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Letter
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# Palbociclib in Acute Leukemias With *KMT2A*-rearrangement: Results of AMLSG 23-14 Trial

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Rearrangements of the *histone-lysine-N-methyltransferase* (*KMT2A*) gene, formerly known as *MLL*, belong to the most frequent chromosomal aberrations with a high number of different fusion partners in patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL).[1,2] AML with t(9;11)(p21.3;q23.3) is recognized as a disease entity.[2] Similarly, the presence of t(4;11)(q21.3;q23.3), which accounts for 8%–10% of B-cell precursor ALL in patients aged >20 years, defines a distinct entity termed B-lymphoblastic leukemia with t(v;11q23).[2,3] AML with t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A* are classified in the intermediate-risk category according to the 2017 and 2022 European LeukemiaNet risk stratification, but the remaining t(v;11q23.3)/*KMT2A*-rearranged AML belong to the adverse-risk group and these leukemias still represent an unmet medical need[1,4–6] given the poor long-term survival depending on the *KMT2A* fusion partner, presence of additional risk factors (eg, age), and postremission treatment.[1]

Using a functional genomic approach indicated that *KMT2A*-rearranged AML cells rely on cyclin-dependent kinase 6 (CDK6) in order to maintain an immature phenotype supporting the hypothesis that catalytic activity of CDK6 is essential for the dependence of *KMT2A*-rearranged AML cells on CDK6 expression.[7] Similar results were observed in *KMT2A*-rearranged ALL cells.[8] These data provided the rationale for a clinical trial with the CDK4/6 inhibitor palbociclib in patients with *KMT2A*-rearranged acute leukemias. Palbociclib is approved by the European Medicines Agency for the treatment of locally advanced or metastatic hormone receptor positive, human epidermal growth factor (HER2)-negative breast cancer.

We here report the results from a prospective, single-arm, open label, multicenter phase Ib/IIa trial (AMLSG 23-14; EudraCT Number 2014-003647-34) of palbociclib in adults with acute leukemia and *KMT2A*-rearrangement conducted by the German-Austrian AML Study Group (AMLSG). Overall, up to 62 patients were planned to be recruited over a period of 2 years, 6–18 patients in the dose-finding phase Ib part to determine the recommended dose for the phase IIa part, and up to 50 patients in the phase IIa part (including 6 patients with the recommended dose from phase Ib). For the phase Ib part, a 3+3 modified Fibonacci design was used with the starting dose level 0 of 125 mg of investigational medicinal product (IMP) palbociclib. This dose of palbociclib corresponds to the standard dose established once daily for 21 days in a 28-day cycle for patients with breast cancer. The recommended dose for the phase IIa of the study was defined as the dose level with maximally 1 of 6 patients with a dose-limiting toxicity (DLT). In case 2 or more, DLTs were observed during this phase Ib of the study, and de-escalation with the following dose levels were intended: 100 mg and 75 mg. The primary objective of the phase IIa phase was to assess the overall response rate to palbociclib, including complete remission (CR), complete remission with incomplete hematologic recovery (CRi), partial remission (PR), and antileukemic efficacy (ALE). The phase IIa phase was planned according to the Simon's optimal 2-stage design with the null hypothesis that the true CR/CRi/PR/ALE rate is ≤0.10, whereas sample size is chosen to achieve a power of 90% to reject the null hypothesis at a true response rate of at least 25%. Therefore, the study is stopped for futility of the investigational therapy after the first stage of 21 treated patients, if 2 or less patients achieved CR,

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CRi, PR, or ALE. If 3 or more patients achieve CR, CRi, PR, or ALE during this first stage, the trial is continued in the second stage with a total sample size of 50 patients.

Treatment duration was estimated between 2 and 6 months, but was not limited in patients with sustained response. Response assessment including bone marrow aspiration was intended after each treatment cycle on day 29 during the first 3 cycles and thereafter every 3 months and at the investigator's discretion.

Overall, 18 patients were recruited between July 2015 and August 2019 at 7 of 25 participating sites of AMLSG in Germany and Austria. Eight of the 18 patients were included in the phase Ib dose-finding part of the trial (2 of them died before starting treatment and, hence, needed to be replaced); additional 10 patients were enrolled in phase IIa. None of the patients received hydroxyurea for cytoreduction before the start of treatment with IMP or while on treatment with IMP. No DLT was observed, neither for the first 3 patients nor for 3 additional patients within the first-dose level in phase Ib part. Therefore, no dose reduction had to be performed and the recommended dose for the expansion phase of study was defined as 125 mg.

**Table 1**

**Baseline and Disease Characteristics of the 18 Patients Enrolled in AMLSG 23-14 Trial**

| Variable | |
|---|---|
| Sex, n (%) | |
| Male | 7 (39) |
| Age (years), median (range) | 64 (21–79) |
| Status of disease at baseline, n (%) | |
| Newly diagnosed | 3 (17) |
| Refractory | 1 (6) |
| Relapsed | 14 (78) |
| 1. relapse | 7 (50) |
| 2. relapse | 5 (36) |
| 3. relapse | 2 (14) |
| Type of leukemia, n (%) | |
| AML | 15 (83) |
| ALL | 3 (17) |
| Type of AML, n (%) | |
| *De novo* AML | 9 (60) |
| Secondary AML after AHD | 1 (7) |
| Treatment-related AML | 5 (33) |
| ECOG performance score, n (%) | |
| 0 | 3 (17) |
| 1 | 10 (56) |
| 2 | 5 (28) |
| *KMT2A-re*arrangement at baseline | |
| t(4;11)(q21.3;q23.3)/*AFF1::KMT2A* | 3 (17) |
| t(6;11)(q27;q23.3)/*AFDN::KMT2A* | 2 (11) |
| t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A* | 7 (39) |
| t(10;11)(p12.3;q23.3)/*MLLT10::KMT2A* | 0 |
| t(11;17)(q23.3;q25.3)/*KMT2A::SEPT9* | 1 (6) |
| t(11;19)(q23.3;p13.1)/*KMT2A::ELL* | 0 |
| t(11;19)(q23.3;p13.3)/*KMT2A::MLLT1* | 3 (17) |
| t(1;11)(p32.3;q23.3)/*EPS15::KMT2A* | 2 (11) |
| HCT-CI score (points), median (range) | 1 (0-4) |
| Hemoglobin (g/dL), median (range) | 10.8 (7.1–13.5) |
| Platelets (G/L), median (range) | 56 (14–284) |
| White blood count (G/L), median (range) | 7.6 (1–143.6) |
| BM blasts (%), median (range) | 70 (7–95) |
| PB blasts (%), median (range) | 19 (0–84) |

AML = acute myeloid leukemia; ALL = acute lymphoblastic leukemia; AHD = antecedent hematologic disorder; AMLSG = AML Study Group; ECOG = Eastern Cooperative Oncology Group; HCT-CI = Hematopoietic Cell Transplantation-specific Comorbidity Index; BM = bone marrow; PB = peripheral blood.

Baseline clinical and disease characteristics are given in Table 1. There were 7 male (39%) and 11 female (61%) patients; the median age of the study cohort was 64 years (range, 21–79 years). Three patients (17%) had ALL and 15 (83%) AML. Among the latter, 9 patients had *de novo* AML, 5 patients treatment-related AML, all after treatment of breast cancer, and there was 1 patient with secondary AML. Three (17%) patients had a newly diagnosed disease, 14 (78%) patients relapsed disease, and 1 (6%) patient refractory disease. The following *KMT2A*-rearrangements were documented at study entry: t(9;11)(p21.3;q23.3) *MLLT3::KMT2A* [n = 7 (39%)], t(11;19)(q23.3;p13.3) *KMT2A::MLLT1* [n = 3 (17%)], t (4;11)(q21.3;q23.3) *AFF1::KMT2A* [n = 3 (17%)], t (6;11)(q27;q23.3) *AFDN::KMT2A* [n = 2 (11%)], t(1;11)(p32.3;q23.3) *EPS15::KMT2A* [n = 2 (11%)], t(11;17)(q23.3;q25.3) *KMT2A::SEPT9* [n = 1 (6%)].

Patients received median 2 cycles of therapy (range, 1–6; Table 2; Suppl. Figure S1). With regard to response to the therapy (Suppl. Table S1; Table 2), 1 patient achieved a CRi after 2 cycles, 1 patient a PR, and 8 patients a stable disease. Six patients had a progressive disease (PD). There was no bone marrow blast reduction in nonresponding patients observed. Only 1 of the 16 patients completed study according to the protocol with 6 cycles; the other 15 patients were prematurely withdrawn due to the following reasons: PD (n = 10), death (n = 2), withdrawal of informed consent for the trial (n = 1), investigator decision (n = 1), and hematopoietic cell transplantation (HCT, n = 1). Two patients died before start of the first treatment cycle. The median overall survival was 2.7 months (Figure 1; range, 9 days to 20.4 months). Three patients died during study treatment (PD, n = 2; suicide, n = 1). The other 13 patients died during the follow-up period. After inclusion of 16 patients during phase IIa, the trial was terminated prematurely due

**Table 2**

**Response to Palbociclib Therapy Within AMLSG 23-14 Trial (Patients Who Started With Study Treatment, n = 16)**

| Outcome | |
|---|---|
| CR, n (%) | 0 |
| CRi, n (%) | 1 (6) |
| PR, n (%) | 1 (6) |
| SD, n (%) | 8 (50) |
| PD, n (%) | 6 (38) |
| Treatment duration, median (range) | 2 cycles (1–6) |
| Discontinuation of treatment, n (%) | 15 (93.8) |

CR = complete remission; CRi = complete remission with incomplete hematologic recovery; AMLSG = AML Study Group; PR = partial remission; SD = stable disease; PD = progressive disease.

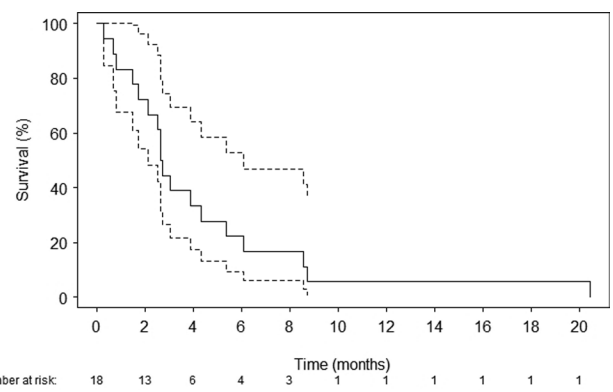


**Figure 1. Kaplan-Meier plot for overall survival of all enrolled patients.**

to a very slow recruitment, which remained behind the initial projections to complete the trial successfully. Thus, response rate was analyzed descriptively, but further analyses reflecting primary and secondary efficacy end points as planned within the protocol were not performed. One reason for the low recruitment might be the patient population itself as adult patients with refractory/relapsed acute leukemias with *KMT2A*-rearrangement are rare; most of the patients have already received an allogeneic HCT due to the fact that AML with *KMT2A*-rearrangements mostly belong to the adverse-risk group. Due to the dynamic course of the relapsed disease and/or posttransplant comorbidities, some potential patients could not be included in the study. Although the trial had 25 active sites, the accrual rate was very slow showing that collaboration of several group on a national or international level may be warranted for a successful conduct of clinical trials in small molecular disease subsets.

Overall, 19 serious adverse events (SAEs) were reported in 10 patients (63%); 6 of these SAEs were related to IMP. The most frequent SAEs were infections (n = 7) and PD (n = 4), followed by fever (n = 2), bone marrow failure, acute coronary syndrome, suicide, rash, worsening of general condition, and dentition disturbance of a wisdom tooth. Eight SAEs were associated with fatal outcome. The observed toxicities were comparable to the spectrum and frequency of toxicities described in other studies in patients with refractory or relapsed acute leukemias.

Although the study population consisted of primarily relapsed or refractory *KMT2A*-rearranged AML patients with a dismal prognosis, achieving only 2 responses observed among 16 patients (CRi, n = 1; PR, n = 1) was not considered clinically meaningful, also in the context of the following new developed drug class. It cannot be excluded that more proliferative cases of *KMT2A*-rearranged leukemias may respond, or that palbociclib at higher doses may exert more antileukemic efficacy. In our previous in vitro studies, which built the rationale for this trial, palbociclib inhibited colony formation in methylcellulose of mononuclear cells from 7 AML patients harboring 5 different *KMT2A*-rearrangements. Furthermore, we could show that Palbociclib induced expression of markers known for myeloid differentiation, for example, CD11b or CEBPA.[7] But in the relapsed/refractory setting, novel agents may demonstrate their antileukemic potential only when administered in combination treatment, as for example, for *KMT2A*-rearranged AML targeting further elements upstream of *KMT2A*-mediated transformation like the interaction between KMT2A and menin or K3K79 methylation by DOT1L in order to generate additive or synergistics effects.[7] Palbociclib is recently evaluated in relapsed/refractory pediatric and young adult patients.[9] Unfortunately, we were not able to perform any *ex vivo* or *in vitro* studies to investigate the possible response of leukemic cells, as we had only 1 patient with CR and 1 patient with PR. So current investigations show promising activity of so-called menin-inhibitors targeting the oncogenic fusion protein of *KMT2A* that is caused by the 11q23.3 chromosomal translocations. These fusion proteins require the interaction with menin for chromatin binding and activation of leukemogenic gene expression and further leukemic transformation.[10] Interestingly, BCL2 and CDK6 are also targeted by treatment with menin-inhibitors; thus, treatment with the combination of the menin-inhibitor SNDX-50469 and the BCL2 inhibitor (venetoclax), or the CDK6 inhibitor (abemaciclib) induces synergistic lethality in cell lines and patient-derived AML cells harboring *KMT2A*-rearrangement or mutation in nucleophosmin-1.[11] Further studies will show whether monotherapy with menin-inhibitors or combination therapy with menin-inhibitors and another targeted therapy have the potential to improve outcome of patients with *KMT2A*-rearranged acute leukemia.

## AUTHOR CONTRIBUTIONS

VIG, PP, RFS, and HD did conception and design. VIG and HD did administrative support. VIG and PP did article writing. All authors did collection and assembly of data, data analysis and interpretation, final approval of the article, and accountable for all aspects of the work.

## DISCLOSURES

VIG: Consulting or advisory board membership: Jazz Pharmaceuticals; Speakers bureau: Abbvie, Janssen, Pfizer; Travel or accommodation expenses: AbbVie. PP: Consulting or advisory board membership: AbbVie, Agios, Astellas, Astex, Bristol-Meyers Squibb, Celgene, Jazz, Novartis, Otsuka, Pfizer, Sunesis; Speakers bureau: AbbVie, Agios, Astellas, Bristol-Meyers Squibb, Celgene, Jazz, Novartis, Pfizer; Travel or accommodation expenses: AbbVie, Amgen, Bristol-Meyers Squibb, Celgene, Janssen, Novartis, Takeda. RFS: Consulting or advisory board membership: Abbvie, Agios, Astellas, Celgene, Daiichi Sankyo, Hexal, Neovio Biotech, Novartis, Pfizer, Roche; research funding: Astellas, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Pfizer, Roche; speakers bureau, Astellas, Pfizer. SF: Consulting or advisory board membership: Bayer, Illumina, Roche; honoraria: Amgen, Eli Lilly, PharmaMar, Roche; research funding: AstraZeneca, Pfizer, PharmaMar, Roche; travel or accommodation expenses: Amgen, Eli Lilly, Illumina, PharmaMar, Roche. AK: Consulting, honoraria, advisory board membership: Roche; research funding: BMS, Roche. RW: Consulting or advisory board: Janssen, Novartis, BMS/Celgene, Amgen, Gilead, Pfizer, Sanofi, Takeda; research funding: Janssen, Sanofi; Honoraria: Abbvie, Sanofi, Takeda, Janssen, Amgen, BMS/Celgene, Gilead, Pfizer. JW: Consulting or advisory board membership: Novartis, Bristol Myers Squibb, Celgene, Amgen, Abbvie, Agios, Jazz, Pfizer, Sanofi, Sobi, Astellas. MdW: Research funding: Pfizer, Abbvie, Novartis, Astellas, Bristol Myers Squibb, AstraZeneca, MorphoSys; speakers honoraria: AstraZeneca, Janssen; travel or accommodation expenses: Astellas, Janssen. WF: Consulting or advisory board membership: AbbVie, Amgen, Celgene, Jazz Pharmaceuticals, MorphoSys AG, Novartis, Pfizer; Stemline and Clinigen; research funding: from Amgen and Pfizer; patents and royalties: Amgen; travel or accommodation expenses: Amgen, Daiichi Sankyo, Gilead, Jazz Pharmaceuticals, and Servier. MH: Consulting or advisory board: Abbvie, BMS/Celgene, Daiichi Sankyo, Jazz Pharmaceuticals, Novartis, Pfizer, Roche, Tolremo. Honoraria: Jazz Pharmaceuticals, Janssen, Novartis; research funding: Astellas, Bayer Pharma AG, BergenBio, Daiichi Sankyo, Jazz Pharmaceuticals, Karyopharm, Novartis, Pfizer, Roche. FT: Consulting or advisory board: Abbvie, Astellas, Bristol Myers Squibb/Celgene, Jazz Pharmaceuticals, Novartis, Pfizer. KD: Consulting or advisory board: Novartis, Celgene/BMS, Abbvie, Jazz Pharmaceuticals; research funding: Novartis; Celgene/BMS, Astellas, Agios, Kronos; Honoraria: Novartis, Celgene/BMS, Jazz Pharmaceuticals. HD: Consulting or advisory board: AbbVie, Agios, Amgen, Astellas, AstraZeneca, Berlin-Chemie, BMS, Celgene, Daiichi Sankyo, Gilead, Janssen, Jazz, Novartis, Servier, Syndax; Clinical Research Funding to Institution: AbbVie, Agios, Amgen, Astellas, Bristol Myers Squibb, Celgene, Jazz Pharmaceuticals, Kronos Bio, Novartis, Pfizer. All the other authors have no conflicts of interest to disclose.

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