Preliminary Phase II Results of Ara-C and Idarubicin in Combination with Selective Inhibitor of Nuclear Export (SINE) Compound Selinexor (KPT-330) in Patients with Relapsed or Refractory AML

Walter Fiedler[1], Michael Heuser[2], Maxim Kebenko[1], Felicitas Thol[2], Arne Trummer[2], Christian Brandts[3], Carsten Bokemeyer[1], Susann Theile[4], Anne Kranich[5]

[1]Department of Internal Medicine II and Clinic (Oncology Center), University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [2]Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany, [3]Department of Medicine II, University Hospital Frankfurt, Frankfurt, Germany, [4]GSO Hamburg, Hamburg, Germany, [5]GSO Global, Amsterdam, Netherlands

Universitätsklinikum Hamburg-Eppendorf

GSO

Background

Acute myeloid leukemia (AML) is the most frequent acute leukemia in adults. Although 70-80% of patients achieve a complete remission (CR), patients with AML who fail to achieve a CR after the first cycle of induction therapy and those with relapsed disease have a bleak prognosis *(1)*. Currently no standard regimen exists for the treatment of patients with relapsed AML and a great clinical need exists for new treatment options *(2)*. Selinexor, an oral first-in-class Selective Inhibitor of Nuclear Export (SINE) compound, inhibits XPO1 mediated nuclear export to induce cytotoxicity in cells with genomic damage such as tumor cells *(3)*. In an *in-vivo* model, selinexor shows high activity against AML cells of leukemic mice without toxicity to normal hematopoietic cells *(4)*. This Phase I clinical study demonstrates encouraging results in AML patients. The role of selinexor as a mono therapy is currently under investigation in Phase II.

Study Design

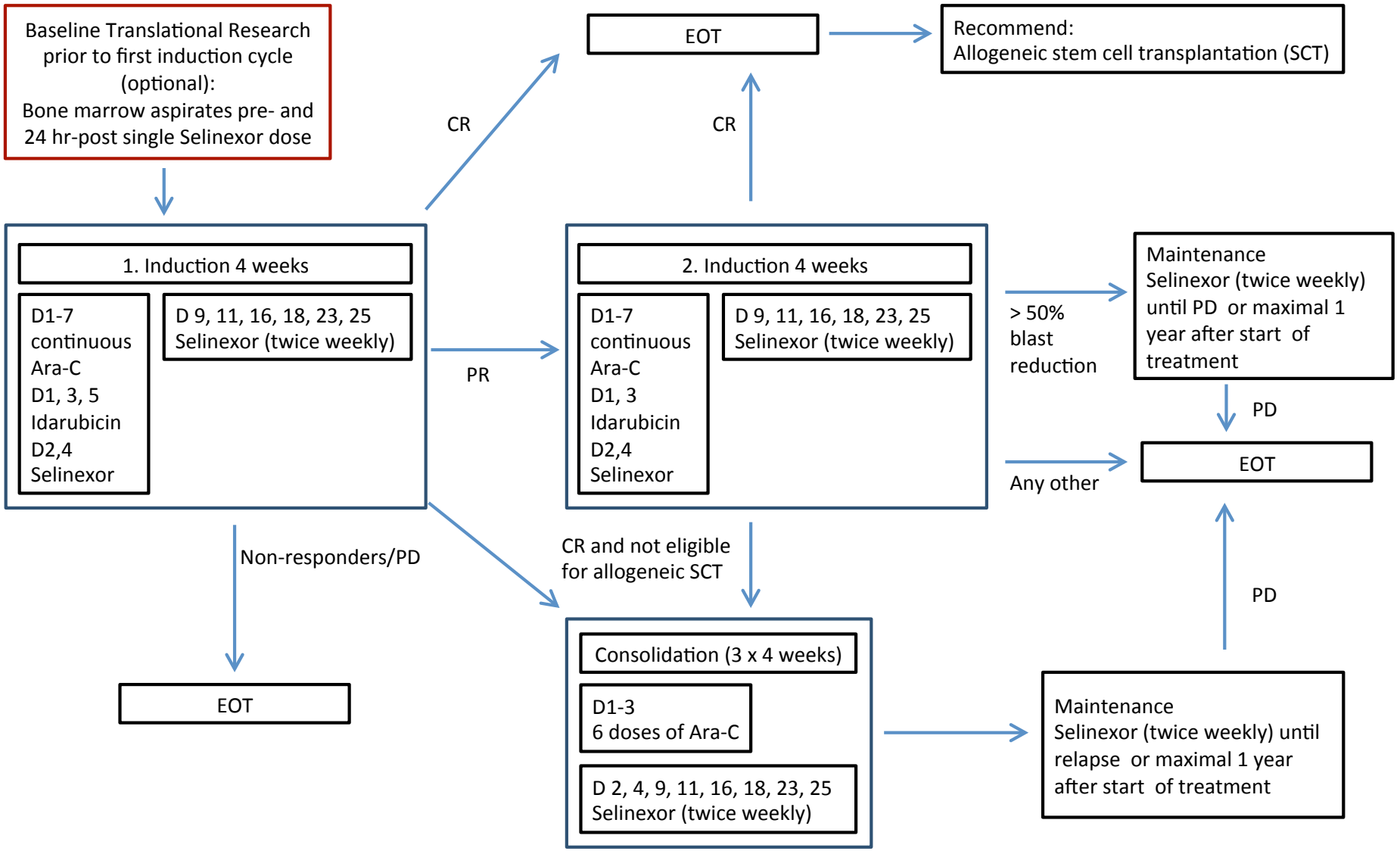
Study Objectives:

- This Phase II trial explores the efficacy & tolerability of Ara-C and idarubicin in combination with selinexor in patients with relapsed or refractory AML.

Study Methods:

- Patients with relapsed/refractory AML are treated with Ara-C (100 mg/m^2, continuous infusion, day 1-7), idarubicin (10 mg/m^2, day 1, 3, 5) every 4 weeks. In a majority of the patients selinexor was administered orally, twice weekly, starting on Day 2 (40 mg/m^2).
    - A small cohort of patients received selinexor after registration and before first induction cycle for correlative studies. The study flow chart is shown in **Figure 1**.
- The primary endpoint is percentage of patients achieving a complete response (CR) or complete remission without normalization of peripheral blood counts (CRi). Other endpoints are partial response (PR) rate, percentage of patients undergoing subsequent allogeneic stem cell transplant (SCT), early death rate, overall survival (OS), event-free survival and toxicity.

Figure 1: Study Flow Chart

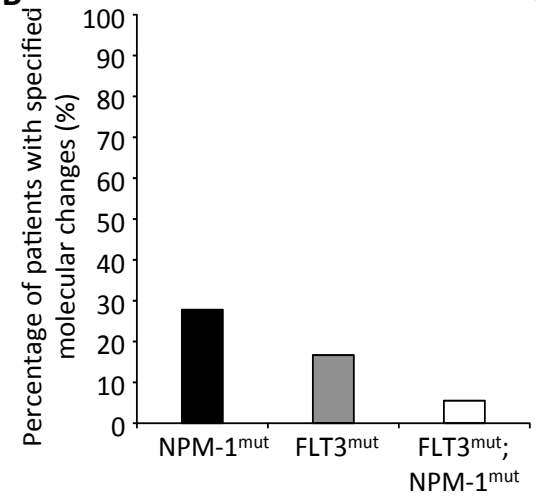


Patient Characteristics

A

Patient characteristics	
Median age	57 (+/- 15)
Gender	
Male	10 (56%)
Female	8 (44%)
Prior therapy	
Prior chemotherapy	2 (+/- 0.8)
Prior SCT/DLi	39% (6% n.n.)

B



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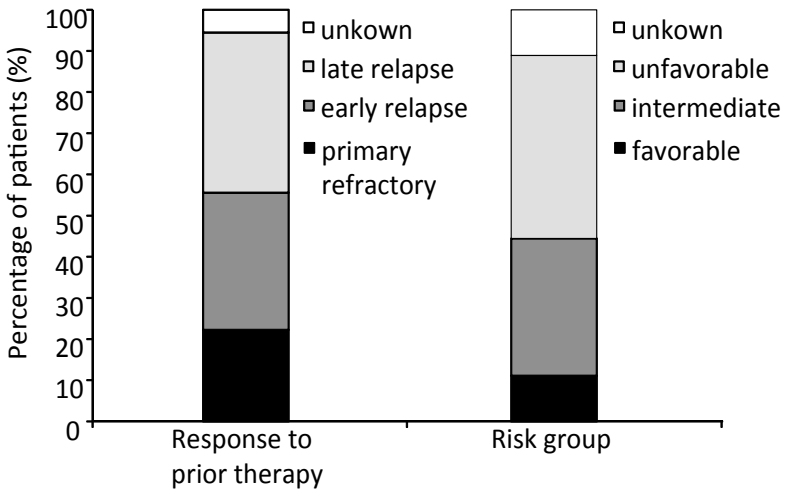


A) Patient demographics (n.n. = not known, n=18). **B)** Percentage of patients with specific molecular abnormalities (n=18). **C)** Disease status at study entry and risk category according to karyotype (n=18). As of 27-April-2015, 18 patients with AML have been enrolled in 3 sites. Median age was 57 years with 56% male and 44% female patients. Over 40% of patients showed molecular changes. On average, patients had received 2 chemotherapies prior to study start and 39% had prior stem cell transplantations (SCT) and donor lymphocyte infusion (DLi). 22% of patients were primary refractory while 33% of patients showed early relapse within 12 month and 39% of patients late relapse. 44% of patients were categorized as unfavourable.

Safety

Drug related adverse events (percentage of patients)		
Event	**CTC grade 3+4**	**CTC grade 1+2**
Anemia	18%	0%
Diarrhea	45%	36%
Constipation	0%	18%
Nausea	18%	45%
Vomiting	9%	55%
Fatigue	18%	27%
Thrombocytopenia	27%	0%
Leukopenia	27%	0%
Hypokalemia	9%	9%
Anorexia	45%	18%

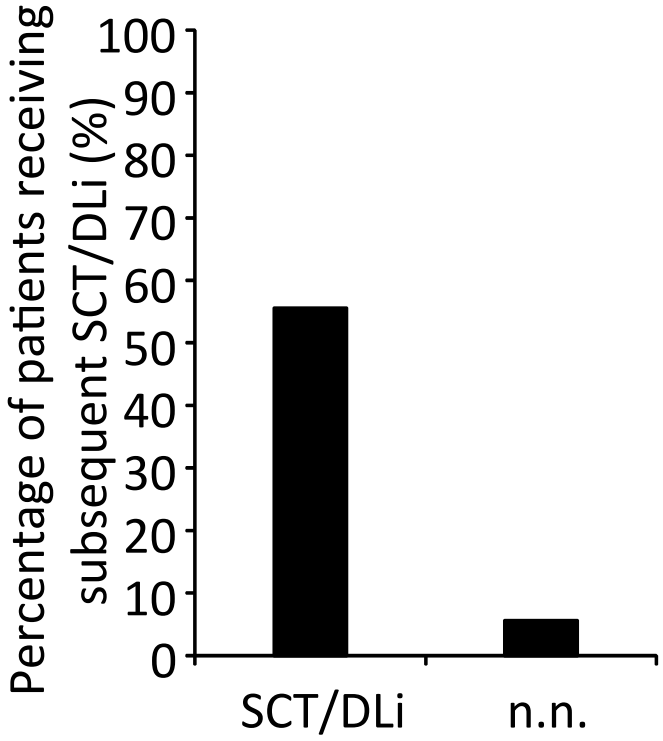
Out of 18 patients, 11 patients were evaluable for tolerability at time of analysis. Drug related adverse events comprised 43% of all CTC grade 3 and 4 and 51% of all CTC grade 1 and 2 events. The most common grade 3 and 4 drug related adverse events and grade 1 and 2 drug related adverse events are shown above. No drug related deaths occurred.

Efficacy

A

Percentage and number of patients with specified response	
Overall response rate	**10 (56%)**
CR	3 (17%)
CRi	6 (33%)
PR	1 (6%)
SD	2 (11%)
PD	6 (33%)

B



A) Percentage of patients showing complete remission (CR), complete remission with incomplete blood count recovery (CRi), partial remission (PR), stable disease (SD) and disease progression (PD) is presented (n=18). **B)** Percentage of patients receiving or planned for stem cell transplantations (SCT) / donor lymphocyte infusion (DLi) are shown (n.n. = not known) (n=18). Overall response rate was 56% (17% CR, 33% CRi, 6% PR,). Fifty-six percent of patients received or were planned for SCT / DLi.

Conclusions

- **The prognosis of relapsed/refractory AML patients is remarkably poor.**

- **Our findings suggest that treatment with Ara-C and idarubicin in combination with selinexor shows a promising complete response rate and may serve as a bridge to transplant for patients with relapsed/refractory AML.**

- **No unexpected toxicities were encountered.**

References

1) Ofran et al., Current opinion in hematology, 2012

2) Ferrara et al., Haematologica, 2004

3) Parikh et al., Journal of hematology & oncology, 2014

4) Etchin et al., British journal of haematology, 2013