Selinexor

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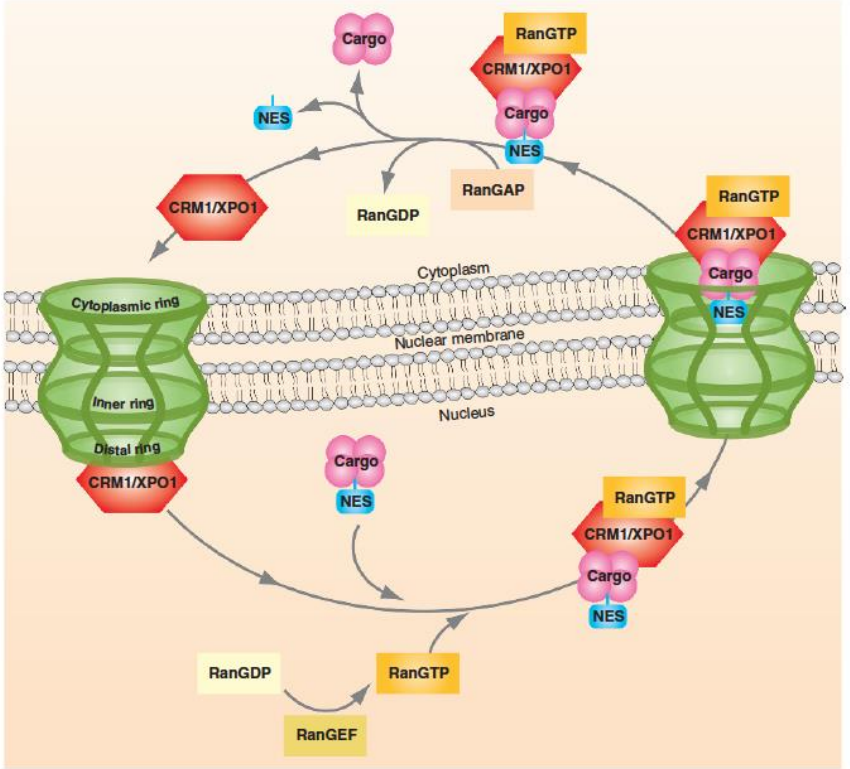
Disclosures of John Kuruvilla

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie			X			X	
BMS			X			X	
Janssen	X		X			X	
Merck			X			X	
Roche	X		X			X	
Gilead			X			X	
Seattle Genetics			X			X	
Karyopharm						X	

Nuclear Pore Complex

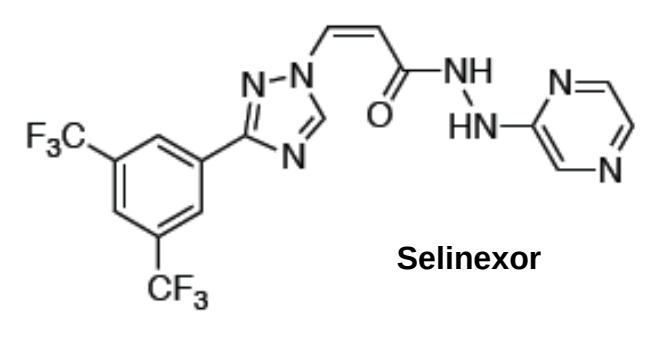


Tan Cancer Discovery 2014

Responsible for protein traffic between cell nucleus and cytoplasm
XPO1 and RanGTP

Cancer targets undergoing XPO1 mediated nuclear export include:
p53, APC, ATF2, BCR-ABL, BOK, BRCA1, CIP2A, p21, p27, ERK, ER-a, FOXO1, FOXO3A, FOXO4, FOXO6, Galectin-3, HSP90, In1/hSNF5, NF2NPM, N-WASP/FAK, RASSF2, RB1, RUNX3, survivin, ErbB-2, Topo1, Topo2A, VDUP1, WEE1

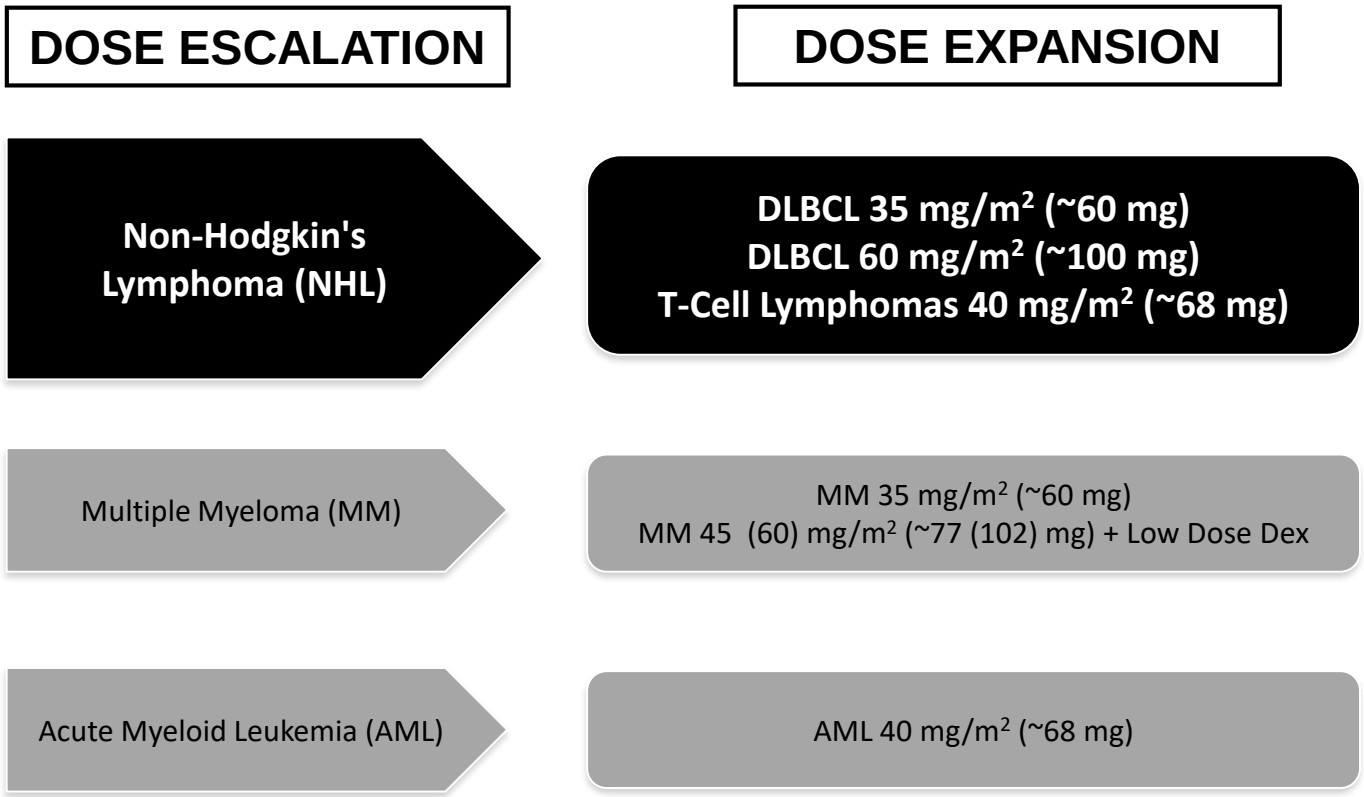
Selinexor:
First-in-Class, Oral Selective Inhibitor of Nuclear Export (SINE) Compound



Selinexor

- Novel, small molecule selective inhibitor of 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
- Potent anti-myeloma, lymphoma and leukemia effects in preclinical models
- Over 2450 patients dosed alone or in combination
- Randomized Phase II/III studies ongoing in advanced hematologic and solid tumors

Study Design: NCT01607892



Treatment and Key Inclusion

- Treatment Scheme
  - Selinexor dosing 10 doses/cycle (2-3 doses/week) or 8 doses/cycle (twice weekly) or 4 doses/cycle (once weekly)
- Doses
  - 3 mg/m^2 – 80 mg/m^2 (~ 5 mg – 136 mg)
- Main Inclusion Criteria
  - Patients ≥18 years old, ECOG performance status 0-1, no available standard treatments
  - ANC >1000/µL, Platelets >30,000/µL
  - Documented disease progression at study entry

Phase 1: Selinexor in R/R NHL to assess safety and determine RP2D

43 R/R DLBCL patients enrolled (79 NHL)

Median age 60 years (range 30-82)

Median of 3 prior therapies (range 2-11)

28% refractory to last therapy, 30% had prior auto SCT

Dose escalation 3-80 mg/m2 in 21 or 28 day cycles

Dose expansion 35-60 mg/m2; 30 or 60 mg flat

Most common grade 3-4 events:

Thrombocytopenia (47%)

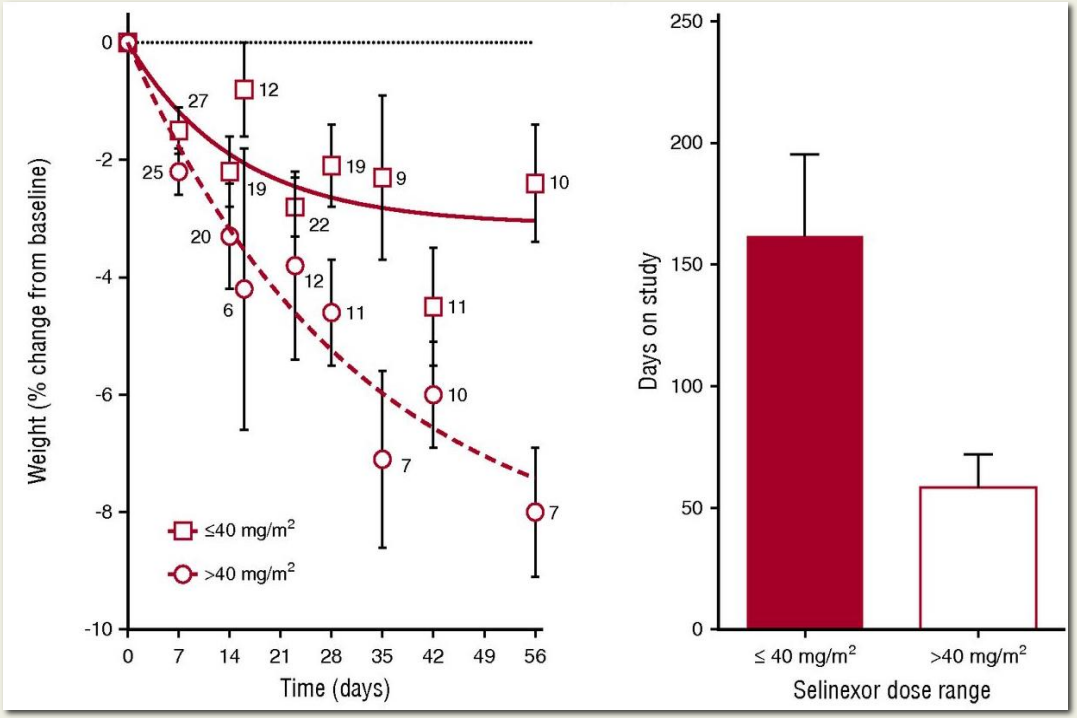
Neutropenia (32%)

Leukopenia (16%)

Fatigue (11%)

Hyponatremia (10%)

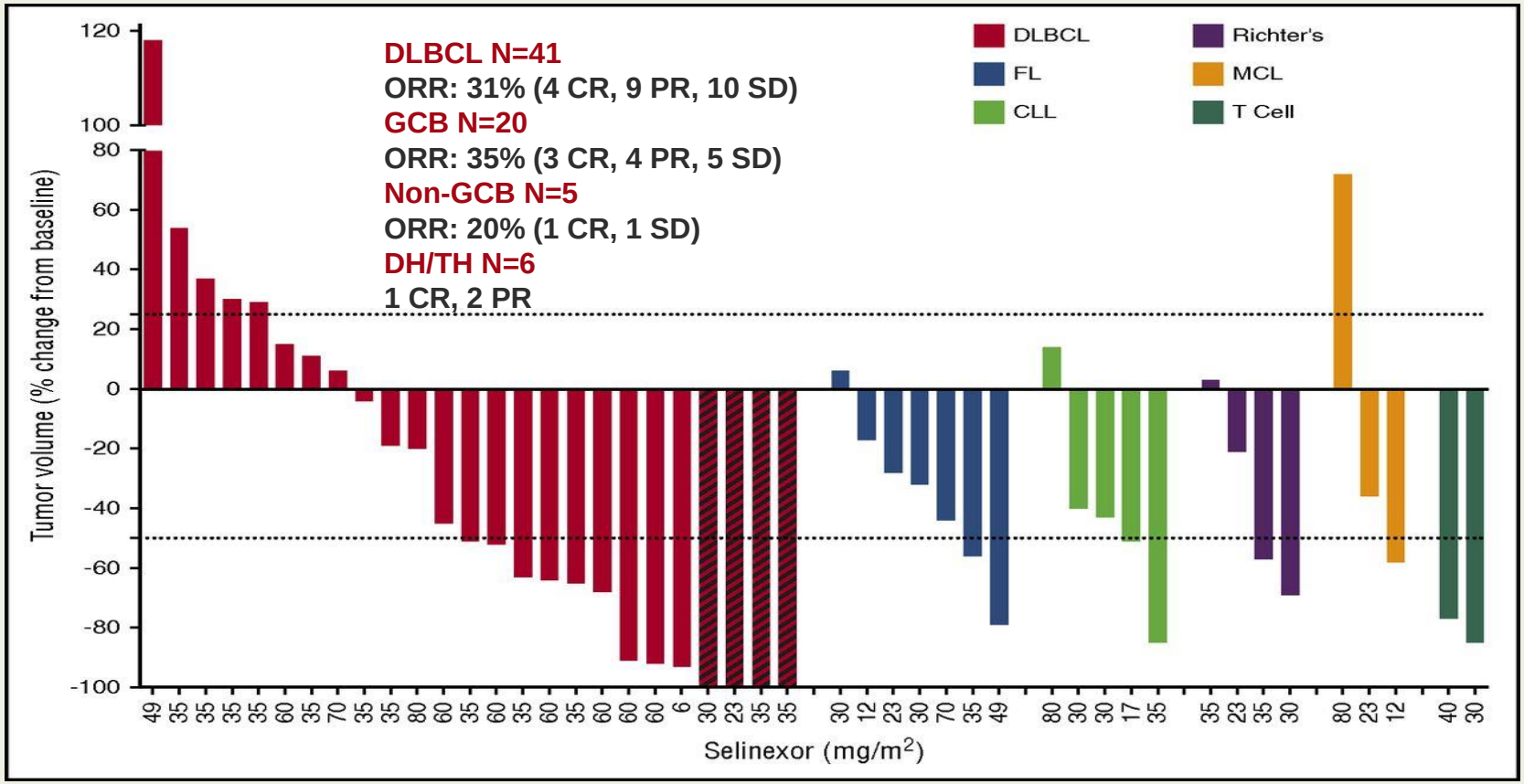
RP2D = 60 mg



Weight Change During Cycles 1-2

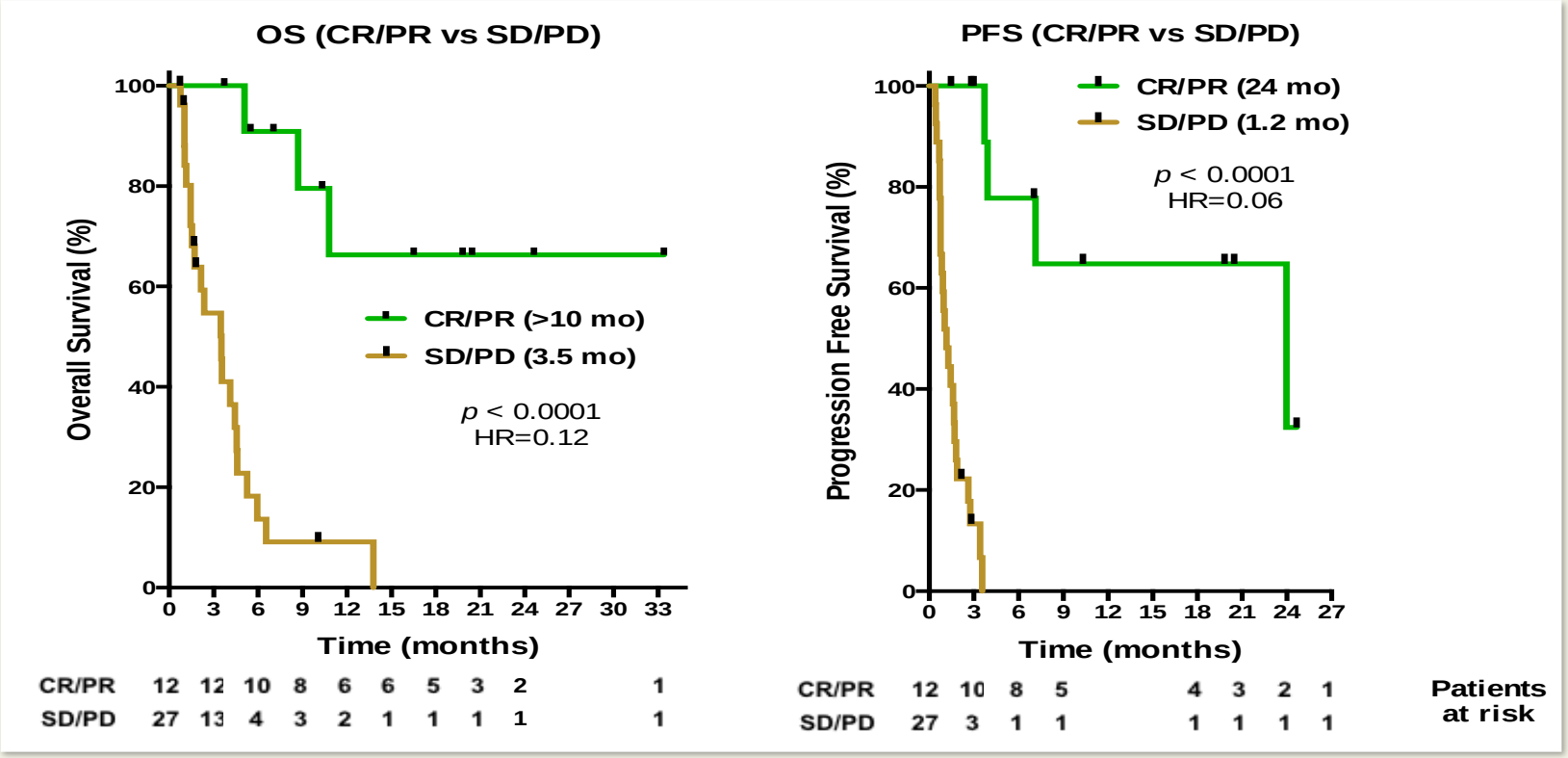
Kuruvilla, Blood 2017

Phase 1 Selinexor in R/R NHL: Waterfall



Kuruvilla , Blood 2017

DLBCL Responses were Durable



Garzon et al., EHA 2015

SADAL[1]: A Phase 2b Study In DLBCL(Pv7)-Ongoing

Ongoing open-label clinical trial evaluating selinexor in patients with relapsed or refractory (≥3rd line) DLBCL; at least 50% of patients with GCB-DLBCL

[1] **S**elinexor **A**gainst **D**iffuse **A**ggressive **L**ymphoma

SADAL: Baseline Patient Characteristics (PV6 ≥14 weeks from last treatment)

A randomized Phase 2B study investigating 60 mg vs.100mg single agent oral selinexor in patients with relapsed or refractory diffuse large B-Cell lymphoma (DLBCL) who are not candidates for transplantation

	60 mg	100 mg
Patients Enrolled as of May 15, 2017 (N=90)	46	44
Median Age, Years (range)	68 (44 – 87)	66 (30 – 83)
Males : Females	29 M : 17 F	28 M : 16 F
de novo DLBCL : Transformed DLBCL	74% de novo : 26% trans	70% de novo : 30% trans
GCB Subtype	22 (48%)	23 (52%)
Non-GCB Subtype	24 (52%)	21 (48%)
Median Prior Regimens (range)	3 (2 – 5)	3 (2 – 5)
- Prior Stem Cell Transplant	13 (28%)	18 (41%)
R-IPI Risk (Sehn 2007)		
- High Risk	7 (15%)	7 (16%)
- High Intermediate Risk	18 (39%)	15 (34%)
- Low Intermediate Risk	14 (31%)	15 (34%)
- Low Risk	6 (13%)	5 (11%)
- Unknown	1 (2%)	2 (5%)

Maerevoet,et al EHA 2017

SADAL: Efficacy: Pre-Specified Interim Analysis First 63 Patients

Best Responses† in the First 63 Patients as of May 15, 2017					
Category	All Patients (N=63)	60 mg (N=32)	100 mg (N=31)	GCB (N=32)	Non-GCB (N=31)
ORR (%)	21 (33.3%)	11 (34.4%)	10 (32.2%)	9 (28.1%)	12 (38.7%)
CR (%)	9 (14.3%)	4 (12.5%)	5 (16.1%)	4 (12.5%)	5 (16.1%)
PR (%)	12 (19.0%)	7 (21.9%)	5 (16.1%)	5 (15.6%)	7 (22.6%)
SD (%)	6 (9.5%)	1 (3.1%)	5 (16.1%)	3 (9.4%)	3 (9.7%)
PD/NE (%)	36 (57.1%)	20 (62.5%)	16 (51.6%)	20 (62.5%)	16 (51.6%)

†Responses were adjudicated according to the Lugano Classification *(Cheson, 2014)* by an independent central radiological review committee. ORR=Overall Response Rate (CR+PR), CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, NE=Non-evaluable. Responses are based on interim unaudited data as of May 15, 2017 for the first 63 patients (of 90 total patients).

Overall response rate as determined by an independent central radiological review

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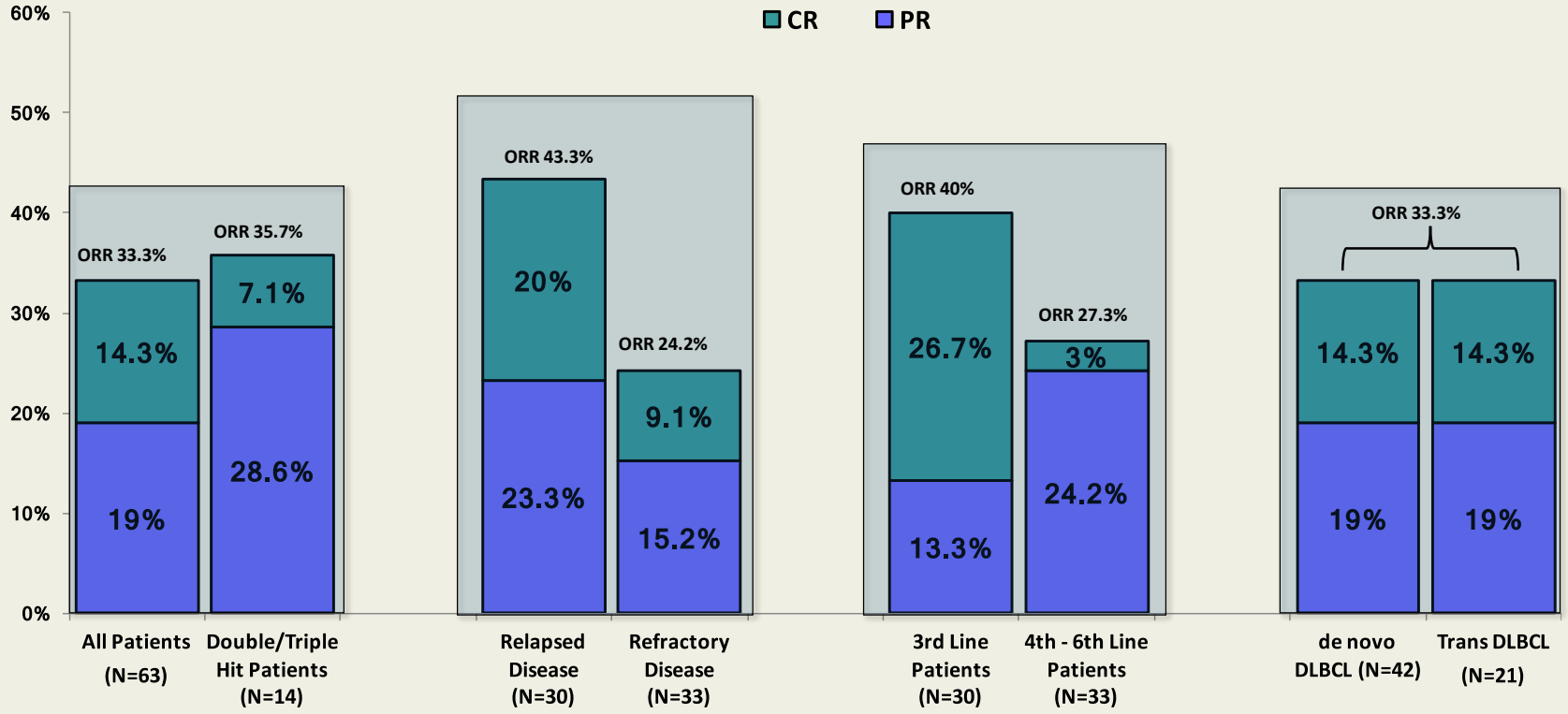
Efficacy: ORR Subgroups



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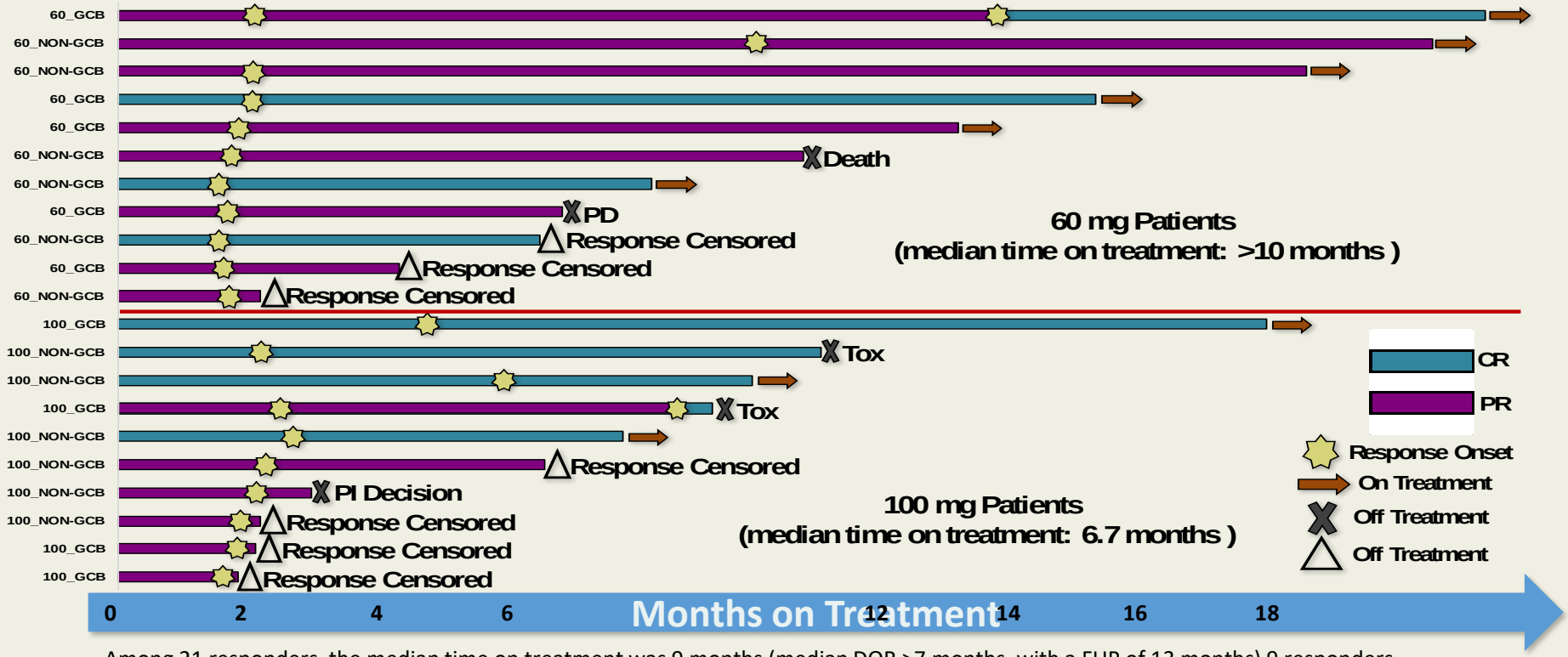
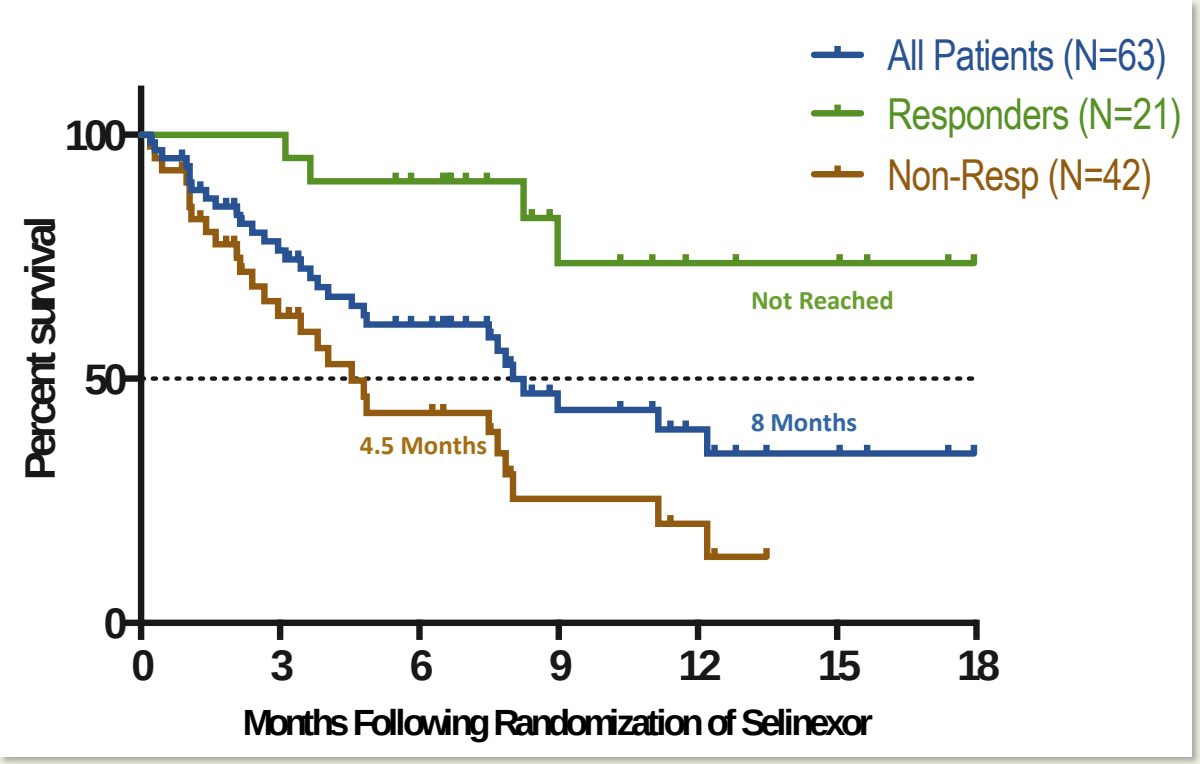
Responders (N=21): Response Onset & Time on Treatment



Among 21 responders, the median time on treatment was 9 months (median DOR >7 months, with a FUP of 13 months) 9 responders remain on treatment including 6 patients in CR; as of March, 2018, several patients have remained on study >24 months

SADAL Efficacy: Overall Survival



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SADAL: Safety-Related Adverse Events Occurring in ≥10% of Patients Rx at 60mg (N=46)

AE Term	60 mg N=46			
Gastrointestinal	**Grade 1/2**	**Grade 3**	**Grade 4**	**G 3/4 Total**
Nausea	21 (45.7%)	3 (6.5%)	--	3 (6.5%)
Anorexia	18 (39.1%)	1 (2.2%)	--	1 (2.2%)
Vomiting	16 (34.8%)	--	--	--
Diarrhea	14 (30.4%)	1 (2.2%)	--	1 (2.2%)
Altered Taste	6 (13%)	--	--	--
Constipation	6 (13%)	--	--	--
Constitutional				
Fatigue/Asthenia	22 (47.8%)	5 (10.9%)	--	5 (10.9%)
Weight Loss	12 (26.1%)	--	--	--
Hematologic				
Thrombocytopenia	6 (13%)	8 (17.4%)	5 (10.9%)	13 (28.2%)
Anemia	8 (17.4%)	7 (15.2%)	--	7 (15.2%)
Neutropenia	4 (8.7%)	5 (10.9%)	3 (6.5%)	8 (17.4%)
Other				
Hyponatremia	1 (2.2%)	3 (6.5%)	--	3 (6.5%)
Dizziness	2 (4.3%)	--	--	--

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Causes of Treatment Discontinuation (N=46)

	60 mg (N=46)
Patients Off Treatment	34 (74%)
Progressive Disease	21 (62%)
Toxicity	6 (18%)
Death	4 (12%)
Other	3 (9%)
Median Dose Received	51 mg

Maerevoet,et al EHA 2017

Selinexor – current single agent DLBCL data

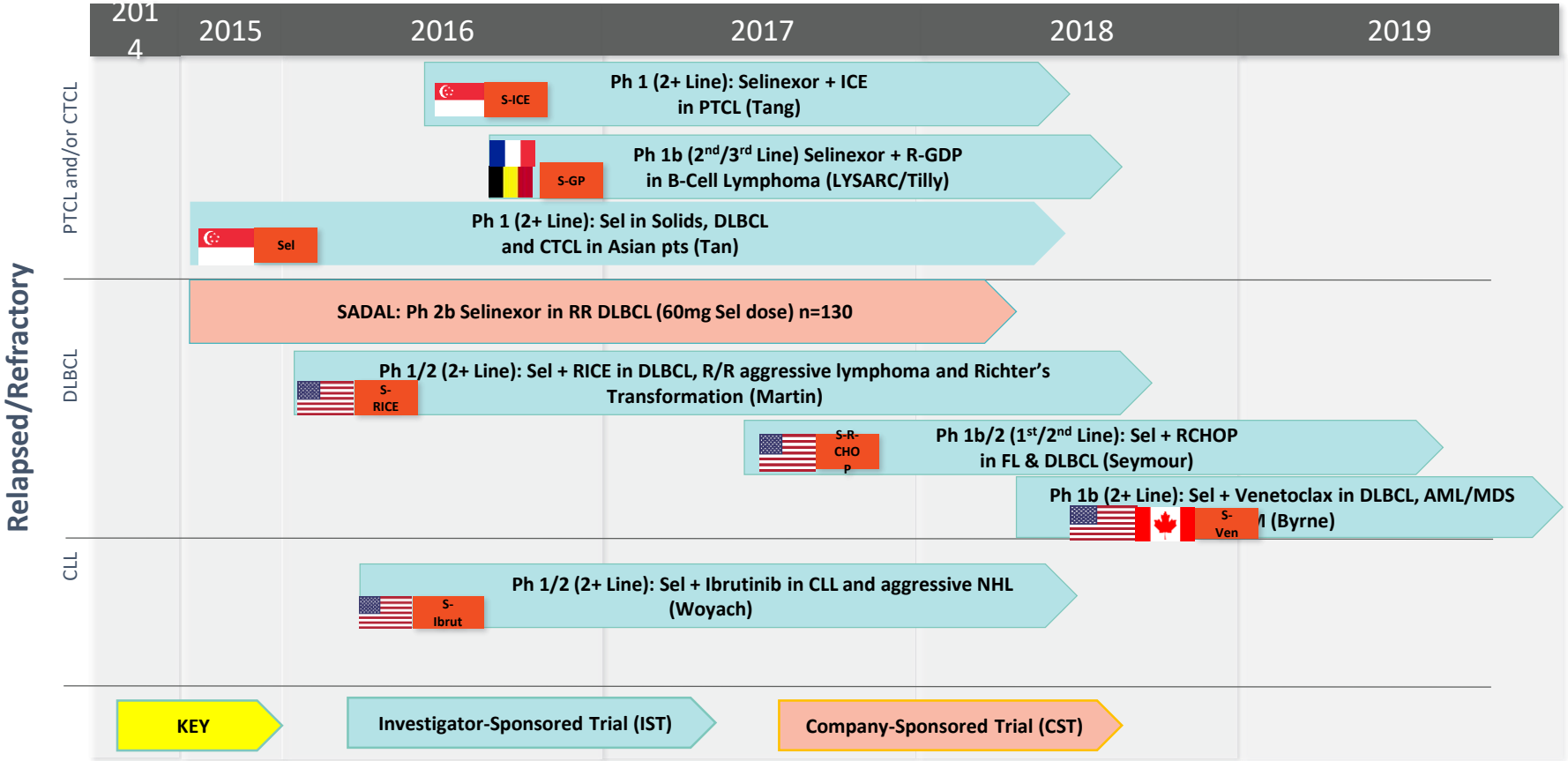
- ORR: approximately 35%
  - Activity in both GCB and non-GCB
- Toxicity
  - Grade 3-4 thrombocytopenia 28%
  - Grade 3-4 neutropenia: 17%
  - Grade 3-4 anemia 15%

  - Grade 3-4 fatigue/asthenia: 11%
  - Grade 1-2 GI tox 40%
  - Grade 3-4 nausea 6.5%

Conclusions from Available Data

- Selinexor has single agent activity in DLBCL
  - Independent of cell of origin
  - Responses seen in poor risk populations
  - No predictive biomarker
- SADAL trial confirms data from phase 1 suggesting 60 mg is optimal dose as monotherapy
- Toxicity is reasonable and can be managed with routine supportive care
- Anti-cancer mechanism in lymphoma unclear
  - Makes rational combination challenging – pre-clinical data with chemotherapy, proteasome inhibitors, BCL2 inhibitor, BTK inhibitor as examples

Selinexor Clinical Development in NHL



Summary – Selinexor in Lymphoma

- Single agent activity demonstrated with reasonable toxicity
  - No biomarker identified for enrichment
  - Mechanism remains unclear
  - Clearest signal in DLBCL
  - Potential activity in other lymphoma subtypes not well explored
  - Combinations possible
- Development plan
  - DLBCL: Confirmatory RCT design undecided
  - Optimal place unclear
  - Other diseases?