

A phase 1 study of XL281, a selective inhibitor of RAF kinases, administered orally to patients with advanced solid tumors

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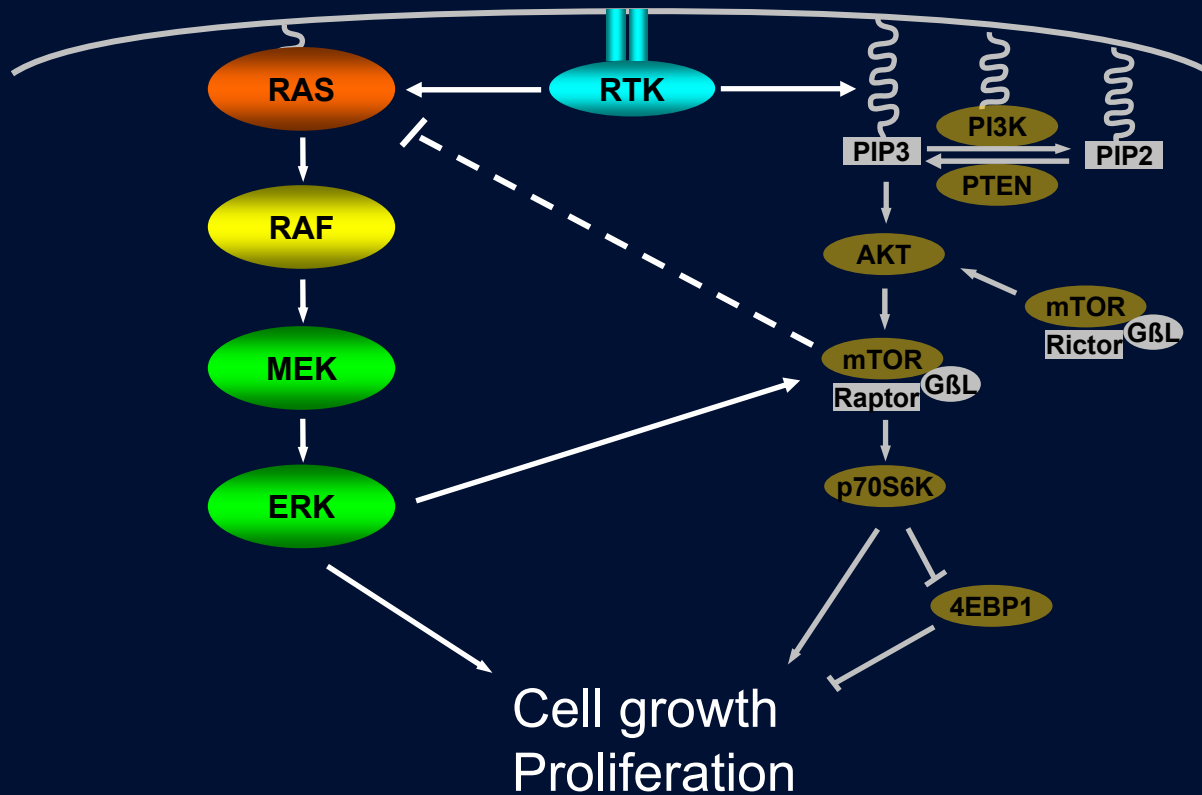
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Disclosure

- This study was sponsored by Exelixis
- G. Schwartz, D. Mendelson, M. Gordon: Clinical investigators for this study
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RAS/RAF/MAPK Signaling Pathway



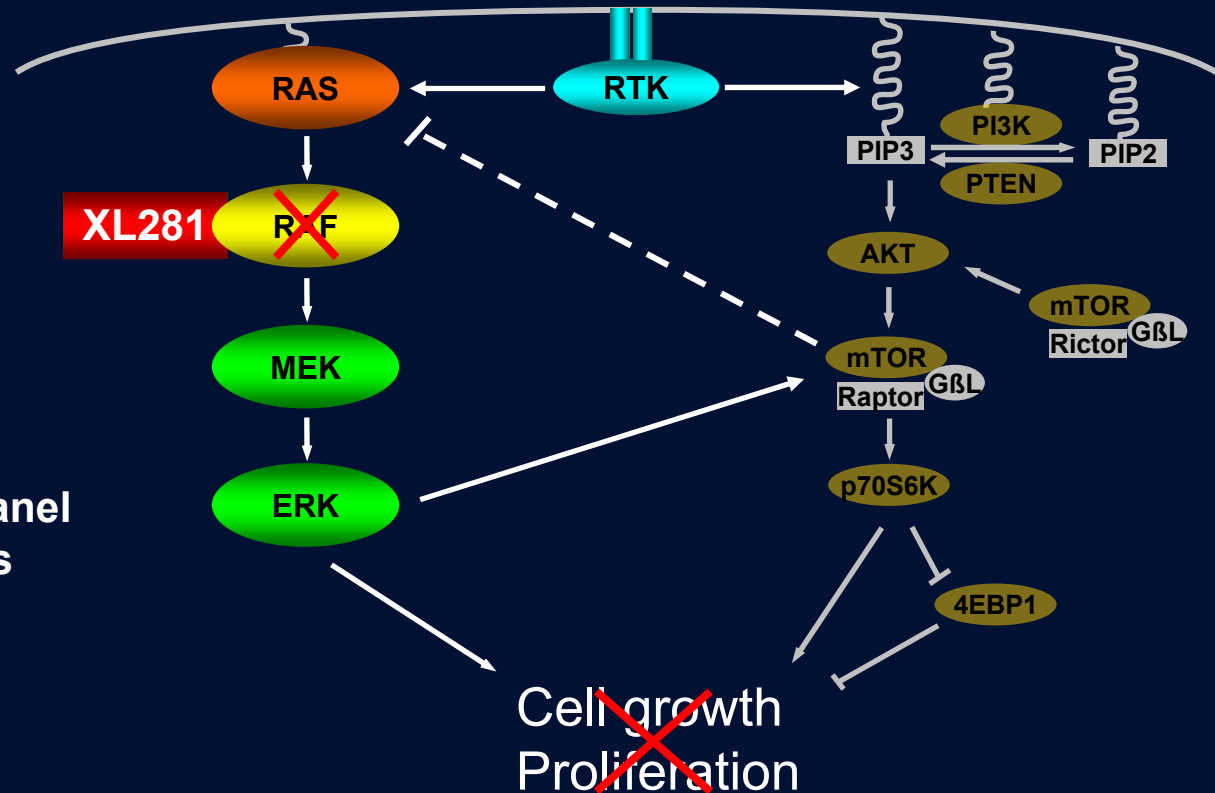
Pathway is mutationally-activated in many cancers

RAS/RAF/MAPK Signaling Pathway

Kinase	IC ₅₀ (nM)
BRAF	4.5
BRAF-V600E	6.0
CRAF	2.6

Highly selective in a panel of >100 protein kinases

ATP competitive, reversible

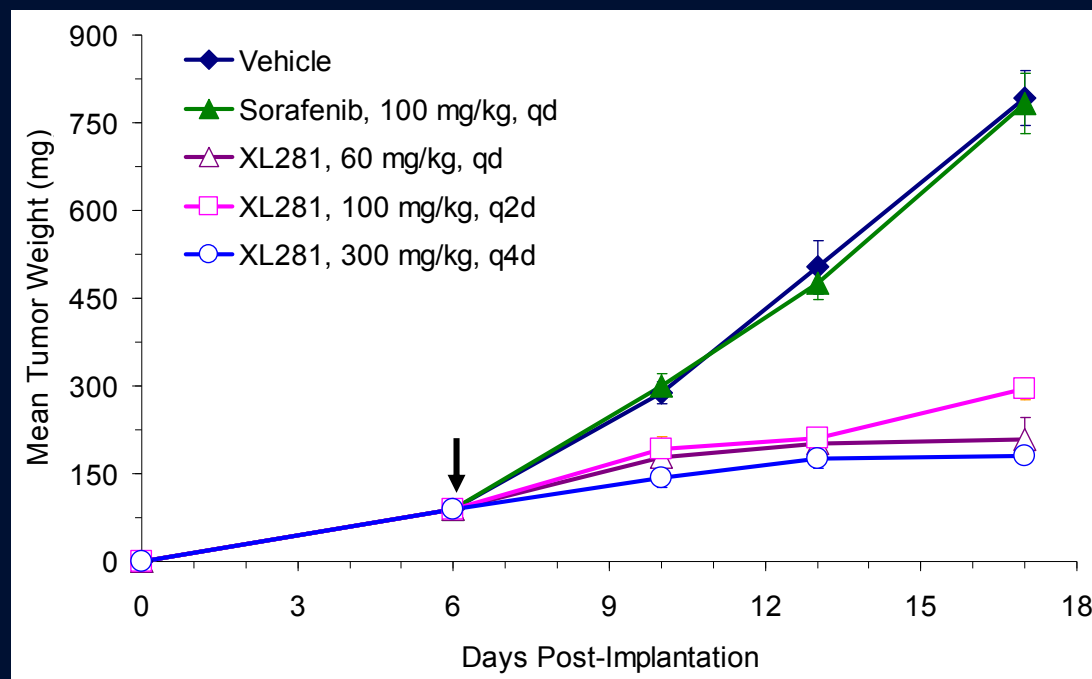
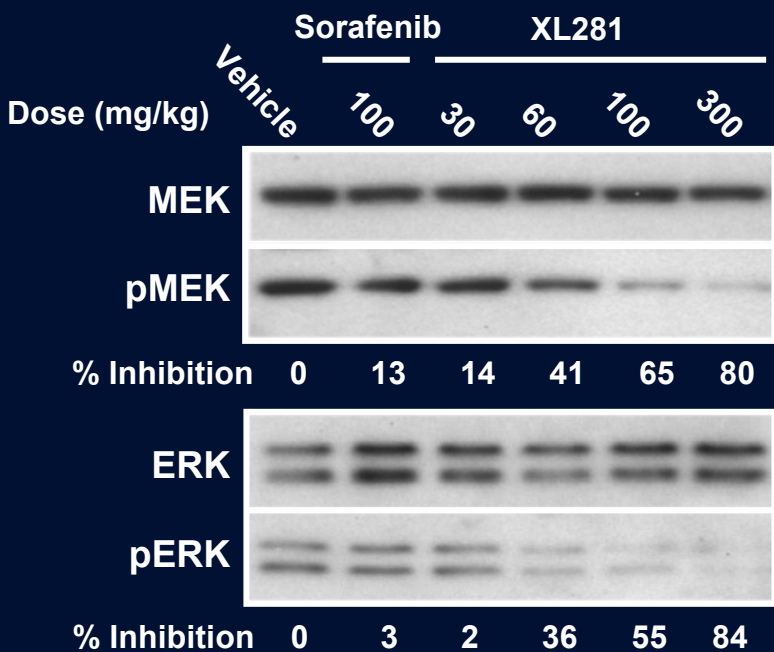


Pathway is mutationally-activated in many cancers

XL281: Potent Inhibitor of RAS/RAF Pathway

A375 (BRAF-V600E)

A431 (wt KRAS/BRAF)



XL281 is active in cell lines and xenograft models with wild type or mutant BRAF or KRAS

XL281 Phase 1: Study Objectives

- Safety and tolerability
- Define MTD
- Plasma Pharmacokinetics
 - PK profiles on Day 1 and Day 22
- Pharmacodynamics
 - Tumor, skin and hair samples: pre- and post- treatment
 - Protein phosphorylation: pERK and pMEK
- Preliminary antitumor activity
 - 'Clinical Benefit' defined as CR/PR or on study ≥ 12 weeks

XL281 Phase 1: Study Design

- “3 + 3” dose escalation design in subjects with refractory solid tumors
- Oral daily dosing
 - Intra-subject dose escalation allowed
- MTD based on Cycle 1 (28 days) XL281-related toxicities
- MTD cohort expansions:
 - Malignant melanoma, CRC, NSCLC & PTC
- Standard phase 1 eligibility criteria and DLT definitions
 - DLT defined during Cycle 1
- Standard safety assessments
 - Ophthalmic exams and QTc monitoring

XL281 Phase 1: Enrollment

Dose Escalation (n=30)	Number of subjects
CRC	7
PTC	5
Melanoma	5
Carcinoid	2
NSCLC	2
Hurthle cell thyroid	2
Prostate, ovarian, adenoca of sweat gland, adenoca unknown primary, pancreas, clear cell uterine, anaplastic thyroid	1 each
MTD Expansions (4 cohorts)	
Melanoma (11), CRC (12), NSCLC (10), PTC (7)	40

XL281 Phase 1: Demographics (N=48*)

Age, median yrs (range) 61 (28-84)

Gender (m / f) 27 / 21

ECOG (0 / 1 / 2) 28 / 19 / 1

Prior Therapy

Cancer Therapy ± Radiation 41 (85%)

Median Regimen # (range) 3.5 (1-9)

Radiation therapy (only) 4 (8%)

No prior therapy 3 (6%)

XL281 Phase 1: Dose Escalation and DLT

Dose	Number of Subjects	Dose Limiting Toxicity (Cycle 1)
Dose Escalation		
10 mg	5	None
20 mg	3	None
40 mg	3	None
60 mg	3	None
100 mg	6*	None
150 mg MTD	7*	None
225 mg DLT	3	Nausea (G4), Fatigue (G3), Diarrhea (G3), Vomiting (G3)
MTD Expansion		
150 mg	37**	Rash (G2)

*Dose levels expanded to determine the MTD

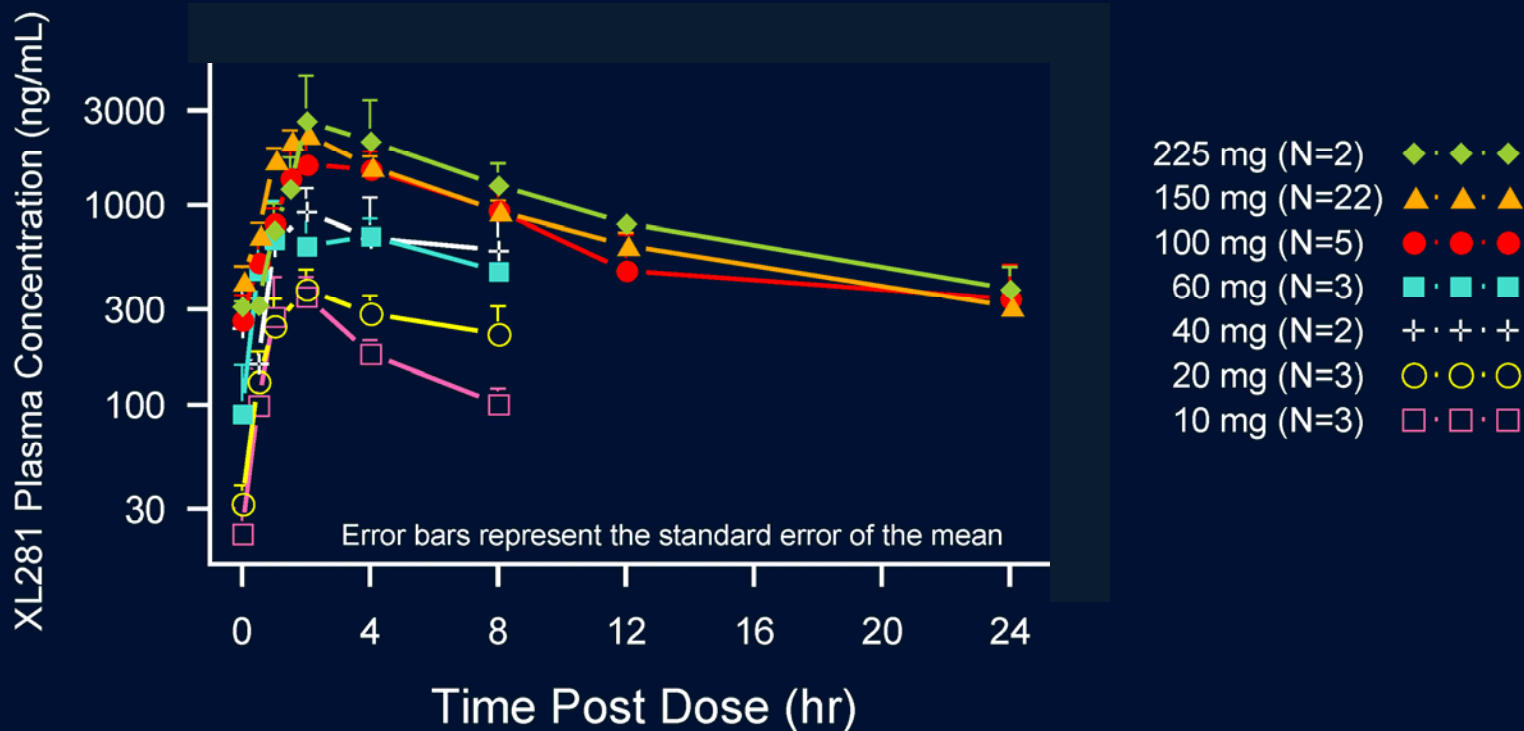
**Evaluable for DLT

XL281 Phase 1: Adverse Events* Occurring in $\geq 15\%$ of Subjects (N=48)

AE Term	Number of subjects (%)			
	Grade 1-2	Grade 3	Grade 4	All Grades
Fatigue	26 (54)	3 (6)	-	29 (60)
Nausea	21 (44)	1 (2)	2(4)	24 (50)
Diarrhea	20 (42)	2 (4)	-	22 (46)
Vomiting	16 (33)	3 (6)	2 (4)	21 (44)
Constipation	12 (25)	-	-	12 (25)
Rash	11 (23)	-	-	11 (23)
Anorexia	9 (19)	-	-	9 (19)
Arthralgia	8 (17)	1 (2)	-	9 (19)
Dyspnea	9 (19)	-	-	9 (19)
Decreased Appetite	8 (17)	-	-	8 (17)
Pyrexia	8 (17)	-	-	8 (17)
Chills	7 (15)	-	-	7 (15)

Cutaneous squamous cell carcinoma or keratoacanthoma reported in four subjects (pending pathology confirmation in 1 subject)

XL281 Phase 1: Pharmacokinetic Profile (Day 22)



Across All Cohorts

At MTD (150 mg)

T_{max} 2 hrs

Accumulation 1.5 (0.7 – 4.3) fold

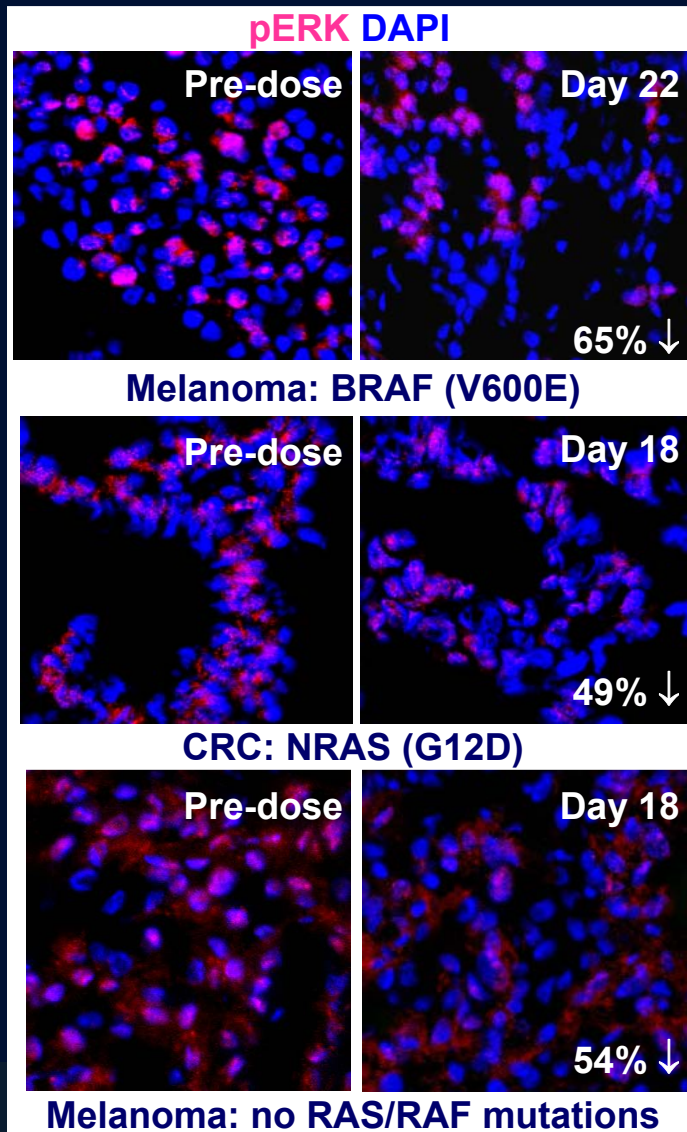
$T_{1/2z}$ 8 (5 – 22) hrs

AUC_{0-24} 14.5 $\mu\text{g}\cdot\text{hr}/\text{mL}$

Steady State by Day 8

CL/F_{ss} 9.6 L/hr

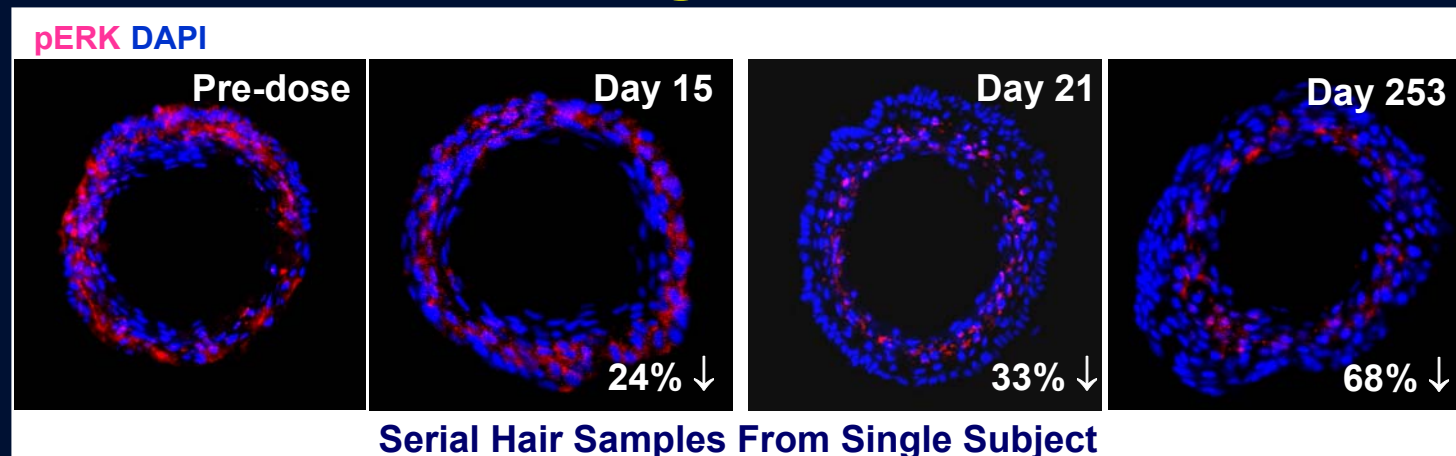
XL281 Phase 1: Pharmacodynamics in Tumor



Tissue	Pts	% ↓ pERK (T202/Y204)	% ↓ pMEK (S217/S221)
Melanoma	5	40 - 66	62 - 65
CRC	2	49 - 70	61
NSCLC	1	83	78
Adenoca Sweat Gland	1	69	85

Robust pathway inhibition observed in tumors → independent of RAS/RAF genotype

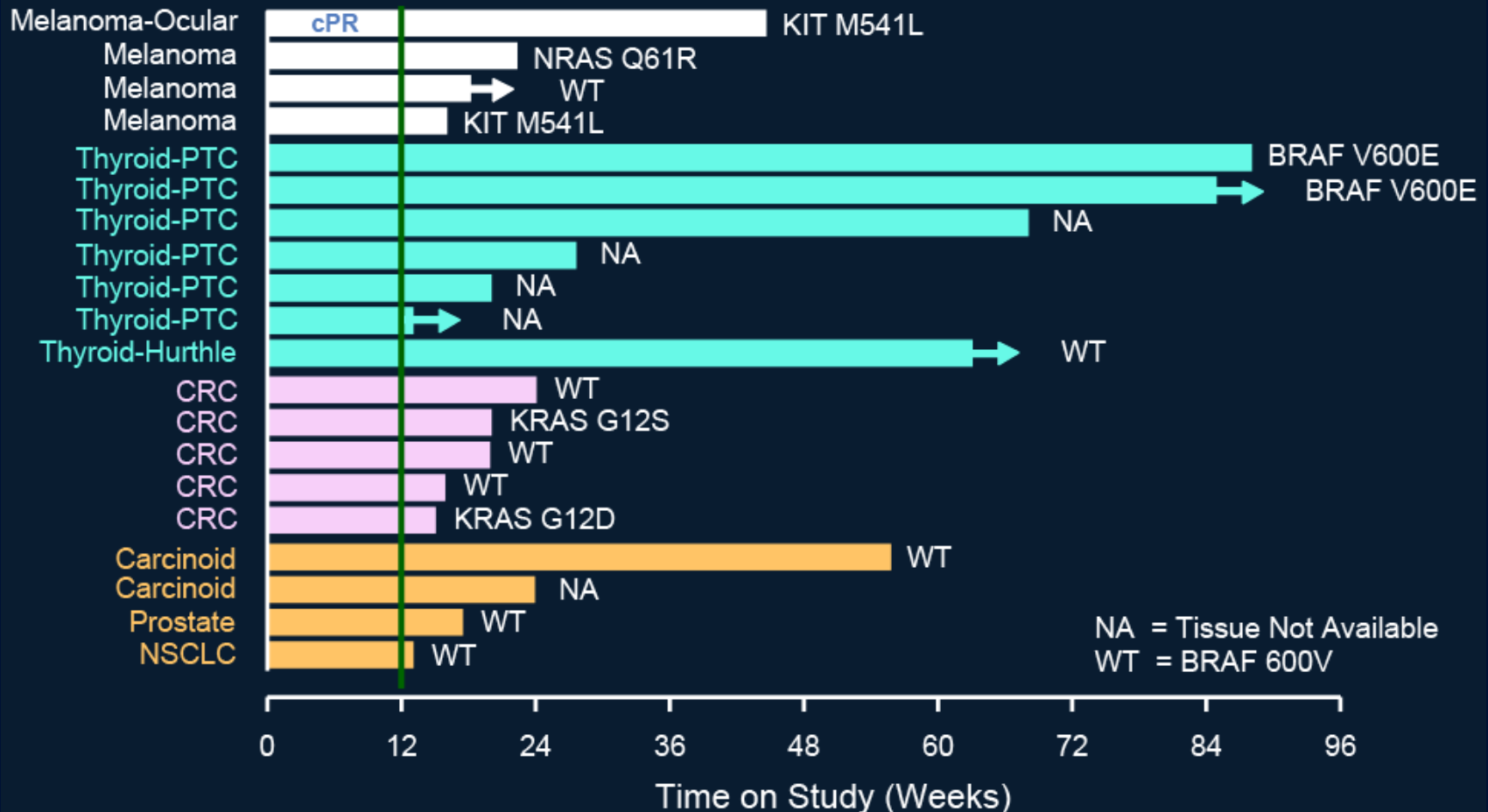
XL281 Phase 1: Pharmacodynamics in Surrogate Tissue



Tissue	Pts	% ↓ pERK (T202/Y204)	% ↓ pMEK (S217/S221)
Hair	4	51 - 68 (n=4)	50 - 61 (n=2)
Skin	3	0 - 58	15 - 55

Increasing pathway inhibition over time
observed in serial hair samples

XL281 Phase 1: Clinical Benefit (CR/PR or on study for ≥ 12 wks)



55 subjects evaluable for clinical benefit
1 cPR + 19 additional subjects on study for ≥ 12 wks
Clinical Benefit Rate = 36% (20/55)

XL281 Summary

- A potent and highly selective RAF inhibitor
- Generally well-tolerated at the MTD of 150 mg
 - Most common AEs were Grade 1 and 2 fatigue, nausea, vomiting and diarrhea
 - Prophylactic use of anti-emetics initiated during the MTD Expansion
- Substantial pathway modulation
 - pERK and pMEK down-regulated in tumor and surrogate tissues
- Evidence of clinical benefit in 36% of subjects
 - 1 cPR in a subject with ocular melanoma (on study ~45 weeks)
 - 19 additional subjects on study \geq 12 weeks (range: 12 – 88+ weeks)
- Future plans
 - Expand MTD cohort in CRC and Melanoma subjects with RAF/RAS mutations
 - Evaluate BID dosing schedule

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