Wake Forest®
School of Medicine

Frontline Selinexor and Chemotherapy Is Highly Active in Older Adults with Acute Myeloid Leukemia (AML)

Timothy S. Pardee, MD, PhD[1], *Kristin M. Pladna, M.S.*[2*], *Susan Lyerly, P.A.-C.*[2*], *Sarah Dralle*[2*], *Megan Manuel, NP*[2*], *Leslie Renee Ellis, MD, MSHPEd*[2], *Dianna S. Howard, MD*[2], *Rupali Bhave, M.D.*[2*] *and Bayard L. Powell, MD*[2]

Conflicts of Interest

- Co-Chief Medical Officer of Rafael Pharmaceuticals
- Speaker/Consultant for (in the last 2 years):
  - Celgene/BMS
  - Amgen
  - Pharmacyclics/Janssen
  - AbbVie
- Advisory Board Member for:
  - CBM Biopharma
- Research Support From
  - Karyopharm
  - Rafael Pharmaceuticals
  - Spherix Intellectual Property

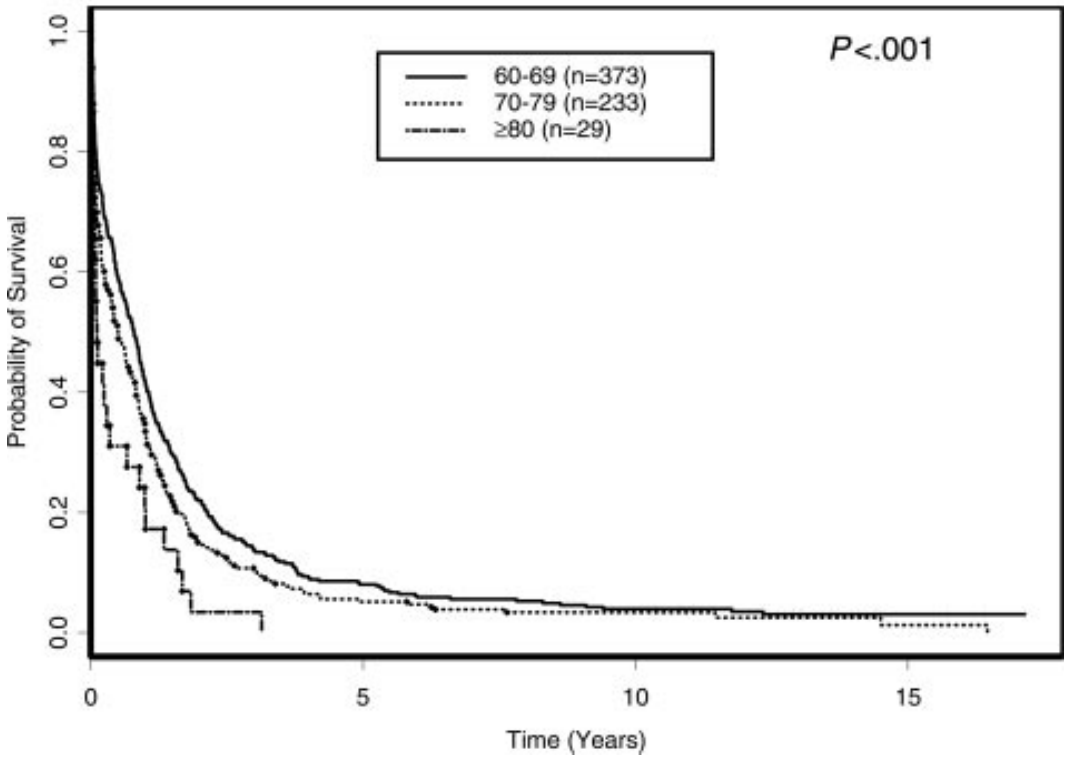
Acute Myeloid Leukemia (AML) Background

- An aggressive, abnormal proliferation of immature myeloid cells (myeloblasts) that fail to differentiate
- Leads to progressive marrow failure and death
- Median age at diagnosis is 68 (disease of older patients)
- An estimated 21,450 new cases in 2019 in the US
- Associated mortality is high with an estimated 10,920 deaths in 2019 in the US
- 28.3% of patients surviving at 5 years (2009-2015)

SEER 19 2011-2015, All Races, Both Sexes

AML Prognosis, Age

AML and Outcome by Age

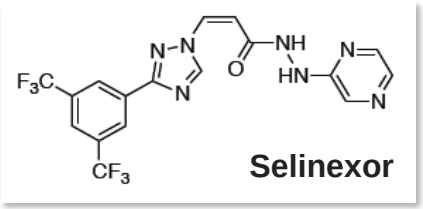


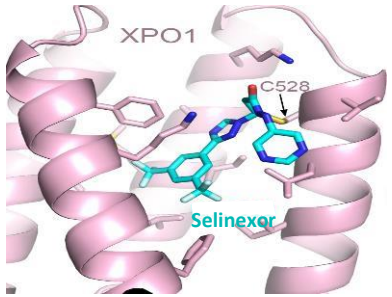
5 yr OS for all comers: 6.6%!!!!!!!

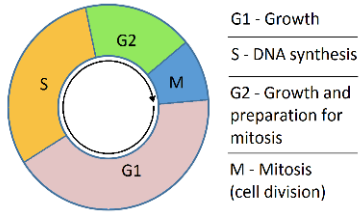
- Median Age at Diagnosis is 68
- 70% of all AML patients are >60
- Outcomes are dismal
- Resistance to standard therapy is common

Farag SS, et.al. *Blood* 2006; 108(1):63-73

Selinexor: Novel, First-in-Class, Small Molecule, Selective Inhibitor of Nuclear Export (SINE) XPO1







- Oral drug given 1-2 times per week (PDn $t_{1/2}$ ~48 hrs)
- No known drug-drug interactions
  - None through CYP450s or other enzymes
  - No effect on QTc intervals
- Forms a covalent adduct at cysteine 528 (C528) in the XPO1 cargo binding pocket
- Inhibits XPO1-mediated nuclear export of TSPs and oncogenic mRNAs resulting in G1/G2 arrest and apoptosis
- Potent anti-myeloma, lymphoma and leukemia effects in preclinical models
- Preclinical evidence of therapeutic window between cancer cells and normal cells
- Has been shown to sensitize AML cells to anthracylines
- Phase I/II studies have been done in Frontline and RR AML

Inclusion Criteria

- Key Inclusion Criteria
  - Patients must have histologically or cytologically documented newly diagnosed de novo Acute Myeloid Leukemia (non-APL) that has not yet been treated. Hydrea is acceptable.
  - Patients must not have a secondary AML (defined as a history of prior radiation therapy or systemic chemotherapy, antecedent MDS, MPN or CMML)
  - Hydroxyurea may be used to control leukocytosis, provided that it is without Grade >2 toxicity, and can be taken until start of therapy.
  - Age >60 years.

Study Design

1:3 Randomization

Cycle 1

Arm 1: S.O.C.	Arm 2: Selinexor
Day 1-7: Cytarabine 100 mg/m^2/day	Day 1-7: Cytarabine 100 mg/m^2/day
Day 1-3: Daunorubicin 60 mg/m^2/day	Day 1-3: Daunorubicin 60 mg/m^2/day
	Days 1 and 3: Twice weekly selinexor 60 mg (flat dose) for 3 weeks

Cycle 2 if needed
(for persistent leukemia)

Day 14: Bone marrow biopsy

Day 1-2: Daunorubicin 60 mg/m^2/day	Day 1-2: Daunorubicin 60 mg/m^2/day
Day 1-5: Cytarabine 100 mg/m^2/day	Day 1-5: Cytarabine 100 mg/m^2/day
	Days 1 and 3: Twice weekly selinexor 60 mg (flat dose) for 3 weeks

Study Design

	Arm 1: S.O.C.	Arm 2: Selinexor
Consolidation therapy (up to 4 cycles)	Remission bone marrow biopsy Day 28-42	
	Day 1-3: High dose Cytarabine ≤ 70 years: 1.5 g/m^2/day > 70 years: 1 g/m^2/day	Day 1-6: High dose Cytarabine ≤ 70 years: 1.5 g/m^2/day > 70 years: 1 g/m^2/day
		Days 1 and 3: Twice weekly selinexor 60 mg for weeks 1-3
Continues until unacceptable toxicity or recurrence		Maintenance therapy
		Once weekly (Days 1 and 8) selinexor 60 mg or highest tolerated dose every 3 weeks until relapse or unacceptable toxicity

Demographics

Cohort	All (n=28)	Standard Arm (n=7)	Selinexor Arm (n=21)
Median Age (range)	69 (60-75)	74 (60-75)	67 (61-73)
Male	12/28	0/7	12/21
ELN 2017 Cytogenetic Risk			
Poor	32% (9/28)	43% (3/7)	29% (6/21)
Intermediate	39% (11/28)	14% (1/7)	48% (10/21)
Good	24% (7/28)	43% (3/7)	19% (4/21)
Unknown	4% (1/28)	0% (0/7)	5% (1/21)

Mutational Data

Cohort	All (n=28)	Standard Arm (n=7)	Selinexor Arm (n=21)
DNMT3A	25% (7/28)	43% (3/7)	19% (4/21)
NPM1	25% (7/28)	43% (3/7)	19% (4/21)
SRSF2	21% (6/28)	14% (1/7)	24% (5/21)
TET2	21% (6/28)	43% (3/7)	14% (3/21)
ASXL1	18% (5/28)	0% (0/7)	24% (5/21)
IDH1	14% (4/28)	14% (1/7)	14% (3/21)
RUNX1	14% (4/28)	14% (1/7)	14% (3/21)
NRAS	11% (3/28)	14% (1/7)	10% (2/21)
WT1	11% (3/28)	43% (3/7)	0% (0/21)
TP53	4% (1/28)	0% (0/7)	5% (1/21)

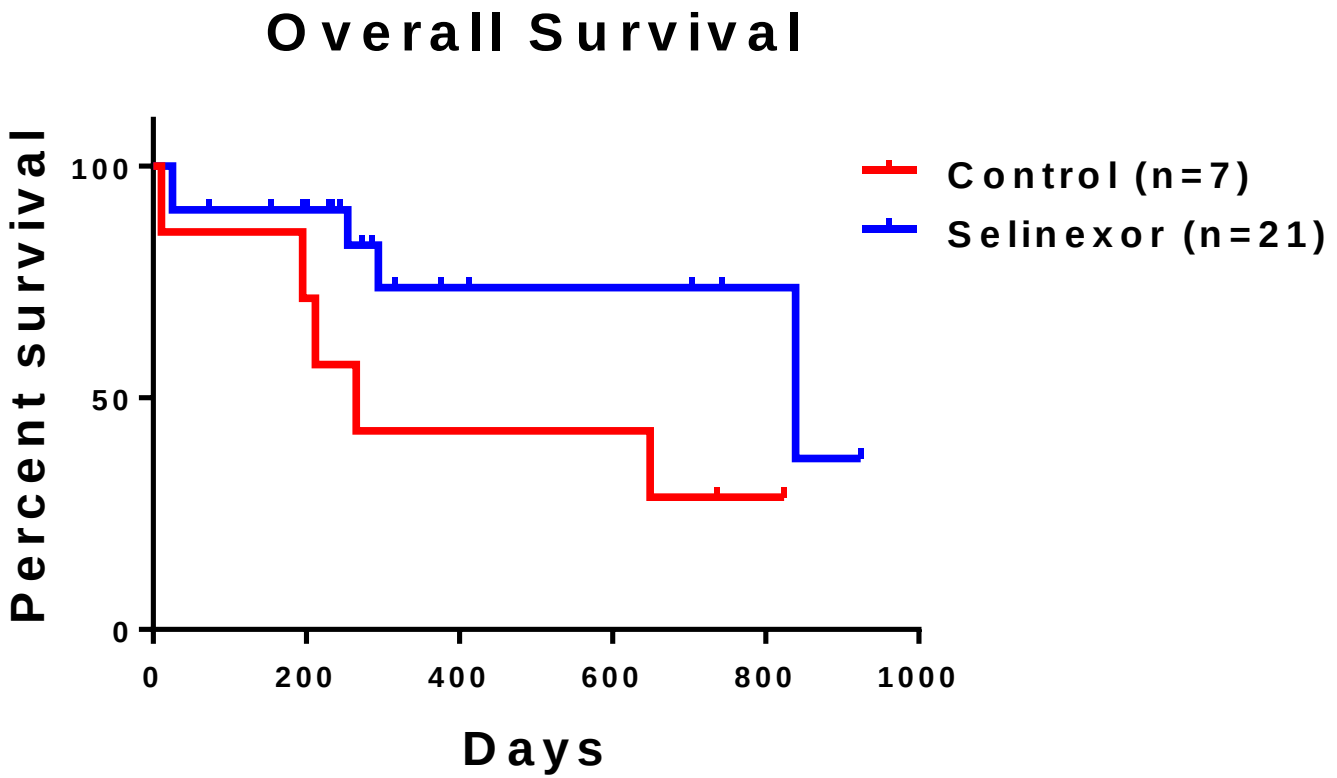
Toxicity

- 60 day mortality 10% (2/21) selinexor arm, 14% (1/7) in SOC arm
- 33% (7/21) patients in selinexor arm with prolonged thrombocytopenia (>4 weeks following neutrophil recovery, transfusion dependent in 1)
- Diarrhea most common AE resulting in dose holding, dose modifications

Efficacy

Cohort	All (n=28)	Standard Arm (n=7)	Selinexor Arm (n=21)
Residual Disease on Nadir Marrow	19% (5/27)	50% (3/6)	10% (2/21)
Complete Remission (CR)	68% (19/28)	43% (3/7)	76% (16/21)
MRD Negative CR	81% (13/16)	NA	81% (13/16)
Overall Response (CR+CRi)	75% (21/28)	43% (3/7)	86% (18/21)
No CR/CRi	26% (7/28)	57% (4/7)	14% (3/21)
Went on to Transplant	29% (8/28)	14% (1/7)	33% (7/21)
Relapsed After CR	24% (5/21)	33% (1/3)	22% (4/18)

Survival

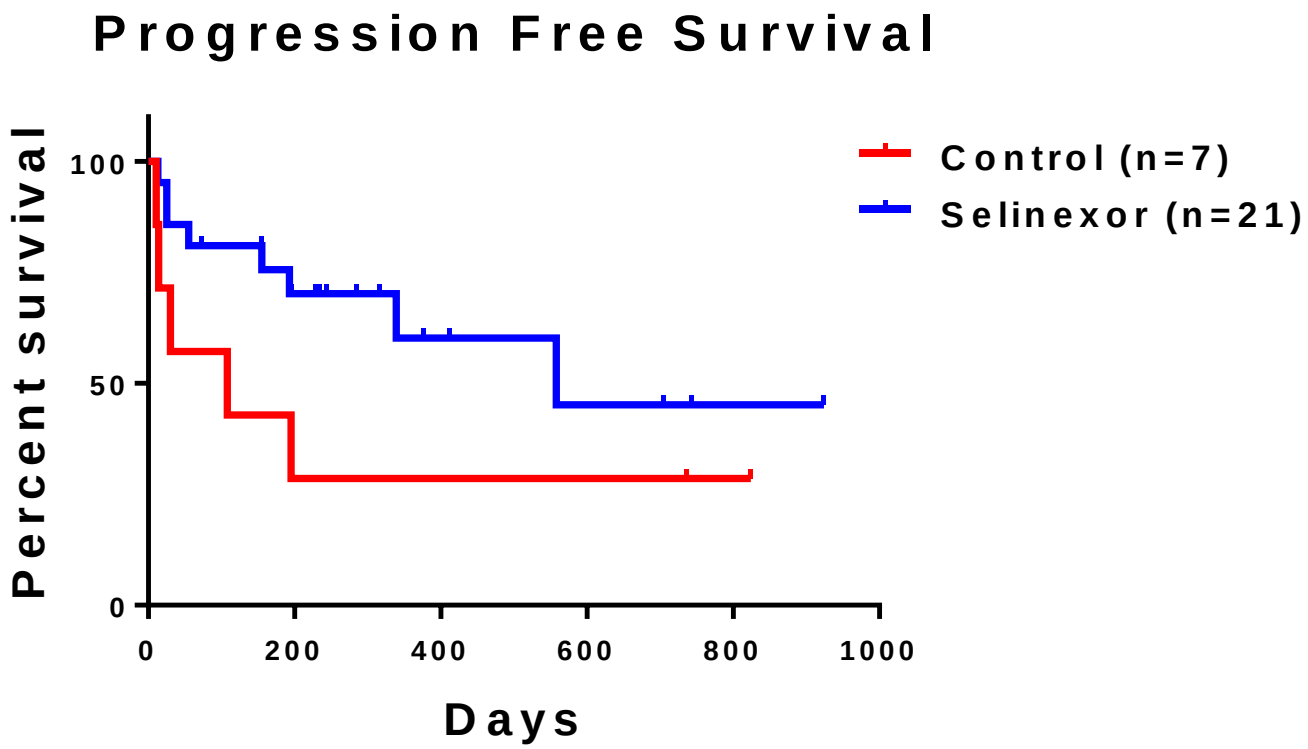


Control Median OS= 265 Days

Selinexor Median OS= 839 Days

p=0.0472

Progression Free Survival

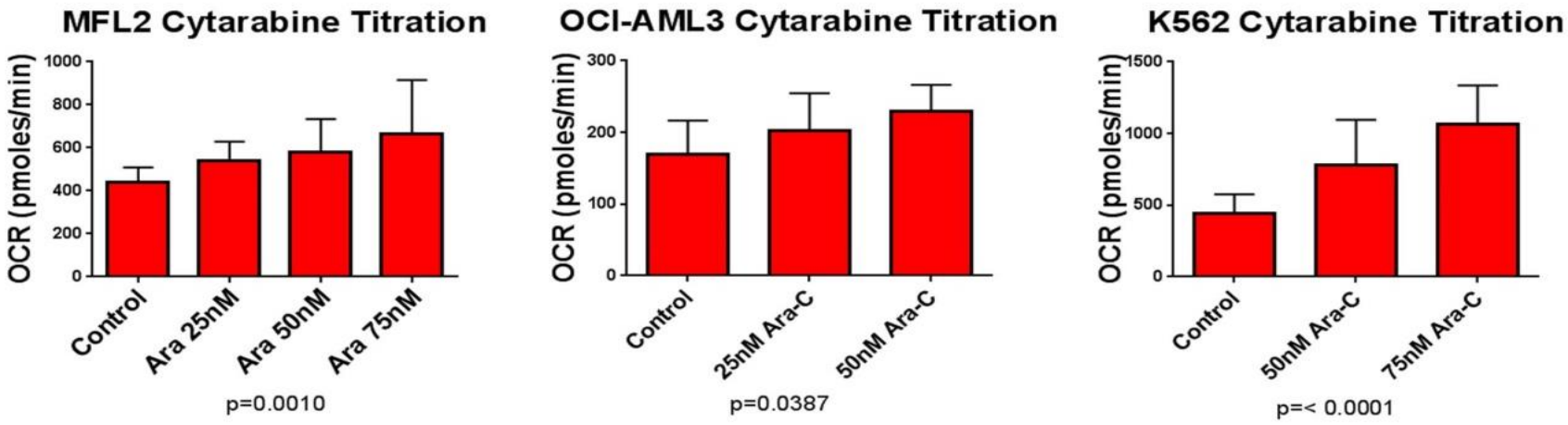


Control Median PFS= 108 Days

Selinexor Median PFS= 558 Days

p=0.1319

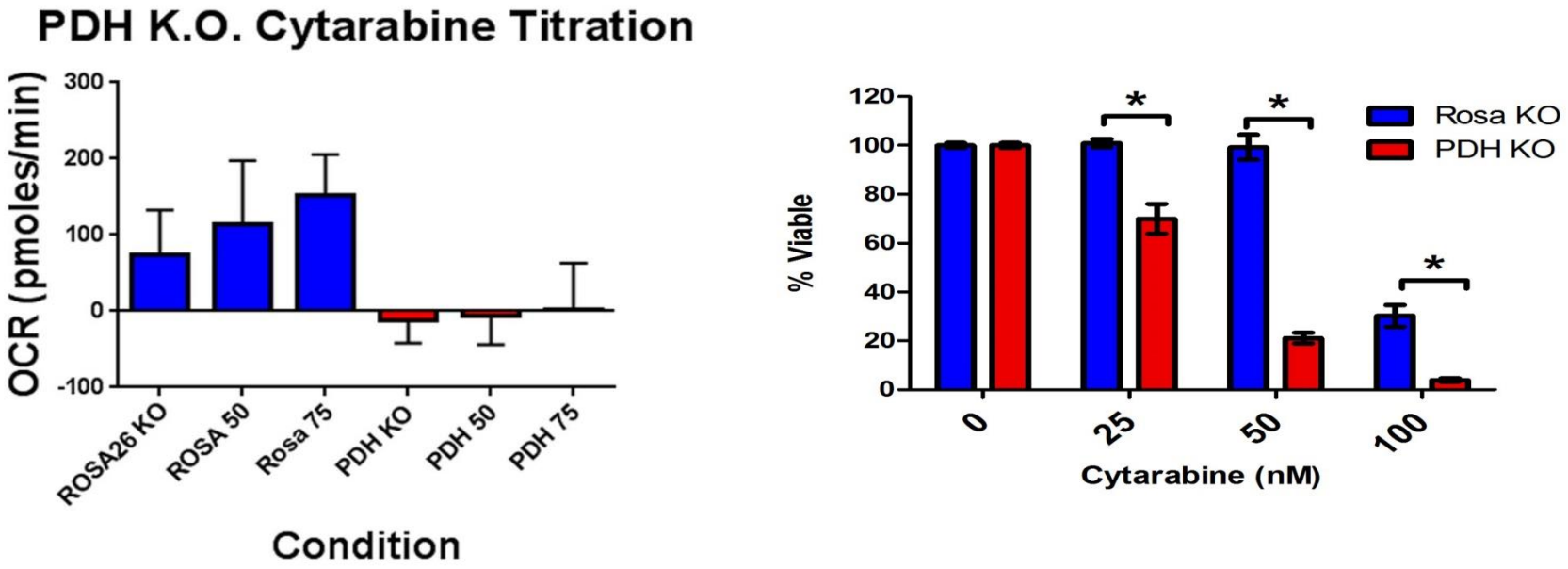
Cytarabine Exposure Induces Oxygen Consumption in AML



Pardee et. al. *Clin Ca Res*. 2018 May 1;24(9):2060-2073

OCR=Oxygen Consumption Rate

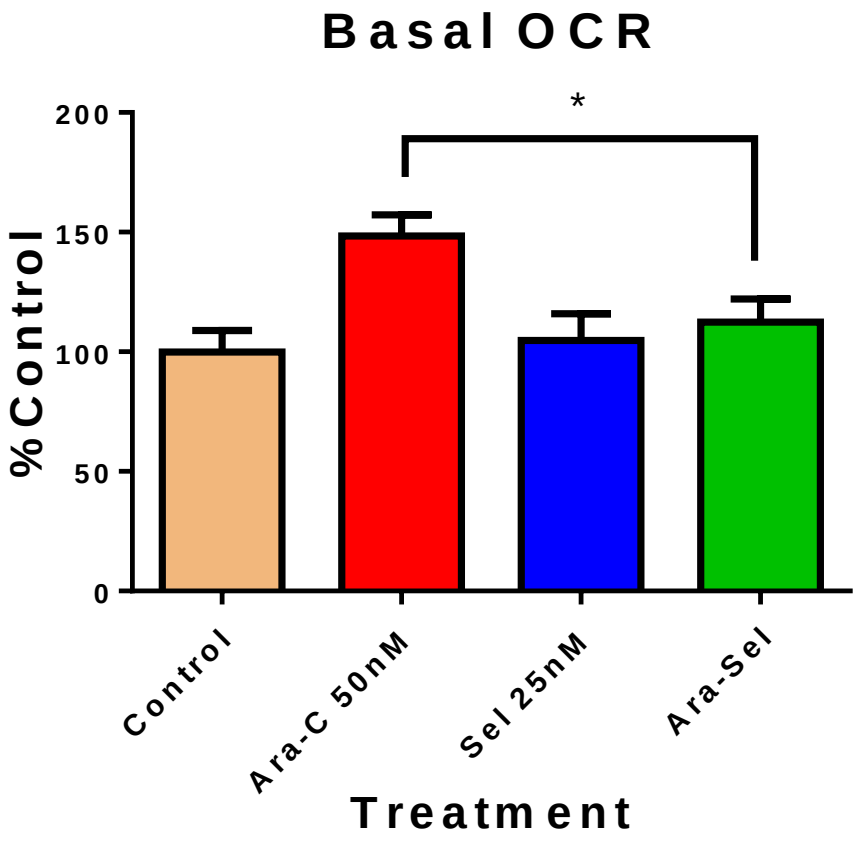
OCR is a Source of Resistance to Cytarabine *In Vitro*



Pardee et. al. *Clin Ca Res*. 2018 May 1;24(9):2060-2073

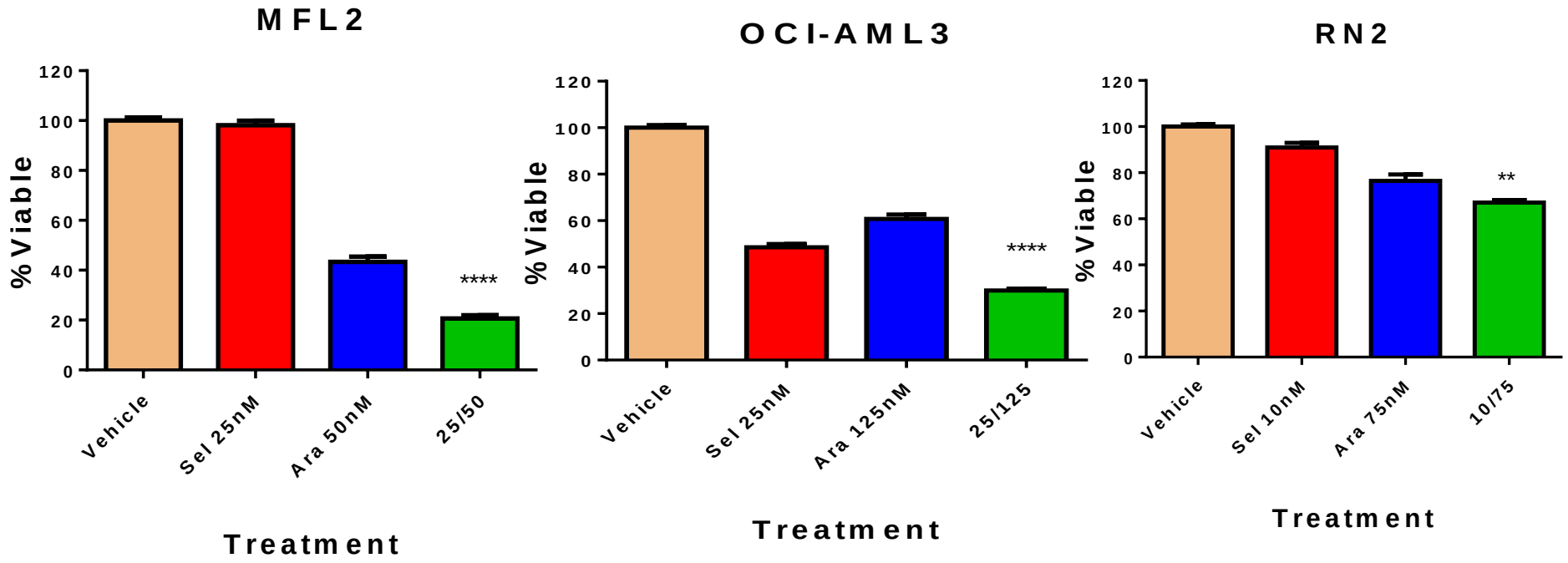
OCR=Oxygen Consumption Rate

Selinexor Blocks Increased OCR



OCR=Oxygen Consumption Rate

Selinexor Sensitizes AML to Ara-C



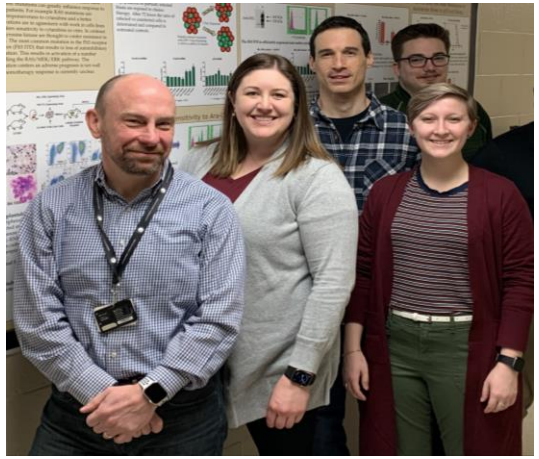
Summary

- Selinexor in combination with 7+3 appears highly active in fit elderly patients
- Selinexor provided a significant survival benefit in this small randomized trial
- Toxicities appeared manageable with similar 60 day mortality
- Fixed 60 mg dose is deserving of additional study in a larger randomized trial
- Selinexor may impair nuclear/mitochondrial communication needed for resistance to cytarabine

Acknowledgements

Pardee Lab:

- Kristi Stadelman
- Rebecca Anderson
- Enzo Palma
- Natty Schramm



Funding:

- Comprehensive Cancer Center of Wake Forest Baptist Health
- Karyopharm

The patients who have enrolled on our studies!