



## How I treat relapsed or refractory AML

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**Treatment of relapsed or refractory acute myeloid leukemia (AML) has presented challenges for hematologists for decades. Despite numerous clinical studies, outcomes are consistently disappointing with 5-year overall survival rates of ~10%. Allogeneic hematopoietic cell transplantation at the time of second complete remission remains the only reliable option with curative potential. However, recent approval of several new agents has transformed treatment paradigms that had been in place for almost half a century in AML. This new therapeutic landscape provides the opportunity to revisit the approach to relapsed or refractory AML. Through illustrative cases, we describe our approach, which increasingly relies on specific disease biology. We focus on treatment outside of the context of clinical trials because such trials are not available in most parts of the world. Primarily, we consider age, fitness to tolerate intensive chemotherapy, remission duration, and presence of a targetable mutation to guide treatment. The coming years will inevitably bring new targets and agents that may prove most effective when combined with each other and/or chemotherapy. Future studies are needed to determine how best to implement this evolving armamentarium of treatment options, to elucidate mechanisms of resistance, and to continue the pursuit of novel drug discovery. (*Blood*. 2020;136(9):1023-1032)**

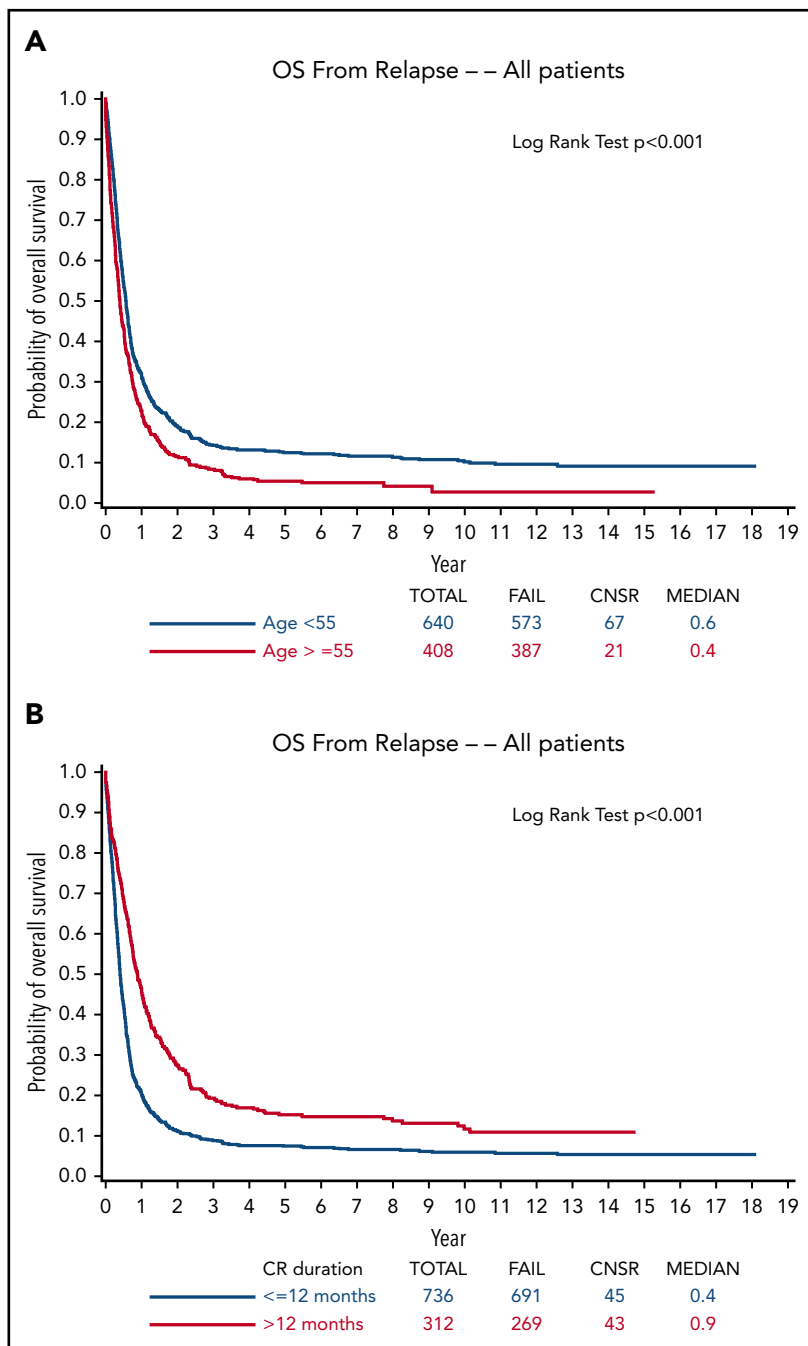
### Introduction

Effective treatment of relapsed or refractory acute myeloid leukemia (AML) has presented a Sisyphean challenge for hematologists for decades. Despite remarkable insights into deciphering the molecular pathogenesis of AML and important albeit modest advances in treatment, >10 000 of the ~20 000 new patients with AML diagnosed in the United States each year die of their disease.<sup>1</sup> Relapse is the most common cause of treatment failure. The 5-year overall survival (OS) for adult patients with AML (non-acute promyelocytic leukemia [non-APL] AML) after disease relapse is only 10% (Figure 1) in both older studies with long-term follow-up<sup>2-4</sup> and in more contemporary series,<sup>5,6</sup> although available data are from studies prior to the promising era of molecular genetics and targeted therapy. Furthermore, ~20% of patients demonstrate primary induction failure (PIF; further defined in the next section).<sup>7,8</sup> Currently, allogeneic hematopoietic cell transplantation (HCT) is the only reliable option with curative potential, with OS estimated at 15% to 25% 3 to 5 years posttransplant.<sup>9,10</sup> Beyond this guiding principle, the optimal treatment of the majority of patients, both older and younger, with relapsed or refractory AML has lacked a uniform treatment strategy,<sup>11</sup> despite the wide variety of regimens administered in numerous clinical trials carried out over >4 decades. However, recent regulatory agency approvals of a number of novel agents have provided the opportunity to revisit the approach to relapsed or refractory AML and may well pave the way for genuine progress in this historically difficult if not stagnant area. Here, we present illustrative cases that capture our treatment approach in the dynamic landscape of new diagnostic capabilities and in view of a burgeoning armamentarium

of both approved and investigational therapies. We focus on treatment outside of a clinical trial because we recognize that clinical trials are not readily available in many parts of the world.

### Definitions

Precise definitions of relapsed and refractory disease are important in the face of perpetually changing response criteria and in an effort to promulgate uniform terminology.<sup>12,13</sup> There is no agreed-upon definition of primary refractory disease (PRD). Some consider PRD to mean failure after 1 cycle of induction chemotherapy. We consider PRD, also known as PIF, to be a state of persistent leukemia with >5% blasts after at least 2 cycles of intensive induction therapy, as put forward in the 2017 European LeukemiaNet (ELN) guidelines<sup>14</sup> (Table 1). This 5% threshold, established decades ago and entrenched in daily practice, is arbitrary and could be revisited because we are now less dependent solely on morphology, with highly sensitive techniques for the detection of minimal/measurable residual disease (MRD). In the past, some argued that 1 cycle should include high-dose cytarabine (HiDAC), given the ability of HiDAC to overcome resistance to standard-dose cytarabine.<sup>15</sup> In the current era with increasing use of nonintensive venetoclax-based regimens and targeted therapy, we speculate that this terminology requires further revision. Guided by recent prospective data,<sup>16,17</sup> we tend to use hypomethylating agents (HMAs) or low-dose cytarabine (LoDAC) combined with venetoclax for 2 cycles before changing; however, some patients take longer to respond and, if tolerating therapy without obvious



**Figure 1. OS from relapse.** Stratified by (A) age (<55 years or  $\geq 55$  years) and (B) duration of first CR ( $\leq 12$  months or  $> 12$  months) from ECOG-ACRIN trials from 1984 to 2008.<sup>4</sup> Reprinted from Ganzel et al<sup>4</sup> with permission. CNSR, censor.

disease progression, we continue this regimen. For targeted therapy, median time to remission is typically over 2 months,<sup>6,18,19</sup> patients can respond after even 4 to 6 months, and thus defining treatment failure is an even greater challenge. We generally continue until clear progressive disease.

Relapsed disease falls into 2 main categories: clear morphologic relapse, which may be in the bone marrow or extramedullary, or the emergence of MRD after initial clearance (Table 1). The presence of 5% or greater leukemic blasts (acknowledging again that this percentage is arbitrary) in the bone marrow or detection of blasts in the peripheral blood fulfills criteria for morphologic relapse, unless another possible etiology to explain the blasts is identified, for example, as a result of robust hematologic

reconstitution or stimulation of myeloid growth factors. In these settings, we repeat a bone marrow evaluation, even weekly if needed, to distinguish between recurrence and anticipated hematologic maturation; often molecular studies or the blast phenotype by flow cytometry can quickly differentiate the 2 processes. MRD describes a state in which the patient has evidence of leukemia detected by highly sensitive techniques such as real-time quantitative polymerase chain reaction, next-generation sequencing, or advanced flow cytometry without the presence of blasts sufficient to meet criteria for relapse.<sup>20-25</sup> The definition is an evolving one based on available assays with varying thresholds of detection, detailed discussion of which is reviewed in Xiao et al.<sup>26</sup> Although the detection of abnormal blasts by flow cytometry with a similar phenotype to the original

**Table 1. Definitions of relapsed and refractory AML**

Category	Definition
PIF (PRD)	Lack of CR or CRi following at least 2 cycles of intensive chemotherapy
Hematologic relapse	Detection of $\geq 5\%$ blasts in the BM, identification of circulating blasts, or emergence of extramedullary disease
MRD	Detection of MRD defined by molecular techniques or multiparameter flow cytometry after an MRD <sup>-</sup> CR

Modified from the ELN guidelines in Döhner et al.<sup>14</sup>

BM, bone marrow; CR, complete remission; CRi, CR with incomplete hematologic recovery; MRD, minimal/measurable residual disease.

disease raises strong suspicion for impending morphologic relapse, the prognostic value of some molecular studies is murkier and may vary by mutation. For some subtypes such as core-binding factor AML and nucleophosmin 1 (NPM1)-mutated AML, molecular MRD is associated with a higher relapse rate.<sup>27</sup> Studies are needed to clarify technical aspects of MRD measurement and the clinical significance of the detection of abnormal clones, some of which may be preleukemic in nature and may not portend inevitable relapse.<sup>14,27</sup>

## Prognostic factors

Historically, duration of first complete remission (CR) was a major factor for risk stratification in relapsed AML, with poorest outcomes seen in patients relapsing within the first year following initial induction therapy.<sup>28-30</sup> Other independent factors that play a role in a patient's clinical course include age, cytogenetics at diagnosis, certain molecular features such as FLT3-internal tandem duplication (ITD) mutation status, and history of prior allogeneic HCT.<sup>23,31-33</sup> Two main prognostic indices were developed to stratify patient outcomes following relapse incorporating some of these variables: the European Prognostic Index (EPI) and the Groupe Ouest Est d'Etude des Leucemies et Autres Maladies du Sang (GOELAMS).<sup>2,34,35</sup> An important caveat about these scoring systems is that, although they give a sense of a patient's general prognosis regardless of risk stratification, the overall outcome is typically poor. Furthermore, these prognostic indices likely require revision in the era of advanced molecular studies and targeted agents. Therefore, in the hustle and bustle of a busy clinic day, we do not routinely rely on these scoring systems, but rather focus on the biology of a patient's disease to guide therapy.

## Patient 1

### Early relapsed AML in a young patient

The first case is a 30-year-old otherwise healthy woman with AML and extramedullary disease at presentation who relapsed only 2 months after intensive induction and consolidation chemotherapy. She originally presented with cervical adenopathy and a white blood cell (WBC) count of  $322 \times 10^3/\mu\text{L}$  requiring emergent leukapheresis. Bone marrow studies revealed a hypercellular marrow with  $>90\%$  abnormal myeloid blasts (CD34<sup>+</sup>, CD11b<sup>+</sup>, CD15<sup>+</sup>, CD33<sup>+</sup>, CD117<sup>+</sup>, CD123<sup>+</sup>, HLA-DR<sup>+</sup>)

and further analyses identified a DNMT3A mutation and normal karyotype. Positron emission tomography-computed tomography detected fluorodeoxyglucose-avid nodes limited to the cervical and pelvic region; lumbar puncture with intrathecal chemotherapy confirmed no malignant cerebrospinal fluid cells. She received induction with cytarabine plus daunorubicin (90 mg/m<sup>2</sup>) and bone marrow 1 month after treatment demonstrated an MRD<sup>-</sup> CR both by flow cytometry and molecular studies. She elected not to pursue allogeneic HCT and received 4 cycles of consolidation therapy with HiDAC. However, 2 months after completing consolidation, her cervical adenopathy returned and bone marrow studies revealed 55% blasts with the same phenotype and mutation profile as her original disease. She was swiftly reinduced with MEC (mitoxantrone/etoposide/cytarabine (MEC), leading to a second morphologic CR with evidence of MRD by flow cytometry (1.8% of WBCs). She proceeded to allogeneic HCT from a matched unrelated donor with an ablative conditioning regimen and remains in CR 1 year after transplant without MRD. Nevertheless, her long-term prognosis is precarious, given that she underwent transplant with MRD<sup>36,37</sup> together with the short duration of the first CR.

The field is rapidly moving away from indiscriminate multiagent conventional cytotoxic chemotherapy. However, in this setting of early relapse in a young patient whose leukemia cells do not express a targetable mutation, in whom cure with allogeneic HCT is the clear goal, we pursue an initial approach with intensive chemotherapy. Individual institutions and investigators often have a preferred chemotherapy regimen for reinduction therapy, but one cannot be dogmatic in the absence of randomized trials. Early studies supporting the use of HiDAC emerged in the late 1980s.<sup>15,38</sup> However, 2 other regimens we frequently consider are MEC<sup>39</sup> and fludarabine/cytarabine/granulocyte colony-stimulating factor (G-CSF)/idarubicin (FLAG-IDA).<sup>40</sup> Prior treatment history and side-effect profile guide our specific reinduction choice, but we use classical HiDAC (3 g/m<sup>2</sup>) less often than in the past in an effort to minimize cytarabine-related toxicities and prolonged cytopenias; we are motivated by studies in consolidation suggesting that lower doses of cytarabine (1.5-2 g/m<sup>2</sup>) appear equally effective and less toxic than classical HiDAC.<sup>41</sup>

The efficacy of these regimens and similar variations is consistently relatively disappointing with CR rates ranging from ~20% to 65% with a median duration of response typically  $< 1$  year.<sup>40,42-50</sup> Although there is no proof that such high- or intermediate-dose regimens are better than repeating standard-dose induction among previously untreated patients if the day 14 marrow shows persistent disease, data from the German AML Cooperative Group suggest that patients with poor-risk disease such as those with  $>40\%$  blasts on day 16 marrow fare better with more intensive cytarabine-containing regimens.<sup>51</sup> Some groups prefer regimens with cladribine (cladribine/arabinoside cytosine/mitoxantrone/G-CSF)<sup>52,53</sup> or clofarabine (clofarabine/cytarabine/G-CSF).<sup>54,55</sup> However, these regimens have yielded similarly relatively poor outcomes despite their initial promise.

### Implications of a FLT3 mutation

A somatic FLT3 mutation is identified in nearly 30% of AML patients and the development of several small molecule inhibitors of FLT3 has created a new treatment paradigm (Table 2).<sup>6,56-59</sup> When in a patient's disease course to administer these

**Table 2. New targeted therapeutics in current clinical use for relapsed or refractory AML**

Agent	Target	CR+CRh/CRi/CRp % (CR %)	Median survival, mo	Approved population	FDA-approval status	Reference for FDA-approved indication and support for use in the unapproved setting
Gilteritinib	FLT3	34 (21.1)	9.3	FLT3-mutated R/R AML	2017	6
Enasidenib	IDH2	26.6 (20.2)	9.3	IDH2-mutated R/R AML	2017	18
Ivosidenib	IDH1	30.4 (21.6)	8.8	IDH1-mutated R/R or untreated AML	2018	19
Gemtuzumab ozogamicin	CD33	33 (26)	8.4	CD33 <sup>+</sup> untreated or R/R AML in adults or pediatric patients 2 y or older	2017	101
HMA/LoDAC + venetoclax	BCL-2	67 (54) <sup>16</sup> ; 54 (26) <sup>17</sup> (untreated)	17.5 <sup>16</sup> ; 10.1 <sup>17</sup> (untreated)	Untreated AML in patients 75 y and older unfit for chemotherapy	2018	16,17,68-74*

BCL-2, B-cell lymphoma 2; CRh, CR with partial hematological recovery; CRp, CR with incomplete platelet recovery; IDH, isocitrate dehydrogenase; R/R, relapsed or refractory. See Table 1 for expansion of other abbreviations.

\*Selected additional recent publications and abstracts.

targeted agents is an area of ongoing investigation, but 1 important randomized trial has contributed to a change in the standard of care for relapsed or refractory patients with FLT3-ITD and/or FLT3-tyrosine kinase domain mutations. Recent data from the ADMIRAL study, a phase 3 trial investigating the potent FLT3 inhibitor gilteritinib in primary refractory or first relapse FLT3-mutated (FLT3-ITD and FLT3-tyrosine kinase domain D835 or I836) disease, not only led to the approval of this agent by the US Food and Drug Administration (FDA) in November 2018 for relapsed or refractory FLT3-mutated disease, but also has led to changes in treatment strategies.<sup>6</sup> Gilteritinib monotherapy resulted in a median OS of 9.3 months compared with 5.6 months in the reinduction chemotherapy (low-dose cytarabine, azacitidine, MEC, or FLAG-IDA) arm. Two subgroups found to have longer survival were patients with high FLT3-ITD allelic ratios (median OS, 7.1 months compared with 4.3 months) and those with certain comutations, such as NPM1 and DNMT3A (median OS, 10.8 months vs 8.9 months).

How would we have treated this patient if her disease had been FLT3-ITD<sup>+</sup>? Occasionally, patients with highly proliferative disease may require urgent cytoreduction with cytotoxic chemotherapy. Guided by the ADMIRAL study, we now strongly consider gilteritinib if the patient has FLT3-mutated AML in first relapse rather than intensive chemotherapy, taking into account the patient's clinical course and disease biology. We evaluate for loss or gain of targetable mutations in all patients with relapse. The poor survival rate in either group in the ADMIRAL study is conspicuous. Whether FLT3 inhibitors with chemotherapy will be more effective than FLT3 inhibitors alone will be determined in future randomized clinical trials. Additionally, several studies suggest a benefit for FLT3 inhibitors after allogeneic HCT as maintenance.<sup>6,58,60-63</sup> Based on these data, we would have encouraged such a strategy following transplant if

our patient had a FLT3-ITD mutation. An ongoing randomized trial will further clarify the role of FLT3 inhibition after allogeneic HCT.<sup>64</sup>

## Patient 2

### PIF in a patient with AML

A 52-year-old man without significant medical history presented with shortness of breath and was found to be anemic with a hemoglobin of 6.2 g/dL with blasts identified in the peripheral blood. A bone marrow biopsy established a diagnosis of AML with inversion(3) by cytogenetics [46,XY,inv(3)(q21q26)] without other associated mutations, a karyotype associated with a particularly poor prognosis. He initially received cytarabine-plus-daunorubicin induction with persistence of over 70% blasts. Then he received classical HiDAC, but had 33% blasts on follow-up marrow evaluation. After failing a clinical trial, he received reinduction with MEC followed again by progression of disease. Finally, 8 months after diagnosis, he received 2 cycles of azacitidine and venetoclax, as this regimen was becoming available, and achieved a morphologic CR, though with MRD by flow cytometry. He proceeded to allogeneic HCT and remained disease-free for over 2 years.

This patient falls into the category of PIF having failed to achieve CR after at least 2 courses of intensive chemotherapy. The emergence of regimens combining the oral B-cell lymphoma 2 (BCL-2) inhibitor venetoclax with HMAs (decitabine or azacitidine) or LoDAC is rapidly changing our treatment approach (Table 2).<sup>16,17,65</sup> If we were treating this patient today, this regimen would have been our first choice for PIF, outside of a trial. Although mechanistically much remains to be learned about this regimen,<sup>66</sup> results from untreated patients are transformative and have been met with unbridled euphoria. Initial studies

with single-agent venetoclax revealed a response rate of only 19% in patients with relapsed or refractory disease.<sup>67</sup> However, when combined with HMAs in older adults with newly diagnosed AML not eligible for standard induction therapy, remarkable apparent synergism resulted in a response rate of over 70%.<sup>16,65</sup> Furthermore, the regimen is typically well tolerated, is not limited to patients with a specific mutation, and often can be given outpatient as we do in our practice usually after the first cycle. Studies are limited in the relapsed or refractory disease setting and are primarily retrospective in nature, though initial clinical experience suggests promising results. However, the variability of reported outcomes in early studies is unsettling and may be due to the small numbers of patients: published CR/CR with incomplete hematologic recovery (CRI) rates range from 12% to 51%.<sup>68-74</sup>

One of the features of HMA plus venetoclax is the relatively rapid clinical response with maximum responses achieved after only 1 to 2 cycles,<sup>16,65</sup> which is an important distinction from single-agent HMA for which responses may take several months of therapy.<sup>75</sup> We typically perform a bone marrow evaluation after the first cycle, particularly if the patient remains cytopenic, to determine whether the cytopenias are attributable to persistent disease or drug-induced aplasia. In some patients, we reduce the duration of venetoclax dosing from 28 days to 21 or even 14 days because of prolonged count recovery.

In eligible patients, we encourage allogeneic HCT after 1 to 2 cycles of therapy, ideally when morphologic CR is achieved. We still pursue transplantation in appropriate patients even with MRD<sup>36,37</sup> and/or incomplete count recovery in the relapsed or refractory setting if it is unlikely that the patient can be rendered MRD<sup>-</sup> and in light of the potential of transplant to cure these patients. If transplant is not the intended course, we continue HMA plus venetoclax indefinitely, as long as the patient has a continued response and acceptable side-effect profile. The optimal duration of therapy remains to be elucidated. That patients survive long enough to ask about the optimal duration of treatment is a victory in itself.

A randomized trial is needed to determine whether, even for older newly diagnosed patients fit for intensive reinduction chemotherapy, a venetoclax-based approach is the most effective, particularly if future studies determine that co-occurring mutations such as isocitrate dehydrogenase 1/2 (IDH1/2) and NPM1 predict response, as is becoming increasingly evident.<sup>17,68</sup> Since the combination of HMA or LoDAC plus venetoclax burst onto the scene, it has been rapidly and enthusiastically embraced not only for untreated patients in particular, but also for those with relapsed or refractory disease without evidence from prospective studies. Although we are optimistic about this regimen, we are highly supportive of clinical studies from which we can learn about venetoclax-based approaches, including in combination with chemotherapy<sup>76,77</sup> or other novel agents.

### Relapse following allogeneic HCT

What if this patient ultimately relapses after undergoing transplantation? The lack of options for relapse following transplantation is well recognized and clinical trials are typically our

preferred approach, unless the patient has a targetable mutation. In patients with CD33<sup>+</sup> disease, gemtuzumab is an option, but there is a risk of veno-occlusive disease, also called sinusoidal obstructive syndrome, particularly if administered in close proximity (within 3 months) to allogeneic HCT (Table 2); therefore, we tend to prefer other therapies, such as targeted agents, if suitable. Other options we consider are HMAs,<sup>78-80</sup> cellular therapies such as donor lymphocyte infusion,<sup>81</sup> a combination of both,<sup>82-84</sup> or a second transplant from a new donor in appropriate patients in second CR.<sup>10</sup> The latter approaches and other investigational cellular therapies are guided by our transplant colleagues.

## Patient 3

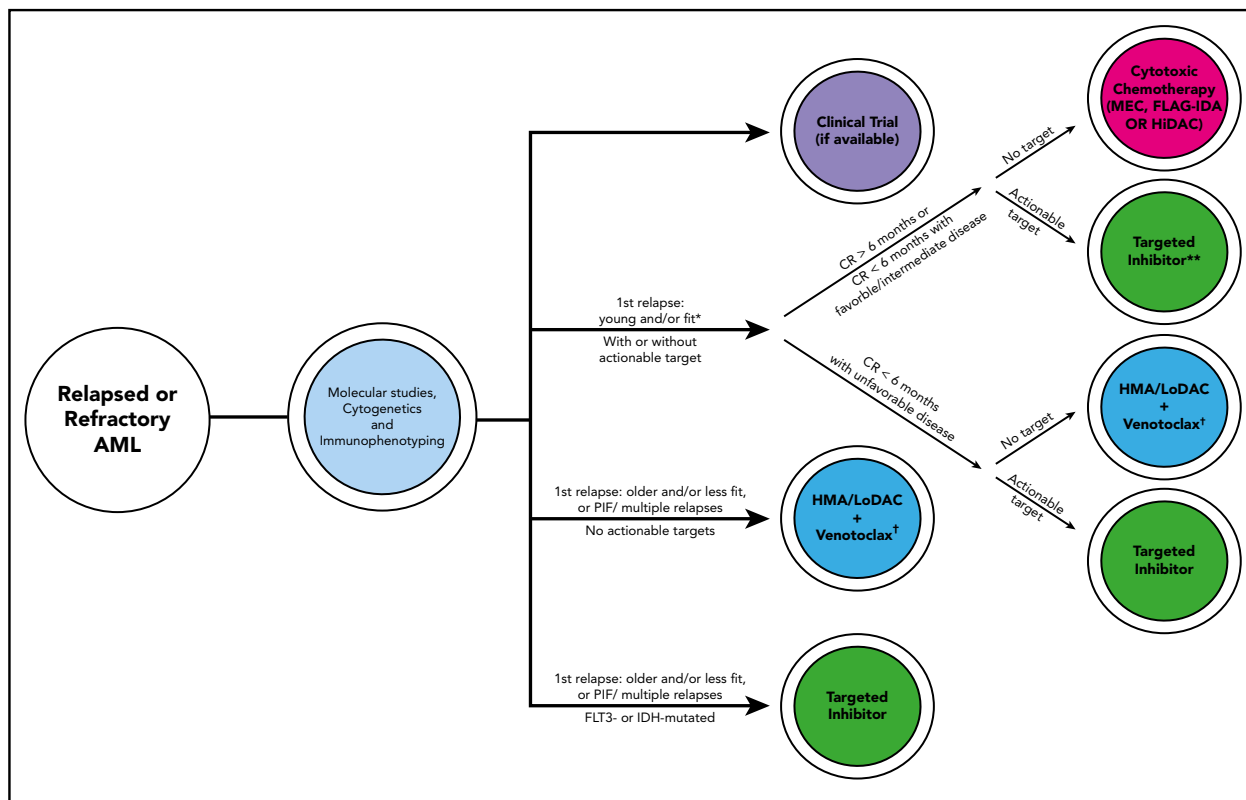
### Relapsed IDH<sup>+</sup> AML in the older patient

An 86-year-old woman was originally treated with azacitidine for AML diagnosed as part of an evaluation of pancytopenia requiring red blood cell transfusions. At diagnosis, a bone marrow biopsy identified 64% blasts with cytogenetics notable for a 5q deletion. Molecular studies were unrevealing. She enjoyed 2 years of excellent response with an improvement in her peripheral blood counts until a bone marrow evaluation detected 30% to 40% blasts along with worsening pancytopenia. A complete molecular evaluation led to discovery of an IDH1 mutation, prompting the initiation of ivosidenib, which had been recently approved. Within weeks her peripheral blood counts began to improve. She continues without evidence of recurrent disease on ivosidenib for over a year following relapse.

Relapsed AML in the older patient presents a distinct challenge as the fitness and wellness of the patient plays as important a role as the disease status.<sup>85</sup> Clinical trial options are frequently limited. We typically avoid intensive chemotherapy. Although we do not impose strict age limits for specific treatment approaches and take into account functional independence, emotional support, and overall goals of treatment, we have great respect for octogenarians.

This case underscores the importance of a complete molecular investigation at the time of relapse. We always check for IDH and FLT3 mutation status. We also perform a more comprehensive panel of mutations by next-generation sequencing, primarily to evaluate for potential clinical trials. The principle of clonal evolution in AML is now well established<sup>86,87</sup> and, in the era of targeted inhibitors, a first step in all relapsed patients is to carry out molecular studies. Ivosidenib and enasidenib are novel oral agents targeting IDH1 and IDH2, respectively, and are specifically included in the 2019 National Comprehensive Cancer Network (NCCN) guidelines for relapsed or refractory patients.<sup>11,18,19,88</sup> The phase 1 study published in 2018 leading to ivosidenib's FDA approval identified a CR rate among relapsed or refractory patients of 21.6% with a median CR duration of 9.3 months.<sup>19</sup> However, long-term data are currently limited and no randomized data have been presented.

The outcome for patients with IDH2 mutations treated with enasidenib is similarly encouraging (Table 2).<sup>18</sup> Both enasidenib and ivosidenib are associated with a risk of IDH differentiation syndrome, a systemic cardiorespiratory distress syndrome associated with the differentiation of immature leukemic cells into a mature phenotype reminiscent of the differentiation syndrome



**Figure 2. Schematic capturing our current general approach for relapsed or refractory patients with AML with some factors guiding the clinical decision process.** Risk stratification by 2017 ELN criteria.<sup>14</sup> Approved targeted inhibitors include gilteritinib (FLT3), ivosidenib (IDH1), enasidenib (IDH2). \*Assuming patient has already received intensive consolidation. \*\*Randomized phase 3 data are only currently available for gilteritinib,<sup>6</sup> not ivosidenib or enasidenib. †HMA alone if venetoclax unavailable. FLAG-IDA, fludarabine/cytarabine/granulocyte colony-stimulating factor/idarubicin; HiDAC, high-dose cytarabine; HMA, hypomethylating agent; IDH, isocitrate dehydrogenase; LoDAC, low-dose cytarabine; MEC, mitoxantrone/etoposide/cytarabine; PIF, primary induction failure.

observed in some patients with APL.<sup>89</sup> Symptoms are non-specific, but include unexplained fever, volume overload, and multisystem organ dysfunction. Steroids are typically effective. We temporarily interrupt targeted therapy if the presentation requires hospitalization or if severe symptoms persist for >48 hours after steroids have been started; we worry less about holding treatment than we do in APL.<sup>18,19,90,91</sup>

Our patient tolerated ivosidenib without side effects at a dose of 500 mg daily. She has monthly electrocardiograms as QT-interval prolongation was seen in 24.6% of patients in the original study.<sup>19</sup> Although in many patients we pursue regular bone marrow biopsies for disease assessment, for older patients we try to minimize invasive procedures. With normal blood counts and no detectable disease in the peripheral blood, we monitor patients with only clinical evaluations and complete blood counts. Because the median time to CR is over 2 months for ivosidenib<sup>19</sup> and enasidenib,<sup>18</sup> we continue treatment as long as patients appear to be deriving some clinical benefit before changing our approach. Stein et al reported that 30% of patients with stable disease after 90 days on enasidenib subsequently had a response.<sup>88</sup> In many parts of the world, IDH inhibitors are not available. Therefore, for IDH-mutated relapsed or refractory patients, we consider HMA or LoDAC plus venetoclax. If venetoclax is not available, we would consider HMA alone or best supportive care.

Not only have the IDH and FLT3 inhibitors already transformed the treatment of AML, but there are also many more targeted

approaches in development, either alone or in combination with HMA or chemotherapy. Approved in Japan, quizartinib is a potent FLT3 inhibitor found to be superior as a single agent to chemotherapy in the phase 3 QuANTUM-R trial in the relapsed or refractory setting.<sup>58</sup> In addition to the trove of promising targeted agents for relapsed or refractory AML, diverse immunotherapies are also under investigation, ranging from checkpoint inhibitors to bispecific T-cell engagers to antibody-drug conjugates.

### Resistance to targeted therapy

Although our patient responded well to ivosidenib, her disease may at some point develop resistance. Detailed investigations have identified new IDH mutations in some patients on IDH-directed therapy, eliminating susceptibility of the disease to inhibitors.<sup>92</sup> Furthermore, second-site mutations may occur in *trans* from the original IDH mutation, which is a novel resistance mechanism. In some patients, disease resistance results from progression of preexisting non-IDH-mutated clones that emerge under the selective pressure of anti-IDH therapy. There are even reports of IDH1 mutations undetected at diagnosis that arise in patients with IDH2-mutated disease receiving enasidenib.<sup>93,94</sup> Secondary mutations in FLT3 or other key signaling pathways such as RAS/MAPK have been identified as 1 resistance mechanism to FLT3 inhibitors.<sup>95-97</sup> Furthermore, not all clones in a patient's relapsed disease may harbor a given mutation, limiting the efficacy of targeted treatment. Combining targeted therapy with other

**Table 3. Our central guiding principles in the setting of relapsed or refractory AML**

Guiding principles for relapsed or refractory AML
1. Enroll patients on clinical trials, when available
2. Perform molecular testing to identify potential for targeted therapy and drug development
3. Decipher mechanisms of treatment resistance
4. Avoid reinduction attempts with multiple sequential courses of intensive cytotoxic chemotherapy
5. Ensure appropriate patients proceed to allogeneic HCT, ideally when patients are MRD <sup>-</sup>

agents such as HMAs may be a powerful approach to overcome some disease resistance.<sup>98,99</sup>

## Conclusions

*If you have built castles in the air, your work need not be lost; that is where they should be.  
Now put the foundations under them.*

—HENRY DAVID THOREAU

Historically, effective treatment of relapsed or refractory AML has been like Thoreau's castle in the air, the material of dreams for hematologists. With molecular testing, targeted agents, and a myriad of novel treatment combinations, we find ourselves in a new era of medicine. A schematic capturing our current approach with factors guiding our decision process is presented in Figure 2. For young and/or fit patients in first relapse after >6 months in CR,<sup>2</sup> we treat with cytotoxic chemotherapy; however, we favor gilteritinib if the patient has an FLT3-ITD mutation. We recognize that this 6-month time period is arbitrary. If relapse occurs <6 months from CR, our approach depends on the biology of the disease: if adverse cytogenetic or molecular abnormalities are present, we treat with an inhibitor if a mutation is present or HMA/LoDAC plus venetoclax if no mutation is present, rather than cytotoxic chemotherapy. If the patient is older, less fit, has PIF, or multiple relapses, we treat with HMA/LoDAC plus venetoclax, unless the patient has a targetable mutation, in which case we treat with the appropriate inhibitor.

## REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69(1):7-34.
2. Breems DA, Van Putten WL, Huijgens PC, et al. Prognostic index for adult patients with acute myeloid leukemia in first relapse. *J Clin Oncol*. 2005;23(9):1969-1978.
3. Forman SJ, Rowe JM. The myth of the second remission of acute leukemia in the adult. *Blood*. 2013;121(7):1077-1082.
4. Ganzel C, Sun Z, Cripe LD, et al. Very poor long-term survival in past and more recent studies for relapsed AML patients: the ECOG-ACRIN experience. *Am J Hematol*. 2018;93(8):1074-1081.
5. Roboz GJ, Rosenblat T, Arellano M, et al. International randomized phase III study of elacytarabine versus investigator choice in patients with relapsed/refractory acute myeloid leukemia. *J Clin Oncol*. 2014;32(18):1919-1926.
6. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. *N Engl J Med*. 2019;381(18):1728-1740.
7. Petersdorf SH, Kopecky KJ, Slovak M, et al. A phase 3 study of gemtuzumab ozogamicin during induction and postconsolidation therapy in younger patients with acute myeloid leukemia. *Blood*. 2013;121(24):4854-4860.
8. Othus M, Appelbaum FR, Petersdorf SH, et al. Fate of patients with newly diagnosed acute myeloid leukemia who fail primary induction therapy. *Biol Blood Marrow Transplant*. 2015;21(3):559-564.
9. Weisdorf D. The role of second transplants for leukemia. *Best Pract Res Clin Haematol*. 2016;29(4):359-364.

## Final thoughts

Propelled by effective oral targeted agents, we are particularly enthusiastic about therapeutic strategies that avoid intensive chemotherapy and prolonged inpatient admissions in an effort to improve overall quality of life (Table 3). Although there may be a rare patient for whom 3 or even more courses of intensive chemotherapy may be effective, such treatment is no longer the only option and is generally not advised.<sup>100</sup> Many advances have occurred since the last "How I treat refractory and early relapsed AML" was published in 2015. We anticipate that the next such publication will address more new targets, more novel targeted agents, and combinations of targeted agents with each other (doublets, triplets, and beyond) and with chemotherapy. The identification of MRD by increasingly sensitive and widely available techniques will likely establish a more definitive role for MRD in guiding therapy. Our major focus should be on prevention of recurrent disease. Indeed, we predict that there will be fewer patients with relapsed or refractory disease as more patients are likely to be cured with initial therapy.

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## Authorship

Contribution: S.D. and M.S.T. wrote and edited the manuscript.

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## Footnote

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10. Christopeit M, Kuss O, Finke J, et al. Second allograft for hematologic relapse of acute leukemia after first allogeneic stem-cell transplantation from related and unrelated donors: the role of donor change. *J Clin Oncol*. 2013;31(26):3259-3271.
11. Tallman MS, Wang ES, Altman JK, et al; OCN. Acute myeloid leukemia, version 3.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2019; 17(6):721-749.
12. Cheson BD, Bennett JM, Kopecky KJ, et al; International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia [published correction appears in *J Clin Oncol*. 2004;22(3):576]. *J Clin Oncol*. 2003;21(24):4642-4649.
13. Bloomfield CD, Estey E, Pleyer L, et al. Time to repeal and replace response criteria for acute myeloid leukemia? *Blood Rev*. 2018; 32(5):416-425.
14. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017; 129(4):424-447.
15. Herzig RH, Wolff SN, Lazarus HM, Phillips GL, Karanes C, Herzig GP. High-dose cytosine arabinoside therapy for refractory leukemia. *Blood*. 1983;62(2):361-369.
16. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naïve, elderly patients with acute myeloid leukemia. *Blood*. 2019;133(1):7-17.
17. Wei AH, Strickland SA Jr., Hou JZ, et al. Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: results from a phase Ib/II study. *J Clin Oncol*. 2019;37(15): 1277-1284.
18. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood*. 2017;130(6):722-731.
19. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med*. 2018;378(25):2386-2398.
20. Buccisano F, Maurillo L, Del Principe MI, et al. Prognostic and therapeutic implications of minimal residual disease detection in acute myeloid leukemia. *Blood*. 2012;119(2): 332-341.
21. Chen X, Xie H, Wood BL, et al. Relation of clinical response and minimal residual disease and their prognostic impact on outcome in acute myeloid leukemia. *J Clin Oncol*. 2015;33(11):1258-1264.
22. Kloco JM, Miller CA, Griffith M, et al. Association between mutation clearance after induction therapy and outcomes in acute myeloid leukemia. *JAMA*. 2015;314(8): 811-822.
23. Ivey A, Hills RK, Simpson MA, et al; UK National Cancer Research Institute AML Working Group. Assessment of minimal residual disease in standard-risk AML. *N Engl J Med*. 2016;374(5):422-433.
24. Getta BM, Devlin SM, Levine RL, et al. Multicolor flow cytometry and multigene next-generation sequencing are complementary and highly predictive for relapse in acute myeloid leukemia after allogeneic transplantation. *Biol Blood Marrow Transplant*. 2017;23(7):1064-1071.
25. Jongen-Lavrencic M, Grob T, Hanekamp D, et al. Molecular minimal residual disease in acute myeloid leukemia. *N Engl J Med*. 2018;378(13):1189-1199.
26. Xiao W, Petrova-Drus K, Roshal M. Optimal measurable residual disease testing for acute myeloid leukemia. *Surg Pathol Clin*. 2019; 12(3):671-686.
27. Schuurhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. *Blood*. 2018;131(12):1275-1291.
28. Keating MJ, Kantarjian H, Smith TL, et al. Response to salvage therapy and survival after relapse in acute myelogenous leukemia. *J Clin Oncol*. 1989;7(8):1071-1080.
29. Uhlman DL, Bloomfield CD, Hurd DD, Peterson BA. Prognostic factors at relapse for adults with acute myeloid leukemia. *Am J Hematol*. 1990;33(2):110-116.
30. Estey E, Kornblau S, Pierce S, Kantarjian H, Beran M, Keating M. A stratification system for evaluating and selecting therapies in patients with relapsed or primary refractory acute myelogenous leukemia. *Blood*. 1996; 88(2):756.
31. Ravandi F, Kantarjian H, Faderl S, et al. Outcome of patients with FLT3-mutated acute myeloid leukemia in first relapse. *Leuk Res*. 2010;34(6):752-756.
32. Weltermann A, Fonatsch C, Haas OA, et al. Impact of cytogenetics on the prognosis of adults with de novo AML in first relapse. *Leukemia*. 2004;18(2):293-302.
33. Szer J. The prevalent predicament of relapsed acute myeloid leukemia. *Hematology Am Soc Hematol Educ Program*. 2012;2012: 43-48.
34. Giles F, Verstovsek S, Garcia-Manero G, et al. Validation of the European Prognostic Index for younger adult patients with acute myeloid leukaemia in first relapse. *Br J Haematol*. 2006;134(1):58-60.
35. Chevallier P, Labopin M, Turlure P, et al. A new Leukemia Prognostic Scoring System for refractory/relapsed adult acute myelogenous leukaemia patients: a GOELAMS study. *Leukemia*. 2011;25(6):939-944.
36. Walter RB, Buckley SA, Pagel JM, et al. Significance of minimal residual disease before myeloablative allogeneic hematopoietic cell transplantation for AML in first and second complete remission. *Blood*. 2013;122(10):1813-1821.
37. Araki D, Wood BL, Othus M, et al. Allogeneic hematopoietic cell transplantation for acute myeloid leukemia: time to move toward a minimal residual disease-based definition of complete remission? *J Clin Oncol*. 2016; 34(4):329-336.
38. Karanes C, Kopecky KJ, Head DR, et al. A phase III comparison of high dose ARA-C (HIDAC) versus HIDAC plus mitoxantrone in the treatment of first relapsed or refractory acute myeloid leukemia Southwest Oncology Group Study. *Leuk Res*. 1999;23(9): 787-794.
39. Amadori S, Arcese W, Isacchi G, et al. Mitoxantrone, etoposide, and intermediate-dose cytarabine: an effective and tolerable regimen for the treatment of refractory acute myeloid leukemia. *J Clin Oncol*. 1991;9(7): 1210-1214.
40. Parker JE, Pagliuca A, Mijovic A, et al. Fludarabine, cytarabine, G-CSF and idarubicin (FLAG-IDA) for the treatment of poor-risk myelodysplastic syndromes and acute myeloid leukaemia. *Br J Haematol*. 1997; 99(4):939-944.
41. Burnett AK, Russell NH, Hills RK, et al. Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the medical research council AML15 trial. *J Clin Oncol*. 2013;31(27):3360-3368.
42. Herzig RH, Lazarus HM, Wolff SN, Phillips GL, Herzig GP. High-dose cytosine arabinoside therapy with and without anthracycline antibiotics for remission induction of acute nonlymphoblastic leukemia. *J Clin Oncol*. 1985;3(7):992-997.
43. Rowe JM, Mazza JJ, Hines JD, et al. Mitoxantrone and etoposide in patients with relapsed and refractory acute nonlymphocytic leukemia. *Haematol Blood Transfus*. 1990;33:326-329.
44. Vogler WR, McCarley DL, Stagg M, et al. A phase III trial of high-dose cytosine arabinoside with or without etoposide in relapsed and refractory acute myelogenous leukemia. A Southeastern Cancer Study Group trial. *Leukemia*. 1994;8(11):1847-1853.
45. Montillo M, Mirto S, Petti MC, et al. Fludarabine, cytarabine, and G-CSF (FLAG) for the treatment of poor risk acute myeloid leukemia. *Am J Hematol*. 1998;58(2): 105-109.
46. Thomas X, Fenaux P, Dombret H, et al. Granulocyte-macrophage colony-stimulating factor (GM-CSF) to increase efficacy of intensive sequential chemotherapy with etoposide, mitoxantrone and cytarabine (EMA) in previously treated acute myeloid leukemia: a multicenter randomized placebo-controlled trial (EMA91 Trial). *Leukemia*. 1999;13(8):1214-1220.
47. Leopold LH, Willemze R. The treatment of acute myeloid leukemia in first relapse: a comprehensive review of the literature. *Leuk Lymphoma*. 2002;43(9):1715-1727.
48. Giles F, O'Brien S, Cortes J, et al. Outcome of patients with acute myelogenous leukemia after second salvage therapy. *Cancer*. 2005;104(3):547-554.
49. Trifilio SM, Rademaker AW, Newman D, et al. Mitoxantrone and etoposide with or without intermediate dose cytarabine for the treatment of primary induction failure or relapsed



- acute myeloid leukemia. *Leuk Res.* 2012; 36(4):394-396.
50. Litzow MR, Wang XV, Carroll MP, et al. A randomized trial of three novel regimens for recurrent acute myeloid leukemia demonstrates the continuing challenge of treating this difficult disease. *Am J Hematol.* 2019; 94(1):111-117.
  51. Halpern AB, Othus M, Huebner EM, et al. Phase I/II trial of cladribine, high-dose cytarabine, mitoxantrone, and G-CSF with dose-escalated mitoxantrone for relapsed/refractory acute myeloid leukemia and other high-grade myeloid neoplasms. *Haematologica.* 2019;104(4):e143-e146.
  52. Büchner T, Hiddemann W, Wörmann B, et al. Double induction strategy for acute myeloid leukemia: the effect of high-dose cytarabine with mitoxantrone instead of standard-dose cytarabine with daunorubicin and 6-thioguanine: a randomized trial by the German AML Cooperative Group. *Blood.* 1999; 93(12):4116-4124.
  53. Wierzbowska A, Robak T, Pluta A, et al; Polish Adult Leukemia Group. Cladribine combined with high doses of arabinoside cytosine, mitoxantrone, and G-CSF (CLAG-M) is a highly effective salvage regimen in patients with refractory and relapsed acute myeloid leukemia of the poor risk: a final report of the Polish Adult Leukemia Group. *Eur J Haematol.* 2008;80(2):115-126.
  54. Becker PS, Kantarjian HM, Appelbaum FR, et al. Clofarabine with high dose cytarabine and granulocyte colony-stimulating factor (G-CSF) priming for relapsed and refractory acute myeloid leukaemia. *Br J Haematol.* 2011;155(2):182-189.
  55. Muluneh B, Buhlinger K, Deal AM, et al. A comparison of clofarabine-based (GCLAC) and cladribine-based (CLAG) salvage chemotherapy for relapsed/refractory AML. *Clin Lymphoma Myeloma Leuk.* 2018;18(1): e13-e18.
  56. Perl AE, Altman JK, Cortes J, et al. Selective inhibition of FLT3 by gilteritinib in relapsed or refractory acute myeloid leukaemia: a multicentre, first-in-human, open-label, phase 1-2 study. *Lancet Oncol.* 2017;18(8): 1061-1075.
  57. Cortes JE, Tallman MS, Schiller GJ, et al. Phase 2b study of 2 dosing regimens of quizartinib monotherapy in FLT3-ITD-mutated, relapsed or refractory AML. *Blood.* 2018;132(6):598-607.
  58. Cortes JE, Khaled S, Martinelli G, 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.* 2019;20(7):984-997.
  59. Perl AE. Availability of FLT3 inhibitors: how do we use them? *Blood.* 2019;134(9): 741-745.
  60. Maziarz RT, Fernandez H, Patnaik MM, et al Radius: Midostaurin (mido) plus standard of care (SOC) after allogeneic stem cell transplant (alloSCT) in patients (pts) with FLT3-internal tandem duplication (ITD)-mutated acute myeloid leukemia (AML). *Biol Blood Marrow Transplant.* 2019;25(suppl 3): S11-S12.
  61. Burchert A, Bug G, Finke J, et al. Sorafenib as maintenance therapy post allogeneic stem cell transplantation for FLT3-ITD positive AML [abstract]. *Blood.* 2018;132(suppl 1). Abstract 661.
  62. Chappell G, Geer M, Gatz E, et al. Maintenance sorafenib in FLT3-ITD AML following allogeneic HCT favorably impacts relapse and overall survival. *Bone Marrow Transplant.* 2019;54(9):1518-1520.
  63. Schlenk RF, Weber D, Fiedler W, et al; German-Austrian AML Study Group. Midostaurin added to chemotherapy and continued single-agent maintenance therapy in acute myeloid leukemia with FLT3-ITD. *Blood.* 2019;133(8):840-851.
  64. Levis MJ, Hamadani M, Logan B, et al. A phase 3, trial of gilteritinib, as maintenance therapy after allogeneic hematopoietic stem cell transplantation in patients with FLT3-ITD+ AML [abstract]. *J Clin Oncol.* 2018; 36(suppl 15). Abstract TPS7075.
  65. DiNardo CD, Pratz KW, Letai A, et al. Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. *Lancet Oncol.* 2018;19(2): 216-228.
  66. Pollyea DA, Stevens BM, Jones CL, et al. Venetoclax with azacitidine disrupts energy metabolism and targets leukemia stem cells in patients with acute myeloid leukemia. *Nat Med.* 2018;24(12):1859-1866.
  67. Konopleva M, Pollyea DA, Potluri J, et al. Efficacy and biological correlates of response in a phase II study of venetoclax monotherapy in patients with acute myelogenous leukemia. *Cancer Discov.* 2016;6(10): 1106-1117.
  68. DiNardo CD, Rausch CR, Benton C, 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.* 2018;93(3):401-407.
  69. Goldberg AD, Horvat TZ, Hsu M, et al. Venetoclax combined with either a hypomethylating agent or low-dose cytarabine shows activity in relapsed and refractory myeloid malignancies [abstract]. *Blood.* 2017;130(suppl 1). Abstract 1353.
  70. Aldoss I, Yang D, Aribi A, et al. Efficacy of the combination of venetoclax and hypomethylating agents in relapsed/refractory acute myeloid leukemia. *Haematologica.* 2018;103(9):e404-e407.
  71. Tenold M, Moskoff B, Benjamin D, Jonas BA. Retrospective analysis of adults with acute myeloid leukemia treated with venetoclax plus hypomethylating agents at a comprehensive cancer center [abstract]. *Blood.* 2018;132(suppl 1). Abstract 1424.
  72. Maiti A, DiNardo CD, Rausch CR, et al Ten-day decitabine with Venetoclax (DEC10-VEN) in acute myeloid leukemia: updated results of a phase II trial [abstract]. *Blood.* 2019;134(suppl 1). Abstract 2637.
  73. Ram R, Amit O, Zuckerman T, et al. Venetoclax in patients with acute myeloid leukemia refractory to hypomethylating agents—a multicenter historical prospective study. *Ann Hematol.* 2019;98(8):1927-1932.
  74. Asghari H, Lee D, Deutsch YE, et al. Outcomes of patients with relapsed or refractory acute myeloid leukemia receiving hypomethylating agent and venetoclax [abstract]. *Blood.* 2019;134(suppl 1). Abstract 1357.
  75. Götze K, Müller-Thomas C, Peschel C. The role of azacitidine in the management of myelodysplastic syndromes (MDS). *Cancer Manag Res.* 2009;1:119-130.
  76. Karol SE, Alexander T, Budraja A, et al. Venetoclax in combination with high-dose chemotherapy is active and well-tolerated in children with relapsed or refractory acute myeloid leukemia [abstract]. *Blood.* 2019; 134(suppl 1). Abstract 178.
  77. Aboudalle I, Konopleva MY, Kadia TM, et al. A phase Ib/II study of the BCL-2 inhibitor venetoclax in combination with standard intensive AML induction/consolidation therapy with FLAG-IDA in patients with newly diagnosed or relapsed/refractory AML [abstract]. *Blood.* 2019;134(suppl 1). Abstract 176.
  78. Jabbour E, Giralt S, Kantarjian H, et al. Low-dose azacitidine after allogeneic stem cell transplantation for acute leukemia. *Cancer.* 2009;115(9):1899-1905.
  79. Platzbecker U, Wermke M, Radke J, et al. Azacitidine for treatment of imminent relapse in MDS or AML patients after allogeneic HSCT: results of the RELAZA trial. *Leukemia.* 2012;26(3):381-389.
  80. Craddock C, Labopin M, Robin M, et al. Clinical activity of azacitidine in patients who relapse after allogeneic stem cell transplantation for acute myeloid leukemia. *Haematologica.* 2016;101(7):879-883.
  81. Schmid C, Labopin M, Nagler A, et al; EBMT Acute Leukemia Working Party. Donor lymphocyte infusion in the treatment of first hematological relapse after allogeneic stem-cell transplantation in adults with acute myeloid leukemia: a retrospective risk factors analysis and comparison with other strategies by the EBMT Acute Leukemia Working Party. *J Clin Oncol.* 2007;25(31):4938-4945.
  82. Schroeder T, Czibere A, Platzbecker U, et al. Azacitidine and donor lymphocyte infusions as first salvage therapy for relapse of AML or MDS after allogeneic stem cell transplantation. *Leukemia.* 2013;27(6): 1229-1235.
  83. Schroeder T, Rachlis E, Bug G, et al. Treatment of acute myeloid leukemia or myelodysplastic syndrome relapse after allogeneic stem cell transplantation with azacitidine and donor lymphocyte infusions—a retrospective multicenter analysis from the German Cooperative Transplant Study Group. *Biol Blood Marrow Transplant.* 2015; 21(4):653-660.
  84. Schroeder T, Rautenberg C, Krüger W, et al. Treatment of relapsed AML and MDS after allogeneic stem cell transplantation with decitabine and DLI—a retrospective multicenter analysis on behalf of the German Cooperative Transplant Study Group. *Ann Hematol.* 2018;97(2):335-342.

85. Ossenkoppele G, Löwenberg B. How I treat the older patient with acute myeloid leukemia. *Blood*. 2015;125(5):767-774.
86. Ding L, Ley TJ, Larson DE, et al. Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing. *Nature*. 2012;481(7382):506-510.
87. Meggendorfer M, Alpermann T, Perglerová K, et al. Genetic patterns of relapsed AML differ significantly from first manifestation and are dependent on cytogenetic risk groups at diagnosis: results in 175 patients with paired samples [abstract]. *Blood*. 2014;124(21). Abstract 1029.
88. Stein EM, DiNardo CD, Fathi AT, et al. Molecular remission and response patterns in patients with mutant-IDH2 acute myeloid leukemia treated with enasidenib. *Blood*. 2019;133(7):676-687.
89. Amatangelo MD, Quek L, Shih A, et al. Enasidenib induces acute myeloid leukemia cell differentiation to promote clinical response. *Blood*. 2017;130(6):732-741.
90. Fathi AT, DiNardo CD, Kline I, et al; AG221-C-001 Study Investigators. Differentiation syndrome associated with enasidenib, a selective inhibitor of mutant isocitrate dehydrogenase 2: Analysis of a Phase 1/2 study. *JAMA Oncol*. 2018;4(8):1106-1110.
91. Birendra KC, DiNardo CD. Evidence for clinical differentiation and differentiation syndrome in patients with acute myeloid leukemia and IDH1 mutations treated with the targeted mutant IDH1 inhibitor, AG-120. *Clin Lymphoma Myeloma Leuk*. 2016;16(8):460-465.
92. Intlekofer AM, Shih AH, Wang B, et al. Acquired resistance to IDH inhibition through trans or cis dimer-interface mutations. *Nature*. 2018;559(7712):125-129.
93. Quek L, David MD, Kennedy A, et al. Clonal heterogeneity of acute myeloid leukemia treated with the IDH2 inhibitor enasidenib. *Nat Med*. 2018;24(8):1167-1177.
94. Harding JJ, Lowery MA, Shih AH, et al. Isoform switching as a mechanism of acquired resistance to mutant isocitrate dehydrogenase inhibition. *Cancer Discov*. 2018;8(12):1540-1547.
95. Smith CC, Wang Q, Chin CS, et al. Validation of ITD mutations in FLT3 as a therapeutic target in human acute myeloid leukaemia. *Nature*. 2012;485(7397):260-263.
96. Man CH, Fung TK, Ho C, et al. Sorafenib treatment of FLT3-ITD(+) acute myeloid leukemia: favorable initial outcome and mechanisms of subsequent non-responsiveness associated with the emergence of a D835 mutation. *Blood*. 2012;119(22):5133-5143.
97. McMahon CM, Ferng T, Canaani J, et al. Clonal selection with RAS pathway activation mediates secondary clinical resistance to selective FLT3 inhibition in acute myeloid leukemia. *Cancer Discov*. 2019;9(8):1050-1063.
98. DiNardo CD, Schuh AC, Stein EM, 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 [abstract]. *Blood*. 2019;134(suppl 1). Abstract 643.
99. Dinardo CD, Stein AS, Stein EM, et al. Mutant IDH1 inhibitor ivosidenib (IVO; AG-120) in combination with azacitidine (AZA) for newly diagnosed acute myeloid leukemia (ND AML) [abstract]. *J Clin Oncol*. 2019;37(suppl 15). Abstract 7011.
100. Farshchi Zarabi S, Chan S, Gupta V, et al. Remissions after third induction chemotherapy for primary non-responders with acute myeloid leukemia (AML) are uncommon and short-lived. *Leuk Lymphoma*. 2018;59(1):237-240.
101. Taksin AL, Legrand O, Raffoux E, 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(1):66-71.