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Acute myeloid leukemia: potential for new therapeutic approaches targeting mRNA translation pathways

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SUMMARY

Despite advances in molecular research related to acute myeloid leukemia (AML) and a better understanding of the mechanisms of leukemogenesis and pathophysiology of the disease, the pharmacological agents used in the treatment of AML have remained essentially unchanged for the last three decades. Advances in the clinical management of AML patients have been achieved by defining better molecular prognostic markers, but there remains a need for new targeted drugs that disrupt non-overlapping pathways in leukemia cells. The mTOR cellular cascade is critical for cell metabolism, growth, proliferation and survival. Extensive preclinical work suggests that targeting mTOR may provide a powerful approach to block AML precursor cells, while other findings suggest enhanced antileukemic effects by combining mTOR inhibitors with traditional chemotherapy. Such combinations may increase antileukemic responses further, offering unique ways to overcome leukemic cell resistance and to eliminate primitive leukemic precursors.

Treatment of acute myeloid leukemia

Anthracycline given in combination with cytarabine has long been considered the standard treatment for adults with newly diagnosed acute myeloid leukemia (AML) who are fit enough for intensive chemotherapy. Clinical trials have been conducted over the last few decades across cooperative groups, and no regimen has proven superior [1–3]. Recent areas of clinical interest have been optimization of anthracycline and cytarabine doses, appropriate regimens for those who are not deemed fit for standard intensive chemotherapy, and targeting molecular aberrations important in leukemogenesis. Despite substantial efforts and emerging advances, the standard therapy for the treatment of adults with newly diagnosed AML has not changed significantly over the last few decades. A major focus of recent clinical leukemia research has been identifying differences in response to treatment with different anthracyclines, and determining the appropriate dose of anthracyclines used in induction. The EORTC and GIMEMA groups induced adults with newly diagnosed AML with a backbone of cytarabine and etoposide and randomized them to receive daunorubicin 50 mg/m² or mitoxantrone 12 mg/m² or idarubicin 10 mg/m² [4]. While the complete

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remission (CR) rates were similar in the three groups, the 5-year disease-free survival was 29% in the daunorubicin arm compared with 37% in each of the mitoxantrone and idarubicin arms [4]. However, a limitation is it is not clear if the doses of *anthracyclines* studied were equivalent.

Two studies were conducted comparing daunorubicin 45 mg/m² to daunorubicin 90 mg/m²; one in younger adults and one in older adults. In younger adults; the higher dose of daunorubicin led to a higher CR rate (70.6 vs 57.3%) and a significant improvement in overall survival (OS) of 23.7 vs 15.7 months [5]. In adults 60 years and older, anthracycline dose intensification led to an improvement in CR rate, but no difference in OS. However, for the subgroup of those 60–65 years of age, patients who received the higher dose of anthracycline had an improvement in OS of 38% compared with 23% [6]. Based on these studies; 45 mg/m² is no longer considered an appropriate dose of daunorubicin, and doses of 60 or 90 mg/m² of daunorubicin or 12 mg/m² of idarubicin in combination with standard dose of cytarabine are recommended options for induction therapy for newly diagnosed AML [7]. Standard practice for the treatment of AML has been the inclusion of high-dose cytarabine in induction or consolidation for adults deemed fit enough to tolerate the toxicities. However, results of recent studies question whether high-dose cytarabine (2000–3000 mg/m²) is required for the treatment of AML, or if lower doses (i.e., 1000 mg/m²) may be sufficient and associated with decreased toxicities [8]. It is currently recommended that older adults who are considered fit for intensive chemotherapy be treated in the context of a well-designed clinical trial. In the absence of a clinical trial, the recommendation is for fit older adults to be treated with standard induction chemotherapy. The expectation is a CR of 50–60% and OS of less than 30% at 2 years [6]. The Eastern Cooperative Oncology Group is currently conducting a randomized Phase III study assessing the role of clofarabine compared with standard daunorubicin/cytarabine for induction of eligible patients.

A number of studies have been conducted in older adults who are not candidates for intensive chemotherapy. The Medical Research Council has dedicated a series of studies to these patients. Using their ‘pick a winner’ approach they have used low-dose Ara-C (LDAC) as their standard arm. Despite many patients studied on many different trials, they have not found a benefit with the addition of any additional agents to this backbone. This group consistently finds a CR rate of 14–18% and OS of 4–6 months [9,10]. Burnett *et al.* recently presented results from AML16 comparing LDAC to clofarabine. In the Phase II study, clofarabine treatment led to a higher CR rate allowing the Medical Research Council to proceed to the randomized Phase III trial. Unfortunately, in the Phase III study there was no difference in OS in the two arms [11].

Owing to both the inconvenience of subcutaneous administration of LDAC and the low CR and OS rates, studies to determine the role of hypomethylating agents have been conducted based on their approval for the treatment of myelodysplastic syndrome (MDS). In fact, in three sequential trials performed by Cancer and Leukemia Group B trials with azacitidine for the treatment of MDS, a small group of patients with AML were included (these were patients enrolled on these trials as refractory anemia with excess blasts in transformation [RAEB-T] and were reclassified as AML by the WHO classification and separately analyzed). The median survival time for the 27 patients with AML randomized to azacitidine was 19.3 months vs 12.9 months for the 25 patients who were randomized to the observation arm [12]. In addition, a Phase III randomized study was conducted in adults with high-risk MDS comparing azacitidine to conventional care (including best-supportive care, low-dose cytarabine or intensive chemotherapy). When these patients were reclassified under the WHO classification, approximately a third had AML (with blast percentage of 20–30%). The median OS for AML patients treated with azacitidine is 24.5 months vs 16.0 months for the conventional care group [13].

Likewise, results of a compassionate-use protocol of 5-azacitidine for 82 patients with AML in Italy was reported in 2012. In the 35 patients who had not previously been treated for AML, the CR/incomplete blood count recovery rate was 31% [14]. A similar study of patients who were considered medically unfit or resistant to chemotherapy was conducted in Germany. For the 20 adults with newly diagnosed AML, the CR rate was 10% [15].

In a recent multicenter Phase II study, decitabine was administered to patients older than 60 years with previously untreated AML. The CR rate was 24% with a median OS of 7.7 months, and a 30-day mortality rate of 7% [16]. A randomized Phase III multicenter trial compared decitabine with supportive care or LDAC in elderly patients (aged >65 years) with newly diagnosed AML [17]. The CR rate was 17.8% and the OS was 7.7 months in the decitabine arm. These results were reviewed by Drugs Advisory Committee and decitabine was not approved by the US FDA for the treatment of AML, as the OS in the LDAC/supportive care arm was 5.0 months with a CR rate of 7.8% and deemed not substantially different than decitabine [17]. Thus, there is a clear need to improve upon the treatment for adults with AML, especially those who are not candidates for induction chemotherapy.

Potential targets based on increasing understanding of leukemogenesis

A recent success in the study of leukemia has been an improvement in the cytogenetic and molecular prognostication. Assessment of cytogenetics provides critical prognostic information in patients with newly diagnosed AML. However, the most common cytogenetic finding in AML is a normal karyotype. These patients have variable prognosis, and it is now recognized that there are a number of molecular mutations, along with epigenetic and miRNA abnormalities that also affect prognosis. Recognition of the roles of these aberrations in leukemogenesis has allowed the study of targeted therapies for specific subtypes of AML. Three notable examples of molecular mutations that are of current interest as novel targets in AML therapy are FLT3, cKit and MLL.

FLT3

FLT3 is a receptor tyrosine kinase mutated in approximately 15–30% of adults with AML [18,19]. The internal tandem duplication is associated with AML that is rapidly proliferative and associated with a lower OS compared with normal karyotype AML. A series of FLT3 inhibitors have been developed and studied in clinical trials with relapsed/refractory AML. These agents include lestaurtinib, midostaurin and quizartinib. Quizartinib has been of particular interest as it appears to be among the most potent and selective of the drugs that inhibit the FLT3-ITD reported to date [20,21].

The results of the Phase II trial of quizartinib for the treatment of relapsed/refractory AML were recently reported, and for adults 60 years of age or older with refractory disease or disease that had relapsed within a year, a response rate of approximately 50% was reported [22]. Similar results were reported at this meeting for younger adults [23]. Further studies with quizartinib are ongoing, with lower doses to decrease toxicities and in combination with chemotherapy for newly diagnosed patients.

Potential future developments of FLT3 inhibitors include combination with induction chemotherapy, combination with less intensive agents, and maintenance strategies. Furthermore, there are additional FLT3 inhibitors in development, including agents that may have more potent activity against the D835 mutation that can occur *de novo* or as a resistance mechanism in those with the FLT3-ITD where the disease stops responding to FLT3-ITD inhibitors [24]. Targeting FLT3 has become an important clinical translational treatment strategy and it is now recognized that the use of FLT3 inhibitors may improve long-term outcome of patients with relapsed and refractory FLT3-ITD mutated AML [25].

In summary, FLT3 inhibitors are quite promising and a prime example of how the recognition of a mutation associated with leukemogenesis and poor prognosis has the potential to be targeted as a single agent or in combination therapy.

MLL

Acute leukemias with rearrangement of the *MLL* gene are associated with a poor prognosis [26]. MLL disease is characterized by a chromosomal translocation involving the *MLL* gene on chromosome 11q23 [27,28]. Approximately 10% of AML in adults have rearrangement of the *MLL* gene [26]. DOT1L, a histone methyltransferase protein, is known to be a driver of cell proliferation in *MLL*-rearranged leukemia. DOT1L is the only enzyme thus far identified that catalyzes the methylation of histone 3 at lysine 79 (H3K79) [29,30]. This is important, as it has been recognized that *MLL*-rearranged leukemia cells are known to have high levels of H3K79 methylation on the *MLL*-fusion target genes. There are now DOT1L inhibitors in very early development being studied in *MLL*-rearranged leukemias [31].

mTOR signaling pathway & its significance in cancer

The mTOR cellular pathway involves a network of kinases and other signaling elements that act upstream and downstream of mTOR to regulate and optimize its kinase activity and functional consequences, and to control signals of importance for the initiation of mRNA translation in normal and malignant cells [32–41]. As the function of this signaling pathway is central for the control of important cellular functions in living organisms, its dysregulation in humans has been associated with disease development and progression [42]. These include metabolic disorders such as diabetes and metabolic syndrome; coronary restenosis and other syndromes associated with inflammation; and neuropsychiatric disorders, such as neurodegenerative disease and depression (reviewed in [42]). Importantly, dysregulation of the mTOR pathway and/or constitutive activation of this cascade has been shown in several neoplasms, including both solid tumors and hematological malignancies [34,37–40,42,43].

Because of the known involvement of mTOR pathways in carcinogenesis, efforts to target the pathway in cases in which there is constitutive activation/dysregulation have led to the development of pharmacological agents with mTOR inhibitory activities and extensive clinical efforts for the treatment of different malignancies [43–55]. Currently, several mTOR inhibitors have been approved in the USA for the treatment of several malignant tumors. Everolimus (RAD001) is approved, among other indications, for the treatment of advanced renal cell carcinoma, progressive advanced neuroendocrine tumors of pancreatic origin and advanced hormone receptor-positive breast cancer in postmenopausal women (together with exemestane). In all these malignancies this mTOR inhibitor has shown significant clinical activity [56–58]. Temsirolimus (CCI-779) has also demonstrated significant activity in renal cell carcinoma [59], and this agent is also approved by the US FDA for the treatment of patients suffering from this malignancy.

Targets of mTOR inhibitors

One major class of mTOR inhibitors includes rapamycin and related drugs, called rapalogs [60]. As mentioned above, two different rapalogs, temsirolimus and everolimus, are already approved by the FDA for the treatment of a limited number of malignancies; rapamycin (sirolimus) is only FDA approved for use as an immunosuppressant in solid-organ transplantation [61]. Rapamycin and rapalogs, including the related ridaforolimus (deferolimus) [60], act as structural inhibitors, specifically blocking mTORC1 complexes, which are composed of the mTOR kinase, Raptor, mLST8, Deptor and PRAS40 [38,40]. It should be noted that mTORC1 complexes are heavily involved in the regulation of protein synthesis in mammals, as they are the mTOR complexes that engage the cascades and

signals that control initiation of mRNA translation, such as the S6K/rpS6 and 4E-BP1 effector pathways [38–40]. On the other hand, rapalogs do not block activation of mTORC2 complexes, which are composed of mTOR, Rictor, mLST8, Sin1, Deptor and Protor [38,40]. These complexes regulate prosurvival cellular conduits, primarily because of their ability to phosphorylate AKT on serine 473 (Ser473), resulting in generation of downstream antiapoptotic signals [38–40]. A new generation of mTOR inhibitors that act by targeting the catalytic domain of mTOR have been developed in recent years, and some of them are currently in clinical trials [43,62]. By blocking the catalytic activity of mTOR, such pharmacological agents have the capacity to block both mTORC1 and mTORC2 complexes, and thus suppress engagement of antiapoptotic pathways downstream of mTOR [43,62]. It should be noted that at this point no specific inhibitors of mTORC2 have been developed, or at least have been reported. Although the *in vitro* and *in vivo* data available so far indicate superior antitumor effects for dual mTORC1/mTORC2 catalytic inhibitors, one cannot exclude with certainty the theoretical possibility that single mTORC2 inhibitors could be more potent in terms of inducing neoplastic cell death than dual mTORC1/mTORC2 inhibitors. This is because there are several negative feedback signaling cascades that are engaged/activated during inhibition of mTORC1, including the S6K/IRS1 feedback loop [63,64] and the Grb10/IR feedback loop [65,66]. Although some of the prosurvival outcomes of such mTORC1-dependent feedback loops can be abrogated by catalytically blocking mTOR, resulting in functional suppression of mTORC2 and inhibition of Ser473–AKT-generated signals, other yet undefined loops may exist that cannot be inhibited by catalytic mTOR inhibitors.

mTOR targeting using rapalogs in AML

As with several other solid tumors and hematological malignancies, there has been previous evidence that the mTOR pathway is dysregulated in AML [46,67,68]. Notably, mTOR has been shown to be activated by the FLT3 kinase and to be constitutively activated in FLT3-mutated AML cells [69]. The identification of mTOR as a potential therapeutic target in AML led to extensive *in vitro* studies that established inhibitory effects by blocking activation of the pathway using rapamycin [70,71] or agents that block upstream effectors such as the PI3 kinase [72,73] or agents that block both the PI3 kinase and mTOR [74,75]. There is also evidence that combinations of rapamycin or everolimus with several other agents with antileukemic properties, including chemotherapeutic agents, potentiate their effects *in vitro* [76–83]. The demonstration of antileukemic properties by mTORC1 inhibitors against AML cells *in vitro* has led to the development of clinical trials for the treatment of patients with AML that demonstrated that rapamycin has antileukemic properties *in vivo* [70,84]. In addition, combination trials of rapamycin [85] or temsirolimus [86] with chemotherapy have been performed and these demonstrated efficacy. A pharmacodynamic approach to monitor mTOR activity in AML patients during mTOR inhibition *in vivo* by determining levels of phosphorylated rpS6 using flow cytometry has also been developed [87]. Altogether, studies with mTORC1 inhibitors have provided evidence for some clinical activity in AML and have raised the prospect that studies with second-generation mTOR inhibitors that block the catalytic domain of mTOR may result in better outcomes.

Second-generation mTOR inhibitors & future directions

The emergence of catalytic inhibitors of mTOR has led to extensive preclinical efforts to assess their efficacy in AML [46,62,88]. The dual catalytic mTORC1/mTORC2 inhibitor, OSI-027, has been shown to exhibit potent antileukemic responses *in vitro* and to suppress primitive leukemic precursors from AML patients [89]. In addition, this dual mTORC1/mTORC2 inhibitor was shown to enhance the antileukemic effects of cytarabine *in vitro*

[89]. Another dual mTORC1/mTORC2 inhibitor, AZD8055, was also shown to have antileukemic effects against AML progenitors, and demonstrated efficacy in AML transplanted mice *in vivo* [90]. Also, PP242 was recently shown to induce apoptosis of AML cells in an experimental system resembling the bone marrow microenvironment [91]. As in preclinical models, catalytic dual mTORC1/mTORC2 inhibitors exhibit much more potent antileukemic effects than rapamycin; it is possible that such agents may prove to be more efficacious for the treatment of AML patients. Thus, clinical trials using dual catalytic mTOR inhibitors alone or in combinations for the treatment of AML would be of interest.

Conclusion & future perspective

Although our understanding of the molecular pathogenesis of AML has improved over the last few decades, this has not yet been translated to substantial advances in the treatment of adults with newly diagnosed AML. Many molecular markers are still investigational and are being evaluated in clinical trials. However, there are promising therapies under development, including FLT3 and DOT1L inhibitors. Molecular pathogenesis is now being used to inform both clinical trial design and appropriate use of targeted therapies for patients with both refractory and newly diagnosed AML. In the future, we expect that this area of clinical research will expand further. In addition, markers of mRNA translation pathways may prove to be useful, and efforts in that direction are warranted.

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References

Papers of special note have been highlighted as:

■ of interest

■ ■ of considerable interest

1. Preisler H, Davis RB, Kirshner J, et al. Comparison of three remission induction regimens and two postinduction strategies for the treatment of acute nonlymphocytic leukemia: a Cancer and Leukemia Group B study. *Blood*. 1987; 69(5):1441–1449. [PubMed: 3552076]
2. Schiller G, Gajewski J, Nimer S, et al. A randomized study of intermediate versus conventional-dose cytarabine as intensive induction for acute myelogenous leukaemia. *Br. J. Haematol*. 1992; 81(2):170–177. [PubMed: 1643014]
3. Weick JK, Kopecky KJ, Appelbaum FR, et al. A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group study. *Blood*. 1996; 88(8):2841–2851. [PubMed: 8874180]
4. Mandelli F, Vignetti M, Suci S, et al. Daunorubicin versus mitoxantrone versus idarubicin as induction and consolidation chemotherapy for adults with acute myeloid leukemia: the EORTC and GIMEMA Groups Study AML-10. *J. Clin. Oncol*. 2009; 27(32):5397–5403. [PubMed: 19826132]
5. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. *N. Engl. J. Med*. 2009; 361(13):1249–1259. [PubMed: 19776406] ■ ■ Examined the benefits of high-dose daunorubicin for younger adults with acute myeloid leukemia (AML).
6. Löwenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. *N. Engl. J. Med*. 2009; 361(13):1235–1248. [PubMed: 19776405] ■ Reports the results of studies using higher-dose daunorubicin in older adults with AML.
7. O'Donnell MR, Abboud CN, Altman J, et al. Acute myeloid leukemia. *J. Natl Compr. Canc. Netw*. 2012; 10(8):984–1021. [PubMed: 22878824]

8. Löwenberg B. Sense and nonsense of high-dose cytarabine for acute myeloid leukemia. *Blood*. 2013; 121(1):26–28. [PubMed: 23287624]
9. Burnett AK, Hills RK, Hunter A, et al. The addition of arsenic trioxide to low-dose Ara-C in older patients with AML does not improve outcome. *Leukemia*. 2011; 25(7):1122–1127. [PubMed: 21475252]
10. Burnett AK, Milligan D, Prentice AG, et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-*trans* retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. *Cancer*. 2007; 109(6):1114–1124. [PubMed: 17315155]
11. Burnett, MD.; Russell, NH.; McMullin, MF., et al. A randomised comparison of clofarabine versus low dose ara-C as first line treatment for older patients with AML. Presented at: American Society of Hematology Annual Meeting; 8–11 December 2012; Atlanta, GA, USA.
12. Silverman LR, McKenzie DR, Peterson BL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *J. Clin. Oncol.* 2006; 24(24):3895–3903. [PubMed: 16921040] ■ Summarizes a series of trials with azacitidine in patients with myelodysplastic syndrome and low-blast-count AML.
13. Fenaux P, Mufti GJ, Hellström-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J. Clin. Oncol.* 2010; 28(4):562–569. [PubMed: 20026804]
14. Maurillo L, Venditti A, Spagnoli A, et al. Azacitidine for the treatment of patients with acute myeloid leukemia: report of 82 patients enrolled in an Italian Compassionate Program. *Cancer*. 2012; 118(4):1014–1022. [PubMed: 21761399]
15. Al-Ali HK, Jaekel N, Junghanss C, et al. Azacitidine in patients with acute myeloid leukemia medically unfit for or resistant to chemotherapy: a multicenter Phase I/II study. *Leuk. Lymphoma*. 2012; 53(1):110–117. [PubMed: 21767242]
16. Cashen AF, Schiller GJ, O'Donnell MR, DiPersio JF. Multicenter, Phase II study of decitabine for the first-line treatment of older patients with acute myeloid leukemia. *J. Clin. Oncol.* 2010; 28(4):556–561. [PubMed: 20026803]
17. Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open-label, Phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *J. Clin. Oncol.* 2012; 30(21):2670–2677. [PubMed: 22689805] ■ Recent report of use of decitabine for the treatment of older adults with AML.
18. Kottaridis PD, Gale RE, Frew ME, et al. The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. *Blood*. 2001; 98(6):1752–1759. [PubMed: 11535508]
19. Grossmann V, Schnittger S, Kohlmann A, et al. A novel hierarchical prognostic model of AML solely based on molecular mutations. *Blood*. 2012; 120(15):2963–2972. [PubMed: 22915647] ■ Details a prognostic model of AML utilizing molecular mutations.
20. Fathi A, Levis M. FLT3 inhibitors: a story of the old and the new. *Curr. Opin. Hematol.* 2011; 18(2):71–76. [PubMed: 21245757]
21. Zarrinkar PP, Gunawardane RN, Cramer MD, et al. AC220 is a uniquely potent and selective inhibitor of FLT3 for the treatment of acute myeloid leukemia (AML). *Blood*. 2009; 114(14):2984–2992. [PubMed: 19654408]
22. Cortes, JE.; Perl, AE.; Dombret, H., et al. Final results of a Phase 2 open-label, monotherapy efficacy and safety study of quizartinib (AC220) in patients ≥ 60 years of age with FLT3 ITD positive or negative relapsed/refractory acute myeloid leukemia. Presented at: American Society of Hematology Annual Meeting; 8–11 December 2012; Atlanta, GA, USA.
23. Levis, MJ.; Perl, AE.; Dombret, H., et al. Final results of a Phase 2 open-label, monotherapy efficacy and safety study of quizartinib (AC220) in patients with FLT3-ITD positive or negative relapsed/refractory acute myeloid leukemia after second-line chemotherapy or hematopoietic stem

- cell transplantation. Presented at: American Society of Hematology Annual Meeting; 8–11 December 2012; Atlanta, GA, USA.
24. Smith, CC.; Lasater, EA.; McCreey, MQ., et al. Crenolanib (CP-868,596) is a potent and selective type I FLT3 inhibitor that retains activity against AC220 resistance-causing FLT3 kinase domain mutants; Presented at: American Society of Hematology Annual Meeting; 8–11 December 2012; Atlanta, GA, USA.
 25. Takahashi K, Kantarjian H, Pemmaraju N, et al. Salvage therapy using FLT3 inhibitors may improve long-term outcome of relapsed or refractory AML in patients with FLT3-ITD. *Br. J. Haematol.* 2013; 161(5):659–66. [PubMed: 23530930]
 26. Bernt KM, Armstrong SA. Targeting epigenetic programs in MLL-rearranged leukemias. *Hematol. Am. Soc. Hematol. Educ. Program.* 2011; 2011:354–360.
 27. Hess JL. MLL: a histone methyltransferase disrupted in leukemia. *Trends Mol. Med.* 2004; 10(10): 500–507. [PubMed: 15464450]
 28. Krivtsov AV, Armstrong SA. MLL translocations, histone modifications and leukaemia stem-cell development. *Nat. Rev. Cancer.* 2007; 7(11):823–833. [PubMed: 17957188]
 29. Feng Q, Wang H, Ng HH, et al. Methylation of H3-lysine 79 is mediated by a new family of HMTases without a SET domain. *Curr. Biol.* 2002; 12:1052–1058. [PubMed: 12123582]
 30. Steger DJ, Lefterova MI, Ying L, et al. DOT1L/KMT4 recruitment and H3K79 methylation are ubiquitously coupled with gene transcription in mammalian cells. *Mol. Cell Biol.* 2008; 28(8): 2825–2839. [PubMed: 18285465]
 31. Daigle SR, Olhava EJ, Therkelsen CA, et al. Selective killing of mixed lineage leukemia cells by a potent small-molecule DOT1L inhibitor. *Cancer Cell.* 2011; 20(1):53–65. [PubMed: 21741596] ■■ Reports EPZ004777's selective killing of cells with the MLL gene translocation and helps form the basis for ongoing clinical-translational efforts.
 32. Hay N, Sonenberg N. Upstream and downstream of mTOR. *Gen. Dev.* 2004; 18(16):1926–1945.
 33. Wullschlegel S, Loewith R, Hall MN. TOR signaling in growth and metabolism. *Cell.* 2006; 124(3):471–484. [PubMed: 16469695]
 34. Sabatini DM. mTOR and cancer: insights into a complex relationship. *Nat. Rev. Cancer.* 2006; 6(9):729–734. [PubMed: 16915295]
 35. Sonenberg N, Hinnebusch AG. Regulation of translation initiation in eukaryotes: mechanisms and biological targets. *Cell.* 2009; 136(4):731–745. [PubMed: 19239892]
 36. Ma XM, Blenis J. Molecular mechanisms of mTOR-mediated translational control. *Nat. Rev. Mol. Cell Biol.* 2009; 10(5):307–318. [PubMed: 19339977]
 37. Efeyan A, Sabatini DM. mTOR and cancer. *Curr. Opin. Cell Biol.* 2010; 22(2):169–176. [PubMed: 19945836]
 38. Zoncu R, Efeyan A, Sabatini DM. mTOR: from growth signal integration to cancer, diabetes and ageing. *Nat. Rev. Mol. Cell Biol.* 2011; 12(1):21–35. [PubMed: 21157483]
 39. Redig AJ, Vakana E, Plataniias LC. Regulation of mammalian target of rapamycin and mitogen activated protein kinase pathways by BCR-ABL. *Leuk. Lymphoma.* 2011; 52(Suppl. 1):S45–S53.
 40. Beauchamp EM, Plataniias LC. The evolution of the TOR pathway and its role in cancer. *Oncogene.* 2012 (Epub ahead of print).
 41. Martin DE, Hall MN. The expanding TOR signaling network. *Curr. Opin. Cell Biol.* 2005; 17(2): 158–166. [PubMed: 15780592]
 42. Dazert E, Hall MN. mTOR signaling in disease. *Curr. Opin. Cell Biol.* 2011; 23(6):744–755. [PubMed: 21963299]
 43. Khokhar NZ, Altman JK, Plataniias LC. Emerging roles for mammalian target of rapamycin inhibitors in the treatment of solid tumors and hematological malignancies. *Curr. Opin. Oncol.* 2011; 23(6):578–586. [PubMed: 21892085]
 44. Gentzler RD, Altman JK, Plataniias LC. An overview of the mTOR pathway as a target in cancer therapy. *Expert Opin. Ther. Targets.* 2012 (Epub ahead of print).
 45. Altman JK, Plataniias LC. Exploiting the mTOR pathway in hematologic malignancies. *Curr. Opin. Hematol.* 2008; 15(2):88–94. [PubMed: 18300753]

46. Altman JK, Sassano A, Plataniias LC. Targeting mTOR for the treatment of AML. New agents and new directions. *Oncotarget*. 2011; 2(6):510–517. [PubMed: 21680954]
47. Younes A, Samad N. Utility of mTOR inhibition in hematologic malignancies. *Oncologist*. 2011; 16(6):730–741. [PubMed: 21632450]
48. Grunt TW, Mariani GL. Targeting the PI3K/AKT/mTOR pathway in breast cancer. *Curr. Cancer Drug Targets*. 2012; 13(2):188–204. [PubMed: 23215720]
49. Chavez-Macgregor M, Gonzalez-Angulo AM. Everolimus in the treatment of hormone receptor-positive breast cancer. *Expert Opin. Investig. Drugs*. 2012; 21(12):1835–1843.
50. Kim DD, Eng C. The promise of mTOR inhibitors in the treatment of colorectal cancer. *Expert Opin. Investig. Drugs*. 2012; 21(12):1775–1788.
51. Yim KL. Everolimus and mTOR inhibition in pancreatic neuroendocrine tumors. *Cancer Manag. Res*. 2012; 4:207–214. [PubMed: 22904642]
52. Kwiatkowska A, Symons M. Signaling determinants of glioma cell invasion. *Adv. Exp. Med. Biol*. 2013; 986:121–141. [PubMed: 22879067]
53. Buitrago-Molina LE, Vogel A. mTOR as a potential target for the prevention and treatment of hepatocellular carcinoma. *Curr. Cancer Drug Targets*. 2012; 12(9):1045–1061. [PubMed: 22873368]
54. Dumont FJ, Bischoff P. Disrupting the mTOR signaling network as a potential strategy for the enhancement of cancer radiotherapy. *Curr. Cancer Drug Targets*. 2012; 12(8):899–924. [PubMed: 22831276]
55. Kotowski A, Ma WW. Emerging therapies in pancreas cancer. *J. Gastrointest. Oncol*. 2011; 2(2): 93–103. [PubMed: 22811835]
56. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled Phase III trial. *Lancet*. 2008; 372(9637):449–456. [PubMed: 18653228]
57. Yao JC, Lombard-Bohas C, Baudin E, et al. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a Phase II trial. *J. Clin. Oncol*. 2010; 28(1):69–76. [PubMed: 19933912]
58. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N. Engl. J. Med*. 2012; 366(6):520–529. [PubMed: 22149876]
59. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N. Engl. J. Med*. 2007; 356(22):2271–2281. [PubMed: 17538086] ■ Key study establishing the activity of temsirolimus in the treatment of advanced renal cell carcinoma.
60. Mahalingam D, Sankhala K, Mita A, Giles FJ, Mita MM. Targeting the mTOR pathway using deforolimus in cancer therapy. *Future Oncol*. 2009; 5(3):291–303. [PubMed: 19374536]
61. Mahalati K, Kahan BD. Clinical pharmacokinetics of sirolimus. *Clin. Pharmacokinet*. 2001; 40(8): 573–585. [PubMed: 11523724]
62. Benjamin D, Colombi M, Moroni C, Hall MN. Rapamycin passes the torch: a new generation of mTOR inhibitors. *Nat. Rev. Drug Discov*. 2011; 10(11):868–880. [PubMed: 22037041]
63. Um SH, Frigerio F, Watanabe M, et al. Absence of S6K1 protects against age- and diet-induced obesity while enhancing insulin sensitivity. *Nature*. 2004; 431(7005):200–205. [PubMed: 15306821]
64. Harrington LS, Findlay GM, Gray A, et al. The TSC1–2 tumor suppressor controls insulin-PI3K signaling via regulation of IRS proteins. *J. Cell Biol*. 2004; 166(2):213–223. [PubMed: 15249583]
65. Yu Y, Yoon SO, Poulogiannis G, et al. Phosphoproteomic analysis identifies Grb10 as an mTORC1 substrate that negatively regulates insulin signaling. *Science*. 2011; 332(6035):1322–1326. [PubMed: 21659605]
66. Hsu PP, Kang SA, Rameseder J, et al. The mTOR regulated phosphoproteome reveals a mechanism of mTORC1-mediated inhibition of growth factor signaling. *Science*. 2011; 332(6035):1317–1322. [PubMed: 21659604]
67. Min YH, Eom JI, Cheong JW, et al. Constitutive phosphorylation of Akt/PKB protein in acute myeloid leukemia: its significance as a prognostic variable. *Leukemia*. 2003; 17(5):995–997. [PubMed: 12750723]

68. Récher C, Dos Santos C, Demur C, Payrastre B. mTOR, a new therapeutic target in acute myeloid leukemia. *Cell Cycle*. 2005; 4(11):1540–1549. [PubMed: 16205124]
69. Chen W, Drakos E, Grammatikakis I, et al. mTOR signaling is activated by FLT3 kinase and promotes survival of FLT3-mutated acute myeloid leukemia cells. *Mol. Cancer*. 2010; 9:292. [PubMed: 21067588]
70. Récher C, Beyne-Rauzy O, Demur C, et al. Antileukemic activity of rapamycin in acute myeloid leukemia. *Blood*. 2005; 105(6):2527–2534. [PubMed: 15550488]
71. Böhm A, Aichberger KJ, Mayerhofer M, et al. Targeting of mTOR is associated with decreased growth and decreased VEGF expression in acute myeloid leukaemia cells. *Eur. J. Clin. Invest.* 2009; 39(5):395–405. [PubMed: 19320940]
72. Xu Q, Simpson SE, Scialla TJ, Bagg A, Carroll M. Survival of acute myeloid leukemia cells requires PI3 kinase activation. *Blood*. 2003; 102(3):972–980. [PubMed: 12702506]
73. Martelli AM, Evangelisti C, Chiarini F, Grimaldi C, Manzoli L, McCubrey JA. Targeting the PI3K/AKT/mTOR signaling network in acute myelogenous leukemia. *Expert Opin. Investig. Drugs*. 2009; 18(9):1333–1349.
74. Park S, Chapuis N, Bardet V, et al. PI-103, a dual inhibitor of Class IA phosphatidylinositide 3-kinase and mTOR, has antileukemic activity in AML. *Leukemia*. 2008; 22(9):1698–1706. [PubMed: 18548104]
75. Kojima K, Shimanuki M, Shikami M, et al. The dual PI3 kinase/mTOR inhibitor PI-103 prevents p53 induction by Mdm2 inhibition but enhances p53-mediated mitochondrial apoptosis in p53 wild-type AML. *Leukemia*. 2008; 22(9):1728–1736. [PubMed: 18548093]
76. Xu Q, Thompson JE, Carroll M. mTOR regulates cell survival after etoposide treatment in primary AML cells. *Blood*. 2005; 106(13):4261–4268. [PubMed: 16150937]
77. Altman JK, Yoon P, Katsoulidis E, et al. Regulatory effects of mammalian target of rapamycin-mediated signals in the generation of arsenic trioxide responses. *J. Biol. Chem.* 2008; 283(4):1992–2001. [PubMed: 18048359]
78. Janus A, Linke A, Cebula B, Robak T, Smolewski P. Rapamycin, the mTOR kinase inhibitor, sensitizes acute myeloid leukemia cells, HL-60 cells, to the cytotoxic effect of arabinoside cytarabine. *Anticancer Drugs*. 2009; 20(8):693–701. [PubMed: 19584709]
79. Calabro A, Tai J, Allen SL, Budman DR. *In vitro* synergism of m-TOR inhibitors, statins, and classical chemotherapy: potential implications in acute leukemia. *Anticancer Drugs*. 2008; 19(7):705–712. [PubMed: 18594212]
80. Nishioka C, Ikezoe T, Yang J, Koeffler HP, Yokoyama A. Blockade of mTOR signaling potentiates the ability of histone deacetylase inhibitor to induce growth arrest and differentiation of acute myelogenous leukemia cells. *Leukemia*. 2008; 22(12):2159–2168. [PubMed: 18784743]
81. Lalic H, Lukinovic-Skudar V, Banfic H, Visnjic D. Rapamycin enhances dimethyl sulfoxide-mediated growth arrest in human myelogenous leukemia cells. *Leuk. Lymphoma*. 2012; 53(11):2253–2261. [PubMed: 22497230]
82. Yang J, Ikezoe T, Nishioka C, Ni L, Koeffler HP, Yokoyama A. Inhibition of mTORC1 by RAD001 (everolimus) potentiates the effects of 1,25-dihydroxyvitamin D(3) to induce growth arrest and differentiation of AML cells *in vitro* and *in vivo*. *Exp. Hematol.* 2010; 38(8):666–676. [PubMed: 20382200]
83. Nishioka C, Ikezoe T, Yang J, Gery S, Koeffler HP, Yokoyama A. Inhibition of mammalian target of rapamycin signaling potentiates the effects of all-*trans* retinoic acid to induce growth arrest and differentiation of human acute myelogenous leukemia cells. *Int. J. Cancer*. 2009; 125(7):1710–1720. [PubMed: 19507250]
84. Boehm A, Mayerhofer M, Herndlhofer S, et al. Evaluation of *in vivo* antineoplastic effects of rapamycin in patients with chemotherapy-refractory AML. *Eur. J. Intern. Med.* 2009; 20(8):775–778. [PubMed: 19892307]
85. Perl AE, Kasner MT, Tsai DE, et al. A Phase I study of the mammalian target of rapamycin inhibitor sirolimus and MEC chemotherapy in relapsed and refractory acute myelogenous leukemia. *Clin. Cancer Res.* 2009; 15(21):6732–6739. [PubMed: 19843663]
86. Amadori S, Stasi R, Martelli AM, et al. Temsirolimus, an mTOR inhibitor, in combination with lower-dose clofarabine as salvage therapy for older patients with acute myeloid leukaemia: results

- of a Phase II GIMEMA study (AML-1107). *Br. J. Haematol.* 2012; 156(2):205–212. [PubMed: 22082314]
87. Perl AE, Kasner MT, Shank D, Luger SM, Carroll M. Single-cell pharmacodynamic monitoring of S6 ribosomal protein phosphorylation in AML blasts during a clinical trial combining the mTOR inhibitor sirolimus and intensive chemotherapy. *Clin. Cancer Res.* 2012; 18(6):1716–1725. [PubMed: 22167413]
88. Markman B, Dienstmann R, Tabernero J. Targeting the PI3K/Akt/mTOR pathway - beyond rapalogs. *Oncotarget.* 2010; 1(7):530–543. [PubMed: 21317449]
89. Altman JK, Sassano A, Kaur S, et al. Dual mTORC2/mTORC1 targeting results in potent suppressive effects on acute myeloid leukemia (AML) progenitors. *Clin. Cancer Res.* 2011; 17(13):4378–4388. [PubMed: 21415215]
90. Willems L, Chapuis N, Puissant A, et al. The dual mTORC1 and mTORC2 inhibitor AZD8055 has anti-tumor activity in acute myeloid leukemia. *Leukemia.* 2012; 26(6):1195–1202. [PubMed: 22143671]
91. Zeng Z, Shi YX, Tsao T, et al. Targeting of mTORC1/2 by the mTOR kinase inhibitor PP242 induces apoptosis in AML cells under conditions mimicking the bone marrow microenvironment. *Blood.* 2012; 120(13):2679–2689. [PubMed: 22826565]

Practice Points

- Cytogenetics and now molecular mutations are important in the classification of prognosis for newly diagnosed acute myeloid leukemia (AML).
- Anthracycline dose intensification is an important concept in the treatment of adults with AML.
- The optimal dose of cytarabine in induction and consolidation is not clear.
- Novel therapeutics are in development for AML targeting specific molecular and cytogenetic aberrations.
- Targeting the mTOR pathway with catalytic inhibitors is an area of active study and interest.
- Targeting mTOR may provide a complementary approach to current treatments, but this hypothesis remains to be directly examined in future studies.