Selinexor in Combination with Cladribine, Cytarabine and G-CSF for Relapsed or Refractory AML

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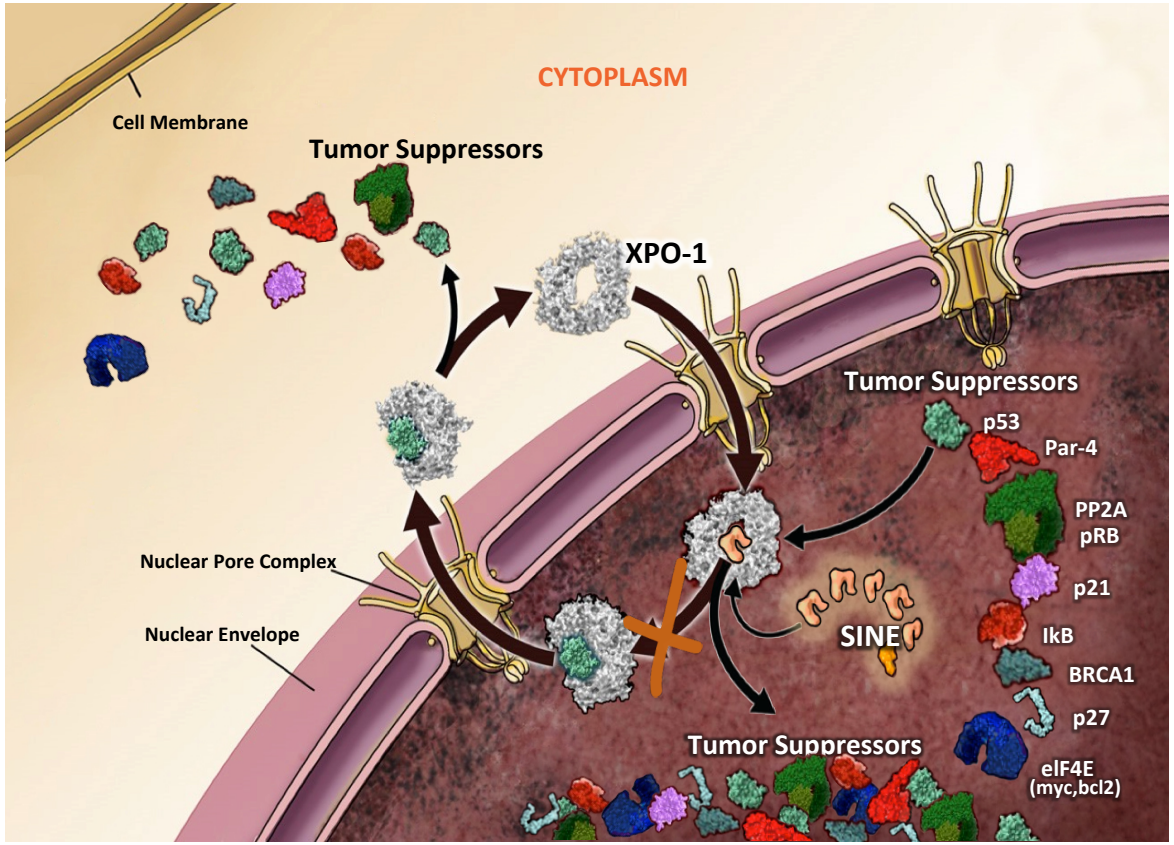
Selinexor (KPT-330) Exportin 1 (XPO1) Antagonist

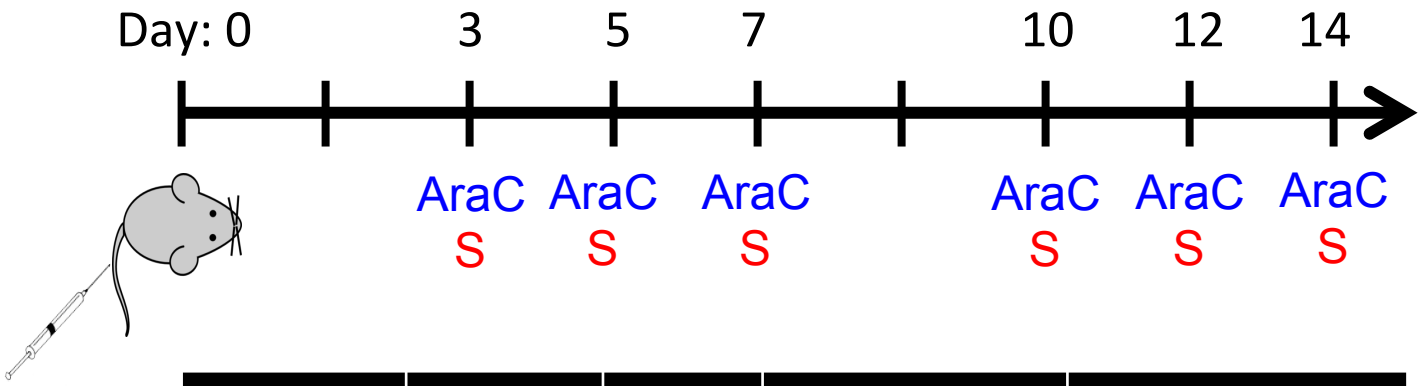
- Oral first in class novel Selective Inhibitor of Nuclear Export
- Activity in broad range of hematologic malignancies
- Postulated mechanisms of action

  a) Nuclear retention of tumor suppressors

  b) Nuclear retention of oncogene mRNAs by reducing eIF4E-dependent export of MYC, BCL2/BCL6, CCND1



Preclinical Data in Murine Model: In Vivo Therapy with Selinexor and AraC

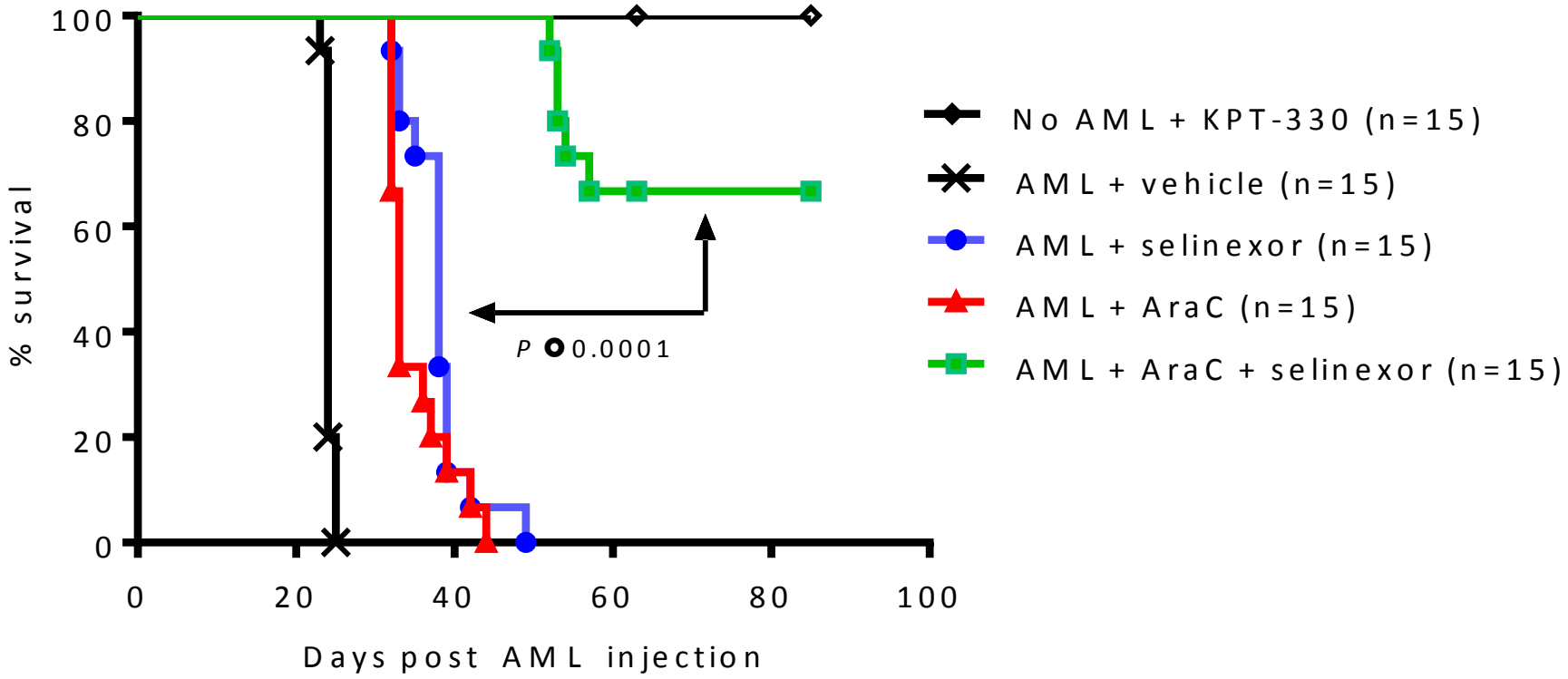


Murine AML
Tumor - B6APL1
(10^6 cells/mouse)

Cohort	No. of mice	AML	Selinexor (15mg/Kg)	AraC (200mg/Kg)
1	15	-	+	-
2	15	+	-	-
3	15	+	+	-
4	15	+	-	+
5	15	+	+	+

Rettig *et al.*, ASH 2013

In Vivo Therapy with AraC and Selinexor



Rettig *et al.*, ASH 2013

Rationale

Addition of Selinexor may augment the effect of AraC based chemotherapy in patients with relapsed or refractory AML

Primary Objective

- To determine the complete remission rate (CR + CRi) for selinexor + CLAG in patients with relapsed or refractory AML.

- Secondary objectives
  - To determine time to hematologic recovery, EFS, OS, RFS and rates of HCT post selinexor-CLAG
  - To characterize effects of selinexor on nuclear transport, cell cycle, and apoptosis

Inclusion Criteria

- Age 18-70
- AML (excluding APL) with one of the following
  - a) primary refractory disease following ≤ 2 cycles of induction chemotherapy
  - b) first relapse with no prior unsuccessful salvage chemotherapy
  - c) relapsed or refractory to hypomethylating agents
- ECOG PS ≤ 3
- Adequate organ function
  - AST, ALT, total bili ≤ 2 x ULN
  - Creatinine clearance ≥ 50 ml/min
  - Left ventricular ejection fraction ≥ 40%

Treatment Plan

	BMBx		BMBx								
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Selinexor (S)	**S**			**S**				**S**			**S**
Cladribine (CL)				**CLAG**	**CLAG**	**CLAG**	**CLAG**	**CLAG**			
AraC (A):											
G-CSF (G)			**G**								

Selinexor 60 mg PO d1,4,8,11
Cladribine 5 mg/m^2/d on Days 4-8
AraC 2000 mg/m^2/d on Days 4-8
G-CSF 300 mcg SC/d on Days 3-8

Maintenance therapy Selinexor 60 mg on Days 1, 8, 15, and 22 of a 28 day cycle permitted for those achieving CR/CRi

Baseline Patient Characteristics

Patient Characteristics (n=33)	
Age, median (range)	56(21-70)
Male (%)	24(73)
Onset of AML n, (%)	
De novo (%)	26(79)
Secondary	7(21)
Indication for therapy, n (%)	
Primary refractory	12(36)
1st Relapse	19(58)
Remission duration, mo (range)	8(1-18)
Hypomethylator refractory	2(6)
Cytogenetic risk, n (%)	
Favorable	2(6)
Intermediate/Unknown	20(61)
Poor	11(33)
WBC K/mm^3, median (range)	2.4(0.6-140)

Response Rate

Treatment Response	N=33	%
CR	8	24%
CRi	7	21%
CR+CRi	**15**	**45%**
Resistant Disease	17	52%
Death prior to AML eval	1	3%

Bridge to alloHCT

- 18 out of first 30 patients (60%)
- 10 pts who achieved CR/CRi with CLAG-Selinexor

Safety and Tolerability

- Time to hematopoietic recovery
  - ANC recovery (≥ 1,000/mm^3) median 33 days (n=22, range 21-52)
  - Platelet recovery (≥ 100,000/mm^3) median 33 days (n=12 range 25-61)
- All cause mortality
  - Two deaths during treatment phase from lung infection / respiratory failure
  - 30 days: n=1 of 33 (3%)
  - 60 day: n= 2 of 33 (6%)
- Serious adverse events (n=20)
  - Primarily related to sepsis (n=7), other infections (n=4)

Selected Common Adverse Events (n=33)

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	%
Gastrointestinal disorders							
Mucositis oral	11	6	3	1		21	64%
Nausea	11	7	1			19	58%
Diarrhea	7	5	3			15	45%
Vomiting	11	4				15	45%
Constipation	3	7				10	30%
General							
Weight loss	11	10				21	64%
Fatigue	4	9	2			15	45%
Chills	12					12	36%
Pain	2	4	1			7	21%
Infections and infestations							
Skin infection		1	9			10	30%
Sepsis				9		9	27%
Bacteremia			8			8	24%
Lung infection			6		1	7	21%

Conclusions

- Completion of accrual expected in Jan 2018
- Selinexor + CLAG is highly active in patients with relapsed or refractory AML and has encouraging rates of CR for a non-anthracycline containing chemotherapy regimen.
- The combination serves as a bridge which allows a high percentage of patients to undergo allogeneic hematopoietic cell transplantation.
- Correlative studies underway to understand the effect of selinexor on nuclear/cytoplasmic trafficking of regulators of leukemogenesis

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