# **SAIL:** Phase II Results of **A**ra-c and **I**darubicin in Combination with the **S**elective Inhibitor of Nuclear Export (SINE™) Compound **S**elinexor (KPT-330) in Patients with Relapsed or Refractory AM**L**

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# Disclosures

Professor Dr. W. Fiedler receives research funding from Amgen and Koltan, holds patents & royalties from Amgen and is a member of an entities Board of Directors or advisory committee for Ariad/Incyte and Novartis. He receives travel reimbursements from Teva, Gilead, Amgen.

Professor Dr. M. Heuser has received research funding from Pfizer, Bayer, Novartis, Tetralogic, BerGenBio and Karyopharm Therapeutics Inc. He receives honoraria from Celgene and consults for Novartis.

Dr. J. Chromik has nothing to disclose.

Dr. F. Thol has nothing to disclose.

Professor Dr. C. Bokemeyer receives research funding from Karyopharm Therapeutics Inc.

S. Theile has nothing to disclose.

I. Lebkuechner has nothing to disclose.

GSO Global B.V. receives funding from Karyopharm Therapeutics Inc.

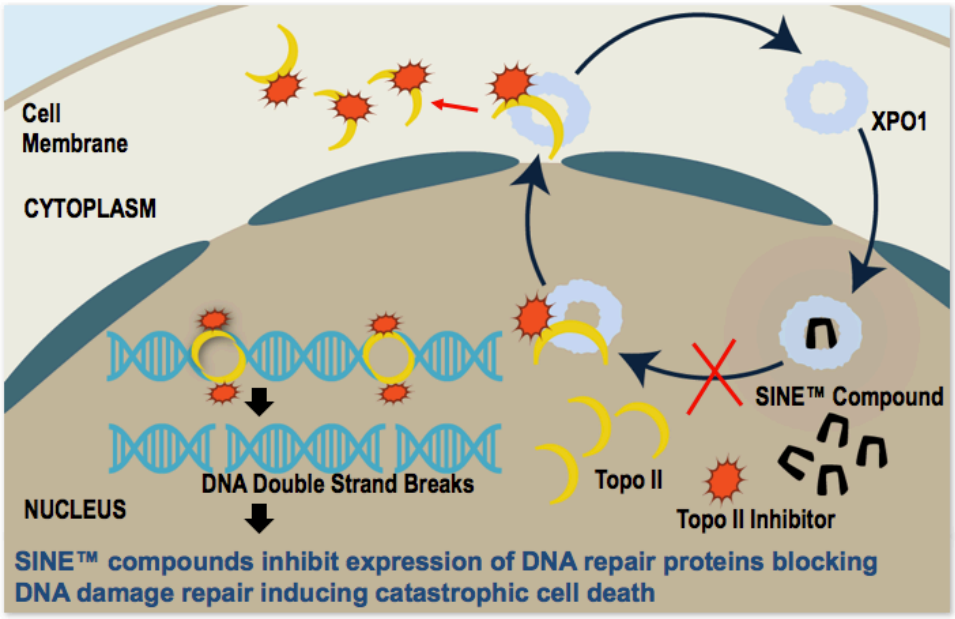
# Introduction: Acute Myeloid Leukemia (AML)

- Second most common form of leukemia and the most frequent cause of leukemia-related deaths in the US[1]
- Complete response (CR) rates can be as high as 80% in patients undergoing initial induction chemotherapy, but the majority relapse[2]
- Patients who fail to achieve CR after a first cycle of induction therapy or have an early relapse within one year after attaining a CR or relapse after Stem Cell Transplant (SCT) have a bleak prognosis independent of the choice of chemotherapy[3,4]
- Therefore, for these patients, there is a high medical need for new therapies


1 Cancer Statistics by American Cancer Society 02/22/2016
2 Lowenberg, B.; Downing, J.R.; Burnett, *A. Acute myeloid leukemia*. *N. Engl. J. Med.* **1999**, *341*,1051–1062.
3 Barrett AJ and Battiwalla M, *Relapse after allogeneic stem cell transplantation*. Expert Rev Hematol. **2010** Aug; 3(4): 429-441.
4 Katarjian HM et al. *The characteristics and outcome of patients with late relapse acute myelogenous leukemia.* J Clin Oncol **1988** Feb;6(2):232-8.

# **Introduction:** Selinexor + Ara-C + Idarubicin

**Blocking Nuclear Export by SINE™ Compounds Re-Sensitize Cancer Cells to TOPO II Inhibitors, Impeding DNA Damage Repair and Enhancing Cell Death**

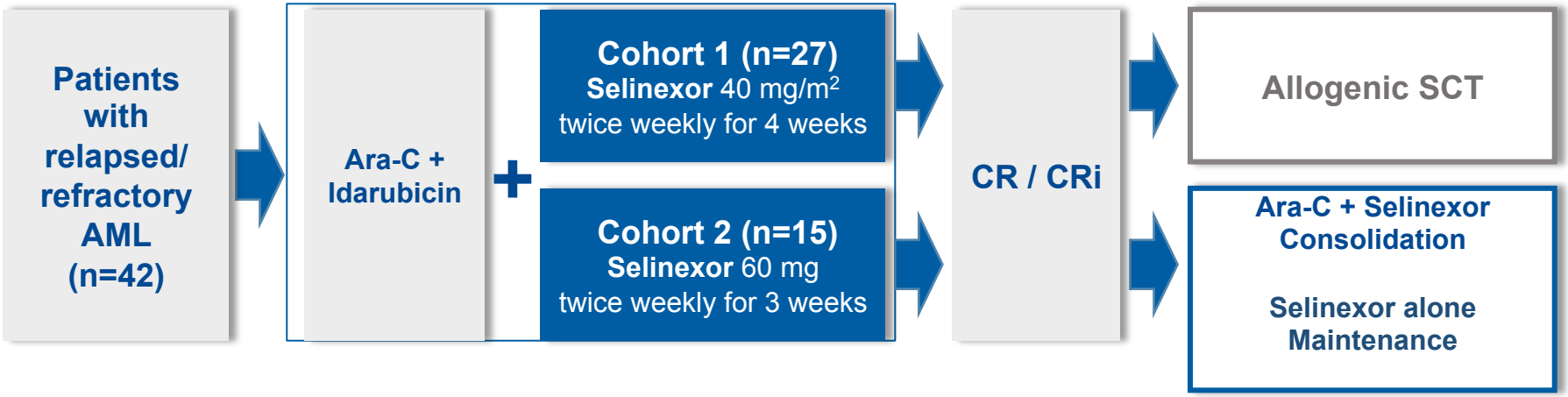



## Synergy Between Selinexor and Anthracyclines

- Aberrant nuclear export and cytoplasmic localization of TOPO IIα has been identified as one of the mechanisms leading to anthracycline resistance in cancer.
- Selinexor treatment results in nuclear retention of TOPO IIα protein, resulting in increased sensitivity to anthracyclines including idarubicin.
- Selinexor treatment of AML cells *in vitro* resulted in a c-MYC dependent reduction of DNA damage repair genes (*Rad51* and *Chk1*) mRNA and protein expression, and subsequent inhibition of homologous recombination.
- Concomitant treatment with selinexor and Topoisomerase II inhibitors results in therapeutic synergy in AML cell lines and patient samples.

Ranganathan *et al.* Clin Cancer Res. 2016

# **Trial design:** Multi-center, open-label, non-randomized, phase II




**Induction (cycle 1 (up to 2 cycles) )**

- Ara-C 100 mg/m² on day 1-7, continuous infusion
- Idarubicin 10 mg/m² on day 1, 3, 5
- Cohort 1: selinexor 40 mg/m² twice weekly for 4 weeks, orally
- Cohort 2: selinexor 60 mg twice weekly for 3 weeks out of a 4 week cycle, orally

**Consolidation (3 x 4 weeks)**

- Ara-C 3000 mg/m² twice daily on day 1-3, 2 hour infusion (patients younger than 60 years and with good performance status) or
- Ara-C 1000 mg/m² twice daily on day 1-3, 2 hour infusion (patients older than 60 years)
- Selinexor twice weekly, dosed as described above for cohort 1 and 2, orally

**Maintenance**

- Selinexor twice weekly, dosed as described above for cohort 1 and 2, orally
  In the absence of relapse, prohibitive toxicity or consent withdrawal, selinexor given ≤1 year after induction

# Objectives

- **Efficacy** of selinexor in combination with standard chemotherapy in patients with relapsed/ refractory AML

- **Primary Endpoint:**
  - CR or CRi

- **Secondary Endpoints:**
  - percentage of patients being transplanted after induction therapy
  - early death rate
  - overall survival (OS)
  - event-free survival

- Overall **safety and tolerability** of selinexor characterized by adverse events (AEs)

# Patient Demographics

| | | Cohort 1 | Cohort 2 |
|---|---|---|---|
| **Number of patients** | | 27 | 15 |
| **Male (%)** | | 16 (59) | 9 (60) |
| **Female (%)** | | 11 (41) | 6 (40) |
| **Median age (range)** | | 58 (22-78) | 60 (29-77) |
| **ECOG at screening (%)** | **0** | 16 (59) | 3 (20) |
| | **1** | 10 (37) | 10 (67) |
| | **2** | 1 (4) | 2 (13) |
| **Median number of prior treatment regimens (range)** | | 2 (1-5) | 1 (1-2) |
| **Prior SCT (%)** | | 10 (37) | 6 (40) |
| **Cytogenetic risk group: unfavorable (%)** | | 9 (33) | 6 (40) |
| **Late relapse (>12 months) (%)** | | 10 (37) | 5 (33) |

# Adverse Events CTCAE Grade 3/4 Independent of Relatedness to Study Medication

| | Cohort 1 (n=27) | | Cohort 2 (n=15) | | Total (n=42) |
|---|---|---|---|---|---|
| | CTCAE Grade 3/4 | Median duration (days) | CTCAE Grade 3/4 | Median duration (days) | CTCAE Grade 3/4 |
| **Diarrhea** | 15 (56%) | 7 | 6 (40%) | 7 | **21 (50%)** |
| **Nausea** | 3 (11%) | 11 | 2 (13%) | 22 | **5 (12%)** |
| **Vomiting** | 1 (4%) | 24 | 1 (7%) | 1 | **2 (5%)** |
| **Neutropenia** | 27 (100%) | 40 | 15 (100%) | 30 | **42 (100%)** |
| **Thrombocytopenia** | 27 (100%) | 42 | 15 (100%) | 35 | **42 (100%)** |

# All Serious Adverse Events Independent of Relatedness to Study Medication

| | Cohort 1 (n=27) | | Cohort 2 (n=15) | | Total (n=42) |
|---|---|---|---|---|---|
| | N of SAEs | CTC Grade | N of SAEs | CTC Grade | N of SAEs |
| **Pneumonia** | 3 | 3 (2x), 5 (1X) | 2 | 4, 5 | **5** |
| **Febrile neutropenia** | 3 | 3 | - | - | **3** |
| **Sepsis /septic shock** | 2 | 4 | 1 | 5 | **3** |
| **Diarrhea** | 1 | 3 | 1 | 4 | **2** |
| **Bone marrow aplasia (prolongation)** | - | - | 2 | 4 | **2** |
| **Asystole** | - | - | 1 | 5 | **1** |
| **Colitis** | 1 | 4 | - | - | **1** |
| **Fever** | 1 | 3 | - | - | **1** |
| **Fracture** | - | - | 1 | 3 | **1** |
| **General weakness** | 1 | 3 | - | - | **1** |
| **GvHD Skin** | 1 | 4 | - | - | **1** |
| **Hemophagocytosis syndrome** | - | - | 1 | 5 | **1** |
| **Hyperbilirubinemia** | 1 | 3 | - | - | **1** |
| **Hypotension** | 1 | 4 | - | - | **1** |
| **Mandibular fracture** | 1 | 3 | - | - | **1** |
| **Multiple brain infarctions** | 1 | 5 | - | - | **1** |
| **Paroxysmal atrial fibrilation** | 1 | 3 | - | - | **1** |
| **SIRS** | 1 | 5 | - | - | **1** |
| **Subarachnoidal intracranial hemorrhage** | 1 | 3 | - | - | **1** |
| **TOTAL** | **20** | - | **9** | - | **29** |

# Deaths Occuring During the Study

| | Cohort 1 (n=27) | Cohort 2 (n=15) | Cohort 1&2 (n=42) |
|---|---|---|---|
| **PD (%)** | 7 (26) | 2 (13) | 9 (21) |
| **Sepsis (%)** | 3 (11) | 1 (7) | 4 (10) |
| **Pneumonia (%)** | 1 (4) | 1 (7) | 2 (5) |
| **Asystole (%)** | - | 1 (7) | 1 (2) |
| **SIRS* (%)** | 1 (4) | - | 1 (2) |
| **Hemophagocytosis syndrome* (%)** | - | 1 (7) | 1 (2) |
| **GvHD (%)** | 1 (4) | - | 1 (2) |
| **Multiple organ failure (%)** | 1 (4) | - | 1 (2) |
| **Multiple brain infarctions (%)** | 1 (4) | - | 1 (2) |
| **∑ of deaths (%)** | **15 (57)** | **6 (42)** | **21 (50)** |

* Possibly drug related

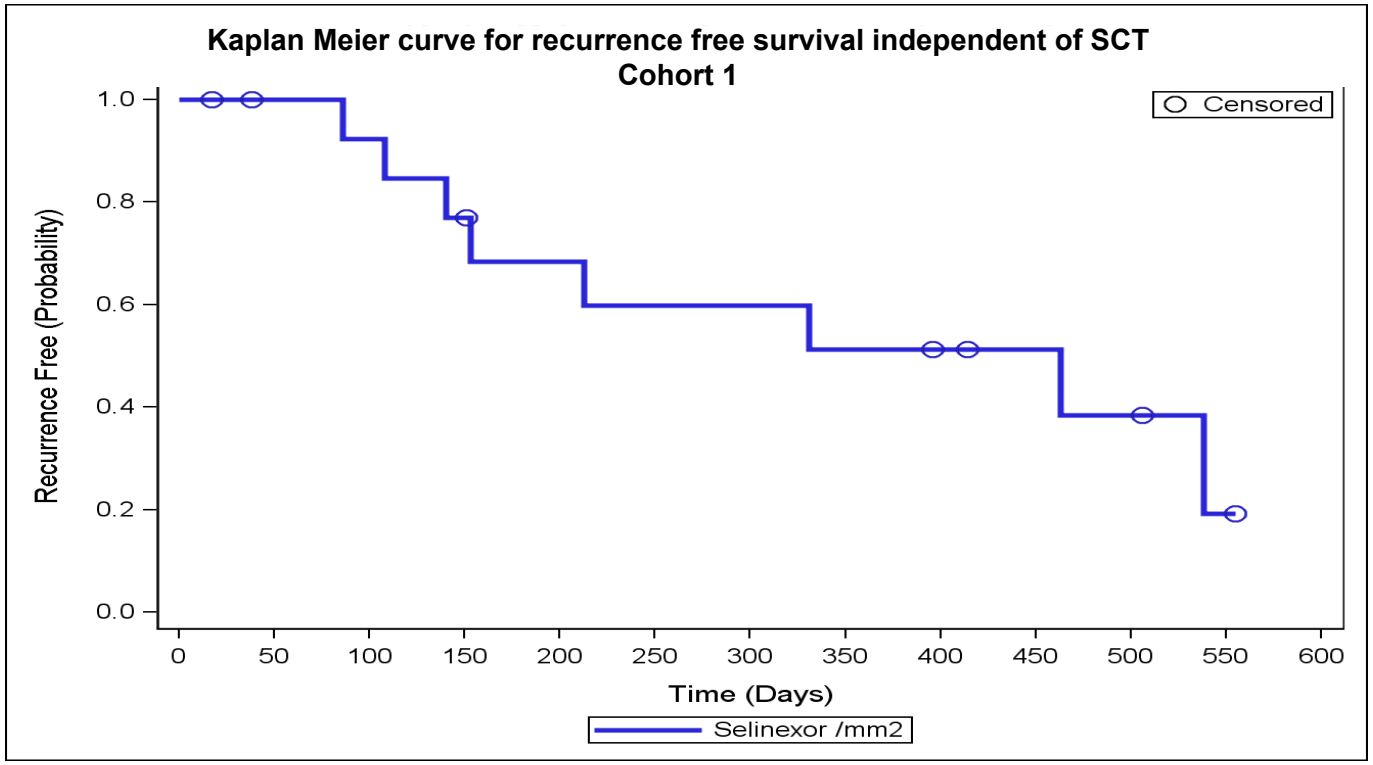
# Overall Response Rate (ORR)
# Remission Status After Induction Cycle 1

| | Cohort 1 (n=27) | Cohort 2 (n=15) |
|---|---|---|
| Evaluated (%) | 27 (100) | 11* (73) |
| **CR (%)** | 6 (22) | 4 (36) |
| **CRi (%)** | 9 (33) | 1 (9) |
| **MLFS (%)** | 0 (0) | 1 (9) |
| **ORR (%)** | **15 (55)** | **6 (54)** |

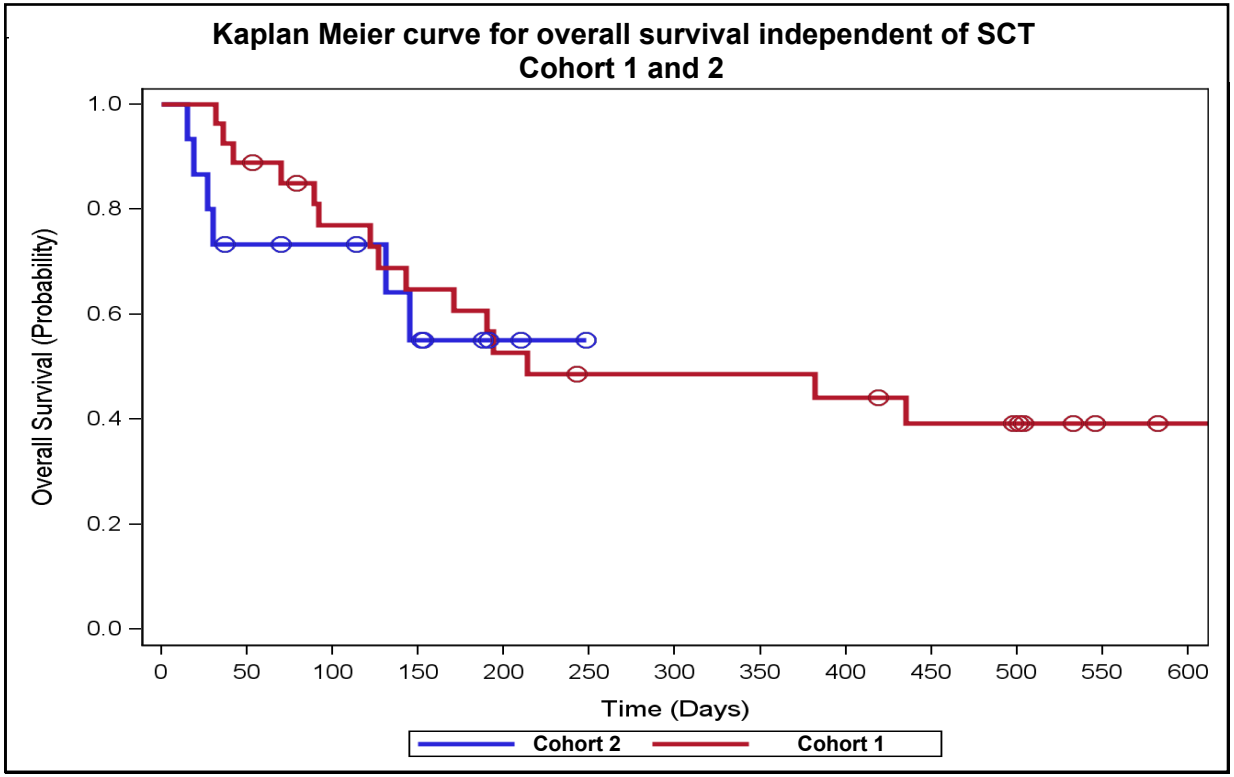
*11 patients were evaluated for efficacy analyses, 4 patients did not have bone marrow analyses after cycle 1 due to early death (sepsis, pneumonia, hemophagocytosis syndrome, asystole) and are not included in ORR calculation of cohort 2.

# SCT, OS and RFS for Cohort 1 Only (Patients Achieving CR/CRi)

| | All (n=15) | SCT (n=7) | No SCT (n=8) |
|---|---|---|---|
| **Relapsed (%)** | 5 ( 33) | 1 (14) | 4 (50) |
| **Median RFS (days)** | 333 | 463 | 272 |
| **Median OS (days)** | 435 | Not reached | 435 |



# Overall Survival (OS) and Observation Period




| | Cohort 1 (n=27) | Cohort 2 (n=15) |
|---|---|---|
| **Patients alive (%)** | 12 (44) | 9 (60) |
| **Median OS (days)** | 214 | Not reached* |

*Due to later introduction of cohort 2 and the set cut-off date (October 2016) the observation time of cohort 2 is shorter than the observation time of cohort 1.

# Current Patient Status

| | Cohort 1 (n=27) | Cohort 2 (n=15) |
|---|---|---|
| **Off-treatment** | 27 | 13 |
| **Withdrawal of consent** | 0 | 1 |
| **Death** | 15 | 6 |
| **Maintenance therapy** | 0 | 2 |
| **In follow-up** | 12 | 6 |

# Conclusions

- The prognosis of relapsed/refractory AML is remarkably poor.
- Our results suggest that combined treatment of Ara-C, idarubicin and selinexor is a mechanism driven and tolerable and effective treatment option for patients with relapsed/refractory AML.
- Nearly half of these heavily pre-treated patients achieved a CR/CRi irrespective of prognosis group, laying in the upper range of salvage regimens.
- Combination therapy with selinexor can successfully serve as a bridge to transplant.
- The lower selinexor dose in combination with chemotherapy is better tolerated and should be further explored in a randomized Phase 3 setting.

# Acknowledgements


- Special thanks to the patients and their families, investigators, study coordinators, and support staff
- The participating centers: P. Kühne, G. Samson, A. Hüls
- The sponsor GSO: U. Deppermann, C. Kohl, R. Reyes, S. Amberg
- GSO Global B.V. receives funding from Karyopharm Therapeutics Inc.