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REVIEW

Targeting the undruggable: menin inhibitors ante portas

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Abstract
Acute myeloid leukaemias harbouring a rearrangement of the mixed lineage leukaemia gene (MLL) are aggressive haematopoietic malignancies that relapse early and have a poor prognosis (event-free survival less than 50%). Menin is a tumour suppressor, however, in MLL-rearranged leukaemias it functions as a co-factor which is mandatory for the leukaemic transformation by interaction with the N-terminal part of MLL, which is maintained in all MLL-fusion proteins. Inhibition of menin blocks leukaemogenesis and leads to differentiation and, in turn, to apoptosis of leukaemic blasts. Furthermore, nucleophosmin 1 (NPM1) binds to specific chromatin targets, which are co-occupied by MLL, and menin inhibition has been shown to trigger degradation of mNPM1 resulting in a rapid decrease in gene expression and activating histone modifications. Therefore, disruption of the menin-MLL axis blocks leukaemias driven by NPM1 mutations for which the expression of menin-MLL target genes (e.g., MEIS1, HOX etc.) is essential. To date at least six different menin-MLL inhibitors are undergoing clinical evaluation as first- and second-line monotherapy in acute leukaemias: DS-1594, BMF-219, JNJ-75276617, DSP-5336, revumenib, and ziftomenib, however, only for revumenib and ziftomenib early clinical data have been reported. In the revumenib phase I/II AUGMENT-101 trial ($N=68$) with very heavily pretreated AML patients the ORR was 53% with a CR rate of 20%. The ORR in patients harbouring MLL rearrangement of mNPM1 was 59%. Patients who achieved a response had a mOS of 7 months. Similar results have been reported for ziftomenib in the phase I/II COMET-001 trial. ORR was 40% and CRc was 35% in AML patients with mNPM1. However, outcome was worse in AML patients with a MLL rearrangement (ORR 16.7%, CRc 11%). Differentiation syndrome was a notable adverse event. The clinical development of novel menin-MLL inhibitors is well in line with the currently ongoing paradigm shift towards targeted therapies seen in the AML treatment landscape. Moreover, the clinical assessment of combinations of these inhibitors with established therapy options in AML could be the fuel for an improved outcome of MLL/NPM1 patients.

Keywords AML · MLL rearrangement · NPM1 · Menin inhibitors · Clinical trials

Introduction

Acute myeloid leukaemias (AMLs) harbouring a rearrangement of the mixed lineage leukaemia gene (MLL, also known as lysine methyltransferase 2A [KMT2A]) are aggressive haematopoietic malignancies that are characterized by hyperleukocytosis, early relapse, high incidence of central nervous system involvement, and poor prognosis. In adults this AML subtype is typically associated with a prior treatment with topoisomerase-II (TOPO-II) inhibitors (e.g., etoposide, teniposide) (Pendleton et al. 2014). To date, chemotherapy, often combined with allogeneic stem cell transplantation in the consolidation setting in patients with a suitable donor, remains the treatment of choice in many cases, however, event-free survival (EFS) is low (approximately 50%), and may patients are not eligible for intensive chemotherapy at all (Clear et al. 2020). The development of novel treatment strategies is, therefore, a high unmet medical need.

During the last two decades over 80 different MLL translocation partner genes and their specific breakpoint regions have been characterized in experimental systems, and some translocations such as ELL (eleven–eighteen lysine-rich leukaemia) or P-TEFb (positive transcription elongation factor

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b) have been identified to act as a HOX (homeobox domain) gene activator in AML cells (Winters et al. 2017). In the vast majority of cases the breakpoint (11q23) is located in the 8.3 kb breakpoint region (Winters et al. 2017). and several lines of research have provided evidence approximately 60% are reciprocal translocation, 11q inversions and deletions are only found in 11% and 18%, respectively (Meyer et al. 2019). By analysing over 760 samples from AML patients, Meyer et al. (2009) could identify 104 different MLL rearrangements suggesting that the rearrangement process appears to be very complex, and many details remain still unknown. However, the research to identify unknown fusion partner genes is ongoing and will help to identify novel treatment targets (Meyer et al. 2023).

Based on this preclinical research two main molecular drivers have been identified as putative therapeutic targets: DOT1L (a histone-3 lysine-79 methyltransferase) and menin, a protein that interacts directly with MLL-fusion proteins (Issa et al. 2021). It has been shown that these two proteins are obligatorily required for MLL-fusion target gene expression and transformation by MLL-fusion proteins (Bernt et al. 2011, Kühn et al. 2015). The importance of DOT1L in AML cells harbouring the MLL rearrangement is well characterized and is regarded to be a critical step for disease progression and chemotherapy resistance since MLL-fusion proteins can lead to an aberrant DOTL1 recruitment (Banday et al. 2020). Although several DOT1L inhibitors (e.g., EPZ-5676, EPZ-004777) have entered the clinic, the clinical activity in phase I/II trials was only modest in MLL-rearranged leukaemias, which formed the basis for the development of highly specific menin inhibitors (Bandey et al. 2020).

Menin is a tumour suppressor, however, in MLL-rearranged leukaemias it functions as a co-factor which is mandatory for the leukaemic transformation (Yokoyama et al. 2005) by interaction with the N-terminal part of MLL, which is maintained in all MLL-fusion proteins. Inhibition of menin blocks leukaemogenesis and leads to differentiation and, in turn, to apoptosis of leukaemic blasts (Chen et al. 2006) (Fig. 1).

Most recently, Perner et al. (2023) provided the first experimental evidence that certain somatic MLL-mutations at the revumenib binding side may cause acquired resistance to revumenib and other menin inhibitors suggesting that this type of chromatin-targeting agents have sufficient selection pressure to drive the evolution of resistance mutations.

Interestingly, in AML cells harbouring a mutant nucleophosmin 1 (mNPM1—detectable in 30% of AML patients), MLL1 is the main oncogenic driver (upregulator) of HOX, MEIS1, and Flt-3 and thereby promoting self-renewal of myeloid progenitor cells (Fiskus et al. 2022). NPM1 mutations often co-occur with Flt-3 mutations (60%) and DNMT3A mutations (50%). NPM1 directly binds to specific chromatin targets, which are co-occupied by MLL, and menin inhibition has been shown to trigger degradation of mNPM1 resulting in a rapid decrease in gene expression

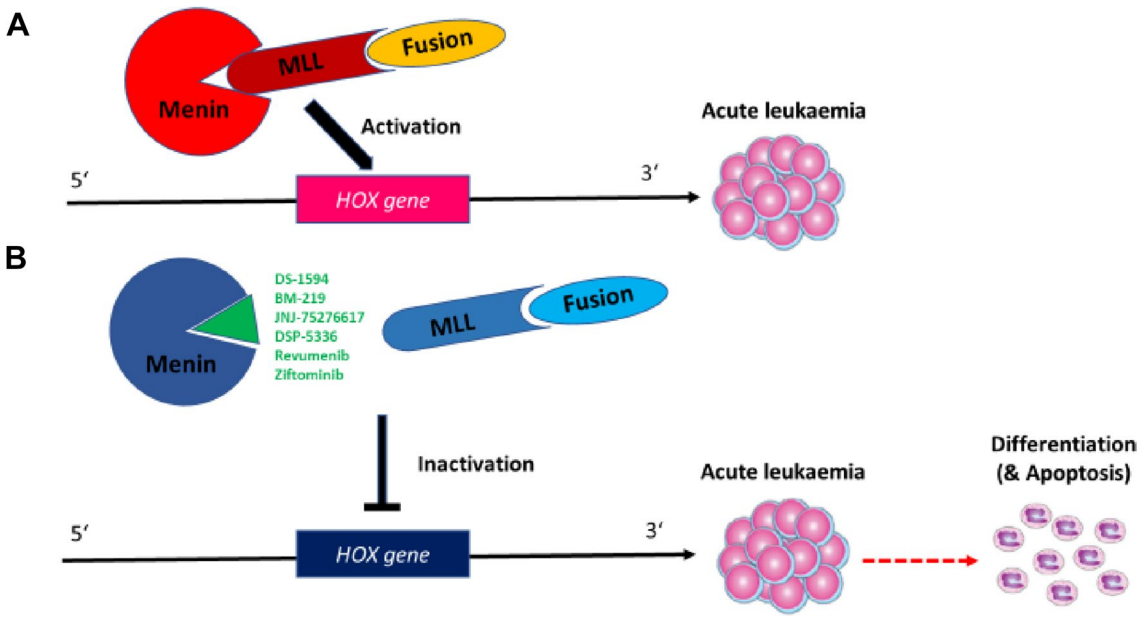

Fig. 1 The menin-MLL interaction is mandatory for the transcription of the HOX gene which is essential for AMLs harbouring a MLL rearrangement (**A**). Small-molecule inhibitors of menin (see Table 1) block the MLL-menin binding side which then results in a shut-down of the HOX gene with subsequent differentiation of leukaemic blasts (**B**). MLL mixed lineage leukaemia gene, HOX homeobox gene (encoding for transcription factors)

and activating histone modifications (Uckelmann et al. 2020, Swamnianthan et al. 2022).

The interaction between MLL and NPM1 was not fully understood and it has remained elusive how NPM1 mutations initiate and maintain the AML phenotype for almost 2 decades (Kühn et al. 2016). In particular, the mechanism by which the expression of mutated NPM1 in leukaemia cells can confer characteristic gene expression profiles was unknown. Seminal experimental data provided by Dr. Armstrong and co-workers (Dana-Farber Cancer Institute, Boston, USA) shed some light on the underlying mechanisms of the MLL-NPM1 interface. These group of researchers could show for the first time that the mutated NPM1 protein binds to specific chromatin targets, which are co-occupied by the MLL1 protein. Thereby, mutated NPM1 can regulate oncogenic gene expression in leukaemic blasts in collaboration with the MLL complex suggesting that NPM1 is a very important target for the menin-MLL inhibition in leukaemia (Uckelmann et al. 2023).

In addition, in an earlier paper the same authors demonstrated for the first time that myeloid progenitor cells harbouring NPM1 mutations exhibit elevated HOX gene expression which is associated with enhanced cell proliferation (Uckelmann et al. 2020). Moreover, the enhanced proliferation could reversed by exposure of cells to VTP-50469, a revumenib analogue). VTP-50469 was found to induce a loss of the MEIS protein and, in turn, a significant differentiation of leukaemic blasts harbouring NPM1 mutations (Uckelmann et al. 2020).

Therefore, disruption of the menin-MLL axis blocks leukaemias driven by NPM1 mutations for which the expression of menin-MLL target genes (e.g., MEIS1, HOX etc.) is essential (Ranieri et al. 2022; Chlaer et al. 2020).

This preclinical observation added further weight to the hypothesis that mNPM1 in collaboration with MLL regulates the expression of oncogenes suggesting that menin inhibitors will also be active in AML patients harbouring mNPM1 (Klossowski et al. 2020).

Clinical trials

To date at least six different menin-MLL inhibitors are currently undergoing clinical evaluation as a novel therapy in r/r AML and are incorporated in salvage therapy trials to bridge the time to allogeneic stem cell transplantation: DS-1594, BMF-219, JNJ-75276617, DSP-5336, revumenib, and ziftomenib (Table 1). So far, the initial results from these studies demonstrated that these orally available inhibitors are well tolerated and have shown very promising clinical activity. However, it should be noted that the spectrum of different toxicities is different between the menin inhibitors currently under clinical development with some toxicities seen with some agents (e.g., differentiation syndrome seen in ziftomenib trials) but not in trials with other agents.

In addition, several trials are also ongoing or planned to combine menin-MLL inhibitors with induction therapy (de novo AML) or in combination with hypomethylating agents and/or venetoclax. Results, however, are not yet available.

In this mini-review we describe the current development of menin-MLL inhibitors and discuss the putative role of these compounds as a new treatment approach for acute leukaemias.

DS-1594

DS-1594 (a or b) (Fig. 2) is a potent and highly selective menin inhibitor which can be administrated orally. In preclinical models DS-1594 has shown significant anti-leukaemic effects against AML and ALL cells harbouring the MLL rearrangement. In addition, robust and durable remission were seen in AML animal models (Numata et al. 2023).

Table 1 Summary of menin inhibitors currently undergoing clinical evaluation

Compound	Manufacturer	Phase	Comments
DS-1594	Daiichi-Sankyo	I/II	Orally available and potent menin inhibitor, phase I/II (alone or in combination with mini-hyper-CVD or venetoclax or azacytidine) is ongoing (r/r AML, ALL)
BMF-219	BioMea	I	Irreversible inhibitor, targets also MYC, COVALENT-101 trial ongoing (various histologies)
JNJ-75276617	Johnson & Johnson	I	Phase I trial (first-in-human) ongoing in r/r AML harbouring MLL or NPM1 alterations, phase I trial in combination with venetoclax or azacitidine is also recruiting (r/r AML)
DSP-5336	Sumitomo Dainippon Pharma	I/II	Trial is ongoing, target population: r/r AML and ALL
Revumenib	Syntax	I/II	ORR 53%, CR rate 30%, mOS 7 months (heavily pretreated AML patients)
Ziftomenib	Kura Oncology	I/II	*mNPM1:* ORR 40%, CRc rate: 35% *MLL rearrangement:* ORR 16.7%, CRc rate: 11% (heavily pretreated patients)

ORR overall response rate, mOS median overall survival, CR complete remission, CRc composite complete remission

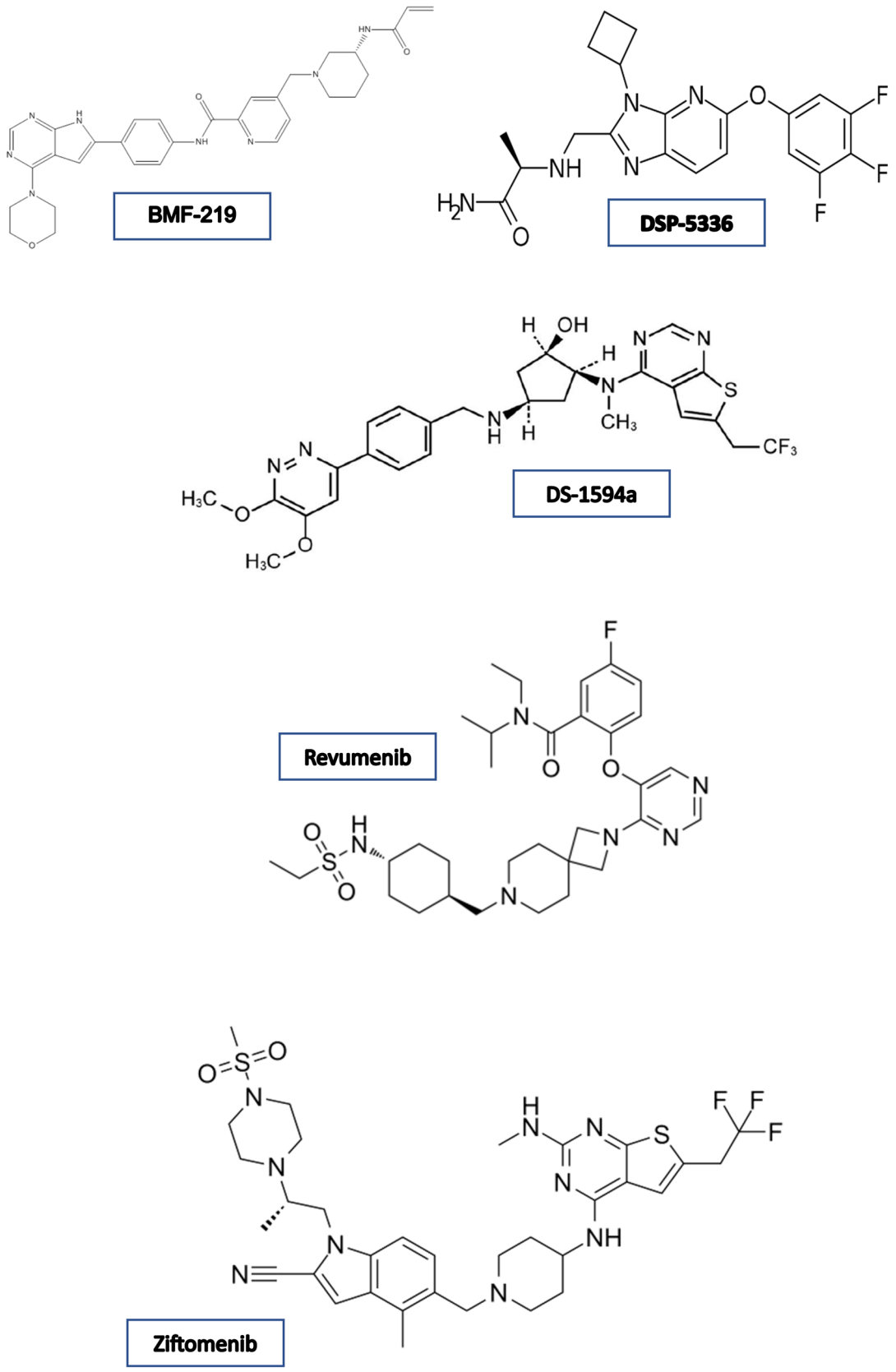

Fig. 2 Chemical structures of menin inhibitors currently undergoing clinical evaluation. The structure of JNJ-75276617 is not available on the public domain

Based on these finding a first-in-human study (NCT04752163) with DS-1594 with or without azacitidine, venetoclax, or mini-HCVD (hyperfractionated cyclophosphamide, vincristine, and dexamethasone) for the treatment of r/r AML or ALL was conducted. The study is active, but not recruiting patients. Results are expected soon.

BMF-219

BMF-219 (Fig. 2) is a highly selective and irreversible inhibitor of menin which has shown very promising activity in in-vitro and in-vivo preclinical tumour models. In addition, since the MYC activity is heavily dependent on its interaction with menin, BM-219 was designed to inhibit MYC as well in preclinical models (Lourenco et al. 2021).

In experimental models the compound was found to exert activity not only in MLL-rearranged acute leukaemias, but also in multiple myeloma, r/r CLL, and diffuse large B cell lymphomas with MYC overexpression.

BMF-219 is currently evaluated in an ongoing phase I trial (COVALENT-101, NCT 05153330); the primary objective is to determine the recommended phase II dose of monotherapy. Enrolment started early in 2022, and results have not yet been reported (Ravandi et al. 2022).

DSP-5336

DSP-5336 (Fig. 2) is a novel orally available selective inhibitor of menin (Daver et al. 2020). Based on the observed activity in preclinical models, DSP-5336 is currently being evaluated as monotherapy in a phase I/II clinical trial to evaluate the safety, efficacy and the recommended phase II dose of the drug in patients with r/r AML/ and ALL with or without MLL rearrangement or NPM1 mutation (NCT04988555). Data are not available yet.

JNJ-75276617

JNJ-75276617 is an orally available, potent, and highly selective inhibitor of the menin-MLL interface. Exposure of AML cells harbouring the MLL rearrangement to JNJ-75276617 resulted in a significant reduction of leukaemic blasts in a dose-dependent manner. Similar results were obtained when using AML-bearing animals (Kwon et al. 2022). Based on these preclinical results a first-in-human study was initiated using JNJ-75276617 as monotherapy in r/r AML patients harbouring either the MLL rearrangement or mNPM1 (NCT04811560).

In addition, another phase I trial (NCT05453903) is ongoing to evaluate the combination of JNJ-75276617 with either venetoclax or azacitidine in r/r AML patients. Both trials are still recruiting patients and results have not been published yet.

Revumenib

Revumenib (also known as SNDX-5613) (Fig. 2) was the first menin inhibitor undergoing clinical evaluation. In several in-vitro models with leukaemic cells harbouring the MLL rearrangement, menin inhibitors (e.g., VTP-5046, a close analogue of revumenib; Gundry et al. 2020) were found to displace menin from MLL (and other proteins) which led to differentiation and subsequently to apoptosis (Krivtsov et al. 2019). In addition, in AML- and ALL-patient-derived mouse xenograft models VTP-5046 induced dramatic reductions of the tumour burden with several animals remained disease-free for more than 12 months (Krivtosov et al. 2019).

Moreover, exposure of cells to the slightly modified compound revumenib was also found to interfere with bcl-2 and CDK6 levels and co-exposure of revumenib with venetoclax or abemaciclib induced overadditive lethality in these cells (Fiskus et al. 2022).

These promising preclinical findings prompted the investigators to conduct a phase I/II trial with revumenib in r/r AML harbouring a MLL rearrangement or a NPM1 mutation (AUGMENT-101, NCT04065399). This trial recruited a total of 68 patients with 82% of whom had AML. Many of the patients recruited had very refractory disease and had failed multiple treatment lines including stem cell transplantation.

The ORR was found to be 53% (60 evaluable patients) with a CR rate of 20%. The ORR in patients harbouring MLL rearrangement of mNPM1 was reported to be 59%. Patients who did achieve a response had a mOS of 7 months (Issa et al. 2023). Treatment was well tolerated with a dose-limiting toxicity of QTc prolongation (grade III in 13% of patients). Eleven patients had a grade II differentiation syndrome which resolved after steroids and/or hydroxyurea application (Issa et al. 2023).

In addition, two other trials with revumenib are currently recruiting patients: the first one evaluates the combination of revumenib in combination with chemotherapy in r/r AML patients (NCT05761171), the second one evaluates the effects of revumenib and chemotherapy in patients with colorectal carcinomas (NCT05731947). The rationale here is the observation that wild-type MLL is expressed in many solid tumours (Parameswaran et al. 2019).

Finally, several other clinical trials with revumenib in acute leukaemias are planned and comprise a first-line combination with venetoclax and azacitidine (BEAT-AML trial), a second-line trial in r/r AML in combination with chemotherapy (AUGMENT-002 trial), and a monotherapy trial in MDR-positive AML patients harbouring the MLL rearrangement or a NPM1 mutation.

Collectively, the mOS of 7 months with revumenib in this heavily pretreated AML population appears to be an

impressive result, which, however, needs to be confirmed in larger randomized trials. Despite this, it underscores the potential of this menin inhibitor for future novel treatment regimens in AML.

Ziftomenib

Ziftomenib (also known as KO-539 (Fig. 2) is a small-molecule menin inhibitor which has been developed as part of the FDA's "Project Optimus" (FDA 2015). Using in-vitro and in-vivo systems the compound was found to effectively inhibit growth of MLL-rearranged leukaemias. Moreover, in two subcutaneous AML xenograft models (MV4;11 and MOLM13), treatment of the animals with ziftomenib resulted in a prolonged und durable survival benefit, and all mice were found to be free of leukaemic blast after 4 weeks. In 40% of the surviving animals, leukaemia was even not detectable after four weeks of cessation of the study (Burrows et al. 2017). In addition, the compound was also found to sensitize AML blasts to venetoclax (Rausch et al. 2022).

Based on these promising results a phase I/II study was conducted (COMET-001, NCT04067336) in which the drug was evaluated in an initial dose escalation part followed by a dose expansion part (evaluation of ziftomenib specifically in patients harbouring the MLL rearrangement or NPM1 mutations). Patients enrolled in this trial were heavily pretreated (median of three prior treatment lines, mainly including venetoclax and 25% of patients with prior stem cell transplantation). The trial demonstrated a good safety profile and ziftomenib was well tolerated (dose: 600 mg; recommended dose for phase II testing). The main dose-limiting toxicity appeared to be the differentiation syndrome that prompted the FDA to place an earlier partial clinical recruitment hold which was then lifted after an agreement on the strategy for mitigating this adverse event. Preliminary efficacy data showed that the 600 mg dose had meaningful efficacy, with an ORR of 40% and CRc in 35% in AML patients with mNPM1. However, outcome was worse in AML patients with a MLL rearrangement (ORR 16.7%, CRc 11%). Differentiation syndrome was a notable adverse event, with at least grade III severity occurring in 27% of MLL-rearrangement patients (one patient died), although no grade III differentiation syndrome occurred in mNPM1 patients. Of note, the differentiation syndrome was associated with improved response (75% of mNPM1 patients), and severity decreased with improved protocol guidance as requested by the FDA (Erba et al. 2022).

Overall, ziftomenib demonstrated an ORR that was comparable to that of revumenib, but the efficacy was lower in the AML population harbouring MLL rearrangements. Currently, a phase I study of venetoclax plus azacitidine or venetoclax in combination with ziftomenib or cytarabine plus daunorubicin ("7 + 3") chemotherapy in combination with ziftomenib for the treatment of AML patients is ongoing (NCT 05735184). Moreover, a clinical trial evaluating the combination of gilteritinib and ziftomenib in NPM1-mutant r/r AML patients is planned since Flt-3 and NPM1 mutations are known to often co-occur in r/r AML patients according to the 5th edition of the World Health Organization Classification of haematolymphoid tumours (Khoury et al. 2022).

Future directions

Even in the area of advanced knowledge of the underlying molecular biology, treatment approaches for acute leukaemias still remain a therapeutic challenge. In particular, AML is known to be associated with a high mortality rate despite the fact that advancements in molecular risk stratification and new treatment opportunities have led to some improvements in the outcomes for some subgroups (Table 2).

During the last four to five decades the underlying molecular alterations of the disease or the AML subtype did not significantly impact front-line induction chemotherapy. Almost all leukaemia centres have treated (and still treat) AML patients being eligible for intensive chemotherapy with an anthracycline (e.g., daunorubicin or idarubicin for 3 consecutive days) plus ara-C (continuous infusion over 7 days)—generally known as the "7 + 3" regimen. A significant breakthrough in terms of mOS benefit was recently demonstrated by a new "7 + 3" formulation (CPX-351, Vyxeos liposomal®) in patients with secondary AML (Lancet et al. 2018).

Although chemotherapy still remains the backbone for all acute leukaemias, its administration is somewhat limited due to the cardiotoxic effects of anthracyclines in the regimens used. To exceed the maximal cumulative dose for anthracyclines used in the treatment of acute leukaemias, novel anthracycline derivatives are currently under development (Dempke et al. 2023). Amongst them, the most advanced compound L-annamycin was found to exert no cardiotoxicity in all patients treated, showed activity even in the mdr-1-positive cells and demonstrated an excellent clinical activity (ORR 80%) (Dempke et al. 2023).

Results from clinical trials with immunotherapy agents (checkpoint inhibitor) in patients with acute leukaemias were disappointing since the immune system of de novo and r/r AML patients appears to be significantly impeded prior to treatment (i.e. due to massive bone marrow infiltration—"immune desert"), checkpoint expression is very low at baseline, and clonal heterogeneity of AMLs appear to be the main causes for treatment failure of therapies relying on patient immune function (Ghosh et al. 2020).

During the last couple of years, the treatment armamentarium for AML patients has significantly changed with the

Table 2 Novel drugs approved for the treatment of AML patients

Drug	Brand Name	Target	Indication	mOS (experimental vs. control)	References
Midostaurin	Rydapt®	Flt-3, PKC, VEGFR	1st line with intensive CTX (Flt-3-positive)	74.7 vs. 25.6 months	Stone et al. (2017)
Gilteritinib	Xospata®	Flt-3	r/r AML (Flt-3-positive)	9.3 vs. 5.6 months	Perl et al. (2019)
Gemtuzumab-ozogamcin	Mylotarg®	CD33	1st line with intensive CTX (CD33-positive)	27.5 vs. 21.8 months	Castaigne et al. (2012)
CPX-351	Yvxeos liposomal®	Liposomal "7 + 3" formulation	1st line (secondary AML)	9.6 vs. 6 months	Lancet et al. (2018)
Azacitidine	Onureg®	DNA methylation	Maintenance following intensive CTX (not eligible for SCT)	24.7 vs. 14.8 months	Wei et al. (2020)
Venetoclax	Venclexa®	Bcl-2	Unfit patients, 1st line	14.7 vs. 9.6 months	DiNardo et al. (2018)
Enasidenib	Idhifa®	IDH-2	r/r AML (mIDH-2-positive) in combination with azacitidine	9.3 months (single arm) (CR/CRi: 27%)	Stein et al. (2017)
Ivosidenib	Tibsovo®	IDH-1	1st or 2nd line AML (alone or in combination with azacitidine) (mIDH-1-positive)	9 months (single arm) (CR/CRi: 35%)	DiNardo et al. (2020)
Glasdegib	Daurismo®	Hedgehog	1st and 2nd line AML in combination with azacitidine (not eligible for SCT)	8.3 vs. 4.3 months	Cortes et al. (2019)

SCT stem cell transplantation, CTX chemotherapy, r/r relapsed or refractory, CR complete remission, CRi complete remission with incomplete recovery

development and approval of several targeted therapies (e.g., inhibitors of Flt-3, IDH1,2, bcl-2, DOT1L, Hedgehog, bromodomain, etc.), and novel targets (e.g., DNA methylation, CD33, CD47, CD70, CD123 etc.) in the first- and second-line setting (Stubbins et al. 2022).

The actual clinical development of novel menin-MLL inhibitors is well in line with the currently ongoing paradigm shift towards targeted therapies we are witnessing in the AML treatment landscape. These compounds appear to be very attractive molecules and represent prototypes of innovative inhibitors of AML driver mutations. In future trials which are currently under development menin inhibitors will also be evaluated together with combination therapy in the first-line setting of AML patients. Moreover, the clinical assessment of combinations of these inhibitors with established therapy options in AML will clearly be the fuel to improve the outcome of AML patients harbouring MLL/NPM1 alterations and thereby will pave the way for a better outcome of AML patients in the not-too-distant future.

Summary

The novel menin inhibitors described here represent a new class of very promising agents in clinical evaluation. Currently, it appears that these compounds are most effective in acute leukaemias harbouring the MLL rearrangement and/or a NPM1 mutation, however, it may also be possible that a subgroup of leukaemias with other molecular alterations could also respond. Of note, BMF-219 is the only menin-MLL inhibitor that also targets the MYC oncogene which might broaden the treatment spectrum of this drug. However, based on the data coming from the dose escalation and expansion parts of the various studies described here are clearly not robust enough to define the "best-in-class" menin inhibitor, and a final judgement can only be made once the data from phase II and III trials (with a longer follow-up) are available.

Finally, combination trials with menin inhibitors are also underway (e.g., combinations with venetoclax, azacitidine, or chemotherapy) in newly diagnosed or r/r AML patients, and results from these trials will clearly help to further evaluate the potential of this new class of agents for the treatment of haematological malignancies.

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Data availability All data within this paper are available from the authors upon request.

Declarations

Conflict of interest The authors declare no conflicts of interest.

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