Annals of Hematology (2019) 98:2467–2483
https://doi.org/10.1007/s00277-019-03820-w

REVIEW ARTICLE

Update on management and progress of novel therapeutics for R/R AML: an Iberian expert panel consensus

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Received: 14 July 2019 / Accepted: 8 October 2019 / Published online: 30 October 2019

Abstract

A significant proportion of adult patients with acute myeloid leukemia (AML) fail to achieve complete remission or will relapse later on after achieving it. Prognosis for relapsed or refractory (R/R) AML patients remains discouraging, with the main curative option still relying on hematopoietic stem cell transplant (HSCT) for those who are eligible. Beyond morphological bone marrow and peripheral blood assessment, evaluation of patient performance status and comorbidities, as well as genetic/molecular characterization, is crucial to make an accurate diagnosis and prognosis, which will be useful to select the most appropriate treatment. Emerging strategies are mainly focusing on the development of immune- and molecular-based approaches. Novel targeted therapies are generally well tolerated, potentially allowing them to be administered alone or in combination with classical chemotherapy agents. Enrolment in clinical trials should be considered first option for R/R AML patients, either as a bridge to HSCT or to benefit from novel therapies that eventually may prolong survival and improve quality of life. An Iberian expert panel has reviewed the recent advances in the management of R/R AML with the aim to develop updated evidence and expert opinion-based recommendations.

Keywords Acute myeloid leukemia · Relapsed · Refractory · Treatment · Targeted therapies

Introduction

Despite progress of modern chemotherapy achieved in recent decades, prognosis of acute myeloid leukemia (AML) remains discouraging, without significant improvement in long-term outcomes. A considerable amount of patients still develops induction failure, or relapse after attaining complete remission (CR) [1]. Although prognosis for relapsed/refractory (R/R) patients is particularly poor, a sizeable proportion can be efficaciously salvaged using chemotherapy-based therapies followed by allogeneic hematopoietic stem cell transplant (allo-HSCT) [2], particularly in younger and fit patients. In addition, many AML patients are not considered candidates for front-line or salvage intensive chemotherapy-based strategies, and therefore should be offered low-intensity regimens. Those non-intensively treated older and unfit patients represent a large AML population in which there is a striking lack of information at the R/R stage. We can state that, given the dismal prognosis and the absence of standard/satisfactory treatment options, patients with R/R AML represent a challenging unmet medical need.

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Definition of refractory disease has largely differed within clinical practice protocols over the years (Table 1), which has consequently hindered comparison of data across studies. Last published European LeukemiaNet (ELN) guidelines define it as failure to attain CR, i.e. a remaining blast count ≥ 5% (by optical cytomorphology), after two intensive induction cycles, regardless of the schedule used in the second cycle [3]. It should be noted that this recent consensus definition has not been consistently used in the past, but it could be adopted in future prospective clinical trials and observations, facilitating comparison of clinical outcomes [4]. This definition contrasts with the bleak diagnosis of patients who do not achieve CR or even partial remission (PR) after a first induction cycle with 3+7 regimen [5]. In contrast, the definition of relapse has been less heterogeneous in the past (i.e. reappearance of ≥ 5% of leukemic blasts in the BM or peripheral blood by optical cytomorphology, or extramedullary infiltration, after a first CR). Of note, relapses are frequently classified based upon time of appearance after first CR (CR1) into early (< 6 months) or late relapse (> months) [6], but this cut-off may vary across different studies (e.g. 12, 18 or 24 months).

Molecular genetic alterations underlying AML pathogenesis have established the basis for the development of targeted therapies, which may particularly benefit R/R AML patients. Herein, we aim to provide a broad overview of current knowledge in R/R AML setting including prognostic factors, diagnosis and treatment strategies, with a special focus on novel therapeutic approaches that are either used in clinical practice or being evaluated in clinical trials. Novel therapies provide a more personalized approach for AML treatment that may eventually help to improve outcomes in R/R AML patients, particularly in those with worse prognosis who are not suitable for intensive salvage chemotherapy.

Search methodology

PubMed and Medline databases were searched for R/R AML publications and clinical studies released until September 2018. Ongoing clinical trials with novel therapeutics have been extracted from ClinicalTrials.gov database (https://clinicaltrials.gov/). Conventional chemotherapy is outside of the scope of this review since it has been widely described in a recently published systematic review [2].

Epidemiology

While CR is achieved in approximately 60–80% of younger newly diagnosed AML patients treated with intensive induction (usually 7+3 cytarabine plus anthracycline schedule) therapy [12], approximately half of the younger patients and up to 90% of those elderly will experience a subsequent relapsed [13]. Outcomes for R/R AML patients are poor, with median overall survival (OS) of only 3 to 7 months and an estimated survival rate at 3 years of 10% [14]. Although most relapses occur within 1 year of remission, the rate of relapse remains high until 3 years from remission date, when it suddenly falls [15]. Refractoriness to 7+3 incidence ranges between 10 and 40% depending on the patient population [6], with a remarkable increased risk in elderly patients as well as in those with high-risk features (i.e. secondary AML, adverse cytogenetics and molecular alterations that carry increased risk of chemoresistance, such as *TP53* mutation and *GATA2enh-MECOM* rearrangement). Although allo-HSCT remains the approach with the greatest probability of cure in patients achieving CR1, this procedure is not feasible for a sizable proportion of patients (due to comorbidities, older age or lack of suitable donor). Also, survival rates after allo-HSCT are about 50%, and post-transplant relapse has been reported in up to 40% of patients [16, 17]. Allo-HSCT has been further studied as initial salvage therapy, being associated with better prognosis in AML patients with low burden disease at diagnosis compared with intensive chemotherapy [18]. Since allo-HSCT as part of the front-line therapy is now more frequently used, those patients relapsing after an allo-HSCT represent an emerging setting of R/R AML which calls for specific management.

Table 1 Definitions for induction failure or primary refractory AML over time

Definition	Reference
No CR or CRi after two courses of intensive induction cycles, excluding patients with death in aplasia or due to indeterminate cause	Döhner H, et al. 2017 [3]
Less than a 50% reduction in blast numbers with > 15% residual blasts after one cycle of induction chemotherapy	Ferguson P, et al. 2016 [5]
> 15% blasts in the bone marrow, 2 weeks after the completion of the cycle	Wheatley K, et al. 1999 [7]
Persistent leukemic blasts in either the peripheral blood or the bone marrow in a patient alive 7 days or more following treatment	Cheson B, et al. 2003 [8] Döhner H, et al. 2010 [9]
< 50% blast percentage reduction following one course of intensive chemotherapy	Schlenk RF, et al. 2003 [10]
Persistence of a significant leukemic blasts 7 days or more following high-dose cytarabine therapy	NCCN Guidelines 2016 [11]

CR, complete remission; *CRi*, CR with incomplete hematologic recovery.

Key points

- Failure to achieve CR1 due to chemoresistance after 3+7-based induction is common, especially in older patients, unfavourable genetics and secondary AML.
- Relapse after CR1 occurs frequently, and relapse after allo-HSCT is an emerging complication.
- Older/unfit patients failing to achieve a CR or progressing after attenuated therapeutic approaches represent a challenging unmet medical need.

Prognosis

According to ELN guidelines and European Prognostic (EPI) score applicable to R/R AML adults aged 15 to 60 years, clinically relevant parameters associated with worse outcomes are shorter relapse-free interval (RFI) after CR1, older age at the time of relapse, unfavourable karyotype at initial diagnosis and allo-HSCT prior to first relapse [3]. It is generally accepted that patients who relapse after 12 or 18 months after CR1 fare better than earlier relapse [19, 20], but this superior prognosis can be questioned in patients relapsing after 5 years through leukemic clonal evolution, in whom results could be poorer [21]. Recently, the impact of FLT3-ITD mutations in R/R AML has been analyzed, revealing a correlation between a mutated phenotype and shorter survival of patients, likely as a result of the lower probability to achieve a second CR (CR2) after intensive chemotherapy in FLT3-mutated patients [2, 13, 22, 23]. Besides lower age and lack of previous HSCT, favourable prognostic factors in R/R AML are the presence of core-binding factor (CBF) AML at diagnosis, of biallelic *CEBPA* mutations and a CR1 > 18 months [13]. Some studies showed contradictory data about the prognostic impact of *t*(8;21) and previous allo-SCT [24, 25]. While *NPM1* mutations seem to lose their favourable value in relapsing patients [26, 27], *CEBPA* mutations remain a positive prognostic factor at relapse [13]. A compilation of the most relevant prognostic factors that have been identified across the available score systems for R/R AML is shown in Table 2.

Higher frequencies of mutations in genes associated with poor prognosis, such as FLT3, *RUNX1* and *DNMT3A,* have been found at diagnosis in cytogenetically normal (CN) relapsed patients [28]. Of these, only FLT3-ITD remains as a negative independent factor at relapse [13, 23, 26, 27]. Interestingly, mutations in epigenetic regulators appear to remain stable at relapse while mutations of genes affecting signalling pathways seem to be gained/lost [28]. Given that most of R/R AML patients harbour a different mutational profile from the time point of initial diagnosis, and mutations in specific genes may drive disease progression through therapy resistance, the relevance of molecular re-testing in clinical practice is evident.

Key points

- Some validated scoring systems could be useful in the routine clinical practice to guide therapeutic decision-taking.
- Apart from CR1 duration, age, prior HSCT and cytogenetics, molecular markers such as *FLT3*-ITD or *CEBPA* biallelic mutations may play a role in the definition of prognosis at R/R AML status.
- It is recommended to use reproducible definitions of refractory AML as well as to describe the main risk factors (or categorize following scoring systems) in clinical trials of R/R AML patients.

Diagnosis and management

Considering that no standard salvage regimen for R/R AML has been yet agreed, enrolment in clinical trials should be a priority for these patients whenever possible [3]. Reassessment of patient fitness and cytogenetics at refractoriness/relapse should be performed prior to trial enrolment, using approved diagnostic tests that ultimately enable administration of the most appropriate therapy to each patient. Besides myeloblast count, evaluation of molecular markers and subsequent clonal evolution could be recommended in the diagnostic workup for R/R AML patients [29]. We should highlight that the screening of druggable mutations is recommendable in light of the evolving strategies for the management of R/R AML (i.e. emergence of IDH1/IDH2 inhibitors and second-generation FLT3 inhibitors). Thus, FLT3 and IDH mutation screening could be recommended for R/R AML patients, even in the absence of these mutations at the primary diagnosis (especially for FLT3 given that these are less stable, with frequent loss or acquisition by clonal selection/evolution) [30]. Current diagnostic procedures for R/R AML are summarized in Table 3.

Intensive salvage therapies, i.e. high-dose cytarabine-based regimens, should be primarily administered to fit R/R AML patients with the aim to achieve disease remission (e.g. CR/CRi) and undergo allo-HSCT (Fig. 1), which has shown to provide the best chance of survival [23]. Nevertheless, it should be noted that indication of a subsequent allo-HSCT could be unfeasible or even controversial in many patients, such as those on borderline age or clinical condition, or very late relapses with favourable genetics [3]. Attenuated approaches, i.e. low-dose cytarabine (LDAC) or hypomethylating agents (HMAs), could be considered for unfit R/R patients, but also as second or beyond salvage therapy for younger/fit subjects [31]. In this regard, available data shows that a CR can be achieved in a higher proportion of patients after intensive salvage approaches, although median OS is not clearly improved compared to attenuated salvage regimens [2, 32]. In contrast, studies with HMAs

Table 2 Prognostic factors for R/R AML based on developed scoring systems

Factor	HOVON-SAKK score [19] *n* = 667 (15–60 years)		GOELAMS score [27] *n* = 133 (19–70 years)		PETHEMA score [26] *n* = 190 (16–76 years)		AMLSG score [13] *n* = 907 (18–80 years)	
	Measure	Points	Measure	Points	Measure	Points	Measure	Points
RFI (months)	> 18 7–18 ≤ 6	0 3 5	≤ 12	1	< 12 > 12 Refractory	4 0 2	> 18	+ 0.5
Cytogenetics at diagnosis	inv(16) *t*(8;21) Other ¥	0 3 5	High-risk cytogenetics*	1	Favourable** Intermediate** Adverse**	0 2 4	CBF-AML Adverse-risk cytogenetics	1 -1
Age at relapse (years)	< 36 36–45 > 45	0 1 2	-	-	-	-	-	-
Prior stem cell transplant	Autologous Allogeneic No	2 2 0	-	-	Autologous Allogeneic No	1 0 1	-	-
FLT3-ITD	-	-	Yes	1	Yes No	2 0	Yes	− 1
Biallelic *CEBPA* mutation	-	-	-		-	-	Yes	1
Definition of risk categories according to calculated score (*n*, %)	Favourable risk 0–6 (57, 9%) Intermediate risk 7–9 (165, 25%) High risk 10–14 (445, 66%)		Favourable risk 0 (36, 27%) Intermediate risk 1 (54, 41%) High risk 2 or 3 (43, 32%)		Good prognosis 1–4 (48, 25%) Intermediate prognosis 5–6 (57, 30%) Poor prognosis 7–11 (85, 45%)		Low CR/CRi probability < 0 (281, 31%) Intermediate CR/CRi probability 0 (369, 41%) High CR/CRi probability = > 0 (257, 28%)	

*According to MRC, Grimwade 2010. **Modified MRC cytogenetics: low risk karyotype (inv.16), intermediate, high risk + *t*(8;21). ¥ Normal, intermediate, unfavourable and unknown cytogenetics. *RFI*, relapse-free interval; *HOVON*, Dutch-Belgian Hemato-Oncology Cooperative Group; *SAKK*, Swiss Group for Clinical Cancer Research Collaborative Group; *GOELAMS*, Groupe Ouest Est des Leucemies et des Autres Maladies du Sang; *PETHEMA*, Programa Español de Tratamientos en Hematología; *AMLSG*, German-Australian *AML* study group

Table 3 Diagnostic tests/procedures for R/R AML according to ELN guidelines 2017 [3]

Morphology (cytomorphology and histopathology)	• Bone marrow blasts ≥ 5% (an aspirate is mandatory, biopsy as clinically indicated) • Reappearance of leukemic blasts in the blood • Development of extramedullary disease (biopsy of suspected site of relapse; CT scan or lumbar puncture to be performed only if clinical suspicion of involvement or site infiltration at primary diagnosis)
Molecular genetic testing (RT-qPCR, NGS*)	• *CBF* rearrangements, *NPM1*, *CEBPA* mutations (define prognosis and disease category, in contrast with secondary AML) • FLT3 mutations (ITD including allelic ratio, associated with poor prognosis, and TKD mutations, potential use of targeted therapy with second-generation FLT3 inhibitors) • IDH1 and IDH2 mutations (potential use of targeted therapy with first-generation IDH inhibitors) • *TP53* mutations (associated with poor prognosis, potential resistance to MDM2 inhibitors)
Performance status	• ECOG performance status • HCT-CI score (for potential candidates for a subsequent allo-SCT)
Cytogenetics (karyotyping, FISH)	• Rearrangements (translocations, inversions) • Gene fusions • Chromosomal gains/loses
Additional procedures to be considered	❖ Immunophenotyping (MFC) ❖ Sensitivity assessment of response (RT-qPCR) ❖ Eligibility assessment for allogeneic HSCT

*This technique has not been widely implemented yet. *NGS*, next generation sequencing; *RT-qPCR*, reverse transcription quantitative polymerase chain reaction; *FISH*, fluorescence in situ hybridization; *MFC*, multiparameter flow cytometry; *HSCT*, human stem cell transplant; *ECOG*, Eastern Cooperative Oncology Group; *ITD*, internal tandem duplication; *TKD*, tyrosine kinase domain

used in monotherapy yielded a CR of 16%, with median OS comparable with intensive salvage approaches for high-risk R/R AML patients (OS of 6.7 months) [33]. Accordingly, less intensive therapies such as HMAs and LDAC are recommended in the NCCN Guidelines for elderly unfit patients with R/R AML who are not eligible for intensive chemotherapy, to control disease progression and minimize treatment-related mortality [31].

Key points

- Enrolment in clinical trials should be a priority for R/R AML patients whenever possible.
- Reassessment of patient fitness, conventional cytogenetics and molecular genetic testing (e.g. FLT3 and IDH1/2) are recommended for the diagnostic workup.
- Despite intensive salvage therapy aimed at achieving disease remission followed by an allo-HSCT is the main curative strategy for younger/fit R/R AML patients, those

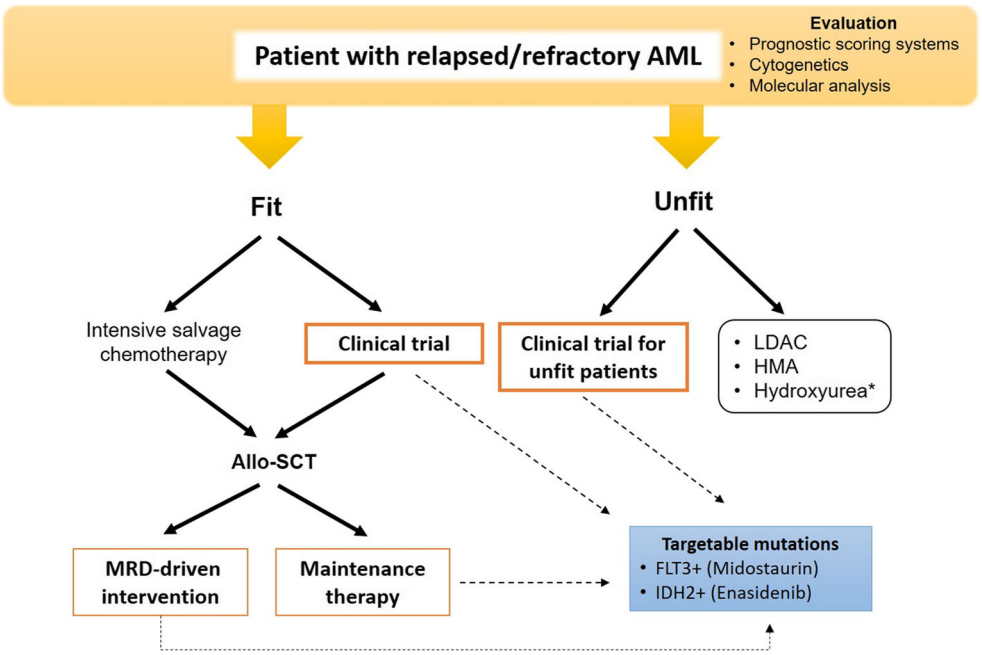

Fig. 1 Treatment algorithm for patients with R/R AML. ADC, antibody drug conjugate; ENA, enasidenib; HMA, hypomethylating agents; IVO, ivosidenib; LDAC, low-dose cytarabine; MRD, minimal residual disease. The asterisk indicates best supportive care

who carry FLT3 mutations are currently able to benefit of more effective and less toxic novel agents, such as FT3 inhibitors quizartinib and gilteritinib.

Intensive therapy and allo-HSCT

Current intensive chemotherapy approaches involve the use of cytarabine (Ara-C) in high or intermediate dose (HiDAC, IDAC, respectively), either in monotherapy or combined with other agents, such as (i) anthracyclines (daunorubicin (Dau), idarubicin (Ida), mitoxantrone (Mito), amsacrine (Amsa)) and (ii) purine analogues (fludarabine, cladribine, clofarabine). A third agent can be also added to the combination of Ara-C + Mito, such as etoposide (MEC regimen) or gemtuzumab ozogamicin (MIDAM regimen). The granulocyte-colony stimulating factor (G-CSF) is frequently administered in combination with Ara-C + fludarabine (FLAG or FLAG-Ida) or Ara-C + cladribine (CLAG).

ELN recommended the following salvage regimens: IDAC with or without an anthracycline (Dau, Ida or Mito), FLAG-Ida and MEC [3].

None of the salvage conventional agents have rendered outstanding OS rates (recently reviewed by Megías-Vericat et al., although some regimens have shown acceptable results in terms of weighted mean CR rates: Ara-C + Amsa (54.3%), MEC (52.5%), MIDAM (59.4%), FLAG (53.5%), CLAG (45.5%), FLAG-Ida (52.9%) and Ara-C + clofarabine (44.2%) [2]. Despite achieving disease remission (CR2) after salvage chemotherapy, the decision to undergo HSCT relies on the risk-benefit ratio, which depends on patient performance status, cytogenetics and molecular genetic features as well as inherent transplantation factors. R/R AML patients with unfavourable cytogenetics (e.g. complex karyotype with *TP53* mutation) and those with FLT3-ITD mutations (especially if allelic ratio > 0.51) show disappointing outcomes in spite of performing an allo-HSCT in ≥ second CR, while it is not recommended in patients with > 25% blasts in bone marrow [6] or peripheral blood blasts before conditioning [34]. Among novel conditioning regimens to improve transplant outcomes, sequential regimen of FLAMSA (i.e. fludarabine, Amsa and Ara-C) followed by reduced-intensity conditioning (RIC)-HSCT has shown encouraging results in R/R AML patients with active disease [35]. However, these data need to be confirmed in well-designed clinical trials, the goal remaining to achieve a new CR before conventional allo-HSCT.

Several recent retrospective studies have consistently shown the prognostic relevance of minimal residual disease (MRD) before allo-HSCT [36–38]. Although these studies analyzed the impact of MRD by different techniques [39], which generally lack standardization, a striking negative impact of MRD "positivity" was observed [40]. However, there are no studies indicating that additional pre-HSCT interventions to turn this MRD into "negative" are valuable (e.g. additional chemotherapy, HMAs, targeted therapy or others).

Key points

- Although there is no standard salvage chemotherapy regimen, some could result in better CR rates (e.g. MIDAM-GO, Ara-C + Amsa, FLAG/FLAG-Ida or MEC).
- Retrospective studies are showing the prognostic relevance of MRD status before allo-HSCT. However, MRD positive status before allo-HSCT does not preclude its indication.

Management of AML relapsing after allo-HSCT

AML patients relapsing after allo-HSCT, performed either during CR1 or CR2, represent a special subset with particularly poor outcomes. Of note, 3-year OS appears to increase as time from HSCT to relapse increases, being estimated at 4%, 12%, 26% and 38% for relapses within 1–6 months, 6 months to 2 years, 2 to 3 years and > 3 years after HSCT, respectively [3]. To achieve a new CR, administration of chemotherapy along with donor lymphocyte infusion (DLI) has demonstrated better efficacy than chemotherapy alone [3]. Second allo-HSCT (HSCT2) can be considered when CR is achieved after relapsed-HSCT, although outcomes are poor and treatment-related mortality rate can reach 42% [3]. Recently, DLI and allo-HSCT2 were compared in 418 post-allograft relapsed AML patients (< 60 years) showing similar survival rates with both treatments, but highlighting that better outcome relied on the achievement of CR before HSCT2/DLI or emergence of relapse > 6 months from HSCT1 [41].

Craddock et al. showed that an increased risk of early relapse appears to be associated with adverse-risk karyotype and FLT3-ITD mutations, whereas late relapse correlates with the absence of *NPM1* mutation and chronic graft-versus-host disease (GvHD) [18]. These observations provide insights for the design and application of novel strategies aimed at reducing the risk of relapse after transplant. To this regard, small molecule FT3 inhibitors, such as sorafenib, have shown promising results for patients in the post-transplant setting, thus prompting currently underway clinical trials in FLT3-ITD+ R/R AML as maintenance therapy [42]. A recent study suggested that early tapering of immunosuppressive agents allows for strengthening graft-versus-leukemia (GVL) effect, which results in reduced relapse rates and durable remissions, thereby improving AML patients' survival after allo-HSCT [43]. Mechanisms of relapse after allo-HSCT could be mostly related to the loss of immunosurveillance exerted by donor immune cells as compared with clonal evolution of AML

cells, commonly observed in patients relapsing after chemotherapy [44]. This observation would reinforce the search of a novel allogeneic immune platform as part of salvage strategy to achieve a durable response.

Key points

- AML patients relapsing after allo-HSCT represent a special subset, with poor outcomes and limited therapeutic options.
- Some studies suggest better outcomes when intensive or attenuated salvage chemotherapy is followed by DLI or a subsequent allo-HSCT.
- Novel strategies aimed at reducing the risk of overt haematological relapse after allo-HSCT should be explored, especially for patients at high risk of relapse (e.g. FLT3-ITD mutated or MRD positive).

Novel approaches

Efforts made during the last decades to understand the complexity underlying AML molecular mechanisms have generated an impressive progress towards the development of more specific and effective treatments. Targeted therapies are antibody-mediated or molecular-based strategies with distinct mechanisms of action (Fig. 2), that are used either in combination with traditional chemotherapy or as single agents. In R/R AML setting, these novel approaches have been intensively evaluated and numerous clinical trials are currently ongoing (Tables 4 and 5).

FLT3 tyrosine kinase inhibitors: *Fms*-like tyrosine kinase 3 (FLT3*)* activating mutations occur in 35% cases of AML, mostly as internal tandem duplications (ITD, 25%) but also as point mutations in the TK domain (TKD, 10%) [13]. FLT3-tyrosine kinase inhibitors (TKIs) are categorized based on their mechanism of action into type I (midostaurin, gilteritinib and crenolanib), that target all FLT3-mutated cells and bind to active/inactive kinases, and type II (sorafenib, quizartinib and ponatinib), that target ITD+ cells but not TKD+ and binding inactive kinases [45]. Besides, FLT3-TKIs are classified into first generation of less specific FLT3 inhibitors (sorafenib, lestaurtinib, sunitinib and midostaurin), or second generation of selective and potent inhibitors (quizartinib, gilteritinib, crenolanib and ponatinib) [46].

First-generation inhibitor sorafenib, administered along with chemotherapy in phase 1/2, showed reduction of

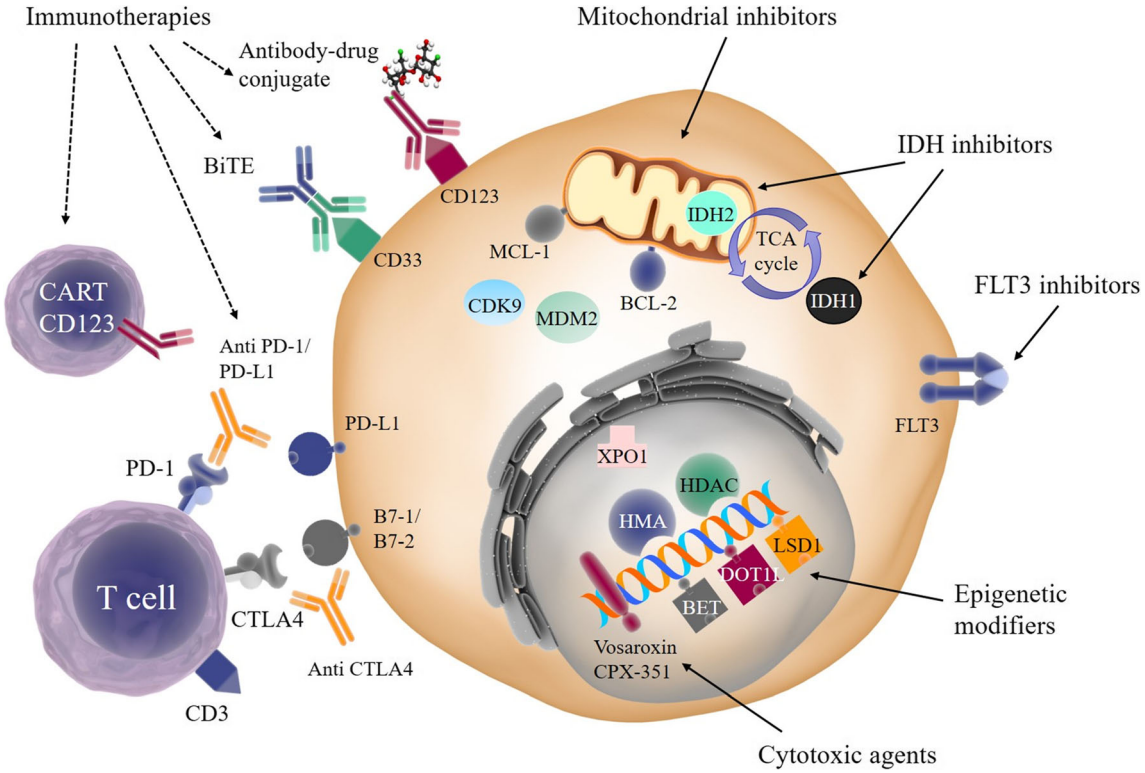

Fig. 2 Mechanism of action of novel therapies in the AML cell. BET, bromodomain and extraterminal proteins; BiTE, bispecific T cell engager; CART, chimeric antigen receptor T cell; CTLA-4, cytotoxic T-lymphocyte associated protein 4; DOT1L, disrupter of telomere silencing-1 like; FLT3, fms-like tyrosine kinase 3; HDAC, histone deacetylase; HMA, hypomethylating agents; IDH, isocitrate dehydrogenase; LSD1, lysine-specific demethylase 1; MDM2, murine double minute 2; PD-1, programmed-death 1; TCA, tricarboxylic acid; XPO, exportin 1

Table 4 Phase 1 and 2 clinical trials with novel therapies in R/R AML (active/recruiting status)

	Drug	Study number	Study design
PK inhibitors			
FLT3 inhibitors	Crenolanib	NCT02400281; NCT01657682	Combined with standard chemotherapy (Ida/AraC, MEC or FLAG-IDA) or Aza; single agent
	Sorafenib	NCT03622541	Single agent in R/R to chemotherapy or SCT
	Ponatinib	NCT01620216	*In vitro* kinase inhibitor panel to select the best targeted therapy
	Quizartinib	NCT03661307; NCT01892371	Combined with decitabine; with Aza or AraC
	Midostaurin Gilteritinib	NCT00819546	Combined with everolimus
Immunotherapy			
CD33-targeted antibody drug conjugates	GO	NCT03374332; NCT02221310¤	Followed by DLI; in combination with chemotherapy followed by SCT
	IMGN779	NCT02674763	Dose-escalation (monotherapy)
	BI836858	NCT03207191	Single agent after relapsed SCT
BiTE® CD33	AMG330	NCT02520427	FIH: safety, tolerability, PKPD
CD38-targeted antibody	Daratumumab	NCT03067571	Efficacy and safety as single agent
CD45-targeted antibody conjugated with Ytrium	BC8	NCT03670966	Dose-escalation combined with chemotherapy previous to allo-SCT
CD123-targeted antibody drug conjugates	IMGN632	NCT03386513	Dose-escalation (monotherapy)
	XmAb14045	NCT02730312	Safety and tolerability
Immune checkpoint inhibitors	Avelumab	NCT02953561	Combined with Aza
	Nivolumab	NCT02397720	Combined with Aza with/without ipilimumab
	Pembrolizumab	NCT02845297; NCT02996474	Combined with Aza; with decitabine
	Ipilimumab	NCT02890329	Combined with decitabine for relapsed after SCT/chemotherapy or refractory to chemotherapy
Adoptive cell transfer	NK cells	NCT03050216¤; NCT02944162; NCT02316964	Haploidentical NK cells; anti-CD33 CAR-NK; haploidentical infusion after decitabine
	CART	NCT02159495§; NCT03631576¤; NCT03126864¤§	CD123-CART; CD123/CLL-1-CART; CD33-CART
	DLI	NCT02017457	Combined with Aza and administered after SCT
Epigenetic modulators			
Hypomethylating agents	Azacitidine	NCT00766116¤, NCT02275663	Combined with GO; with FLAG
	Decitabine	NCT03063203	Single agent in TP53-mutated patients
	Guadecitabine	NCT02684162	Combined with DLI in relapsing post-allogeneic SCT
Inhibitors of BET proteins	FT-1101	NCT02543879	Alone or in combination with Aza
	GSK525762	NCT01943851	Dose-escalation (monotherapy), safety and PKPD
Epigenetic modulators			
Histone deacetylase inhibitors	Panobinostat	NCT01451268; NCT02676323§	Combined with standard immunosupressive therapy after SCT; with fludarabine + AraC
	Vorinostat	NCT03263936§	Combined with decitabine before and during chemotherapy with FLAG
	Entinostat	NCT01305499¤	Combined with Aza
IDH inhibitors	Enasidenib	NCT01915498	

Table 4 (continued)

	Drug	Study number	Study design
			Dose-escalation (monotherapy), safety and PKPD in IDH2-mutated patients
	Ivosidenib FT-2102	NCT02074839	Dose-escalation (monotherapy), safety and PKPD in IDH1-mutated patients
Mitochondrial inhibitors			
CDK inhibitors	Alvocidib	NCT03441555; NCT03563560; NCT02520011	Combined with venetoclax (PKPD); with CM or CD; with CM with/without alvocidib
	HDM2012		
	Dinaciclib	NCT03484520	Combined with venetoclax (PKPD)
MDM2 inhibitors	Milademetan	NCT03634228; NCT03552029	Combined with LDAC; with quizartinib
BCL-2 inhibitors	Venetoclax	NCT03194932[§]; NCT03404193; NCT03214562; NCT03625505	Combined with chemotherapy (pediatric); with decitabine; with FLAG-Ida; with gilteritinib
	AMG-176	NCT02675452	FIH: dose exploration and safety
Inhibitors of nuclear export	Selinexor	NCT02416908[¤]; NCT02249091; NCT03071276[§]	Combined with intensive chemotherapy: CLAG; AraC + Ida; AraC + fludarabine
Chemotherapy			
Inhibitors of DNA synthesis	CPX-351	NCT02019069[¤]; NCT01943682[§]	Monotherapy in R/R after HMA therapy; safety and PK in children

[¤] Inclusion of patients > 65 years, [§] Mainly in children and/or young adults < 24 years. *FIH*, first in human; *FLAG*, fludarabine, cytarabine, G-CSF (granulocyte-colony stimulating factor); *Ida*, idarubicin; *CM*, cytarabine + mitoxantrone; *CD*, cytarabine+daunorubicin; *LDAC*, low-dose cytarabine; *CLAG*, cladribine, G-CSF, cytarabine; *GO*, gemtuzumab ozogamicin; *DLI,* donor lymphocyte infusion; *AraC*, cytarabine; *Aza*, azacitidine; *SCT*, stem cell transplant

leukemic burden in R/R AML ITD+ patients [47]. Its combination with azacitidine and DLI has shown promising efficacy as salvage therapy for relapse post-HSCT, but well-designed studies are needed to confirm the potential benefit of this combination [48]. Midostaurin treatment as single agent in phase 2 studies resulted only in a reduction of peripheral blasts in R/R patients with FLT3 mutations (ITD and TKD) [49], and an overall response rate (CR+CRi+PR) of 33% when combined with azacitidine [50].

Encouraging outcomes have been shown from phase 1/2 studies conducted in R/R AML ITD+ patients with the second-generation inhibitor quizartinib, with CR/CRi rates of nearly 50% [51] and roughly one-third of younger patients bridging to HSCT [52]. Combined with azacitidine or LDAC, quizartinib therapy showed a 73% CR/CRi rate [53], while its use as single agent to prevent relapse post-HSCT was shown tolerable [54]. Gilteritinib clinical responses in R/R patients (phase 1/2 studies) occurred independently of ITD or TKD mutations but reached higher CR/CRi rate among ITD+ patients (60–62%) [55, 56]. Subsequently, the FDA accepted the new drug application of gilteritinib to treat FLT3-mutated R/R AML. Final results of quizartinib and gilteritinib phase 3 trials NCT02421939 and NCT02039726, respectively (Table 5), have been recently released. Compared with salvage chemotherapy, these potent FLT3 inhibitors showed a favourable safety profile with higher response rates and significantly longer survival of FLT3-mutated R/R AML patients [57, 58].

Crenolanib and ponatinib are second-generation inhibitors that could tackle the problem of resistance to previously developed TKIs [44]. As single agent, crenolanib produced CR/CRi rates of 62% in FL3-TKI naïve patients [59], whereas, when combined with chemotherapy, CR/CRi was reached in 66% of patients failing ≤ 2 therapies [60]. Phase I trial with ponatinib in refractory patients suggested early clinical efficacy in those ITD+ [61] and in animal models with resistance to quizartinib [62], which led to a subsequent phase 2 trial (Table 4).

Antibodies and immunotherapies: CD33-antibody drug conjugate (ADC) gemtuzumab ozogamicin (GO) was withdrawn from the market in 2010 but it has been re-approved by the FDA in 2017 for R/R CD33+ AML patients using a lower-dose fractionated regimen [63], and several phase 1/2 trials are currently underway (Table 4). CD33-ADC vadastuximab talirine, which was designed to overcome cytotoxic off-target activities of GO [64], demonstrated a safe profile and single-agent activity in R/R AML but a subsequent

randomized front-line phase 3 trial in elderly had to be closed due to increased fatal infections [65]. First in human (FIH) trials for IMGN779 (a novel CD33-ADC) and AMG330 (a CD3/CD33- Bispecific T cell engaging [BiTE] antibody) have recently started (Table 4), based upon high selectivity and robust efficacy against leukemic cells revealed in preclinical studies [66–68].

The finding that CD123 is differentially expressed on AML stem cells in comparison with normal hematopoietic cells [69] led to the development of CD123-ADC. Recently, several of these ADC have entered clinical phases based upon encouraging preclinical outcomes [70–72]. A phase 1 safety trial with IMGN632 has already finished, while similar trials with SGN-CD123 and XmAb14045 are still ongoing (Table 4). Flotetuzumab, a CD123 x CD3 dual-affinity re-targeting (DART®) molecule, has shown encouraging anti-leukemic activity in phase 1, with durable responses in R/R AML patients. In vitro data supports the combination of flotetuzumab and anti-PD-1 monoclonal antibody MGA012 to potentially enhance T cell–mediated cytotoxicity against leukemic cells [73].

Therapeutic blockade of immune checkpoint pathways has become a potentially active approach to enhance the anti-leukemic immune response. Therefore, novel antibodies targeting immune checkpoint inhibitors, such as programmed-death 1 (PD-1) receptor, PD-1 ligand (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), have been deployed [67]. Moreover, synergism between these inhibitors and HMAs was reported [74] and subsequent phase 1/2 studies are being conducted in elderly unfit R/R AML patients (Table 4).

Consolidation therapy with haploidentical NK cell infusion has shown to be a safe and feasible approach to reduce the risk of relapse post-HSCT in poor-prognosis patients [75], fostering the GVL effect [74]. However, these preliminary results should be confirmed in well-designed clinical trials. Administration of donor lymphocyte infusion (DLI) along with chemotherapy at relapse post-HSCT has shown to increase both CR and OS rates compared with chemotherapy alone, especially in female patients with favourable karyotype and low disease burden [76]. Phase 1/2 studies in R/R AML patients with both NK cell and lymphocyte infusion strategies are ongoing (Table 4). An ongoing phase 1 study with lentivirally transduced CD123-chimeric antigen receptor (CAR) T cells has shown a clinical response in 83% of relapsed patients [77]. Given that human C-type lectin-like molecule-1 (CLL-1) is highly expressed in leukemic stem cells but absent in hematopoietic stem cells [78], a dual-targeted CD123/CLL-1 CART approach is currently being explored (Table 4).

Epigenetic modulators: Hypomethylating agent (HMA) azacitidine has shown significant clinical activity in R/R setting, with possible achievement of CR but a relatively short remission duration [79]. Current clinical trials are therefore pursuing an increased and durable efficacy through its combination with other agents, such as HDACs (panobinostat, vorinostat,

Table 5 Main phase 3 clinical trials with novel therapies in R/R AML

	Drug	Study number	Study design
PK inhibitors			
FLT3 inhibitors	Crenolanib	NCT02298166 NCT03250338¤	Combined with standard chemotherapy (CM) Administered following salvage chemotherapy (FLAG-Ida or HAM)
	Gilteritinib	NCT03182244 NCT02421939	Compared with salvage chemotherapy (LDAC, MEC, FLAG) Compared with salvage chemotherapy (LDAC, MEC, FLAG-Ida)
	Quizartinib	NCT02039726	Compared with salvage chemotherapy (LDAC, MEC, FLAG-Ida)
Immunotherapy			
CD33-targeted antibody drug conjugates	GO	NCT00049517	Following high-dose or standard daunorubicin, compared with HDAC, prior to autologous SCT
Epigenetic modulators			
Hypomethylating agents	Guadecitabine	NCT02920008	Compared with high- (HDAC, MEC, FLAG-Ida) or low-intensity (LDAC, Aza, Dec) chemotherapy or BSC
IDH2 inhibitor	Enasidenib	NCT02577406¤	Combined with BSC, compared with low-intense regimens (Aza, LDAC, IDAC)
Mitochondrial inhibitors			
MDM2 inhibitor	Idasanutlin	NCT02545283	Combined with AraC, includes wt and *TP53* mutated patients
BCL-2 inhibitor	Venetoclax	NCT02670044	Combined with idasanutlin versus cobimetinib

¤ Inclusion of patients > 65 years. *BSC*, best supportive care; *AraC*, cytarabine; *IDAC*, intermediate-dose AraC; *Dec*, decitabine; *FLAG*, fludarabine, cytarabine, G-CSF (granulocyte-colony stimulating factor); *Ida*, idarubicin; *CM*, cytarabine + mitoxantrone; *HAM*, high-dose AraC + mitoxantrone; *LDAC*, low-dose AraC; *GO*, gemtuzumab ozogamicin; *Aza*, azacitidine; *SCT*, stem cell transplant

entinostat), immunotherapeutic, chemotherapeutic and targeted agents (Table 4). Single-agent decitabine showed 21% CR/CRi rate in R/R AML patients, allowing 44% of them to perform a subsequent HSCT [80], although a lower response rate (16%) has been recently reported in real-life patients [33]. Guadecitabine is a "second-generation" HMA designed to protect decitabine from intracellular degradation, and its administration following induction chemotherapy has resulted in 23% CR rate and 1- and 2-year survival of 28% and 19%, respectively [81]. A phase 3 trial with guadecitabine versus treatment of choice for adult R/R AML patients recently achieved its enrolment goal (Table 5).

Bromodomain and extraterminal (BET) inhibitors, which repress transcription of oncogenic *c-MYC* [82], have recently entered clinical phase trials (Table 4). Despite their encouraging in vitro activity, they appear to generate early resistance [83] and combination strategies should be therefore devised. Lysine- specific demethylase 1 (LSD1) inhibitor ORY-1001 demonstrated a potent and selective activity in preclinical studies as a single agent, producing blast cell differentiation in 64% of treated R/R AML patients [84]. Another LSD-1 inhibitor, GSK2879552, has been evaluated in a dose-escalation phase 1 trial with R/R AML patients [85], but this study terminated because of the poor risk/benefit ratio obtained.

Despite its poor activity and inadequate safety in elderly R/R AML patients [86], the histone deacetylase (HDAC) inhibitor panobinostat might be effective mitigating GvHD in high-risk patients, as shown by the low relapse rate observed in preliminary results from a phase 1/2 trial [87]. Preclinical evidence supporting synergy between HDAC inhibitors and HMAs [88] led to vorinostat evaluation combined with decitabine, achieving 35% CR in young R/R AML patients [89]. This combination is being further evaluated along with FLAG chemotherapy, while novel HDAC inhibitor entinostat is being tested combined with azacitidine (Table 4). Disrupter of telomere silencing 1-like (DOT1L) inhibitor pinometostat, in early clinical development for R/R AML patients harbouring *KMTA2A* (*MLL*)-rearranged target genes [1], has shown acceptable safety with transient blast reduction in children, although clinical response was only attained in 12% of adult subjects [90].

Isocitrate dehydrogenase (IDH) mutations occur in roughly 15–20% of AML patients [14], and IDH inhibitors enasidenib and ivosidenib have shown promising activity as single agents with CR/CRi plus PR rates of 40% and 36%, respectively [91]. Both inhibitors have shown to be safe and well tolerated. Ivosidenib produced durable and even molecular remissions [92] while enasidenib induced differentiation and maturation of myeloblasts without affecting normal cells [93]. Enasidenib was approved by FDA in 2017 for R/R AML patients with susceptible IDH2 mutation and ivosidenib received approval in July 2018 for those carrying IDH1 mutation. An ongoing phase 3 trial is evaluating enasidenib versus conventional care regimens in IDH2-mutated elderly R/R AML patients (Table 5).

Mitochondrial inhibitors: Alvocidib (Flavopiridol) is a CDKN2/9 inhibitor producing tumour lysis syndrome and blast clearance as a single agent for R/R AML [94, 95]. The timed-sequential therapy FLAM (alvocidib [96] followed by Ara-C continuous infusion and Mito) was developed after preclinical observations of increased Ara-C-induced apoptosis by alvocidib [97]. FLAM treatment resulted in CR rates of 36% in R/R AML [98], and preliminary results from a phase 2 trial have revealed outstanding CR in 75% refractory patients showing MCL1 dependency (44% of them proceeding to HSCT) [99].

Murine double minute 2 (MDM2) inhibitors, such as idasanutlin and milademetan, could restore p53-mediated apoptosis pathways in leukemic cells [100]. Idasanutlin has shown promising response rates in early phase studies [101] and it is being further explored as salvage therapy in combination with IDAC (Table 5). The BCL-2 antagonist venetoclax displayed moderate activity as single agent [85, 102], although its combination with low-intensity therapy has demonstrated to be a feasible salvage option, particularly in patients with diploid/intermediate cytogenetics, *RUNX1* and/or IDH1/2 mutations [103]. The combination of venetoclax with HMAs achieved 21% CR rate, whereas preliminary data of the association to FLAG-Ida regimen has shown 74% [104]. Based on their synergistically anti-leukemic activity [105], venetoclax and CDKN2/9 inhibitors (dinaciclib and alvocidib) are currently combined in clinical trials (Table 4). Recently, the myeloid cell leukemia-1 (MCL-1) inhibitor AMG176, with promising anti-tumour activity in animal models [106], has entered FIH trials (Table 4). Through release of tumour suppressor proteins from the nucleus, selinexor, a selective inhibitor of exportin 1 (XPO1), is relatively safe as single agent [107] and apparently tolerable in combination with HiDAC/Mito in R/R AML patients [108]. It is being tested in combination with intensive chemotherapy regimens in phase 1/2 trials (Table 4).

Chemotherapeutic agents: Novel chemotherapy approaches rely on the improvement of AML induction therapy backbone, i.e. traditional 7+3 regimen. Combination of Ara-C and vosaroxin, a non-anthracycline quinolone derivative, has resulted in increased and durable remission rates compared with IDAC alone, especially in patients aged more than 60 years old [109, 110], but the randomized phase 3 trial failed in its primary endpoint of OS ($p = 0.06$). The liposomal formulation of Ara-C and daunorubicin (CPX-351) has demonstrated increased efficacy in animal models [111], but only slightly higher CR compared with conventional 7+3 (37% vs. 32%) in R/R AML studies [112].

Key points

- Targeted therapies, such as FLT3 and IDH inhibitors, have shown a striking activity as single agents in FLT3 or IDH-mutated R/R AML patients; thus, they could be valuable and broadly available options in this setting.
- Immunotherapies and mitochondrial inhibitors, alone or in combination, constitute promising strategies under development.

Conclusions

There is a lack of valuable information about the characteristics and outcomes of R/R AML in the real-life population since information derived from phase 1 to 3 clinical trials (or from collaborative group registries in the context of protocols) is generally focused on < 60-year-old patients treated with a selected salvage regimen. Intensive chemotherapy has provided the greatest benefit in R/R AML to date and it is therefore unlikely that current targeted therapies may replace standard cytotoxic drugs in the short term. Nevertheless, some targeted therapies and novel agents targeting alternative mechanisms of action could increase the anti-leukemic efficacy when combined with conventional chemotherapy, while maintaining an appropriate safety profile. Targeted therapies, either as single agents or in combination, could offer a unique treatment opportunity for specific AML patient populations. Targeted agents could play a role in post-transplant setting, and recent studies aimed at reducing the risk of relapse after HSCT emphasize the importance of both maintenance strategies and early interventions, triggered by measurable residual disease evaluation in high-risk patients. The emergence of some new effective therapies may change the diagnostic approach to R/R AML, leading to the inclusion of a systematic screening for some druggable mutations (e.g. IDH and FLT3) and potential biomarkers of response to some of these novel agents in the current practice.

Clinical trial enrolment should be considered first option for all subsets of R/R AML patients using appropriate study designs and therapeutic approaches, according to a previously defined patient profile based upon performance, cytogenetic and molecular testing.

Author contributions The authors met the criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development and approved the final version that reflects the authors' interpretations and conclusions.

Funding information Financial support for medical editorial assistance, copyright permission and publication costs was provided by Daiichi Sankyo, Inc., a member of the Daiichi Sankyo Group.

Compliance with ethical standards

Conflict of interest PM has received research funding from Teva, Celgene, Janssen, Novartis, Daiichi Sankyo, Pfizer and Karyopharm; has received honoraria from Teva, Celgene, Janssen, Novartis, Daiichi Sankyo, Pfizer and Incyte; and has served in a consulting or advisory role for Teva, Celgene, Janssen, Novartis, Daiichi Sankyo, Pfizer, Karyopharm, Incyte and Abbvie. JS has received research funding from Novartis and Amgen; has received honoraria from Novartis, Abbvie, Pfizer, Daiichi Sankyo and Astellas; and has served in a consulting or advisory role for Novartis, Abbvie, Pfizer, Daiichi Sankyo, Gilead, Astellas, Celgene and Roche. JS is a member of DMC from Gamida Cell. JI has received honoraria from Novartis and Daiichi Sankyo, and has served in a consulting or advisory role for Daiichi Sankyo. JE has received research funding from Celgene and Novartis; has received honoraria from Celgene, Janssen, Novartis, Daiichi Sankyo and Astellas; and has served in a consulting or advisory role for Celgene, Janssen, Novartis, Pfizer, Daiichi Sankyo, Jazz Pharmaceuticals, Abbvie, Roche, Teva and Incyte. JEG has received a speaker honorarium (speaker's fees) from Abbvie, Amgen, Janssen, Pfizer and Daiichi Sankyo; and has served in a consulting or advisory role for Abbvie, Pfizer, Roche and Daiichi Sankyo.

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

References

1. Lim SH, Dubielecka PM, Raghunathan VM (2017) Molecular targeting in acute myeloid leukemia. J Transl Med 15(183):1–13. https://doi.org/10.1186/s12967-017-1281-x
2. Megías-Vericat JE, Martínez-Cuadrón D, Sanz MA, Montesinos P (2018) Salvage regimens using conventional chemotherapy agents for relapsed/refractory adult AML patients: a systematic literature review. Ann Hematol 97(7):1115–1153. https://doi.org/10.1007/s00277-018-3304-y
3. 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
4. Ravandi F (2011) Primary refractory acute myeloid leukaemia - in search of better definitions and therapies. Br J Haematol 155(4):413–419. https://doi.org/10.1111/j.1365-2141.2011.08869.x
5. Ferguson P, Hills RK, Grech A, Betteridge S, Kjeldsen L, Dennis M, Vyas P, Goldstone AH, Milligan D, Clark RE, Russell NH, Craddock C, UK NCRI AML Working Group (2016) An operational definition of primary refractory acute myeloid leukemia allowing early identification of patients who may benefit from allogeneic stem cell transplantation. Haematologica 101(11):1351–1358. https://doi.org/10.3324/haematol.2016.148825
6. Thol F, Schlenk RF, Heuser M, Ganser A (2015) How I treat refractory and early relapsed acute myeloid leukemia. Blood 126(3):319–327. https://doi.org/10.1182/blood-2014-10-551911
7. Wheatley K, Burnett AK, Goldstone AH, Gray RG, Hann IM, Harrison CJ, Rees JK, Stevens RF, Walker H (1999) A simple,

robust, validated and highly predictive index for the determination of risk-directed therapy in acute myeloid leukaemia derived from the MRC AML 10 trial. United Kingdom Medical Research Council's Adult and Childhood Leukaemia Working Parties. Br J Haematol 107(1):69–79

8. Cheson BD, Bennett JM, Kopecky KJ et al (2003) Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 21(24):4642–4649. https://doi.org/10.1200/jco.2003.04.036
9. Döhner H, Estey EH, Amadori S, Appelbaum FR, Büchner T, Burnett AK, Dombret H, Fenaux P, Grimwade D, Larson RA, Lo-Coco F, Naoe T, Niederwieser D, Ossenkoppele GJ, Sanz MA, Sierra J, Tallman MS, Löwenberg B, Bloomfield CD, European LeukemiaNet (2010) Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood 115(3):453–474. https://doi.org/10.1182/blood-2009-07-235358
10. Schlenk RF, Benner A, Hartmann F, del Valle F, Weber C, Pralle H, Fischer JT, Gunzer U, Pezzutto A, Weber W, Grimminger W, Preiss J, Hensel M, Fröhling S, Döhner K, Haas R, Döhner H, AML Study Group Ulm (AMLSG ULM) (2003) Risk-adapted postremission therapy in acute myeloid leukemia: results of the German multicenter AML HD93 treatment trial. Leukemia 17(8):1521–1528. https://doi.org/10.1038/sj.leu.2403009
11. National Comprehensive Cancer Network (NCCN) Guidelines: acute myeloid leukemia. 2016. (2016).
12. Ramos NR, Mo CC, Karp JE, Hourigan CS (2015) Current approaches in the treatment of relapsed and refractory acute myeloid leukemia. J Clin Med 4(4):665–695. https://doi.org/10.3390/jcm4040665
13. Schlenk RF, Frech P, Weber D, Brossart P, Horst HA, Kraemer D, Held G, Ringhoffer M, Burchardt A, Kobbe G, Götze K, Nachbaur D, Fischer T, Lübbert M, Salih HR, Salwender H, Wulf G, Koller E, Wattad M, Fiedler W, Kremers S, Kirchen H, Hertenstein B, Paschka P, Gaidzik VI, Teleanu V, Heuser M, Thol F, Döhner K, Krauter J, Ganser A, Döhner H, the German-Austrian AMLSG (2017) Impact of pretreatment characteristics and salvage strategy on outcome in patients with relapsed acute myeloid leukemia. Leukemia 31(5):1217–1220. https://doi.org/10.1038/leu.2017.22
14. Bose P, Vachhani P, Cortes JE (2017) Treatment of relapsed/refractory acute myeloid leukemia. Curr Treat Options in Oncol 18(3):17–30. https://doi.org/10.1007/s11864-017-0456-2
15. Estey E (2016) Why are there so few randomized trials for patients with primary refractory acute myeloid leukemia? Best Pract Res Clin Haematol 29(4):324–328. https://doi.org/10.1016/j.beha.2016.10.003
16. Bejanyan N, Weisdorf DJ, Logan BR, Wang HL, Devine SM, de Lima M, Bunjes DW, Zhang MJ (2015) Survival of patients with acute myeloid leukemia relapsing after allogeneic hematopoietic cell transplantation: a center for international blood and marrow transplant research study. Biol Blood Marrow Transplant 21(3):454–459. https://doi.org/10.1016/j.bbmt.2014.11.007
17. Vosberg S, Hartmann L, Metzeler KH et al (2018) Relapse of acute myeloid leukemia after allogeneic stem cell transplantation is associated with gain of WT1 alterations and high mutation load. Haematologica. https://doi.org/10.3324/haematol.2018.193102
18. Craddock C, Versluis J, Labopin M, Socie G, Huynh A, Deconinck E, Volin L, Milpied N, Bourhis JH, Rambaldi A, Chevallier P, Blaise D, Manz M, Vellenga E, Vekemans MC, Maertens J, Passweg J, Vyas P, Schmid C, Löwenberg B, Ossenkoppele G, Mohty M, Cornelissen JJ, Nagler A, Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation and HOVON-SAKK (2018) Distinct factors determine the kinetics of disease relapse in adults transplanted for acute myeloid leukaemia. J Intern Med 283(4):371–379. https://doi.org/10.1111/joim.12720
19. Breems DA, Van Putten WL, Huijgens PC et al (2005) Prognostic index for adult patients with acute myeloid leukemia in first relapse. J Clin Oncol 23(9):1969–1978. https://doi.org/10.1200/jco.2005.06.027
20. Estey E, Kornblau S, Pierce S, Kantarjian H, Beran M, Keating M (1996) A stratification system for evaluating and selecting therapies in patients with relapsed or primary refractory acute myelogenous leukemia. Blood 88(2):756
21. Verma D, Kantarjian H, Faderl S, O'Brien S, Pierce S, Vu K, Freireich E, Keating M, Cortes J, Ravandi F (2010) Late relapses in acute myeloid leukemia: analysis of characteristics and outcome. Leuk Lymphoma 51(5):778–782. https://doi.org/10.3109/10428191003661852
22. Ravandi F, Kantarjian H, Faderl S, Garcia-Manero G, O'Brien S, Koller C, Pierce S, Brandt M, Kennedy D, Cortes J, Beran M (2010) Outcome of patients with FLT3-mutated acute myeloid leukemia in first relapse. Leuk Res 34(6):752–756. https://doi.org/10.1016/j.leukres.2009.10.001
23. Wattad M, Weber D, Döhner K, Krauter J, Gaidzik VI, Paschka P, Heuser M, Thol F, Kindler T, Lübbert M, Salih HR, Kündgen A, Horst HA, Brossart P, Götze K, Nachbaur D, Köhne CH, Ringhoffer M, Wulf G, Held G, Salwender H, Benner A, Ganser A, Döhner H, Schlenk RF (2017) Impact of salvage regimens on response and overall survival in acute myeloid leukemia with induction failure. Leukemia 31(6):1306–1313. https://doi.org/10.1038/leu.2017.23
24. Qin YZ, Zhu HH, Jiang Q, Jiang H, Zhang LP, Xu LP, Wang Y, Liu YR, Lai YY, Shi HX, Jiang B, Huang XJ (2014) Prevalence and prognostic significance of c-KIT mutations in core binding factor acute myeloid leukemia: a comprehensive large-scale study from a single Chinese center. Leuk Res 38(12):1435–1440. https://doi.org/10.1016/j.leukres.2014.09.017
25. Hospital MA, Prebet T, Bertoli S et al (2014) Core-binding factor acute myeloid leukemia in first relapse: a retrospective study from the French AML Intergroup. Blood 124(8):1312–1319. https://doi.org/10.1182/blood-2014-01-549212
26. Bergua JM, Montesinos P, Martínez-Cuadrón D et al (2016) A prognostic model for survival after salvage treatment with FLAG-Ida +/- gemtuzumab-ozogamicine in adult patients with refractory/relapsed acute myeloid leukaemia. Br J Haematol 174(5):700–710. https://doi.org/10.1111/bjh.14107
27. Chevallier P, Labopin M, Turlure P, Prebet T, Pigneux A, Hunault M, Filanovsky K, Cornillet-Lefebvre P, Luquet I, Lode L, Richebourg S, Blanchet O, Gachard N, Vey N, Ifrah N, Milpied N, Harousseau JL, Bene MC, Mohty M, Delaunay J (2011) A new Leukemia Prognostic Scoring System for refractory/relapsed adult acute myelogeneous leukaemia patients: a GOELAMS study. Leukemia 25(6):939–944. https://doi.org/10.1038/leu.2011.25
28. Greif PA, Hartmann L, Vosberg S, Stief SM, Mattes R, Hellmann I, Metzeler KH, Herold T, Bamopoulos SA, Kerbs P, Jurinovic V, Schumacher D, Pastore F, Bräundl K, Zellmeier E, Ksienzyk B, Konstandin NP, Schneider S, Graf A, Krebs S, Blum H, Neumann M, Baldus CD, Bohlander SK, Wolf S, Görlich D, Berdel WE, Wörmann BJ, Hiddemann W, Spiekermann K (2018) Evolution of cytogenetically normal acute myeloid leukemia during therapy and relapse: an exome sequencing study of 50 patients. Clin Cancer Res 24(7):1716–1726. https://doi.org/10.1158/1078-0432.ccr-17-2344
29. Uy GL, Duncavage EJ, Chang GS, Jacoby MA, Miller CA, Shao J, Heath S, Elliott K, Reineck T, Fulton RS, Fronick CC, O'Laughlin M, Ganel L, Abboud CN, Cashen AF, DiPersio J, Wilson RK, Link DC, Welch JS, Ley TJ, Graubert TA,

Westervelt P, Walter MJ (2017) Dynamic changes in the clonal structure of MDS and AML in response to epigenetic therapy. Leukemia 31(4):872–881
30. Kronke J, Bullinger L, Teleanu V et al (2013) Clonal evolution in relapsed NPM1-mutated acute myeloid leukemia. Blood 122(1): 100–108. https://doi.org/10.1182/blood-2013-01-479188
31. O'Donnell MR, Tallman MS, Abboud CN et al (2017) Acute myeloid leukemia, version 3.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw 15(7):926–957. https://doi.org/10.6004/jnccn.2017.0116
32. Araki D, Othus M, Walter RB, Becker PS, Sandhu V, Estey EH (2016) Does outcome of second salvage therapy in relapsed or refractory acute myeloid leukemia depend on intensity of either first or second salvage therapy? Leuk Lymphoma 57(5):1205–1207. https://doi.org/10.3109/10428194.2015.1079316
33. Stahl M, DeVeaux M, Montesinos P, Itzykson R, Ritchie EK, Sekeres MA, Barnard JD, Podoltsev NA, Brunner AM, Komrokji RS, Bhatt VR, al-Kali A, Cluzeau T, Santini V, Fathi AT, Roboz GJ, Fenaux P, Litzow MR, Perreault S, Kim TK, Prebet T, Vey N, Verma V, Germing U, Bergua JM, Serrano J, Gore SD, Zeidan AM (2018) Hypomethylating agents in relapsed and refractory AML: outcomes and their predictors in a large international patient cohort. Blood Advances 2(8):923–932. https://doi.org/10.1182/bloodadvances.2018016121
34. Abutalib S, Tallman MS (2008) Relapsed and refractory acute myeloid leukemia. In: Acute leukemias. Springer, Berlin Heidelberg, pp 57–76. https://doi.org/10.1007/978-3-540-72304-2_4
35. Schmid C, Schleuning M, Ledderose G, Tischer J, Kolb HJ (2005) Sequential regimen of chemotherapy, reduced-intensity conditioning for allogeneic stem-cell transplantation, and prophylactic donor lymphocyte transfusion in high-risk acute myeloid leukemia and myelodysplastic syndrome. J Clin Oncol 23(24):5675–5687. https://doi.org/10.1200/jco.2005.07.061
36. Bastos-Oreiro M, Pérez-Corral A, Martínez-Laperche C et al (2014) Prognostic impact of minimal residual disease analysis by flow cytometry in patients with acute myeloid leukemia before and after allogeneic hemopoietic stem cell transplantation. Eur J Haematol 93(3):239–246. https://doi.org/10.1111/ejh.12336
37. Araki D, Wood BL, Othus M, Radich JP, Halpern AB, Zhou Y, Mielcarek M, Estey EH, Appelbaum FR, Walter RB (2016) Allogeneic hematopoietic cell transplantation for acute myeloid leukemia: time to move toward a minimal residual disease-based definition of complete remission? J Clin Oncol 34(4):329–336. https://doi.org/10.1200/jco.2015.63.3826
38. Guolo F, Minetto P, Clavio M, Miglino M, Galaverna F, Raiola AM, di Grazia C, Colombo N, Pozzi S, Ibatici A, Bagnasco S, Guardo D, Kunkl A, Ballerini F, Ghiggi C, Lemoli RM, Gobbi M, Bacigalupo A (2017) Combining flow cytometry and WT1 assessment improves the prognostic value of pre-transplant minimal residual disease in acute myeloid leukemia. Haematologica 102(9):e348–e351. https://doi.org/10.3324/haematol.2017.167254
39. Ravandi F, Walter RB, Freeman SD (2018) Evaluating measurable residual disease in acute myeloid leukemia. Blood Adv 2(11): 1356–1366. https://doi.org/10.1182/bloodadvances.2018016378
40. Paietta E (2018) Consensus on MRD in AML? Blood 131(12): 1265–1266. https://doi.org/10.1182/blood-2018-01-828145
41. Kharfan-Dabaja MA, Labopin M, Polge E, Nishihori T, Bazarbachi A, Finke J, Stadler M, Ehninger G, Lioure B, Schaap N, Afanasyev B, Yeshurun M, Isaksson C, Maertens J, Chalandon Y, Schmid C, Nagler A, Mohty M (2018) Association of second allogeneic hematopoietic cell transplant *vs*. donor lymphocyte infusion with overall survival in patients with acute myeloid leukemia relapse. JAMA Oncology 4(9):1245–1253. https://doi.org/10.1001/jamaoncol.2018.2091
42. Li GX, Wang L, Yaghmour B, Ramsingh G, Yaghmour G (2018) The role of FLT3 inhibitors as maintenance therapy following hematopoietic stem cell transplant. Leuk Res Rep 10:26–36. https://doi.org/10.1016/j.lrr.2018.06.003
43. Yang J, Cai Y, Jiang J, Wan L, Bai H, Zhu J, Li S, Wang C, Song X (2018) Early tapering of immunosuppressive agents after HLA-matched donor transplantation can improve the survival of patients with advanced acute myeloid leukemia. Ann Hematol 97(3):497–507. https://doi.org/10.1007/s00277-017-3204-6
44. Christopher MJ, Petti AA, Rettig MP, Miller CA, Chendamarai E, Duncavage EJ, Klco JM, Helton NM, O'Laughlin M, Fronick CC, Fulton RS, Wilson RK, Wartman LD, Welch JS, Heath SE, Baty JD, Payton JE, Graubert TA, Link DC, Walter MJ, Westervelt P, Ley TJ, DiPersio J (2018) Immune escape of relapsed AML cells after allogeneic transplantation. N Engl J Med 379(24):2330–2341. https://doi.org/10.1056/NEJMoa1808777
45. Larrosa-García M, Baer MR (2017) FLT3 inhibitors in acute myeloid leukemia: current status and future directions. Mol Cancer Ther 16(6):991–1001. https://doi.org/10.1158/1535-7163.mct-16-0876
46. El Fakih R, Rasheed W, Hawsawi Y, Alsermani M, Hassanein M (2018) Targeting FLT3 mutations in acute myeloid leukemia. Cells 7(1). https://doi.org/10.3390/cells7010004
47. Zhang W, Konopleva M, Shi YX, McQueen T, Harris D, Ling X, Estrov Z, Quintás-Cardama A, Small D, Cortes J, Andreeff M (2008) Mutant FLT3: a direct target of sorafenib in acute myelogenous leukemia. J Natl Cancer Inst 100(3):184–198. https://doi.org/10.1093/jnci/djm328
48. Rautenberg C, Nachtkamp K, Dienst A, Schmidt PV, Heyn C, Kondakci M, Germing U, Haas R, Kobbe G, Schroeder T (2017) Sorafenib and azacitidine as salvage therapy for relapse of FLT3-ITD mutated AML after allo-SCT. Eur J Haematol 98(4):348–354. https://doi.org/10.1111/ejh.12832
49. Fischer T, Stone RM, Deangelo DJ, Galinsky I, Estey E, Lanza C, Fox E, Ehninger G, Feldman EJ, Schiller GJ, Klimek VM, Nimer SD, Gilliland DG, Dutreix C, Huntsman-Labed A, Virkus J, Giles FJ (2010) Phase IIB trial of oral Midostaurin (PKC412), the FMS-like tyrosine kinase 3 receptor (FLT3) and multi-targeted kinase inhibitor, in patients with acute myeloid leukemia and high-risk myelodysplastic syndrome with either wild-type or mutated FLT3. J Clin Oncol 28(28):4339–4345. https://doi.org/10.1200/jco.2010.28.9678
50. Strati P, Kantarjian H, Ravandi F, Nazha A, Borthakur G, Daver N, Kadia T, Estrov Z, Garcia-Manero G, Konopleva M, Rajkhowa T, Durand M, Andreeff M, Levis M, Cortes J (2015) Phase I/II trial of the combination of midostaurin (PKC412) and 5-azacytidine for patients with acute myeloid leukemia and myelodysplastic syndrome. Am J Hematol 90(4):276–281. https://doi.org/10.1002/ajh.23924
51. Cortes JE, Perl AE, Dombret H et al (2012) Final results of a phase 2 open-label, monotherapy efficacy and safety study of quizartinib (AC220) in patients ≥60 years of age with FLT3 ITD positive or negative relapsed/refractory acute myeloid leukemia. Blood 120(21):48
52. Levis M (2013) Quizartinib in acute myeloid leukemia. Clin Adv Hematol Oncol 11(9):586–588
53. Borthakur G, Kantarjian HM, O'Brien S et al (2014) The combination of quizartinib with azacitidine or low dose cytarabine is highly active in patients (Pts) with FLT3-ITD mutated myeloid leukemias: interim report of a phase I/II trial. Blood 124(21): 388–388
54. Sandmaier BM, Khaled SK, Oran B et al (2014) Results of a phase 1 study of quizartinib (AC220) as maintenance therapy in subjects with acute myeloid leukemia in remission following allogeneic hematopoietic cell transplantation. Blood 124(21):428–428

55. Perl AE, Altman JK, Cortes JE et al (2016) Final results of the chrysalis trial: a first-in-human phase 1/2 dose-escalation, dose-expansion study of gilteritinib (ASP2215) in patients with relapsed/refractory acute myeloid leukemia (R/R AML). Blood 128(22):1069–1069
56. Altman JK, Perl AE, Cortes JE et al (2015) Antileukemic activity and tolerability of ASP2215 80 mg and greater in FLT3 mutation-positive subjects with relapsed or refractory acute myeloid leukemia: results from a phase 1/2, open-label, dose-escalation/dose-response study. Blood 126(23):321–321
57. Cortes JE, Khaled S, Martinelli G et al (2019) Quizartinib *versus* salvage chemotherapy in relapsed or refractory FLT3-ITD acute myeloid leukaemia (QuANTUM-R): a multicentre, randomised, controlled, open-label, phase 3 trial. Lancet Oncol. https://doi.org/10.1016/s1470-2045(19)30150-0
58. Perl AE, Martinelli G, Cortes JE *et al.* CT184 - Gilteritinib significantly prolongs overall survival in patients with FLT3-mutated (FLT3mut+) relapsed/refractory (R/R) acute myeloid leukemia (AML): results from the phase III ADMIRAL trial In: Proceedings of the 110th Annual Meeting of the American Association for Cancer Research, Atlanta, GA, 2019.
59. Randhawa JK, Kantarjian HM, Borthakur G et al (2014) Results of a phase II study of crenolanib in relapsed/refractory acute myeloid leukemia patients (Pts) with activating FLT3 mutations. Blood 124(21):389–389
60. Ohanian M, Kantarjian HM, Borthakur G et al (2016) Efficacy of a type I FLT3 inhibitor, crenolanib, with idarubicin and high-dose ara-C in multiply relapsed/refractory FLT3+ AML. Blood 128(22):2744–2744
61. Shah NP, Talpaz M, Deininger MW et al (2013) Ponatinib in patients with refractory acute myeloid leukaemia: findings from a phase 1 study. Br J Haematol 162(4):548–552. https://doi.org/10.1111/bjh.12382
62. Smith CC, Lasater EA, Zhu X, Lin KC, Stewart WK, Damon LE, Salerno S, Shah NP (2013) Activity of ponatinib against clinically-relevant AC220-resistant kinase domain mutants of FLT3-ITD. Blood 121(16):3165–3171. https://doi.org/10.1182/blood-2012-07-442871
63. Jen EY, Ko CW, Lee JE, del Valle P, Aydanian A, Jewell C, Norsworthy KJ, Przepiorka D, Nie L, Liu J, Sheth CM, Shapiro M, Farrell AT, Pazdur R (2018) FDA approval: gemtuzumab ozogamicin for the treatment of adults with newly diagnosed CD33-positive acute myeloid leukemia. Clin Cancer Res 24(14):3242–3246. https://doi.org/10.1158/1078-0432.ccr-17-3179
64. Boddu P, Kantarjian H, Ravandi F, Daver N (2017) Emerging molecular and immune therapies in acute myeloid leukemia. Ame J Hematol/Oncol 13(4):12
65. Stein EM, Walter RB, Erba HP et al (2017) A phase 1 trial of vadastuximab talirine as monotherapy in patients with CD33 positive acute myeloid leukemia (AML). Blood. https://doi.org/10.1182/blood-2017-06-789800
66. Kovtun Y, Noordhuis P, Whiteman KR, Watkins K, Jones GE, Harvey L, Lai KC, Portwood S, Adams S, Sloss CM, Schuurhuis GJ, Ossenkoppele G, Wang ES, Pinkas J (2018) IMGN779, a novel CD33-targeting antibody-drug conjugate with DNA-alkylating activity, exhibits potent antitumor activity in models of AML. Mol Cancer Ther 17(6):1271–1279. https://doi.org/10.1158/1535-7163.mct-17-1077
67. Friedrich M, Henn A, Raum T, Bajtus M, Matthes K, Hendrich L, Wahl J, Hoffmann P, Kischel R, Kvesic M, Slootstra JW, Baeuerle PA, Kufer P, Rattel B (2014) Preclinical characterization of AMG 330, a CD3/CD33-bispecific T-cell-engaging antibody with potential for treatment of acute myelogenous leukemia. Mol Cancer Ther 13(6):1549–1557. https://doi.org/10.1158/1535-7163.mct-13-0956
68. Gbolahan OB, Zeidan AM, Stahl M et al (2017) Immunotherapeutic concepts to target acute myeloid leukemia: focusing on the role of monoclonal antibodies, hypomethylating agents and the leukemic microenvironment. Int J Mol Sci 18(8)
69. Testa U, Pelosi E, Frankel A (2014) CD 123 is a membrane biomarker and a therapeutic target in hematologic malignancies. Biomark Res 2(1):4. https://doi.org/10.1186/2050-7771-2-4
70. Adams S, Wilhelm A, Harvey L et al (2016) IMGN632: a CD123-targeting antibody-drug conjugate (ADC) with a novel DNA-alkylating payload, is highly active and prolongs survival in acute myeloid leukemia (AML) Xenograft Models. Blood 128(22):2832–2832
71. Lichtenegger FS, Krupka C, Haubner S, Köhnke T, Subklewe M (2017) Recent developments in immunotherapy of acute myeloid leukemia. J Hematol Oncol 10:142
72. Li F, Sutherland MK, Yu C, Walter RB, Westendorf L, Valliere-Douglass J, Pan L, Cronkite A, Sussman D, Klussman K, Ulrich M, Anderson ME, Stone IJ, Zeng W, Jonas M, Lewis TS, Goswami M, Wang SA, Senter PD, Law CL, Feldman EJ, Benjamin DR (2018) Characterization of SGN-CD123A, a potent CD123-directed antibody-drug conjugate for acute myeloid leukemia. Mol Cancer Ther 17(2):554–564. https://doi.org/10.1158/1535-7163.mct-17-0742
73. Godwin JE (2017) Preliminary results of a phase 1 study of flotetuzumab, a CD123 x CD3 bispecific DART protein, in patients with relapsed/refractory acute myeloid leukemia and myelodysplastic syndrome. Paper presented at the 59th Annual Meeting of the American Society of Hematology (ASH), Atlanta
74. Isidori A, Loscocco F, Ciciarello M, Corradi G, Lecciso M, Ocadlikova D, Parisi S, Salvestrini V, Amadori S, Visani G, Curti A (2018) Immunosenescence and immunotherapy in elderly acute myeloid leukemia patients: time for a biology-driven approach. Cancers (Basel) 10(7). https://doi.org/10.3390/cancers10070211
75. Miller JS, Soignier Y, Panoskaltsis-Mortari A, McNearney S, Yun GH, Fautsch SK, McKenna D, le C, Defor TE, Burns LJ, Orchard PJ, Blazar BR, Wagner JE, Slungaard A, Weisdorf DJ, Okazaki IJ, McGlave P (2005) Successful adoptive transfer and in vivo expansion of human haploidentical NK cells in patients with cancer. Blood 105(8):3051–3057. https://doi.org/10.1182/blood-2004-07-2974
76. Orti G, Barba P, Fox L, Salamero O, Bosch F, Valcarcel D (2017) Donor lymphocyte infusions in AML and MDS: enhancing the graft-versus-leukemia effect. Exp Hematol 48:1–11. https://doi.org/10.1016/j.exphem.2016.12.004
77. Budde L, Song J, Kim Y, *et al.* Remissions of acute myeloid leukemia and blastic plasmacytoid dendritic cell neoplasm following treatment with CD123-specific CAR T cells: a first-in-human clinical trial. Abstract #811. In: ASH Annual Meeting, Atlanta, GA, December 11 2017.
78. Jiang YP, Liu BY, Zheng Q, Panuganti S, Chen R, Zhu J, Mishra M, Huang J, Dao-Pick T, Roy S, Zhao X, Lin J, Banik G, Hsi ED, Mandalam R, Junutula JR (2018) CLT030, a leukemic stem cell–targeting CLL1 antibody-drug conjugate for treatment of acute myeloid leukemia. Blood Adv 2(14):1738–1749. https://doi.org/10.1182/bloodadvances.2018020107
79. Ram R, Gatt M, Merkel D, Helman I, Inbar T, Nagler A, Avivi I, Ofran Y (2017) Second line azacitidine for elderly or infirmed patients with acute myeloid leukemia (AML) not eligible for allogeneic hematopoietic cell transplantation-a retrospective national multicenter study. Ann Hematol 96(4):575–579. https://doi.org/10.1007/s00277-016-2914-5
80. Khan N, Hantel A, Knoebel RW et al (2017) Efficacy of single-agent decitabine in relapsed and refractory acute myeloid leukemia. Leuk Lymphoma 58(9):1–7. https://doi.org/10.1080/10428194.2017.1289524

81. Daver N, Kantarjian HM, Roboz GJ et al (2016) Long term survival and clinical complete responses of various prognostic subgroups in 103 relapsed/refractory acute myeloid leukemia (r/r AML) patients treated with guadecitabine (SGI-110) in phase 2 studies. Blood 128(22):904–904
82. Coude MM, Braun T, Berrou J et al (2015) BET inhibitor OTX015 targets BRD2 and BRD4 and decreases c-MYC in acute leukemia cells. Oncotarget 6(19):17698–17712. https://doi.org/10.18632/oncotarget.4131
83. Braun T, Gardin C (2017) Investigational BET bromodomain protein inhibitors in early stage clinical trials for acute myelogenous leukemia (AML). Expert Opin Investig Drugs 26(7):803–811. https://doi.org/10.1080/13543784.2017.1335711
84. Somervaille T, Salamero O, Montesinos P et al (2016) Safety, phamacokinetics (PK), pharmacodynamics (PD) and preliminary activity in acute leukemia of Ory-1001, a first-in-class inhibitor of lysine-specific histone demethylase 1A (LSD1/KDM1A): initial results from a first-in-human phase 1 study. Blood 128(22):4060–4060
85. Shafer D, Grant S (2016) Update on rational targeted therapy in AML. Blood Rev 30(4):275–283. https://doi.org/10.1016/j.blre.2016.02.001
86. Schlenk RF, Krauter J, Raffoux E, Kreuzer KA, Schaich M, Noens L, Pabst T, Vusirikala M, Bouscary D, Spencer A, Candoni A, Gil JS, Berkowitz N, Weber HJ, Ottmann O (2018) Panobinostat monotherapy and combination therapy in patients with acute myeloid leukemia: results from two clinical trials. Haematologica 103(1):e25–e28
87. Bug G, Burchert A, Wagner EM, Kröger N, Berg T, Güller S, Metzelder SK, Wolf A, Hünecke S, Bader P, Schetelig J, Serve H, Ottmann OG (2017) Phase I/II study of the deacetylase inhibitor panobinostat after allogeneic stem cell transplantation in patients with high-risk MDS or AML (PANOBEST trial). Leukemia 31:2523–2525. https://doi.org/10.1038/leu.2017.242
88. Stahl M, Zeidan AM (2017) Hypomethylating agents in combination with histone deacetylase inhibitors in higher risk myelodysplastic syndromes: is there a light at the end of the tunnel? Cancer 123(6):911–914. https://doi.org/10.1002/cncr.30532
89. Mims AS, Klisovic RB, Garzon R et al (2016) A novel regimen for acute myeloid leukemia with MLL partial tandem duplication: results of a phase 1 study NCI 8485. Blood 128(22):900–900
90. Stein EM, Garcia-Manero G, Rizzieri DA et al (2015) A phase 1 study of the DOT1L inhibitor, pinometostat (EPZ-5676), in adults with relapsed or refractory leukemia: safety, clinical activity, exposure and target inhibition. Blood 126(23):2547–2547
91. Schlenk RF, Muller-Tidow C, Benner A, Kieser M (2017) Relapsed/refractory acute myeloid leukemia: any progress? Curr Opin Oncol 29(6):467–473. https://doi.org/10.1097/cco.0000000000000404
92. DiNardo CD, Stein EM, de Botton S, Roboz GJ, Altman JK, Mims AS, Swords R, Collins RH, Mannis GN, Pollyea DA, Donnellan W, Fathi AT, Pigneux A, Erba HP, Prince GT, Stein AS, Uy GL, Foran JM, Traer E, Stuart RK, Arellano ML, Slack JL, Sekeres MA, Willekens C, Choe S, Wang H, Zhang V, Yen KE, Kapsalis SM, Yang H, Dai D, Fan B, Goldwasser M, Liu H, Agresta S, Wu B, Attar EC, Tallman MS, Stone RM, Kantarjian HM (2018) Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. N Engl J Med 378(25):2386–2398. https://doi.org/10.1056/NEJMoa1716984
93. Stein EM, DiNardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, Stone RM, DeAngelo D, Levine RL, Flinn IW, Kantarjian HM, Collins R, Patel MR, Frankel AE, Stein A, Sekeres MA, Swords RT, Medeiros BC, Willekens C, Vyas P, Tosolini A, Xu Q, Knight RD, Yen KE, Agresta S, de Botton S, Tallman MS (2017) Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. Blood 130(6):722–731. https://doi.org/10.1182/blood-2017-04-779405
94. Karp JE, Smith BD, Levis MJ, Gore SD, Greer J, Hattenburg C, Briel J, Jones RJ, Wright JJ, Colevas AD (2007) Sequential flavopiridol, cytosine arabinoside, and mitoxantrone: a phase II trial in adults with poor-risk acute myelogenous leukemia. Clin Cancer Res 13(15 Pt 1):4467–4473. https://doi.org/10.1158/1078-0432.ccr-07-0381
95. Fathi AT, Karp JE (2009) New agents in acute myeloid leukemia: beyond cytarabine and anthracyclines. Curr Oncol Rep 11(5):346–352
96. LaCerte C, Ivaturi V, Gobburu J, Greer JM, Doyle LA, Wright JJ, Karp JE, Rudek MA (2017) Exposure-response analysis of alvocidib (flavopiridol) treatment by bolus or hybrid administration in newly diagnosed or relapsed/refractory acute leukemia patients. Clin Cancer Res 23(14):3592–3600. https://doi.org/10.1158/1078-0432.ccr-16-2629
97. Karp JE, Ross DD, Yang W, Tidwell ML, Wei Y, Greer J, Mann DL, Nakanishi T, Wright JJ, Colevas AD (2003) Timed sequential therapy of acute leukemia with flavopiridol: in vitro model for a phase I clinical trial. Clin Cancer Res 9(1):307–315
98. Zeidner JF, Karp JE (2015) Clinical activity of alvocidib (flavopiridol) in acute myeloid leukemia. Leuk Res 39(12):1312–1318. https://doi.org/10.1016/j.leukres.2015.10.010
99. Zeidner JF, Vigil CE, Lin T *et al.* Phase II study incorporating a novel BH3-profiling biomarker approach of alvocidib followed by cytarabine and mitoxantrone in relapsed/refractory acute myeloid leukemia (AML). Poster PF243. In: 23rd Annual Congress of the European Hematology Association, Stockholm, Sweden, June 15 2018.
100. Kojima K, Konopleva M, Samudio IJ, Shikami M, Cabreira-Hansen M, McQueen T, Ruvolo V, Tsao T, Zeng Z, Vassilev LT, Andreeff M (2005) MDM2 antagonists induce p53-dependent apoptosis in AML: implications for leukemia therapy. Blood 106(9):3150–3159
101. Reis B, Jukofsky L, Chen G, Martinelli G, Zhong H, So WV, Dickinson MJ, Drummond M, Assouline S, Hashemyan M, Theron M, Blotner S, Lee JH, Kasner M, Yoon SS, Rueger R, Seiter K, Middleton SA, Kelly KR, Vey N, Yee K, Nichols G, Chen LC, Pierceall WE (2016) Acute myeloid leukemia patients' clinical response to idasanutlin (RG7388) is associated with pretreatment MDM2 protein expression in leukemic blasts. Haematologica 101(5):e185–e188
102. Konopleva M, Pollyea DA, Potluri J, Chyla B, Hogdal L, Busman T, McKeegan E, Salem AH, Zhu M, Ricker JL, Blum W, DiNardo C, Kadia T, Dunbar M, Kirby R, Falotico N, Leverson J, Humerickhouse R, Mabry M, Stone R, Kantarjian H, Letai A (2016) Efficacy and biological correlates of response in a phase II study of venetoclax monotherapy in patients with acute myelogenous leukemia. Cancer Discov 6(10):1106–1117. https://doi.org/10.1158/2159-8290.cd-16-0313
103. DiNardo CD, Rausch CR, Benton C, Kadia T, Jain N, Pemmaraju N, Daver N, Covert W, Marx KR, Mace M, Jabbour E, Cortes J, Garcia-Manero G, Ravandi F, Bhalla KN, Kantarjian H, Konopleva M (2018) Clinical experience with the BCL2-inhibitor venetoclax in combination therapy for relapsed and refractory acute myeloid leukemia and related myeloid malignancies. Am J Hematol 93(3):401–407. https://doi.org/10.1002/ajh.25000
104. DiNardo C, Albitar M, Kadia T et al (2018) Venetoclax in combination with FLAG-IDA chemotherapy (FLAG-V-I) for fit, relapsed/refractory AML patients: interim results of a phase 1b/2 dose escalation and expansion study paper presented at the American Society of Hematology (ASH) Annual Meeting. San Diego, California

105. Bogenberger J, Whatcott C, Hansen N et al (2017) Combined venetoclax and alvocidib in acute myeloid leukemia. Oncotarget 8(63):107206–107222. https://doi.org/10.18632/oncotarget.22284
106. Caenepeel SR, Belmontes B, Sun J et al (2017) Abstract 2027: preclinical evaluation of AMG 176, a novel, potent and selective Mcl-1 inhibitor with robust anti-tumor activity in Mcl-1 dependent cancer models. Cancer Res 77(13 Supplement):2027–2027. https://doi.org/10.1158/1538-7445.am2017-2027
107. Garzón R, Savona M, Baz R et al (2017) A phase 1 clinical trial of single-agent selinexor in acute myeloid leukemia. Blood 129(24):3165–3174. https://doi.org/10.1182/blood-2016-11-750158
108. Wang AY, Weiner H, Green M, Chang H, Fulton N, Larson RA, Odenike O, Artz AS, Bishop MR, Godley LA, Thirman MJ, Kosuri S, Churpek JE, Curran E, Pettit K, Stock W, Liu H (2018) A phase I study of selinexor in combination with high-dose cytarabine and mitoxantrone for remission induction in patients with acute myeloid leukemia. J Hematol Oncol 11(1):4. https://doi.org/10.1186/s13045-017-0550-8
109. Ravandi F, Ritchie EK, Sayar H, Lancet JE, Craig MD, Vey N, Strickland SA, Schiller GJ, Jabbour E, Erba HP, Pigneux A, Horst HA, Recher C, Klimek VM, Cortes J, Roboz GJ, Odenike O, Thomas X, Havelange V, Maertens J, Derigs HG, Heuser M, Damon L, Powell BL, Gaidano G, Carella AM, Wei A, Hogge D, Craig AR, Fox JA, Ward R, Smith JA, Acton G, Mehta C, Stuart RK, Kantarjian HM (2015) Vosaroxin plus cytarabine versus placebo plus cytarabine in patients with first relapsed or refractory acute myeloid leukaemia (VALOR): a randomised, controlled, double-blind, multinational, phase 3 study. Lancet Oncol 16(9):1025–1036. https://doi.org/10.1016/s1470-2045(15)00201-6
110. Ravandi F, Ritchie EK, Sayar H et al (2016) Durable overall survival benefit in patients ≥60 years with relapsed or refractory AML treated with vosaroxin/cytarabine *vs.* placebo/cytarabine: updated results from the Valor Trial. Blood 128(22):903–903
111. 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
112. Saygin C, Carraway HE (2017) Emerging therapies for acute myeloid leukemia. J Hematol Oncol 10(1):93. https://doi.org/10.1186/s13045-017-0463-6