First in class, first in human phase I trial of KPT-330, a Selective Inhibitor of Nuclear Export (SINE) in patients with advanced solid tumors

Albiruni RA Razak[1], Morten M Sorensen[2], Amit Mahipal[3], Sharon Shacham[4], Cindy YF Yau[5], Ulrik Lassen[2], Dilara McCauley[4], Jennifer Cooksey[3], David SP Tan[1], Jean-Richard Saint-Martin[4], Yossi Landesman[4], Greg Pond[5], Amit Oza[5], Michael Kauffman[4], Lillian L. Siu[1], Mansoor R Mirza[4]

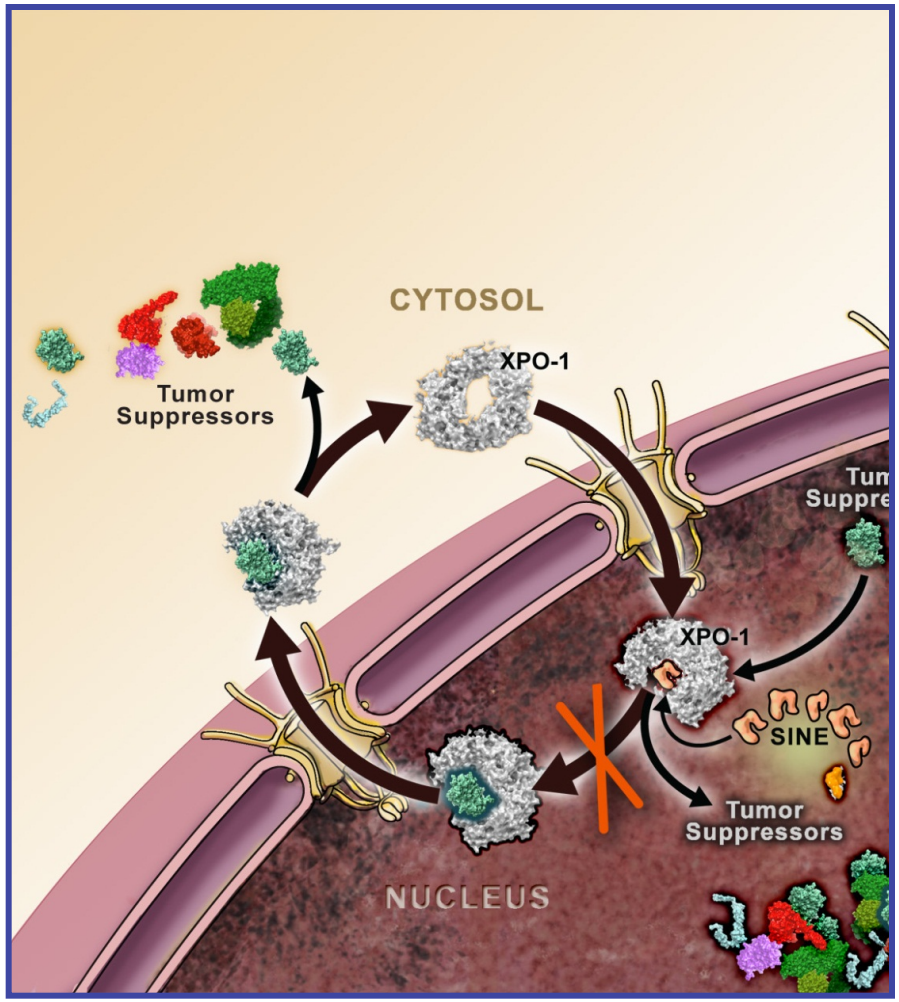
(1) Drug Development Program, Princess Margaret Cancer Center, Toronto, Canada; (2) Dept. of Oncology, Rigshospitalet, Copenhagen, Denmark; (3) Moffitt Cancer Center, Tampa, FL, USA; (4) Karyopharm Therapeutics, Natick, MA, USA; (5) Ozmosis Research Inc, Toronto, Canada.

Presenter Disclosures

- **Employment or Leadership Position:** None
- **Consultant/Advisory Role:** None
- **Stock Ownership:** None
- **Honoraria:** None
- **Research Funding:** None
- **Expert Testimony:** None
- **Other Remuneration:** None

Selective Inhibition of Nuclear Export (SINE)

- Cancer cells can inactivate their Tumor Suppressor Proteins (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
- KPT-330 is a covalent, oral selective inhibitor of nuclear export against XPO1



Study Design

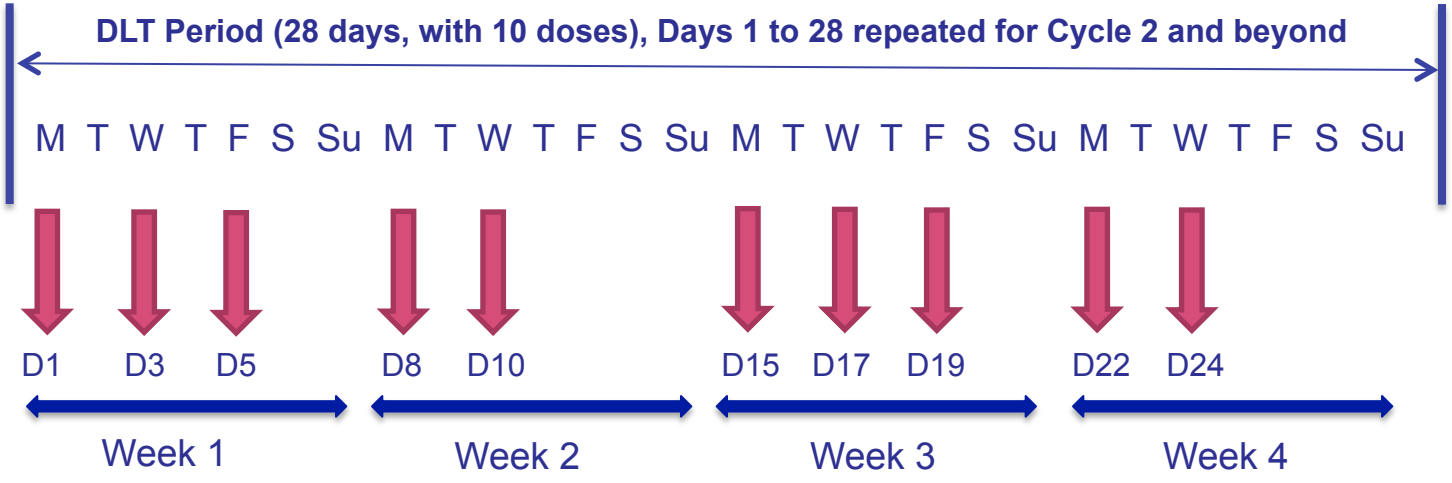
- Objectives
  - Primary: Safety, tolerability and Recommended Phase 2 Dose (RP2D) of KPT-330;
  - Secondary: Pharmacokinetics (PK), pharmacodynamics (PDn), anti-tumor response; confirmation of RP2D of KPT-330

- 3+3 design

- Major eligibility criteria:
  - Solid tumor patients with no available standard treatments
  - ECOG 0-1
  - Documented progression at study entry
  - Stable, asymptomatic brain metastases permissible

Dosing

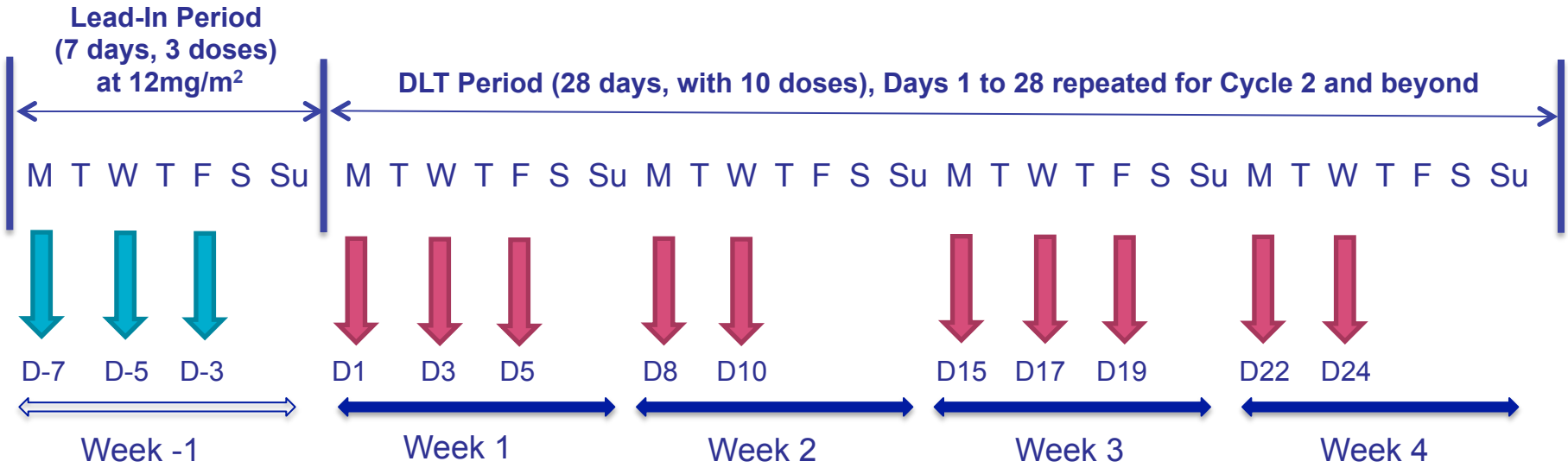
- FPFV on 18th June 2012; at 3mg/m^2 dose level, po od on dosing days



KPT-330 Dosing Days

Dosing

- FPFV on 18th June 2012; at 3mg/m^2 dose level, po od on dosing days



KPT-330 Dosing Days (Lead-In Period only for dose level > 12mg/m^2)

KPT-330 Dosing Days

DLT Criteria

- ≥ 3 missed doses in 28 days
- Discontinuation of a patient due a toxicity in cycle 1
- Non Hematologic:
  - Grade ≥ 3 (nausea/vomiting, electrolyte imbalances must be supported first and AST/ALT lasting more than 7 days)
- Hematologic:
  - Grade 4 neutropenia ≥7 days
  - Febrile neutropenia
  - Grade 4 thrombocytopenia that persists for ≥5 days, or Grade 3 with bleeding

Patient characteristics

Characteristic	N=39
Median age (range)	62 (33-72)
Male /Female	22/17
Median prior lines of treatment (range)	2 (1-7)
ECOG performance status, 0/1	7/32
Disease site	
-Colorectal	19
-Pancreas	4
-Head & Neck	3
-Small Bowel	2
-Ovarian	2
-Cervical	2
-Sarcoma	2
-Other (uterine, thymic, melanoma, lung, bladder ca)	5

Dose Levels, DLT and MTD

Cohort #	Dose Level (mg/m2)	DLT Evaluable Patients (n=28)	Patients with DLT	DLTs
1	3	1	0	
2	6	3	0	
3	12	4	0	
4	16.8	3	0	
5	23	3	0	
6	30	4	0	
7	**40**	**3**	**2**	**Grade 3 Dehydration and Fatigue Missed >3 doses (Grade 2 Fatigue)**
8 (Expansion)	30	7	N/A	

Adverse Events (at least possibly related)

Preferred term	Grade	Incidence at different dose levels n(%)							All N=35
		3 mg/m^2 N= 1	6 mg/m^2 N=3	12 mg/m^2 N=4	16.8 mg/m^2 N=4	23mg/m^2 N=5	30 mg/m^2 N=13	40 mg/m^2 N=6	
Nausea	All 3/4	0(0) 0(0)	3(100) 0 (0)	4 (100) 0 (0)	4(100) 1 (25)	4(80) 1 (20)	10(77) 0 (0)	4 (80) 1 (20)	29 (83) 3 (9)
Fatigue	All 3/4	1(100) 1(100)	2 (67) 0 (0)	3 (75) 0 (0)	4(100) 1 (25)	5(100) 0(0)	10(77) 0 (0)	3(60) 2(40)	28 (80) 4 (11)
Anorexia	All 3/4	1 (100) 1 (100)	2 (67) 0 (0)	4 (100) 0 (0)	3 (75) 0(0)	3(60) 0(0)	11(85) 0(0)	4(80) 1 (20)	28 (80) 2 (6)
Vomiting	All 3/4	0 (0) 0 (0)	1 (33) 0 (0)	3 (75) 0 (0)	3 (75) 0(0)	5(100) 1(20)	8(62) 1(8)	3(60) 0(0)	23 (66) 2(6)
Weight Loss	All 3/4	0 (0) 0 (0)	1 (33) 0 (0)	3 (75) 0 (0)	2 (50) 0(0)	3(60) 0(0)	9(69) 0(0)	1(20) 0(0)	19 (54) 0 (0)
Dysgeusia	All 3/4	1 (100) 0 (0)	2 (67) 0 (0)	4 (100) 0 (0)	3(75) 0(0)	1(20) 0(0)	6(46) 0(0)	1(20) 0(0)	18 (51) 0 (0)
Blurred vision	All 3/4	0 (0) 0 (0)	0 (0) 0 (0)	1 (25) 0 (0)	1(25) 0(0)	1(20) 0(0)	1(8) 0(0)	2(40) 0(0)	6 (17) 0(0)
Anemia	All 3/4	1 (100) 1 (100)	0 (0) 0 (0)	1 (25) 0 (0)	1(25) 0(0)	1(20) 0(0)	3(23) 1(8)	2(40) 0(0)	9(26) 2(6)
Hyponatremia	All 3/4	0 (0) 0 (0)	0 (0) 0 (0)	1 (25) 1 (25)	0(0) 0(0)	0(0) 0(0)	3(23) 3(23)	1(20) 1(20)	5(14) 5(14)
Low Platelets	All 3/4	0 (0) 0 (0)	0 (0) 0 (0)	0 (0) 0 (0)	1(25) 0(0)	1(20) 1(20)	3(23) 2(15)	(0) 0(0)	5(14) 3(9)

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Anorexia	All 3/4	1 (100) 1 (100)	2 (67) 0 (0)	4 (100) 0 (0)	3 (75) 0(0)	3(60) 0(0)	11(85) 0(0)	4(80) 1 (20)	28 (80) 2 (6)
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Dysgeusia	All 3/4	1 (100) 0 (0)	2 (67) 0 (0)	4 (100) 0 (0)	3(75) 0(0)	1(20) 0(0)	6(46) 0(0)	1(20) 0(0)	18 (51) 0 (0)
Blurred vision	All 3/4	0 (0) 0 (0)	0 (0) 0 (0)	1 (25) 0 (0)	1(25) 0(0)	1(20) 0(0)	1(8) 0(0)	2(40) 0(0)	6 (17) 0(0)
Anemia	All 3/4	1 (100) 1 (100)	0 (0) 0 (0)	1 (25) 0 (0)	1(25) 0(0)	1(20) 0(0)	3(23) 1(8)	2(40) 0(0)	9(26) 2(6)
Hyponatremia	All 3/4	0 (0) 0 (0)	0 (0) 0 (0)	1 (25) 1 (25)	0(0) 0(0)	0(0) 0(0)	3(23) 3(23)	1(20) 1(20)	5(14) 5(14)
Low Platelets	All 3/4	0 (0) 0 (0)	0 (0) 0 (0)	0 (0) 0 (0)	1(25) 0(0)	1(20) 1(20)	3(23) 2(15)	(0) 0(0)	5(14) 3(9)

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Vomiting	All 3/4	0 (0) 0 (0)	1 (33) 0 (0)	3 (75) 0 (0)	3 (75) 0(0)	5(100) 1(20)	8(62) 1(8)	3(60) 0(0)	23 (66) 2(6)
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Hyponatremia	All 3/4	0 (0) 0 (0)	0 (0) 0 (0)	1 (25) 1 (25)	0(0) 0(0)	0(0) 0(0)	3(23) 3(23)	1(20) 1(20)	5(14) 5(14)
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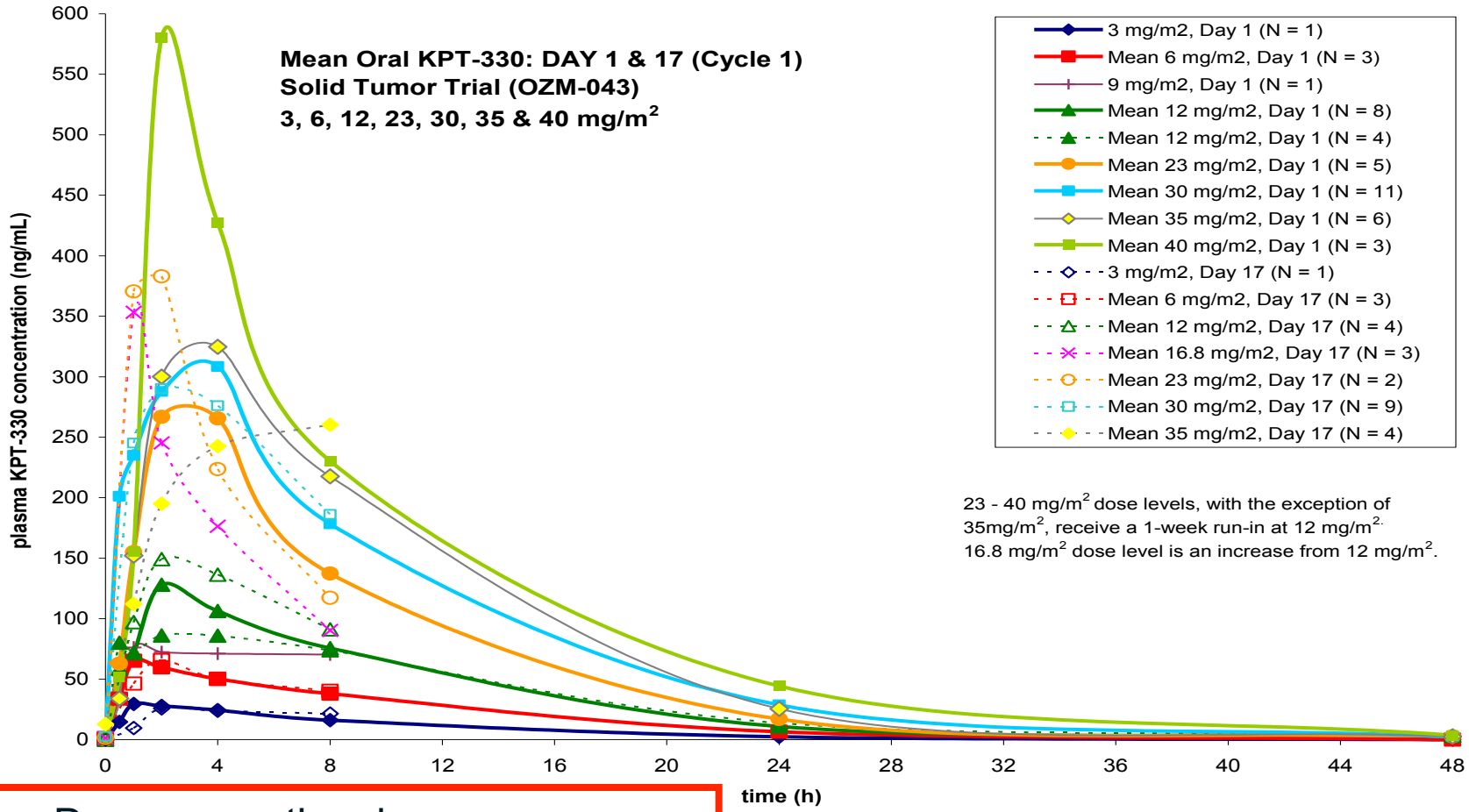
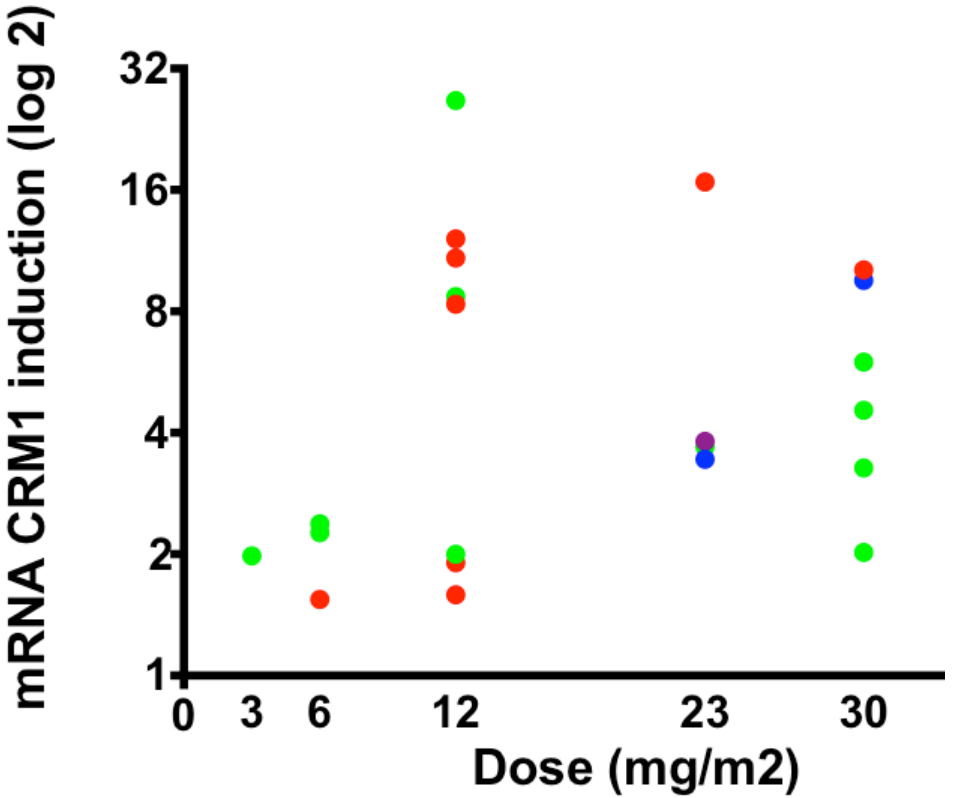
Pharmacokinetics of KPT-330



- Dose proportional exposure
- No accumulation
- Half life of 5-7 hours at all doses

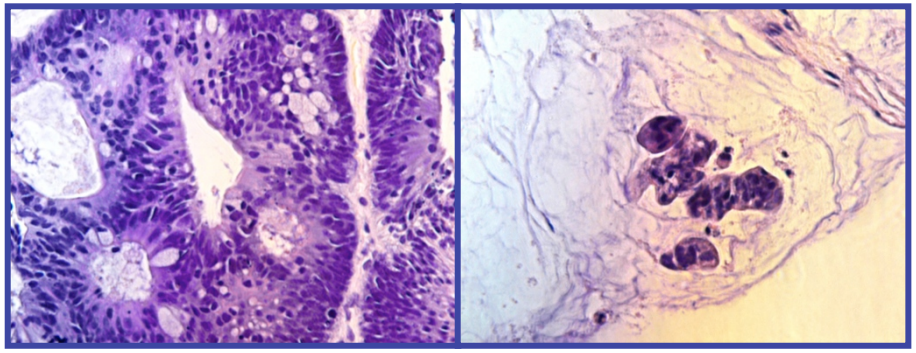
Pharmacodynamic (XPO1 mRNA)

- XPO1 mRNA induction following KPT-330 exposure in pre-clinical studies
- mRNA from leukocyctes
- 1.5-2 fold induction at lower doses
- >5 fold induction at dose level 12mg/m^2 or higher
- No correlation to clinical activity

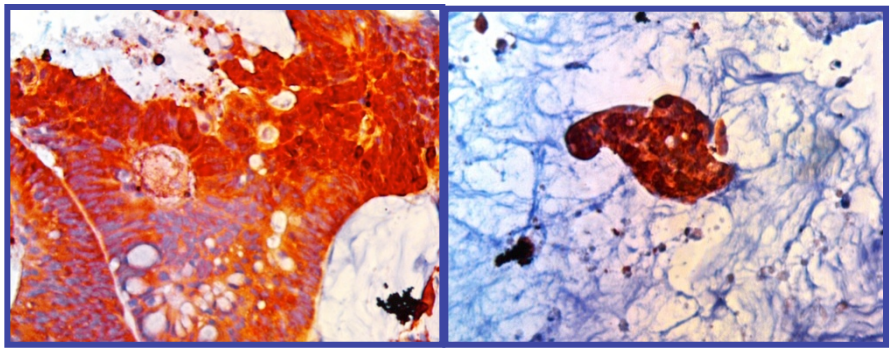


Pharmacodynamic (Paired Biopsies)

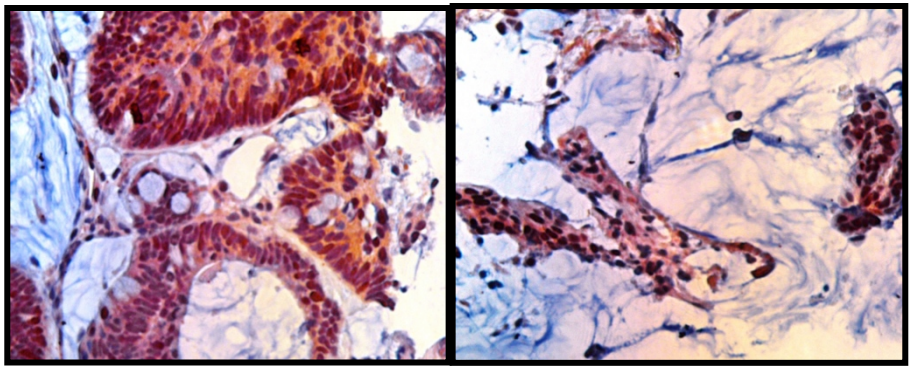
Biopsies at 3 weeks: less tumor cellularity and increased nuclear retention for IκB, p53 and FOXO1



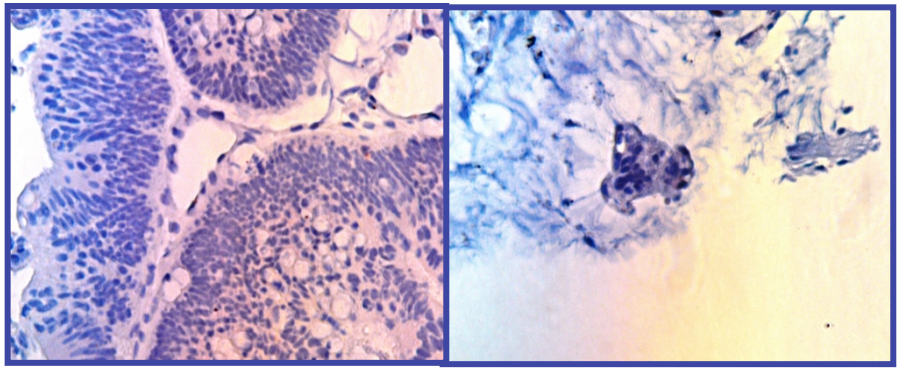
Pre-Treatment H&E 3 weeks



Pre-Treatment IκB 3 weeks



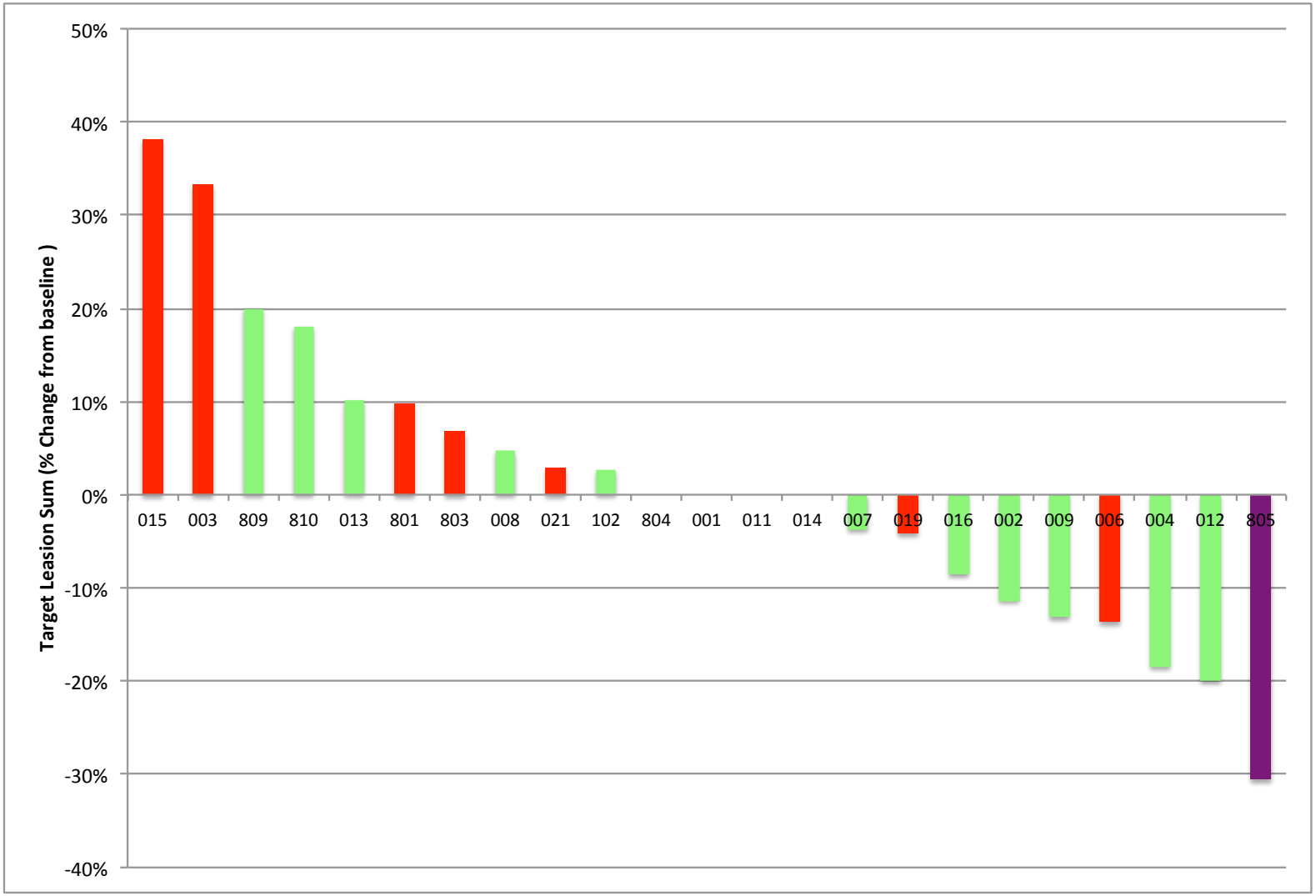
Pre-Treatment p53 3 weeks



Pre-Treatment FOXO1 3 weeks

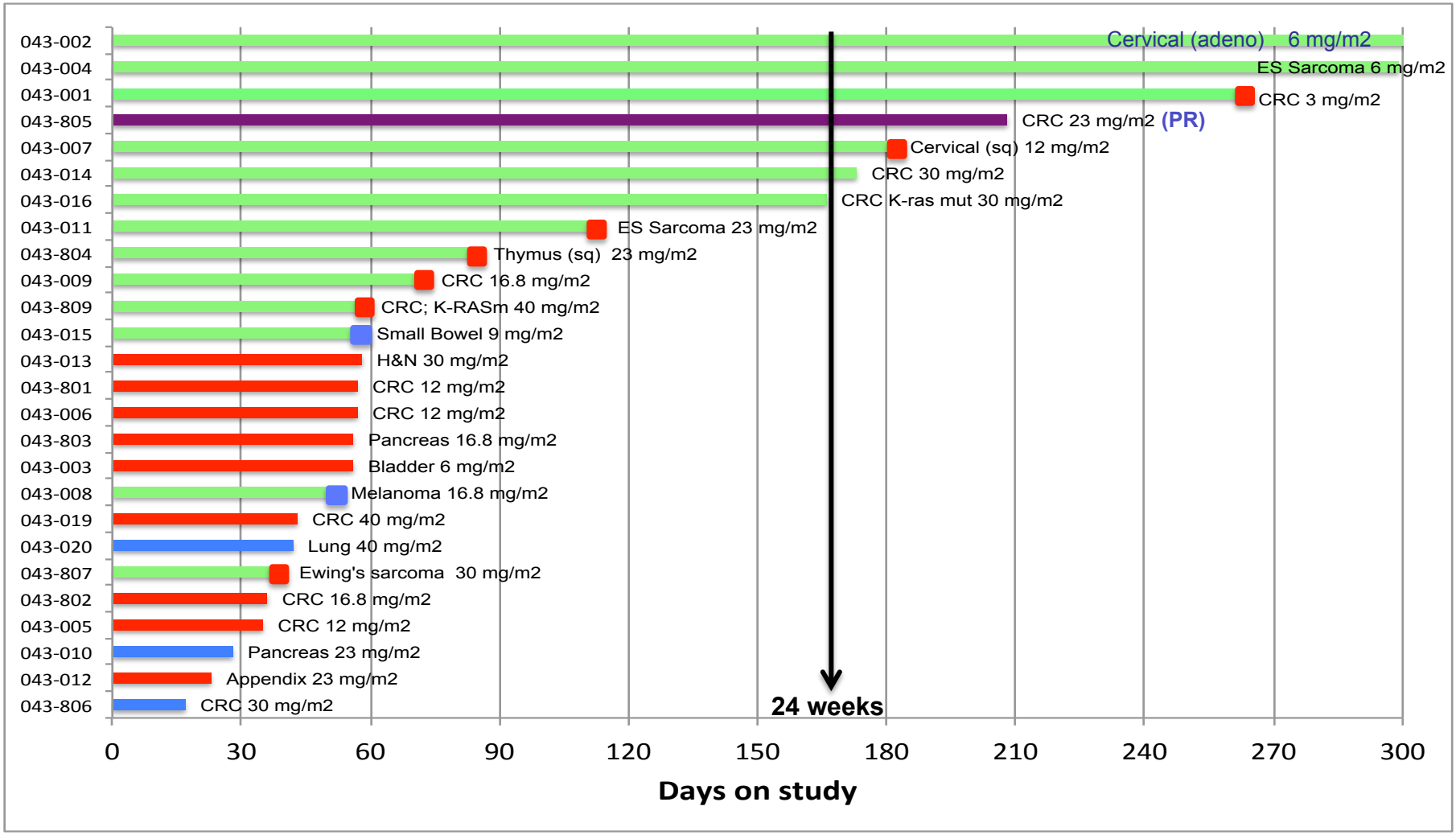
10x magnification

Waterfall Plot



PD SD PR

KPT-330: Clinical Activity



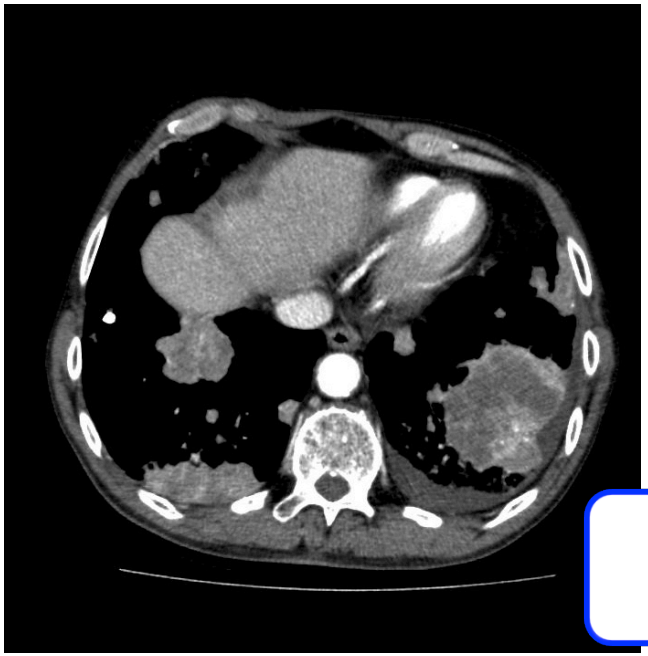
Partial Response (n=1); Stable Disease ≥24 weeks (n=6)

PD SD PR Withdrew Consent

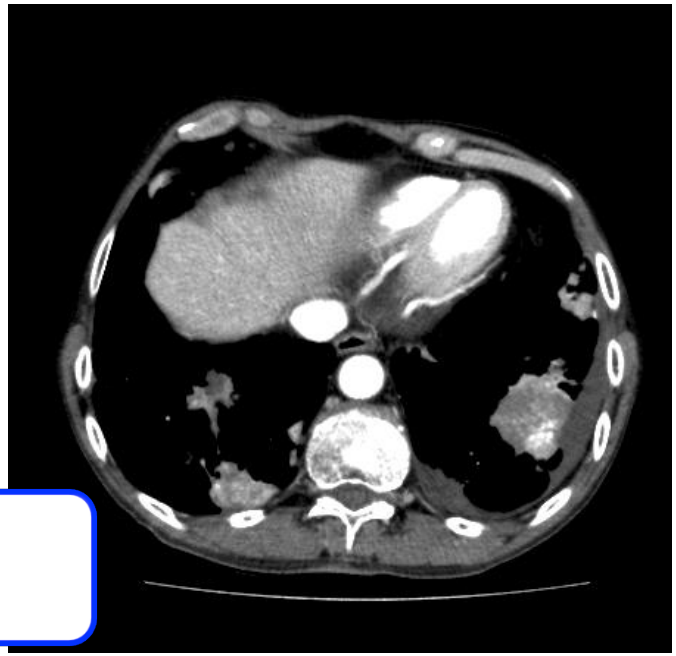
Patient 043-805: Colorectal Cancer

- 70 y.o. male with lung metastases. *KRAS* mutant disease
- 2 lines of treatment in the metastatic setting
- October 2012: KPT-330 at 23 mg/m^2

Baseline



Cycle 4



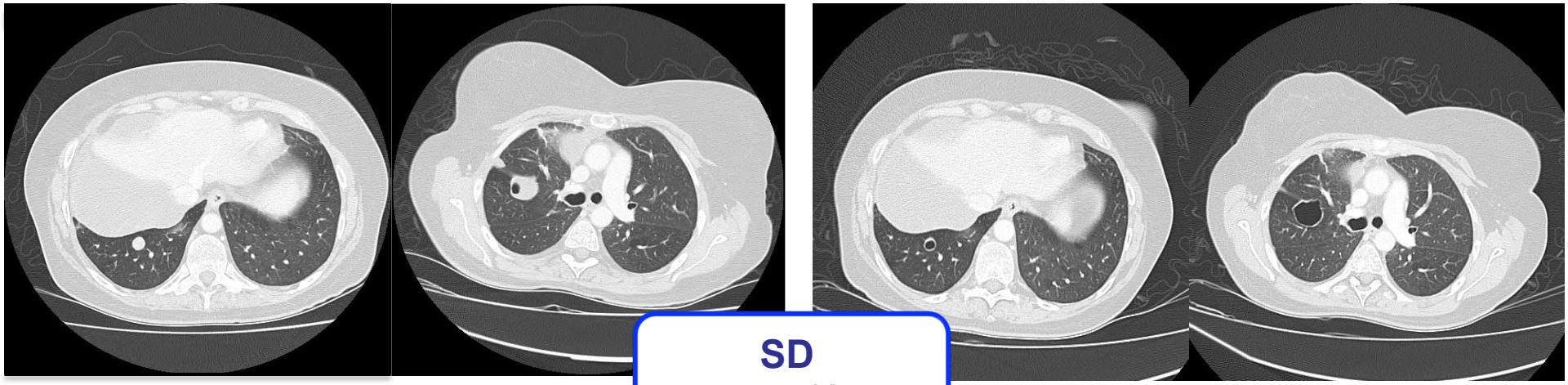
PR
–31%

Patient 043-004: Endometrial Stromal Sarcoma

- 48 y.o. female with lung metastases
- 3 lines of treatment in the metastatic setting
- August, 2012: KPT-330 at 6 mg/m^2

Baseline

Cycle 10



SD
–20%

Conclusions

- KPT-330 can safely be administered as monotherapy.
  - Main toxicities: Nausea, Fatigue and Anorexia
  - RP2D is being evaluated at 30mg/m2 on the 10 days q 28 schedule
  - MTD has been reached at 40mg/m^2 on the 10 days q 28 schedule
- KPT-330 has favorable PK and PD characteristics
- First signs of clinical efficacy in heavily pre-treated patients have been observed with a number of patients with prolonged stable disease, even at low dose levels
- Determination of RP2D, alternative dose scheduling and dose expansion in indicated tumour types are on-going

Acknowledgments

- We would like to thank:
  - Patients and their families
  - Investigators, co-investigators and the study teams at each participating center
    - Princess Margaret Cancer Centre, Toronto – P Bedard, L Stayner & DDP Fellows
    - Rigshospitalet, Copenhagen – G Kjeldsen & B Find
    - Moffitt Cancer Centre, Tampa
    - Karmanos Cancer Centre, Detroit

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