Phase 1 study of safety and tolerability of Selinexor in Asian patients with advanced solid cancers

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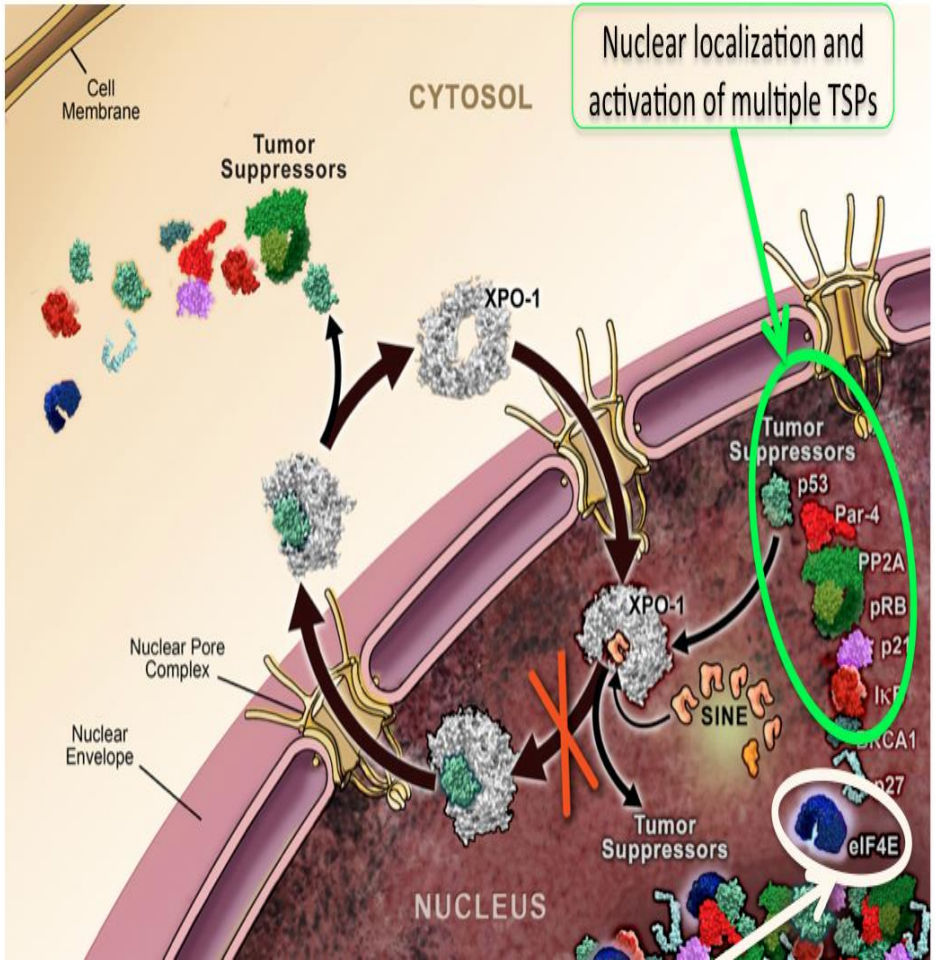
Selective Inhibitors of Nuclear Export (SINE)

- Tumor Suppressor Proteins (TSPs) exert anti-neoplastic effects in the nucleus.
- Cancer cells can inactivate TSPs via the nuclear export mechanism
- Exportin 1 (XPO1) is the nuclear exporter of most TSPs
- Blockade of XPO1 leads to nuclear retention and activation of multiple TSPs and reduced translation of key oncogenes (myc, BCL2/BCL6)
- Selinexor is a covalent, oral selective inhibitor of nuclear export against XPO1
- First in class Asian patients, phase 1 study



Study design

- Objectives
  - Primary: Safety, tolerability and Recommended Phase 2 Dose (RP2D) of selinexor in Asian patients with solid tumour and lymphoma
  - Secondary: Pharmacokinetics (PK), pharmacodynamics (PDn), anti-tumor response
- Modified 3+3 design
- Major eligibility criteria:
  - Advanced or metastatic solid tumour and lymphoma
  - ECOG 0-1
  - Documented progression at study entry
  - Stable brain metastases permissible

Treatment schedules

Schedule 1 (S1):

- Twice weekly continuous 28 day cycle at 40 mg/m^2
- S1 was stopped due to persistent drug-related adverse events (AEs) – two additional schedules were subsequently explored:

Schedule 2 (S2):

- Once weekly for a 28 day cycle, starting at 50 mg/m^2

Schedule 3 (S3):

- Twice weekly for 2 weeks of a 21 day cycle, starting at 40 mg/m^2

DLT criteria

- Discontinuation of a patient due to toxicity in cycle 1
- Non Hematologic: Gd ≥3 (nausea/vomiting, diarrhea, fatigue > 5 days, AST/ALT > 7days, electrolyte abnormalities despite adequate supplements)
- Hematologic: Gd 4 neutropenia ≥ 7 days, febrile neutropenia, Gd 4 thrombocytopenia ≥ 5 days or Gd 3 associated with bleeding

Patient demographics and disease characteristics

Characteristic	N=40
Median age (range)	60 (25 – 76)
Male /Female	25 /15
Median prior lines of treatment (range)	4 (1 – 9)
ECOG performance status, 0/1	22/18
Disease site	
-Colorectal	15
-Lymphoma	7
- Lung	4
-Pancreas	4
-Head & Neck	3
-Ovarian	2
-Liver	2
-Other (esophagus, thymic, RCC, sarcoma)	4

Dose levels, DLT and MTD

Shedule 1: Twice a week continuous schedule			
Dose Level (mg/m2)	DLT Evaluable Patients (n=6)	**Pts with DLT**	**DLT**
40	6	1	G3 diarrhea
Ceased due to chronic, persistent drug related toxicity			

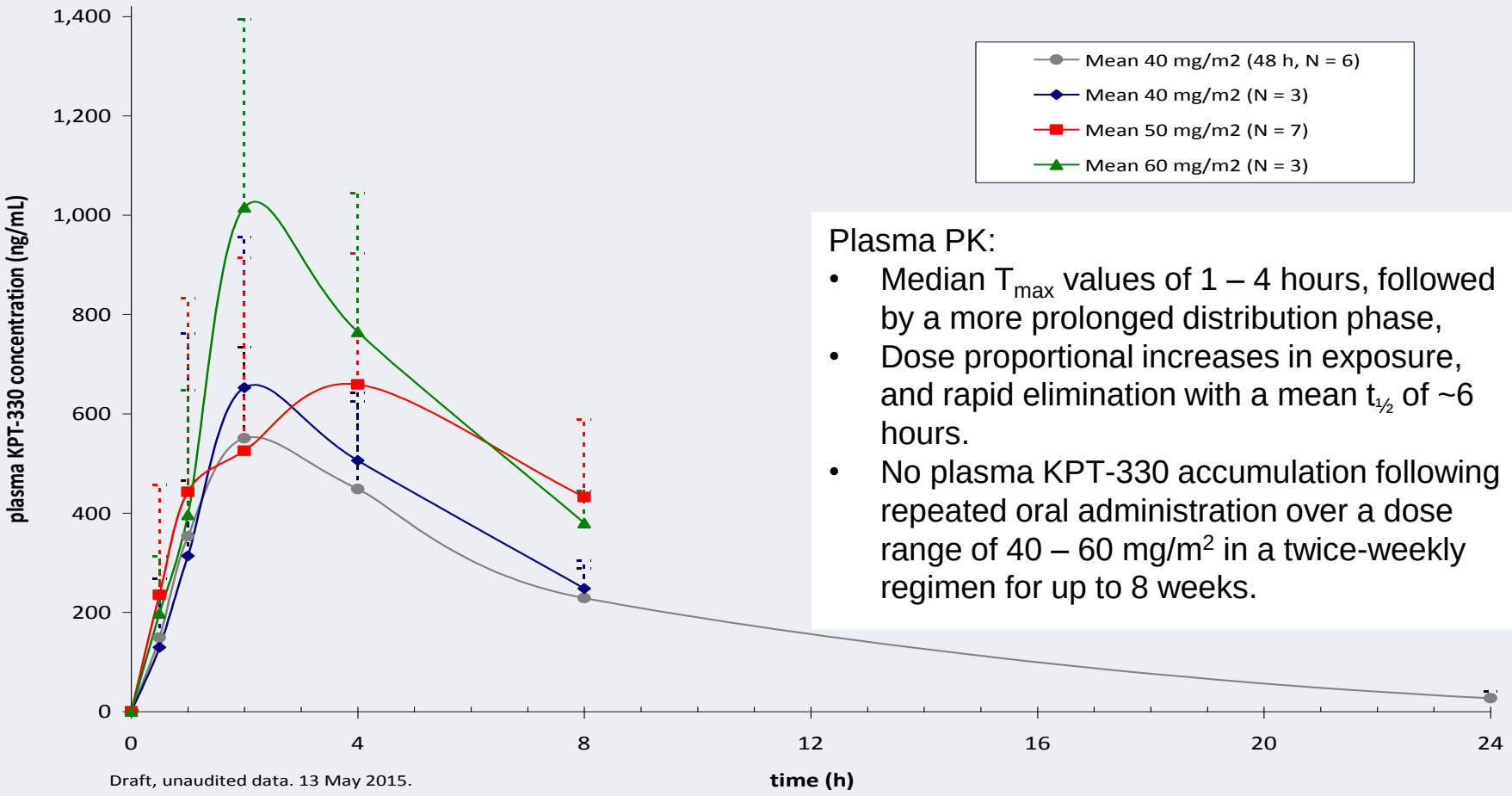
Schedule 2: Once weekly continuous			
Dose Level (mg/m2)	DLT Evaluable Patients (n=12)	Pts with DLT	**DLT**
50	3	0	-
60	3	0	-
70	6 (+4)	1/6 + (0/4)	G3 fatigue > 5days

Schedule 3: Twice a week, 2 out of 3 weeks			
Dose Level (mg/m2)	DLT Evaluable Patients (n=9)	Pts with DLT	**DLT**
40	3	0	-
50	6 (+4)	1/6 + (1/4)	G3 N/V; G3 fatigue > 5 days

Most common treatment-related AEs

Preferred term N(%)	All (N=40) N (%)	Schedule 1 (twice weekly continuous)	Schedule 2 (weekly continuous)			Schedule 3 (twice a week 2 out of 3 weeks)	
		40mg/m²(n=6)	**50mg/m² (n=3)**	**60mg/m² (n=3)**	**70mg/m² (n=12)**	**40mg/m² (n=3)**	**50mg/m² (n=13)**
		≥ Grade 3 N(%)	≥ Grade 3 N(%)			**≥ Grade 3 N(%)**	
Fatigue	33 (82.5)	2 (33.3)	0	0	2(16.7)	1(33.3)	2(15.4)
Nausea	17 (42.5)	0	0	1(33.3)	0	0	1(7.69)
Anorexia	25 (62.5)	0	0	0	0	0	1(7.69)
Vomiting	12 (30.0)	0	0	1(33.3)	1(8.33)	0	0
Weight Loss	10 (25.0)	0	0	0	0	0	0
Diarrhea	11 (27.5)	1(16.7)	0	0	0	0	0
Thrombocytopenia	11 (27.5)	1(16.7)	0	0	2(16.7)	0	0
Anemia	10 (25)	1(16.7)	0	1(33.3)	1(8.33)	0	2(15.4)
Hyponatremia	30 (75)	5 (83.3)	0	1(33.3)	0	2(66.7)	4(30.8)
Dehydration	3 (7.5)	1(16.7)	0	0	0	0	2(15.4)
Hypomagnesiemia	11 (27.5)	0	0	0	0	0	0
Neutropenia	2 (5.0)	0	0	0	2(16.7)	0	0

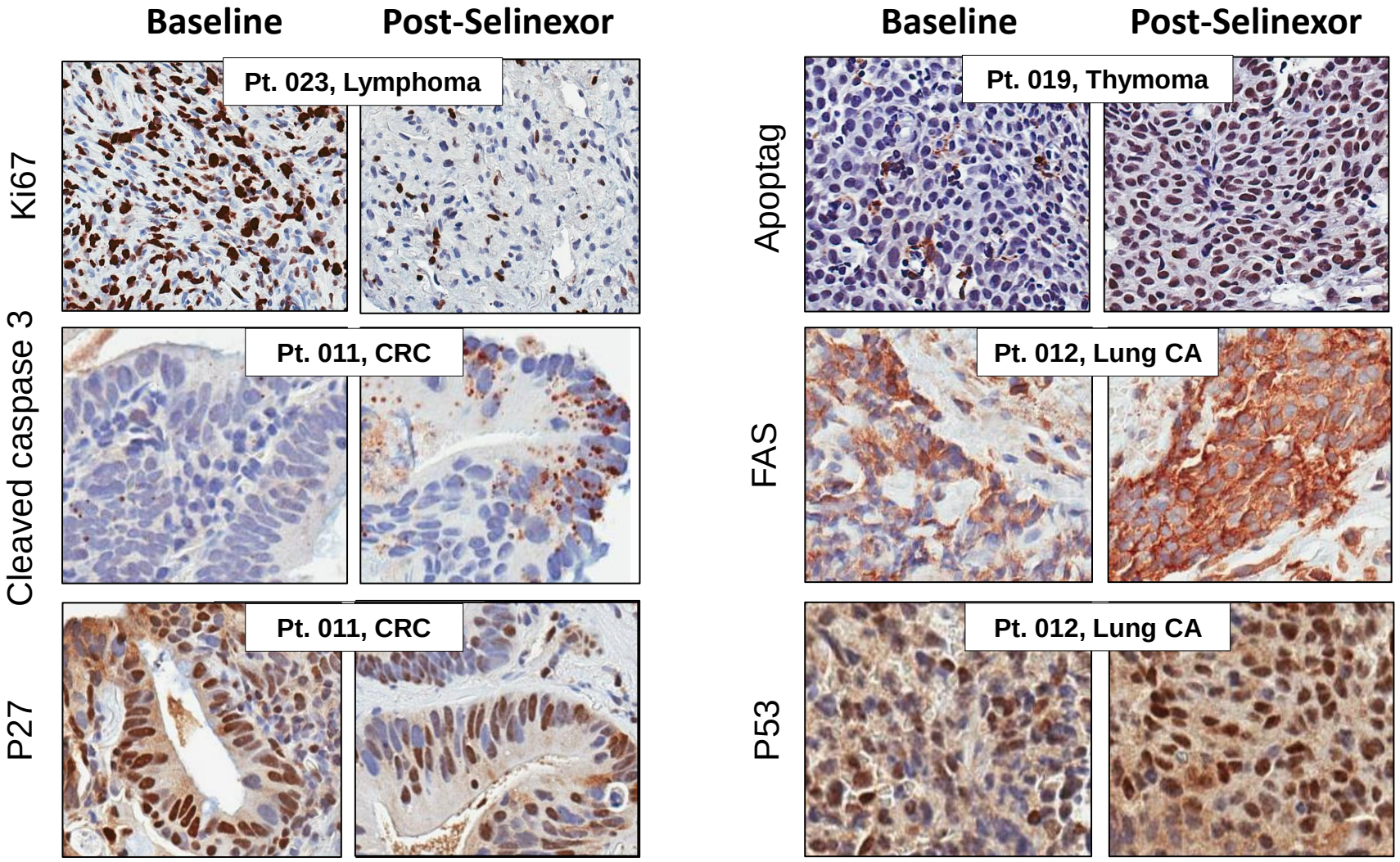
Plasma Pharmacokinetics: Mean ± SD plasma selinexor concentration vs. time following oral administration at 40 - 60 mg/m2 to asian patients with solid tumor malignancies, Day 1



Plasma PK:

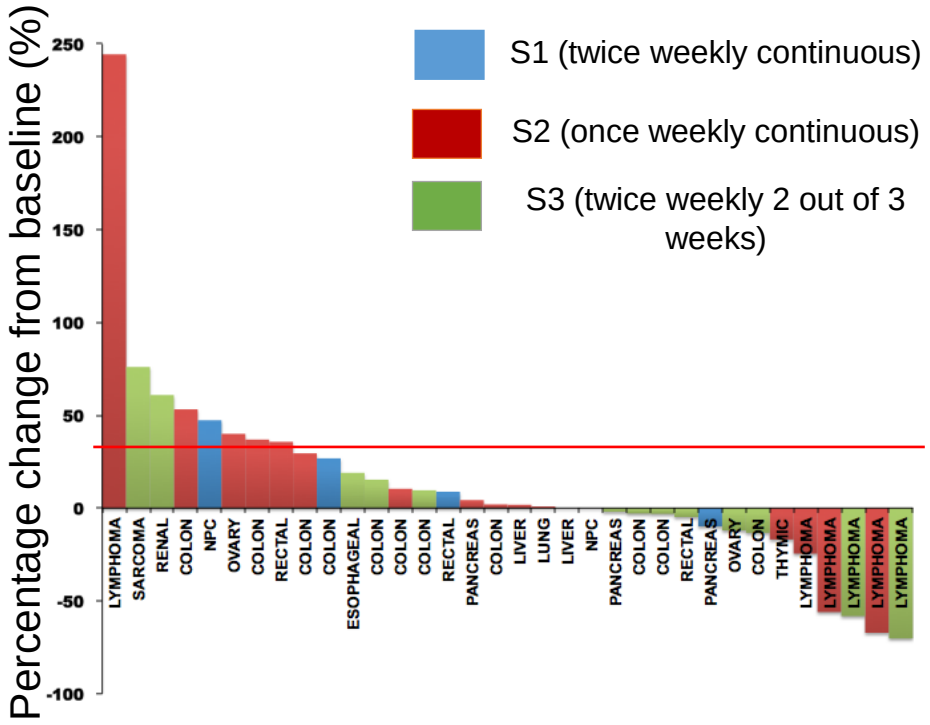
- Median T_{max} values of 1 – 4 hours, followed by a more prolonged distribution phase,
- Dose proportional increases in exposure, and rapid elimination with a mean $t_{½}$ of ~6 hours.
- No plasma KPT-330 accumulation following repeated oral administration over a dose range of 40 – 60 mg/m^2 in a twice-weekly regimen for up to 8 weeks.

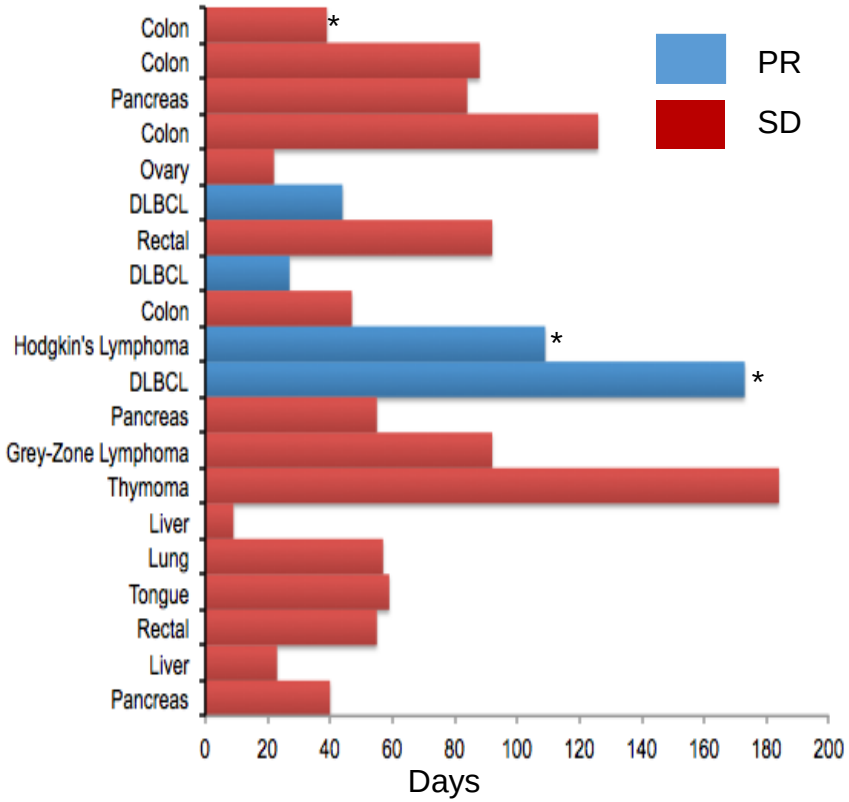
Tumour Pharmacodynamics: Reduced proliferation and increased nuclear staining of XPO1 cargos and major tumor suppressor proteins post selinexor treatment



Clinical activity: best tumour response and duration of best response

Percentage change in size of target lesion from baseline at best response (n=34 evaluable)	• Duration of best response for PR and SD (days)





* Treatment ongoing

Biomarker – RAS mutants/ cytoplasmic p27

Oncogene (2011) 30, 2846–2858

www.nature.com/onc

ORIGINAL ARTICLE

Cytoplasmic p27 is oncogenic and cooperates with Ras both *in vivo* and *in vitro*

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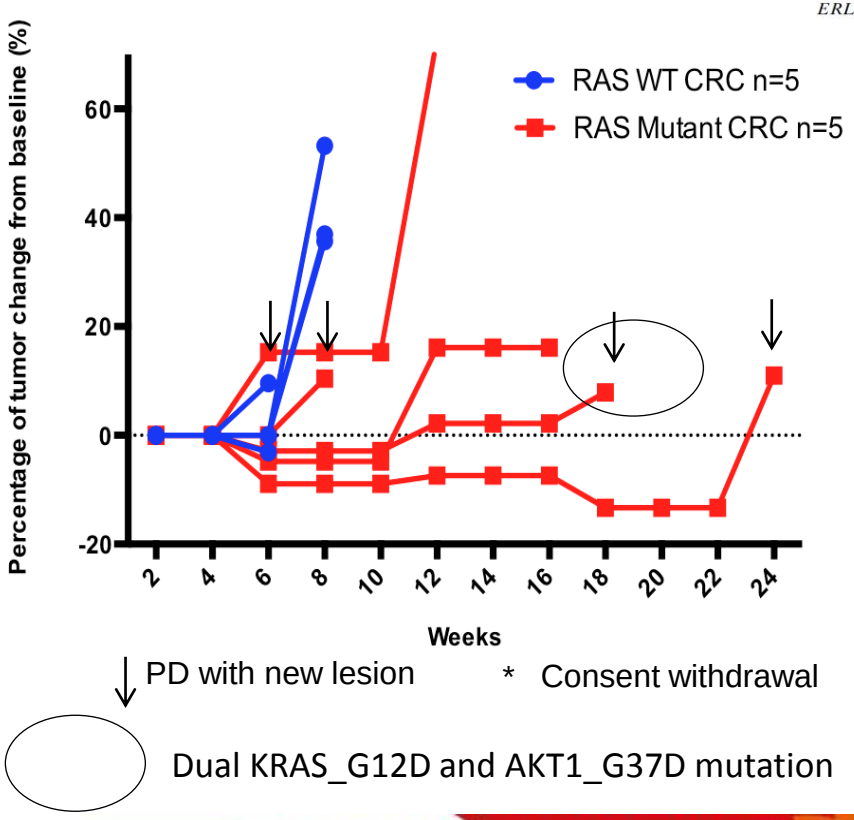
Tumor response for patients with colorectal cancer according to RAS mutation (n=10)



↓ PD with new lesion

* Consent withdrawal

Dual KRAS_G12D and AKT1_G37D mutation

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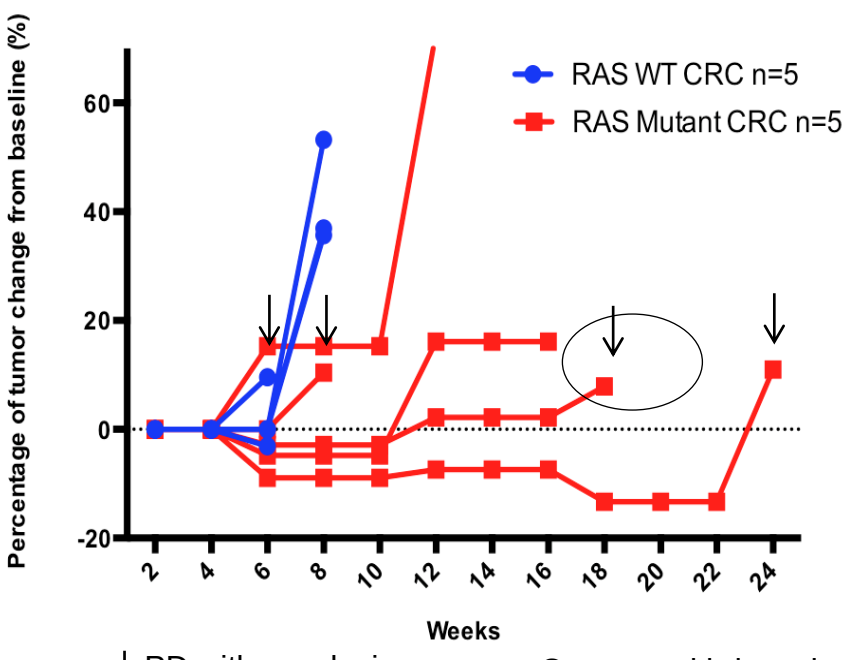

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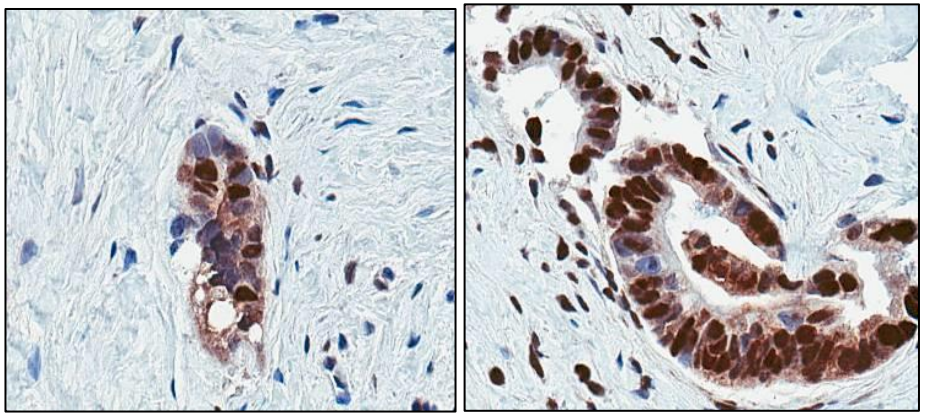
P27 IHC

Pre Post



P27 IHC: Pt 037 with CRC, AKT_G37D and KRAS_G12D mutation treated with selinexor

Hua Chang

Conclusion

- Inhibition of the nuclear-cytoplasmic export pathway is a viable anti-cancer strategy

- XPO1 inhibitor selinexor given weekly or twice weekly is tolerable with manageable toxicities at current escalated dose levels
- Schedule 2 (weekly): Current recommended phase 2 dose (RP2D) at 70 mg/m^2
- Schedule 3 (2 x weekly/ 3 weeks): Current RP2D at 50 mg/m^2
- 3 times a week at 20 mg/m^2 currently being explored
  →Phase 1b expansion

- Proof of mechanism in peripheral blood cells and tumours

- Promising antitumor activity was observed in Asian patients with highly refractory tumours

- → Predictive Biomarkers: ?p27 cytoplasmic expression

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