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REVIEW ARTICLE

The leukemia strikes back: a review of pathogenesis and treatment of secondary AML

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Abstract

Secondary AML is associated with a disproportionately poor prognosis, consistently shown to exhibit inferior response rates, event-free survival, and overall survival in comparison with de novo AML. Secondary AML may arise from the evolution of an antecedent hematologic disorder, or it may arise as a complication of prior cytotoxic chemotherapy or radiation therapy in the case of therapy-related AML. Because of the high frequency of poor-risk cytogenetics and high-risk molecular features, such as alterations in *TP53*, leukemic clones are often inherently chemoresistant. Standard of care induction had long remained conventional 7 + 3 until its reformulation as CPX-351, recently FDA approved specifically for secondary AML. However, recent data also suggests relatively favorable outcomes with regimens based on high-dose cytarabine or hypomethylating agents. With several investigational agents being studied, the therapeutic landscape becomes even more complex, and the treatment approach involves patient-specific, disease-specific, and therapy-specific considerations.

Keywords Secondary AML · Therapy-related AML · AML with myelodysplasia-related changes · Liposomal daunorubicin and cytarabine · FLAG · Hypomethylating agents

Introduction

While the standard of care for acute myeloid leukemia (AML) has remained relatively unchanged for decades, the need for novel therapy is even more pronounced in secondary AML (sAML). Arising from an antecedent hematologic disorder (AHD) or prior leukemogenic chemotherapy/radiation therapy, sAML is a subset of AML that comprises 25 to 35% of AML cases [1, 2]. The incidence of sAML appears to be on the rise, potentially due to the increasing survivorship from prior malignancies, changing strategies in chemotherapy (such as expanding adjuvant treatment to lower-risk patients with breast cancer) [3], and more precise epidemiological documentation in registration processes [4].

Compared to de novo AML, patients with sAML tend to exhibit worse clinical outcomes, including significantly inferior complete remission rates, relapse-free survival, and overall survival [1, 5, 6]. Predictive models incorporate the presence of sAML as a risk factor for early death [7, 8]. Given the etiology of sAML, hematopoietic reserves are often depleted from prior chemotherapy/radiation therapy (XRT) or AHD [1]. Additionally, the median age of patients with sAML is significantly older; thus, they are more likely to present with comorbidities and may be unable to tolerate intensive chemotherapy. Baseline renal, hepatic, pulmonary, and cardiac function may be compromised due to vascular and parenchymal damage from prior chemotherapy/XRT for a primary malignancy preceding sAML. In addition, a higher proportion of patients with sAML have adverse cytogenetic and molecular features such as complex karyotype, monosomy 5 or 7, and *TP53* alterations which are associated with chemotherapy resistance [5, 9–11]. Interestingly, the poor prognosis of sAML has even been shown to be independent of age and cytogenetics [1]. For example, patients with core binding factor (CBF) abnormalities have worse survival in sAML versus de novo

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AML, even though CBF mutations are considered favorable-risk cytogenetics [6]. Patient-reported outcomes are also less favorable, as patients with sAML experience more severe symptom burden, distress, and quality of life problems after induction chemotherapy [12].

Despite disproportionately high morbidity and mortality, the standard of care for AML induction has remained surprisingly stagnant for decades, pivoting largely on 7 + 3 with minor variations as the standard of care for both de novo and secondary AML. This changed in 2017 with the FDA approvals of liposomal cytarabine and daunorubicin (CPX-351, Vyxeos®) for sAML, midostaurin, and enasidenib for patients with specific mutations, and gemtuzumab ozogamicin (GO) after a temporary removal from the market. In light of the expanding armamentarium of treatment options for sAML and the complicated underlying pathophysiology, we provide a comprehensive review on the background of sAML and synthesize the current evidence for the treatment of sAML.

Pathophysiology

Etiology

Secondary AML may arise from an AHD or prior chemotherapy/XRT, with characteristic genomic changes and associated hypotheses for molecular pathogenesis. The most common AHD preceding sAML is myelodysplastic syndrome (MDS), a genetically heterogeneous class of disorders resulting in ineffective hematopoiesis. Approximately one third of MDS patients progress to sAML [13]. The risk of MDS transformation to AML may be assessed with the Revised International Prognostic Scoring System (IPSS-R), which stratifies patients based on cytogenetics, marrow aspirate blast percentage, and extent of cell lines affected (neutropenia, thrombocytopenia, and anemia) [14]. Although genome sequencing data implies that the underlying pathophysiology of sAML evolution involves multiple stages of clonal evolution [15], a large population-based database has determined that the risk of transformation remains largely constant over the time elapsed from MDS diagnosis, suggesting the postulate that transformation may be driven by a single genetic or epigenetic event [16]. Besides a documented AHD, patients may present with AML with myelodysplasia-related changes (AML-MRC), as sAML may undergo an undiagnosed MDS prodrome [17]. Per the 2016 revision to the World Health Organization (WHO) classification of AML, patients with multilineage dysplasia (50% or more dysplastic cells in at least two cell lines) without NPM1 or biallelic CEBPα mutations as well as those with specific MDS-related cytogenetic abnormalities are included in this category for a diagnosis of AML-MRC [18].

Another group of indolent hematopoietic cell malignancies with the potential to transform into AML are myeloproliferative neoplasms (MPN), encompassing chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocytopenia (ET), chronic myelomonocytic leukemia (CMML), primary myelofibrosis (PMF), and other disorders of myeloid origin [19]. AML arising from an MPN has been associated with worse survival than AML originating from MDS, possibly due to a higher frequency of aberrant cytogenetics [1]. Although the BCR-ABL1-negative MPN (such as PV and ET) are frequently characterized by mutated JAK2, AML transformation may correlate instead with alterations in *TP53* and *RUNX1* [20]. In patients with JAK2 V617F-mutated AML, complex karyotype and TET2 mutations were more common in AML secondary to MPNs compared to de novo AML, suggesting similar genomic instability [21].

Aplastic anemia also has the potential to evolve into AML, with a proposed mechanism that mutated clones may have a survival advantage in a bone marrow environment rendered dysfunctional with autoimmune damage [22]. Compared to MDS, these other disorders are less common, and the molecular events leading to sAML transformation are less well understood.

Therapy-related sAML arises as a complication of prior cytotoxic therapy/XRT, most commonly for breast cancer, gynecologic cancers, and lymphomas due to the mutagenic treatment agents [5, 10, 23]. The incidence of therapy-related sAML is 0.8 to 6.3% at 20 years after conventional therapy, with a notably reduced risk after 10 years [24]. The most well-studied chemotherapy agents associated with sAML include alkylating agents and topoisomerase II inhibitors. Alkylating agents form cross-links in DNA, leading to single- and double-strand breaks in the repair process. The cytogenetics of subsequent sAML are commonly unbalanced, with partial or whole losses of chromosomes 5 or 7 [25]. The pathogenesis of sAML induced by alkylating agents appears to be gradual, often with a preceding MDS phase [26] and a median latency period of 5 years (range 1 to 14 years) from initial exposure [23]. In contrast, sAML following topoisomerase II inhibitor therapy exhibits a shorter latency period at a median of 1.5 years [23], typically presenting as a rapidly progressive disease without a recognized antecedent MDS [26]. The leukemogenic mechanism of topoisomerase II inhibitors is based on its interference with DNA re-ligation and chromosomal breakage, yielding chromosomal translocations involving *KMT2A* at 11q23 and *RUNX1* at 21q22 [25, 27, 28]. Genetic aberrations in hematopoietic stem cells and progenitor cells exposed to cytotoxic therapy may confer a survival advantage that leads to clonal proliferation and ultimately manifests as sAML.

Since radiation therapy is often given along with chemotherapy as part of multi-modality therapy, there is debate over the leukemogenic role of radiation therapy itself and the

specific cytogenetic abnormalities involved [23]. The association between radiation therapy and sAML is best documented in breast cancer, where studies show that radiation therapy increases the relative risk of sAML development two- to six-fold [29–31] after adjusting for other therapies received. The time course is not well defined, with a median onset of 4.5 years after exposure in a breast cancer study [31], in contrast to a markedly long latency period with a median of 18 years in a pooled analysis of patients with sAML [23]. Similar to alkylating agents, radiation therapy induces double-strand DNA breaks [32] and has been associated with unbalanced cytogenetics [23] that suggests a similar pathogenesis. Most cases of therapy-related sAML therefore involve the propagation of a myeloid clone with genetic instability induced by prior chemotherapy and/or radiation. An altered bone marrow environment may facilitate the expansion of pathogenic clones, as is the case in sAML due to an AHD.

Other causes of therapy-related sAML have been explored, such as the immunomodulatory agent lenalidomide [33] (especially in the immediate post-transplant setting) and the immunosuppressant azathioprine [34]. Lastly, occupational and residential chemicals such as benzene, vinyl chlorides, dyes, tanning solutions, soot, and coal dust have shown statistically significant association with sAML in epidemiology studies, though exposures account for only a small percentage of cases [35]. This review encompasses AML-MRC and therapy-related AML as defined by the WHO [18]. These malignancies are collectively referred to as secondary AML (sAML) throughout the review, as both follow a similar treatment approach.

Genomics

At the molecular level, AML exhibits a lower number of coding mutations per exome compared to other cancers [36]. However, variations in gene expression, DNA methylation, and the bone marrow microenvironment are factors contribute to the incredibly heterogeneous phenotype of sAML. Ontogeny studies have sought to track the clonal evolution throughout the pathogenesis of sAML.

The Cancer Genome Atlas Project analyzed genomes of de novo AML patients and found certain mutational patterns to be non-random and mutually exclusive, suggesting specific deregulatory pathways [37]. Mutations could be grouped into functional categories for signaling (e.g., *FLT3*, *RAS*), DNA methylation (e.g., *IDH1*, *IDH2*), myeloid transcription factors (e.g., *RUNX1*), chromatin-modification (e.g., *ASXL1*, *EZH2*), nucleo-cytoplasmic shuttling (e.g., *NPM1*), tumor suppressors (e.g., *TP53*), spiceosome complex (e.g., *SRSF2*), and cohesin complex (e.g., *STAG2*); each of which correlates to a mechanistic role in leukemogenesis. Genomic instability tends to be uncommon, except for complex/monosomal karyotypes that were strongly associated with *TP53*.

According to clonal composition analysis, mutations of genes involved in epigenetic regulation, such as those related to DNA methylation (*DNMT3A*, *TET2*, *IDH*1, *IDH2*) and chromatin modification (*ASXL1*), tend to occur early in the founding clone during the MDS phase [17]. In fact, mutations in genes regulating chromatin (*ASXL1*, *STAG2*, *BCOR*, and *EZH2*) and RNA splicing (*SRSF2*, *SF3B1*, *U2AF1*, and *ZRSR*2) have been found to be over 95% specific for AML with myelodysplasia-related changes. These mutations often found in high-risk MDS patients may be drivers of dysplastic differentiation and ineffective hematopoiesis in MDS. By enabling a survival advantage over non-mutated hematopoietic stem cells during chemotherapy, these epigenetic mutations may be responsible for clonal expansion during remission in MDS, resulting in relapse and transformation to sAML [38–40].

In contrast to epigenetic mutations that tend to be present in preleukemic hematopoietic clones, mutations in signal transduction proteins (*FLT3*, *RAS*), myeloid transcription factors (*RUNX1*, *CEBPA*, *GATA2*), and nucleo-cytoplasmic shuttling proteins (*NPM1*) are usually not present in MDS and instead occur late in leukemogenesis [17, 36]. *NPM1* and *FLT3* mutations have been associated with de novo AML [5, 17, 41]. Mutations in de novo AML are generally more susceptible to chemotherapy and are lost during remission, while mutations that drive sAML inherently confer relative chemoresistance and thus result in worse clinical outcomes.

Similar to the findings of non-random mutations for de novo AML, the pathogenesis of therapy-related sAML may also be driven by a limited number of cooperative pathways [26]. Alkylator-induced therapy-related sAML commonly presents with unbalanced cytogenetics such as deletions in chromosomes 5 or 7 and haploinsufficiency of tumor suppressor gene *EGR1* on chromosome 5q has been shown to be an initiating event in the pathogenesis of AML [42]. However, loss of multiple tumor suppressor genes in addition to other mutations may be ultimately necessary for transformation, which is consistent with the relatively long latency of alkylator-induced, therapy-related sAML. On the other hand, topoisomerase-induced sAML is associated with balanced rearrangements and shorter latency. Following translocations resulting in the fusion of a dominant oncogene such as *KMT2A* at 11q23, fewer subsequent mutations would be necessary for transformation to a leukemic phenotype [26].

Alterations in the tumor suppressor gene *TP53*, found at a higher incidence in sAML than de novo AML, are commonly associated with complex/monosomal cytogenetics and poor prognosis [43]. *TP53* is important for regulating cellular response to genotoxic stress, and alterations in *TP53* may harbor a selective proliferative advantage [44]. Similar to sAML pathogenesis from secondary-type mutations, *TP53* alterations

may be acquired early in a founding clone and allowed to preferentially expand after chemotherapy. Therapy-related AML commonly manifests as complex and monosomal karyotypes, likely due to the selection of resistant clones conferred by *TP53* alterations during prior chemotherapy [10, 11, 44]. The mechanism by which secondary-type and *TP53* alterations lead to sAML therefore suggests inherent chemoresistance, explaining the poor prognosis of sAML and underscoring the need for novel therapies.

Treatment

Because patients with sAML often constitute a small subset of AML clinical trials or are excluded altogether [45], the optimal approach to therapy for sAML remains unclear. The low number of patients with sAML also precludes analysis of subgroups within sAML that may benefit from particular treatment strategies. Further complicating treatment options are the sequelae of prior therapies that patients have been exposed to while treating a hematologic disorder/other malignancy preceding transformation into sAML. Given the generally poor overall outcomes, consolidation with allogeneic hematopoietic cell transplant (alloHCT) is encouraged in all patients who are candidates, since it is potentially the only curative treatment. Although adverse risk cytogenetics is an independent risk factor for post-transplant relapse, alloHCT likely offers the greatest odds of long-term remission. For those undergoing alloHCT in first remission, patients with de novo and secondary AML seem to have comparable overall survival, disease-free survival, relapse rate, and non-relapse mortality [46, 47].

The poor outcomes in sAML may therefore be driven by a failure to achieve and maintain remission, and the choice of optimal induction regimen indeed remains a topic of clinical debate. Recent advances in sAML therapy such as the liposomal agent CPX-351, the reintroduction of GO, and rational combinations under study add complexity to the treatment landscape, and it is important to objectively delineate the place in therapy of new agents that show promise in a malignancy that has proven difficult to treat.

7 + 3

The treatment of AML has remained relatively unchanged since the 1970s, when the standard of care was established as the "7 + 3" regimen with cytarabine and an anthracycline [48]. Complete remission (CR) rates with this approach range from 30 to 60%, and median overall survival is approximately 9 months for patients with sAML [1, 49–51]. Treatment-related mortality is 5 to 10%, and median time to neutrophil and platelet recovery is 26 days [52, 53] . Clinical trials of 7 + 3 reporting subgroup analyses demonstrate that patients with sAML are approximately half as likely to achieve complete remission, 1.3 to 1.4 times more likely to experience mortality at 2 years, and twice as likely to experience mortality at 4 years compared to those with de novo AML [49, 54]. Patients with sAML are particularly poor responders to treatment, as confirmed in a large national population-based cohort study in Denmark that reported inferior outcomes in patients with sAML, most of whom received standard 7 + 3 induction chemotherapy [1]. Compared to those with de novo AML, patients with sAML were half as likely to achieve complete remission, and the poor response corresponded to approximately 14 to 25% increased risk of mortality at 3 years. On adjusted analyses, the inferior outcomes are statistically significant for all types of sAML, including etiologies of MDS, non-MDS AHD, and prior chemotherapy.

Therapeutic resistance in AML may be mediated by overexpression of efflux pumps such as p-glycoprotein, decreasing exposure to anthracyclines. MDR1 expression and the resulting functional efflux via p-glycoprotein has been shown to increase with age, from 17% in patients under 35 years old to 39% in patients for those 50 years old and above [55]. In fact, a cohort study showed p-glycoprotein expression to be higher in patients with AML transformed from MDS than that in patients with de novo AML (69%, 9 of 13 versus 40%, 55 of 138; $p = 0.041$) [56]. P-glycoprotein expression was also an independent predictor for failing to attain CR with 7 + 3 induction chemotherapy. Hence, p-glycoprotein expression may be at least partially responsible for the poor outcomes with anthracycline-based regimens in the elderly and/or patients with sAML.

CPX-351

CPX-351 (Vyxeos®) is a liposomal formulation of cytarabine and daunorubicin recently FDA approved for the treatment of AML with myelodysplasia-related changes or therapy-related AML. The reformulation of 7 + 3 is thought to optimize the pharmacodynamics and pharmacokinetics. One unit of CPX-351 contains 1.0 mg of cytarabine and 0.44 mg of daunorubicin. The liposomal nano-scale drug delivery system of CPX-351 was designed to maintain a 5:1 ratio correlating with maximal synergistic activity in vitro and in vivo [57]. The encapsulated liposomal formulation enhances delivery of CPX-351 to the bone marrow to more selectively target leukemic cells. It has also been proposed to overcome resistance mechanisms such as P-glycoprotein efflux and other first-pass metabolism [58]; however, once the chemotherapy is released intracellularly, P-glycoprotein may still efflux the individual drug components. The formulation of CPX-351 also resulted in an extended half-life and accumulation at each dose [59]. Beyond these theoretical pharmacodynamics and pharmacokinetic advantages, it is unknown why CPX-351 is associated with efficacy specifically in patients with sAML.

Reflecting the gravity of the unmet need in the treatment of sAML, the FDA had designated CPX-351 as an orphan drug.

The benefit of CPX-351 in the sAML subgroup was first identified in a preplanned analysis of a phase II study comparing induction and consolidation of CPX-351 to 7 + 3 in newly diagnosed AML in adults 60 to 75 years old [60]. Although there was no statistically significant survival benefit in the study population as a whole, the subgroup of 52 patients with sAML were found to have improved overall survival with CPX-351. The efficacy and safety of CPX-351 in sAML were confirmed in a phase III open-label trial, in which 309 patients 60 to 75 years old with newly diagnosed sAML were randomized to CPX-351 versus 7 + 3 [61]. Treatment with CPX-351 resulted in significantly improved CR/CRi rates at 47.1% versus 33.3% ($p = 0.016$), with approximately 10% CRi (complete remission with incomplete count recovery) in both arms. Event-free survival (2.53 months for CPX-351 versus 1.31 months for 7 + 3; $p = 0.021$) and overall survival (9.56 versus 5.95 months, respectively; $p = 0.005$) also favored CPX-351, although event-free survival was very low in both arms and median remission duration were similar (6.93 versus 6.11 months; $p = 0.291$). Subgroup analyses showed the survival benefit over 7 + 3 to be consistent by age stratification and in those with therapy-related sAML. However, other subgroups exhibited non-significant differences in median overall survival, and these include patients with unfavorable cytogenetics (6.60 versus 5.16 months; hazard ratio, HR 0.73; 95% confidence interval, 95% CI 0.51 to 1.06), de novo AML with MDS karyotype (10.09 versus 7.36 months; HR 0.71, 95% CI 0.42 to 1.20), and prior HMA exposure (5.65 versus 5.90 months for CPX-351 versus 7 + 3, respectively; HR 0.86, 95% CI 0.59 to 1.26). This is concerning, given that a majority of patients with sAML have poor-risk cytogenetics and that several patients with sAML arising from MDS have been previously treated with HMA (Table 1).

It is noteworthy to point out that the control arm may not accurately represent standard practice at many centers. First, a second induction was allowed: the selection of patients to receive second induction adds another factor for potential bias, and the double induction may have contributed to the high incidence of early mortality. Importantly, the control arm utilized 7 + 3 induction with 5 + 2 consolidation, which while an NCCN guideline option [69], is not standard practice for several institutions. Some consider this consolidation inferior to high-dose cytarabine, although there is a lack of data in older populations to support the optimal consolidation strategy. This possibly contributed to the lower event-free survival and overall survival of patients in the control arm. Also noteworthy is the somewhat surprisingly low response rates (CR/CRi) to 7 + 3 in this trial: 33% (CR 26% and CRi 8%). This is numerically lower than the 40 to 60% CR rate observed in a large epidemiological study [1], despite real-world patients being potentially less fit than clinical trial subjects, and the historical context of the epidemiological study encompassing 2000 to 2013 versus the CPX-351 phase III trial from 2012 to 2014. Previous trials of 7 + 3 in patients over 65 years old and those with adverse cytogenetic risk demonstrated an approximately 20% probability of overall survival at 30 months [49, 52], compared to the 12% 30-month survival in patients receiving 7 + 3 in the CPX-351 trial. Although cross-trial comparisons are limited by inherently different patient cohorts, the apparent underperformance of the control arm and use of the 5 + 2 re-induction and consolidation raises inquiry regarding how representative this is as a standard control group.

In both the phase II and III trials, CPX-351 treatment resulted in a higher rate of CRi than 7 + 3, suggesting that its efficacy may be contingent upon pharmacokinetic and pharmacodynamic properties. While this may improve the ability of CPX-351 to deliver chemotherapy to the bone marrow, there are consequences of substantially prolonged myelosuppression. Patients receiving CPX-351 required a longer median time to neutrophil (35 versus 29 days) and platelet recovery (37 versus 29 days, for CPX-351 versus 7 + 3, respectively) [61].Given the duration of myelosuppression, one should anticipate that the length of stay in the hospital during induction is prolonged in patients receiving CPX-351. Duration of neutropenia is known to be an independent risk factor for invasive fungal infections despite appropriate anti-fungal prophylaxis [70, 71]. Further, the prolonged thrombocytopenia did appear to correlate with an increased incidence of hemorrhage in the phase II and III trials. Bleeding events of any grade were 75% versus 60%, and grades 3 to 5 hemorrhage were 12% versus 9% for patients treated with CPX-351 versus the control arm, respectively, in the phase III trial. CPX-351 was also associated with a higher incidence of rash and lower incidence of alopecia, and other non-hematological adverse event rates were similar. The incidence of reduced ejection fraction was comparable between the two arms. CPX-351 did not appear to mitigate cardiotoxicity, although long-term follow-up is lacking and patients with significant myocardial impairment were excluded from the trial. Lastly, the phase III study claims that CPX-351 may be a safer treatment option after normalizing to an adverse event rate per patient-year. This may not be an accurate means of assessing safety in clinical practice, as the extended treatment for CPX-351 is likely related to the prolonged myelosuppression and ongoing supportive care.

CPX-351 has been proposed to be suitable as a bridge to transplant. A combined analysis of patients with sAML in the phase II and III trials found that patients treated with CPX-351 were more likely to receive HCT (32% versus 25%; odds ratio 1.47, 95% CI 0.924 to 2.349), although this difference was not statistically significant [72]. Patients receiving HCT in the phase III trial demonstrated favorable long-term outcomes; by 100 days post-transplant, mortality in transplant patients was 9.6% for patients receiving CPX-351 compared to 20.5% for 7 + 3 [73]. However, the decision to transplant was not randomized; thus, a number of variables such as donor selection and graft type could influence outcomes besides induction therapy, and this exploratory analysis may be subject to confounders. In

Table 1 Efficacy and safety of current secondary AML treatment options

Regimen	CR/CRi	CR	Median EFS	Median OS	Key adverse effects
7 + 3 [1, 49, 62]	–	45 to 61%	2-year EFS 9–6%	9.1 months	Myelosuppression, mucositis, cardiotoxicity
7 + 3 (CPX-351 phase III trial) [61]	33.3%	25.6%	1.31 months	5.95 months	
7 + 3 (FLAG cohort study) [63]	45%	34.8%	5 months	9.1 months	
CPX-351 [61]	47.7%	37.3%	2.53 months	9.56 months	Prolonged myelosuppression, febrile neutropenia, hemorrhage, cardiotoxicity
FLAG [63]	65%	52.5%	4 months	8.5 months	Myelosuppression, febrile neutropenia
GCLAC* [64]	–	76%	–	24.3 months	Myelosuppression, febrile neutropenia
HiDAC with daunorubicin and etoposide** [65]	–	86%	6-year EFS 21%	6-year OS 24%	Myelosuppression, febrile neutropenia
HiDAC with mitoxantrone [66]	–	66%	DFS 13.6 months	13.1 months	Myelosuppression, febrile neutropenia
HMA [62]	20%	–	–	10.8 months	Myelosuppression
Venetoclax with HMA [67]	67%	–	–	Not reached (95% CI 14.6 months—not reached)	Myelosuppression
Low-dose cytarabine [62]	–	43%	–	7.1 months	Well tolerated
Best supportive care [68]	–	–	–	4 months	N/A
GO monotherapy [68]	25%	–	–	7.2 months	Sinusoidal obstruction syndrome, myelosuppression

CR, CR/CRi rates, EFS, and OS are reported based on the largest available subgroup analyses of patients with sAML unless otherwise stated. Studies for CPX-351 and FLAG consisted entirely of patients with sAML. Outcomes of patients receiving 7 + 3 are also reported from the studies of CPX-351 and FLAG, in order to assess the validity of the control arm

CR complete remission; CRi complete remission with incomplete count recovery; DFS disease-free survival; EFS event-free survival; FLAG = fludarabine, cytarabine, G-CSF; GCLAC G-CSF, clofarabine, cytarabine; GO gemtuzumab ozogamicin; HiDAC high-dose cytarabine; HMA hypomethylating agent; OS overall survival; − not reported; N/A not applicable; 95% CI 95% confidence interval

*Consisted of 25 patients with sAML (50% of study population), **consisted of 46 patients with sAML (2% of study population)

fact, there is evidence of imbalances between the two arms in the trial. According to this exploratory analysis, a higher proportion of patients in the 7 + 3 arm were taken to transplant not having attained a CR/CRi compared with the group treated with CPX-351 [73]. The external validity of the different outcomes with CPX-351 is also limited by the use of 5 + 2 consolidation in the control arm, which may have contributed to a lower depth of remission in the control arm going into transplant. In addition, the prolonged cytopenias associated with CPX-351 is expected to result in a selection bias, since only relatively fit patients are likely to tolerate CPX-351 induction and be able to proceed to transplant. This may be evidenced by the fact that although 47.7% of patients who received CPX-351 attained CR/CRi, only 34% of patients proceeded to transplant. The remarkable survival with CPX-351 post-transplant may therefore reflect consequences of these confounders.

The prolonged myelosuppression associated with CPX-351 limits the utility in elderly patients, leading one to consider the feasibility of dose reduction without compromising efficacy. Two phase II studies assessed the efficacy and safety of CPX-351 dose reduction in patients at risk for induction mortality, with risk factors such as advanced age, Eastern Cooperative Oncology Group (ECOG) performance status greater 2, renal dysfunction, and/or unfavorable cytogenetics [74, 75]. These characteristics may better reflect real-world AML patients, as the pivotal phase II and phase III trials excluded patients with end organ dysfunction and poor performance status. Dose reductions including 32 units/m^2, 50 units/m^2, 64 units/m^2, and 75 units/m^2 were tested, but overall resulted in unsatisfactory response rates. Adverse effects did not appear to be mitigated with dose reduction, as 80% of patients in one study experienced grades 3 to 4 adverse events despite dose reduction. Frail patients may be particularly prone to mortality from sepsis, hemorrhage, other myelosuppressive complications associated with CPX-351. The practicality of dose adjustment is also limited by the availability of a single vial size and the fixed molar ratio. Therefore, the most reasonable strategy based on current evidence would be to use full-dose CPX-351 in relatively fit patients who are expected to tolerate it, and to pursue alternative regimens for those deemed at high enough risk for treatment-related mortality.

Purine analog and high-dose cytarabine combinations

Regimens with high-dose cytarabine (HiDAC) have demonstrated the most apparent benefit in patients with sAML in subgroup analyses. The EORTC-GIMEMA AML-12 trial

combined high-dose cytarabine (3 g/m^2 twice daily on days 1, 3, 5, and 7) with etoposide and daunorubicin, and it included 105 patients with sAML [65]. Compared to those receiving standard-dose cytarabine, patients with sAML treated with the HiDAC had clinically meaningful improvements in CR (94.1% versus 59.1% for HiDAC versus standard-dose cytarabine in 15- to 45-year olds, and 82.8% versus 52.9% in 45- to 60-year olds). The survival benefit also reached statistical significance in the younger subgroup of patients with sAML; 76.5% of HiDAC-treated patients reached 6-year overall survival, compared to 28.7% of patients with standard-dose cytarabine (HR 0.23, 99% CI 0.08 to 0.89). A small single-center prospective study in 32 patients with therapy-related myeloid neoplasms reported high-dose cytarabine (3 g/m^2 once on days 1 and 5) with mitoxantrone to be feasible, with a CR rate of 66%, 30-day treatment mortality of 9%, and an overall survival of 72% at 1 year for patients who proceeded to alloHCT [66]. Published studies on alternatives to standard 7 + 3 therefore intimate the potential benefit of a high-dose cytarabine-based strategy in patients with sAML.

Purine analogs can be added to synergize with cytarabine. Intracellularly, cytarabine (Ara-C) is sequentially phosphorylated to produce its active metabolite arabinofuranosylcytosine triphosphate (Ara-CTP). The rate-limiting step is the initial phosphorylation via deoxycytidine kinase, an enzyme in the nucleoside salvage pathway typically leading to the production of endogenous deoxycytidine triphosphosphate (dCTP). dCTP is a deoxyribonucleotide that can also be produced from ribonucleotides via ribonucleotide reductase. Because purine analogs inhibit ribonucleotide reductase to suppress deoxynucleotide triphosphate (dNTP) production, purine analogs in effect upregulate deoxycytidine kinase to increase dCTP to compensate for the decreased dNTP pools and thus also increases the formation of Ara-CTP. Indeed, in vitro studies have shown that pretreatment with fludarabine 4 h before cytarabine resulted in nearly doubled levels of Ara-CTP levels [76]. It is also thought that the combination of cytarabine with a purine analog may reduce the risk of neurotoxicity, since more cytarabine is retained intracellularly instead of being extracellularly converted to arabinofuranosyluracil triphosphate (Ara-UTP). AML regimens thus combine fludarabine or clofarabine with high-dose cytarabine to harness synergy, in addition to adding G-CSF to theoretically increase myeloblast sensitivity to the cytotoxic agents. In addition, it is rational to utilize chemotherapy agents besides P-glycoprotein substrates such as anthracyclines, as patients with sAML may be predisposed to chemoresistance mediated by P-glycoprotein efflux [55].

Because the GCLAC regimen (G-CSF priming with clofarabine and high-dose cytarabine) had shown efficacy in the relapsed or refractory setting, a prospective cohort study sought to determine outcomes in untreated AML/high-grade MDS or MPN patients of which 46% had sAML due to an AHD and 4% had therapy-related sAML [64]. In this study of 50 patients (including 39 patients with AML) with a median age of 53 years, the CR rate with GCLAC was 76% in the overall cohort and 65% for patients with an AHD. Patients in the overall cohort had a median overall survival of 24.3 months, 54% proceeded to alloHCT; the 60-day mortality was only 2%. With 76% of patients experiencing grade 3 and 20% experiencing grade 4 adverse effects (most of which were infection-related), as well as a transient transaminitis in the majority of patients, clofarabine is not without safety concerns in sAML patients at high risk for treatment-related mortality.

Bashey et al. assessed FLAG (fludarabine, high-dose cytarabine, and G-CSF) induction in 24 patients in which 57% had AHD-related sAML [77], and Ferrera et al. investigated a modified FLAG regimen using continuous fludarabine and cytarabine infusion in 64 patients with AML secondary to MDS [78]. Despite the elderly age distribution with patients at least 60 years old, both cohorts showed that efficacy and safety were favorable and surprisingly comparable to that achieved in the CPX-351 trials: in the overall cohorts in Bashey et al. and Ferrara et al., patients experienced a CR rate of 58% and 64%, a CR/CRi rate of 75% and 67%, HCT consolidation in 29% and 20%, and early induction mortality (predominantly attributed to infectious complications) in 12% and 16%, respectively. There were no cases of cardiotoxicity, mucositis, cerebellar toxicity, or other non-hematologic adverse effects more severe than grade 2, except for 7% of patients with liver function test elevations or diarrhea in Ferrara et al. Overall survival was 54% at 1 year in Bashey et al. and a median of 8 months in Ferrara et al.

The retrospective, single-institution FOSSIL study further suggested FLAG's potential benefit as an alternative frontline induction strategy in sAML patients [63]. Patients receiving FLAG had an overall response rate of 70% versus 48% with 7 + 3 ($p = 0.043$), which correlated to more patients being able to proceed to alloHCT (33% with FLAG versus 15% with 7 + 3, $p = 0.051$) and experience long-term benefit (5-year overall survival 22% with FLAG versus 6% with 7 + 3, $p = 0.054$). Induction mortality within 30 days was also lower at 3% with FLAG and 8% with 7 + 3, and patients receiving FLAG only experienced a median of 16 days of neutropenia, compared to 23 days for 7 + 3 ($p < 0.001$) and 35 days for CPX-351 [61]. There were also no cases of cerebellar toxicity despite the elderly patient population with a median age of 63 years.

Based on limited data from retrospective cohort studies and subgroup analyses of HiDAC-based approaches, FLAG or GCLAC are promising sAML treatment options that are significantly less costly and potentially better tolerated and more efficacious than CPX-351. The lack of anthracyclines in the regimen is beneficial for patients with reduced ejection fraction at baseline and other cardiac comorbidities. It may also contribute to the decreased time to neutrophil recovery, which

is an important consideration given the significant infection-related morbidity and mortality in this highly immunocompromised patient population.

Hypomethylating agent-based approaches

An alternative treatment that may be preferred in elderly and/or unfit patients is the use of hypomethylating agents (HMA), azacitidine and decitabine. Because HMA exert anti-tumor effects primarily via epigenetic modification to induce re-expression of tumor suppressor genes, acute toxicities typical of intensive induction chemotherapy are minimized; however, response is often delayed. Clinical responses typically require 2 to 3 months of treatment, scheduled every 4 weeks to maintain epigenetic effects [79–83].

Although the response to HMA is typically less rapid than conventional cytotoxic chemotherapy, these agents may have a unique role for patients with sAML. In this more elderly, unfit, and more heavily pretreated patient population, those unable to tolerate the acute and potentially serious adverse effects of intensive chemotherapy would benefit from treatment with a HMA. From an efficacy standpoint, the re-expression of tumor suppressor genes via HMA may be particularly advantageous in sAML, which is typically associated with the loss of tumor suppression as reflected by alterations in *TP53* and DNA methylation genes, as well as losses on chromosomes 5 and 7 and complex/monosomal karyotypes. In fact, a cohort study of patients with AML or MDS found a 100% response rate with a 10-day course of decitabine in 21 patients with *TP53* alterations [84].

Another single-center cohort study in patients with AML or MDS and/or chromosomes 5 and 7 abnormalities found higher rates of CR of 41% versus 35% ($p = 0.395$), more durable CR at a median of 45 versus 23 weeks ($p = 0.153$), and superior overall survival at a median of 9 versus 5 months ($p = 0.019$) for HMA in comparison to cytarabine-based regimens (with the majority of patients receiving either cytarabine with an anthracycline, or clofarabine with or without low-dose cytarabine) [85]. Thus, treatment with a HMA appears to overcome at least some of the chemoresistance in patients with poor-risk cytogenetics and myelodysplasia, but the incomplete clearance of leukemia cells harboring driver mutations may contribute to the lack of a durable response and eventual relapse.

Because HMA often require multiple cycles to induce remission, and remissions tend to be short-lived, the combination of a HMA with the BCL-2 (anti-apoptotic B cell lymphoma 2 protein) inhibitor venetoclax is under study. Ex vivo data suggest synergistic cytotoxicity between venetoclax and azacitidine [86], although the exact mechanism is not well characterized. The activation of multiple pro-apoptotic signals is speculated to enhance "apoptotic primedness," resulting in an increased therapeutic index for cytotoxicity against myeloid blasts. This in turn may translate to efficacy in sAML in which alterations such as *TP53* interfere with apoptotic processes. A non-randomized open label phase 1B dose-escalation study in elderly patients with AML found evidence of clinical activity and tolerability with azacitidine (7 days) or decitabine (5 days) combined with venetoclax [67]. For 145 patients in the dose-escalation cohorts, 67% attained a response, approximately half of which were CRi. The CR/CRi rate was equally high among patients with sAML (67%) and in those with poor risk cytogenetics (60%). The combination regimen induced a response in a median of 1 month, which is faster than HMA monotherapy, and the remission was also sustained to a median duration of 11 months. Median time to best response was 2.1 months. Overall survival was also favorable at a median of 17.5 months; among those with sAML, survival was not reached (95% CI 14.6 months—not reached). Early data with decitabine for 10 days in combination with venetoclax have also been recently reported. Patients with sAML achieved a CR/CRi rate of 71% ($n = 7$), while patients with de novo AML demonstrated a 92% CR/CRi rate ($n = 24$) [87]. This therapeutic combination warrants further study as another potential treatment option in patients with sAML.

A large retrospective study assessing outcomes of different treatment modalities highlights the benefits of HMA for sAML in the real-world setting [62]. Despite statistically significant lower CR rates in lower intensity therapies, patients treated with HMA or low-dose cytarabine had superior median overall survival compared to those receiving high- or intermediate-dose cytarabine (6.9 versus 5.4 months, respectively; $p = 0.048$). Of note, the majority of the high-dose cytarabine regimens contained anthracyclines or chemotherapy agents outside of more traditional purine analog and cytarabine combinations, which likely contributed to toxicity in this group. Additionally, although the percentages were small, more patients receiving lower intensity treatments were able to proceed to transplant (10.3% versus 4.3%, $p = 0.001$), possibly because they were able to continue receiving subsequent cycles of the better tolerated therapy. In fact, the median survival with low-intensity treatments was comparable to that of patients receiving CPX-351. In another observational study of elderly patients of AML, half of which had sAML, those treated with MEC (mitoxantrone, etoposide, and cytarabine) had higher CR rates compared to azacitidine, but 3-year overall survival were similar between the two cohorts after propensity-score matching [88]. As responses tend to require more time with HMA, intermediate-intensity regimens such as FLAG with quicker responses and reasonable tolerability may be able to bridge patients to transplant more promptly. Overall, HMA represent a viable option for patients not eligible for or declining intensive chemotherapy, particularly those who are not alloHCT candidates.

Besides aberrant methylation, histone acetylation is another epigenetic mechanism of gene regulation that is disrupted in leukemic cells. Panobinostat, vorinostat, entinostat, and pracinostat are histone deacetylase inhibitors studied primarily in combination with HMA or intensive chemotherapy in AML. However, there is no current clinical evidence to suggest a specific advantage in sAML. Another investigational agent in early phase development is pinometostat (EPZ-5676), a DOT1L inhibitor. DOTL1 has histone methyltransferase activity that is thought to be responsible for downstream oncogenic effects of KMT2A fusion proteins, a common mutation in therapy-related sAML. It remains to be tested whether hypothetical advantages based on the epigenetic pathophysiology of sAML translates to significant improvements in clinical outcomes with these new DNA methyltransferase and histone deacetylate inhibitors.

Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin (GO) is an antibody-drug conjugate that uses an anti-CD33 antibody to selectively deliver ozogamicin, a highly potent calicheamicin-derived cytotoxin causing DNA incision, to AML blasts that express CD33. GO initially received accelerated FDA approval for relapsed AML in May 2000, but was voluntarily withdrawn in June 2010 due to a lack of benefit when added to standard therapy in a phase III confirmatory trial [89] and safety concerns primarily associated with the risk of sinusoidal obstruction syndrome. It was reapproved in September 2017 based on new findings of improved event-free survival and reasonable safety with a lower fractionated dosing regimen [90], improved 5-year overall survival due to a lower risk of relapse in certain subgroups [91], and improved survival over best supportive care in elderly patients [68].

Select GO trials included 40 to 90 patients with sAML (about 5 to 15% of the study population), and outcomes were largely unchanged with or without GO. Earlier trials and a meta-analysis suggested that GO conferred some degree of survival benefit in patients with favorable- (especially CBF) and intermediate-risk cytogenetics [91–93]. However, patients with sAML experienced approximately 10% numerically lower response rates when GO was added, and survival was unchanged [92, 93]. The lack of apparent efficacy of GO for sAML is expected, since patients with sAML often have poor-risk cytogenetics, a group that did not benefit from GO in any trial or overall in the meta-analysis [91]. A trial assessing sequential GO with MEC identified patients with sAML less than 70 years old as the only subgroup that showed any benefit with GO, with 3-year overall survival plateauing at 20% with GO versus 5% without GO [94]. It is difficult to conclude the true utility of GO in this subgroup, since this was based on a post hoc analysis and is inconsistent with previous studies. CR rate in patients with sAML have also been disappointingly low across studies, and was only 25% in a study of GO monotherapy [68]. Thus, there is currently no clear clinical scenario in which patients with sAML would benefit from GO, and there are significant toxicity concerns.

A novel approach under investigation is the use of GO following standard chemotherapy. Since CD33-positive cells in peripheral blood may limit the effectiveness of GO in the bone marrow, GO may have increased activity in bone marrow blasts after initial chemotherapy reduces the CD33 antigen load in peripheral blood [95, 96]. A phase II trial studied FLAI-GO induction, with fludarabine, HiDAC, and idarubicin immediately followed by low-dose GO in patients 65 years old or younger [97]. Patients responded favorably, with a CR/CRi rate of 85% with predominantly CR (82%), as well as a low induction mortality of 3%. In the subgroup of 34 patients with sAML, CR rates were significantly lower at 67% ($p = 0.003$). It is difficult to conclude the advantage of GO per se given the lack of an active comparator, and the benefit for sAML is unclear in this subgroup analysis. GO may be a useful adjunct in young and fit patients with CD33-positive AML, but more long-term data, randomized controlled trials, and studies in patients with sAML are needed.

Vadastuximab talirine (SGN-CD33A) is another antibody-drug conjugate directed against CD33 with a more stable linker that is thought to limit free cytotoxin, reducing the risk of SOS [98]. The use of pyrrolobenzodiazepine as a conjugated cytotoxin is potentially more potent, and vadastuximab talirine also has the advantage of better loading of the anti-CD33 antibody with the toxic payload. However, the phase III CASCADE trial was terminated early due to higher rates of death observed in patients receiving vadastuximab talirine. Although there was no apparent correlation with hepatotoxicity, there was a higher rate of fatal infections with vadastuximab talirine. The trial enrolled patients with untreated de novo or secondary AML with intermediate or adverse risk cytogenetics. In a phase 1 trial combining HMA with vadastuximab talirine for previously untreated CD33-positive AML, nearly half of the patients had sAML. Even with advanced age (median 77 years old) and the majority of adverse-risk cytogenetics (75%), this subgroup of 24 patients with sAML achieved high response rates at a CR/CRi of 75% (CR rate 42%). Another subgroup of patients with adverse-risk cytogenetics also demonstrated surprisingly favorable efficacy at a CR/CRi of 80% (CR rate 50%). The exclusion of patients with prior HMA treatment in this phase I study is a current limitation in applying this strategy to patients with sAML arising from MDS. More data are needed on the efficacy, safety, and optimal regimens in sAML.

Investigational agents

As the unmet therapeutic need in sAML is becoming increasingly recognized, many clinical trials are openly targeting

patients with sAML. However, given the lack of clearly identified targetable driver mutations in sAML and the low relative prevalence compared to de novo AML, most trials of investigational agents include both types of AML with subgroup analyses to identify potential benefits in sAML. Because of limited long-term survival with current treatment options, the National Comprehensive Cancer Network (NCCN) strongly encourages participation in a clinical trial.

A number of investigational agents involve modifications on existing treatment options in order to improve efficacy and safety. However, theoretical advantages do not always translate from bench to beside. Amonafide is a new topoisomerase II inhibitor thought to have utility in sAML because it is not prone to p-glycoprotein efflux as anthracyclines are. Unfortunately, a phase III trial failed to show differences in CR rates for amonafide with cytarabine versus conventional 7 + 3 in sAML [99].

Given the increasing prevalence of epigenetic mutations found in sAML, various epigenetic modifiers are under study. *IDH1* and *IDH2* mutations lead to hypermethylation and are associated with clonal hematopoiesis in healthy elderly patients [36]. *IDH1* and/or *IDH2* inhibitors may be useful for targetable mutations, particularly in sAML transformed from MDS or MPNs as *IDH* mutations are implicated in the pathogenesis [100]. Other epigenetic targets are being investigated, as monotherapy and in combination with existing treatments. The rational combination of direct-acting cytotoxic agent with a slow-onset epigenetic modifier, such as venetoclax with a HMA, may be able to provide rapid reduction of tumor burden with long-term restoration of endogenous tumor suppression.

Immunotherapy approaches are also in early phases of development, including monoclonal antibodies, bispecific antibodies, chimeric antigen receptor (CAR) T cells, and checkpoint inhibitors. A promising target is CD123, also known as interleukin-3 receptor alpha chain. Because it is overexpressed on AML blasts, CD123 may be a useful targeting signal and is being combined with T cell-mediated cytotoxicity via CD123/CD3 bispecific antibodies and CAR T cells. With T cells generally thought to be preserved in AML, checkpoint inhibitors may help to augment the response of endogenous T cells against AML blasts. The PD-1 pathway has been linked to in immune invasion during AML progression [101], and anti-PD-1 monoclonal antibodies are being studied as maintenance therapy for patients in remission. Another therapeutic approach is utilizing an immunomodulatory priming effect of HMA in combination with checkpoint inhibitors, as HMA have been shown to upregulate PD-1 and PD-L1 [102]. The precise role of immunotherapy in AML is not well defined, and results of clinical trials are necessary in order to elucidate the benefits of immunotherapy in both de novo and sAML.

Other agents are exploring different mechanisms of cytotoxicity. Venetoclax induces BH3-dependent apoptosis, and MDM2 inhibitors induce *TP53*-dependent apoptosis. Veliparib is a PARP inhibitor, hindering the DNA repair process. In vitro synergy has been observed with topotecan, and the phase I study showed notable activity in AML arising from MPN [103]. The cyclin-dependent kinase inhibitor alvocidib (also known as flavopiridol) has demonstrated a favorable CR rate of 60% compared to 35% with 7 + 3 in a phase II trial of FLAM for induction (flavopiridol, cytarabine, and mitoxantrone) that included 78 patients with sAML (47% of the study population) [104]. Although *FLT3* inhibitors are widely studied for *FLT3*-mutated AML, use in sAML is likely limited as the mutation occurs predominantly in de novo AML [17]. With improving but limited efficacy of current agents, identification of novel pharmacological modes of action and targetable mutations is crucial to expanding treatment options for sAML.

Table 2 summarizes investigational agents currently under study that specify inclusion of adult patients with sAML. Even with the currently changing treatment options of sAML, new agents and rational combinations are needed.

Guideline recommendations

While the European Medicines Agency (EMA) recently favored marketing authorization for CPX-351, European LeukemiaNet (ELN) guidelines have not delineated a treatment approach for sAML [105]. Interestingly, the National Institute for Health and Care Excellence (NICE) has recommended against employing CPX-351 for routine use in the United Kingdom, given the high cost and uncertainty regarding the cost-effectiveness [106]. In the USA, the NCCN guideline recommendations largely follow the prescribing information for CPX-351 [69]. CPX-351 is listed as an option for treatment induction, re-induction, and consolidation in patients with sAML secondary to MDS/CMML, sAML with myelodysplasia-related changes, or therapy-related sAML. The recommendation grading is stronger (category 1) for patients of 60 years of age and older compared to that for younger patients (category 2A), based on the patient population of the phase II and phase III CPX-351 trials enrolling patients at least 60 years old. For elderly patients with AHD, therapy-related AML, or unfavorable cytogenetic or molecular features and who are candidates for intensive induction therapy, the NCCN guidelines also list HMA or 7 + 3 with or without midostaurin as category 2A recommendations.

The NCCN guidelines specify that CPX-351 should not be used for therapy-related sAML with CBF mutations or acute promyelocytic leukemia (APL). Therapy-related APL is successfully managed with standard APL treatment, and APL was an exclusion criterion in the CPX-351 trials. On the other hand, the utility of CPX-351 in patients with CBF is unknown, as the phase II and III trials excluded patients with favorable cytogenetics. CBF translocations are rare in sAML, are classified under favorable-risk cytogenetics, and are known to be

Table 2 Investigational agents including patients with secondary AML

Class	Mechanism	Drug	Regimen studied	Patient population	Phase	NCT number
Pro-apoptotic	BCL-2 inhibitor	Venetoclax	With low-dose cytarabine	Untreated, unfit	III	03069352
			With decitabine	Untreated elderly or R/R	II	03404193
			With FLAG-IDA	Untreated or R/R, fit	II	032214562
			With FLAI	Fit	II	03455504
	MDM2 inhibitor	Idasanutlin	With cytarabine	R/R	III	0254583
Cytotoxic	Topoisomerase II inhibitor	Vosaroxin	With cytarabine	Untreated	II	02658487
			Monotherapy	Untreated, elderly	II	00607997
			With decitabine	Untreated, elderly	I/II	01893320
Epigenetic	Hypomethylating agent	Guadecitabine	Monotherapy	MDS-sAML, failed HMA	II	02197676
	HDAC inhibitor	Vorinostat	With 7 + 3	Untreated, fit	III	01802333
			With decitabine and cytarabine	R/R	I	01130506
		Pracinostat	With azacitidine	Untreated	III	03151408
		Panobinostat	With 7 + 3	Untreated, elderly	I	01463046
			Monotherapy	R/R	II	00880269
			Monotherapy	Maintenance after alloHCT	I/II	01451268
		Etinostat	With azacitidine	Untreated, elderly	II	01305499
	LSD1 inhibitor	Tranylcypromine	With ATRA	R/R	I	02273102
Adoptive T cell therapy	Anti-CD123	CD123 CAR T	Monotherapy	R/R, CD123+	I	02159495
Bispecific antibody	Anti-CD123/CD3	XmAb14045	Monotherapy	R/R	I	02730312
		Flotetuzumab (MGD006)	Monotherapy	R/R	I	02152956
Immunotherapy	Anti-PD/PD1	Nivolumab	With azacitidine, with or without ipilumumab	R/R, untreated, elderly	II	02397720
			With oral cyclophosphamide	R/R	II	0317154
			Monotherapy	In remission, at risk for relapse	II	02532231
		Pembrolizumab	With azacitidine	Untreated, elderly	II	02845297
		Durvalumab	With azacitidine	Elderly, unfit	II	02775903
		Aveluamab	With azacitidine	R/R	I/II	02953561
	Anti-CTLA4	Ipilimumab	With decitabine	Elderly	I	02890329
Targeted	IDH2 inhibitor	Enasidenib (AG-221)	Monotherapy	Elderly, R/R, IDH2 mutation	III	02577406
			With azacitidine	Untreated, IDH1 or IDH2 mutation	I/II	02677922
	IDH1 inhibitor	Ivosidenib (AG-120)	With azacitidine	Untreated, IDH1 mutation	III	03173248
			With azacitidine	Untreated, unfit, IDH1 or IDH2 mutation	I/II	02677922
		Enaidinib (AG-221) or ivosidenib (AG-120)	With 7 + 3	Untreated, IDH1 or IDH2 mutation	I	02632708

Table 2 (continued)

Class	Mechanism	Drug	Regimen studied	Patient population	Phase	NCT number
	JAK2 inhibitor	Ruxolitinib	With decitabine	Untreated, R/R, post-MPN sAML	I/II	02076191
			With cytarabine	Post-MPN sAML	I/II	03558607
	FLT3 inhibitor	Midostaurin, others	Monotherapy or with HMA or induction/consolidation	FLT3-ITD or FLT3-TKD mutation		Various
Other	Polo-like kinase inhibitor	Volasertib	With low-dose cytarabine	Unfit	III	01721876
	Cyclin-dependent kinase inhibitor	Alvocidib	FLAM (flavopiridol, cytarabine, mitoxantrone)		III	Pending
			With 7 + 3	Untreated	I	03298984
	Aminopeptidase inhibitor	Tosedostat	With HMA or cytarabine	Untreated, R/R	I/II	01636609, 01567059
	PARP inhibitor	Veliparib	With topotecan and carboplatin	Untreated, R/R, post-MPN AML	II	03289910
	Nucleoside inhibitor	8-Chloro-adenosine	Monotherapy	R/R	I/II	02509546

Trials listed specify inclusion of patients with sAML, though benefits in sAML are primarily established subgroup analyses. Few trials are exclusively enrolling patients with sAML. Mechanism, synergy, and adverse effect profile are considerations when designing rational combinations with investigational agents

MPN myeloproliferative neoplasm, R/R relapsed/refractory, sAML = secondary AML

sensitive to high-dose cytarabine in de novo AML. However, there is conflicting data on the prognostic impact of CBF in sAML [6], and the efficacy of CPX-351 in patients with sAML and CBF mutations is unknown as these patients were excluded in clinical trials.

Because the NCCN AML guidelines identify sAML as a high-risk feature, the treatment algorithms group sAML together with poor-risk cytogenetics or molecular abnormalities and recommend consideration of alloHCT in young and fit patients due to increased risk of relapse. The European LeukemiaNet guidelines similarly suggest alloHCT at CR due to the otherwise high risk of relapse [105].

Principles in clinical practice

The optimal treatment approach depends on a thorough consideration of several patient-specific factors, including cytogenetics, comorbidities, prior chemotherapy received, and goals of therapy. The decision may be dynamic, depending on response to therapy and ongoing new evidence from clinical trials. Because alloHCT offers the best odds of long-term survival, the initial assessment should pivot on whether the goal of treatment is bridging to alloHCT for fit patients, or prolonging survival through less intensive treatments that unfit patients could better tolerate. A suggested treatment approach is outlined in Fig. 1, and a summary of outcomes from key clinical trials of each regimen is compiled in Table 1.

For patients who are fit alloHCT candidates, the goal of induction chemotherapy should be attaining a deep remission, as detectable minimal residual disease at alloHCT has been associated with risk of relapse [107]. Among frontline treatment options for sAML, FLAG demonstrates notable efficacy and safety, based on retrospective data [63]. FLAG has been associated with a favorable CR/CRi of 65%, which is comparable to that expected in de novo AML. It is also generally well tolerated (reported to be feasible at full dose up to 82 years of age in a cohort study) and has correlated with a relatively shorter duration of myelosuppression. GCLAC is another HiDAC-based regimen with a purine analog, but FLAG may be less myelosuppressive and has greater numbers of patients in sAML reports. HMA with venetoclax is also an appropriate choice in fit, older alloHCT candidates, with similarly promising CR/CRi rates (67%), excellent tolerability, and long-term survival rates [67]. The downside of this approach is the relatively slow attainment of CR/CRi (median time to best response of 2.1 months) in patients awaiting alloHCT.

While CPX-351 is currently the only FDA approved agent for sAML, clinical trials with methodological limitations, as detailed above, render many questions unanswered. The CPX-351 CR/CRi rate of 48% [51] is numerically lower than the 65% with FLAG (although retrospective data) [63], despite the higher proportion of patients with poor-risk cytogenetics in the FLAG study. Suboptimal response with CPX-351 has

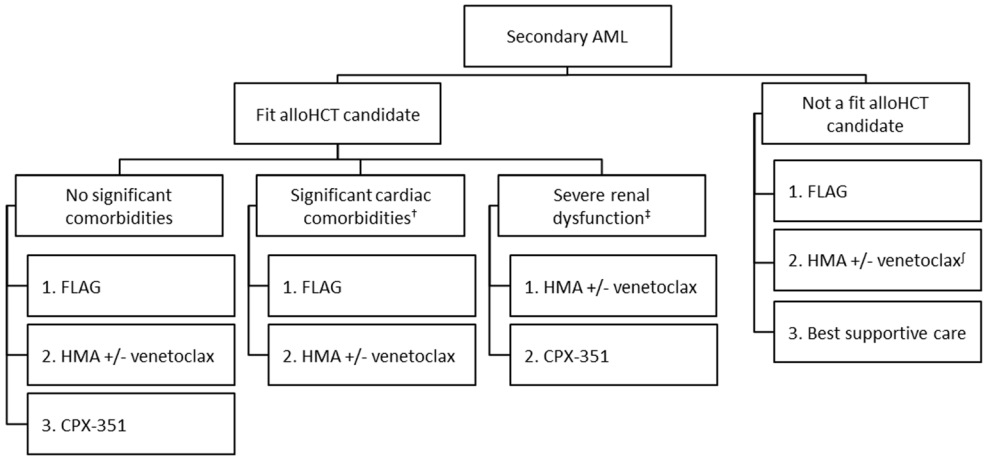

Fig. 1 Treatment approach and considerations in secondary AML. AlloHCT allogeneic hematopoietic cell transplant, HMA hypomethylating agent. †Cardiac comorbidities may be based on institutional criteria on candidates for anthracyclines. Considerations may include reduced left ventricular ejection fraction (less than approximately 40–50%), New York Heart Association class III or IV, or other cardiac comorbidities. ‡Renal dysfunction may be defined as baseline serum creatinine greater than 2 mg/dL or dependent on hemodialysis. ∫Consider prioritizing HMA therapy for patients with *TP53* mutations, if mutational status available upfront. Because alloHCT is likely the only potentially curative option, an initial assessment of whether a patient is a fit alloHCT candidate can help guide the choice of an induction regimen. In addition to efficacy and tolerability, comorbidities, value-based care, and patient preference are factors in determining an optimal patient-specific regimen, particularly in patients opting for lower intensity treatments. Figure created using Microsoft PowerPoint, 2010 version

been reported in a large retrospective cohort study [62]; this may reflect real-world patients as more elderly, less fit, and with more poor-risk disease compared to those enrolled in clinical trials. In addition, complications such as febrile neutropenia and fatal hemorrhage resulting from prolonged cytopenias with CPX-351 are concerning. An HMA-based strategy remains an option in patients who prefer to undergo a less intense induction compared to CPX-351 or HiDAC-based regimen. In patients previously treated with HMA for MDS transformed to sAML, leukemic clones may have arisen from selective pressures of HMA, and improved responses may be observed with other treatments. A recent multicenter retrospective review demonstrated high response rates (CR/CRi 53%) to purine-analogue and high-dose cytarabine combinations in sAML patients with prior HMA therapy, irrespective of the amount of prior HMA given [108].

While cost should not be the main driver for a decision in treatment options, value-based care is an evolving paradigm that cannot be overlooked, especially with the anticipated advent of new treatments that are likely high-cost. Not only is the drug cost of CPX-351 itself considerably high across the globe; it is compounded with other non-negligible direct and indirect costs of treatment-related adverse effects such as hospitalization for neutropenic complications and monitoring while awaiting count recovery. With the efficacy and tolerability benefits as outlined above, as well as significantly lower drug costs, other regimens such as FLAG may therefore be more cost-effective.

Comorbidities may limit available treatment options for an individual patient. In patients with significant cardiac dysfunction, such as left ventricular ejection of less than 45% or heart failure of New York Heart Association (NYHA) class III or IV, anthracyclines including CPX-351 should be avoided. In patients with severe renal dysfunction, manifested as baseline serum creatinine greater than 2 mg/dL or dependent on hemodialysis, HiDAC-based regimens such as FLAG should be avoided due to accumulation of the neurotoxic Ara-U metabolite.

In patients who are not alloHCT candidates, goals of care and patient preference are essential considerations driving treatment selection. As highlighted in the retrospective cohort study by Boddu et al., CR does not necessarily correlate with overall survival in the elderly and unfit patient population. It also should be noted that although HMA are generally considered the best tolerated agent, patients often experience prolonged pancytopenia and clinically significant fatigue. In contrast, FLAG yields an acute period of myelosuppression and risks of associated complications but may allow for more expeditious improvement in quality of life after achieving remission and count recovery. In patients with *TP53* alterations, response may be improved with a HMA-based approach. Best supportive care with transfusion and symptom management may be another option, depending on goals for patient comfort and quality of life.

For consolidation, the corresponding regimen at appropriate doses is recommended; for example, CPX-351, FLAG, or HMA induction with remission should be followed by the respective consolidation regimens. In patients with F*LT3* mutations, the addition of a *FLT3* inhibitor may be considered, though data are limited in sAML.

There is no standard of care for relapsed or refractory AML, in neither secondary nor de novo AML. Switching strategies from prior treatment likely improve the odds of a response. For example, a patient who has relapsed on FLAG but who is still fit and aiming to pursue aggressive treatment may benefit from a trial of CPX-351, which has preliminary evidence of activity in the relapsed setting [109]. Other salvage regimens such as MEC may also be considered, although treatment-related mortality can be substantial in intensive regimens. Thus, less intensive regimens such as hypomethylating agents, with or without venetoclax, in this older population are often preferred. Actionable mutations should be assessed to determine the appropriateness of using targeted therapy as an adjunct or monotherapy. Available clinical trials of novel agents or combinations should always be considered. Although new treatment regimens have modestly improved response rates and overall survival, ongoing research is vital to maintaining long-term remission in this high-risk malignancy.

Conclusion

The treatment of sAML has evolved substantially in recent years after decades of standard 7 + 3 induction, and the dynamic flux of ongoing research is beginning to show signs of progress in a malignancy that has long been considered of very poor prognosis. CPX-351 seems to increase CR rates compared to standard 7 + 3 and may be the new standard of care in sAML, although significant myelosuppression and limitations of clinical trial design lead to unanswered questions. Though not FDA-approved for sAML, FLAG appears to be effective and well tolerated based on retrospective and small prospective cohort data. HMA-based approaches result in reasonable response rates in sAML, and are a suitable option, particularly in unfit patients not eligible for alloHCT. Investigational agents may be an option in all cases, especially in the relapsed and refractory setting. As more patients with sAML hopefully achieve more prolonged remission durations, further inquiries regarding the role of maintenance therapy, the optimal sequence during relapse, and late-onset adverse effects will arise. An understanding of the molecular and genomic pathogenesis of sAML may help identify novel therapeutic targets and rational combinations with current treatment options of known efficacy and safety.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

References

1. Granfeldt Østgård LS, Medeiros BC, Sengeløv H, Nørgaard M, Andersen MK, Dufva IH, Friis LS, Kjeldsen E, Marcher CW, Preiss B, Severinsen M, Nørgaard JM (2015) Epidemiology and clinical significance of secondary and therapy-related acute myeloid leukemia: a National Population-Based Cohort Study. J Clin Oncol 33(31):3641–3649. https://doi.org/10.1200/JCO.2014.60.0890
2. Hulegårdh E, Nilsson C, Lazarevic V, Garelius H, Antunovic P, Rangert Derolf Å, Möllgård L, Uggla B, Wennström L, Wahlin A, Höglund M, Juliusson G, Stockelberg D, Lehmann S (2015) Characterization and prognostic features of secondary acute myeloid leukemia in a population-based setting: a report from the Swedish acute leukemia registry. Am J Hematol 90(3):208–214. https://doi.org/10.1002/ajh.23908
3. Valentini CG, Fianchi L, Voso MT, Caira M, Leone G, Pagano L (2011) Incidence of acute myeloid leukemia after breast cancer. Mediterr J Hematol Infect Dis 3(1):e2011069. https://doi.org/10.4084/MJHID.2011.069
4. Craig BM, Rollison DE, List AF, Cogle CR (2012) Underreporting of myeloid malignancies by United States cancer registries. Cancer Epidemiol Biomark Prev 21(3):474–481. https://doi.org/10.1158/1055-9965.EPI-11-1087
5. Kayser S, Döhner K, Krauter J et al (2011) The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. Blood 117(7):2137–2145. https://doi.org/10.1182/blood-2010-08-301713
6. Borthakur G, Lin E, Jain N, Estey EE, Cortes JE, O'Brien S, Faderl S, Ravandi F, Pierce S, Kantarjian H (2009) Survival is poorer in patients with secondary core-binding factor acute myelogenous leukemia compared with de novo core-binding factor leukemia. Cancer 115(14):3217–3221. https://doi.org/10.1002/cncr.24367
7. Krug U, Röllig C, Koschmieder A, Heinecke A, Sauerland MC, Schaich M, Thiede C, Kramer M, Braess J, Spiekermann K, Haferlach T, Haferlach C, Koschmieder S, Rohde C, Serve H, Wörmann B, Hiddemann W, Ehninger G, Berdel WE, Büchner T, Müller-Tidow C (2010) 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 376(9757):2000–2008. https://doi.org/10.1016/S0140-6736(10)62105-8
8. Walter RB, Othus M, Borthakur G, Ravandi F, Cortes JE, Pierce SA, Appelbaum FR, Kantarjian HA, Estey EH (2011) 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 29(33):4417–4424. https://doi.org/10.1200/JCO.2011.35.7525
9. Smith SM, Le Beau MM, Huo D et al (2003) Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: the University of Chicago series. Blood 102(1):43–52. https://doi.org/10.1182/blood-2002-11-3343
10. Larson RA (2007) Etiology and Management of Therapy-Related Myeloid Leukemia. Hematology 2007(1):453–459. https://doi.org/10.1182/asheducation-2007.1.453
11. Christiansen DH, Andersen MK, Pedersen-Bjergaard J (2001) Mutations with loss of heterozygosity of p53 are common in therapy-related myelodysplasia and acute myeloid leukemia after exposure to alkylating agents and significantly associated with deletion or loss of 5q, a complex karyotype, and a poor prognosis.

J Clin Oncol 19(5):1405–1413. https://doi.org/10.1200/JCO.2001.19.5.1405

12. Kayastha N, Wolf SP, Locke SC, Samsa GP, El-Jawahri A, LeBlanc TW (2018) The impact of remission status on patients' experiences with acute myeloid leukemia (AML): an exploratory analysis of longitudinal patient-reported outcomes data. Support Care Cancer 26(5):1437–1445. https://doi.org/10.1007/s00520-017-3973-4
13. Tefferi A, Vardiman JW (2009) Myelodysplastic syndromes. N Engl J Med 361(19):1872–1885. https://doi.org/10.1056/NEJMra0902908
14. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, Bennett JM, Bowen D, Fenaux P, Dreyfus F, Kantarjian H, Kuendgen A, Levis A, Malcovati L, Cazzola M, Cermak J, Fonatsch C, le Beau MM, Slovak ML, Krieger O, Luebbert M, Maciejewski J, Magalhaes SMM, Miyazaki Y, Pfeilstocker M, Sekeres M, Sperr WR, Stauder R, Tauro S, Valent P, Vallespi T, van de Loosdrecht AA, Germing U, Haase D (2012) Revised international prognostic scoring system for myelodysplastic syndromes. Blood 120(12):2454–2465. https://doi.org/10.1182/blood-2012-03-420489
15. Walter MJ, Shen D, Ding L, Shao J, Koboldt DC, Chen K, Larson DE, McLellan MD, Dooling D, Abbott R, Fulton R, Magrini V, Schmidt H, Kalicki-Veizer J, O'Laughlin M, Fan X, Grillot M, Witowski S, Heath S, Frater JL, Eades W, Tomasson M, Westervelt P, DiPersio JF, Link DC, Mardis ER, Ley TJ, Wilson RK, Graubert TA (2012) Clonal architecture of secondary acute myeloid leukemia. N Engl J Med 366(12):1090–1098. https://doi.org/10.1056/NEJMoa1106968
16. Shukron O, Vainstein V, Kündgen A, Germing U, Agur Z (2012) Analyzing transformation of myelodysplastic syndrome to secondary acute myeloid leukemia using a large patient database. Am J Hematol 87(9):853–860. https://doi.org/10.1002/ajh.23257
17. Lindsley RC, Mar BG, Mazzola E, Grauman PV, Shareef S, Allen SL, Pigneux A, Wetzler M, Stuart RK, Erba HP, Damon LE, Powell BL, Lindeman N, Steensma DP, Wadleigh M, DeAngelo DJ, Neuberg D, Stone RM, Ebert BL (2015) Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. Blood 125(9):1367–1376. https://doi.org/10.1182/blood-2014-11-610543
18. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW (2016) The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 127(20):2391–2405. https://doi.org/10.1182/blood-2016-03-643544
19. Vardiman J, Hyjek E (2011) World health organization classification, evaluation, and genetics of the myeloproliferative neoplasm variants. Hematol Am Soc Hematol Educ Program 2011(1):250–256. https://doi.org/10.1182/asheducation-2011.1.250
20. Cerquozzi S, Tefferi A (2015) Blast transformation and fibrotic progression in polycythemia vera and essential thrombocythemia: a literature review of incidence and risk factors. Blood Cancer J 5(11):e366. https://doi.org/10.1038/bcj.2015.95
21. Aynardi J, Manur R, Hess PR et al (2018) JAK2 V617F-positive acute myeloid leukaemia (AML): a comparison between de novo AML and secondary AML transformed from an underlying myeloproliferative neoplasm. A study from the Bone Marrow Pathology Group. Br J Haematol. https://doi.org/10.1111/bjh.15276
22. Yoshizato T, Dumitriu B, Hosokawa K, Makishima H, Yoshida K, Townsley D, Sato-Otsubo A, Sato Y, Liu D, Suzuki H, Wu CO, Shiraishi Y, Clemente MJ, Kataoka K, Shiozawa Y, Okuno Y, Chiba K, Tanaka H, Nagata Y, Katagiri T, Kon A, Sanada M, Scheinberg P, Miyano S, Maciejewski JP, Nakao S, Young NS, Ogawa S (2015) Somatic mutations and clonal hematopoiesis in aplastic Anemia. N Engl J Med 373(1):35–47. https://doi.org/10.1056/NEJMoa1414799
23. Mauritzson N, Albin M, Rylander L, Billström R, Ahlgren T, Mikoczy Z, Björk J, Strömberg U, Nilsson PG, Mitelman F, Hagmar L, Johansson B (2002) Pooled analysis of clinical and cytogenetic features in treatment-related and de novo adult acute myeloid leukemia and myelodysplastic syndromes based on a consecutive series of 761 patients analyzed 1976-1993 and on 5098 unselected cases reported in the literature 1974-2001. Leukemia 16(12):2366–2378. https://doi.org/10.1038/sj.leu.2402713
24. Bhatia S (2013) Therapy-related myelodysplasia and acute myeloid leukemia. Semin Oncol 40(6):666–675. https://doi.org/10.1053/j.seminoncol.2013.09.013
25. Schoch C, Kern W, Schnittger S, Hiddemann W, Haferlach T (2004) Karyotype is an independent prognostic parameter in therapy-related acute myeloid leukemia (t-AML): an analysis of 93 patients with t-AML in comparison to 1091 patients with de novo AML. Leukemia 18(1):120–125. https://doi.org/10.1038/sj.leu.2403187
26. Godley LA, Larson RA (2008) Therapy-related myeloid leukemia. Semin Oncol 35(4):418–429. https://doi.org/10.1053/j.seminoncol.2008.04.012
27. Olney HJ, Mitelman F, Johansson B, Mrózek K, Berger R, Rowley JD (2002) Unique balanced chromosome abnormalities in treatment-related myelodysplastic syndromes and acute myeloid leukemia: report from an international workshop. Genes Chromosom Cancer 33(4):413–423 http://www.ncbi.nlm.nih.gov/pubmed/11921275. Accessed 18 June 2018
28. Pedersen-Bjergaard J, Andersen MK, Andersen MT, Christiansen DH (2008) Genetics of therapy-related myelodysplasia and acute myeloid leukemia. Leukemia 22(2):240–248. https://doi.org/10.1038/sj.leu.2405078
29. Smith RE, Bryant J, DeCillis A, Anderson S (2003) National Surgical Adjuvant Breast and bowel project experience. Acute myeloid leukemia and myelodysplastic syndrome after doxorubicin-cyclophosphamide adjuvant therapy for operable breast cancer: the National Surgical Adjuvant Breast and bowel project experience. J Clin Oncol 21(7):1195–1204. https://doi.org/10.1200/JCO.2003.03.114
30. Curtis RE, Boice JD, Stovall M et al (1992) Risk of leukemia after chemotherapy and radiation treatment for breast Cancer. N Engl J Med 326(26):1745–1751. https://doi.org/10.1056/NEJM199206253262605
31. Zhang W, Becciolini A, Biggeri A, Pacini P, Muirhead CR (2011) Second malignancies in breast cancer patients following radiotherapy: a study in Florence, Italy. Breast Cancer Res 13(2):R38. https://doi.org/10.1186/bcr2860
32. Borrego-Soto G, Ortiz-López R, Rojas-Martínez A (2015) Ionizing radiation-induced DNA injury and damage detection in patients with breast cancer. Genet Mol Biol 38(4):420–432. https://doi.org/10.1590/S1415-475738420150019
33. Dimopoulos MA, Richardson PG, Brandenburg N, Yu Z, Weber DM, Niesvizky R, Morgan GJ (2012) A review of second primary malignancy in patients with relapsed or refractory multiple myeloma treated with lenalidomide. Blood 119(12):2764–2767. https://doi.org/10.1182/blood-2011-08-373514
34. Ertz-Archambault N, Kosiorek H, Taylor GE, Kelemen K, Dueck A, Castro J, Marino R, Gauthier S, Finn L, Sproat LZ, Palmer J, Mesa RA, al-Kali A, Foran J, Tibes R (2017) Association of Therapy for autoimmune disease with myelodysplastic syndromes and acute myeloid leukemia. JAMA Oncol 3(7):936. https://doi.org/10.1001/jamaoncol.2016.6435
35. Poynter JN, Richardson M, Roesler M, Blair CK, Hirsch B, Nguyen P, Cioc A, Cerhan JR, Warlick E (2017) Chemical exposures and risk of acute myeloid leukemia and myelodysplastic

syndromes in a population-based study. Int J Cancer 140(1):23–33. https://doi.org/10.1002/ijc.30420
36. Bullinger L, Döhner K, Döhner H (2017) Genomics of acute myeloid leukemia diagnosis and pathways. J Clin Oncol 35(9):934–946. https://doi.org/10.1200/JCO.2016.71.2208
37. Cancer Genome Atlas Research Network, Ley TJ, Miller C et al (2013) Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med 368(22):2059–2074. https://doi.org/10.1056/NEJMoa1301689
38. Ding L, Ley TJ, Larson DE, Miller CA, Koboldt DC, Welch JS, Ritchey JK, Young MA, Lamprecht T, McLellan MD, McMichael JF, Wallis JW, Lu C, Shen D, Harris CC, Dooling DJ, Fulton RS, Fulton LL, Chen K, Schmidt H, Kalicki-Veizer J, Magrini VJ, Cook L, McGrath SD, Vickery TL, Wendl MC, Heath S, Watson MA, Link DC, Tomasson MH, Shannon WD, Payton JE, Kulkarni S, Westervelt P, Walter MJ, Graubert TA, Mardis ER, Wilson RK, DiPersio JF (2012) Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing. Nature 481(7382):506–510. https://doi.org/10.1038/nature10738
39. Welch JS, Ley TJ, Link DC, Miller CA, Larson DE, Koboldt DC, Wartman LD, Lamprecht TL, Liu F, Xia J, Kandoth C, Fulton RS, McLellan MD, Dooling DJ, Wallis JW, Chen K, Harris CC, Schmidt HK, Kalicki-Veizer JM, Lu C, Zhang Q, Lin L, O'Laughlin MD, McMichael JF, Delehaunty KD, Fulton LA, Magrini VJ, McGrath SD, Demeter RT, Vickery TL, Hundal J, Cook LL, Swift GW, Reed JP, Alldredge PA, Wylie TN, Walker JR, Watson MA, Heath SE, Shannon WD, Varghese N, Nagarajan R, Payton JE, Baty JD, Kulkarni S, Klco JM, Tomasson MH, Westervelt P, Walter MJ, Graubert TA, DiPersio JF, Ding L, Mardis ER, Wilson RK (2012) The origin and evolution of mutations in acute myeloid leukemia. Cell 150(2):264–278. https://doi.org/10.1016/j.cell.2012.06.023
40. Shlush LI, Zandi S, Mitchell A, Chen WC, Brandwein JM, Gupta V, Kennedy JA, Schimmer AD, Schuh AC, Yee KW, McLeod JL, Doedens M, Medeiros JJF, Marke R, Kim HJ, Lee K, McPherson JD, Hudson TJ, Pan-Leukemia Gene Panel Consortium THALT, Brown AMK, Yousif F, Trinh QM, Stein LD, Minden MD, Wang JCY, Dick JE (2014) Identification of pre-leukaemic haematopoietic stem cells in acute leukaemia. Nature 506(7488):328–333. https://doi.org/10.1038/nature13038
41. Milosevic JD, Puda A, Malcovati L, Berg T, Hofbauer M, Stukalov A, Klampfl T, Harutyunyan AS, Gisslinger H, Gisslinger B, Burjanivova T, Rumi E, Pietra D, Elena C, Vannucchi AM, Doubek M, Dvorakova D, Robesova B, Wieser R, Koller E, Suvajdzic N, Tomin D, Tosic N, Colinge J, Racil Z, Steurer M, Pavlovic S, Cazzola M, Kralovics R (2012) Clinical significance of genetic aberrations in secondary acute myeloid leukemia. Am J Hematol 87(11):1010–1016. https://doi.org/10.1002/ajh.23309
42. Joslin JM, Fernald AA, Tennant TR, Davis EM, Kogan SC, Anastasi J, Crispino JD, le Beau MM (2007) Haploinsufficiency of EGR1, a candidate gene in the del(5q), leads to the development of myeloid disorders. Blood 110(2):719–726. https://doi.org/10.1182/blood-2007-01-068809
43. Rücker FG, Schlenk RF, Bullinger L et al (2012) TP53 alterations in acute myeloid leukemia with complex karyotype correlate with specific copy number alterations, monosomal karyotype, and dismal outcome. Blood 119(9):2114–2121. https://doi.org/10.1182/blood-2011-08-375758
44. Wong TN, Ramsingh G, Young AL, Miller CA, Touma W, Welch JS, Lamprecht TL, Shen D, Hundal J, Fulton RS, Heath S, Baty JD, Klco JM, Ding L, Mardis ER, Westervelt P, DiPersio JF, Walter MJ, Graubert TA, Ley TJ, Druley TE, Link DC, Wilson RK (2015) Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. Nature 518(7540):552–555. https://doi.org/10.1038/nature13968
45. Larson RA (2012) Cytogenetics, not just previous therapy, determines the course of therapy-related myeloid neoplasms. J Clin Oncol 30(19):2300–2302. https://doi.org/10.1200/JCO.2011.41.1215
46. Michelis FV, Atenafu EG, Gupta V, Kim DD, Kuruvilla J, Lipton JH, Loach D, Seftel MD, Uhm J, Alam N, Lambie A, McGillis L, Messner HA (2015) Comparable outcomes post allogeneic hematopoietic cell transplant for patients with de novo or secondary acute myeloid leukemia in first remission. Bone Marrow Transplant 50(7):907–913. https://doi.org/10.1038/bmt.2015.59
47. Tang F-F, Huang X-J, Zhang X-H, Chen H, Chen YH, Han W, Chen Y, Wang FR, Wang Y, Wang JZ, Yan CH, Sun YQ, Mo XD, Liu KY, Xu LP (2016) Allogeneic hematopoietic cell transplantation for adult patients with treatment-related acute myeloid leukemia during first remission: comparable to de novo acute myeloid leukemia. Leuk Res 47:8–15. https://doi.org/10.1016/j.leukres.2016.05.005
48. Yates JW, Wallace HJ, Ellison RR, Holland JF Cytosine arabinoside (NSC-63878) and daunorubicin (NSC-83142) therapy in acute nonlymphocytic leukemia. Cancer Chemother Rep 57(4):485–488 http://www.ncbi.nlm.nih.gov/pubmed/4586956. Accessed 28 Jul 2018
49. Löwenberg B, Ossenkoppele GJ, van Putten W, Schouten HC, Graux C, Ferrant A, Sonneveld P, Maertens J, Jongen-Lavrencic M, von Lilienfeld-Toal M, Biemond BJ, Vellenga E, Kooy MM, Verdonck LF, Beck J, Döhner H, Gratwohl A, Pabst T, Verhoef G (2009) High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med 361(13):1235–1248. https://doi.org/10.1056/NEJMoa0901409
50. Boddu P, Kantarjian HM, Garcia-Manero G, Ravandi F, Verstovsek S, Jabbour E, Borthakur G, Konopleva M, Bhalla KN, Daver N, DiNardo CD, Benton CB, Takahashi K, Estrov Z, Pierce SR, Andreeff M, Cortes JE, Kadia TM (2017) Treated secondary acute myeloid leukemia: a distinct high-risk subset of AML with adverse prognosis. Blood Adv 1(17):1312–1323. https://doi.org/10.1182/bloodadvances.2017008227
51. Lancet JE, Uy GL, Cortes JE et al (2016) 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 34(15):Suppl 7000. https://doi.org/10.1200/JCO.2016.34.15_SUPPL.7000
52. Fernandez HF, Sun Z, Yao X, Litzow MR, Luger SM, Paietta EM, Racevskis J, Dewald GW, Ketterling RP, Bennett JM, Rowe JM, Lazarus HM, Tallman MS (2009) Anthracycline dose intensification in acute myeloid leukemia. N Engl J Med 361(13):1249–1259. https://doi.org/10.1056/NEJMoa0904544
53. Löwenberg B, Pabst T, Vellenga E, van Putten W, Schouten HC, Graux C, Ferrant A, Sonneveld P, Biemond BJ, Gratwohl A, de Greef GE, Verdonck LF, Schaafsma MR, Gregor M, Theobald M, Schanz U, Maertens J, Ossenkoppele GJ (2011) Cytarabine dose for acute myeloid leukemia. N Engl J Med 364(11):1027–1036. https://doi.org/10.1056/NEJMoa1010222
54. Lee J-H, Joo Y-D, Kim H, Bae SH, Kim MK, Zang DY, Lee JL, Lee GW, Lee JH, Park JH, Kim DY, Lee WS, Ryoo HM, Hyun MS, Kim HJ, Min YJ, Jang YE, Lee KH, for the Cooperative Study Group A for Hematology (2011) A randomized trial comparing standard versus high-dose daunorubicin induction in patients with acute myeloid leukemia. Blood 118(14):3832–3841. https://doi.org/10.1182/blood-2011-06-361410
55. Leith CP, Kopecky KJ, Chen IM et al (1999) 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 94(3):1086–1099 http://www.ncbi.nlm.nih.gov/pubmed/10419902. Accessed 19 June 2018

56. Tsuji K, Wang Y-H, Takanashi M, Odajima T, Lee GA, Sugimori H, Motoji T (2012) Overexpression of lung resistance-related protein and P-glycoprotein and response to induction chemotherapy in acute myelogenous leukemia. Hematol Rep 4(3):e18. https://doi.org/10.4081/hr.2012.e18
57. Tardi P, Johnstone S, Harasym N, Xie S, Harasym T, Zisman N, Harvie P, Bermudes D, Mayer L (2009) In vivo maintenance of synergistic cytarabine:daunorubicin ratios greatly enhances therapeutic efficacy. Leuk Res 33(1):129–139. https://doi.org/10.1016/j.leukres.2008.06.028
58. Brunetti C, Anelli L, Zagaria A, Specchia G, Albano F (2017) CPX-351 in acute myeloid leukemia: can a new formulation maximize the efficacy of old compounds? Expert Rev Hematol 10(10):853–862. https://doi.org/10.1080/17474086.2017.1369400
59. Feldman EJ, Kolitz JE, Trang JM, Liboiron BD, Swenson CE, Chiarella MT, Mayer LD, Louie AC, Lancet JE (2012) Pharmacokinetics of CPX-351; a nano-scale liposomal fixed molar ratio formulation of cytarabine:daunorubicin, in patients with advanced leukemia. Leuk Res 36(10):1283–1289. https://doi.org/10.1016/j.leukres.2012.07.006
60. Lancet JE, Cortes JE, Hogge DE, Tallman MS, Kovacsovics TJ, Damon LE, Komrokji R, Solomon SR, Kolitz JE, Cooper M, Yeager AM, Louie AC, Feldman EJ (2014) 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 123(21):3239–3246. https://doi.org/10.1182/blood-2013-12-540971
61. Lancet JE, Uy GL, Cortes JE, Newell LF, Lin TL, Ritchie EK, Stuart RK, Strickland SA, Hogge D, Solomon SR, Stone RM, Bixby DL, Kolitz JE, Schiller GJ, Wieduwilt MJ, Ryan DH, Hoering A, Banerjee K, Chiarella M, Louie AC, Medeiros BC (2018) CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia. J Clin Oncol 36:JCO2017776112. https://doi.org/10.1200/JCO.2017.77.6112
62. Boddu PC, Kantarjian HM, Ravandi F, Garcia-Manero G, Verstovsek S, Jabbour EJ, Takahashi K, Bhalla K, Konopleva M, DiNardo CD, Ohanian M, Pemmaraju N, Jain N, Pierce S, Wierda WG, Cortes JE, Kadia TM (2017) Characteristics and outcomes of older patients with secondary acute myeloid leukemia according to treatment approach. Cancer 123(16):3050–3060. https://doi.org/10.1002/cncr.30704
63. Vulaj V, Perissinotti AJ, Uebel JR, Nachar VR, Scappaticci GB, Crouch A, Bixby DL, Burke PW, Maillard I, Talpaz M, Marini BL (2018) The FOSSIL study: FLAG or standard 7+3 induction therapy in secondary acute myeloid leukemia. Leuk Res 70:91–96. https://doi.org/10.1016/j.leukres.2018.05.011
64. Becker PS, Medeiros BC, Stein AS, Othus M, Appelbaum FR, Forman SJ, Scott BL, Hendrie PC, Gardner KM, Pagel JM, Walter RB, Parks C, Wood BL, Abkowitz JL, Estey EH (2015) G-CSF priming, clofarabine, and high dose cytarabine (GCLAC) for upfront treatment of acute myeloid leukemia, advanced myelodysplastic syndrome or advanced myeloproliferative neoplasm. Am J Hematol 90(4):295–300. https://doi.org/10.1002/ajh.23927
65. Willemze R, Suciu S, Meloni G, Labar B, Marie JP, Halkes CJM, Muus P, Mistrik M, Amadori S, Specchia G, Fabbiano F, Nobile F, Sborgia M, Camera A, Selleslag DLD, Lefrère F Sr, Magro D, Sica S, Cantore N, Beksac M, Berneman Z, Thomas X, Melillo L, Guimaraes JE, Leoni P, Luppi M, Mitra ME, Bron D, Fillet G, Marijt EWA, Venditti A, Hagemeijer A, Mancini M, Jansen J, Cilloni D, Meert L, Fazi P, Vignetti M, Trisolini SM, Mandelli F, de Witte T (2014) 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 32(3):219–228. https://doi.org/10.1200/JCO.2013.51.8571
66. Godley LA, Njiaju UO, Green M, Weiner H, Lin S, Odenike O, Rich ES, Artz A, van Besien K, Daugherty CK, Zhang Y, le Beau MM, Stock W, Larson RA (2010) Treatment of therapy-related myeloid neoplasms with high-dose cytarabine/mitoxantrone followed by hematopoietic stem cell transplant. Leuk Lymphoma. 51(6):995–1006. https://doi.org/10.3109/10428191003763468
67. DiNardo CD, Pratz K, Pullarkat V et al (2018) Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood. https://doi.org/10.1182/blood-2018-08-868752
68. Amadori S, Suciu S, Selleslag D, Aversa F, Gaidano G, Musso M, Annino L, Venditti A, Voso MT, Mazzone C, Magro D, de Fabritiis P, Muus P, Alimena G, Mancini M, Hagemeijer A, Paoloni F, Vignetti M, Fazi P, Meert L, Ramadan SM, Willemze R, de Witte T, Baron F (2016) 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 34(9):972–979. https://doi.org/10.1200/JCO.2015.64.0060
69. Abboud CN, ξ, Þ, Altman JK, et al (2018) NCCN Guidelines Version 2.2018 Acute Myeloid Leukemia. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed 13 Oct 2018
70. Maertens J (2007) Evaluating prophylaxis of invasive fungal infections in patients with haematologic malignancies. Eur J Haematol 78(4):275–282. https://doi.org/10.1111/j.1600-0609.2006.00805.x
71. Cornely OA, Böhme A, Reichert D, Reuter S, Maschmeyer G, Maertens J, Buchheidt D, Paluszewska M, Arenz D, Bethe U, Effelsberg J, Lövenich H, Sieniawski M, Haas A, Einsele H, Eimermacher H, Martino R, Silling G, Hahn M, Wacker S, Ullmann AJ, Karthaus M, Multinational Case Registry of the Infectious Diseases Working Party of the German Society for Hematology and Oncology (2008) Risk factors for breakthrough invasive fungal infection during secondary prophylaxis. J Antimicrob Chemother 61(4):939–946. https://doi.org/10.1093/jac/dkn027
72. Lancet JE, Ritchie EK, Uy GL et al (2017) Efficacy and Safety of CPX-351 Versus 7+3 in Older Adults with Secondary Acute Myeloid Leukemia: Combined Subgroup Analysis of Phase 2 and Phase 3 Studies. Blood 130(Suppl 1) http://www.bloodjournal.org/content/130/Suppl_1/2657?sso-checked=true. Accessed 19 June 2018
73. Lancet JE, Uy GL, Cortes JE, et al (2017) Analysis of Transplantation Rate and Overall Treatment Efficacy By Age for Patients Aged 60 to 75 with Untreated Secondary Acute Myeloid Leukemia (AML) Given CPX-351 Liposome Injection Versus Conventional Cytarabine and Daunorubicin in a Phase III Trial. BMT Tandem Meetings. https://bmt.confex.com/tandem/2017/meetingapp.cgi/Paper/8916. Published 2017. Accessed 19 June 2018
74. Walter RB, Othus M, Orlowski KF, McDaniel EN, Scott BL, Becker PS, Percival MEM, Hendrie PC, Medeiros BC, Chiarella MT, Louie AC, Estey EH (2018) Unsatisfactory efficacy in randomized study of reduced-dose CPX-351 for medically less fit adults with newly diagnosed acute myeloid leukemia or other high-grade myeloid neoplasm. Haematologica 103(3):e106–e109. https://doi.org/10.3324/haematol.2017.182642
75. Assi R, Kantarjian HM, Verstovsek S et al (2016) CPX-351 for the Treatment of High-Risk Patients with Acute Myeloid Leukemia. Blood 128(22) http://www.bloodjournal.org/content/128/22/4047?sso-checked=true. Accessed 19 June 2018

76. Gandhi V, Estey E, Keating MJ, Plunkett W (1993) Fludarabine potentiates metabolism of cytarabine in patients with acute myelogenous leukemia during therapy. J Clin Oncol 11(1):116–124. https://doi.org/10.1200/JCO.1993.11.1.116
77. Bashey A, Liu L, Ihasz A, Medina B, Corringham S, Keese K, Carrier E, Castro JE, Holman P, Lane TA, Hassidim K, Ball ED (2006) Non-anthracycline based remission induction therapy for newly diagnosed patients with acute myeloid leukemia aged 60 or older. Leuk Res 30(4):503–506. https://doi.org/10.1016/j.leukres.2005.09.002
78. Ferrara F, Palmieri S, Izzo T, Criscuolo C, Riccardi C (2010) Continuous sequential infusion of fludarabine and cytarabine for elderly patients with acute myeloid leukaemia secondary to a previously diagnosed myelodysplastic syndrome. Hematol Oncol 28(4):202–208. https://doi.org/10.1002/hon.943
79. Fenaux P, Mufti GJ, Hellström-Lindberg E, Santini V, Gattermann N, Germing U, Sanz G, List AF, Gore S, Seymour JF, Dombret H, Backstrom J, Zimmerman L, McKenzie D, Beach CL, Silverman LR (2010) Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J Clin Oncol 28(4):562–569. https://doi.org/10.1200/JCO.2009.23.8329
80. Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, Kumar R, Cavenagh J, Schuh AC, Candoni A, Recher C, Sandhu I, Bernal del Castillo T, al-Ali HK, Martinelli G, Falantes J, Noppeney R, Stone RM, Minden MD, McIntyre H, Songer S, Lucy LM, Beach CL, Dohner H (2015) International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood 126(3):291–299. https://doi.org/10.1182/blood-2015-01-621664
81. Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, Gau JP, Chou WC, Buckstein R, Cermak J, Kuo CY, Oriol A, Ravandi F, Faderl S, Delaunay J, Lysák D, Minden M, Arthur C (2012) 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 30(21):2670–2677. https://doi.org/10.1200/JCO.2011.38.9429
82. Pleyer L, Stauder R, Burgstaller S, Schreder M, Tinchon C, Pfeilstocker M, Steinkirchner S, Melchardt T, Mitrovic M, Girschikofsky M, Lang A, Krippl P, Sliwa T, Egle A, Linkesch W, Voskova D, Angermann H, Greil R (2013) Azacitidine in patients with WHO-defined AML—results of 155 patients from the Austrian Azacitidine registry of the AGMT-study group. J Hematol Oncol 6(1):32. https://doi.org/10.1186/1756-8722-6-32
83. Dumas P-Y, Bertoli S, Bérard E et al (2017) Azacitidine or intensive chemotherapy for older patients with secondary or therapy-related acute myeloid leukemia. Oncotarget 8(45):79126–79136. https://doi.org/10.18632/oncotarget.15988
84. Welch JS, Petti AA, Miller CA, Fronick CC, O'Laughlin M, Fulton RS, Wilson RK, Baty JD, Duncavage EJ, Tandon B, Lee YS, Wartman LD, Uy GL, Ghobadi A, Tomasson MH, Pusic I, Romee R, Fehniger TA, Stockerl-Goldstein KE, Vij R, Oh ST, Abboud CN, Cashen AF, Schroeder MA, Jacoby MA, Heath SE, Luber K, Janke MR, Hantel A, Khan N, Sukhanova MJ, Knoebel RW, Stock W, Graubert TA, Walter MJ, Westervelt P, Link DC, DiPersio JF, Ley TJ (2016) *TP53* and Decitabine in acute myeloid leukemia and myelodysplastic syndromes. N Engl J Med 375(21):2023–2036. https://doi.org/10.1056/NEJMoa1605949
85. Ravandi F, Issa J-P, Garcia-Manero G, O'Brien S, Pierce S, Shan J, Borthakur G, Verstovsek S, Faderl S, Cortes J, Kantarjian H (2009) Superior outcome with hypomethylating therapy in patients with acute myeloid leukemia and high-risk myelodysplastic syndrome and chromosome 5 and 7 abnormalities. Cancer 115(24):5746–5751. https://doi.org/10.1002/cncr.24661
86. Bogenberger JM, Delman D, Hansen N, Valdez R, Fauble V, Mesa RA, Tibes R (2015) *Ex vivo* activity of BCL-2 family inhibitors ABT-199 and ABT-737 combined with 5-azacytidine in myeloid malignancies. Leuk Lymphoma. 56(1):226–229. https://doi.org/10.3109/10428194.2014.910657
87. Maiti A, DiNardo CD, Cortes JE, et al (2018) Interim analysis of phase II study of Venetoclax with 10-day Decitabine (DEC10-VEN) in acute myeloid leukemia and myelodysplastic syndrome. https://ash.confex.com/ash/2018/webprogram/Paper113749.html. Accessed 17 Nov 2018
88. Maurillo L, Buccisano F, Spagnoli A, Voso MT, Fianchi L, Papayannidis C, Gaidano GL, Breccia M, Musto P, de Bellis E, del Principe MI, Lunghi M, Lessi F, Martinelli G, Venditti A (June) Comparative analysis of azacitidine and intensive chemotherapy as front-line treatment of elderly patients with acute myeloid leukemia. Ann Hematol 97:1767–1774. https://doi.org/10.1007/s00277-018-3374-x
89. Petersdorf SH, Kopecky KJ, Slovak M, Willman C, Nevill T, Brandwein J, Larson RA, Erba HP, Stiff PJ, Stuart RK, Walter RB, Tallman MS, Stenke L, Appelbaum FR (2013) A phase 3 study of gemtuzumab ozogamicin during induction and postconsolidation therapy in younger patients with acute myeloid leukemia. Blood 121(24):4854–4860. https://doi.org/10.1182/blood-2013-01-466706
90. Castaigne S, Pautas C, Terré C et al (2014) Final Analysis of the ALFA 0701 Study. Blood 124(21) http://www.bloodjournal.org/content/124/21/376?sso-checked=true. Accessed 19 June 2018
91. Hills RK, Castaigne S, Appelbaum FR, Delaunay J, Petersdorf S, Othus M, Estey EH, Dombret H, Chevret S, Ifrah N, Cahn JY, Récher C, Chilton L, Moorman AV, Burnett AK (2014) Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. Lancet Oncol 15(9):986–996. https://doi.org/10.1016/S1470-2045(14)70281-5
92. Burnett AK, Hills RK, Milligan D, Kjeldsen L, Kell J, Russell NH, Yin JAL, Hunter A, Goldstone AH, Wheatley K (2011) Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. J Clin Oncol 29(4):369–377. https://doi.org/10.1200/JCO.2010.31.4310
93. Burnett AK, Russell NH, Hills RK, Kell J, Freeman S, Kjeldsen L, Hunter AE, Yin J, Craddock CF, Dufva IH, Wheatley K, Milligan D (2012) Addition of Gemtuzumab Ozogamicin to induction chemotherapy improves survival in older patients with acute myeloid leukemia. J Clin Oncol 30(32):3924–3931. https://doi.org/10.1200/JCO.2012.42.2964
94. Amadori S, Suciu S, Stasi R, Salih HR, Selleslag D, Muus P, de Fabritiis P, Venditti A, Ho AD, Lübbert M, Thomas X, Latagliata R, Halkes CJM, Falzetti F, Magro D, Guimaraes JE, Berneman Z, Specchia G, Karrasch M, Fazi P, Vignetti M, Willemze R, de Witte T, Marie JP (2013) Sequential combination of gemtuzumab ozogamicin and standard chemotherapy in older patients with newly diagnosed acute myeloid leukemia: results of a randomized phase III trial by the EORTC and GIMEMA consortium (AML-17). J Clin Oncol 31(35):4424–4430. https://doi.org/10.1200/JCO.2013.49.0771
95. van der Velden VHJ, Boeckx N, Jedema I, te Marvelde JG, Hoogeveen PG, Boogaerts M, van Dongen JJM (2004) High CD33-antigen loads in peripheral blood limit the efficacy of gemtuzumab ozogamicin (Mylotarg) treatment in acute myeloid leukemia patients. Leukemia 18(5):983–988. https://doi.org/10.1038/sj.leu.2403350
96. Dowell JA, Korth-Bradley J, Liu H, King SP, Berger MS (2001) Pharmacokinetics of gemtuzumab ozogamicin, an antibody-targeted chemotherapy agent for the treatment of patients with acute myeloid leukemia in first relapse. J Clin Pharmacol 41(11):

1206–1214 http://www.ncbi.nlm.nih.gov/pubmed/11697753. Accessed 19 June 2018

97. Candoni A, Papayannidis C, Martinelli G, Simeone E, Gottardi M, Iacobucci I, Gherlinzoni F, Visani G, Baccarani M, Fanin R (2018) Flai (fludarabine, cytarabine, idarubicin) plus low-dose Gemtuzumab Ozogamicin as induction therapy in CD33-positive AML: final results and long term outcome of a phase II multicenter clinical trial. Am J Hematol 93(5):655–663. https://doi.org/10.1002/ajh.25057
98. Stein EM, Walter RB, Erba HP, Fathi AT, Advani AS, Lancet JE, Ravandi F, Kovacsovics T, DeAngelo DJ, Bixby D, Faderl S, Jillella AP, Ho PA, O'Meara MM, Zhao B, Biddle-Snead C, Stein AS (2018) A phase 1 trial of vadastuximab talirine as monotherapy in patients with CD33-positive acute myeloid leukemia. Blood 131(4):387–396. https://doi.org/10.1182/blood-2017-06-789800
99. Stone RM, Mazzola E, Neuberg D, Allen SL, Pigneux A, Stuart RK, Wetzler M, Rizzieri D, Erba HP, Damon L, Jang JH, Tallman MS, Warzocha K, Masszi T, Sekeres MA, Egyed M, Horst HA, Selleslag D, Solomon SR, Venugopal P, Lundberg AS, Powell B (2015) Phase III open-label randomized study of Cytarabine in combination with Amonafide L-malate or Daunorubicin as induction therapy for patients with secondary acute myeloid leukemia. J Clin Oncol 33(11):1252–1257. https://doi.org/10.1200/JCO.2014.57.0952
100. Cazzola M (2010) IDH1 and IDH2 mutations in myeloid neoplasms–novel paradigms and clinical implications. Haematologica 95(10):1623–1627. https://doi.org/10.3324/haematol.2010.030015
101. Boddu P, Kantarjian H, Garcia-Manero G, Allison J, Sharma P, Daver N (2018) The emerging role of immune checkpoint based approaches in AML and MDS. Leuk Lymphoma 59(4):790–802. https://doi.org/10.1080/10428194.2017.1344905
102. Yang H, Bueso-Ramos C, DiNardo C, Estecio MR, Davanlou M, Geng QR, Fang Z, Nguyen M, Pierce S, Wei Y, Parmar S, Cortes J, Kantarjian H, Garcia-Manero G (2014) Expression of PD-L1, PD-L2, PD-1 and CTLA4 in myelodysplastic syndromes is enhanced by treatment with hypomethylating agents. Leukemia 28(6):1280–1288. https://doi.org/10.1038/leu.2013.355
103. Pratz KW, Rudek MA, Gojo I, Litzow MR, McDevitt MA, Ji J, Karnitz LM, Herman JG, Kinders RJ, Smith BD, Gore SD, Carraway HE, Showel MM, Gladstone DE, Levis MJ, Tsai HL, Rosner G, Chen A, Kaufmann SH, Karp JE (2017) A phase I study of Topotecan, carboplatin and the PARP inhibitor Veliparib in acute Leukemias, aggressive myeloproliferative neoplasms, and chronic Myelomonocytic leukemia. Clin Cancer Res 23(4):899–907. https://doi.org/10.1158/1078-0432.CCR-16-1274
104. Zeidner JF, Foster MC, Blackford AL, Litzow MR, Morris LE, Strickland SA, Lancet JE, Bose P, Levy MY, Tibes R, Gojo I, Gocke CD, Rosner GL, Little RF, Wright JJ, Doyle LA, Smith BD, Karp JE (2015) Randomized multicenter phase II study of flavopiridol (alvocidib), cytarabine, and mitoxantrone (FLAM) versus cytarabine/daunorubicin (7+3) in newly diagnosed acute myeloid leukemia. Haematologica 100(9):1172–1179. https://doi.org/10.3324/haematol.2015.125849
105. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, Dombret H, Ebert BL, Fenaux P, Larson RA, Levine RL, Lo-Coco F, Naoe T, Niederwieser D, Ossenkoppele GJ, Sanz M, Sierra J, Tallman MS, Tien HF, Wei AH, Löwenberg B, Bloomfield CD (2017) Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 129(4):424–447. https://doi.org/10.1182/blood-2016-08-733196
106. (NICE) NI for H and CE (2018) Appraisal Consultation Document-Liposomal Cytarabine and Daunorubicin for Untreated Acute Myeloid Leukaemia Liposomal Cytarabine and Daunorubicin for Untreated Acute Myeloid Leukaemia. https://www.nice.org.uk/guidance/gid-ta10230/documents/appraisal-consultation-document. Accessed 17 Nov 2018
107. Ommen HB (2016) Monitoring minimal residual disease in acute myeloid leukaemia: a review of the current evolving strategies. Ther Adv Hematol 7(1):3–16. https://doi.org/10.1177/2040620715614529
108. Talati C (2018) Comparison of induction strategies and responses for acute myeloid leukemia patients after resistance to Hypomethylating agents for antecedent myeloid malignancy. https://ash.confex.com/ash/2018/webprogram/Paper119879.html. Accessed 10 Dec 2018
109. Cortes JE, Goldberg SL, Feldman EJ, Rizzeri DA, Hogge DE, Larson M, Pigneux A, Recher C, Schiller G, Warzocha K, Kantarjian H, Louie AC, Kolitz JE (2015) Phase II, multicenter, randomized trial of CPX-351 (cytarabine:daunorubicin) liposome injection versus intensive salvage therapy in adults with first relapse AML. Cancer 121(2):234–242. https://doi.org/10.1002/cncr.28974