THE UNIVERSITY OF CHICAGO MEDICINE

# Combination of Selinexor with High-Dose Cytarabine and Mitoxantrone for Remission Induction in Acute Myeloid Leukemia is Feasible and Tolerable – A Phase I Study (NCT02573363)

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# Disclosure

- **Study was sponsored by Karyopharm Therapeutics**
- **No financial relationships to disclose**
- **Other disclosures:**

  **Hongtao Liu, MD** *(Principal Investigator)*

  - Consultant for: MedImmune/AstraZeneca, Pfizer, Novartis
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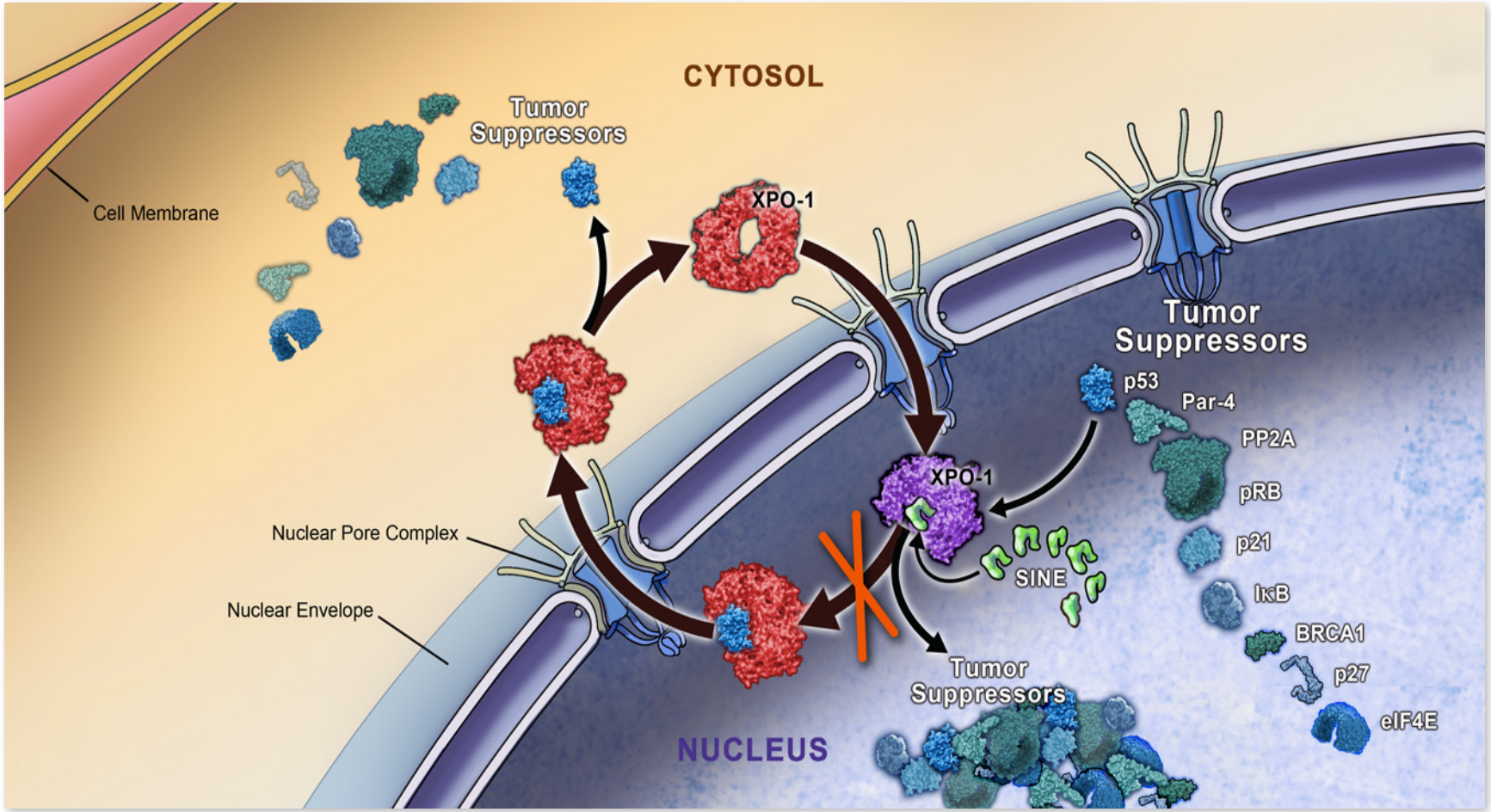
# Background

- **Acute myeloid leukemia (AML) is a disease with poor prognosis**
- **Standard induction chemotherapy regimen involves combination of cytarabine with anthracycline**
- **High-dose cytarabine (HiDAC) with mitoxantrone (Mito) is frequently used at U. Chicago with good response rates**
  - HiDAC/Mito in high risk AML patients: Overall Response Rate (ORR) of 55% (Larson *et al*., 2012)
  - HiDAC/Mito in untreated therapy-related myeloid neoplasms: ORR 82% (Godley *et al*., 2010)

# Selinexor: Novel Oral Anti-Cancer Agent Restores Tumor Suppressors & Reduces Oncoproteins

- **Selinexor (KPT-330) is a selective inhibitor of nuclear export (SINE™) that inhibits exportin 1 (XPO1)**
- **Mechanism 1:** Nuclear Retention and Activation of Tumor Suppressor Proteins
- **Mechanism 2:** Reduction of Oncoproteins Through Nuclear Retention of their mRNAs
- **Mechanism 3:** Inhibition of DNA damage repair



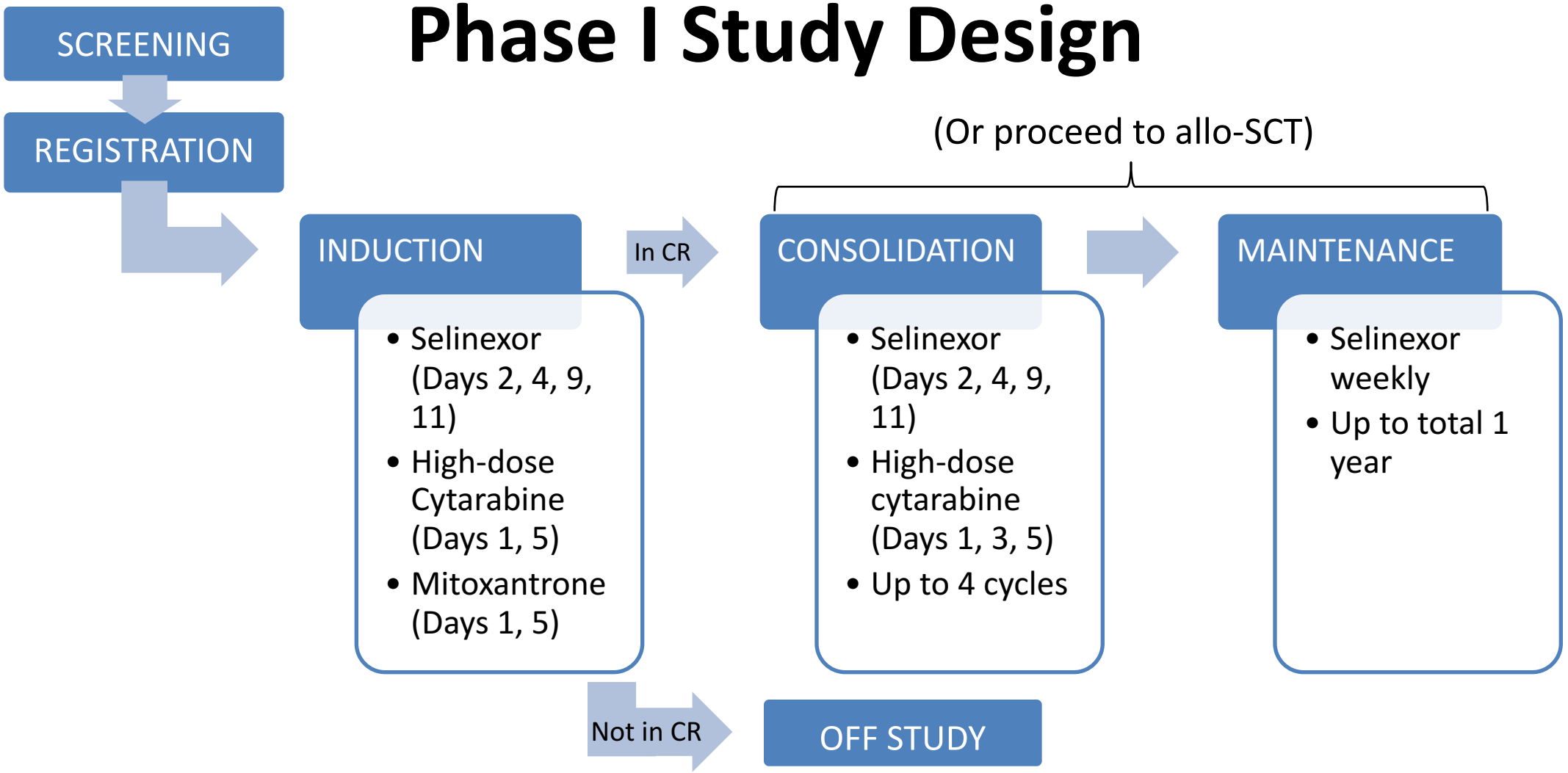
# Selinexor is Tolerable with Anti-Leukemic Effects

- **A phase I study of selinexor monotherapy in relapsed/refractory AML showed that it is well-tolerated and efficacious[1,2]**
- **Karyopharm's Phase II trial (SOPRA) using single-agent selinexor in patients with relapsed AML is close to full enrollment**
  - **60 mg selinexor flat dosing twice weekly (RP2D)**
- **Other clinical trials that combine selinexor with cytarabine-based regimens show favorable safety and efficacy profiles (NCT02403310, NCT02249091)**
- **Treatment with selinexor and topoisomerase II inhibitors (e.g. Idarubicin) demonstrated therapeutic synergy recently[3]**

## We hypothesized that adding selinexor to HiDAC/Mito is feasible and has synergistic anti-leukemic effects.

[1]Garzon et al., Blood, 2013. [2]Yee et al., J Clin Onc, 2014. [3]Ranganathan et al., Clin Cancer Res, 2016.

# Phase I Study Design




- Open-label, dose escalation of selinexor with expansion cohort
  - 3+3 design
  - 60mg (35mg/m$^2$) and 80mg (50mg/m$^2$)

References: KCP-330-001, KCP-330-002, KCP-330-003

# Study Objectives

- **Primary Objective**
  - To determine the Maximum Tolerated Dose (MTD) of selinexor to combine with HiDAC+mito
- **Secondary Objectives**
  - To determine the Complete Remission (CR) rate following induction chemotherapy
  - To determine the toxicities of the combination regimen during induction, consolidation, and maintenance
  - To determine the Relapse-free Survival (RFS) and Overall Survival (OS) rates during consolidation and maintenance treatment
  - To determine the Stem Cell Transplantation (SCT) success rate

# Key Eligibility Criteria

- **Approximately 27 patients to be enrolled**
- **Inclusion criteria:**
  - Newly diagnosed or relapsed/refractory AML patients suitable for intensive therapy
  - LVEF >50%
  - ECOG performance status ≤2
  - Meets laboratory criteria for renal and hepatic function
- **Exclusion criteria:**
  - Treatment with any investigational agent within 2 weeks
  - AML with CNS involvement
  - Significant co-morbidities that could compromise patient's safety

# Patient Characteristics (as of Nov 2016)

| Patient Characteristics | Number (%) |
|---|---|
| Total Patients Enrolled | 20 |
| Selinexor 60 mg | 3 |
| Selinexor 80 mg | 17 |
| # Female | 14 (70%) |
| Median age | 61 (range 44-76) |
| Initial AML Diagnosis | |
| De novo AML | 12 (60%) |
| Secondary AML | 8 (40%) |
| Disease state on enrollment | |
| Newly diagnosed AML | 12 (60%) |
| Relapsed/Refractory (R/R) AML | 8 (40%) |
| Median # of prior regimens (R/R only) | 1.5 (range 1-3) |
| European Leukemia Net risk group | |
| Favorable | 4 (20%) |
| Intermediate I/II | 8 (40%) |
| Adverse | 8 (40%) |

**19/20 patients are evaluable for safety and efficacy, as of 11/15/2016**

# Definition of DLT

- **Dose Limiting Toxicity (DLT)**
  - Observation period: up to 56 days
  - Any grade 3* or greater treatment-related, non-hematologic toxicity, except
    - Transient (<48 hours) nausea/vomiting and liver function abnormalities
    - Electrolyte abnormalities correctable with supportive therapy
  - Persistent bone marrow aplasia lasting >56 days in the absence of disease
  - DLTs were not evaluated in patients enrolled in dose expansion

***Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) 4.03**

# No DLTs Were Observed During Dose-Escalation

- **No DLTs based on protocol definition**
  - 1 patient in expansion cohort had aplastic marrow beyond day 56; however, she had pre-existing hypocellular marrow
  - 1 patient in expansion cohort died during induction of hemorrhagic stroke with a platelet of 4K
- **RP2D: Selinexor 80 mg+HiDAC+mitoxantrone**

# Non-Hematologic Adverse Events

| Adverse Events | Total | Grade 1&2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| Febrile neutropenia | 14 (74%) | 0 | 14 (74%)# | 0 | 0 |
| Diarrhea | 6 (32%) | 6 (32%) | 0 | 0 | 0 |
| Anorexia | 5 (26%) | 5 (26%) | 0 | 0 | 0 |
| Electrolyte abnormalities | 5 (26%) | 5 (26%) | 0 | 0 | 0 |
| Bacteremia | 5 (26%) | 0 | 5 (26%) | 0 | 0 |
| Nausea/vomiting | 4 (21%) | 4 (21%) | 0 | 0 | 0 |
| Fatigue | 4 (21%) | 4 (21%) | 0 | 0 | 0 |
| Typhlitis/colitis | 4 (21%) | 3 (16%) | 1 (5%) | 0 | 0 |
| Cardiac toxicity | 4 (21%) | 2 (11%) | 2 (11%) | 0 | 0 |
| Alopecia | 3 (16%) | 3 (16%) | 0 | 0 | 0 |
| Line-associated DVT | 3 (16%) | 0 | 3 (16%) | 0 | 0 |
| Pneumonia | 2 (11%) | 0 | 2 (11%) | 0 | 0 |
| Syncope/Pre-syncope | 2 (11%) | 1 (5%) | 1 (5%) | 0 | 0 |
| Hypoxia | 1 (5%) | 0 | 1 (5%) | 0 | 0 |
| Urinary tract infection* | 1 (5%) | 0 | 1 (5%) | 0 | 0 |
| Cerebellar toxicity* | 1 (5%) | 0 | 1 (5%) | 0 | 0 |
| Hemorrhagic stroke* | 1 (5%) | 0 | 0 | 0 | 1 (5%)& |
| Cellulitis* | 1 (5%) | 0 | 1 (5%) | 0 | 0 |
| Endocarditis* | 1 (5%) | 0 | 1 (5%) | 0 | 0 |
| Diverticulitis | 1 (5%) | 1 (5%) | 0 | 0 | 0 |
| Total | 68 | 34 | 33 | 0 | 1 |

*= **Serious Adverse Events** (5/19 = 26%)

#= 64% in HiDAC+mitoxantrone *(Larson et al., 2012)*

&=Intracranial bleeding after 2nd selinexor dose on day 4 of induction

# Selinexor + HiDAC/Mito is Tolerable

- **The most common non-infectious adverse effects were all Grade 1 or 2 and manageable with supportive care**
  - Diarrhea, anorexia, electrolyte abnormalities, nausea/vomiting, fatigue
- **19/20 patients completed induction therapy**
  - 1 induction death
  - All responding patients went onto consolidation or stem cell transplant

# Response Rates by Selinexor Dose

| Dose Level | # Patients Evaluated | Response | | | | |
|---|---|---|---|---|---|---|
| | | TF | CR | CRi | PR | ORR |
| 60 mg | 3 | 2 | 1 | 0 | 0 | 1 |
| 80 mg | 16 | 4 | 8 | 3 | 1 | 12 |
| **Total** | **19** | **6 (32%)** | **9 (47%)** | **3 (16%)** | **1 (5%)** | **13 (68%)** |

CR = complete remission
CRi = remission with incomplete count recovery
PR = partial remission
ORR = overall response rate
DLT = dose limiting toxicity
TF = treatment failure

**ORR = 13/19 = 68.4%**

**CR/CRi rate = 12/19 = 63%**

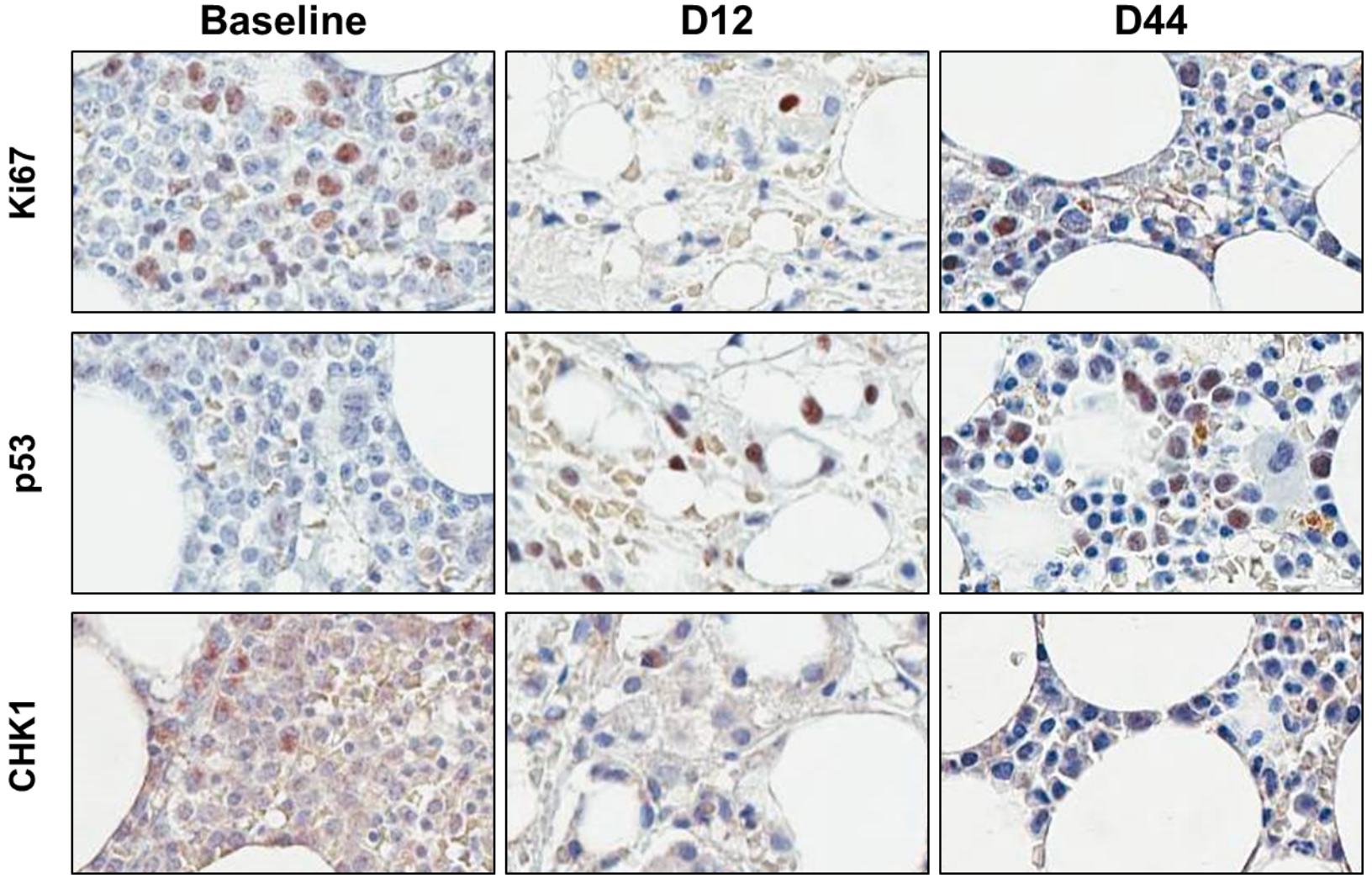
# Subgroup Response Rates

| | CR | CRi | PR | TF | Total | ORR |
|---|---|---|---|---|---|---|
| **AML Risk** | | | | | | |
| Newly diagnosed | 6 (55%) | 3 (27%) | 1 (9%) | 1 (9%) | 11 | 10 (91%) |
| Relapsed/Refractory | 3 (38%) | 0 | 0 | 5 (63%) | 8 | 3 (38%) |
| **European Leukemia Net Risk Group** | | | | | | |
| Favorable | 3 (100%) | 0 | 0 | 0 | 3 | 3 (100%) |
| Int I/II | 3 (38%) | 2 (25%) | 0 | 3 (38%) | 8 | 5 (63%) |
| Adverse | 3 (38%) | 1 (13%) | 1 (13%) | 3 (38%) | 8 | 5 (63%) |
| **Age** | | | | | | |
| Age >60 | 3 (33%) | 2 (22%) | 0 | 4 (44%) | 9 | 5 (56%) |
| Age ≤60 | 6 (60%) | 1 (10%) | 1 (10%) | 2 (20%) | 10 | 8 (80%) |

# Reduction of DNA Damage Response Protein and Nuclear Localization of P53 by Selinexor

**Patient #2**

- Female
- Selinexor 60mg
- De novo
- Adverse risk
- Achieved CR



# Conclusions

- **Combination of Selinexor with HiDAC/Mitoxantrone is well tolerated with RP2D of selinexor at 80 mg**
- **The most common toxicities included febrile neutropenia and GI-related toxicities, such as anorexia, diarrhea, and nausea.**
- **Selinexor with HiDAC/Mitoxantrone has a promising ORR of 68% out of 19 patients, as well as an ORR of 91% in patients with newly diagnosed AML**
- **The combination of selinexor + HiDAC + mitoxantrone warrants further investigation in a larger study**

# Acknowledgements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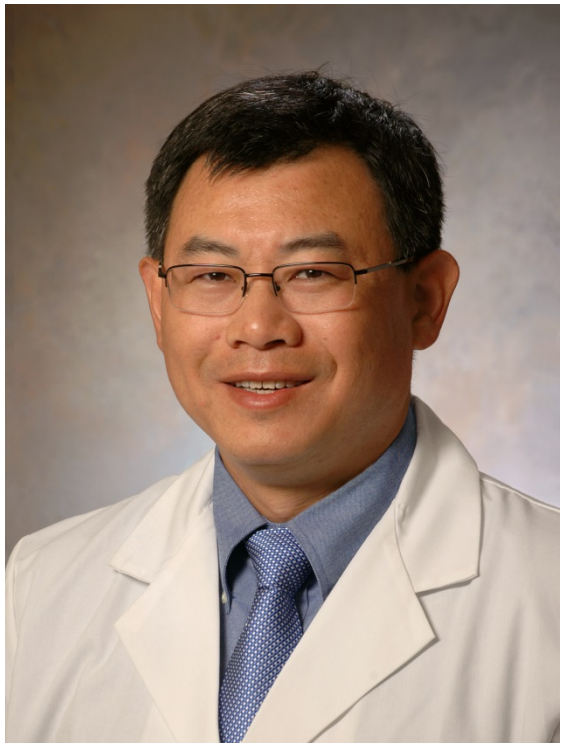

**Dr. Hongtao Liu**

# Post-induction Outcomes

- **4 total deaths**
  - 2 TF with progression of disease
  - 1 relapse after remission x 5 months
  - 1 induction death
- **Post-induction plan for those in remission:**
  - 6 have undergone allogeneic SCT
  - 4 went on to consolidation
  - 2 are planning for SCT
  - 1 awaiting for count recovery

# Treatment History

| Prior Treatment | Number (%) |
|---|---|
| Untreated | 12 (60%) |
| 1st relapse | 3 (15%) |
| Beyond 1st relapse | 1 (5%) |
| Primary refractory | 4 (20%) |
| Prior therapies | • Combination cytarabine with anthracycline<br>• HiDAC<br>• Hypomethylating agents (eg. Decitabine)<br>• Tyrosine kinase inhibitors<br>• FLAG-IDA<br>• ATRA<br>• Clinical trial agents |

# Results

- **Median time to CR: 35 days**
  - With G-CSF: 31 days
  - Without G-CSF: 37.5 days

# Post-Induction Outcomes

| Patient ID | Diagnosis | Selinexor Dose | Response | Outcome |
|---|---|---|---|---|
| 1 | De novo | 60mg | TF | Off study |
| 2 | De novo | 60mg | CR | In consolidation |
| 3 | Refractory | 60mg | TF | Off study |
| 4 | Relapsed | 80mg | TF | Off study; died of disease progression |
| 5 | De novo | 80mg | CR | In remission for 5 months before relapse; died of disease progression |
| 6 | Refractory | 80mg | TF | Off study |
| 7 | De novo | 80mg | CR | Allo-SCT |
| 8 | De novo | 80mg | CRi | Early relapse, then decitabine bridge to allo-SCT |
| 9 | De novo | 80mg | PR | Selinexor bridge to allo-SCT |
| 10 | De novo | 80mg | CR | Sorafenib bridge to allo-SCT |
| 11 | Refractory | 80mg | CR | Allo-SCT |
| 12 | De novo | 80mg | CRi | Allo-SCT |
| 13 | Relapsed | 80mg | CR | In consolidation |
| 14 | De novo | 80mg | CR | In maintenance |
| 15 | De novo | 80mg | CRi | Awaiting count recovery |
| 16 | Relapsed | 80mg | TF | Off study |
| 17 | De novo | 80mg | CR | In consolidation, planning for allo-SCT |
| 18 | Refractory | 80mg | CR | In consolidation, planning for allo-SCT |
| 19 | Relapsed | 80mg | TF | Off study; died during induction of hemorrhagic stroke |
| 20 | De novo | 80mg | Pending | n/a |