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Emerging therapeutic modalities for acute myeloid leukemia (AML) in older adults

Li-Wen Huang¹ and Rebecca L. Olin^{*,2}

Department of Medicine, Division of Hematology/Oncology, University of California San Francisco, USA

Abstract

Treatment for the older adult with acute myeloid leukemia (AML) is challenging, due to both more aggressive disease biology as well as patient-related risk factors that limit tolerance of intensive chemotherapy. The use of prognostic models and comprehensive geriatric assessments can help hematologists evaluate the suitability of intensive chemotherapy for individual patients. For older patients considered fit for intensive chemotherapy, standard induction therapy should be given, followed by consideration of reduced intensity allogeneic stem cell transplantation. Patients considered unfit for intensive therapy are standardly treated with hypomethylating agents. Several new therapeutic agents have shown promising results either by improving intensive chemotherapy (CPX-351), by improving upon lower intensity therapy (venetoclax, antibody drug conjugates), or by targeting somatic mutations (FLT3 inhibitors and others).

Keywords

Acute myeloid leukemia; Older adults; Induction chemotherapy; Hypomethylating agents; Novel agents

1. Introduction

Acute myeloid leukemia (AML) is a disease of older adults, with a median age of diagnosis of 67 years and one third of patients aged ≥ 75 years [1]. Increasing age has been associated with higher treatment-related mortality (TRM), lower complete remission (CR) rates, higher relapse risk, and shorter overall survival (OS) [2–4]. Concerns about poor efficacy and high toxicity contribute to less than half of patients with newly diagnosed AML aged ≥ 65 receiving any chemotherapy in the US [5].

*Corresponding author. li-wen.huang@ucsf.edu (L.-W. Huang), rebecca.olin@ucsf.edu (R.L. Olin).

¹Mailing address: 505 Parnassus Ave, Hematology/Oncology office, M1286, San Francisco, CA 94143, USA.

²Mailing address: 400 Parnassus Ave Box 0324, San Francisco, CA 94143, USA.

Author Contributions

Concept and design: R. Olin.

Data collection: R. Olin and L. Huang.

Analysis and interpretation of data: R. Olin and L. Huang.

Manuscript writing and approval: R. Olin and L. Huang.

2. Risk Stratification

Poor outcomes in older patients are a result both of disease biology and patient characteristics. Older patients have a higher incidence of secondary AML and unfavorable cytogenetics. Older patients with favorable cytogenetics have worse prognosis than their younger counterparts [2,6]. Leukemic blasts in older patients are also more likely to be resistant to chemotherapeutic agents due to higher expression of the multidrug resistance gene MDR1 [7]. In addition to more aggressive disease biology, many older patients with AML tolerate chemotherapy poorly, due to comorbidities including age-related renal and hepatic dysfunction. Geriatric syndromes such as functional impairment, cognitive impairment, and polypharmacy also influence treatment decision-making.

2.1. Prognostic Models

To identify patients who would benefit from and can tolerate intensive chemotherapy, prognostic models have been created to estimate probabilities of TRM and CR; some of these models are available as online tools [8,9]. These models tend to rely on age and performance status (PS) as markers of treatment tolerance. However, chronologic age is simply a surrogate for physiologic age, and PS alone may not fully assess patients' functional impairment.

2.2. Geriatric Assessments

Comprehensive geriatric assessments (CGA) are standardized, in depth evaluations of physical function, comorbidity, polypharmacy, nutritional status, cognition, depression, and social support that help improve risk stratification for older patients. They are better than PS scales at identifying patients who may not be frail but nevertheless have vulnerabilities that impact treatment tolerance [10]. For example, in a prospective study of AML patients aged 60 treated with induction chemotherapy, CGA measures of objective physical performance (Short Physical Performance Battery < 9) and cognitive impairment (Modified Mini-Mental State Exam < 77) were independently associated with OS after accounting for other tumor and clinical characteristics such as age and PS [11].

3. Treatment Approach

When an older patient is diagnosed with AML, the first step in treatment decision-making is to determine whether the patient is fit for intensive induction chemotherapy (IC), which depends on the above disease- and patient-related factors as well as patient preference. One must also determine the overall goal of the therapeutic plan—curative, life-prolonging, or palliative (Fig. 1). In general, patients who are not candidates for IC due to comorbidities or other patient-related factors are likely not candidates for a curative approach. However, selecting a strategy upfront does not preclude changing course later. If a very good response is achieved and any necessary improvements in PS and organ function occur with a lower intensity regimen, patients may “crossover” to a curative strategy of reduced intensity allogeneic transplantation.

Determination of fitness is clearly a significant challenge. Our current approach is to consider PS, comorbidities, and other geriatric domains such as cognition. Social support

and a strong caregiving team are particularly critical in an older patient with any vulnerabilities. The current state of the literature does not support a consistent approach to this determination; more and larger studies are needed to clarify the best use of CGA and/or its components.

3.1. Intensive Chemotherapy

3.1.1. Induction Chemotherapy—Several studies have attempted to address whether an intensive approach (standard “7+ 3” regimen of standard dose cytarabine plus an anthracycline) improves outcomes compared to lower intensity therapy in older adults. Retrospective studies are inevitably confounded by patient selection bias. Studies from the 1980s showed improved survival with IC versus best supportive care (BSC), but a non-significant benefit of IC when compared to low-dose cytarabine (LDAC) [12,13]. However, these studies were not performed in the era of modern supportive care. The best modern data supporting the use of IC comes from the retrospective Swedish registry study assessing “real-world” outcomes in different areas of Sweden which differed in physician willingness to administer IC. IC was associated with better outcomes even in patients aged 70–79 [3]. The 7+3 regimen also appears to be superior to single agent clofarabine in patients aged > 60 [14]. Based on this data, IC remains a reasonable standard of care for older patients with AML who are considered fit enough to receive it.

It is controversial, however, whether certain subsets of patients who may be fit for IC should in fact not receive it. Some evidence suggests patients with secondary AML, poor risk cytogenetics, or AML with myelodysplasia-related change may benefit more from hypomethylating agents (HMA), or simply are less likely to benefit from 7 + 3 [14–16]. Data to answer this question is still emerging. Our practice is to continue to offer IC to fit older patients, but for patients with borderline fitness and the above high-risk disease features, we may be more likely to consider HMA.

3.1.2. Post-remission Therapy—If an intensive strategy is selected and remission is achieved, the clinician then needs to determine the optimal post-remission therapy. Several trials have examined the role of higher doses of cytarabine as part of a consolidation regimen and have consistently not shown any benefit in survival [17]. Thus, there is currently no clear standard of care for chemotherapy-based consolidation in first remission.

Given that higher intensity consolidation does not seem to improve the generally poor outcome of older AML, the development of non-myeloablative or reduced intensity conditioning (RIC) regimens has made allogeneic stem cell transplantation an increasingly attractive option for post-remission therapy. Studies show that older adults with AML who proceed to RIC allogeneic transplantation can achieve 2-year survival rates of 34–48% [18,19]. Preliminary results from a prospective biologic assignment study (“donor versus no donor”) of patients aged 60–75 years in first remission suggest that, compared to chemotherapy consolidation, allogeneic transplantation results in lower relapse rates and higher disease-free survival, but higher non-relapse mortality, with a non-significant trend toward improved OS [20].

3.2. Lower Intensity Therapy

The HMAs decitabine and azacitidine represent the current lower intensity regimen of choice for older patients with AML. This is based on trials which randomized patients to receive HMA versus patient/physician choice of BSC, LDAC, or in some trials, IC (Table 1). One international phase 3 study compared azacitidine to conventional care regimens (IC, LDAC, or BSC) in patients with AML and >30% bone marrow blasts. Azacitidine resulted in median OS of 10.4 versus 6.5 months with conventional care regimens, although the primary endpoint was not met. The study was not powered to detect an OS difference in the group pre-selected for IC, though patients in this group who received azacitidine and IC had similar median OS (13.3 vs 12.2 months). Interestingly, for patients with poor risk cytogenetics or myelodysplasia-related change, azacitidine was superior to conventional care regimens, with median OS of 6.4 compared to 3.2 months [15]. Another study found that patients with unfavorable risk cytogenetics or TP53 mutation treated with decitabine had higher response rates and similar OS compared to patients with intermediate risk cytogenetics [16].

4. Emerging Therapies

Whenever possible, older patients with AML should be enrolled on a clinical trial. Numerous new drugs are emerging from the drug development pipeline with the potential to greatly enrich the limited therapeutic options for older AML patients; some of these are highlighted below.

4.1. CPX351

The 7 + 3 regimen has been a standard in AML treatment since the 1970s, and multiple attempts to improve upon it have largely been unsuccessful, except in younger and favorable risk subsets [21–24]. CPX-351 is a liposomal formulation of cytarabine and daunorubicin in a fixed 5:1 molar ratio, chosen based on in vitro studies showing this ratio to be maximally synergistic. Subset analysis of a phase 2 trial of CPX-351 showed an encouraging signal in secondary AML [25]. Therefore, a phase 3 trial was conducted randomizing older patients aged 60–75 with previously untreated secondary AML to receive 7+3 versus CPX-351. Results showed a higher CR rate (37.3% vs 25.6%), improved OS (9.56 vs 5.95 months, $p = 0.005$), decreased early death in 60 days (13.7% vs 21.1%), and more patients proceeding to allogeneic transplant (34% vs 25%) in the CPX-351 arm [26]. Although early deaths due to toxicity were similar, there were fewer early deaths due to progressive AML. Landmark analysis from time of transplant also showed that patients who received CPX-351 had better post-transplant survival. Why CPX-351 prolongs survival—decreased toxicity, better efficacy, more patients transplanted, or a combination—remains unclear. CPX-351 (Vyxeos) was approved by the FDA in August 2017 for therapy-related AML and AML with myelodysplasia-related change and will become a new standard of care for older adults with secondary AML.

4.2. Small Molecule Inhibitors

4.2.1. Venetoclax—Venetoclax is a potent BCL2 inhibitor which binds selectively to BCL2, promoting programmed cell death. Ongoing phase 1b trials combining venetoclax

with azacitidine and decitabine in adults aged ≥ 65 with untreated AML unfit for IC show overall response rate (ORR) of 62% across all treatment arms, with median duration of response of 8.4 months [27]. These results are promising compared to historical results for azacitidine alone with ORR of only 29% [15]. In 2016, venetoclax received breakthrough designation in combination with HMA for patients with AML who are unfit for IC.

4.2.2. FLT3 Inhibitors—FLT3 mutations occur in 30% of AML patients, and FLT3 internal tandem duplication (ITD) mutations are associated with poor prognosis. Small molecule FLT3 inhibitors have emerged as an attractive therapeutic option. Type II inhibitors such as sorafenib are vulnerable to the secondary development of D835 mutations, resulting in resistance. Type I inhibitors, such as midostaurin, crenolanib, and gilteritinib, are able to bind FLT3 despite the presence of the D835 mutation. Midostaurin was recently shown to prolong survival in combination with chemotherapy, but this trial did not include older patients [28]. Studies are ongoing with other FLT3 inhibitors including crenolanib and gilteritinib in combination with chemotherapy or with HMA, and as monotherapy for post-transplant maintenance.

Several drugs targeting novel small molecular targets are in development for the treatment of AML, which are summarized in Table 2. Though not specifically aimed at older patients with AML, these novel therapies represent promising treatment options for older adults whose options may otherwise be limited.

4.3. Antibody-Drug Conjugates

Antibody-drug conjugates (ADC) targeting CD33 are a promising class of agents for older adults with AML. Gemtuzumab ozogamicin (GO) is an ADC comprised of a monoclonal antibody targeting CD33 linked to the cytotoxic agent calicheamicin. GO was approved in 2000 for use in older patients with relapsed, CD33 positive AML, but was withdrawn from the market in 2010 when the confirmatory phase 3 study showed no benefit but increased toxicity, including hepatic veno-occlusive disease, when used for younger patients in combination with 7+3 [29]. However, low dose GO as first-line monotherapy significantly improved OS compared to BSC in older AML patients ineligible for IC [30], and is now being reviewed by the FDA for use in combination with 7 + 3 based on the ALFA-0701 trial showing a survival benefit for patients aged 50–70 [31].

Vadastuximab talirine (SGN-CD33A) is a new anti-CD33 ADC which in a phase 1b study in combination with HMA for older patients with treatment naïve AML showed promising CR rate of 73% [32]. However, in June 2017 all trials of vadastuximab were halted due to a higher rate of death in a phase 3 trial in older adults.

5. Conclusion

The treatment approach for older patients with AML generally consists of IC for the fit patient and HMA for the unfit. The development of CPX-351 for secondary AML and increasing utilization of RIC allogeneic transplantation may improve both the tolerability and long-term outcome of an intensive treatment strategy. Emerging novel agents such as venetoclax, ADCs, and small molecular inhibitors that are effective and tolerable, as well as

drug combinations, will be invaluable additions to the treatment landscape for older patients with AML.

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References

1. Howlader N, Noone A, Krapcho M, Miller D, Bishop K, Altekruse S, et al. SEER cancer statistics review, 1975–2013. Bethesda, MD: National Cancer Institute; Apr, 2016. [http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site]
2. Appelbaum FR, Gundacker H, Head DR, Slovak ML, Willman CL, Godwin JE, et al. Age and acute myeloid leukemia. *Blood*. 2006; 107(9):3481–5. [PubMed: 16455952]
3. Juliusson G, Antunovic P, Derolf A, Lehmann S, Mollgard L, Stockelberg D, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood*. 2009; 113(18):4179–87. [PubMed: 19008455]
4. Grimwade D, Walker H, Harrison G, Oliver F, Chatters S, Harrison CJ, et al. The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial. *Blood*. 2001; 98(5):1312–20. [PubMed: 11520776]
5. Oran B, Weisdorf DJ. Survival for older patients with acute myeloid leukemia: a population-based study. *Haematologica*. 2012; 97(12):1916–24. [PubMed: 22773600]
6. Prebet T, Boissel N, Reutenauer S, Thomas X, Delaunay J, Cahn JY, et al. Acute myeloid leukemia with translocation (8;21) or inversion (16) in elderly patients treated with conventional chemotherapy: a collaborative study of the French CBF-AML intergroup. *J Clin Oncol*. 2009; 27(28):4747–53. [PubMed: 19720919]
7. Leith CP, Kopecky KJ, Chen IM, Eijdens L, Slovak ML, McConnell TS, et al. Frequency and clinical significance of the expression of the multidrug resistance proteins MDR1/P-glycoprotein, MRP1, and LRP in acute myeloid leukemia: a Southwest Oncology Group Study. *Blood*. 1999; 94(3):1086–99. [PubMed: 10419902]
8. Krug U, Rollig C, Koschmieder A, Heinecke A, Sauerland MC, Schaich M, et al. Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. *Lancet*. 2010; 376(9757):2000–8. [PubMed: 21131036]
9. Walter RB, Othus M, Borthakur G, Ravandi F, Cortes JE, Pierce SA, et al. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: a novel paradigm for treatment assignment. *J Clin Oncol*. 2011; 29(33):4417–23. [PubMed: 21969499]
10. Klepin HD, Rao AV, Pardee TS. Acute myeloid leukemia and myelodysplastic syndromes in older adults. *J Clin Oncol*. 2014; 32(24):2541–52. [PubMed: 25071138]
11. Klepin HD, Geiger AM, Tooze JA, Kritchevsky SB, Williamson JD, Pardee TS, et al. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. *Blood*. 2013; 121(21):4287–94. [PubMed: 23550038]
12. Lowenberg B, Zittoun R, Kerkhofs H, Jehn U, Abels J, Debusscher L, et al. On the value of intensive remission-induction chemotherapy in elderly patients of 65+ years with acute myeloid leukemia: a randomized phase III study of the European Organization for Research and Treatment of Cancer Leukemia Group. *J Clin Oncol*. 1989; 7(9):1268–74. [PubMed: 2475589]

13. Tilly H, Castaigne S, Bordessoule D, Casassus P, Le Prise PY, Tertian G, et al. Low-dose cytarabine versus intensive chemotherapy in the treatment of acute nonlymphocytic leukemia in the elderly. *J Clin Oncol*. 1990; 8(2):272–9. [PubMed: 2299370]
14. Foran JM, Sun Z, Claxton DF, Lazarus HM, Thomas ML, Melnick A, et al. North American leukemia, intergroup phase III randomized trial of single agent clofarabine as induction and post-remission therapy, and decitabine as maintenance therapy in newly-diagnosed acute myeloid leukemia in older adults (age ≥ 60 years): a trial of the ECOG-ACRIN Cancer Research Group (E2906). *Blood*. 2015; 126(23):217.
15. Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with greater than 30% blasts. *Blood*. 2015; 126(3):291. [PubMed: 25987659]
16. Welch JS, Petti AA, Miller CA, Fronick CC, O'Laughlin M, Fulton RS, et al. TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. *N Engl J Med*. 2016; 375(21):2023–36. [PubMed: 27959731]
17. Stone RM. Should older adults with AML receive post-remission therapy? *Best Pract Res Clin Haematol*. 2015; 28(2–3):106–11. [PubMed: 26590766]
18. Devine SM, Owzar K, Blum W, Mulkey F, Stone RM, Hsu JW, et al. Phase II study of allogeneic transplantation for older patients with acute myeloid leukemia in first complete remission using a reduced-intensity conditioning regimen: results from Cancer and Leukemia Group B 100103 (Alliance for Clinical Trials in Oncology)/Blood and Marrow Transplant Clinical Trial Network 0502. *J Clin Oncol*. 2015; 33(35):4167–75. [PubMed: 26527780]
19. McClune BL, Weisdorf DJ, Pedersen TL, Tunes da Silva G, Tallman MS, Sierra J, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. *J Clin Oncol*. 2010; 28(11):1878–87. [PubMed: 20212255]
20. Niederwieser D, Al-Ali HK, Krahl R, Kahl C, Wolf H-H, Kreibich U, et al. Higher leukemia free survival after post-induction hematopoietic cell transplantation compared to consolidation therapy in patients greater than 60 years with acute myelogenous leukemia (AML): report from the AML 2004 East German Study Group (OSHO). *Blood*. 2014; 124(21):280.
21. Burnett AK, Russell NH, Hills RK, Hunter AE, Kjeldsen L, Yin J, et al. Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the medical research council AML15 trial. *J Clin Oncol*. 2013; 31(27):3360–8. [PubMed: 23940227]
22. Burnett AK, Russell NH, Hills RK, Kell J, Cavenagh J, Kjeldsen L, et al. A randomized comparison of daunorubicin 90 mg/m² vs 60 mg/m² in AML induction: results from the UK NCRI AML17 trial in 1206 patients. *Blood*. 2015; 125(25):3878–85. [PubMed: 25833957]
23. Willemze R, Suci S, Meloni G, Labar B, Marie JP, Halkes CJ, et al. High-dose cytarabine in induction treatment improves the outcome of adult patients younger than age 46 years with acute myeloid leukemia: results of the EORTC-GIMEMA AML-12 trial. *J Clin Oncol*. 2014; 32(3):219–28. [PubMed: 24297940]
24. Bishop JF, Lowenthal RM, Joshua D, Matthews JP, Todd D, Cobcroft R, et al. Etoposide in acute nonlymphocytic leukemia. Australian Leukemia Study Group. *Blood*. 1990; 75(1):27–32. [PubMed: 2403818]
25. Lancet JE, Cortes JE, Hogge DE, Tallman MS, Kovacsics TJ, Damon LE, et al. Phase 2 trial of CPX-351, a fixed 5:1 molar ratio of cytarabine/daunorubicin, vs cytarabine/daunorubicin in older adults with untreated AML. *Blood*. 2014; 123(21):3239. [PubMed: 24687088]
26. Lancet JE, Uy GL, Cortes JE, Newell LF, Lin TL, Ritchie EK, et al. Final results of a phase III randomized trial of CPX-351 versus 7 + 3 in older patients with newly diagnosed high risk (secondary) AML. *J Clin Oncol*. 2016; 34(suppl) abstr 7000.
27. Pollyea DA, Dinardo CD, Thirman MJ, Letai A, Wei AH, Jonas BA, et al. Results of a phase 1b study of venetoclax plus decitabine or azacitidine in untreated acute myeloid leukemia patients 65 years ineligible for standard induction therapy. *J Clin Oncol*. 2016; 34(suppl) abstr 7009.
28. Stone RM, Mandrekas S, Sanford BL, Geyer S, Bloomfield CD, Dohner K, et al. The multi-kinase inhibitor midostaurin (M) prolongs survival compared with placebo (P) in combination with daunorubicin (D)/cytarabine (C) induction (ind), high-dose C consolidation (consol), and as maintenance (maint) therapy in newly diagnosed acute myeloid leukemia (AML) patients (pts) age

- 18–60 with FLT3 mutations (mut): an international prospective randomized (rand) P-controlled double-blind trial (CALGB 10603/RATIFY [Alliance]). *Blood*. 2015; 126(23):26. [PubMed: 25827831]
29. Petersdorf SH, Kopecky KJ, Slovak M, Willman C, Nevill T, Brandwein J, et al. A phase 3 study of gemtuzumab ozogamicin during induction and postconsolidation therapy in younger patients with acute myeloid leukemia. *Blood*. 2013; 121(24):4854–60. [PubMed: 23591789]
30. Amadori S, Succi S, Selleslag D, Aversa F, Gaidano G, Musso M, et al. Gemtuzumab Ozogamicin versus best supportive care in older patients with newly diagnosed acute myeloid leukemia unsuitable for intensive chemotherapy: results of the randomized phase III EORTC-GIMEMA AML-19 trial. *J Clin Oncol*. 2016; 34(9):972–9. [PubMed: 26811524]
31. Castaigne S, Pautas C, Terre C, Raffoux E, Bordessoule D, Bastie JN, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. *Lancet*. 2012; 379(9825):1508–16. [PubMed: 22482940]
32. Fathi AT, Erba HP, Lancet JE, Stein EM, Ravandi F, Faderl S, et al. Vadastuximab Talirine plus hypomethylating agents: a well-tolerated regimen with high remission rate in frontline older patients with acute myeloid leukemia (AML). *Blood*. 2016; 128(22):591.
33. Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *J Clin Oncol*. 2012; 30(21):2670–7. [PubMed: 22689805]
34. Fenaux P, Mufti GJ, Hellström-Lindberg E, Santini V, Gattermann N, Germing U, 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):562–9. [PubMed: 20026804]

Fig. 1.
Treatment algorithm for older AML patients.

Table 1

Trials evaluating hypomethylating agents in acute myeloid leukemia in older adults. BSC = best supportive care, LDAC = low dose cytarabine, IC = intensive chemotherapy, CR = complete remission, OS = overall survival, MDS = myelodysplastic syndrome, WHO = World Health Organization, AML= acute myeloid leukemia.

Trial	No. of patients	CR (%)	p-Value	Median OS (months)	p-Value	Comments
<i>Kantarjian [33]</i>						
Decitabine	243	17.8	0.001	7.7	0.108	Age 65, poor/intermediate risk cytogenetics.
BSC or LDAC	242	7.8		5.0		Unplanned analysis with 446 deaths show same median OS with p = 0.037.
<i>Fenaux [34]</i>						
Azacitidine	55	18	0.80	24.5	0.005	Age 18 (median age 70), 20–30% blasts (subset of MDS trial meeting WHO criteria for AML).
BSC, LDAC, IC	58	16		16.0		CR rates with IC 55%, LDAC 15%, BSC 0%.
<i>Dombret [15]</i>						
Azacitidine	241	27.8	0.54	10.4	0.10	Age 65, >30% blasts.
BSC, LDAC, IC	247	25.1		6.5		CR rates with IC 48%, LDAC 26%, BSC 0%.

Table 2

Novel therapeutic targets for AML. BCL2 = B cell lymphoma 2, FLT3 = fms like tyrosine kinase 3, Plk = polo like kinase, IDH = isocitrate dehydrogenase, MEK = mitogen-activated protein kinase enzyme, MDM2 = murine double minute chromosome 2, HDAC = histone deacetylase, CTLA4 = cytotoxic T-lymphocyte-associated protein 4, PDL = programmed cell death ligand, BiTE = bispecific T cell engager, CAR-T = chimeric antigen receptor T cells

Therapeutic approach	Drug
<i>Small molecule inhibitors</i>	
BCL2	Venetoclax
FLT3	Midostaurin, sorafenib, crenolanib, lestaurtinib, gilteritinib
Plk	Volasertib, rigosertib
IDH1/2	AG-120, AG-221
MEK	Trametinib, cobimetinib
MDM2	AMG-232
HDAC	Pracinostat, panobinostat, entinostat
<i>Antibody-drug conjugates</i>	
Anti-CD33	SGN33A (vadastuximab), AC225 (lintuzumab)
Anti-CD123	SL-401
<i>Immunotherapy</i>	
Anti-CTLA4	Ipilimumab
Anti-PD1/PDL1	Nivolumab, pembrolizumab, PDR001, MBG453
BiTE and DART antibody constructs	AMG 330, MGD006
CAR-T cells	CART123