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 FLT3mut AML. While patients with NPM1mut, IDH1/2mut experience favorable outcomes, those with TP53mut 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

(© 2022 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal. ISSN: 1528-9117)

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 low at 5% to 20%, with worse outcomes in high-risk subgroups.5

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.

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 BCL-2’s 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.

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, AbbVie, and AstraZeneca; consulting/honorarium from AbbVie, Genentech, F. Hoffman La-Roche, Stemline Therapeutics, Aegerion, Forty-Seven, Kisqali, 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.
similar to or better than intensive chemotherapy (HR for death, responders, and median OS of 7.8 months with overall outcomes day decitabine with venetoclax, which conferred 30-day mortality 94%.32,33 Evaluation of cytarabine and daunorubicin (7 + 3) with CR/CRi rates of 90% to 95%, negative MRD in 94% to 96% of has shown very promising results with 30-day mortality of 0%, composite CR (CRc) rate of 37%, negative MRD in 18% 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 (G-CSF), 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 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

| Agent(s) | Trial Phase | Prior Therapy | N Age, y | Cytemedication | Cyogenetic Risk per ELN | CR/Cri, % | CR, % | Median OS/1-y OS Reference |
|----------|-------------|---------------|--------|---------------|------------------------|---------|-------|--------------------------|
| Single agent | II | None/HMA/IC/SCT | 32 71 (19–84) | Nonfavorable | 19 6 | .. | .. | 4.7 |
| AZA 7 d | III | None | 286 76 (49–91) | Nonfavorable | 66 37 | 37 | 14.7 |
| AZA 7 d | III | None | 72 74 (65–86) | Nonfavorable | 33–76 | 27 | 9.8–NR |
| DEC 5 d | III | None | 73 74 (64–86) | Nonfavorable | 60–73 | 35 | 14.2–NR |
| DEC 10 d* | II | None | 85 72 (63–89) | Nonfavorable | 81 | 61 | 12.4 |
| DEC 10 d* | II | HMA/IC/SCT | 83 66 (18–85) | Nonfavorable | 41 | 23 | 6.8 |
| LDAC | III | None/HMA | 143 76 (36–93) | Any | 48 | 27 | 8.4 |
| Clad-LDAC/AZA | II | None | 48 68 (57–84) | Nonfavorable | 94 | 77 | 80 |
| 5 + 2 Ara-c Ida | II | None/HMA | 51 72 (63–80) | Any | 72 | 41 | 83 |
| FLAG-Ida | II | None | 29 45 (20–65) | Non-APL | 90 | 69 | 96 |
|FLAG-Ida | II | HMA/IC/SCT | 23 47 (22–66) | Non-APL | 61 | 48 | 79 |
| CLIA | II | HMA | 41 48 (18–64) | Non-APL | 95 | 85 | 94 |
| CPX-351 | II | HMA/IC/VEN/SCT | 18 51 (29–71) | Nonfavorable | 37 | 6 | 14 |
| Gilteritinib | II | Veri/FLT3/IC/SCT | 56 63 (21–85) | Non-APL | 76 | 18 | .. |
| Ivosidenib | II | None/HMA/IC/SCT | 12 69 (44–84) | Nonfavorable | 83 | 50 | 40 |
| Triplet regimen | DEC10 quizartinib | II | None | 5 69 (65–85) | Nonfavorable | 100 | 100 | 80 |
| DEC10 quizartinib | II | HMA/IC/FLT3/SCT | 23 50 (23–86) | Nonfavorable | 65 | 13 | 36 |
| AZA ivosidenib | II | None/HMA/IC/SCT | 13 65 (56–76) | Nonfavorable | 85 | 54 | 42 |
| AZA pevonedstat | II | None/HMA | 12 74 (61–79) | Nonfavorable | 70 | 50 | 7.4 |

*Concomitant FLT3 inhibitors were allowed.
†Includes CRh with partial hematologic recovery.
‡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; FLA-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. Prospective Clinical Trials Evaluating Venetoclax-Based Regimens in AML

© 2022 The Author(s). Published by Wolters Kluwer Health, Inc.
www.journalppo.com | 3
(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 NPM1mut and IDH1/2mut.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

**5+2 VEN**

Among patients with favorable-risk NPM1mut 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

---

**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.

---

**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 NPM1mut and IDH1/2mut.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

**NPM1mut AML**

Among patients with favorable-risk NPM1mut 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

---

**TABLE 1.**

| Regimen          | Induction | Consolidation | Comments |
|------------------|-----------|---------------|----------|
| **VEN 400 mg/d** | D1-21,28  | D1-7 to 21    |          |
| **AZA-VEN**      |           |               |          |
| Aza 75 mg/m²/d   | D1-7      | D1-7          |          |
| **DEC10-VEN**    |           |               |          |
| Dec 20 mg/m²/d   | D1-10     | D1-5          |          |
| **DEC5-VEN**     |           |               |          |
| Dec 20 mg/m²/d   | D1-5      | D1-5          |          |
| **LDAC-VEN**     |           |               |          |
| Ven 600 mg/d     | D1-28     | D1-28         | VEN dose of 50-70 mg was strong for CYP3A4 or 300 mg with moderate CYP3A4i |
| LDAC 20 mg/m²/d  | D1-10     | D1-10         |          |
| **Clad-LDAC a/w AZA - VEN** | | | |
| Ven 400 mg/d     | D1-21     | D1-7 to 21    | Induction: up to 2 cy |
| Clad 5 mg/m²/d   | D1-5      | D1-3          | Consolidation: 2 cy of Clad-LDAC alternating with 2 cy of AZA for up to total 18 cy |
| LDAC 20 mg BID   | D1-10     | D1-10         |          |
| Aza 75 mg/m²/d   | D1-7      |               |          |
| **HMA VEN FLT3i** |           |               |          |
| Ven 400 mg/d     | D1-14     | D1-7 to 21    | Induction: 14 days of venetoclax + FLT3i. BMBx on D1-7 and hold therapy if blasts ≤5%. Consolation: FLT3i continuously at one dose level lower. |
| DECS-10 or A2A7  | 10/7 days | DEC5 / A2A7  |          |
| FLT3i inhibitor   | D1-14 DL 0|               |          |
| **5+2 VEN**      |           |               |          |
| Ven 600 mg/d     | D-6 to 7  | D-(-6) to 7   | Induction: up to 1 cy |
| Ara-c 100 mg/m²/d| D1-5      | D1-2          | Consolidation: up to 4 cy. Maintenance: VEN x14d x14d q28d x7cy |
| Idarubicin 12 mg/m²/d | D2-3 | D1 |          |
| **FLAG-IDA VEN** |           |               |          |
| Ven 400 mg/d     | D1-14     | D1-7          | Induction: 1-2 cy |
| Filgrastim 5 mcg/kg/d | D1-6  | D1-4 | Consolation: up to 4-6 cy. "IDA dose is 6 mg/m²/d on D4-6 for induction in R/R AML. IDA is optional in up to 2 consolidation cy per physician discretion. |
| Fludarabine 30 mg/m²/d | D2-6  | D2-4 |          |
| Ara-c 1.5 g/m²/d  | D2-6      | D2-4          |          |
| Idarubicin 8/6* g/m²/d | D4-6* | D3-4 |          |
| Pegfilgrastim 6 mg | D7       | D5            |          |
| **CLA VEN**      |           |               |          |
| Ven 400 mg/d     | D2-8      | D2-8          | Induction: 1-2 cy |
| Clad 5 mg/m²/d   | D1-5      | D1-3          | Consolidation: up to 4-5 cy with IDA 8 mg/m² For pts ≥60 yrs, ara-c dose was 1.5 g/m² for induction 0.75 g/m² for consolidation |
| Idarubicin 10/8* g/m²/d | D1-3 | D1-2 |          |
| Ara-c 1.5/1 g/m²/d | D1-5     | D1-3 |          |

---

© 2022 The Author(s). Published by Wolters Kluwer Health, Inc.
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\(^{\text{mut}}\) 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\(^{\text{mut}}\)** AML

Among patients with FLT3\(^{\text{mut}}\) 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\(^{\text{mut}}\) 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.\(^{49,51}\) 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\(^{\text{mut}}\)** AML

Patients with IDH1/2\(^{\text{mut}}\) AML have overall favorable outcomes with HMA-VEN. In the frontline setting, CR/CRi rate in IDH1\(^{\text{mut}}\) AML is 75% to 100%, with median OS not reached and 1-year OS of 72%, and CR/CRi in IDH2\(^{\text{mut}}\) AML is 75% to 86% with median OS of 29.6 months.\(^{21,52}\) 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\(^{\text{mut}}\) AML of 53%, with median OS not reached and 1-year OS of 66%, and CR/CRi in IDH2\(^{\text{mut}}\) AML of 54%, with median OS of 14.7 months.\(^{33}\) 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\(^{\text{mut}}\) 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\(^{\text{mut}}\)** 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.\(^{32–57}\) 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.\(^{25,59}\) 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 14. In case of residual disease with BM blasts >5%, we perform BM evaluation at 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 × 10^9/L and platelet count >100 × 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 |
|                 | • Cyto reduction to WBC count <10 to 25 × 10⁹/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 |
|                 | • Avoid CYP3A4 inhibitor during dose ramp-up |
| Optimizing venetoclax dose | • Avoid CYP3A4 inhibitor in case of myelosuppression |
| Renal impairment | • Ensure appropriate dose reduction with CYP3A4 or P-glycoprotein inhibitors |
| Liver dysfunction | • Avoid in glomerular filtration rate <30 mL/min due to lack of pharmacokinetic data |
| Minimizing myelosuppression | • For severe liver dysfunction (Child-Pugh class C), reduce dose by 50% |

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 55% and marrow cellularity 15%–30% → reduce HMA or LDAC dose to 30% |
• 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 × 10⁹/L |
• For consolidation or maintenance, consider prophylactic pegfilgrastim 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
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. 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. Incidence of clinical TLS has been lower with reported rates of 0% to 2.7%. Such low incidence is likely the result of aggressive measures to ensure white blood cell (WBC) count less than 10⁹/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 × 10⁹/L using hydroxyurea and/or cytarabine 100 mg/m² IV daily or up to 2 g/m². 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.

Minimizing Myelosuppression

Venetoclax-based regimens are associated with significant myelosuppression. Median time to ANC recovery to CRh threshold of 0.5 × 10⁹/L ranged from 32 to 40 days with lower-intensity therapy and 27 to 37 days with intensive chemotherapy. 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. Absolute neutrophil count recovery to 0.5 × 10⁹/L may take longer up to 44 to 47 days with “FLT3 inhibitor triplets.” 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. 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. 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                                        |                 |
| 600 mg*         | ≤300 mg                                         | (50 mg with posaconazole)                       | 50–70 mg        |

*For venetoclax with LDAC or 5 + 2 regimen of cytarabine with Idarubicin.
dose level or by 20% to 33% of planned doses. For FLAG-Ida venetoclax regimen, we administer lower dose of Ida in salvage setting and do not administer Ida routinely during consolidation. 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) | Azacitidine   | ✓             | ✓           | 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         | NCT04150509   |
| 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          |               |               |             |           |               |
| Gilbertinib                | Oral decitabine| ✓             | ✓           | 1/2       | NCT05010122   |
| Gilbertinib                | Azacitidine   | ✓             | ✓           | 1/2       | NCT04140487   |
| CA-4948 (IRAK4 inhibitor)  | Azacitidine   | ✓             | ✓           | 1/2       | NCT04278768   |
| IDH inhibitor              | Oral decitabine| ✓             | ✓           | 1/2       | NCT04774393   |
| Quizartinib                | Decitabine    | ✓             | ✓           | 1/2       | NCT03765875   |
| 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   |
| Idasanulin                 | ✓             | ✓             | ✓           | 1/2       | NCT04029688   |
| HDM201                     | ✓             | ✓             | ✓           | 1         | NCT03940352   |
| Miscellaneous agents       |               |               |             |           |               |
| Pitavastatin               | ✓             | ✓             | ✓           | 1         | NCT04512105   |
| Tamibarotene (RARα agonist)| ✓             | ✓             | ✓           | 2         | NCT04905407   |
| Salsalate (nonsteroidal anti-inflammatory drug) | HMA | ✓ | ✓ | 2 | NCT04140638 |
| Uproleselan (E-selectin inhibitor) | Azacitidine | ✓ | ✓ | 1 | NCT04964505 |
| CC-90011 (LSD-1 inhibitor) | ✓             | ✓             | ✓           | 1         | NCT04748848   |
| OPB-11107 (STAT3 inhibitor) | Decitabine    | ✓             | ✓           | 1         | NCT03063944   |
| CC-90009 (CELERMoD)        | Azacitidine   | ✓             | ✓           | 1/2       | NCT04369828   |
| DS-1594b (menin inhibitor) | Azacitidine   | ✓             | ✓           | 1/2       | NCT04752163   |
| Omacetaxine                | ✓             | ✓             | ✓           | 1/2       | NCT04874194   |
| Selinexor (XPO1 inhibitor) | ✓             | ✓             | ✓           | 1         | NCT04898894   |

TRAIL indicates tumor necrosis factor–related apoptosis-inducing ligand.
on cycle 1 day 21, or day 14 with FLT3 inhibitor triplet, we use daily filgrastim until ANC trends greater than 1.5 × 10⁹/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. 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. Similarly, we recommend mold-active triazole antifungals prophylaxis due to significant reduction in death related to fungal infections. Itraconazole or posaconazole may have better tolerance than voriconazole in this regard. 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 toazole 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. 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 × 10⁹/L occurred in 46% of patients. 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 non-intensive chemotherapy regimens. In addition, up to 40% of responding patients may experience relapse following response to HMA-VEN. 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.\textsuperscript{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 intrinsin 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.\textsuperscript{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.\textsuperscript{75,76} 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.\textsuperscript{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/aml.html.
2. Vass 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. Bhart VR, Shroott 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 triple antimicrobial prophylaxis—mediated antileukemic effector function. New Engl J Med. 2020;383:81–89.
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. Domínguez MJ, Seymour JF, Rutmum 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, Lohaghi S, et al. Treatment with a 5-day versus a 10-day schedule of decitabine in older patients with newly diagnosed acute myeloid leukemia: a randomised phase 2 trial. Lancet Haematol. 2016;3:e141–e149.
11. Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. New Engl J Med. 2015;373:1136–1152.
12. Löwenberg B, Ossenpinkke GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. New Engl J Med. 2009;361:1235–1248.
13. Fernandez HF, Sun Z, Yao X, et al. Anthracylidine dose intensification in acute myeloid leukemia. New Engl J Med. 2009;361:1289–1295.
14. Holowicki 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. Holowicki 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;20:6971–6982.
17. Roboz GJ, Rosenblat T, Arenallo 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, Leverston JD, Boghuerts 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. Schoppele M, Polyne A, Patrholi 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. New Engl J Med. 2020;383:617–629.
22. Prat 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, Prat K, Rutjens JA, Riddell S, et al. Safety and preliminary efficacy of venetoclax with or without azacitidine in elderly patients with previously untreated acute myeloid leukemia: a non-randomised, open-label, phase Ib study. Lancet Oncol. 2018;19:216–226.
24. DiNardo CD, Prat K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naïve, elderly patients with acute myeloid leukemia. Blood. 2019;133:7–17.
25. DiNardo CD, Maiti A, Rasch CR, et al. 10-Day decitabine with venetoclax for newly diagnosed intensive chemotherapy ineligible, and relapsed or refractory acute myeloid leukemia: 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/I clinical trial. 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, Lachowicz 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 leukemia or high-risk myelodysplastic syndrome: a cohort from a single-centre, single-arm, phase 2 trial. Lancet Haematol. 2021;8:e55–e56.

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 [Internet]. ASH; 2020. Cited August 21, 2021. Available at: https://library.ehaweb.org/eha/2021-virtual-congress/324543/jessica.k.altman.efficacy.and.safety.of.venetoclax.in.combination.with.html.

36. Lachowicz CA, Borthakur G, Loghavi S, et al. A phase Ib/Iib 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 and venetoclax (triplet) is highly active in patients with FLT3-ITD mutated acute myeloid leukemia (AML) [Internet]. ASH. 2021. 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.

38. Short N, Bose P, DiNardo C, et al. Preliminary results of a phase I/II study of azacitidine, venetoclax and penvonostat 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. Shahvarw 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 leukemia. 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 outcome for relapsed/refractory acute myeloid leukemia. Blood. 2020;136:24–29.

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. Lachowicz 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://onlineibrary.wiley.com/doi/abs/10.1002/ajh.25929.

46. Konopleva M, Thurman J, Patriz K, et al. Results of venetoclax and azacitidine combination in chemotherapy ineligible untreated patients with acute myeloid leukemia with FLT3 mutations. Blood. 2020;136:6–10.

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 trial. 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) [Internet]. ASH. 2020. 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.

51. 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 [Internet]. ASH; 2020. 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.

52. Pollyea DA, Winters A, Jordan CT, et al. Allogeneic transplant improves outcome for relapsed/refractory acute myeloid leukemia: a systematic review and meta-analysis. Haematologica. 2020;105:2659–2663.

53. Plunkett V, Patriz K, Dohner H, et al. Venetoclax and azacitidine combination in chemotherapy ineligible untreated patients with therapy-related myeloid neoplasms, antecedent myelodysplastic syndromes, or myelodyplastic/myeloproliferative neoplasms. J Clin Oncol. 2021;39(suppl 15):7011.

54. 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.

55. 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.

56. DiNardo CD, Wei AH. How I treat acute myeloid leukemia in the era of new drugs. Blood. 2020;135:85–96.

57. Diao S, Nichols ED, DiNardo C, et al. Incidence of tumor lysis syndrome in patients with AML evolving from MPNs. Blood Adv. 2021;5:2156–2164.
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, Marin 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;21:53–56.

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 anti-leukemic activity by increasing ROS production. *Blood*. 2021;138:234–245.

78. Khellilapp FJ, Haribhai D, Mathew R, et al. Venetoclax increases intratumoral effector T cell 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.