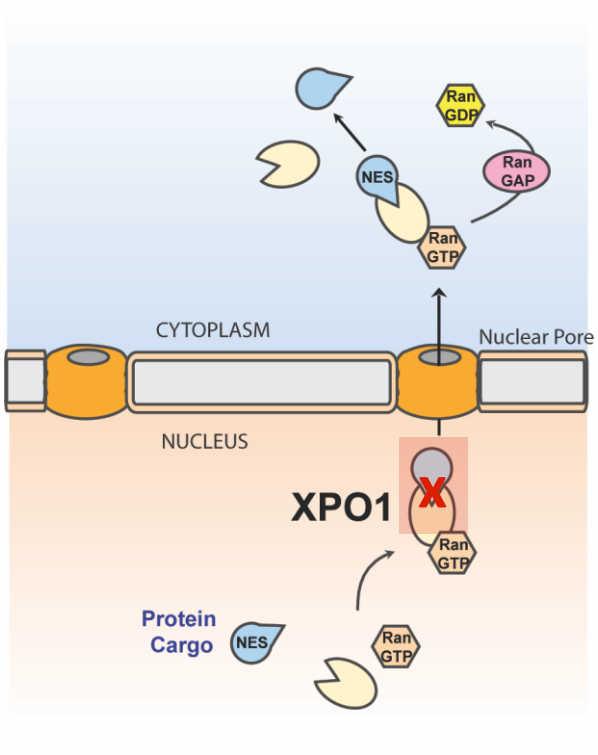
Selinexor, a First-in-Class XPO1 Inhibitor, Is Efficacious and Tolerable in Patients with Myelodysplastic Syndromes (MDS) Refractory to Hypomethylating Agents

Justin Taylor, MD, Morgan Coleman, MPH, Kelsey Alvarez, RN, Margaret Nelsen, Janine Pichardo, Filiz Sen, MD, Stephen S. Chung, MD, Raajit K. Rampal, MD, PhD, Jae H. Park, MD, Eytan M. Stein, MD, Martin S. Tallman, MD, Omar Abdel-Wahab, MD and Virginia M. Klimek, MD

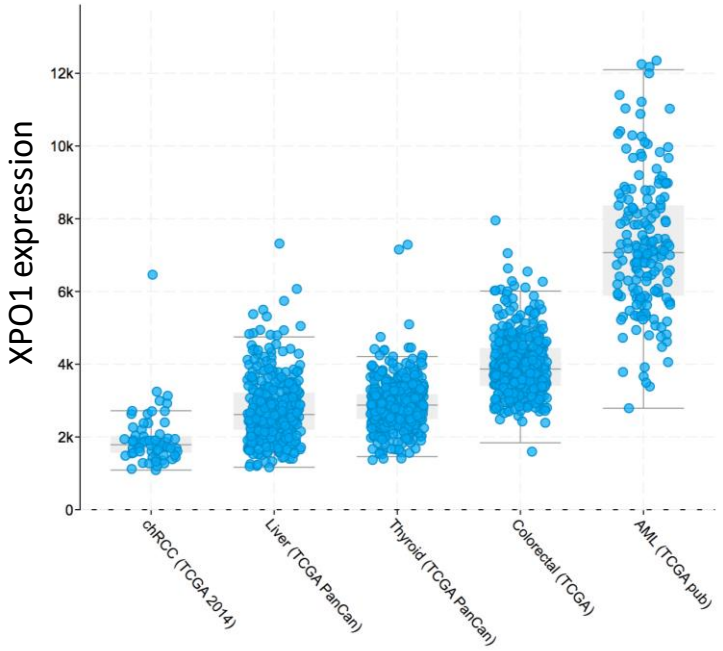
Memorial Sloan Kettering Cancer Center

Selinexor is an oral, slowly-reversible, first-in-class Selective Inhibitor of Nuclear Export (SINE)

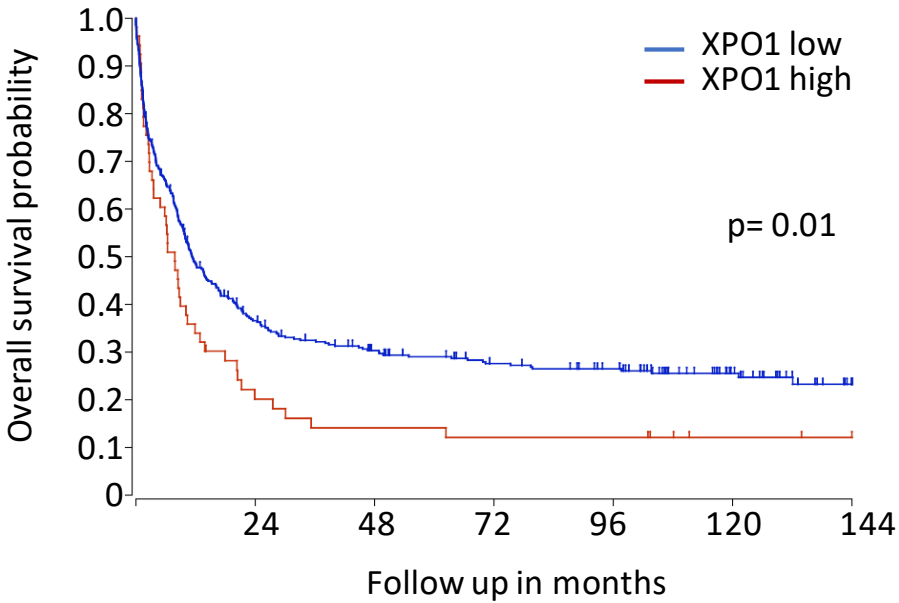


- XPO1 is the main nuclear export protein in eukaryotic cells and is essential for cell homeostasis
- Selinexor binds Cysteine-528 of XPO1 blocking cargo binding
- XPO1 inhibition induces cell-cycle arrest and apoptosis

XPO1 over-expression is seen in MDS/AML and is associated with decreased survival

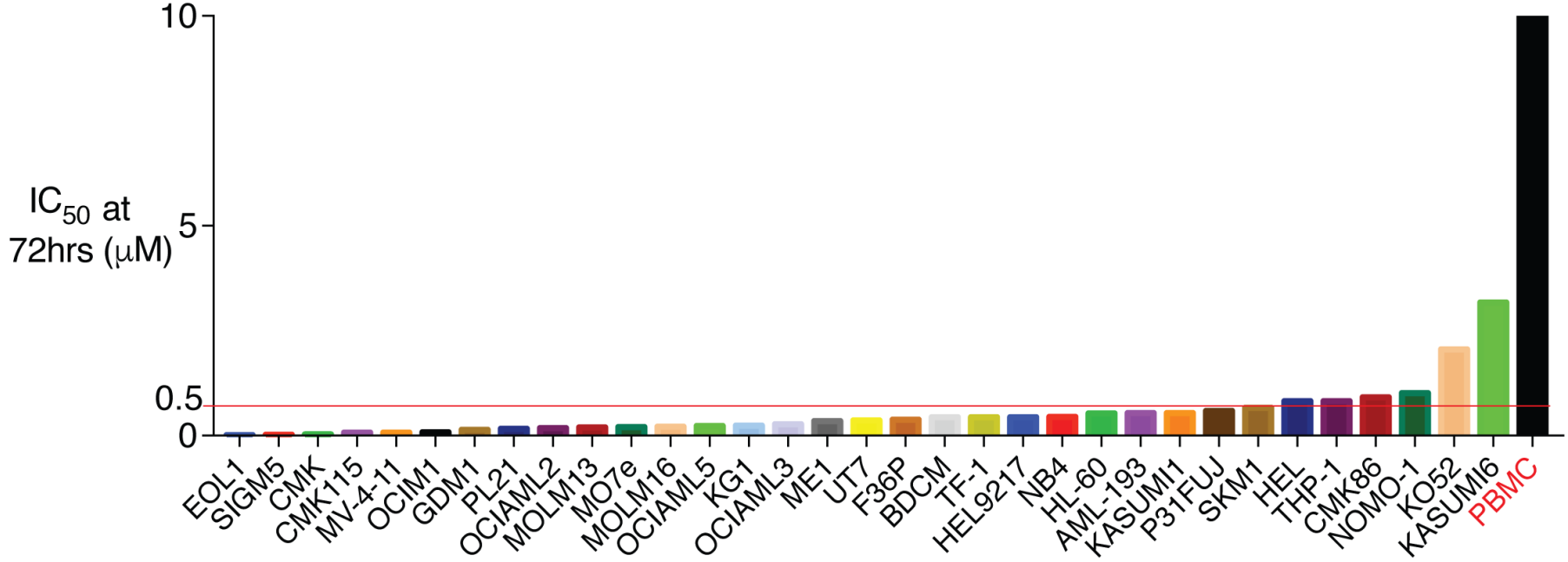


cBioportal.org



Li Z, *et al*, J Clin Oncol. 2013 Mar 20;31(9): 1172-81

Selinexor has broad cytotoxicity in myeloid leukemia cell lines at <0.5μM IC_{50} range



High need for new therapies in patients with MDS refractory to hypomethylating agents (HMA)

- Standard treatment options are limited after HMA
  - AML induction therapy (if appropriate)
  - Allogeneic SCT (if appropriate)
  - Supportive care

- Survival is short following HMA failure
  - IPSS Int-2/High Risk: approx. 5-6 months[1]
  - IPSS Low/Int-1 Risk: approx. 16-17 months[2,3]

1. Prebet T, *et al*, J Clin Oncol. 2011;29(24): 3322-7
2. Prebet T, *et al*, Haematologica 2013;98(2): e18-e19
3. Jabbour EJ, *et al*, Cancer 2015;121(6): 876-82

Investigator-initiated, single-arm, Phase 2 trial of selinexor in HMA refractory MDS

Primary Endpoint:

ORR (CR+mCR+PR+HI)

(Cheson BD, *et al*, Blood 2006;108: 419–425)

Secondary Endpoints:

Safety, Duration of Response, Survival

Exploratory Objectives:

Genetics, RNA Expression, Protein Levels as Biomarkers

Allowable selinexor dose reductions on 3-week schedule:

- 40mg twice weekly for 2 weeks
- 80mg once weekly for 2 weeks

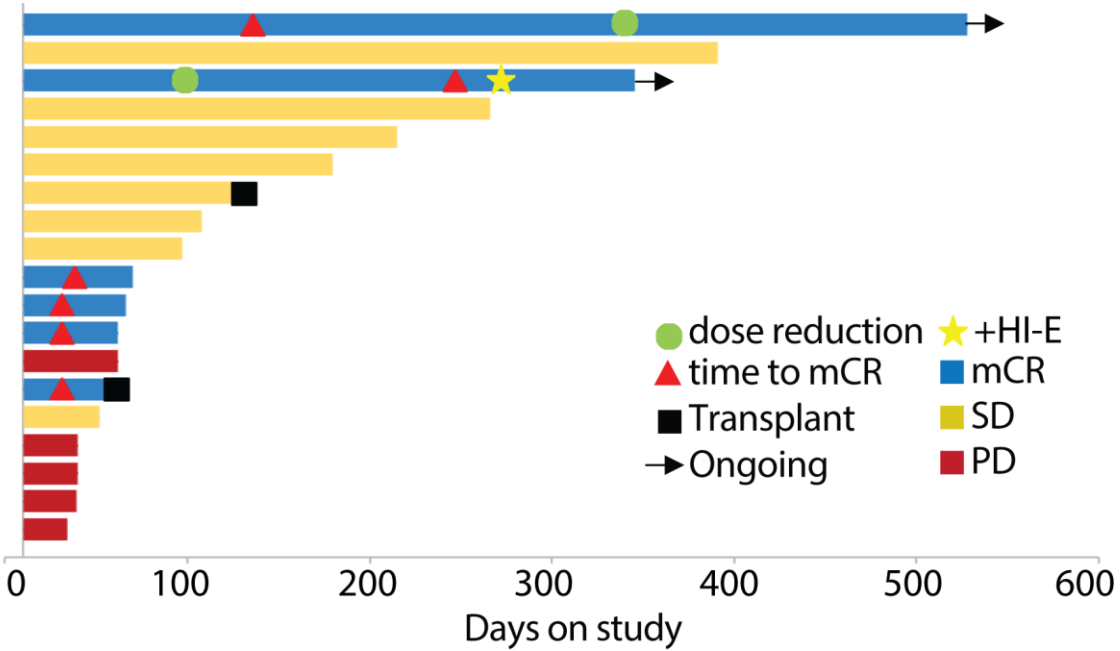
Trial included older patient population with high-risk MDS characteristics

Baseline characteristics (n=25)

	# Pts	% Pts
Median Age (years)	77 (50 - 86)	
Female	4	16%
Male	21	84%
De novo	19	76%
Therapy-Related	6	24%
WHO Subtype		
RAEB-1	4	16%
RAEB-2	12	48%
AML	4	16%
RCUD	1	4%
RCMD	3	12%
MDS/MPN	1	4%
IPSS-R Risk Group		
Very Low	0	0%
(≥)Low	2	8%
(≥)Intermediate	5	20%
(≥)High	7	28%
Very High	11	44%

	# Pts	% Pts
BM BLASTS		
< 5%	2	8%
5-10%	6	24%
11-20%	13	52%
21-30%	4	16%
IPSS-R Cytogenetics		
Very Good	1	4%
Good	4	16%
Intermediate	7	28%
Poor	3	12%
Very Poor	5	20%
Unknown	5	20%
PRIOR THERAPY		
MEDIAN CYCLES	13 (3 - 67)	
Azacitidine	14	56%
Decitabine	3	12%
Aza & DAC	6	24%
HMA & Other	3	12%

Selinexor is associated with a 32% ORR (n=19 patients evaluable for efficacy*)



- Response duration 6.8 mo
- 2 ongoing responses >1 yr
- An additional 42% had SD

*6 patients did not receive 1 complete cycle:
PD/death (n=4), withdrawal (n=1), concurrent illness (n=1)

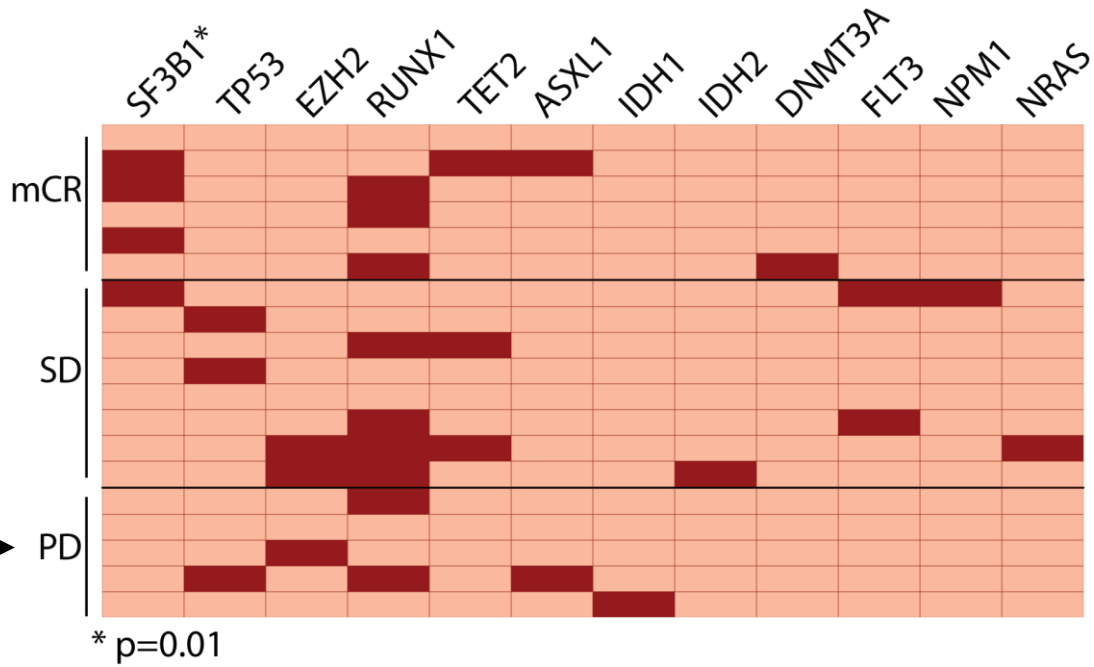
Responses and associated disease-related parameters (n=19 evaluable for response)

	Time to Best Response	Time on Study (appx. days)	IPSS-R Risk Category	IPSS Cytogenetics	WHO Subtype
mCR * +HI-E	21	52	Intermediate	Unknown	RAEB-1
	126	390	Intermediate	Very Good	RAEB-2
	21	63	Very High	Poor	RAEB-2
	28	72	High	Good	RAEB-2
	237	321	* High	Intermediate	RAEB-2
	21	105	High	Intermediate	RAEB-1
SD	20	133	Intermediate	Unknown	RCMD
	21	90	Very High	Very Poor	RAEB-2
	28	16	High	Unknown	AML (20%)
	21	62	Very High	Very Poor	RAEB-2
	21	217	High	Intermediate	AML (25%)
	20	259	High	Good	MDS/MPN
	21	63	Very High	Intermediate	RAEB-1
	21	21	Very High	Good	RAEB-2
	21	52	High	Good	RAEB-2
PD	21	42	Very High	Poor	AML (20%)
	28	35	High	Intermediate	AML (20%)
	21	36	Very High	Very Poor	RCUD
	21	42	Very High	Very Poor	RCMD-RS

Responses by molecular abnormalities (n=19 evaluable for response)

SF3B1 mutation was significantly associated with response

TP53 mutation or >3 mutations non-significantly enriched in non-responders



Selinexor is safe and tolerable in MDS at 60mg flat dose given twice weekly

% Adverse Effect By Grade and Cycle Length (n=25)

4-week (35mg/m^2)

3-week (60mg flat)

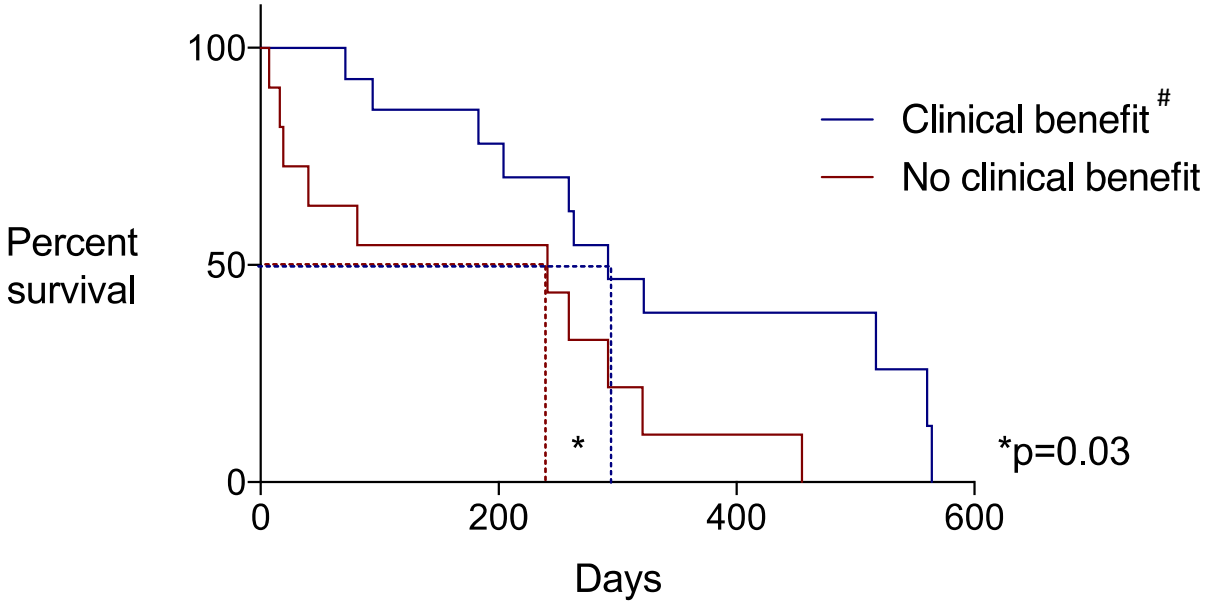
	Gr 1		Gr 2		Gr 3		Gr 4	
cycle length	*4wk*	*3wk*	*4wk*	*3wk*	*4wk*	*3wk*	*4wk*	*3wk*
ALT Increased		13						
AST Increased		6.3						
Anemia				6.3	40			
Anorexia/Weight Loss		31.3	40	6.3				
Back Pain		6.3						
Blood Bilirubin Increased		6.3						
Blurred Vision				6.3				
Diarrhea	20	6.3		6.3		6.3		
Dizziness		6.3						
Dysgeusia		18.8		6.3				
Dehydration			20					
Dry Mouth		6.3						
Dyspnea	20							
Fatigue	20		60	31.3	20	12.5		
Febrile Neutropenia						12.5		
Flu Like Symptoms		6.3						
Headache		6.3						
Hypotension								6.3
Hyperglycemia	40	12.5	20	12.5		12.5		
Hyperkalemia	40							
Hypoalbuminemia	60	18.8						
Hypocalcemia		6.3	20			6.3		
Hyponatremia	40	25			20	25		
INR Increaded		6.3						
Lethargy			20					
Lung Infection						6.3		
Malaise	20		20					
Mucosal Infection				6.3				
Nausea/Constipation	40	50		12.5	20			
Neutrophil Count Decreased				12.5		12.5	20	
Oral Hemorrhage		6.3						
Platelet Count Decreased	20	6.3		6.3		12.5	40	18.8
Weakness			20					
White Blood Cell Decreased	20			6.3	20		20	

>10% decrease with 60mg twice weekly

>10% increase with 60mg twice weekly

Using patients' highest grade per toxicity

Selinexor improves survival in HMA refractory MDS compared to historical cohorts

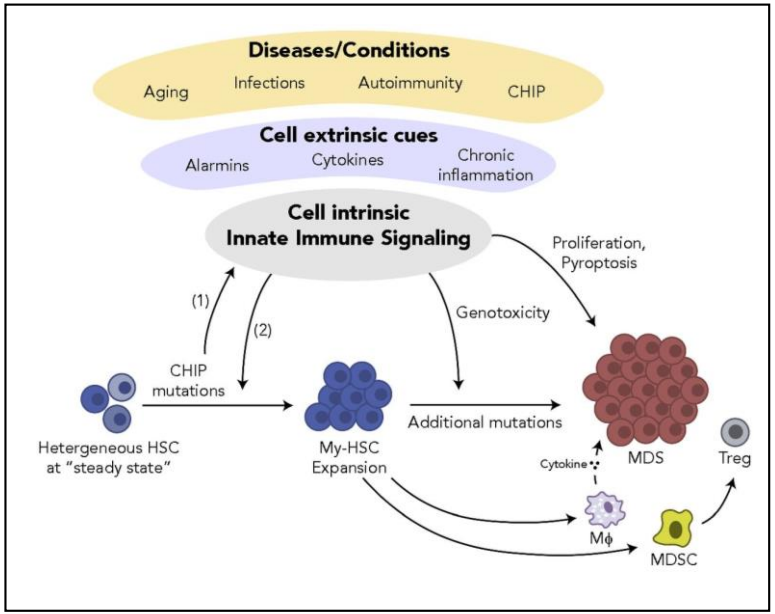


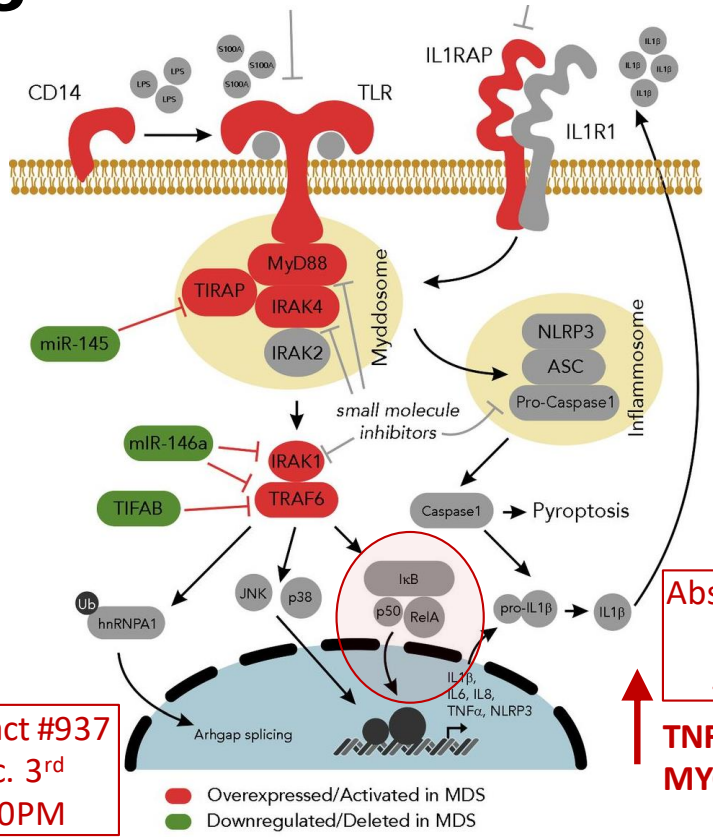
- Median OS = 9.7 months
- Historical survival 5-6 months in high-risk pts

(Prebet *et al*, JCO. 2011)

Clinical benefit includes patients with SD

Recent data implicate innate immune activation in the pathogenesis of MDS





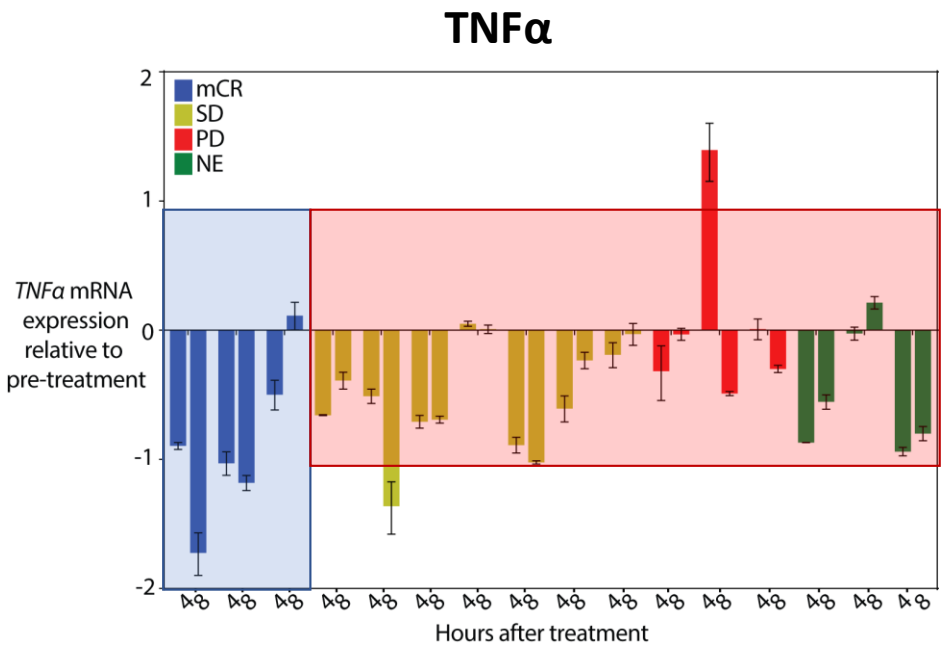
Barreyro L, *et al*, Blood 2018;132:1553-1560
Lee SCW *et al*, Cancer Cell 2018; 34:225-241

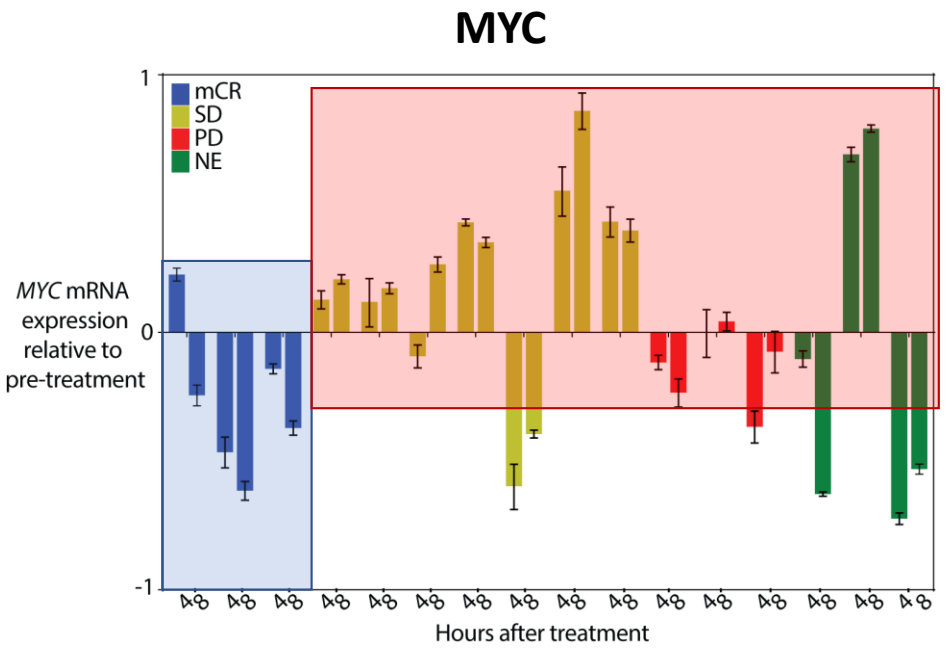
Abstract #937
Dec. 3rd
4:30PM

Abstract #882
Dec. 3rd
5:45PM

TNFα, MYC

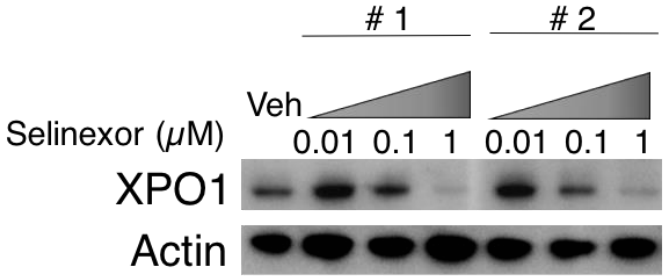
Selinexor decreases NF-κB target genes and alters MYC transcription levels



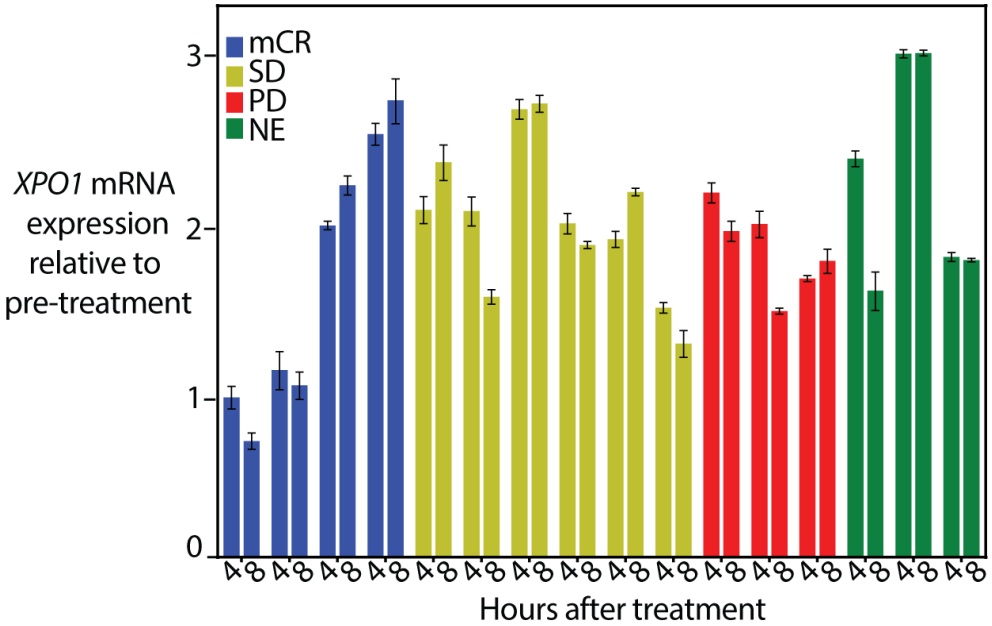


Measured from Peripheral Blood Mononuclear Cells

XPO1 mRNA levels are increased at 4 and 8 hours after selinexor administration



Preclinical degradation of XPO1 with exposure to selinexor



***XPO1* mRNA increase may be a biomarker for SINE target effect**

*XPO1 protein levels in pt samples ongoing

Conclusions

- Primary efficacy endpoint was reached with ORR = 32%
- 60mg flat dose given twice weekly for 3 weeks was tolerable and PD markers suggest sufficient for target engagement
- Median overall survival was 9.7 months compared to historical control of 5-6 months
- *SF3B1* mutation significantly associated with response

Acknowledgements

MSKCC

Morgan Coleman
Margaret Nelsen
Kelsey Alvarez, RN
Filiz Sen, MD- Pathology
Omar Abdel-Wahab lab
Virginia Klimek, MD
Leukemia Service

NYP-Columbia

Gary Schwartz lab

MSKCC patients and their families

Karyopharm Therapeutics

Memorial Sloan Kettering Cancer Center

CYCLE FOR SURVIVAL

MEMORIAL SLOAN KETTERING | EQUINOX