

How we treat older patients with acute myeloid leukaemia

Avraham Frisch,¹ Jacob M. Rowe^{1,2,3}  and Yishai Ofran^{1,3} 

¹Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, Haifa, ²Department of Hematology, Shaare Zedek Medical Center, Jerusalem, and ³The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel

Summary

After decades when intensive chemotherapy remained the only effective anti-acute myeloid leukaemia (AML) treatment, a torrent of novel, less toxic agents are about to revolutionise AML therapy. Prolonged remissions with good quality of life become achievable for many patients previously considered only for palliative care because they could not tolerate intensive therapy. As treatment options multiply, the importance of genetic profile is recognised, even for advanced-age patients for whom cure is unlikely. With lack of randomised comparative trials for most treatment regimens, one can only extrapolate data from existing studies to make evidence-based decisions. We herein present seven common clinical scenarios illustrating the complexity of treating older AML patients and describe our approach to their management. In each case, up-to-date data on relevant agents to be offered to a particular patient are discussed. The current review is limited to the drugs, available and approved in the Western world and many promising agents, still under investigation, are not discussed.

Keywords: acute myeloid leukaemia, older adults, molecular profile, intensive chemotherapy, novel agents.

Acute myeloid leukaemia (AML) is the most prevalent acute leukaemia in adults, with a median age at diagnosis of 68 years. For decades, the main treatment option for newly-diagnosed AML patients has been intensive chemotherapy, which optimally offers a complete remission (CR) rate of 70% and a long-term survival of about 40%.¹ Specifically for patients with advanced age, not only is the remission rate significantly inferior, but also toxicity and treatment-related mortality are excessive compared to younger patients. Fortunately, in recent years, novel, effective and less toxic drugs

have become available. Moreover, improvements in supportive care, and better tools for risk stratification and patient selection for allogeneic stem cell transplantation (allo-SCT), have all contributed to an improved outcome. Choosing wisely from the many treatment options available for AML patients with advanced age is currently a common clinical dilemma with no simple textbook answer. It is challenging to translate the accumulating but limited data regarding the effectiveness of each drug into a reliable, effective and evidence-based approach. We herein, with the use of six vignettes, present common treatment options and discuss a few case scenarios, aiming to apply principles that can be used in common clinical practice.

Case 1: Is there still a role for intensive chemotherapy for elderly AML patients?

A previously healthy 72-year-old woman is referred because of increased fatigue. Her complete blood count (CBC) shows a white blood cell (WBC) count of 1,300/ μ l with 6% blasts, 32,000/ μ l platelets and haemoglobin of 6.5 g/dl. Her marrow is infiltrated with myeloid blasts, and molecular mutation analysis is negative for NPM1, FLT3-ITD mutations and for core binding factor (CBF) aberrations. Her echocardiogram demonstrates normal left systolic and diastolic functions without pulmonary hypertension or wall motion abnormalities. She has normal renal and liver functions. Cytogenetic results will be available within a week. What is the optimal approach for this patient? Should cytogenetics impact the chosen strategy?

This is a case of an apparently fit patient who, had she been 10 years younger, would have been considered for intensive chemotherapy by most physicians. The question therefore is whether intermediate- and/or adverse-risk patients should be treated differently in an advanced age. To answer this question, it is prudent to consider both the immediate treatment plan and post-remission therapy. It has been well-known for decades that achieving CR in the end of induction is a prerequisite but insufficient condition for long-term remission. A substantial number of patients will relapse early after achieving CR, if no consolidation therapy

Correspondence: Yishai Ofran, Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, 8 Ha'Aliya st., Haifa 3109601, Israel.

E-mail: y_ofran@rambam.health.gov.il

CELGENE 2082
APOTEX v. CELGENE
IPR2023-00512

First published online 30 April 2020
doi: 10.1111/bjh.16701

© 2020 British Society for Haematology and John Wiley & Sons Ltd
British Journal of Haematology, 2020, **191**, 682–691

is prescribed.^{2,3} Thus, an immediate/induction treatment plan should be such as to allow optimal post-remission therapy, particularly in fit patients, preserving the option for allo-SCT.

Following intensive chemotherapy, fit patients aged 70–80 years with intermediate-risk AML have about 60–65% probability to achieve CR, with a 10–15% early death risk.^{1,4} It should be noted that in the large prospective study by the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network Cancer Research Group (ECOG-ACRIN, E2906) exploring intensive chemotherapy in patients with advanced age, minimal residual disease (MRD) negativity was achieved in 58/147 (39.5%) of patients who achieved remission. These MRD-negative patients have an excellent long-term survival rate.⁵ Further improvement of intensive regimes in older patients is challenging. The addition of gemtuzumab ozogamicin (GO) in induction, known to improve CR and survival in younger patients, is probably too toxic for patients over 70 years.^{6,7} As GO increases induction toxicity by prolonging the time to bone marrow recovery⁸ and increasing early mortality,⁹ its use in combination with intensive chemotherapy for older patients cannot be recommended.

For long-term remission in fit older patients, allo-SCT remains the most effective post-remission strategy, with 38% 2-year overall survival (OS) in CR1 for patients older than 69 years and a 3-year OS of 49% for patients older than 60 years.^{10,11}

A novel alternative for this patient, considered by some, is using venetoclax with hypomethylating agents (HMA) or low-dose cytarabine (LDAC; discussed later in case 2). Although data from phase Ib/II studies reported CR + CR with incomplete blood count recovery (CRi) rates as high as 73% and low early mortality rates, early results from the phase III trial studying the LDAC and venetoclax combination found a much lower response rate of 47% and a median OS of 7.2 months only. Furthermore, updated results of using an HMA + venetoclax combination in both NPM1 and IDH2 wildtype AML patients demonstrated a 2-year OS of 26.6%.¹² Of note, given SCT ineligibility of most patients included in the phase Ib/II trials, data about the outcome of patients fit to be transplanted are insufficient. Interestingly, in 21 patients (out of 145) initially treated with HMAs and venetoclax combination and then transplanted,^{13,14} the median OS is reported to be as high as 24.4 months. However, the required depth of response and optimal timing for SCT after induction with a venetoclax combination still need to be assessed.

Therefore, as long-term data are lacking, and in the absence of prospective comparisons between intensive chemotherapy and venetoclax combinations, it seems that for fit intermediate-risk AML patients, outcomes are better when intensive chemotherapy rather than venetoclax combinations is used.

Assuming that our patient has AML with adverse-risk cytogenetics would lead to complicated decision-making. Available data in patients with advanced age suggest that, for patients presenting with a monosomal/complex karyotype, the CR rates with intensive chemotherapy are as low as 30–35% and become even lower if TP53 is mutated/deleted.^{4,15,16} Moreover, early death rates are higher, presumably because of prolonged cytopenia and the need for additional chemotherapy.

Novel agents (e.g., venetoclax + azacitidine) offer at least the same CR with reduced early death rates. However, as discussed earlier, to achieve a long-term outcome, the feasibility and efficacy of allo-SCT after these novel therapies need to be demonstrated in prospective studies.

Older patients who are not candidates for allo-SCT but are in remission after chemotherapy are commonly offered at least one cycle of intermediate-dose cytarabine. The overall results, however, remain disappointing, with a relapse-free survival (RFS) of only 16% after 4 years.²

Historically, maintenance therapy with various agents consistently failed to demonstrate OS advantage. Exceptions are three early studies showing an event-free survival (EFS) benefit with LDAC^{17,18} and with IL-2 and histamine combination,¹⁹ but this has not been adopted in clinical practice, particularly in the U.S. Recently, the Haemato-Oncology Foundation for Adults in the Netherlands (HOVON) published a phase III trial where patients >60 years who received intensive chemotherapy and achieved remission were randomised to azacitidine maintenance or observation alone. This study reported an EFS benefit without OS prolongation.²⁰ Other studies established an OS benefit for azacitidine maintenance, but with some limitations. Oliva *et al.* presented at the 23rd European Hematology Association Congress a phase III trial where azacitidine maintenance, preceded by intermediate-dose cytarabine consolidation, led to improved OS compared to non-maintenance.²¹ Notably, the number of patients participating in that study was relatively small. A phase II ECOG-ACRIN trial as an ancillary to the large prospective E2906 study included a randomisation for patients who achieved CR1 with intensive chemotherapy. One year of decitabine maintenance was shown to improve OS in the FLT3-ITD-negative subgroup.²² Finally, the most exciting breakthrough confirming the value of HMA maintenance therapy is in the results of the phase III randomised placebo-control QUAZAR AML-001 study. In this trial, CC-486, an oral formulation of azacitidine, was tested as maintenance therapy for both *de novo* and secondary AML patients aged 55 and older. The drug was given until relapse or allo-SCT, and was reported to double EFS and OS.^{23,24}

Our suggestion is to treat this patient with a curative intent, comprising intensive chemotherapy and, if possible, an allo-SCT. If a decision to consolidate her with chemotherapy is taken, at least 1 year of post-remission maintenance with HMAs should also be considered.

Case 2: Initial therapy in an unfit older patient

An active 74-year-old male presents with AML. His ECOG performance status (PS) is 1. He is known to have type II diabetes and hypertension, a prior cerebrovascular accident (CVA) from which he recovered with no sequelae and chronic obstructive pulmonary disease (COPD) with moderate pulmonary hypertension. His WBC count is 60 000/ μ l, he has no disseminated intravascular coagulation (DIC) and no evidence of end-organ injury on admission. Two months previously, his blood counts were within normal limits. He has a normal karyotype and molecularly is FLT3-ITD-negative/NPM1-positive. Is there a preferred targeted approach for this patient?

Older patients with comorbidities have lower CR rates and higher mortality with intensive chemotherapy than younger patients. Assessing fitness for intensive induction is problematic and biased by considerable subjectivity; thus, published data need to be carefully scrutinised. In general, truly unfit patients have an early mortality rate of approximately 30% with standard chemotherapy, as reported by real-world data from the Swedish registry.¹

Despite the good PS, his comorbidities, which can be evaluated using either Hematopoietic Cell Transplantation Comorbidities Index or Charlson Comorbidities Index, are predictive of early mortality.^{25,26} Thus, treatment with intensive chemotherapy should to be discouraged.

Few low-intensity options are currently approved for unfit newly-diagnosed AML patients. These regimens have not been directly compared; thus, recommending a particular regimen for this patient is based on a careful review of the available data.

Venetoclax

BCL2 superfamily proteins regulate mitochondrial apoptotic signalling, with BCL2, MCL1 and BCL_{XL} proteins being the key anti-apoptotic members. Venetoclax is a potent oral specific BCL2-inhibitor which has only a modest activity against AML blasts as a single agent, possibly due to MCL1-dependent apoptosis evasion.²⁷ However, based on phase I-II trials, the combination of venetoclax with either HMA or LDAC was approved by the FDA (though not the European Medicines Agency) for newly-diagnosed older or unfit AML patients.

DiNardo *et al.*^{13,14} demonstrated that a combination of venetoclax with HMA in newly-diagnosed patients (median age 74 years) who were HMA-naïve induced CR/CRi rates of 67%, compared with the historic rates of 20–25% CR/CRi for azacytidine or decitabine when used as monotherapy.^{28,29} Moreover, high response rates were reported even in patients with poor cytogenetics or P53 mutations, with 60% and 47% CR/CRi rates, respectively. With a median follow-up of 15 months, the median OS was not reached in NPM1-

mutated AML patients. With the same duration of follow-up, the median OS was not reached if isocitrate dehydrogenase (IDH) 1/2 was also mutated. Early mortality rates were as low as 3% in the first 30 days and 8% in 60 days. Interestingly, MRD-negativity was defined using a low-sensitivity threshold of 10^{-3} and was reached in 30% of responsive patients. An optimal venetoclax dose, when prescribed in combination with HMA, was determined to be 400 mg/day, with no additive value for 800 mg/day and excessive toxicity in the 1200 mg/day dose.

Another phase II trial examined the combination of LDAC (20 mg/day for 10 days) with 600 mg venetoclax. This study also included patients who failed previous treatment with HMA (about a third of the patients). The CR/CRi rates were 26 and 28% respectively, but were dramatically influenced by presence of secondary AML or prior HMA treatment. For patients without prior HMA treatment the CR/CRi rates were 62%, and the median OS was 13.5 months. Of note, patients with NPM1 mutation had favourable response to this combination, with 89% CR/CRi rates.²⁴

Retrospective observations report encouraging results of venetoclax combinations even in the relapse setting. Studies demonstrate a response spectrum of 21–64%, emphasising the heterogeneity of these select reports, with higher responses in IDH1/2-mutated AML, intermediate-risk cytogenetics and RUX1-mutated AML.^{30–32}

The kinetics of response in the newly-diagnosed AML and relapse settings are similar. The vast majority of the patients who respond to venetoclax-containing regimens do so in the first two cycles.^{13,14,24,30} It is therefore rational to assess response after two cycles.

Venetoclax-containing regimens have a few important limitations. The major haematologic toxicity is neutropenia, which may often be profound. If severe neutropenia is evolving while the patient is in remission, granulocyte-colony stimulating factor (G-CSF) support provides a short and minimal benefit; therefore, reducing or withholding doses is advised. Detailed dose modification varies and relies on minimal data. Published recommendations include withholding venetoclax administration until neutrophil recovery and then resuming treatment in lower dose (50–75% full dose), reducing the HMA/LDAC doses or extending intervals between treatment cycles.³³ The two latter might be advised when marrow hypocellularity or pancytopenia is evident. Such recommendations are based on clinical experience/observation of dose modifications that lead to peripheral count recovery in some patients. Experience in the practical use of venetoclax is crucial, and precise data regarding the long-term effect of any modifications on survival and relapse are lacking.

Venetoclax is metabolised via CYP3A4, and thus strong CYP3A4 inhibitors, commonly used for other indications in AML patients, may increase venetoclax blood levels. Commonly used azoles, particularly voriconazole and posaconazole, and quinolone antibiotics may have a strong interaction

with venetoclax. It is recommended to reduce the venetoclax dose by 75% when co-administering strong CYP3A4 inhibitors, like the aforementioned azoles, and by 50% for moderate CYP3A4 inhibitors.^{24,34} However, as previously noted, these recommendations are based on limited pharmacokinetic data with no clinical evidence supporting the long-term effect of these dose modifications.

A major limitation for venetoclax-containing regimens is venetoclax resistance, as lack of response to venetoclax-based treatment is usually associated with prolonged cytopenias. Moreover, as other options for first-line treatment are available, prediction of response to venetoclax-based therapy will become very important. Venetoclax resistance is driven mainly by overexpression or mutations in MCL1 and BCL-X_L, the two other anti-apoptotic proteins of the BCL-2 family.³⁵ Recent studies suggested that high BCL2 expression or BCL2/MCL1 ratio can predict for good response to venetoclax. It was also shown that HMA and chemotherapy suppress MCL1 expression and thus synergise with venetoclax.^{36,37} A few recently-published articles demonstrate that AML cells with monocytic differentiation respond poorly to venetoclax, possibly because of low BCL2/MCL1 ratio, and that CD14 can serve as a marker for venetoclax sensitivity.^{37–40} Other pathways/mechanisms which confer venetoclax resistance are currently being actively investigated, as are other venetoclax combinations, such as those with MEK inhibitor, MDM2 inhibitor and FLT3-ITD inhibitors.^{41–44}

Glasdegib

Glasdegib is a specific inhibitor of Smoothened (SMO), a receptor regulating the hedgehog pathway. SMO inhibition in cell lines is found to reduce the percentage of G0 cells, especially in leukaemic stem cells, and to abrogate cytarabine resistance. In mouse model, SMO inhibition is demonstrated to attenuate leukaemia-initiation potential of AML cells, presumably by targeting leukaemic stem cells.⁴⁵ Based on these results, a phase II study was conducted, comparing LDAC to LDAC + glasdegib in AML patients and high-risk myelodysplastic syndrome (MDS) patients. The glasdegib + LDAC combination was found to have an OS benefit in AML patients (median OS 8.8 months, compared to 4.9 months with LDAC alone), which was consistent in all cytogenetic risk groups, albeit less pronounced in high-risk cytogenetics. Despite the survival advantage, only 27% patients achieved CR/CRi. Notably, 17% of patients who received the combination were previously treated with HMAs. Most adverse events more common with glasdegib were gastrointestinal symptoms, mostly grade I/II.⁴⁶ Based on these results, glasdegib was approved by the FDA for relapsed/refractory patients over 75 years or those with comorbidities, and a phase III trial for newly-diagnosed patients combining glasdegib with either intensive chemotherapy or HMAs was initiated in 2018.

Our priority for this patient is a combination of venetoclax with azacytidine. While LDAC is a perfectly reasonable option, we prefer the combination with HMA due to the lower dose of venetoclax, used with less risk of drug interactions.

Case 3: Treatment of an unfit AML patient with IDH1/2 mutation

A 77-year-old female presents with normal karyotype, NPM1wt/FLT3-ITD-negative/IDH1-positive *de novo* AML. She is known to have hypertension, treated with valsartan/amlodipine. She had a hip fracture 4 months ago, for which she underwent total hip replacement. She is assisted with a walker, and her ECOG PS is 2. On CBC, she is pancytopenic with WBC of 2500/μl, absolute neutrophil count (ANC) of 1200/μl, 72 000/μl platelets, haemoglobin 7.9 g/dl. The patient is a widow, and her children live abroad. She is afraid that she would not be able to attend frequent visits to the clinic.

Is a total ambulatory care possible in this patient?

IDH1/2 inhibitors

IDH1 and IDH2 mutations are present in about 20% of AML cases, predominantly in normal karyotype AML. The IDH1 inhibitor ivosidenib and the IDH2 inhibitor enasidenib will be discussed together, since their safety profiles and efficacies are very similar. In relapsed/refractory AML, each of these IDH inhibitors is effective as a single agent, with as much as 30% CR + CRi rates and a median survival of over 1 year for CR/CRi responders. Also, many patients who achieved only partial response (PR) had prolonged survival and became transfusion-independent.^{47,48} Based on these results, the IDH inhibitors gained FDA approval for relapsed/refractory AML. Interestingly, patients with FLT3-ITD co-mutation and RAS co-mutations respond poorly to IDH inhibition. For newly-diagnosed older patients, both IDH inhibitors were tested in phase I studies as single agents. Ivosidenib treatment achieved 55% ORR and 42% CR/CRh rates, with more than 60% of responses lasting for 12 months. Based on these data, ivosidenib was approved by the FDA for this indication.⁴⁹ Enasidenib achieved 31% ORR, with median duration response not reached.⁵⁰ Adverse effects with these drugs are minor. Leukocytosis associated with differentiation syndrome is unique but uncommon, and possible QT prolongation, particularly with co-administration of CYP3A4 inhibitors such as azoles, may also occur.

IDH inhibitors were also tested in combination with azacytidine, demonstrating relatively high CR rates of 50–57% and ORR of 68–78%. Grade 3–4 neutropenia occurred in about 30%, whereas grade 3–4 febrile neutropenia occurred in 12% of patients treated with enasidenib and 39% of patients treated with ivosidenib combinations.^{13,51}

Given that IDH inhibitors are oral anti-leukaemic agents with a remarkable safety profile, this would easily be our preference for older unfit patients who clearly elect to avoid hospitalisations. The sustained response and easy administration of single agent ivosidenib make this an exciting therapeutic strategy. However, in cases where immobilisation is less of a problem, venetoclax combinations, very effective also in IDH1/2-mutated AML, would be offered to this patient, given the overall greater likelihood of achieving a longer disease-free interval.

Case 4: Treating an older patient with FLT3-ITD-mutated AML

A 75-year-old obese male, known to have diabetes and restrictive lung disease with hypoventilation syndrome, presents to the emergency room with dyspnoea. On examination, his O₂ saturation is 86% in ambient air, and chest radiography demonstrates bilateral pulmonary infiltrates. His CBC shows a WBC count of 140 000/μl with 85% circulating monoblasts, 60 000/μl platelets and haemoglobin 8.4 g/dl. He is treated with supplement oxygen, broad-spectrum antibiotics and hydroxyurea 6 g/day. Two days later, his WBC is 25 000/μl and his lungs are clear. The molecular AML work-up comes back with the diagnosis of normal karyotype, NPM1 wt/FLT3-ITD-mutated (allelic ratio 1.5) AML.

FLT3 is a transmembrane tyrosine kinase receptor, which, upon binding to its ligand, promotes proliferation and survival of normal haematopoietic progenitors through various intracellular pathways. Mutations in FLT3, resulting in constitutive activation of FLT3, are among the most common in AML in younger patients and are less frequent in advanced age. These mutations can be sub-divided into mutations in the juxtamembrane domain (FLT3-ITD mutation) and the tyrosine kinase domain (typically D835 point mutation).⁵² FLT3-ITD is a well-known adverse prognostic marker, and is associated with high proliferation index and reduced RFS and OS.⁵³ The poor prognosis is more pronounced if high allelic ratio (AR) FLT3-ITD mutation (defined as >0.5) is noted.⁵⁴ Guidelines of the National Comprehensive Cancer Network and the European LeukemiaNet categorise AML with FLT3-ITD mutation as poor-risk AML, based on the high relapse risk after intensive chemotherapy, and recommend allo-SCT as the preferred post-remission treatment. As for FLT3-TKD mutations, their prognostic impact is more uncertain due to conflicting evidence,^{55–57} and therefore they are not considered currently as poor prognostic markers.

FLT3-ITD-mutated AML patients treated with low-intensity regimens with no FLT3 inhibitors have poor responses. CR rates of 44% for venetoclax + LDAC and 33% for glasdegib + LDAC were reported, which were lower than results in patients with no FLT3 mutations. The OS was also inferior, with only one-third of patients treated with venetoclax + LDAC being alive after a year. Similar results were

recently published, demonstrating 53.3% CR/CRi rates and median OS of 12.4 months for FLT3-ITD-mutated AML patients receiving venetoclax-based combinations.⁵⁸ Thus, FLT3-ITD-mutated AML in older patients should be considered separately with novel agents. FLT3 inhibitors have a substantial role in treatment of AML patients presenting with FLT3 mutations. Midosturin, a first-generation FLT3 inhibitor, was the first to be approved as first-line therapy, in combination with 7 + 3 intensive chemotherapy, based on CR and survival benefit demonstrated in a prospective phase III study.^{59,60} Sorafenib, another first-generation FLT3 inhibitor, which is biologically active only against FLT3-ITD and not against TKD mutations, was also tested prospectively in combination with either intensive chemotherapy or azacytidine. Addition of sorafenib to chemotherapy during induction and consolidation, with use as a single agent in 1-year maintenance, was found to improve the CR and survival rates in FLT3-ITD-mutated young AML patients.⁶¹ The same survival benefit was demonstrated for FLT3-ITD-mutated AML patients aged 60–69, but not in a more elderly group, presumably because of adverse effects.⁶² This is in line with a prior report regarding increased early mortality for patients >60 years treated with chemotherapy combined with sorafenib.⁶³

The combination of sorafenib and azacytidine was tested in a phase II trial for newly-diagnosed AML and relapsed/refractory patients and resulted in considerable response rates of 32% for the relapsed patients and 67% for newly-diagnosed ones. Notably, about half of responses to sorafenib combined with azacytidine were CRi and not CR.^{64,65}

Next-generation FLT3 inhibitors are more specific and more potent than first-generation inhibitors. Quizartinib was tested against chemotherapy for relapsed/refractory FLT3-ITD + AML patients in a phase III trial, demonstrating improved OS with manageable toxicity. Over 20% of patients receiving quizartinib achieved only PR as best response considered an event, which might have contributed to a less-pronounced EFS advantage.⁶⁶ Due to the very short EFS with this drug, the FDA has not approved it for use yet. Gilteritinib is another next-generation FLT3 inhibitor, which was tested as monotherapy against intensive and non-intensive salvage chemotherapy in a phase III trial. Based on improved OS in this setting, it was approved by the FDA for relapsed/refractory AML. Interestingly, only 21% of patients achieved CR/CRh, but nevertheless many others became transfusion-independent and/or could be referred to allo-SCT. It remains to be seen whether adding chemotherapy or a targeted agent to gilteritinib will improve the outcome in advanced FLT3-positive AML. These two next-generation inhibitors are currently being explored in various combinations in other scenarios, including newly-diagnosed AML patients.

This patient has serious comorbidities that preclude him from standard chemotherapy. He also has a highly proliferative AML with high allelic-ratio FLT3-ITD mutation, which

would argue for the addition of an FLT3 inhibitor. There are no good options here, and the therapeutic intent is limited.

In the absence of a clinical trial and the lack of mature data using second-generation FLT3 inhibitors in newly-diagnosed AML, our preferred choice would be to treat him with the combination of sorafenib and azacytidine. The importance of FLT3 inhibition should be appreciated. Recently, DiNardo *et al.* reported treatment failure in AML patients receiving venetoclax combinations, frequently attributed to expansion of kinase bearing clones, with domination of FLT3 mutation.¹² Interestingly, a recent report⁶⁷ described the feasibility of adding an FLT3 inhibitor to venetoclax-based regimens, without additive toxicity and with improved outcomes, but the results are not mature enough to allow clear recommendation. In any event, the monocytic phenotype described in this case may predict for venetoclax failure.

Case 5: An older patient with treatment-related AML

A 73-year-old active female (ECOG PS-1) is diagnosed with AML. Eight years ago, she had triple-negative breast cancer, for which she received 4 cycles of adriamycin and cyclophosphamide followed by taxol for 12 successive weeks. After completion of neo-adjuvant therapy, she underwent mastectomy with negative sentinel lymph node biopsy. She has had routine annual oncologic surveillance with no evidence of disease. In the past year, she developed mild leukopenia and deteriorating anaemia, for which she did not undergo any investigation. She now presents with WBC of 5600/ μ l, 30% of which are circulating blasts, 23 000/ μ l platelets and haemoglobin 6.1 g/dl. Molecular analysis is negative for NPM1, FLT3 and IDH mutations. Cytogenetic analysis reveals 47XX with trisomy 8. On geriatric evaluation, she is considered fit for intensive chemotherapy.

For this fit patient, is 3 + 7 the best option?

This case illustrates a fit patient with a secondary AML based on prior exposure to anthracyclines and alkylators. Her cumulative anthracycline dose is 240 mg/m², which is low enough to allow further anthracycline exposure. The probability to achieve CR with intensive chemotherapy is estimated to be 50% at most in treatment-related AML^{4,68} but with a 2-year OS of only 20%.⁴

CPX351

CPX351 is a liposomal formulation of cytarabine and daunorubicin at a fixed molar ratio of 1:5. A phase II trial comparing CPX351 to 7 + 3 demonstrated higher response rates, particularly more CRi without increased toxicity. In secondary AML patients, it also demonstrated a survival advantage.⁶⁸ A successive phase III trial conducted in patients aged 60–75 years reported that therapy with CPX351 achieved better outcomes in treatment-related AML patients,

as well as in AML patients with antecedent MDS/chronic myelomonocytic leukaemia and AML with complex karyotype. Toxicity profile of CPX351 is similar to that of intensive chemotherapy, but early mortality rate is reduced. Time will tell if CPX351 is indeed superior to 3 + 7, or if this advantage merely reflects optimised anthracycline/cytarabine ratio.⁶⁹ In a prespecified subgroup analysis, two subgroups, including patients previously treated with HMAs and patients with FLT3-mutated AML, seemed to have no benefit from CPX351, the latter despite an acceptable CR rate.⁷⁰ However, the standard deviation in these groups was wide and no definitive conclusions could be made. As FLT3 inhibitors were prohibited in that study, it is possible that, if used, the combination of CPX351 and FLT3 inhibitor would have the same advantage in FLT3-mutated AML patients. CPX351 is currently the only drug found to be better than standard IC for secondary AML patients in a phase III trial.

Following cardiac evaluation with echocardiography, confirming normal heart function, the patient can be offered treatment with CPX351. Once remission is achieved, the patient may be referred for allo-SCT with reduced-intensity conditioning if possible, or two cycles of consolidation therapy with CPX351 (total cumulative dose of anthracyclines of 488 mg/m²) if deemed unfit for transplant. One can also consider maintenance treatment with azacytidine or CC-486, although this has not been studied after CPX351 but rather after conventional intensive chemotherapy only.

Venetoclax-based therapy is also a reasonable option for a patient with secondary AML, with an encouraging CR/CRi rate of 67% when used with HMAs.¹⁴ Interestingly, the combination of venetoclax with LDAC yielded much lower CR and OS rates. Such preliminary data need to be confirmed.

Case 6: A patient with a relapse

Is there an optimal strategy?

A 67-year-old male was diagnosed with normal karyotype/NPM1mut/FLT3-ITD-negative AML. He was treated with the 7 + 3 regimen and two consolidations with HIDAC, and achieved a stable CR. Eighteen months after the last chemotherapy, the patient was admitted due to CVA, which led to severe functional deterioration. He now requires assistance with activities of daily living and is mobilised with a wheelchair. On a routine check-up, pancytopenia was noticed and a bone marrow evaluation demonstrated 20% of CD33⁺ myeloid blasts, with the same molecular profile as at diagnosis. The patient has very limited social support systems.

This patient is experiencing a late relapse of AML, but due to significant comorbidity he is precluded from receiving intensive treatment. First, in such cases, the mutation status of IDH1/2 should be tested. As no IDH mutation has been identified in this case, the remaining effective alternatives to chemotherapy may be venetoclax-based regimens that can offer relatively high remission rates in a relapsed patient (see

discussion in case no. 2); but, in this case, the administration of HMA or LDAC for 7–10 days a month is access-limited.

GO is an antibody-conjugated drug, directed against CD33-expressing cells, observed in most AML cases. The active conjugated agent calicheamicin is basically a chemotherapy that, similar to anthracyclines, causes double-strand DNA breakage. GO is basically a vehicle that allows targeting the diseased cells with chemotherapy. Consequently, it is not surprising that, when used as part of first-line therapy, GO is most beneficial for standard-risk AML and not for the poor-risk karyotypes that are often chemo-resistant.^{9,71–73} NPM1-mutated AML, known to be highly responsive to chemotherapy, is sensitive to GO; yet in a patient with advanced age, the combination of chemotherapy and GO is reported to be highly toxic.^{6,73}

The use of single-agent GO as a salvage treatment for patients in first relapse resulted in 26–31% CR/CR without platelet recovery (CRp) in several phase II trials.^{72,74} There was no difference in response rates between young and older patients. GO was also studied as consolidation/maintenance therapy in older patients who failed peripheral stem cell collection. In a study conducted by Capelli *et al.*,⁷⁵ GO was administered at a dose of 3mg/m² every month for 3 months, followed by the same dose every 3 months for a total of 3 additional doses, and led to disease-free survival of 45.3% in 8 years.

A specific polymorphism in the enhancer region of the CD33 gene leads to alternative splicing of the CD33 protein and eliminates the binding site of GO. Conflicting evidence has been reported regarding its role in GO resistance.^{76–78}

Adverse reactions to GO include myelosuppression in almost all patients, with about a month to granulocyte recovery.^{72,74} Platelet recovery can also be prolonged, particularly in older patients.⁷⁴ In addition, patients often have liver injury, with transaminitis being much more frequent than veno-occlusive disease (30–60% vs. 0–5%).

We would opt for offering GO to this patient, preferably after testing the CD33 gene polymorphism. This treatment offers him very convenient and short administration with only few clinic visits, and since his AML is NPM1mut and the relapse was late, achieving remission is likely. After achieving remission, he should be re-evaluated for allo-SCT and, if not suitable, he can be offered consolidations with GO.

Decision-making when considering palliative care: can palliative care include anti-leukaemic agents?

A 78-year-old male is referred to the clinic with mucosal bleeding in the past 2 weeks. He is a heavy smoker with active COPD (gold criteria stage 4) necessitating bronchodilators and inhaled steroids. Three years ago, the patient was diagnosed with colon cancer, for which he underwent right hemicolectomy with adjuvant chemotherapy. His blood count is WBC 3000/μl, with 8000/μl platelets and haemoglobin of 8.5 g/dl. His blood smear shows 20% myeloid blasts,

and bone marrow examination confirms the diagnosis of AML, with blasts negative for FLT3-ITD and NPM1 mutations. Cytogenetic analysis demonstrates a complex karyotype with 17p- deletion. The TP53 deletion is confirmed by FISH.

This is a case of a high-risk patient with treatment-related AML, who is definitely not a candidate for intensive therapy due to comorbidities. CPX351 is approved for treatment of secondary AML, but its benefit is mainly for patients who undergo allo-SCT. The median remission duration with CPX351 is only 7 months, and the toxicity profile shows very high rates of febrile neutropenia, with 20–25% probability for either pneumonia or hypoxia, which are expected to be poorly tolerated by this patient. Venetoclax-based regimens can afford 47% CR + CRi rates, but the median remission duration is only 5.6 months. Specifically for TP53-mutated AML, decitabine treatment can offer remission, albeit of short duration.^{79,80}

As a curative option is not realistic in this patient, a discussion regarding palliative care predominantly includes quality-of-life issues. Checking the IDH status is reasonable, as meaningful responses to IDH inhibition have been reported.^{47,50,81} Moreover, encouraging results with the use of ivosidenib/venetoclax⁸² and enasidenib/azacitidine^{13,14} combinations have been recently reported. Of course, use of such novel agents should be weighed against the dismal progression-free period that sometimes can be maintained with supportive care only.

Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

A.F, J.M.R and Y.O wrote the paper.

References

1. Juliusson G, Antunovic P, Derolf A, Lehmann S, Mollgard L, Stockelberg D, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood*. 2009;113:4179–87.
2. Mayer RJ, Davis RB, Schiffer CA, Berg DT, Powell BL, Schulman P, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. *N Engl J Med*. 1994;331:896–903.
3. Stone RM, Berg DT, George SL, Dodge RK, Paciucci PA, Schulman PP, et al. Postremission therapy in older patients with de novo acute myeloid leukemia: a randomized trial comparing mitoxantrone and intermediate-dose cytarabine with standard-dose cytarabine. *Blood*. 2001;98:548–53.
4. Löwenberg B, Ossenkoppele GJ, van Putten W, Schouten HC, Graux C, Ferrant A, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med*. 2009;361:1235–48.
5. Foran JM, Sun Z, Paietta E, Racevskis J, Claxton DF, Lazarus HM, et al. FLT3-ITD mutations are prevalent and significantly impact outcome after intensive therapy in elderly adults with acute myeloid leukemia (AML): analysis of the North American Intergroup E2906 phase III trial in patients age ≥60 years. *Blood*. 2018;132(Supplement 1):3995.

6. Schlenk, RF, Paschka, P, Krzykalla, J, Weber, D & Kapp-Schwoerer, S, et al. Gemtuzumab ozogamicin in NPM1-mutated acute myeloid leukemia: early results from the prospective randomized AMLSG 09–09 phase III study. *J Clin Oncol.* 2020;**38**:623–32.
7. Burnett AK, Russell NH, Hills RK, Kell J, Freeman S, Kjeldsen L, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy improves survival in older patients with acute myeloid leukemia. *J Clin Oncol.* 2012;**30**:3924–31.
8. Castaigne S, Pautas C, Terre C, Raffoux E, Bordessoule D, Bastie JN, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. *Lancet.* 2012;**379**:1508–16.
9. Hills RK, Castaigne S, Appelbaum FR, Delaunay J, Petersdorf S, Othus M, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. *Lancet Oncol.* 2014;**15**:986–96.
10. Pohlen M, Groth C, Sauer T, Gorlich D, Mesters R, Schliemann C, et al. Outcome of allogeneic stem cell transplantation for AML and myelodysplastic syndrome in elderly patients (60 years). *Bone Marrow Transplant.* 2016;**51**:1441–8.
11. Ringden O, Boumendil A, Labopin M, Canaani J, Beelen D, Ehninger G, et al. Outcome of allogeneic hematopoietic stem cell transplantation in patients age >69 years with acute myelogenous leukemia: on behalf of the acute leukemia working party of the European Society for blood and marrow transplantation. *Biol Blood Marrow Transplant.* 2019;**25**:1975–83.
12. DiNardo CD, Tiong IS, Quaglieri A, MacRaild S, Loghavi S, Brown FC, et al. Molecular patterns of response and treatment failure after frontline venetoclax combinations in older patients with AML. *Blood.* 2020;**135**:791–803.
13. DiNardo CD, Schuh AC, Stein EM, Fernandez PM, Wei A, De Botton S, et al. Enasidenib plus azacitidine significantly improves complete remission and overall response compared with azacitidine alone in patients with newly diagnosed acute myeloid leukemia (aml) with isocitrate dehydrogenase 2 (IDH2) mutations: interim phase II results from an ongoing, randomized study. *Blood.* 2019a;**134**:643.
14. DiNardo CD, Pratz K, Pullarkat V, Jonas BA, Arellano M, Becker PS, et al. Venetoclax combined with decitabine or azacitidine in treatment-naïve, elderly patients with acute myeloid leukemia. *Blood.* 2019;**133**:7–17.
15. Rucker FG, Schlenk RF, Bullinger L, Kayser S, Teleanu V, Kett H, et al. TP53 alterations in acute myeloid leukemia with complex karyotype correlate with specific copy number alterations, monosomal karyotype, and dismal outcome. *Blood.* 2012;**119**:2114–21.
16. Seifert H, Mohr B, Thiede C, Oelschlägel U, Schäkel U, Illmer T, et al. The prognostic impact of 17p (p53) deletion in 2272 adults with acute myeloid leukemia. *Leukemia.* 2009;**23**:656–63.
17. Lowenberg B, Suci S, Archimbaud E, Haak H, Stryckmans P, de Cataldo R, et al. Mitoxantrone versus daunorubicin in induction-consolidation chemotherapy—the value of low-dose cytarabine for maintenance of remission, and an assessment of prognostic factors in acute myeloid leukemia in the elderly: final report. European Organization for the Research and Treatment of Cancer and the Dutch-Belgian Hemato-Oncology Cooperative Hovon Group. *J Clin Oncol.* 1998;**16**:872–81.
18. Robles C, Kim KM, Oken MM, Bennett JM, Letendre L, Wiernik PH, et al. Low-dose cytarabine maintenance therapy vs observation after remission induction in advanced acute myeloid leukemia: an Eastern Cooperative Oncology Group Trial (E5483). *Leukemia.* 2000;**14**:1349–53.
19. Brune M, Castaigne S, Catalano J, Gehlsen K, Ho AD, Hofmann WK, et al. Improved leukemia-free survival after postconsolidation immunotherapy with histamine dihydrochloride and interleukin-2 in acute myeloid leukemia: results of a randomized phase 3 trial. *Blood.* 2006;**108**:88–96.
20. Huls G, Chitu DA, Havelange V, Jongen-Lavrencic M, van de Loosdrecht AA, Biemond BJ, et al. Azacitidine maintenance after intensive chemotherapy improves DFS in older AML patients. *Blood.* 2019;**133**:1457–64.
21. Oliva EN, Martino B, Salutati P, Alati C, Mauro E, Cortelezzi A, et al. Randomized open-label, phase III multicenter trial to evaluate azacitidine post-remission therapy in elderly patients with acute myeloid leukemia. *HemaSphere.* 2018;**2**:PS983.
22. Foran JM, Sun Z, Claxton DF, Lazarus HM, Arber DA, Rowe JM, et al. Maintenance decitabine (DAC) improves disease-free (DFS) and overall survival (OS) after intensive therapy for acute myeloid leukemia (AML) in older adults, particularly in FLT3-ITD-negative patients: ECOG-ACRIN (E-A) E2906 randomized study. *Blood.* 2019;**134**:115.
23. Wei AH, Garcia JS, Borate U, Fong CY, Baer MR, Nolte F, et al. A phase 1b study evaluating the safety and efficacy of venetoclax in combination with azacitidine in treatment-naïve patients with higher-risk myelodysplastic syndrome. *Blood.* 2019a;**134**:568.
24. Wei AH, Strickland SA Jr, Hou JZ, Fiedler W, Lin TL, Walter RB, et al. Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: results from a phase 1b/II study. *J Clin Oncol.* 2019b;**37**:1277–84.
25. Giles FJ, Borthakur G, Ravandi F, Faderl S, Verstovsek S, Thomas D, et al. The haematopoietic cell transplantation comorbidity index score is predictive of early death and survival in patients over 60 years of age receiving induction therapy for acute myeloid leukaemia. *Br J Haematol.* 2007;**136**:624–7.
26. Oran B, Weisdorf DJ. Survival for older patients with acute myeloid leukemia: a population-based study. *Haematologica.* 2012;**97**:1916–24.
27. Konopleva M, Pollyea DA, Potluri J, Chyla B, Hogdal L, Busman T, et al. Efficacy and biological correlates of response in a phase II study of venetoclax monotherapy in patients with acute myelogenous leukemia. *Cancer Discov.* 2016;**6**:1106–17.
28. Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, 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**:291–9.
29. Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, 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**:2670–7.
30. Aldoss I, Yang D, Aribi A, Ali H, Sandhu K, Al Malki MM, et al. Efficacy of the combination of venetoclax and hypomethylating agents in relapsed/refractory acute myeloid leukemia. *Haematologica.* 2018;**103**:e404–e407.
31. DiNardo CD, Rausch CR, Benton C, Kadia T, Jain N, Pemmaraju N, et al. Clinical experience with the BCL2-inhibitor venetoclax in combination therapy for relapsed and refractory acute myeloid leukemia and related myeloid malignancies. *Am J Hematol.* 2018a;**93**:401–7.
32. Ram R, Amit O, Zuckerman T, Gurion R, Raanani P, Bar-On Y, et al. Venetoclax in patients with acute myeloid leukemia refractory to hypomethylating agents—a multicenter historical prospective study. *Ann Hematol.* 2019;**98**:1927–32.
33. DiNardo CD, Wei AH. How I treat acute myeloid leukemia in the era of new drugs. *Blood.* 2020;**135**:85–96.
34. Agarwal SK, DiNardo CD, Potluri J, Dunbar M, Kantarjian HM, Humerickhouse RA, et al. Management of venetoclax-posaconazole interaction in acute myeloid leukemia patients: evaluation of dose adjustments. *Clin Ther.* 2017;**39**:359–67.
35. Bose P, Gandhi V, Konopleva M. Pathways and mechanisms of venetoclax resistance. *Leuk Lymphoma.* 2017;**58**:1–17.
36. Teh TC, Nguyen NY, Moujalled DM, Segal D, Pomilio G, Rijal S, et al. Enhancing venetoclax activity in acute myeloid leukemia by co-targeting MCL1. *Leukemia.* 2018;**32**:303–12.
37. Kuusanmaki H, Leppä AM, Polonen P, Kontro M, Dufva O, Deb D, et al. Phenotype-based drug screening reveals association between venetoclax response and differentiation stage in acute myeloid leukemia. *Haematologica.* 2020;**105**:708–20.
38. White BS, Khan SA, Ammad-ud-din M, Potdar S, Mason MJ, Tognon CE, et al. Comparative Analysis of independent ex vivo functional drug screens

- identifies predictive biomarkers of BCL-2 inhibitor response in AML. *Blood*. 2018;**132**:2763.
39. Pei S, Pollyea DA, Gustafson A, Minhajuddin M, Stevens BM, Ye H, et al. Developmental plasticity of acute myeloid leukemia mediates resistance to venetoclax-based therapy. *Blood*. 2019;**134**:185.
 40. Zhang H, Wilmot B, Bottomly D, Kurtz SE, Eide CA, Damnerisawad A, et al. Biomarkers predicting venetoclax sensitivity and strategies for venetoclax combination treatment. *Blood*. 2018;**132**:175.
 41. BCL2/MDM2 inhibitor combo effective in AML. *Cancer Discov*. 2019;**9**:156.
 42. Chyla B, Daver N, Doyle K, McKeegan E, Huang X, Ruvolo V, et al. Genetic biomarkers of sensitivity and resistance to venetoclax monotherapy in patients with relapsed acute myeloid leukemia. *Am J Hematol*. 2018;**93**(8):E202–E205.
 43. Han L, Zhang Q, Dail M, Shi C, Cavazos A, Ruvolo VR, et al. Concomitant targeting of BCL2 with venetoclax and MAPK signaling with cobimetinib in acute myeloid leukemia models. *Haematologica*. 2020;**105**:697–707.
 44. Ma J, Zhao S, Qiao X, Knight T, Edwards H, Polin L, 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**:6815–26.
 45. Fukushima N, Minami Y, Kakiuchi S, Kuwatsuka Y, Hayakawa F, Jamieson C, et al. Small-molecule Hedgehog inhibitor attenuates the leukemia-initiation potential of acute myeloid leukemia cells. *Cancer Sci*. 2016;**107**:1422–9.
 46. Cortes JE, Heidel FH, Hellmann A, Fiedler W, Smith BD, Robak T, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. *Leukemia*. 2019a;**33**:379–89.
 47. DiNardo CD, Stein EM, de Botton S, Roboz GJ, Altman JK, Mims AS, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med*. 2018b;**378**:2386–98.
 48. Stein EM, DiNardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood*. 2017;**130**:722–31.
 49. Roboz JG, Dinardo CD, Stein EM, de Botton S, Mims AS, Prince GT, et al. Ivosidenib (IVO; AG-120) in IDH1-mutant newly-diagnosed acute myeloid leukemia (ND AML): updated results from a phase 1 study. *J Clin Oncol*. 2019;**37**:7028.
 50. Pollyea DA, Tallman MS, de Botton S, Kantarjian HM, Collins R, Stein AS, et al. Enasidenib, an inhibitor of mutant IDH2 proteins, induces durable remissions in older patients with newly diagnosed acute myeloid leukemia. *Leukemia*. 2019;**33**:2575–84.
 51. Dinardo CD, Stein AS, Stein EM, Fathi AT, Frankfurt O, Schuh AC, et al. Mutant IDH1 inhibitor ivosidenib (IVO; AG-120) in combination with azacitidine (AZA) for newly diagnosed acute myeloid leukemia (ND AML). *J Clin Oncol*. 2019c;**37**(15_suppl):7011.
 52. Grafone T, Palmisano M, Nicci C, Storti S. An overview on the role of FLT3-tyrosine kinase receptor in acute myeloid leukemia: biology and treatment. *Oncol Rev*. 2012;**6**:e8.
 53. Port M, Bottcher M, Thol F, Ganser A, Schlenk R, Wasem J, et al. Prognostic significance of FLT3 internal tandem duplication, nucleophosmin 1, and CEBPA gene mutations for acute myeloid leukemia patients with normal karyotype and younger than 60 years: a systematic review and meta-analysis. *Ann Hematol*. 2014;**93**:1279–86.
 54. Schlenk RF, Kayser S, Bullinger L, Kobbe G, Casper J, Ringhoffer M, et al. Differential impact of allelic ratio and insertion site in FLT3-ITD-positive AML with respect to allogeneic transplantation. *Blood*. 2014;**124**:3441–9.
 55. Bacher U, Haferlach C, Kern W, Haferlach T, Schnittger S. Prognostic relevance of FLT3-TKD mutations in AML: the combination matters—an analysis of 3082 patients. *Blood*. 2008;**111**:2527–37.
 56. Mead AJ, Linch DC, Hills RK, Wheatley K, Burnett AK, Gale RE. FLT3 tyrosine kinase domain mutations are biologically distinct from and have a significantly more favorable prognosis than FLT3 internal tandem duplications in patients with acute myeloid leukemia. *Blood*. 2007;**110**:1262–70.
 57. Yanada M, Matsuo K, Suzuki T, Kiyoi H, Naoe T. Prognostic significance of FLT3 internal tandem duplication and tyrosine kinase domain mutations for acute myeloid leukemia: a meta-analysis. *Leukemia*. 2005;**19**:1345–9.
 58. Chyla BJ, Harb J, Mantis C, Riehm JJ, Ross JA, Sun Y, et al. Response to venetoclax in combination with low intensity therapy (LDAC or HMA) in untreated patients with acute myeloid leukemia patients with IDH, FLT3 and other mutations and correlations with BCL2 family expression. *Blood*. 2019;**134**(Supplement_1):546–546.
 59. Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. *N Engl J Med*. 2017;**377**:454–64.
 60. Berger T, Rozovski U, Moshe Y, Yaari S, Frisch A, Hellmann I, et al. Midostaurin in combination with intensive chemotherapy is safe and associated with improved remission rates and higher transplantation rates in first remission—a multi-center historical control study. *Ann Hematol*. 2019;**98**:2711–7.
 61. Sasaki K, Kantarjian HM, Kadia T, Patel K, Loghavi S, Garcia-Manero G, et al. Sorafenib plus intensive chemotherapy improves survival in patients with newly diagnosed, FLT3-internal tandem duplication mutation-positive acute myeloid leukemia. *Cancer*. 2019;**125**:3755–66.
 62. Uy GL, Mandrekar SJ, Laumann K, Marcucci G, Zhao W, Levis MJ, et al. A phase 2 study incorporating sorafenib into the chemotherapy for older adults with FLT3-mutated acute myeloid leukemia: CALGB 11001. *Blood Adv*. 2017;**1**:331–40.
 63. Serve H, Krug U, Wagner R, Sauerland MC, Heinecke A, Brunnberg U, et al. Sorafenib in combination with intensive chemotherapy in elderly patients with acute myeloid leukemia: results from a randomized, placebo-controlled trial. *J Clin Oncol*. 2013;**31**:3110–8.
 64. Ohanian M, Garcia-Manero G, Levis M, Jabbour E, Daver N, Borthakur G, et al. Sorafenib combined with 5-azacytidine in older patients with untreated FLT3-ITD mutated acute myeloid leukemia. *Am J Hematol*. 2018;**93**:1136–41.
 65. Ravandi F, Alattar ML, Grunwald MR, Rudek MA, Rajkhowa T, Richie MA, et al. Phase 2 study of azacytidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation. *Blood*. 2013;**121**:4655–62.
 66. Cortes JE, Khaled S, Martinelli G, Perl AE, Ganguly S, Russell N, et al. Quizartinib versus salvage chemotherapy in relapsed or refractory FLT3-ITD acute myeloid leukaemia (QuANTUM-R): a multicentre, randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2019b;**20**:984–97.
 67. Maiti A, Rausch CR, Cortes JE, Pemmaraju N, Daver NG, Ravandi F, et al. Outcomes in molecular subgroups and resistance patterns with ten-day decitabine and venetoclax (DEC10-VEN) in acute myeloid leukemia. *Blood*. 2019;**134**(Supplement_1):645.
 68. Lancet JE, Cortes JE, Hogge DE, Tallman MS, Kovacsics TJ, Damon LE, et al. Phase 2 trial of CPX-351, a fixed 5:1 molar ratio of cytarabine/daunorubicin, vs cytarabine/daunorubicin in older adults with untreated AML. *Blood*. 2014;**123**:3239–46.
 69. Stein EM, Tallman MS. Emerging therapeutic drugs for AML. *Blood*. 2016;**127**:71–8.
 70. Lancet JE, Uy GL, Cortes JE, Newell LF, Lin TL, Ritchie EK, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. *J Clin Oncol*. 2018;**36**:2684–92.
 71. Burnett AK, Hills RK, Milligan D, Kjeldsen L, Kell J, Russell NH, et al. Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. *J Clin Oncol*. 2011;**29**:369–77.
 72. Taksin AL, Legrand O, Raffoux E, de Revel T, Thomas X, Contentin N, et al. High efficacy and safety profile of fractionated doses of Mylotarg as induction therapy in patients with relapsed acute myeloblastic leukemia: a prospective study of the alfa group. *Leukemia*. 2007;**21**:66–71.
 73. Lambert J, Pautas C, Terre C, Raffoux E, Turlure P, Caillot D, et al. Gemtuzumab ozogamicin for de novo acute myeloid leukemia: final efficacy

- and safety updates from the open-label, phase III ALFA-0701 trial. *Haematologica*. 2019;**104**:113–9.
74. Larson RA, Sievers EL, Stadtmauer EA, Lowenberg B, Estey EH, Dombret H, et al. Final report of the efficacy and safety of gemtuzumab ozogamicin (Mylotarg) in patients with CD33-positive acute myeloid leukemia in first recurrence. *Cancer*. 2005;**104**:1442–52.
 75. Capelli D, Chiarucci M, Poloni A, Saraceni F, Mancini G, Trappolini S, et al. Mobilization-driven postconsolidation therapy in elderly patients with acute myeloid leukemia: feasibility and efficacy of autologous stem cell transplantation versus low-dose gemtuzumab ozogamicin. *Biol Blood Marrow Transplant*. 2014;**20**:1399–406.
 76. Gale RE, Popa T, Wright M, Khan N, Freeman SD, Burnett AK, et al. No evidence that CD33 splicing SNP impacts the response to GO in younger adults with AML treated on UK MRC/NCRI trials. *Blood*. 2018;**131**:468–71.
 77. Lamba JK, Chauhan L, Shin M, Loken MR, Pollard JA, Wang YC, et al. CD33 splicing polymorphism determines gemtuzumab ozogamicin response in de novo acute myeloid leukemia: report from randomized phase III Children's Oncology Group Trial AAML0531. *J Clin Oncol*. 2017;**35**:2674–82.
 78. Stanchina M, Pastore A, Devlin S, Famulare C, Stein E, Taylor J. CD33 splice site genotype was not associated with outcomes of patients receiving the anti-CD33 drug conjugate SGN-CD33A. *J Hematol Oncol*. 2019;**12**:85.
 79. Chang CK, Zhao YS, Xu F, Guo J, Zhang Z, He Q, et al. TP53 mutations predict decitabine-induced complete responses in patients with myelodysplastic syndromes. *Br J Haematol*. 2017;**176**:600–8.
 80. Welch JS, Petti AA, Miller CA, Fronick CC, O'Laughlin M, Fulton RS, et al. TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. *N Engl J Med*. 2016;**375**:2023–36.
 81. Stein EM, DiNardo CD, Fathi AT, Pollyea DA, Stone RM, Altman JK, et al. Molecular remission and response patterns in patients with mutant-IDH2 acute myeloid leukemia treated with enasidenib. *Blood*. 2019;**133**:676–87.
 82. DiNardo CD, Stein AS, Stein EM, Fathi AT, Frankfurt O, Schuh AC, et al. Mutant IDH1 inhibitor ivosidenib (AG-120) in combination with azacitidine for newly diagnosed acute myeloid leukemia. *HemaSphere*. 2019b;**3**:460–1.