SELINEXOR, ARA-C AND IDARUBICIN: AN EFFECTIVE AND TOLERABLE COMBINATION IN PATIENTS WITH RELAPSED, REFRACTORY AML: A MULTICENTER PHASE II STUDY

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Background

Acute myeloid leukemia (AML) is the second most common form of leukemia and the most frequent cause of leukemia-related deaths in the United States. While complete response rates can be as high as 80% in patients undergoing initial induction chemotherapy, the majority of AML patients will relapse. Refractory or relapsed patients have a bleak prognosis (1). As there is currently no standard regimen for these patients, 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 inducing cytotoxicity in cells with genomic damage (3). Preclinical data with Ara-C and selinexor significantly prolonged the survival of leukemic mice (4). A phase I clinical study demonstrated encouraging results in relapsed or refractory (r/r) AML patients. The role of selinexor as mono-therapy or in combination is currently under investigation in phase II trials of AML (ClinicalTrials.gov NCT 02088541).

Objectives, Materials, & Methods

Primary Objective: This phase II trial investigates the efficacy & tolerability of Ara-C and Idarubicin in combination with selinexor in patients with relapsed or refractory AML.

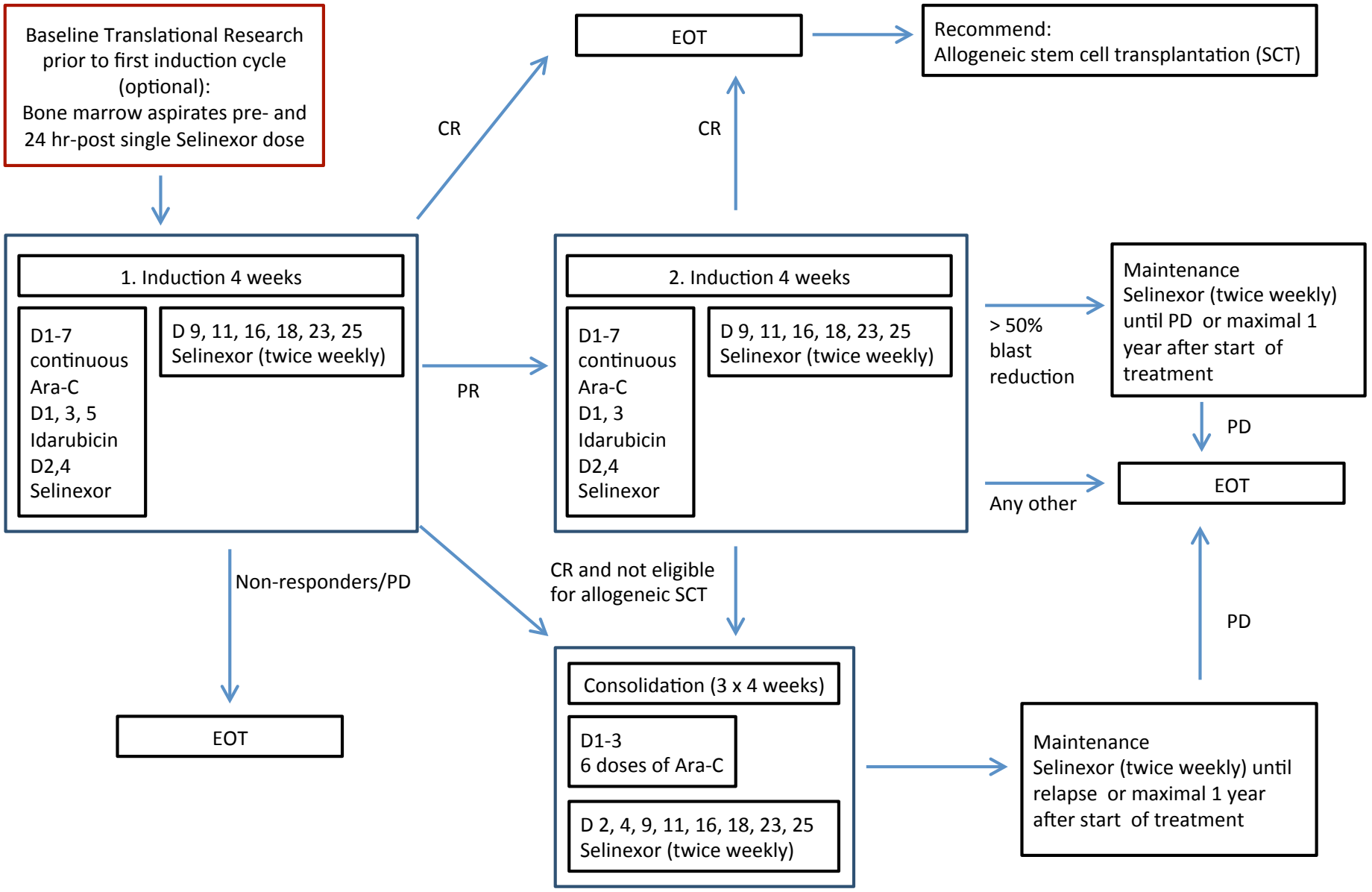
Materials & Methods: Patients with relapsed/refractory AML were treated with Ara-C (100 mg/m^2, continuous infusion, day 1-7), idarubicin (10 mg/m^2, day 1, 3, 5) every 4 weeks.

Selinexor was administered twice weekly orally 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 primary endpoint was percentage of patients achieving a complete response or complete remission without normalization of peripheral blood counts (CRi). Secondary endpoints were partial response rate, percentage of patients undergoing subsequent allogeneic stem cell transplant, early death rate, overall survival (OS), event-free survival and toxicity.

This clinical trial was conducted according to all applicable ICH/GCP Guidelines. Furthermore, 100% Source Data Verification (SDV) was performed.

Study Flow Chart

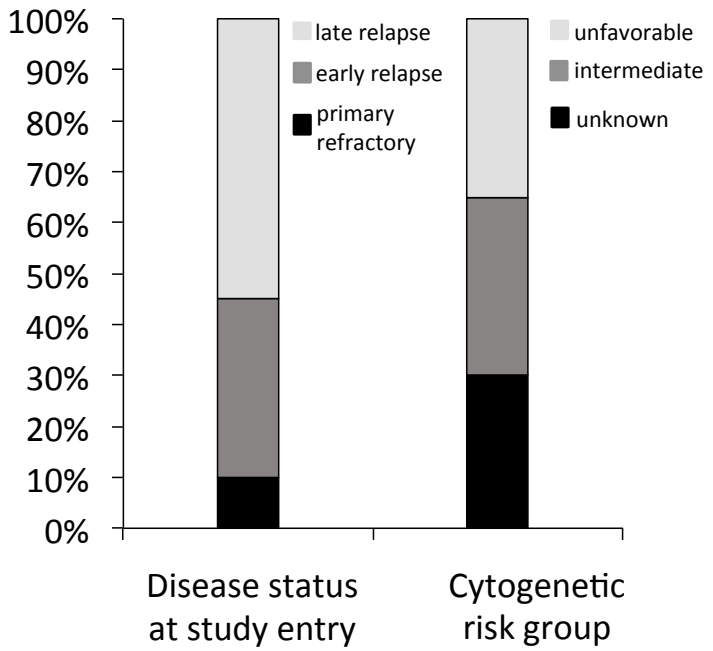


Patient Characteristics

A

Patient characteristics	
Median age	59 (+/- 14)
Gender	
Male	11 (55%)
Female	9 (45%)
Prior therapy	
Prior chemotherapy	3.5 (1 -6)
Prior SCT/DLi	5 SCT/ 2 DLi (35%)

B



As of June-16-2015, 21 patients with AML have been enrolled at 3 sites in Germany (NCT02249091) after obtaining informed consent of which 20 had received ≥ 1 induction cycle and were evaluable for efficacy and toxicity. Median age was 59 (range 22-78) years. Seven patients had a complex and 6 a normal karyotype (unknown at screening timepoint in 7 cases). On average, patients had received 3.5 (range 1-6) prior therapies. Two patients had primary refractory disease and 11 patients an early relapse and 7 patients a late relapse. 7 patients had prior allogeneic transplantation. Overall, the patient cohort had an especially adverse risk profile. **A)** Patient demographics (n=20) **B)** Disease status at study entry and cytogenetic risk category according to karyotype (n=20)

Adverse Events

A

Adverse events: Diarrhoea and Fatigue			n=20
Event	**CTC grade 3+4**	**Average time to event**	**Average duration of event**
Diarrhoea	12/20 (60%)	17 d	3 d
Fatigue	5/20 (25%)	11 d	7 d

Adverse Events Summary

The most frequent non-hematologic AEs were vomiting, diarrhoea, nausea, fatigue, anorexia and neutropenic fever. Diarrhoea could be managed by medical therapy including liquid opium and was self limited after a few days. One treatment-related death occurred. The patient developed subarachnoid haemorrhage during thrombocytopenia grade 4 and died.

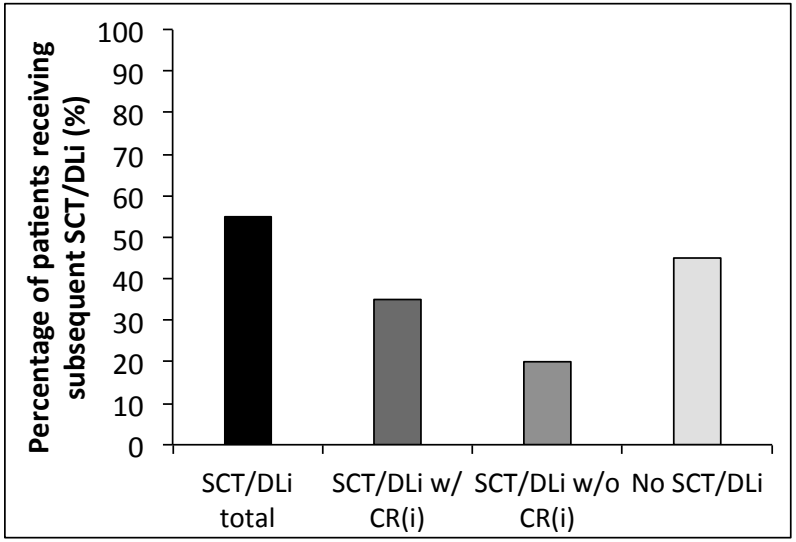
A) Percentage of patients experiencing diarrhoea and fatigue with CTC grade 3 and 4 are shown (n=20); Average of days before onset of events starting from Induction cycle 1; Average duration of events starting from Induction cycle 1

Efficacy

A

Outcome (Remission Status after induction therapy)	
Overall response rate	**12 (60%)**
CR	9* (45%)
CRi	1 (5%)
PR	2 (10%)
SD	4 (20%)
PD	4 (20%)

B



Overall response rate was 60% (45% of patients achieved CR, 5% of patients achieved CRi, 10% of patients achieved PR) representing a remarkable CR rate for this patient cohort with a highly adverse risk profile. At the end of Induction cycle 1, one patient did not recover in blood values, but in blasts, achieving a partial response. Sixty percent of patients received stem cell transplantation or donor lymphocyte infusion. Median time to recovery of neutrophiles and platelets was relatively long with 5-6 weeks. In an amendment a lower dose of selinexor has been implemented to evaluate if recovery of blood counts can be shortened with maintained efficacy. **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) (n=20). *2 patients achieved a CR directly after Induction cycle 1. Due to a prolonged time to blood recovery, 7 patients achieved a CR at a later stage but prior to next therapy. **B)** Total percentage of patients received stem cell transplantations (SCT); percentage of patients received SCT / donor lymphocyte infusion (DLi) with CR / CRi or without CR / CRi as well as percentage of patients not received SCT / DLi (n=20)

Efficacy

A

Remission status n=10 (CR/CRi)	
Patient in remission at time cut-off	5 (50%)
Patient died without relapse	2 (20%)
Patient with relapse	3 (30%)
Duration of remission	
Range	71 – 305 days
Median	206(+/- 64) days

B

Time to blood recovery	Average duration to recovery (days)	n=10 Achieved by # of patients
ANC 500/µl	39 d	10/10
ANC 1000/µl	40 d	10/10
PLT 50k/µl	43 d	9/10
PLT 100k/µl	48 d	9/10

Remission and Blood Recovery

A) Remission status and duration of remission for all patients (n=10) who achieved CR/CRi. Median duration of remission was 206 (range 71-305) days.

B) Time to recovery blood counts: average of ANC 500/µl, ANC 1000/µl; average of PLT 50k/µl, PLT 100k/µl; number of patients received blood recovery. Only patients with CR/CRi included (n=10).

Summary and Conclusions

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

- Our findings suggest that Ara-C and Idarubicin in combination with selinexor resulted in a remarkable response rate and is a promising regimen in this particularly unfavourable cohort of patients without unexpected toxicities enabling the majority of them to proceed to first or second allogeneic stem cell transplantation.

Conflict of Interest / References

- **COI Disclosure**: The following investigators W. Fiedler, J. Chromik, M. Heuser and GSO Global B.V. received research support from Karyopharm Therapeutics.

- **References**:

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