65. Pelcovits A, Moore J, Bakow B, et al. Tumor lysis syndrome risk in outpatient versus inpatient administration of venetoclax and hypomethlators for acute myeloid leukemia. *Support Care Cancer*. 2021;29:5323–5327.
66. Kadia TM, Cortes J, Ravandi F, et al. Cladribine and low-dose cytarabine alternating with decitabine as front-line therapy for elderly patients with

acute myeloid leukaemia: a phase 2 single-arm trial. *Lancet Haematol*. 2018;5:e411–e421.
67. Wojenski DJ, Barreto JN, Wolf RC, et al. Cefpodoxime for antimicrobial prophylaxis in neutropenia: a retrospective case series. *Clin Ther*. 2014; 36:976–981.
68. Gøtzsche PC, Johansen HK. Routine versus selective antifungal administration for control of fungal infections in patients with cancer. *Cochrane Database Syst Rev [Internet]*. 2002;CD000026. Cited August 29, 2021; (2). Available at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000026/full.
69. Bose P, McCue D, Wurster S, et al. Isavuconazole as primary antifungal prophylaxis in patients with acute myeloid leukemia or myelodysplastic syndrome: an open-label, prospective, phase 2 study. *Clin Infect Dis*. 2021;72:1755–1763.
70. Samanta P, Clancy CJ, Marini RV, et al. Isavuconazole is as effective as and better tolerated than voriconazole for antifungal prophylaxis in lung transplant recipients. *Clin Infect Dis*. 2021;73:416–426.
71. Stern A, Su Y, Lee YJ, et al. A single-center, open-label trial of Isavuconazole prophylaxis against invasive fungal infection in patients undergoing allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2020;26:1195–1202.
72. Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. *J Clin Oncol*. 2018;36:3043–3054.
73. Sandherr M, Hentrich M, von Lilienfeld-Toal M, et al. Antiviral prophylaxis in patients with solid tumours and haematological malignancies—update of the guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO). *Ann Hematol*. 2015;94:1441–1450.
74. Maiti A, Andreeff M, Konopleva MY. Beyond BCL-2 inhibition in acute myeloid leukemia: other approaches to leverage the apoptotic pathway. *Clin Lymphoma Myeloma Leuk*. 2021;21:S3–S6.
75. Maiti A, Rausch CR, Cortes JE, et al. Outcomes of relapsed or refractory acute myeloid leukemia after frontline hypomethylating agent and venetoclax regimens. *Haematologica*. 2021;106:894–898.
76. Pei S, Pollyea DA, Gustafson A, et al. Monocytic subclones confer resistance to venetoclax-based therapy in patients with acute myeloid leukemia. *Cancer Discov*. 2020;10:536–551. CD-19-0710.
77. Lee JB, Khan DH, Hurren R, et al. Venetoclax enhances T cell–mediated antileukemic activity by increasing ROS production. *Blood*. 2021;138:234–245.
78. Kohlhapp FJ, Haribhai D, Mathew R, et al. Venetoclax increases intratumoral effector T cells and antitumor efficacy in combination with immune checkpoint blockade. *Cancer Discov*. 2021;11:68–79.
79. Siblany L, Gaugler B, Stocker N, et al. Venetoclax does not impair activated T-cell proliferation. *Bone Marrow Transplant*. 2021;56:1740–1742.
80. Yang M, Wang L, Ni M, et al. Pre-sensitization of malignant B cells through venetoclax significantly improves the cytotoxic efficacy of CD19.CAR-T cells. *Front Immunol*. 2020;11:608167.