ACUTE MYELOID LEUKEMIA (AML) BIOLOGY AND PROGNOSIS

Revised risk stratification criteria for children with newly diagnosed AML

Currently, most phenotypic, cytogenetic or molecular markers identified in children with acute myeloid leukemia (AML) are not used for risk stratification or treatment assignment. To develop an improved risk stratification strategy, Cooper et al. conducted a comprehensive retrospective evaluation of potential biomarkers that have been reported using available karyotype, immunophenotype and next generation sequencing (NGS) data from patients treated on AAML0531 (a study that enrolled 1,022 patients and randomized to standard therapy with or without gemtuzumab ozogamicin). Table 1 shows the cytogenetic, molecular, and immunophenotypic markers that were used in this new risk stratification model.

Increased prevalence of AML-defining mutations in peripheral blood years prior to the development of overt leukemia

It is known that AML is preceded by the serial acquisition of somatic mutations, but the exact pattern is unknown. A study reported by Desai et al. analyzed 212 subjects with a centrally adjudicated AML diagnosis with a peripheral blood sample prior to the diagnosis of overt AML and 212 healthy non-AML matched controls. Myeloid specific mutations were detected in 35.4% of controls and in 59.04% of cases. The most commonly found mutations and their frequencies among cases and controls respectively were DNMT3A (22.8% and 10%), TET2 (19.5% and 4.2%) and ASXL1/ASXL2 (8% and 6.8%). TP53 (6.6%) and RUNX1 (2%) mutations were only seen in participants who eventually developed AML and were absent in controls. There was an increased prevalence of myeloid specific mutation among cases compared to controls (OR[95%CI]: 2.87[1.90-4.37], p< 0.001). Also, the presence of a pathogenic myeloid mutation was significantly different among cases and controls (p value <.0001). In this matched case control analysis, the presence of a myeloid specific mutation at baseline was associated with the development of AML (OR: 2.9, p< 0.001). Strikingly, all participants with a RUNX1 and TP53 and most patients with the targetable Ariez International, Ghent, Belgium

Please send all correspondence to: T. Feys, Ariez international, Oude Houtlei 118, 900 Ghent, E-mail: t. feys@ariez.com, Tel: 0479/567890

Conflict of interest: The selection of the abstracts discussed here is the sole responsibility of the publisher and was not influenced by third parties.
IDH2R140Q mutation (10/11) eventually developed AML many years later. These findings suggest that subclonal stepwise acquisition of mutations may occur years prior to disease onset and that deep molecular monitoring using NGS may enable early intervention in selected patients.

**TREATMENT**

**Targeting FLT3 mutations in AML.**

Patients with AML and a FLT3 mutation have poor outcomes. In a phase III study (RATIFY) reported by Stone et al. in the New England Journal of Medicine, 717 patients with newly diagnosed AML and a FLT3 mutation were randomly assigned to receive standard chemotherapy (induction therapy with daunorubicin and cytarabine and consolidation therapy with high-dose cytarabine) plus either midostaurin or placebo. Patients who were in remission after consolidation therapy entered a maintenance phase in which they received either midostaurin or placebo. The OS was significantly longer in the midostaurin group than in the placebo group (HR: 0.78; one-sided p= 0.009), as was the event-free survival (EFS) (HR: 0.78; one-sided p= 0.002). The benefit of midostaurin was consistent across all FLT3 subtypes (point mutation in the tyrosine kinase domain [TKD] or internal tandem duplication [ITD] mutation with either a high ratio or a low ratio of mutant to wild-type allele). The rate of severe adverse events was similar in the two groups.

During the 2017 annual ASH meeting, Döhner et al. presented a subgroup analysis of the RATIFY study evaluating the prog-

---

### TABLE 1. Revised risk stratification criteria for children with newly diagnosed AML

<table>
<thead>
<tr>
<th>High Risk Prognostic Markers</th>
<th>Low Risk Prognostic Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECOM (3q26.2)</strong></td>
<td>t(8;21)(q22;q22)</td>
</tr>
<tr>
<td>- inv(3)(p14q26)</td>
<td>inv(16)/t(16;16)(p13.1q22)</td>
</tr>
<tr>
<td>- t(3;3)(p21;q26.2)</td>
<td><strong>NPM1</strong> positive</td>
</tr>
<tr>
<td>- t(3;21)(p26.2;q22)</td>
<td><strong>CEBPA</strong> positive</td>
</tr>
<tr>
<td>- t(3;5)(q25;q34)/(NPM1-MLF1)</td>
<td><strong>KMT2A(MLL)</strong> (11q23.3)</td>
</tr>
<tr>
<td>t(6;9)(p23;q34.1) [DEK-NUP214]</td>
<td>- t(4;11)(q21;q23)</td>
</tr>
<tr>
<td>Monosomy 7</td>
<td>- t(6;11)(q27;q23)</td>
</tr>
<tr>
<td>Monosomy 5/5q-[EGR1(5q31) deleted]</td>
<td>- t(10;11)(p11.2;q23)</td>
</tr>
<tr>
<td><strong>KMT2A(MLL)</strong> (11q23.3)</td>
<td>- t(10;11)(p12;q23)</td>
</tr>
<tr>
<td>- t(11;19)(q23;p13.3)</td>
<td>- t(11;11)(q23;q23)</td>
</tr>
<tr>
<td><strong>NUP98</strong> (11p15.5)</td>
<td><strong>RBM15-MKL1</strong></td>
</tr>
<tr>
<td>- t(7;11)(p15;p15)</td>
<td></td>
</tr>
<tr>
<td>- t(5;11)(q35.3;p15)(cryptic)</td>
<td></td>
</tr>
<tr>
<td>- t(X;11)(q28;p15) [NUP98-HMGB3]</td>
<td></td>
</tr>
<tr>
<td>- t(2;11)(q31;p15) [NUP98-HOXD13]</td>
<td></td>
</tr>
<tr>
<td>12p abnormalities (ETV6)</td>
<td></td>
</tr>
<tr>
<td>- 12p loss or rearrangement</td>
<td></td>
</tr>
<tr>
<td>- t(7;12)(q36;p13)</td>
<td><strong>Standard Risk assignment/MRD negative at end of 1st induction</strong></td>
</tr>
</tbody>
</table>

---

29
nostic impact of NPM1/FLT3-ITD genotypes on the outcome. This analysis included data from 438 patients who gave informed consent for biomarker analyses and who could be categorized to one of the 4 ELN NPM1/FLT3-ITD subgroups: NPM1mut/FLT3-ITDlow (N= 85), NPM1mut/FLT3-ITDhigh (N=159), NPM1wt/FLT3-ITDlow (N= 75), and NPM1wt/FLT3-ITDhigh (N= 109). The OS was shown to be significantly different among the 4 groups (p= 0.001). The median OS times was not reached, 27 months, 20 months and 17 months for NPM1mut/FLT3-ITDlow, NPM1mut/FLT3-ITDhigh, NPM1wt/FLT3-ITDlow, and NPM1wt/FLT3-ITDhigh patients, respectively. This effect was even more pronounced when censoring patients at the time of allogeneic hematopoietic cell transplantation (allo SCT). Similar to OS, non-censored EFS significantly differed among the 4 groups (p= 0.001); median EFS times were 16, 8, 4, and 4 months for NPM1mut/FLT3-ITDlow, NPM1mut/FLT3-ITDhigh, NPM1wt/FLT3-ITDlow, and NPM1wt/FLT3-ITDhigh patients, respectively.

A second (unplanned) analysis of the RATIFY study presented at ASH 2017 sought to evaluate the contribution of the maintenance treatment to the overall outcome. A complete response (CR) was achieved within the protocol-specified 60 days (CR60) by 403 patients in the study (36%) with no significant difference between arms (59% on midostaurin arm 54% on placebo). In total, 174 of the 403 CR60 patients began maintenance therapy still in CR1. Overall, the maintenance therapy was well tolerated, and the median duration of exposure was similar in both arms (336 days). Discontinuation due to adverse events was infrequent (8% for midostaurin; 6% for placebo). Using a landmark analysis, the disease-free survival (DFS) was not different between the 2 arms during the 12 cycles of maintenance (HR[95%CI]: 0.83[0.48-1.43]; p= 0.49). There were 16 post-maintenance DFS events (all relapses) on the midostaurin arm and 9 DFS events on the placebo arm (7 relapses, 2 deaths). Using a landmark analysis from the end of maintenance, there was no difference in DFS between the 2 arms (HR[95%CI]: 1.4 [0.63-3.3]; p= 0.38). The DFS at 1-year from the end of maintenance was 75% for midostaurin and 91% for placebo. Overall, midostaurin was well-tolerated, but the definitive impact of maintenance strategies with midostaurin will need to be addressed by randomization.

Next to midostaurin, several other, selective, FLT3 inhibitors are under development. In a study including patients aged ≥60 years with FLT3 mutated AML, induction treatment with cytarabine/anthracycline and the selective FLT3-inhibitor crenolanib, resulted in a CR in 24/29 (83%) patients. With a median follow up of 14 months, only one systemic and one isolated CNS relapse occurred in these 24 patients who achieved a CR. These data suggest that adding crenolanib to standard induction chemotherapy in younger patients with FLT3-mutated AML may be associated with a low relapse rate, especially if SCT is routinely used. A phase 3 trial of crenolanib in combination with 7+3 vs. midostaurin in combination with 7+3 is being initiated. ASH 2017 also featured an interim report of a phase I/II trial evaluating the combination of the FLT3-inhibitor quizartinib with azacitidine or low dose cytarabine (LDAC) in FLT3-ITD mutated myeloid leukemias (patients age >60 years with untreated MDS/CMMML/AML or any age receiving first salvage treatment for AML with FLT3-ITD). In total, 61 (phase I: 12, phase II: 49) patients with a median age of 68 years have been enrolled: 38 to the azacitidine arm and 23 to the LDAC arm. Forty-three patients (14 in LDAC arm [67%] and 29 in the azacitidine arm [76%]) of the 59 evaluable patients responded with an overall response rate (ORR) of 73% (CR: 10, CRp: 6, CRi: 20, PR: 2). In total, 5 patients (12%) were MRD negative. Twelve patients were previously untreated and 11 of them responded (ORR 92%). At a median follow-up of 20 months, 11 of the 43 responders remain in CR: 6 had a stem cell transplantation (SCT), 4 are continuing study therapy and 1 discontinued due to insurance issues. In summary, the combination of quizartinib and azacitidine or LDAC is highly active in AML patients with a FLT3-ITD mutation.

Finally, preliminary phase I results of a study evaluating the FLT3-inhibitor gilteritinib in combination with induction and consolidation chemotherapy were presented. Gilteritinib was combined with 7+3 induction and high-dose cytarabine (HiDAC) consolidation, and was administered as single-agent maintenance therapy in 50 patients aged ≥18 years with newly diagnosed AML. The median age in the study was 59 years and 23 patients harbored a FLT3 mutation (15 with an ITD). In this study, a complete CR rate (Cr + CRp + CRi) of 71.5% was reported (91.3% in FLT3-mutant patients, 56% in the FLT3-wildtype cohort). For the total study population, the median EFS was 327 days with a median DFS of 297 days. Of note, FLT3-mutant subjects had a longer median EFS (327 days) and DFS (134 days) than FLT3-wildtype patients (EFS, 80 days; DFS, not estimable).

IDH1/2 mutations in AML

Approximately 10% of patients with newly diagnosed AML harbor mutations in IDH1 or IDH2. Typical mutation hotspots are IDH1R132, IDH2R172, IDH2R172 and IDH1/2 mutations are enriched in patients with a normal karyotype. The prognostic impact of these mutations is currently controversial. Enasidenib (AG-221/CC-90007) is a first-in-class, oral, selective inhibitor of mutant-IDH2 enzymes. In a first-in-human phase 1/2 study, enasidenib 100 mg once daily was selected...
for the expansion phase based on pharmacokinetic and pharmacodynamic profiles and demonstrated efficacy. Grade 3 to 4 enasidenib-related adverse events included indirect hyperbilirubinemia (12%) and IDH-inhibitor-associated differentiation syndrome (7%). Among patients with relapsed or refractory AML, the ORR was 40.3%, with a median response duration of 5.8 months. Responses were associated with cellular differentiation and maturation, typically without evidence of aplasia. The median OS among relapsed/refractory patients was 9.3 months, and for the 34 patients (19.3%) who attained complete remission, the OS was 19.7 months. During ASH 2017, specific data were presented on the clinical outcomes for older patients with previously untreated IDH2-mutant AML who received enasidenib monotherapy. Of the 239 patients in the phase 1 dose-escalation and study expansion, 37 patients (15.5%) had previously untreated IDH2-mutant AML. In total, seven patients (19%) attained a CR, with a median time to CR of 5.6 months. The ORR in the study was 37.8%. The median duration of CR was not reached, while the median duration of any response was 12.2 months. Three patients proceeded to transplant; at data cutoff, all 3 patients remained in remission. Among all 37 patients, the median OS was 10.4 months and the median EFS was 11.3 months. Among responding patients, the median OS was 19.8 months as compared to 5.4 months for non-responders. The most frequent treatment emergent adverse event (TEAEs) were fatigue (43%), nausea (41%), and decreased appetite (41%). The most frequent TEAEs were hyperbilirubinemia (30%) and nausea (22%). The only serious TEAEs reported in more than 1 patient were IDH differentiation syndrome (N=3, 8%) and tumor lysis syndrome (N=2, 5%).

Ivosidenib (AG-120) is a potent, selective, oral, small-molecule inhibitor of the mutant IDH1 protein and represents a promising therapeutic candidate for the treatment of patients with IDH1-mutant AML. In a presented phase I study, 258 patients with relapsed/refractory, or untreated AML and other advanced hematologic malignancies including myelodysplastic syndrome received ivosidenib as a single agent orally once daily (QD) or twice daily (BID) in 28-day cycles. In this trial, differentiation syndrome was observed in 29 of 258 (11.2%) patients. Among patients with relapsed/refractory AML, the CR + CRh rates reached 30.4%. Finally, Dinardo et al. reported the results of a phase Ib/II study evaluating enasidenib, or ivosidenib in combination with azacitidine in patients with newly diagnosed AML. In

![FIGURE 1. Significantly longer OS with midostaurin plus chemotherapy than with placebo-chemotherapy in FLT3-positive AML.](image-url)
this study, both combinations were generally well tolerated, with 10 of the initial 13 patients remaining on-study at data cutoff, and only 2 discontinuations due to disease progression.12

Other emerging therapeutic strategies in AML

Flotetuzumab is a novel T-cell redirecting (CD123 x CD3) bispecific DART® protein. In a phase 1 study in 45 patients with relapsed/refractory AML and MDS (89% AML and 11% MDS) flotetuzumab demonstrated a manageable toxicity, with infusion-related reaction/CRS (IRR/CRS) as the most common toxicity (76%, grade 3 in 13%). Fourteen patients were treated with at least 500 mg/kg/day dose and completed at least one cycle of treatment and had a post-treatment bone marrow biopsy. Anti-leukemic activity was documented in 57% (8/14) patients. In total, 6 patients reached IWG criteria (3 CR, 1 CRi, 1 MLF, 1 PR) for an ORR of 43%. Two additional patients had stable disease and bone marrow (BM) blast reduction of 20% and 25% from baseline, respectively.13

CD123-chimeric antigen receptor (CAR) T-cell therapy previously demonstrated preclinical activity in AML. The CD123 CAR contains an anti-CD123 single-chain variable fragment, an optimized IgG4 CH2CH3 linker, a CD28 co-stimulatory domain, and a CD3 zeta signaling domain. In the study at hand, donor-derived or autologous T-cells from leukapheresed peripheral blood mononuclear cells were lentivirally transduced with the CD123 CAR vector. Prior to the T-cell infusion, all patients underwent a lymphodepleting regimen including fludarabine (25-30 mg/m² daily for 3 days) and cyclophosphamide (300 mg/m² daily for 3 days). Patients then received a single dose of CD123 CAR T-cells with an option for a second infusion. In total, 14 patients have been enrolled and 7 were treated (6 AML cases and 1 case of blastic plasmacytoid dendritic cell neoplasm [BPDCN]). This first-in-human clinical trial of CD123 CAR T-cell therapy demonstrated the feasibility and safety of targeting CD123. In addition, promising anti-leukemic activity was seen in both AML and BPDCN. Importantly, no myeloablative effects have been observed.14

Venetoclax: In a single center study, the combination of venetoclax with azacitidine was evaluated in untreated, elderly AML patients who were unfit for induction chemotherapy. In total, 33 patients were enrolled and received at least 1 day of therapy. After a median follow up time of 351 days, the ORR (CR + CRi + PR + morphologic leukemia free state [MLFS]), was 30/33 (91%) with 19 patients (58%) having a CR, 9 (27%) with a CRi, 1 patient with a PR and 1 obtaining a MLFS. Of note, all five patients with a monosomal karyotype and all patients with a FLT3 or TP53 mutation (N=7) responded. Three patients proceeded to SCT and none relapsed after 14, 8 and 4 months. The median response duration was not yet reached (mean 484 days), while the median PFS was 294 days.15

A second AML study with venetoclax evaluated the combination with low dose cytarabine (LDAC) in 71 elderly AML patients (at least 65 years) who were unfit for intensive chemotherapy. The median age of patients in the study was 74 years. Ten received venetoclax at a dose of 800 mg and 61 received it at a lower 600 mg dose. In total, 38 patients (62%) achieved CR/CRi with a median duration of CR/CRi of 14.9 months. The median OS was 11.4 months, with a 12-month OS rate of 46%. The safety profile of the combination was acceptable.16 Currently, the 600 mg dose of venetoclax combined with LDAC is being tested in an ongoing phase 3 study.

Nivolumab: PD-1 positive CD8 T-cells are increased in the bone marrow of patients with AML and PD-1 inhibition has previously shown activity in AML. During ASH 2017, results were presented of a phase 2 study testing the combination of cytarabine, idarubicin, and nivolumab as initial therapy for patients with newly diagnosed AML and high-risk MDS. The treatment included 1 or 2 induction cycles of ara-C 1.5 g/m² over 24 hours (days 1-4) and idarubicin 12 mg/m² (days 1-3). Nivolumab at a dose of 3 mg/kg was started on day 24 ± 2 days and was continued every 2 weeks for up to a year. In total, 32 patients with a median age of 53 were treated of whom 23 (72%) achieved a CR/CRi (19 CR, 4 CRi). Nine patients underwent an allo SCT. As such, adding nivolumab to ara-C and anthracycline induction chemotherapy was shown to be feasible and safe in younger patients with AML. Of note, among patients proceeding to alloSCT the risk of GVHD was not significantly increased.17

Selinexor induces cell cycle arrest, inhibits DNA damage repair and modulates the expression of NF-κB in cancer cell lines. It has demonstrated broad activity across several hematologic malignancies including AML. Selinexor was tested in combination with chemotherapy in patients with relapsed or refractory AML, between 18-70 years of age. Selinexor 60 mg/d was administered on days 1, 5, 10, and 12 in combination with CLAG, (cladribine 5 mg/m²/d on d4-8, cytarabine 2000 mg/m²/d on d4-8 and G-CSF 300 mcg/d on d3-8). In this study, 30 patients with a median age of 56 years have been enrolled. The cumulative CR rate among 28 evaluable patients was 50%, (7 CR, 7 CRi). Of the initial 25 patients treated, 15 underwent a subsequent alloSCT (60%). As such, selinexor + CLAG is highly active in patients with relapsed or refractory AML and has encouraging rates of CR. Furthermore, the combination serves as a bridge which allows a high percentage of patients to undergo an allo SCT.18
Maintenance azacitidine in elderly AML patients

The prevention of relapse is the major therapeutic challenge in older patients with AML who have obtained a CR on intensive chemotherapy. There is no established post-remission treatment for the prevention of relapse in this setting, except allo SCT. HOVON97 is a randomized phase III study in older patients (≥60 years) with AML or MDS-RAEB in CR/CRi after at least 2 cycles of intensive chemotherapy that evaluates the value of azacitidine as post remission therapy (in comparison to observation) with respect to DFS (primary endpoint) and OS (secondary endpoint). In total 117 patients were randomly assigned to either observation or azacitidine maintenance (50 mg/m², s.c., day 1-5, q4 weeks), until relapse for a maximum of 12 cycles. The difference in DFS between the two arms was statistically significant in the cohort of patients in this pre-final analysis (p=0.005). The 12-month DFS rate was estimated at 39% for the control group and at 63% for the azacitidine group (Figure 2). The difference in OS between the two groups was not statistically significant at the time of the analysis (p=0.35). The 12-month OS rate (after censoring allo SCT) was estimated at 64% for the control group and at 83% for the azacitidine group. A planned subgroup analysis (CR vs. CRi at inclusion) revealed that patients with a platelet count ≥100 x 10⁹/L had a significantly better OS with azacitidine maintenance treatment (logrank p=0.01).¹⁹

RELEVANCE OF MINIMAL RESIDUAL DISEASE (MRD) IN AML

WT1 overexpression is frequently identified in AML and has been reported as a potential marker for MRD monitoring. However, the role of WT1 MRD response as prognostic and/or treatment stratifying factor is still under debate. In a study reported by Lambert et al. the prognostic value of the post-induction WT1 MRD level, as well as the interaction between post-induction WT1 MRD response and the effect of allo SCT in first CR was evaluated in a cohort of AML patients aged 18 to 59 years old. In total, 539 of the 713 patients enrolled in ALFA-0702 study had an overexpression of WT1 at diagnosis (75.6%). After induction therapy, 473 patients achieved a CR (87.7%). Post-induction WT1 MRD evaluation was available in 339 of these patients (71.7%): 279 patients were MRD negative and 60 were MRD positive. The analysis revealed that post-induction MRD response remained of strong prognostic value. At 4 years, the RFS was 60.9% vs. 24.9% (HR[95%CI]: 2.69[1.89-3.83]; p< 0.001) and the

![FIGURE 2. Significantly longer DFS with azacitidine maintenance versus observation in the HOVON97 study.¹⁹)](https://example.com/figure2.png)

---

OS rate was 71.6% vs. 43.3% (HR[95%CI]: 2.34[1.56-3.51]; p< 0.001) in MRD negative and MRD positive patients, respectively. The study further showed that early WT1 MRD response retained its prognostic value among patients independently of allo SCT in first CR. The prospective RELAZA2 trial evaluated MRD-guided treatment with azacitidine in MDS/AML patients at imminent risk of relapse. In total, 205 patients with either advanced MDS (N=27) or AML (N=178) in CR after either conventional chemotherapy only (N=58) or after consecutive allogeneic SCT (N=147) have been prospectively studied in 11 centers in Germany. Monthly MRD monitoring in bone marrow or peripheral blood was performed after completion of the last therapy. 53 out of 205 (26%) patients became MRD positive while being in hematological CR and started an azacitidine-based pre-emptive treatment. Six months after the start of the MRD-guided therapy, 31 out of 53 patients were still in CR, while a total of 22 patients (42%) relapsed after a median of 3 azacitidine cycles. Twenty-one patients (40%) responded with a decline of MRD, while a stabilization in the absence of relapse was achieved in 10 patients (19%). After a median follow-up of 13 months, the OS and PFS rates were 76% and 42%, respectively. As such, pre-emptive MRD-guided therapy with azacitidine can prevent or substantially delay hematologic relapse in patients with MDS and AML at high-risk of relapse.

AML12 is a prospective, risk-adapted phase II trial of intensive chemotherapy followed or not by auto or allo SCT based on genetic data and MRD status. The study included 500 patients with primary AML with a median age of 55 years. Induction chemotherapy consisted of 3+7 idarubicin (12 mg/m²) and cytarabine (200 mg/m²) and was followed by consolidation courses with high-dose cytarabine. The CR rate was 75% (N=374). An auto or allo SCT was performed depending on MRD levels after consolidation. In total, 133 (38%) patients were in the genetics-MRD favorable category (FR), 81 (24%) had an intermediate risk (IR) score and 129 (38%) were classified as high risk (AR). Of the AR patients, 94 (73%) received an allo SCT in first CR. Ten patients (4%) moved from the FR or IR group to the AR group because of high MRD. Nine patients from the FR became MRD positive during follow-up and all were allografted. RFS rates at 4 years were 77% in the FR group, 40% in the IR and 36% in the AR group (due to significantly different cumulative relapse incidence: 18%, 43% and 46%, respectively). This study shows that risk adapted therapy for primary AML based on genetics and MRD is feasible. The proportion of patients in whom the risk of an allo SCT in first CR may be avoided is 38% when considering cytogenetics, molecular findings and MRD information after the end of consolidation. MRD assessment at the end of consolidation moved 4% of patients from FR and IR to AR. Allo SCT in AR patients was feasible in most instances, even in the AR group. Despite this, relapses remain above 40% in the intermediate and adverse AML categories and further approaches after transplant, such as novel agents and immune therapy deserve investigation. A late breaking abstract presented at ASH 2017 defined prospective molecular MRD detection by next generation sequencing (NGS) as a powerful independent predictor for relapse and survival in adults with newly diagnosed AML. In the HOVON-SAKK clinical trials, 482 AML patients (<65 years) were treated with 2 cycles of standard induction chemotherapy followed by consolidation. NGS was performed to detect mutations in a panel of 54 genes frequently mutated in myeloid malignancies (Illumina) at diagnosis and in bone marrow in morphological CR after completion of induction therapy. In 430 out of 482 (89.2%) AML patients, somatic driver mutations were found to be present at diagnosis. In 51.4% of subjects, persisting mutations were detected in bone marrow in morphological CR. The most prominent persisting mutations were seen in in DNMT3A (78.7%), TET2 (54.2%) and ASXL1 (51.6%), but these mutations did not associate with the incidence of relapse. This indicates a stage of clonal hematopoiesis rather than a condition of impending relapse. In contrast, in the subset of AML patients with persisting DTA mutations, a significant correlation with relapse was observed when any other persistent non-DTA mutation was considered. A multivariable analysis including the data of all 430 AML patients revealed that NGS MRD expresses profound independent prognostic significance for RFS (HR[95%CI]:1.89[1.34-2.63]; p< 0.001) and OS (HR[95%CI]:1.64 [1.18-2.27]; p= 0.003). ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) PH+ ALL During ASH 2017, the first results of the GIMEMA LAL1811 phase II study were presented. This is a prospective study evaluating the combination of steroids with ponatinib as frontline therapy for elderly or unfit patients with Ph+ ALL. In this study, 44 patients with untreated Ph+ ALL, older than 60 years or unfit for intensive chemotherapy and stem cell transplantation, were treated with ponatinib (45 mg/day) for 8 consecutive courses of 6 weeks. Steroids were administered from day -14 to day 29 during course 1 and intrathecal therapy with methotrexate, cytarabine and dexmethasone was performed every 28 days for central nervous system (CNS) disease prophylaxis. A complete hematologic response (CHR) was obtained in 40/42 patients (95.2%) after one course. Thirty-eight out of 42 patients (90.5%)
were still in CHR after 8 courses (after 24 weeks). A complete molecular response (CMR) was detected in 11/24 patients at week 24 (45.8%; 14/38 patients not evaluable). Considering a CMR test sensitivity of at least 10,000 ABL molecules and testing peripheral blood whenever a bone marrow was not obtained, 20/33 patients (60.6%; 5/38 patients not evaluable) were in CMR at week 24. The median follow-up of the enrolled patients was 11.4 months (range 6-34.5). The OS rates at 6 months and at 1 year were 97.6% and 87.5%, respectively. As such, ponatinib plus steroids shows a high efficacy in newly diagnosed unfit/elderly Ph+ ALL patients. Toxicities were manageable and cardiovascular AEs were limited. In the small cohort of patients who relapsed in the study, relapse mechanisms were unclear. Only one patient had evidence of mutations that caused resistance to ponatinib.

Inotuzumab ozogamicin is a CD22 monoclonal antibody bound to calicheamicin that was shown to be active in

<table>
<thead>
<tr>
<th>Study outcome measures</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall CR/CRh/CRi rate</td>
<td>119/271</td>
<td>43.9</td>
</tr>
<tr>
<td>Patients receiving blinatumomab maintenance</td>
<td>27/119</td>
<td>22.7</td>
</tr>
<tr>
<td>Best response during maintenance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>21/27</td>
<td>77.8</td>
</tr>
<tr>
<td>CRh</td>
<td>1/27</td>
<td>3.7</td>
</tr>
<tr>
<td>Blast-free hypoplastic/aplastic BM</td>
<td>1/27</td>
<td>3.7</td>
</tr>
<tr>
<td>Hematological relapse</td>
<td>2/27</td>
<td>7.4</td>
</tr>
<tr>
<td>Non-evaluable</td>
<td>2/27</td>
<td>7.4</td>
</tr>
</tbody>
</table>

**FIGURE 3.** Response to blinatumomab maintenance in the phase III TOWER trial (top) and OS according to maintenance status (bottom).
relapsed/refractory ALL. Bosutinib in the other hand is a tyrosine kinase inhibitor (TKI) that is approved for the treatment of chronic, accelerated, or blast phase CML with resistance or intolerance to prior therapy. In a phase I/II study, Jain et al. combined these two agents in the treatment of patients with Ph+ ALL and CML in lymphoid blast phase (LBPH).

In the phase I part of this trial, three dose levels of bosutinib were evaluated (300 mg daily, 400 mg daily, and 500 mg daily). Bosutinib was initiated on cycle 1 day 1 and was continued daily. Inotuzumab was administered IV weekly during cycle 1 (0.8 mg/m² day 1; 0.5 mg/m² day 8; 0.5 mg/m² day 15). For patients achieving a response, the subsequent cycles of inotuzumab (1 mg/m²) were given once every 4 weeks. A total of 6 cycles of inotuzumab were planned. Fourteen patients with a median age of 62 years were treated in the study (12 with Ph+ ALL and 2 with CML LBPH). Eleven patients (79%) had a CR/CRi and ten of the responders (91%) achieved a complete cytogenetic remission. Eight responders (73%) were negative by flow-cytometry and 6 (55%) achieved undetectable BCR-ABL levels. The median EFS and OS were 8.1 and 8.2 months, respectively. Five patients underwent a subsequent allo SCT (+ of these are alive and in remission post-SCT).²⁵

IMMUNOTHERAPY

A recent randomized phase 3 study of blinatumomab (TOWER), a bispecific T-cell engager antibody construct, in patients with relapsed/refractory Ph- B-precursor ALL, included a maintenance treatment phase to allow patients in hematologic remission to continue blinatumomab. In an exploratory analysis presented at ASH 2017, Rambaldi et al. examined the OS for patients who received blinatumomab maintenance therapy and compared outcomes with data from patients who did not receive maintenance therapy in the phase 3 and phase 2 blinatumomab trials.²⁶ In TOWER, adult patients were randomized to either blinatumomab or standard of care chemotherapy. Patients randomized to blinatumomab received this treatment by continuous intra- venous infusion (4 weeks on, 2 weeks off; 9 μg/day on days 1-7 of Cycle 1 and 28 μg/day thereafter) during induction and consolidation cycles. Patients could receive an SCT at any time after cycle 1. Patients who received blinatumomab, and had bone marrow blasts <5% after two induction and three consolidation cycles of blinatumomab, were eligible for blinatumomab maintenance, administered for up to an additional 12 months (4 weeks on therapy, 8 weeks off). Maintenance therapy was discontinued in case of transition to SCT, investigator discretion, toxicity, relapse, or use of protocol-excluded medications. At data cut-off, 119 of 271 (43.9%) patients receiving blinatumomab achieved a best response of CR/CRh/CRi within two treatment cycles, and 27 patients continued to the blinatumomab maintenance phase. Three patients completed the maintenance phase, 4 transitioned to SCT, and one discontinued due to adverse events (AE). Overall, 21 (77.8%) patients had a best response of CR during maintenance, 1 (3.7%) patient each had CRh or blast free hypoplastic or aplastic bone marrow, and 2 (7.4%) patients each had hematologic relapse or were not evaluable. The relative OR for OS was calculated at 0.59 (95%CI: 0.20 – 1.73) comparing maintenance vs. no maintenance (p=0.33). This represents a 41% reduction in the risk of death associated with maintenance therapy, but this was not statistically significant. Among patients receiving blinatumomab who entered the maintenance phase, the incidence of adverse events of interest was generally lower than the incidence seen during the induction or consolidation phases.

REFERENCES

19. Huis G, Chitu D, Havelange V, et al. Randomized Maintenance Therapy with Azacitidine (Vidaza) in Older Patients (≥ 60 years of age) with Acute Myeloid Leukemia (AML) and Refractory Anemia with Excess of Blasts (RAEB, RAEB-1). Results of the HOVON97 Phase II Randomized Multicentre Study (EudraCT 2008-001290-15). Presented at ASH 2017; Abstract 463.
22. Sierra J, Garrido A, Vives S, et al. Therapy for Acute Myeloid Leukemia (AML) Adjusted to Genetic Data and Minimal Residual Disease: Results of the AML2 Trial of the Spanish Cetlam Group in Adults up to the Age of 70 Years. Presented at ASH 2017; Abstract 567.