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Leukemia (PH Wiernik, Section Editor)

Treatment of Relapsed/Refractory Acute Myeloid Leukemia

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Opinion statement

Approximately 40–45% of younger and 10–20% of older adults with acute myeloid leukemia (AML) will be cured with current standard chemotherapy. The outlook is particularly gloomy for patients with relapsed and/or refractory disease (cure rates no higher than 10%). Allogeneic hematopoietic stem cell transplantation (HSCT), the only realistic hope of cure for these patients, is an option for only a minority. In recent years, much has been learned about the genomic and epigenomic landscapes of AML, and the clonal architecture of both de novo and secondary AML has begun to be unraveled. These advances have paved the way for rational drug development as new "drugable" targets have emerged. Although no new drug has been approved for AML in over four decades, with the exception of gemtuzumab ozogamycin, which was subsequently withdrawn, there is progress on the horizon with the possible regulatory approval soon of agents such as CPX-351 and midostaurin, the Food and Drug Administration "breakthrough" designation granted to venetoclax, and promising agents such as the IDH inhibitors AG-221 and AG-120, the smoothened inhibitor glasdegib and the histone deacetylase inhibitor pracinostat. In our practice, we treat most patients with relapsed/refractory AML on clinical trials, taking into consideration their prior treatment history and response to the same. We utilize targeted sequencing of genes frequently mutated in AML to identify "actionable" mutations, e.g., in *FLT3* or *IDH1/2*, and incorporate small-molecule inhibitors of these oncogenic kinases into our therapeutic regimens whenever possible. In the absence of actionable mutations, we rationally combine conventional agents with other novel therapies such as monoclonal antibodies and other targeted drugs. For fit patients up to the

age of 65, we often use high-dose cytarabine-containing backbone regimens. For older or unfit patients, we prefer hypomethylating agent-based therapy. Finally, all patients with relapsed/refractory AML are evaluated for allogeneic HSCT.

Introduction

The treatment of relapsed/refractory (R/R) acute myeloid leukemia (AML) remains one of the most formidable challenges in oncology today. With a long-term disease-free survival of only approximately 30 to 40% after standard chemotherapy, and a paucity of treatment options besides the standard cytarabine and anthracyclines, disease persistence or recurrence occurs in most patients with AML. Outcomes for patients with relapsed or refractory AML are poor, with overall survival (OS) estimated at no more than 10% at 3 years [1, 2]. In physically fit patients, intensive chemotherapy (IC) with the goal of achieving a second complete remission (CR2) so as to proceed to allogeneic hematopoietic stem cell transplantation (HSCT) is often given, but long-term survival rates remain low, because of the common failure to achieve the necessary response required to achieve the desired "bridge to transplant" and the comorbidities, age considerations, residual toxicities, limited availability of donors, and other factors that limit this approach for a large majority of patients. Thus, the notion that patients can frequently be salvaged with this approach has been termed a "myth" by some experts [3]. Low-intensity therapies, e.g., epigenetic modifiers, are typically offered to patients who are deemed ineligible to receive IC because of age or comorbidities, as in the frontline setting, but in the salvage setting are palliative at best in most instances.

In recent years, better understanding of the molecular complexity and biology of AML has led to the development of new strategies to treat AML. Many new agents from different therapeutic classes have been investigated in patients with R/R AML, with particular interest in nonchemotherapeutic strategies. Although no new drugs have been approved for the treatment of AML for over 50 years (with the exception of gemtuzumab ozogamycin, GO, Mylotarg which was eventually withdrawn from the market) [4], the improved OS seen in phase III trials of CPX-351 (Vyxeos™) [5••] and the *fms*-like tyrosine kinase 3 (FLT3) inhibitor, midostaurin, [6••] in secondary and *FLT3*-mutated AML, respectively, in the frontline setting, have made approval of these agents likely. In this manuscript, we review some of the most notable recent advances in the treatment of R/R AML, with a focus on those with the most mature or promising clinical data. It is important to emphasize that the list of agents included is by necessity partial and incomplete. This deficiency, however, highlights the very active and promising ongoing research that will undoubtedly break the impasse that has characterized the treatment of AML in the last 50 years.

Cytotoxic Chemotherapy: Novel Agents and Combinations

Vosaroxin

Vosaroxin is a first-in-class, anti-cancer quinolone derivative that inhibits topoisomerase II and intercalates DNA, inducing cell cycle arrest and p53-independent apoptosis [7]. Preclinical evidence of synergism with cytarabine [8] and encouraging results in an early phase combination trial [9] led to the phase III, placebo-controlled, VALOR study in 711 patients with AML in first relapse after or refractory to 1 or 2 cycles of previous anthracycline-containing induction chemotherapy [10••]. Patients were randomized 1:1 to receive cytarabine (1 g/m^2 on days 1–5) in combination with vosaroxin (90 mg/m^2 on days 1 and 4 in cycle 1; 70 mg/m^2 in subsequent cycles) or placebo. Median OS (the primary endpoint) was 7.5 months in the vosaroxin group and 6.1 months in the placebo group (p = 0.061) [10]. Complete remission (CR) rates were significantly higher in the vosaroxin group (30 versus 16%, $p < 0.0001$).

Thirty- and 60-day mortality rates were virtually identical in the two groups, although grade ≥3 adverse events (AEs) such as febrile neutropenia (FN), neutropenia, stomatitis, hypokalemia, bacteremia, sepsis, and pneumonia were all more frequent in the vosaroxin cohort [10]. Treatment-related serious AEs (SAEs) occurred in 33 and 17% of patients in the vosaroxin and placebo cohorts, respectively. A number of prespecified secondary and subgroup analyses showed significantly improved OS in the vosaroxin group. Older patients and those with early relapse derived the greatest benefit from vosaroxin and cytarabine [10]. The survival benefit seen in patients ≥60 years of age (median 7.1 versus 5 months, $p = 0.003$) was maintained after a median of 39.9 months of follow-up and was particularly pronounced among those with refractory disease or early relapse [11]. Additionally, post hoc, exploratory analyses showed OS benefits in patients with unfavorable cytogenetic abnormalities and those with *FLT3* mutations. The trial did not meet its primary endpoint; thus, vosaroxin has not gained regulatory approval. However, vosaroxin remains an attractive agent for patients with AML. Promising results were reported in a single-arm, nonrandomized study in combination with decitabine in older patients in the frontline setting. This study identified 70 mg/m^2 of vosaroxin on days 1 and 4 in combination with standard dose decitabine as the preferred dose [12•]. However, the combination of vosaroxin with low-dose cytarabine (LDAC) did not improve CR/complete remission with incomplete count recovery (CRi) rates or survival in a randomized comparison with LDAC alone in older, untreated adults with AML, mainly due to excess early mortality in the combination arm [13]. In this "pick a winner" trial, single-agent vosaroxin was also separately compared to LDAC; CR/CRi rates were similar, and 12-month OS was inferior in the vosaroxin group (12 versus 31%, $p = 0.003$) [13].

CPX-351 (Vyxeos™)

CPX-351 is a liposomal formulation of cytarabine and daunorubicin in a fixed molar ratio of 5:1 that may be particularly effective in secondary AML [14]. A phase II study randomized 125 patients with AML in first relapse after a first complete remission (CR1) of ≥1 month 2:1 to CPX-351 or investigators' choice of first salvage chemotherapy [15]. CR/CRi rates were numerically higher with CPX-351, but 1-year OS was not significantly different (36 versus 27%, $p = 0.33$). However, patients categorized as poor risk by the European Prognostic Index ($n = 85$) appeared to benefit from CPX-351 (12-month OS 28 versus 9%, $p = 0.02$) [15]. These findings led to a randomized trial in which 309 patients aged 60 to 75 years with newly diagnosed secondary AML were randomized to receive CPX-351 (Vyxeos™; 100 units/m^2 on days 1, 3, and 5) or standard chemotherapy ("7 + 3"; cytarabine 100 mg/m^2/day on days 1–7 and daunorubicin 60 mg/m^2/day on days 1–3). Treatment with CPX-351 resulted in improved OS (the primary endpoint of the study), with a median of 9.56 versus 5.95 months with standard chemotherapy ($p = 0.005$), as well as significantly higher response rates (CR/CRi rate 47.7 versus 33.3%; $p = 0.016$) [5••]. Thirty-day (5.9 versus 10.6%) and 60-day (13.7 versus 21.2%) mortality also favored CPX-351 [5••]. A more detailed discussion of this important first-line trial is outside the scope of this review focused on the treatment of R/R AML.

FLAM

Flavopiridol (alvocidib) is a pan-cyclin-dependent kinase (CDK) inhibitor that induces cell cycle arrest and apoptosis and also transcriptionally downregulates the antiapoptotic protein, MCL-1, via inhibition of CDK9 [16]. Based on preclinical studies showing synergism with standard chemotherapeutic agents, the regimen of "timed sequential therapy" with flavopiridol, cytarabine, and mitoxantrone (FLAM) was developed [17, 18]. FLAM yielded significantly superior CR rates in comparison to 7 + 3 (70 versus 46%, $p = 0.003$) in a randomized, phase II study in newly diagnosed, younger adults with intermediate and poor risk AML, although no differences in OS or event-free survival (EFS) were observed [19]. Because of flavopiridol's effects on MCL-1, which is critical to the development and maintenance of AML [20••], an ongoing phase II trial (NCT02520011) of the FLAM regimen in patients with R/R AML is restricted to patients who have evidence of MCL-1 dependence of their AML by a specific BH3-profiling assay that uses the proapoptotic "BH3-only" protein, Noxa, which antagonizes MCL-1 [21]. Flavopiridol has received "orphan drug" designation from the FDA for AML [22].

Epigenetic Therapy: New Agents and Targets

Guadecitabine

Guadecitabine (SGI-110) is a second-generation hypomethylating agent (HMA) that is a dinucleotide of decitabine and deoxyguanosine, making it resistant to deamination by cytidine deaminase [23•]. In a phase 1 trial that enrolled patients with either R/R AML ($n = 74$) or myelodysplastic syndrome (MDS, $n = 19$) and tested various schedules of guadecitabine administered subcutaneously, a maximal tolerated dose (MTD) was not identified in patients with AML, while among those with MDS, 90 mg/m^2/day for five consecutive days every 4 weeks was defined as the MTD (DLTs at the 125 mg/m^2/day dose level included grade 4 cytopenias and FN, resulting in one case in grade 5 sepsis) [23•]. Potent dose-related DNA demethylation occurred on the daily × 5 regimen, reaching a plateau at 60 mg/m^2, which was thus the recommended phase 2 dose (RP2D) [23•]. Six patients each with AML and MDS responded. In a phase II trial, patients with R/R AML received either 10 days ($n = 53$) or 5 days ($n = 50$) of guadecitabine per cycle; additionally, those receiving 5 days were randomized to receive either 60 or 90 mg/m^2/day [24]. Patients receiving the drug for 10 days per cycle received 60 mg/m^2/day. CR rates were 19 and 6%, respectively, in the 10- and 5-day groups ($p = 0.074$). When comparing the sum of CR, CRi, and complete remission with incomplete platelet recovery (CRp) rates (designated the composite CR (CRc) rate), the percentages were 30 and 16% in the 10- and 5-day groups, respectively ($p = 0.106$). The longer 10-day dosing induced significantly more potent and longer demethylation and led also to significantly more anemia and thrombocytopenia. Median OS was 7.1 months with 10-day dosing and 5.7 months with 5-day dosing ($p = 0.505$). There were no significant differences in 30- or 60-day

mortality between the two schedules [24]. Significantly worse OS was observed among patients with performance status 2, poor risk cytogenetics, and those enrolled within 6 months from their previous therapy [25]. An identically designed phase II trial of guadecitabine was conducted in the frontline setting in patients with AML who were not candidates for IC [26]. There were no major differences in clinical responses, demethylation, OS, or safety between 60 and 90 mg/m^2/day on the 5-day regimen [27], or between the 5- and 10-day cohorts for the composite primary endpoint (CR + CRi + CRp), median OS, grade ≥3 AEs, or 30-, 60-, and 90-day all-cause mortality; response rates and median OS were numerically higher in the 5-day cohort [26]. Based upon these findings, guadecitabine is currently being tested in treatment-naive patients with AML in a pivotal phase III trial using the 60 mg/m^2/day for 5 days schedule (ASTRAL-1, NCT02348489). Based on the upregulation by HMAs of tumor-associated antigens and of programmed death ligand-1/2 (PD-L1/2) as a possible mechanism of escape from immune surveillance, an ongoing trial combines guadecitabine with the anti-PD-L1 monoclonal antibody atezolizumab for the treatment of patients with treatment-naive or R/R AML (NCT02892318).

Other Epigenetic Modifiers

A major focus in epigenetics research in recent years has been on the development of targeted therapies against epigenetic "readers" called bromodomains [28, 29]. Their mechanism of action in AML appears to involve induction of hexamethylene bisacetamide-inducible protein 1 (HEXIM1) [30]. Several small-molecule inhibitors of bromodomain and extra-terminal (BET) proteins have been developed, e.g., FT1101, GSK525762, and MK-8628 (OTX015). In a phase I trial of OTX015 (MK-8628), 3 of 36 patients with R/R AML achieved CR/CRp lasting 2 to 5 months [31]. Preclinical studies have suggested synergism between BET and FLT3 or histone deacetylase (HDAC) inhibitors [32, 33]. Such combinations will be entering the clinic in the near future. Another epigenetic target of interest, especially in mixed lineage leukemia (*MLL*)-rearranged AML, is the histone lysine (H3K79) methyltransferase disruptor of telomeric silencing 1-like (DOT1L) [34••, 35••]. Pinometostat (EPZ-5676) is a potent and highly selective inhibitor of DOT1L currently in early stages of clinical development [36]. In a first-in-human (FIH) phase I trial, an MTD was not identified and pharmacodynamic evidence of target inhibition and clinical responses (including CRs) were observed in heavily pretreated patients with *MLL*-rearranged leukemias across a range of doses [36]. Interestingly, DOT1L may also be a therapeutic target in *DNMT3A*-mutated AML [37], which has been shown to carry an adverse prognosis [38•]. Inhibitors of lysine-specific demethylase 1 (LSD1) may reactivate the all-trans-retinoic acid (ATRA) differentiation pathway in AML, and there is preclinical evidence of synergism between ATRA and the LSD1 inhibitor, tranylcypromine, a regimen that may also target leukemia-initiating cells [39]. A number of clinical trials are exploring ATRA/LSD1 inhibitor

combinations in R/R AML (NCT02842827, NCT02273102, NCT02261779, NCT02717884). Synergism between LSD1 inhibitors and HDAC inhibitors against AML has also been demonstrated, both in vitro and in vivo [40]. In a FIH phase I trial, the first-in-class LSD1 inhibitor, Ory-1001, was found to be well-tolerated; objective responses were seen in 5 of 14 (36%) patients with R/R AML in an extension cohort at a dose of 140 μg/m^2/day [41].

Antibody-Drug Conjugates, Bispecific T-Cell Engagers, and Dual Affinity Retargeting Molecules

CD33-Targeted ADCs

GO (Mylotarg®) is an antibody drug conjugate (ADC) targeted to CD33 that consists of a monoclonal antibody against CD33 linked to a semisynthetic derivative of the cytotoxic antibiotic, calicheamicin. It was approved by the FDA in May 2000 for older (≥60) patients with CD33-expressing AML in first relapse, based on a 26% overall response rate (ORR) in this population [42•]. Among 142 patients in untreated first relapse (median age 61), the CR/CRp rate was 30% (16% CRs) [42•]. Unfortunately, however, a confirmatory phase III trial conducted by the Southwest Oncology Group (SWOG) found no benefit to the addition of GO to standard "7 + 3" induction chemotherapy in 595 younger (18–60) patients with newly diagnosed AML, in terms of CR rate, relapse-free or overall survival [43•]. Of note, the dose of daunorubicin used in this trial during induction was only 45 mg/m^2/day on days 1–3. There was also no improvement in disease-free survival with the use of GO post-consolidation among patients remaining in CR after consolidation [43•]. In contrast to the findings of the SWOG trial [43•], a number of other phase III trials have documented a survival benefit for this agent with little to no increase in toxicity [44••, 45••, 46••]. The improved OS seen with the addition of GO to IC appears restricted to patients with nonadverse cytogenetics [47•]. An in-depth discussion of these trials in the upfront setting is not presented here, but GO is expected to become available again soon, based on these data.

Like GO, vadastuximab talirine (SGN-33A) is also a CD33-directed ADC that employs pyrrolobenzodiazepine instead of calicheamicin, the toxin attached to the anti-CD33 antibody in GO. Pyrrolobenzodiazepine is not known to be associated with liver toxicity, thus eliminating the potential for hepatic veno-occlusive disease (VOD, also known as sinusoidal obstruction syndrome (SOS)) seen with GO [48•]. Thirty-four patients with AML that had relapsed after achievement of CR1 and 52 who had declined IC (40 of whom had received 1–2 prior low-intensity therapies, predominantly HMAs) participated in a phase I trial of SGN-33A [48•]. Most patients had intermediate (51%) or adverse (31%) cytogenetics, and 54% had AML with MDS-related changes. DLTs included grade 4 hematologic toxicity, grade 3 mucositis and pulmonary embolism, and grade 5 sepsis. The most frequent grade ≥3 AEs included febrile neutropenia (FN, 69%), thrombocytopenia (29%), and anemia (23%). Fatigue (48%), decreased appetite (28%), constipation, diarrhea, dyspnea, nausea (26% each), and peripheral edema (25%) were common. Thirty-day mortality was 6%, and 40 mcg/kg every 4 weeks was declared the RP2D. Of 21 patients treated at this dose and evaluable for efficacy, 7 (33%) (3 treatment-naive; (14%)) achieved CR/CRi [48•]. A phase I study of vadastuximab talirine

(10 mcg/kg) in combination with an HMA (azacitidine or decitabine) for 5 days every 4 weeks in previously untreated patients with AML who declined or were unfit for IC reported a CR/CRi rate of 73% among evaluable patients (n = 49) with 30- and 60-day mortality of 2 and 8%, respectively [49]. This agent has also been combined safely with IC in both the induction [50] and consolidation [51] settings in younger, newly diagnosed and post-remission [51, 54•] patients, respectively, as well as administered alone as maintenance after IC and/or HSCT [51]. In combination with 7 + 3 induction chemotherapy, vadastuximab talirine produced a CR/CRi rate of 78%, 94% of which occurred with 1 cycle and 74% of which were MRD-negative, among 40 evaluable, newly diagnosed patients with AML, with 30- and 60-day mortality of 0 and 7%, respectively [50]. IMGN779 is yet another CD33-targeted ADC that utilizes a different toxin (DGN462, a novel alkylating agent); this drug is currently in a phase I trial for patients with R/R AML (NCT02674763).

Anti-CD33 BiTE®s

A novel approach to targeting CD33, expression of which is nearly universal on myeloblasts, uses bispecific T-cell engager (BiTE®) technology. AMG 330 is a CD33/CD3 BiTE antibody that recruits and expands T-cells that efficiently lyse autologous blasts in primary AML samples [52•]. At least in some cell lines, epigenetic modifiers, e.g., panobinostat (HDAC inhibitor) and azacitidine increase CD33 expression and augment AMG 330-induced cytotoxicity [53•]. AMG 330, currently in a FIH phase I trial (NCT02520427), has been shown to significantly prolong survival of xenograft mouse models of human *FLT3*-mutated AML [54•]. Interestingly, in preclinical studies, AMG 330 cytotoxicity against primary AML cells is higher in specimens from newly diagnosed patients and those with favorable-risk disease [55]. AMG 330 strongly upregulates programmed death ligand 1 (PD-L1) on primary AML cells in a cytokine-dependent manner, and blockade of the programmed death 1 (PD-1)/PD-L1 axis significantly enhances AMG 330-mediated cell lysis, T-cell proliferation, and interferon-γ secretion, making a compelling argument for combining this agent with anti-PD-1/PD-L1 monoclonal antibodies [56].

Targeting CD123

The interleukin-3 (IL-3) receptor alpha chain, CD123, is highly and differentially (but not exclusively) expressed in leukemic progenitors compared with normal hematopoietic stem and progenitor cells. JNJ-63709178 is a humanized CD123 x CD3 "DuoBody" that is being studied in a FIH phase I trial in patients with R/R AML (NCT02715011). A conceptually similar but structurally distinct strategy to target CD123 involves the use of dual affinity re-targeting (DART) molecules that are generated from antibodies to CD3 and CD123 and redirect T-cells against AML blasts [57•]. MGD006 is a CD3 x CD123 DART currently in a phase I trial in R/RAML and higher risk MDS (NCT02152956). Xmab®14045 is a bispecific monoclonal antibody that binds to both CD3 on T-cells and CD123 on tumor cells via separate antigen recognition and binding sites, thereby cross-linking them to induce potent cell lysis of $CD123^+$ myeloblasts in AML; this agent is now in a broad, phase I trial in patients with R/R $CD123^+$ hematologic malignancies (NCT02730312). SL-401 is a fusion protein consisting of a truncated diphtheria toxin conjugated to IL-3 that represents another

mechanism of therapeutically targeting CD123. SL-401 is under phase I/II evaluation in AML, both in the R/R setting (NCT02113982) and as consolidation for patients in CR1 (NCT02270463). In the limited experience reported to date, best response in the R/R AML population has been stable disease (SD) [58]. CSL362 (JNJ-56022473) is an anti-CD123 monoclonal antibody engineered to bind with high affinity to CD16 on natural killer (NK) cells, leading to enhanced antibody-dependent cellular cytotoxicity (ADCC). This agent is now in a phase II clinical trial in combination with decitabine (versus decitabine alone) for previously untreated patients with AML for whom IC is not considered appropriate (NCT02472145).

Molecularly Targeted Therapy: Isocitrate Dehydrogenase 1/2 (IDH1/2) Inhibitors

Mutations in *IDH1* and *IDH2* each occur in approximately 8–12% of patients with AML; are generally associated with older age, intermediate-risk cytogenetics, *FLT3* and nucleophosmin 1 (*NPM1*) mutations; and appear not to have an adverse impact on prognosis [59]. However, these mutant enzymes produce an abnormal oncometabolite, 2-hydroxyglutarate (2-HG), instead of the normal metabolite, α-ketoglutarate (α-KG). 2-HG inhibits the α-KG-dependent enzyme, ten-eleven translocation 2 (TET2), leading to a hypermethylated genome with a resultant block in differentiation [60••]. A number of small-molecule inhibitors of mutant IDH1 and/or IDH2 have been developed, of which AG-120 (IDH1 inhibitor) and AG-221 (IDH2 inhibitor) are the most advanced. IDHENTIFY is a phase III clinical trial of AG-221 versus standard of care for older patients with R/R AML harboring an *IDH2* mutation (NCT02577406). In a phase I/II trial (NCT01915498), 198 patients with an *IDH2*-mutated hematologic malignancy (70% R/R AML, 17% untreated AML, 7% MDS, 6% other) received AG-221 once or twice daily in continuous 28-day cycles [61•]. Most (64%) patients with R/R AML had received ≥2 prior therapies. An MTD was not reached. The most common AG-221-related AEs were indirect hyperbilirubinemia (19%) and nausea (18%). Objective responses were seen in 52 of 128 (41%) efficacy-evaluable R/R AML patients (CR in 18%, CRp and CRi in 1% each, morphologic CR in 6% and partial remission (PR) in 15%), with a median response duration of 6 months [61•]. Improvements in the absolute neutrophil count (ANC) occurred in 56% of R/R AML patients. Responses may occur as early as the first cycle and in many instances have been sustained for 24+ months. However, the allelic burden of mutant *IDH2* did not decrease in responders [61•]. A similar trial was conducted in patients with advanced, *IDH1*-mutated, hematologic malignancies using the IDH1 inhibitor AG-120 (NCT02074839) [62•]. A MTD was not reached in the dose escalation phase up to a dose of 1200 mg daily. Most AEs were grade 1 or 2, the most common being diarrhea (23%), fatigue (22%), and fever (22%); FN (11%) was the most frequent grade ≥3 AE. The overall response rate (ORR) was 36% with a median duration of 5.6 months, and the CR rate 18% [62•]. Three dose expansion cohorts are currently enrolling at 500 mg daily: R/R AML (n = 125), untreated AML (n = 25), and other *IDH1*-mutated advanced hematologic malignancies (n = 25) [62•]. Plasma levels of 2-HG have been identified as a useful biomarker

of the biologic and clinical activity of these inhibitors as they typically go down significantly upon administration of the IDH inhibitor. An important phenomenon is the development of a differentiation syndrome in the first few weeks of therapy, characterized by a rapid increase in blasts that is followed by maturation with subsequent decrease and a corresponding increase in neutrophils. Both AG-221 and AG-120 are being explored in combination with standard IC (NCT02632708) and azacitidine (NCT02677922), respectively, for fit and unfit adults with newly diagnosed *IDH1/2*-mutated AML. IDH305 and FT-2102 are other inhibitors of mutant IDH1 that are currently undergoing phase I testing in advanced malignancies (including AML, NCT02381886) and AML (NCT02719574) with *IDH1* R132 mutations, respectively. Preliminary data from an ongoing phase I trial in patients with advanced, *IDH1*-mutated malignancies suggest that IDH305 has a favorable safety profile and promising antitumor activity in *IDH1*-mutated R/R AML (ORR = 33%, *n* = 21) [63]. AG-881 is an inhibitor of both mutant IDH1 and IDH2 that exhibits excellent blood-brain barrier penetration and is under investigation in separate phase I trials in *IDH1/2*-mutated advanced hematologic malignancies (NCT02492737) and solid tumors (e.g., gliomas, cholangiocarcinoma, NCT02481154).

Molecularly Targeted Therapy: FLT3 Inhibitors

FLT3 mutations are encountered in approximately 30–35% of cases of AML. These include internal tandem duplications (ITD) that occur in approximately 25% of patients with AML, and point mutations, most frequently at residue D835 affecting the tyrosine kinase domain (TKD), in 5–10% [64]. While *FLT3*-ITD is clearly associated with high relapse rates and poor outcomes, the prognostic significance of TKD mutations is less well understood and inconsistent across studies [64]. Remarkably, although the subject of intense investigation for many years, no FLT3 inhibitor is specifically approved for AML, although this is expected to change in light of positive OS data with midostaurin from the RATIFY trial (discussed below) [6••]. A number of FLT3 tyrosine kinase inhibitors (TKIs) have been developed, and these may be subdivided into type I (e.g., crenolanib, midostaurin) or type II (e.g., sorafenib, quizartinib, ponatinib) inhibitors depending on the conformation of the kinase to which they bind (Table 1) [65]. The five FLT3 inhibitors with the most clinical data available are discussed individually below. Other FLT3 inhibitors, including FLX925 and E6201, are in earlier phases of clinical testing (NCT02335814, NCT02418000).

Sorafenib

The multi-kinase inhibitor sorafenib (Nexavar®), approved for the treatment of advanced hepatocellular and renal cell carcinoma, is a potent inhibitor of FLT3-ITD but not wild-type FLT3 or D835-mutated FLT3 [66]. Its efficacy was first reported in the phase 1 setting, demonstrating rapid reduction in blast count and some instances of CRi, but rarely CR, and with typically short-lived responses. Studies of sorafenib in conjunction with LDAC in the upfront setting in unselected patients with AML resulted in modest clinical benefit [67–69]. Encouraging results were reported in a phase I/II trial (*n* = 43; 40 of them with FLT3-ITD, 6 not previously treated) of sorafenib, 400 mg twice daily

Table 1. Major FLT-3 inhibitors, along with their kinome and efficacy and safety data in relapsed/refractory AML

FLT3 inhibitor	Kinases inhibited	Efficacy in major phase I/II trials	Major adverse events
Sorafenib (BAY 43-9006, Bayer/Onyx)	FLT3 ITD; VEGFR, RAF, RET, c-KIT, PDGFR-β	Sorafenib with azacitidine in AML (93% FLT3-ITD$^+$, 84% of evaluable pts had R/R AML): ORR = 46% (CR + CRi = 43%, PR = 3%), OS in responders 7.8 m, in nonresponders 6.0 m; 16% bridged to HSCT [70•].	All grades: fatigue (47%), rash and diarrhea (20–30%), hyperbilirubinemia (~60%), AST/ALT elevation (30–40%). Most common grade 3/4: cytopenias, FN[70•].
Midostaurin (PKC412, Novartis)	FLT3 WT, ITD, TKD; VEGFR-2, PKC, c-KIT, PDGFR-β	Midostaurin with azacitidine in AML/MDS (94% with AML; 74% FLT3-ITD$^+$, 76% previously treated, 24% had received prior FLT3 inhibitor): ORR = 26% (CR + CRi + MLFS = 24%, PR = 2%). ORR = 33% in FLT3-ITD$^+$ FLT3 inhibitor-naïve pts. OS = 22 weeks [78].	Grade 3/4: Neutropenia (96%), thrombocytopenia (94%), anemia (61%), infections (56%), LVEF reduction (11%) [78].
Quizartinib (AC-220, Daiichi Sankyo)	FLT3 WT, ITD; c-KIT, PDGFR-α	Quizartinib in R/R AML: (1) ≥ 60 yrs., relapsed in <1 year or refractory to first-line chemo: for FLT3-ITD$^+$, ORR = 66%, OS = 25.3 weeks; for FLT3-ITD$^-$, ORR = 32%, OS = 19 weeks [82]. (2) ≥ 18 years, R/R to second-line chemo or HSCT: for FLT3-ITD$^+$, ORR = 68%, OS = 23.1 weeks; for FLT3-ITD$^-$, ORR = 47%, OS =25.6 weeks. ~1/3 of pts successfully bridged to HSCT [83].	Grade 3/4: anemia (~25%), neutropenia (12%), FN (20–25%), thrombocytopenia (12–15%), QT prolongation (10–13%; 3% at 30 or 60 mg daily dose in another study) [82, 83, 85].
Crenolanib (CP-868-596, AROG)	FLT3 WT, ITD, TKD; PDGFR	Crenolanib in R/R FLT3$^+$ AML: (1) No prior FLT3 TKI: CRi = 39%, PR = 11%, OS = 234 days. (2) Prior FLT3 TKI: ORR = 31%, OS = 94 days [94•].	All grades: nausea/vomiting, transaminitis, and fluid retention [94•].
Gilteritinib (ASP2215, Astellas)	FLT3 ITD, TKD; AXL	Gilteretinib in R/R FLT3+ AML: for doses ≥80 mg, overall ORR = 52% (CRc = 41%, PR = 11%). ORR = 56% in FLT3 inhibitor-naive pts vs. 42% in prior FLT3 inhibitor-treated pts. ORR = 55% in FLT3-ITD AML. OS ~31 weeks [99•].	All grades: diarrhea (16%), fatigue (15%) [99•].

CR complete remission, *CRi* CR with incomplete bone marrow recovery, *CRc* composite CR, *LVEF* left ventricular ejection fraction, *HSCT* hematopoietic stem cell transplant, *MLFS* morphologic leukemia-free state, *ORR* objective response rate, *OS* overall survival, *PR* partial remission, *R/R* relapsed/refractory, *FN* febrile neutropenia, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ITD* internal tandem duplication, *TKD* tyrosine kinase domain, *VEGFR* vascular endothelial growth factor receptor, *PDGFR* platelet-derived growth factor receptor, *WT* wild type, *PKC* protein kinase C, *TKI* tyrosine kinase inhibitor, *OS* overall survival, *AML* acute myeloid leukemia, *MDS* myelodysplastic syndromes, *pts* patients

continuously, administered in combination with azacitidine, 75 mg/m^2/day on days 1–7 of each monthly cycle [70•]. The ORR was 46%, with 16% CR, 27% CRi, and 3% PR and a median time to response of 2 months (2 cycles). The median duration of response (DOR) was 2.3 months, and six patients were bridged to allogeneic HSCT [70•]. The commercial availability of both sorafenib and azacitidine makes this a commonly used regimen for patients with R/R (or newly diagnosed if unfit for IC) *FLT3*-ITD$^+$ AML who are unable to enroll on a clinical trial of a FLT3 inhibitor. While the addition of sorafenib to IC has been reported to yield CR/CRp rates as high as 95% among newly diagnosed younger patients with *FLT3*-ITD$^+$ AML [71], two placebo-controlled trials of the addition of sorafenib to IC in unselected patients with previously untreated AML reached opposite conclusions. Serve et al. found no benefit of adding sorafenib to 7 + 3 induction chemotherapy followed by up to 2 cycles of intermediate-dose cytarabine consolidation among elderly patients with AML, including in the *FLT3*-ITD$^+$ subgroup, and higher toxicity during induction in the sorafenib arm [72]. In contrast, Rollig et al. reported significantly improved EFS, at the expense of increased toxicity, with the addition of sorafenib to 7 + 3 induction followed by 3 cycles of high-dose cytarabine (HiDAC) consolidation in a trial in younger subjects with AML that also used "maintenance" sorafenib for 12 months [73••]. Maintenance sorafenib may have a role in decreasing the risk of relapse after allogeneic HSCT for patients with R/R *FLT3*-ITD$^+$ AML [74].

Midostaurin

Midostaurin (formerly PKC412) is another multi-kinase inhibitor that inhibits FLT3 and is active in patients with both *FLT3*-mutated and wild-type AML [75, 76]. Midostaurin 75 mg three times daily induced a ≥50% reduction in circulating and/or bone marrow (BM) blast count in 14 of 20 patients (70%) with FLT3-mutated R/R AML or high-grade MDS who were not candidates for IC [75]. In a phase IIb trial, 95 patients with AML or MDS with either wild-type (n = 60) or mutated (n = 35) *FLT3* were randomized to receive oral midostaurin, 50 or 100 mg twice daily [76]. Seventy-one percent of patients with *FLT3*-mutant and 42% of those with *FLT3* wild-type disease achieved ≥50% reduction in circulating or BM blasts [76]. Midostaurin was well-tolerated, and there were no differences in toxicity or response rate according to the dose of midostaurin.

Preclinical studies showed synergism between hypomethylating agents and midostaurin against *FLT3*-ITD AML [77]. The combination of midostaurin and azacitidine was evaluated in a phase I/II study (n = 54) in patients with AML (95%) or MDS (5%) [78]. Although patients were eligible regardless of their mutation status, 74% of patients had a *FLT3* mutation (68% ITD alone, 6% with both ITD and D835). Seventy-six percent had received prior therapy (median, 2 prior regimens; 43% had received a HMA and 24% a FLT3 TKI). The ORR was 26% (CR and PR in 1 patient each, CRi in 6 patients and a morphologic leukemia-free state (MLFS) in 6). Among patients with *FLT3*-ITD not previously treated with FLT3 inhibitors, the ORR was 33%. Overall, 79% of patients had a reduction (median 68% reduction) in BM blast percentage from baseline, with 53% of patients experiencing a ≥50% reduction. The combination was well-tolerated, with some reduction (median 15%) in cardiac ejection fraction (EF) seen in 6 (11%) patients, all of whom had predisposing factors

[78]. A phase I study was also performed in 16 patients with AML (8 newly diagnosed, 8 relapsed, 2 with *FLT3*-ITD) of the combination of midostaurin and decitabine [77]. Based on the clinical activity observed in a phase IB trial evaluating the combination of midostaurin with 7 + 3 induction and HiDAC consolidation in younger, newly diagnosed patients with AML (80% CR rate with midostaurin 50 mg twice daily, 74% in *FLT3*-wild type and 92% in *FLT3*-mutated patients) [79], the phase III RATIFY (Cancer and Leukemia Group B 10603) trial (n = 717) was conducted and recently reported. All patients had *FLT3* mutations, and midostaurin (50 mg twice daily) or placebo was administered on days 8–22 during both 7 + 3 induction (daunorubicin, 60 mg/m^2 on days 1–3, and cytarabine, 200 mg/m^2 on days 1–7) and HiDAC consolidation (3 g/m^2 every 12 h on days 1, 3, and 5), as well as maintenance for a year [6••]. Despite similar CR rates in the two arms, the trial showed statistically significant benefits in both EFS and OS for patients treated with midostaurin across *FLT3* mutation subtypes. While a detailed discussion of this frontline study is outside the scope of this review, these results establish midostaurin in combination with standard chemotherapy as standard therapy for younger, newly diagnosed patients with *FLT3*-ITD AML [6••].

Quizartinib

Quizartinib (formerly AC220) is a potent FLT3 inhibitor with increased selectivity for this kinase [80]. Inhibition of other kinases such as c-KIT requires approximately tenfold higher concentrations in preclinical studies. In a FIH phase I study, 76 patients with R/R AML received quizartinib, irrespective of *FLT3* mutation status [81]. 23 (30%) patients responded, with 2 achieving CR, 3 CRp, 5 CRi and 13 PR. The ORR was 53% among patients with *FLT3*-ITD patients (one CR, one CRp, two CRis, five PRs), 14% among FLT3-ITD$^-$ negative patients and 22% among those with unknown FLT3 status. As with other FLT3 inhibitors, responses to single-agent quizartinib are typically transient. The DLT was QT prolongation, and the MTD was 200 mg/day. Drug-related AEs that occurred at a frequency of >10% included nausea (16%), prolonged QT interval (12%), vomiting (11%), and dysgeusia (11%); most were grade ≤2 [81]. In a large phase II study (n = 333), the safety and efficacy of quizartinib monotherapy was examined in two cohorts: older (≥60) patients with AML that had relapsed within a year or was refractory to first-line chemotherapy [82], and younger adults with AML R/R to second-line salvage chemotherapy or relapsed after HSCT [83]. In both cohorts, high rates of composite CR (CRc = CR + CRp + CRi) were observed for *FLT3*-ITD$^+$ patients (54% in the older cohort and 44% in the younger cohort); importantly, approximately one third of patients in the younger cohort (8% in the older cohort) were successfully bridged to HSCT [82, 83]. A comparison of the outcomes of 97 *FLT3*-ITD$^+$ patients from the younger cohort with those of 183 matched patients from the UK Medical Research Council/National Cancer Research Institute database suggested an improvement in OS in the patients receiving quizartinib [84]. In an effort to minimize the incidence of grade ≥3 QT prolongation with this agent (13 and 10%, respectively, in the older and younger cohorts above), 76 patients with R/R *FLT3*-ITD$^+$ AML were randomized 1:1 to receive either 30 or 60 mg daily of quizartinib in another phase II study. These reduced doses yielded response rates nearly identical to those reported with higher doses, with CRc of

approximately 50% in both arms, while the incidence of grade 3 QT prolongation decreased significantly to 3% at the lowest dose [85]. In this trial, 29% of patients treated at 30 mg/day and 37% of those receiving 60 mg/day (33% overall) were successfully bridged to HSCT. Quizartinib is now being investigated in a pivotal phase III trial versus salvage chemotherapy in subjects with *FLT3*-ITD AML refractory to prior therapy or in early first relapse (QUANTUM-R, NCT02039726), and a placebo-controlled, phase III study of quizartinib in combination with IC for previously untreated, younger (18–75) patients with *FLT3*-ITD AML (QuANTUM-First, NCT02668653). It is also being studied in a phase II study in combination with azacitidine or LDAC in older (≥60) patients with newly diagnosed, *FLT3*-ITD$^+$ myeloid leukemias or in patients of any age receiving first salvage treatment (NCT01892371). The phase I portion of this study enrolled patients with R/R AML, MDS, or chronic myelomonocytic leukemia (CMML) irrespective of *FLT3* mutation and salvage status. Results in the first 52 patients (12 in phase I, 40 in phase II; 38 in the azacitidine arm, 14 in the LDAC arm) included an ORR of 67% overall and 73% in patients with *FLT3*-ITD (n = 48) [86]. Like sorafenib, quizartinib has been studied in the post-transplant maintenance setting in patients with *FLT3*-ITD$^+$ AML and reported to reduce relapse rates in comparison to historical controls [87].

Crenolanib

The emergence of resistance-conferring point mutations in the kinase domain of FLT3, e.g., at the D835 residue, under the selective pressure of type II FLT3 inhibitors (e.g., sorafenib, quizartinib) occurs in approximately 20–25% of patients [88, 89••, 90]. Molecular docking studies have suggested that D835 mutations primarily confer resistance by stabilizing an active Asp-Phe-Gly in ("DFG-in") kinase conformation unfavorable to the binding of type II FLT3 TKIs, which target a "DFG-out" inactive conformation [65]. Crenolanib is a next-generation, type I, pan-FLT3 inhibitor with activity against TKD point mutations, including D835 and F691, that confer resistance to highly potent type II inhibitors like quizartinib [91•, 92•, 93•]. Crenolanib (100 mg three times daily or 200 mg/m^2/day in three divided doses) was tested in a phase II study in patients with R/R *FLT3*-mutated AML [94•]. Among 18 de novo AML patients who were FLT3-TKI-naive, the ORR was 50% (39% CRi + 11% PR) and median OS was 234 days. Thirty-six de novo AML patients had received prior FLT3 inhibitor therapy; the ORR in this cohort was 31% (17% CRi + 14% PR) and median OS 94 days. Crenolanib provided only transient benefit to patients with secondary *FLT3*-mutated AML (n = 11, median OS 55 days) [94•]. The safety of adding crenolanib, 100 mg three times daily, to both idarubicin/HiDAC (in the R/R setting) and 7 + 3 induction plus HiDAC consolidation (in the upfront setting) has been demonstrated [95, 96]. In the former study, 13 patients received idarubicin (12 mg/m^2/day for 3 days) plus HiDAC (1.5 g/m^2/day for 4 days (for 3 days if over 60 years of age), followed by crenolanib [95]. Responding patients could proceed to HSCT or receive consolidation with cytarabine (750 mg/m^2/day for 3 days) and idarubicin (8 mg/m^2/day for 2 days), followed by crenolanib. Patients could then continue on maintenance crenolanib unless they received an allograft. No DLTs were observed at any of the dose levels explored, and no dose reductions were required [95]. All non-hematologic AEs were grade 1 in severity. The ORR among 11 evaluable patients

was 36%. Among the six patients who had received ≤2 prior AML therapies, the ORR was 67% (all CR or CRi) and median OS was 259 days [95]. Several studies are ongoing investigating crenolanib in combination with IC in newly diagnosed (NCT02283177) and R/R (NCT02400281, NCT02298166) *FLT3*-mutated AML. NCT02400281 also contains an arm in which crenolanib is combined with azacitidine for patients with R/R *FLT3*-mutated AML. Additionally, single-agent crenolanib is being investigated as maintenance post-HSCT (NCT02400255).

Gilteretinib

Gilteretinib (formerly ASP-2215) is a highly selective FLT3 and AXL inhibitor that displays activity against both *FLT3*-ITD and D835 mutations, as well as the "gatekeeper" mutation F691 with minimal activity against wild-type *FLT3* [97]. In a FIH phase I/II trial (NCT02014558) in patients with R/R AML, the drug was found to be well-tolerated across a range of doses (20–300 mg), and antileukemic activity was seen in patients with *FLT3*-mutated AML treated at doses ≥80 mg daily [98]. Several dose levels were then expanded with subjects with *FLT3*-mutated AML. Out of a total of 252 patients with R/R AML in this trial (Chrysalis), 159 had *FLT3*-ITD, 13 had a D835 mutation, and 16 had both. Diarrhea (16%) and fatigue (15%) were the most common treatment-related AEs of any grade [99•]. Only 11 patients (<5%) had a maximum post-baseline-corrected QT interval >500 ms. Among 169 patients with *FLT3*-mutated AML who received doses ≥80 mg/day, the ORR was 52% (55% in *FLT3*-ITD$^+$ subjects, 17% in D835 mutant subjects, and 62% in subjects with both mutations). The ORR was higher (56%) in patients without prior TKI exposure than among those with prior TKI exposure (42%). Median OS was ~31 weeks [99•]. There are a number of ongoing studies of gilteritinib in *FLT3*-mutant AML, including a phase III, randomized trial which is investigating the efficacy of gilteretinib versus salvage chemotherapy in the R/R setting (NCT02421939). In newly diagnosed AML patients, gilteretinib is being investigated in combination with IC without regard to *FLT3* mutational status (NCT02236013, NCT02310321) and with azacitidine (NCT02752035) for those with mutant FLT3 not eligible for IC. Finally, for patients with FLT3 ITD AML, it is also being studied as maintenance therapy in first CR after induction and consolidation therapy (NCT02927262) and after HSCT (NCT02997202).

Other Targeted Therapies

Venetoclax

Venetoclax (Venclexta™) is a "BH3-mimetic" antagonist of the antiapoptotic protein, BCL-2, with high efficacy in relapsed/refractory chronic lymphocytic leukemia, including in patients with a 17p deletion, for whom it is currently approved [100••]. Venetoclax efficiently caused on-target cell death through induction of the mitochondrial pathway of apoptosis in AML cell lines, primary patient samples, and murine primary xenografts [101••]. In a phase II study in patients with R/R AML or deemed unfit for IC, venetoclax produced an ORR of 19% and demonstrated antileukemic activity in an additional 19% of patients [102•]. Common AEs included nausea, diarrhea and vomiting (all grades), FN, and hypokalemia (grade 3/4) [102•]. The FDA has granted venetoclax

"breakthrough" designation in AML. In a phase IB study in treatment-naive older (≥65) patients with cytogenetically intermediate or poor risk AML ineligible for IC, the combination of venetoclax with an HMA (azacitidine or decitabine) yielded an ORR of 76% [103••]. It was higher (82%) in patients with *IDH1/2* mutations, an abnormality that had been shown in preclinical studies to confer enhanced susceptibility to BCL-2 inhibition [104••]. The most common treatment-emergent AEs (TEAEs) were nausea (54%), FN (41%), diarrhea (44%), decreased appetite (33%), and peripheral edema (31%). FN (41%) and neutropenia (33%) were the most common grade 3/4 TEAEs, but no DLT were reported [103••]. A similar trial has been conducted with venetoclax in combination with LDAC (NCT02287233). The ORR was 75% in this 20-patient study, with most responses (14 of 15) being CR/CRi [105]. The 12-month OS was 74.7% for all patients and 86.7% among the responders. Febrile neutropenia (35%), hypertension (20%), and hypophosphatemia (20%) constituted the most common nonhematologic grade 3/4 AEs [105].

MDM2 (HDM2) Inhibitors

Pharmacologic inhibition of murine double minute 2 (MDM2, or its human homolog, HDM2), a physiologic antagonist of p53, activates p53 and induces apoptosis or cell cycle arrest in wild-type p53-expressing AML; however, this strategy is not useful against mutant p53 [106]. The level of pretreatment MDM2 protein expression in leukemic blasts appears to be an important biomarker for prediction of response to the MDM2 inhibitor, idasanutlin (RG7388), among patients with R/R AML [107]. A phase IB trial in 75 patients with R/R AML [108] explored the combination of idasanutlin once or twice a day for 5 days and cytarabine 1 g/m^2/day for 6 days. In the dose escalation phase (n = 23), patients could be R/R or untreated but not candidates for IC. The CR rate was 25%, the CRc rate was 29%, and when patients achieving MLFS were also considered, the rate was 33% [108]. The median DOR was 6.4 months [108]. A phase III placebo-controlled trial in patients with R/R AML in combination with cytarabine (NCT02545283) is currently underway. DS-3032b is another MDM2 inhibitor currently in a phase I trial (NCT02319369) in advanced hematological malignancies. The MTD was determined to be 160 mg daily on a 21/28 days schedule [109]. Reduction in bone marrow blasts by the end of cycle 1 (4 weeks) was seen in 15 of 38 patients with R/R AML or high-risk MDS. CR was achieved in two patients with AML, and one patient with MDS achieved a marrow CR with platelet improvement [109]. Ninety-three percent of patients experienced a grade ≥3 TEAE. The most common TEAEs (any grade) were nausea (73%), diarrhea (57%), vomiting (33%), fatigue (37%), anemia (33%), thrombocytopenia (33%), neutropenia (20%) hypotension (30%), hypokalemia (23%), and hypomagnesemia (20%) [109].

Immune Checkpoint Inhibitors

Immune checkpoints refer to a number of inhibitory pathways that are critical for maintaining self-tolerance and modulating physiological immune responses in order to minimize collateral tissue damage. These pathways are often co-opted by tumor cells to escape immune-mediated destruction [110]. The immune checkpoint pathways consisting of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and its ligands CD80 and CD86, as well as the

programmed cell death protein 1 (PD-1) and its ligands PD-L1 and PD-L2 have come to the forefront given that their blockade has been clinically efficacious in numerous different tumor types such as melanoma, lung cancer, head and neck cancer, Hodgkin's lymphoma, and urothelial and renal cell carcinoma (reviewed in [111]).

In a phase I/IB study, the anticytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody, ipilimumab, was administered to 28 patients with hematologic malignancies that had relapsed post-allogeneic HSCT [112••]. CRs occurred in four patients with extramedullary AML and one patient with MDS evolving into AML, all at a dose of 10 mg/kg (every 3 weeks for 4 doses, then every 12 weeks for up to 60 weeks) [112••]. Immune-related AEs were reported in six patients (21%; one of them grade 5), and graft-versus-host disease (GVHD) precluding further administration of ipilimumab in four (14%) [112••]. There is preclinical evidence for upregulation of CTLA-4 and both PD-1 and its ligands, PD-L1 and PD-L2, on T-cells and neoplastic cells by azacitidine in AML and MDS [113, 114]. Based on this, the combination of azacitidine and the anti-PD-1 monoclonal antibody, nivolumab, is under investigation in patients with R/R AML and older patients (>65) with newly diagnosed AML (NCT02397720). Preliminary results on the first 51 patients, all with R/R AML, enrolled to this trial were recently presented [115•]. Of 35 response-evaluable patients, 6 (17%) obtained CR/CRi, 5 (14%) had hematologic improvement (HI), 9 (26%) had ≥50% BM blast reduction, and 3 (9%) had SD for >6 months. The median OS of 9.3 months observed in this study compared favorably to that reported for historical patients treated with azacitidine-based salvage protocols at the MD Anderson Cancer Center (4.1 months). Immune-related AEs (grade 3/4 in 14% and grade 2 in 12%) responded rapidly to steroids in 12 of 13 episodes and these patients were successfully re-challenged with nivolumab, but one patient died from grade 4 pneumonitis/epiglottitis [115•]. There is also preclinical evidence that blockade of the inhibitory killer-cell immunoglobulin receptors (KIRs), which negatively regulate NK cell-mediated killing of human leukocyte antigen (HLA) class I-expressing tumors, may have antileukemic effects [116]. Twenty-one patients with relapsed AML have been treated with the combination of the anti-KIR monoclonal antibody lirilumab and azacitidine in an ongoing phase IB/II study [117]. No DLTs were observed and lirilumab 3 mg/kg was established as the RP2D in combination with standard dose azacitidine. Of 12 patients evaluable for response, 1 achieved CR and 1 CRi, 2 had ≥50% BM blast reduction, and 2 HI lasting >6 months. Immune-related AEs occurred in three (14%) patients, all of whom responded rapidly to steroids and were re-challenged safely with lirilumab [117].

Rational Combinations

While targeted approaches to specific molecular abnormalities are attractive, AML is a molecularly complex disease with multiple aberrant pathways involved. It is therefore unlikely that blockade of any one specific pathway will lead to prolonged remissions and cures in more than a fraction of the patient population. Thus, combination strategies are likely to be the required to improve outcome. To date, most of the combinations have used a targeted agent

combined with standard agents such as anthracyclines, cytarabine, or hypomethylating agents. Rationally designed combinations that will more specifically and directly alter the biology of the disease are required. The number of such rational combinations possible is virtually limitless. The discussion that follows will focus on some promising approaches that have been shown to be synergistic in laboratory studies, some of which are being pursued in clinical trials (Table 2). This presentation should be considering only a sampling of what is to come rather than an exhaustive discussion of such approaches or a declaration of partiality for specific combinations.

As noted previously, *IDH1/2* mutations induce BCL-2 dependence in AML [104••]. The production by mutant IDH enzymes of 2-HG instead of the normal metabolite, α-KG, creates a dependence of the *IDH*-mutated cells on glutamine as their primary source of α-KG, which can be exploited therapeutically by pharmacologic inhibitors of glutaminase. Thus, *IDH*-mutated AML may be particularly sensitive to glutaminase inhibition [118•]. Glutamine levels also control mitochondrial oxidative phosphorylation (OXPHOS) in AML cells, and glutaminase inhibitors, e.g., CB-839, can reduce OXPHOS, leading to leukemic cell proliferation arrest and apoptosis [119•]. Inhibition of glutaminase by CB-839 activates mitochondrial apoptosis and sensitizes leukemic cells to venetoclax [119•]. These preclinical observations provide a compelling rationale for combining glutaminase inhibitors with BCL-2 antagonists in the clinic.

The major mediator of resistance to BCL-2/-xL inhibition in AML is the antiapoptotic protein, MCL-1 [120]. There is, thus, significant interest in combining venetoclax with drugs that downregulate MCL-1, such as mitogen-activated protein kinase (MEK) inhibitors [121] or sorafenib [122]. Synergism has also been demonstrated between venetoclax and idasanutlin, both in vitro and in vivo [123]. These findings form the basis of an ongoing phase I/II clinical trial (NCT02670044) investigating the combination of venetoclax with cobimetinib, a MEK inhibitor, and with idasanutlin in older patients (≥60) with R/R AML who are not eligible for IC. While MEK inhibitors have limited single-agent activity in R/R AML (with perhaps some preference for patients with *RAS* mutations) [124], synergistic induction of apoptosis is seen in AML cells with combined blockade of MEK and MDM2 [125]. FLT3 signals downstream to members of the BCL-2 family, and synergistic induction of cell death in AML cell lines by the combination of sorafenib and the BCL-2/-xL inhibitor, ABT-737, has been shown [126]. Accordingly, combining sorafenib with venetoclax might improve the outcome observed with FLT3 inhibitors alone in patients with *FLT3*-ITD, and may increase the observed responses to FLT3 inhibitors such as quizartinib and gilteritinib seen among patients with wild-type *FLT3*. MDM2 inhibitors also potentiate apoptosis induction by FLT3 inhibitors through multiple mechanisms [127, 128]. Similar to MDM2 inhibition, another therapeutic strategy to stabilize wild-type p53 is pharmacologic inhibition of chromosomal region maintenance 1 (CRM1), a nuclear export receptor, blockade of which results in nuclear retention of p53 [129]. Selective inhibitors of nuclear export (SINEs) synergize with MDM2 inhibitors in apoptosis induction of patient-derived AML cells [129]. NCT02530476 is an ongoing phase I/II study of sorafenib plus the SINE, selinexor (KPT-330), in patients with R/R *FLT3*-mutated AML. Studies of selinexor in combination with quizartinib and with MDM2 inhibitors in R/R AML are planned. Sequential treatment of AML

Table 2. Selected rational combinations in early phase trials for relapsed/refractory AML

Combination	Mechanism/rationale	Clinicaltrials.gov identifier
Venetoclax (BCL-2 inhibitor) + Idasanutlin (MDM2 antagonist)	Venetoclax inhibits anti-apoptotic BCL-2. Idasanutlin antagonizes MDM2 and activates p53, thereby enhancing the proapoptotic effects of venetoclax.	NCT02670044
Venetoclax (BCL-2 inhibitor) + Cobimetinib (MEK inhibitor)	Venetoclax inhibits antiapoptotic BCL-2, but not MCL-1. Cobimetinib, by blocking the MAPK pathway, downregulates MCL-1. MCL-1 is critical to the development and maintenance of AML.	NCT02670044
Sorafenib (FLT3 inhibitor) + Selinexor (SINE)	CRM1 (XPO1) mediates nuclear export of proteins, including p53. CRM1 expression is increased in FLT3-ITD$^+$ AML and correlates with worse outcomes. SINEs inhibit CRM1 and induce blast differentiation, besides down-regulating FLT3 and c-KIT. Sorafenib inhibits FLT3-ITD. Combination treatment has synergistic/additive pro-apoptotic effects in FLT3-mutant AML cells and suppresses the MAPK and Akt pathways.	NCT02530476
Fludarabine, Cytarabine (chemotherapy) + prexasertib (Chk1 inhibitor)	Nucleoside analogs cause DNA damage. This activates Chk1, which then causes cell cycle arrest, stabilizes stalled replication forks, activates DNA repair, and suppresses apoptosis. Chk1 inhibitors increase cytotoxicity of DNA-damaging chemotherapy by inducing cell death through "mitotic catastrophe."	NCT02649764
Belinostat (HDACI) + AZD1775 (Wee1 inhibitor)	HDACIs induce DNA damage and inhibit DNA repair. HDACIs also downregulate Chk1, thus abrogating its activation in response to Wee1 inhibition. Together, Wee1 inhibitors and HDACIs interact reciprocally to disrupt both the G1/S and G2/M cell cycle checkpoints.	NCT02381548
Idarubicin, Cytarabine + LY2510924 (CXCR4 antagonist)	Inhibition of the CXCR4-CXCL12 interaction blocks homing of AML blasts to protective bone marrow microenvironmental niches and makes them more susceptible to killing by chemotherapy.	NCT02652871
Azacitidine (HMA) + Pevonedistat (NAE Inhibitor)	Pevonedistat inhibits NAE, a critical step in the neddylation process, leading to impaired CRL function and causing accumulation of many CRL substrates including RRM2, a mediator of resistance to many cytotoxic anticancer agents. Azacitidine antagonizes RRM2.	NCT02610777
Azacitidine (HMA) + Nivolumab (anti-PD1 antibody)	Azacitidine upregulates CTLA-4, PD-1, PD-L1, and PD-L2. PD-1/PD-L1 interaction contributes to T-cell inactivation, decreased proliferation and effector function, and apoptosis. Nivolumab interferes with the PD-1/PD-L1 interaction.	NCT02397720

BCL-2 B-cell lymphoma 2, *MCL-1* myeloid cell leukemia 1, *MAPK* mitogen-activated protein kinase, *MEK* MAPK kinase, *FLT3* fms-like tyrosine kinase 3, *ITD* internal tandem duplication, *CRL* cullin-RING ligase, *HDACI* histone deacetylase inhibitor, *HMA* hypomethylating agent, *NAE* NEDD8-activating enzyme, *SINE* selective inhibitor of nuclear export, *PD-1* programmed death-1, *PD-L1* programmed death ligand-1, *PD-L2* programmed death ligand-2, *RRM2* ribonucleotide reductase regulatory subunit M2, *CTLA-4* cytotoxic T-lymphocyte antigen 4, *Chk1* checkpoint kinase 1, *CXCR4* C-X-C chemokine receptor type 4, *CXCL12* C-X-C motif chemokine 12, *AML* acute myeloid leukemia

blasts with decitabine followed by selinexor (decitabine "priming") enhances the antileukemic effects of selinexor, possibly through re-expression of tumor suppressor proteins, e.g., CDKN1A and FOXO3A, that are epigenetically silenced by DNA methylation [130]. These preclinical findings were translated to a phase I clinical trial in 24 patients with R/R (n = 19) or previously untreated (n = 5, age ≥ 60, unfit) AML (NCT02093403) [131]. The rate of CR/CRi/marrow CR was 80% in older, untreated and 21% in R/R AML patients. However, selinexor has considerable toxicities, which were somewhat ameliorated by twice weekly, flat (60 mg) dosing [131].

Pevonedistat (MLN4924) is a first-in-class inhibitor of protein neddylation that is active against AML cell lines, primary patient specimens, and xenograft models [132], and also exhibits modest single-agent efficacy in patients with R/R AML [133•]. Pevonedistat synergizes with azacitidine in AML cells [134] and is currently being evaluated in combination with azacitidine (versus azacitidine alone) in a randomized, phase II clinical trial in patients with low blast count AML, MDS, or CMML (NCT02610777). In a separate, dose-escalation study in treatment-naive patients with AML ≥60 years of age, the MTD of the combination was found to be 20 mg/m^2/day of pevonedistat, administered on days 1, 3, and 5, along with 75 mg/m^2/day of azacitidine, administered on days 1–5, 8, and 9 in 4-week cycles [135]. The ORR was 60% among 52 evaluable patients (18 CR + 5 CRi + 8 PR) with a median DOR of 8.3 months; 6-month survival was 52% after a median follow-up of 16.4 months [135]. A clinical trial of pevonedistat in combination with the HDAC inhibitor, belinostat, in R/R AML is planned based on in vitro and in vivo evidence of synergism [136].

Cell cycle checkpoint dysfunction is universal in neoplastic cells, and a synthetic lethal therapeutic strategy that exploits this phenomenon is the combination of checkpoint kinase (e.g., Chk1, Wee1) inhibitors with DNA-damaging chemotherapy to trigger cell death by "mitotic catastrophe" [137]. The development of some Chk1 inhibitors, e.g., MK-8776, has been discontinued [138], but newer, potentially more potent ones, such as LY2606368, are in clinical trials in R/R AML in combination with IC (NCT02649764). There also exists strong preclinical rationale to combine inhibitors of Chk1 or Wee1 with HDAC inhibitors [139, 140], and a phase I clinical trial, primarily in R/R AML patients, of the combination of the Wee1 inhibitor, MK-1775, and belinostat is ongoing (NCT02381548).

Conclusion

After a long drought of new drug approvals in AML, regulatory approval of several new agents is expected in 2017. The OS benefit seen with some of these agents has brought renewed hope to investigators, physicians and patients. A comprehensive discussion of all the drugs in development for R/R AML is beyond the scope of this review. Table 3 lists some additional agents not covered in the text that are currently in clinical trials for patients with R/R AML. There are yet other agents, such as the histone deacetylase inhibitor pracinostat [141•], and the smoothened (Hedgehog pathway) inhibitor glasdegib [142••], which have shown great promise in previously untreated patients and are expected to be active in salvage settings as well. It is expected that with our improved understanding of the biology of AML and our ability to

Table 3. Miscellaneous agents currently in early phase clinical development for relapsed/refractory AML

Agent	Agent class	Phase of development	Clinicaltrials.gov identifier
Ibrutinib	BTK inhibitor	II	NCT02351037, NCT02635074
Ulixertinib (BVD-523, VRT752271)	ERK1/2 inhibitor	I/II	NCT02296242
BGB324	Axl inhibitor	I	NCT02488408
INCB053914	pan-PIM kinase inhibitor	I/II	NCT02587598
ONC201 (TIC10)	TRAIL pathway-inducer, triggers p53-independent apoptosis through ATF4 induction and atypical integrated stress response	I/II	NCT02392572
IACS-010759	Oxidative phosphorylation inhibitor (selectively inhibits complex I of the electron transport chain)	I	NCT02882321
BP-100-1.01	Liposomal Grb-2 (adaptor protein) antisense oligonucleotide	I	NCT01159028
FF-10501-01	Inosine 5′-monophosphate dehydrogenase (IMPDH) inhibitor	I/II	NCT02193958
APTO-253 (LOR-253, LT-253)	Induces expression of tumor suppressor transcription factor KLF4	I	NCT02267863
ADCT-301	CD25-directed antibody-drug conjugate (toxin: pyrrolobenzodiazepine)	I	NCT02588092
AGS67E	CD37-directed antibody-drug conjugate (toxin: monomethyl Auristatin E)	I	NCT02610062

BTK Bruton's tyrosine kinase, *ERK* extracellular signal-regulated kinase, *TRAIL* tumor necrosis factor alpha-related apoptosis inducing ligand, *ATF4* activating transcription factor 4, *KLF4* Kruppel-like factor 4

translate this knowledge into effective therapies, the outcome of patients with AML will improve in a more definitive way in the coming years. Challenges in the definition of relevant endpoints, adequate clinical trial design, access to ever more costly drugs, and others still have to be addressed to make this reality more universal.

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Compliance with Ethical Standards

Conflict of Interest

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Pankit Vachhani declares that he has no conflict of interest.
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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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