Editorial Commentary

Further validation of poor prognosis for pediatric *KMT2A*-rearranged leukemia and the need for rapid integration of targeted therapies for these patients

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While the 5-year overall-survival rate for pediatric acute lymphoblastic leukemia (ALL) now exceeds 90%, unfavorable ALL subtypes face a far inferior prognosis (1,2). Event-free and overall survival of lysine methyltransferase 2A [*KMT2A*, formerly mixed lineage leukemia (*MLL*)]-rearranged (*KMT2A*-r) ALL lag behind other high risk cytogenetics abnormalities (2,3). Rearrangements involving 11q23/*KMT2A* occur in approximately 75% of infantile ALL, 5% of childhood ALL in non-neonates, and 18% of pediatric acute myeloid leukemia (AML), with different *KMT2A* fusion partners yielding varied but overall poor prognoses (2,4,5). With greater than 100 translocation partners, better characterization of each *KMT2A* rearrangement and its prognostic impact across the ALL landscape is essential to guiding the next generation of clinical trial development, especially since targeted therapy with menin inhibitors has entered into Phase I/II clinical trials (6,7).

The recent report from Attarbaschi *et al.* confirms that childhood *KMT2A*-r ALL outcomes in patients treated on contemporary cytotoxic chemotherapy regimens remain unsatisfactory both with regard to event-free and overall survival (4). This patient cohort desperately requires novel treatment strategies, potentially with bispecific T-cell engager antibodies, chimeric antigen receptor T-cell therapy, and menin inhibitors. While induction failure in childhood *KMT2A*-r ALL was rare, achievement of negative end-of-induction (EOI) minimal residual disease (MRD) across the reported cohort lagged behind non *KMT2A*-r patients. A complete response (CR), defined as an M1 marrow, was observed in 93% of patients (4). However, of evaluable patients, only 56% were MRD negative at EOI at a threshold of <0.05%, indicating that a significant cohort of these patients was predicted to have a high relapse rate (4). This MRD cutoff notably is higher than currently used cutoffs for either flow or high throughput sequencing-based MRD, so even MRD-negative patients as presented may be MRD positive in current practice (8,9). B cell ALL (B-ALL) patients with the most common t(4;11)(q21;q23)/KMT2A::AFF1 rearrangement only were EOI MRD negative 51% of the time while MRD negativity for B-ALL patients with t(10;11)(p12;q23)/KMT2A::MLLT10 reached 75% (4). T cell ALL (T-ALL) patients, while smaller in number, faced even more varied rates of EOI MRD negativity as low as 17% (n=6) for t(9;11)(p21;q23)/KMT2A::MLLT3 patients and 71% (n=7) for t(6;11)(q27;q23)/KMT2A::MLLT4 patients (4). Five-year event-free survival (EFS) was 69% for the entire

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cohort, with sub-stratification by rearrangement partner hovering within 10% of the overall cohort with two notable exceptions. Five year EFS among two T-ALL cohorts demonstrates the variability for therapy response among *KMT2A*-r patients, with an EFS of 91% (n=34) for t(11;19)(q23,p13.3)/KMT2A::MLLT1 patients and only 42% (n=19) for t(9;11) patients (4). For comparison, *KMT2A*-r infants treated on Interfant-06 achieved CR1 91% of the time with 60% EOI MRD negative, and 85% of patients achieved an M1 marrow with 68% EOI MRD negative on the MLL-10 study (5,10,11). These recent studies highlight the difficulty in achieving a deep remission for *KMT2A*-r ALL patients and are even more sobering since neither chemotherapy intensification nor allogenic hematopoietic stem cell transplant improved outcomes (4,5). These outcomes additionally all are inferior to the overall disease-free survival reported among very high-risk patients on the most recent Children's Oncology Group (COG) high risk trial AALL1131 (12). Furthermore, the publication of this childhood ALL cohort validates the prognostic value of the most common *KMT2A* rearrangement partners as seen in both infantile ALL and pediatric AML (5,13-15).

This impressive report from the Ponte-di-Legno Childhood ALL Working Group also must be balanced against contemporary ALL studies that incorporate frontline immunotherapy (4). The drastic improvement of 2 year EFS to 82% from 49% with the addition of blinatumomab to Interfant-06 therapy suggests a significant role for blinatumomab across all *KMT2A*-r ALL, especially since half of these patients presented with t(4;11) rearrangements and responded to therapy (10). Sustaining this impressive response with the addition of blinatumomab especially would be noteworthy since when patients were risk stratified as per Interfant-06 to allow direct comparison, MLL-10 achieved a similar 3-year EFS of 82% in intermediate risk patients but only 45% for high risk patients (11). Adults with *KMT2A*-r leukemia also have responded well to either blinatumomab or inotuzumab (16). Ongoing standard and high-risk B-ALL trials through COG will determine if blinatumomab and/or inotuzumab become the upfront pediatric standards of care, with upfront blinatumomab already gaining significant traction based on efficacy and tolerability in pediatric patients unfit to continue conventional chemotherapy and among adults treated on the E1910 study (17,18). Lineage switching of t(4;11) ALL to AML has been reported, but given the overwhelmingly positive data supporting upfront blinatumomab use, it must be assumed that subsequent *KMT2A*-r rearranged patients will receive upfront immunotherapy (19).

In addition to the added benefit of upfront immunotherapy, *KMT2A*-r patients hopefully will benefit from targeted therapy with menin inhibitors now that they have reached Phase I/II clinical trials. The AUGMENT-101 trial using revumenib (SNDX-5613) in relapsed/refractory leukemias with *KMT2A*-r or nucleophosmin 1 (*NPM1*) mutations includes pediatric patients and published its initial analysis (20). Among the first 68 evaluable patients, 11 presented with ALL, one with MPAL, and the remaining 56 with AML. Fifty-three percent of patients responded to monotherapy, with superior responses seen in patients harboring *KMT2A* rearrangements over *NPM1* mutations. Of the 30 patients with at least a CRh (CR with incomplete hematologic recovery), 78% were also MRD negative with a median time to MRD negativity of 1.9 months. Among the evaluable *KMT2A* fusion partners, only patients with t(4;11) (n=6, 9%) failed to document a response, furthering the robust evidence that t(4;11) patients present with the most aggressive disease (4,13,20,21). The now open COG protocol AALL2121 will evaluate revumenib with chemotherapy in relapsed infantile ALL. While the data are not as mature, the KOMET-007 trial using another menin inhibitor ziftomenib (KO-539) in relapsed/refractory AML notably reported a complete remission rate of 35% in patients harboring *NPM1* mutations (22). Ziftomenib is under study for *de novo* infantile ALL in the recently launched TINI 2 trial that is recruiting (NCT05848687). Additional menin inhibitors are under Phase I/II investigation, with a summary of open and pending trials included in *Table 1*. Hope for an even more impressive response when given as frontline therapy cannot be understated given the promising responses in relapsed/refractory patients. There also remains potential for targeted therapy with disrupter of telomeric silencing 1-like (DOT1L) inhibition, but promising preclinical data thus far has only translated to a modest impact in an early Phase I study (23,24).

In conclusion, expanded outcomes data for pediatric *KMT2A*-r ALL stratified by fusion partner validate the need to bring novel therapies to the bedside (4). Routine use of upfront immunotherapy may drive overall survival closer to the 90% benchmark quoted to the majority of pediatric ALL patients, but even if this occurs, the preclinical and early clinical data supporting menin inhibition cannot be ignored when designing the next iteration of upfront and relapsed clinical trials. The Ponte-di-Legno group should be commended for validating the poor overall prognosis

Table 1 Active and pending clinical trials utilizing menin inhibitors[†]

Investigational agent	Clinical trial identification	Clinical trial phase	Patient population	Incorporation of chemotherapy
BMF-219	NCT05153330 (COVALENT-101)	I	Adults[‡] with relapsed/refractory AML, ALL, DLBCL, CLL/SLL, or multiple myeloma	No
BMF-219	NCT05631574 (COVALENT-102)	I	Adults with *KRAS*-mutated non-small cell lung cancer, pancreatic cancer, colorectal cancer	No
BMF-219	NCT05731544 (COVALENT-111)	I	Adults with type 2 diabetes mellitus	N/A
BMF-219	NCT06152042 (COVALENT-112)	II	Adults aged 18–60 with type 1 diabetes mellitus	N/A
BN104	NCT06052813	I/II	Adults with relapsed/refractory AML with *KMT2A* or *NPM1* alterations, relapsed ALL with *KMT2A* alterations	No
DSP-5336	NCT04988555	I/II	Adults with relapsed/refractory AML, ALL, or acute leukemia of ambiguous lineage. Need for *KMT2A* or *NPM1* alterations varies by cohort	No
JNJ-75276617	NCT04811560	I	Adults with relapsed/refractory AML or ALL with *KMT2A* or *NPM1* alterations	No
JNJ-75276617	NCT05453903	I	Adults with AML with *KMT2A* or *NPM1* alterations	Azacitidine, venetoclax (arms A and B) Cytarabine, daunorubicin or idarubicin (arm C)
JNJ-75276617	NCT05521087	I	Patients less than 30 years with relapsed/refractory leukemia with *KMT2A* or *NPM1* alterations	Fludarabine, cytarabine (AML) Vincristine, dexamethasone, pegaspargase (ALL)
KO-539 (ziftomenib)	NCT04067336 (KOMET-001)	I/II	Adults with relapsed/refractory AML with *KMT2A* or *NPM1* alterations	No
KO-539 (ziftomenib)	NCT05735184 (KOMET-007)	I	Adults with relapsed/refractory AML with *KMT2A* or *NPM1* alterations	Azacitidine, venetoclax, daunorubicin, cytarabine
KO-539 (ziftomenib)	NCT06001788 (KOMET-008)	I	Adults with relapsed/refractory AML with *KMT2A* or *NPM1* alterations, including a *FLT3* cohort	Fludarabine, cytarabine, idarubicin, gilteritinib (*FLT3* cohort)
KO-539 (ziftomenib)	NCT05848687 (TINI 2)	I/II	Infants <1 year of age with *KMT2A* rearranged ALL, undifferentiated, or biphenotypic leukemia	Dexamethasone, mitoxantrone, pegaspargase, bortezomib, vorinostat, mercaptopurine, methotrexate, blinatumomab
SNDX-5613 (revumenib)	NCT04065399 (AUGMENT-101)	I/II	Patients with relapsed/refractory leukemia with *KMT2A* or *NPM1* alterations	No

Table 1 (*continued*)

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Investigational agent	Clinical trial identification	Clinical trial phase	Patient population	Incorporation of chemotherapy
SNDX-5613 (revumenib)	NCT05326516 (AUGMENT-102)	I	Patients with relapsed/refractory leukemia with *KMT2A* or *NPM1* alterations	Vincristine, prednisone, pegaspargase/calaspargase, daunorubicin, etoposide, cyclophosphamide (regimen 1) Fludarabine, cytarabine (regimen 2)
SNDX-5613 (revumenib)	NCT05360160 (SAVE)	I/II	Patients 12 years and older with relapsed/refractory AML or MPAL with myeloid phenotype	Decitabine/cedazuridine and venetoclax
SNDX-5613 (revumenib)	NCT05761171 (AALL2121)	II	Patients <6 years old with relapsed/refractory ALL, MPAL with *KMT2A* rearrangement with initial diagnosis <2 years old	Vincristine, prednisone, calaspargase (regimen A) Fludarabine, cytarabine (regimen B)
SNDX-5613 (revumenib)	NCT05886049	I	Adults with newly diagnosed AML with *KMT2A* or *NPM1* alterations	Daunorubicin plus cytarabine
SNDX-5613 (revumenib)	NCT05731947	I/II	Adults with progressive metastatic colorectal cancer (phase I) or solid tumors (phase II)	Phase II will compare SYDX-5613 response against trifluridine/tipiracil and regorafenib
SNDX-5613 (revumenib)	NCT06177067	I	Patients 1–30 years old with relapsed/refractory AML with *KMT2A*, *NPM1*, and other eligible alterations	Azacitidine, venetoclax

[†], listed trials on clinicaltrials.gov using search terms "menin", "revumenib", and "ziftomenib" as of January 7, 2024; [‡], patient is 18 years of age or older. AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; CLL, chronic lymphocytic lymphoma; SLL, small lymphocytic lymphoma; MPAL, mixed phenotype acute leukemia; *KRAS*, Ki-ras2, Kirsten rat sarcoma viral oncogene homolog; *KMT2A*, lysine methyltransferase 2A; *NPM1*, nucleophosmin 1; *FLT3*, FMS-related receptor tyrosine kinase 3.

of *KMT2A*-r patients as their report only will hasten the introduction of novel therapies, including immunotherapy and targeted therapies, to these patients.

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