Early Development of LY2835219, a Novel Cell Cycle Inhibitor with Activity against CDK4 and CDK6

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Lee Rosen, MD

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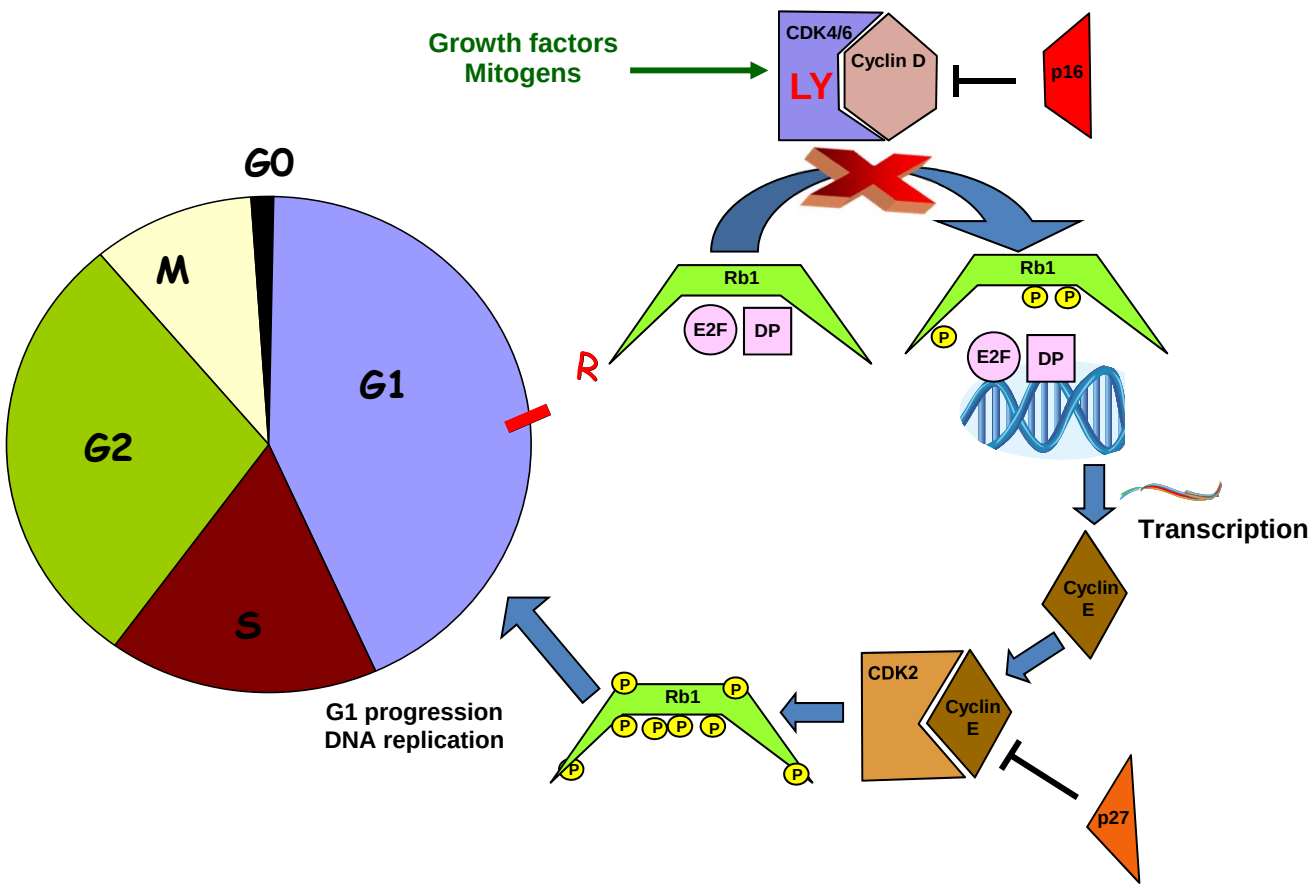
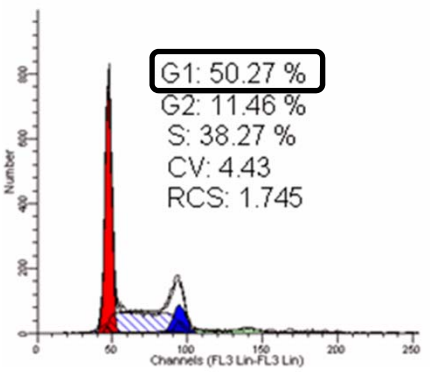
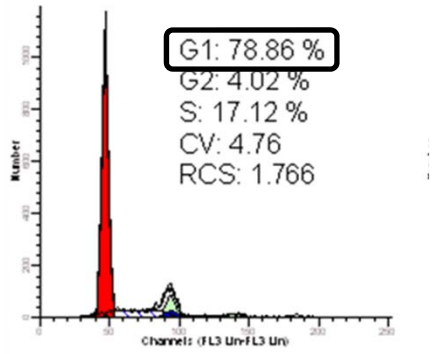
I intend to reference unlabeled / unapproved uses of drugs or products in my presentation: LY2835219

CDK4/6 Regulates G1→ S Cell Cycle Progression by Inactivating the Rb Tumor Suppressor Protein





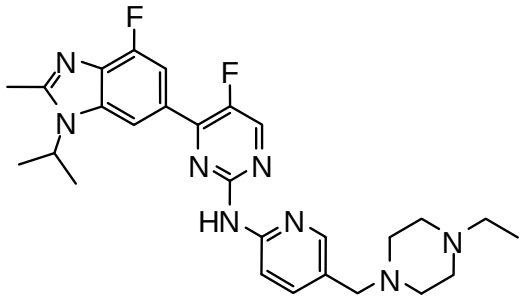
Vehicle



LY 0.16 μM

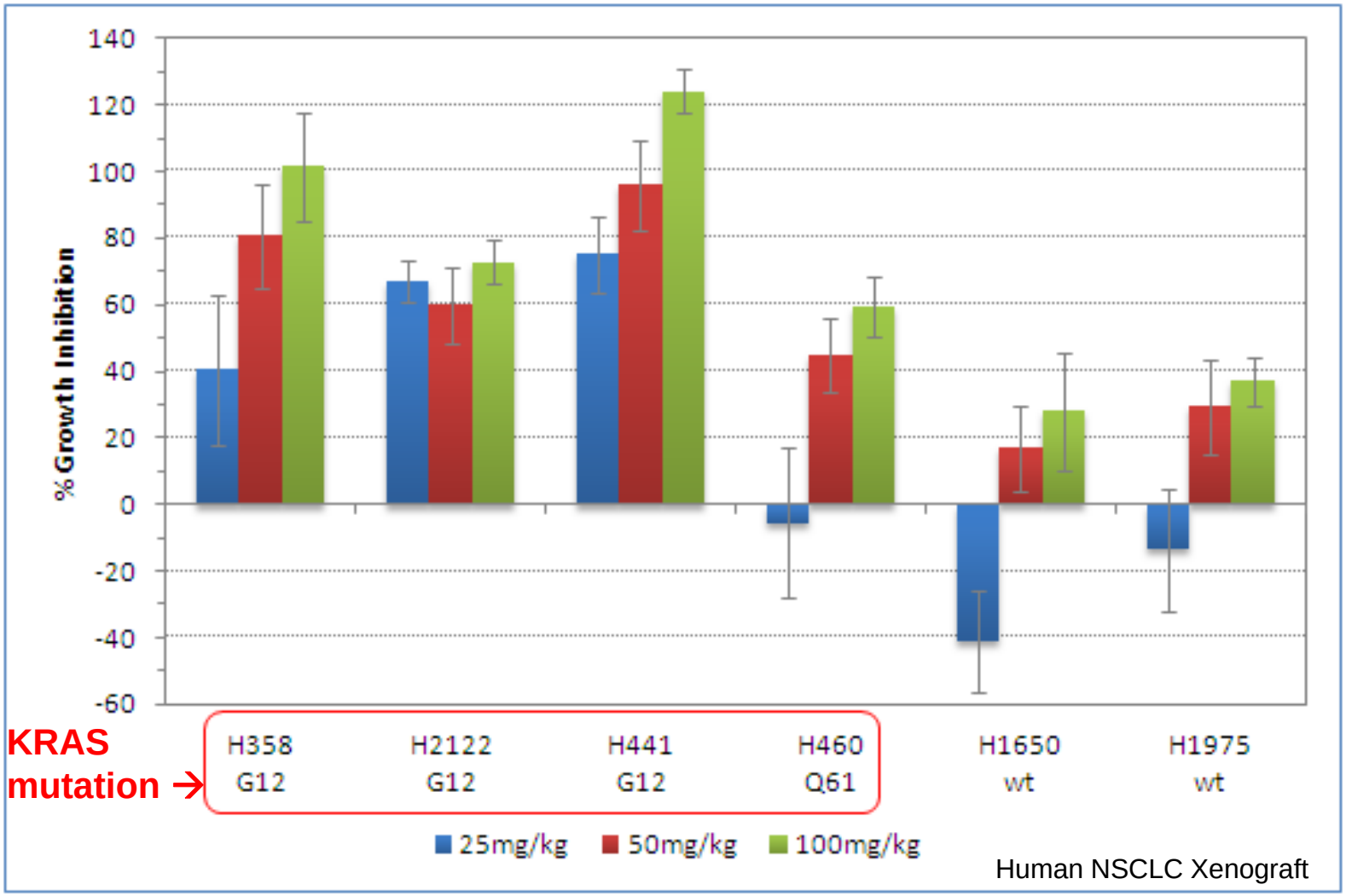
LY inhibits CDK4/6 and induces G1 arrest in breast cancer cells (MDA-MB-231)

LY2835219

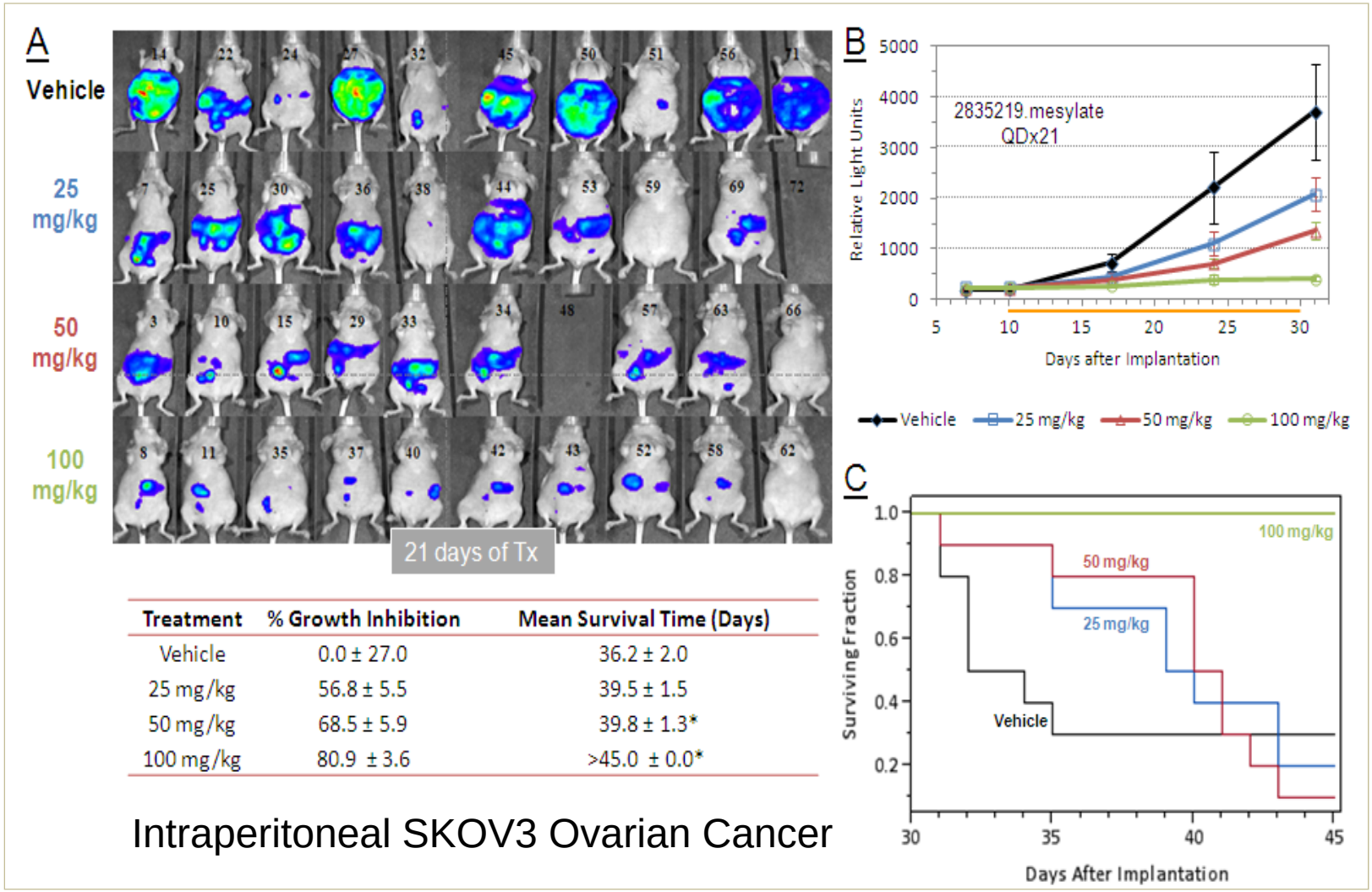


- ATP-competitive small molecule inhibitor of CDK4/6
  - Inhibits CDK4 (IC50 = 2 nM) and CDK6 (IC50 = 9.9 nM)
  - Selective for CDK4 (IC50 = 2 nM) relative to CDK1 (IC50 = 1627 nM)
- Nonclinical ADME
  - Moderate to high oral bioavailability
  - Biliary excretion
  - Distributes efficiently to the brain
- Nonclinical toxicology
  - Bone marrow and gastrointestinal tract
  - Toxicities were either partially or completely reversible
- Demonstrates antitumor activity in multiple preclinical models of human cancer including non-small cell lung cancer (NSCLC), ovarian cancer, and breast cancer

Non-Small Cell Lung Cancer



Ovarian Cancer



Treatment	% Growth Inhibition	Mean Survival Time (Days)
Vehicle	0.0 ± 27.0	36.2 ± 2.0
25 mg/kg	56.8 ± 5.5	39.5 ± 1.5
50 mg/kg	68.5 ± 5.9	39.8 ± 1.3*
100 mg/kg	80.9 ± 3.6	>45.0 ± 0.0*

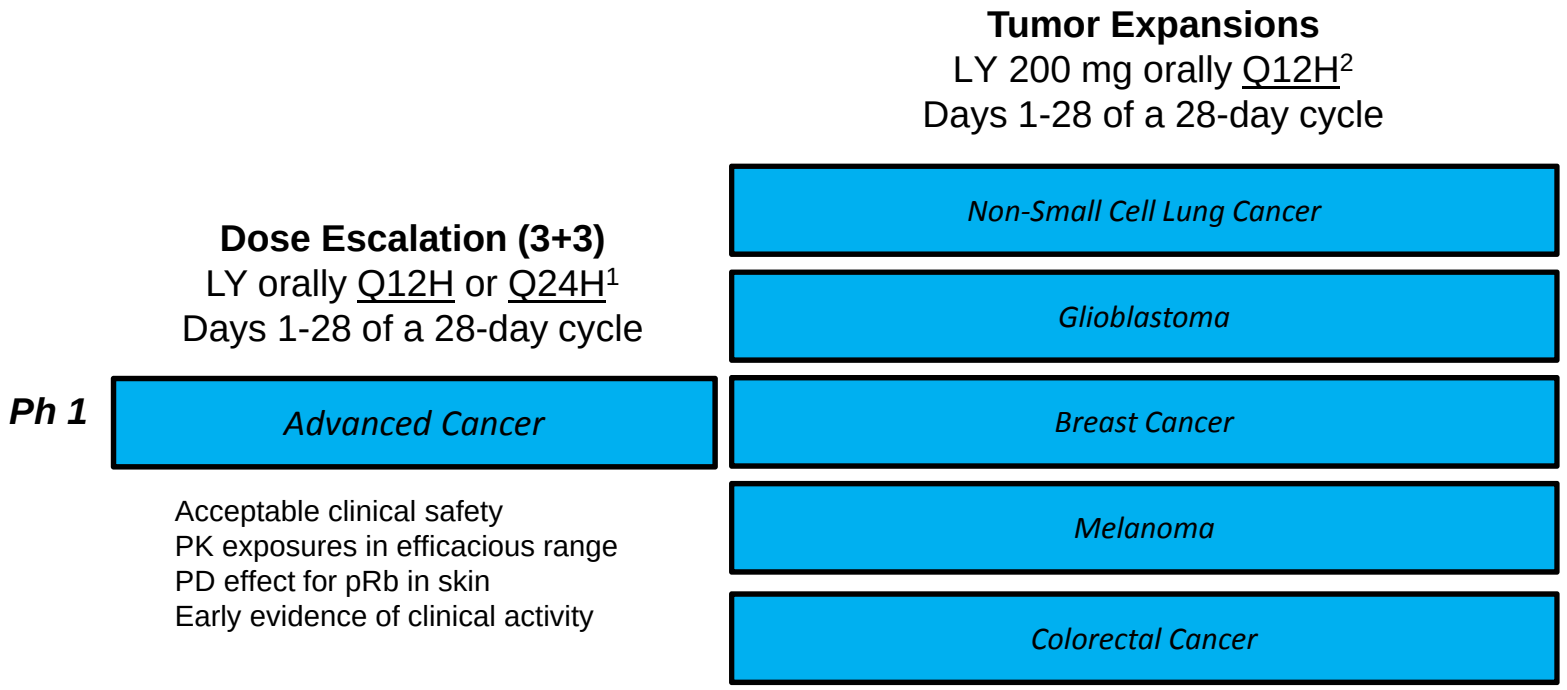
Intraperitoneal SKOV3 Ovarian Cancer

Phase 1 Objectives

- Primary
  - Evaluate safety and tolerability of LY2835219 for patients with advanced cancer
- Secondary
  - Determine pharmacokinetics of LY2835219
  - Evaluate pharmacodynamic and predictive biomarkers
  - Document antitumor activity of LY2835219
  - Establish a recommended dose for Phase 2 studies

Study Design

(non-randomized, open label)



[1]LY dosed initially Q24H, then subsequently Q12H in order to increase steady state exposures
[2]LY dosed Q12H in the tumor expansions

Patient Characteristics

Total Patients Treated	n = 75
Median age	60 yrs (range: 38-78)
Gender	**n (%)**
Male	27 (36)
Female	48 (64)
ECOG Performance Status	
0	25 (33)
1	46 (61)
2	4 (5)
Prior Systemic Therapies	74 (99)
1	7 (9)
2	15 (20)
3	13 (17)
4 or more	39 (52)
Prior Surgery	64 (85)
Prior Radiotherapy	39 (52)
Brain Metastasis	9 (12)

Dose-Limiting Toxicities

Q24H Dose (mg)	n	Q12H Dose (mg)	N
50	4	75	3
100	3	100	4
150	3	150	3
225	3	200	7
-	-	275	3

- LY dosed initially Q24H, then subsequently Q12H in order to increase steady state exposures
- MTD for the Q24H schedule was not reached
- DLT for the Q12H schedule was fatigue (Gr 3)
  - 200 mg (1/6 evaluable pts)
  - 275 mg (2/3 evaluable pts)
- MTD for the Q12H schedule was 200 mg

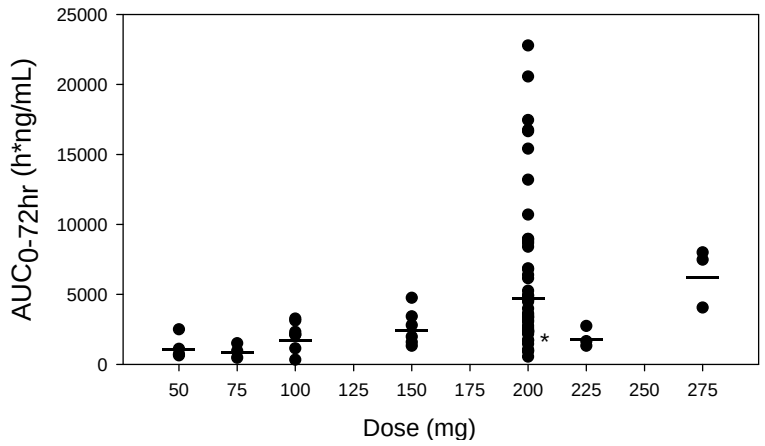
Most Common Treatment-Emergent Adverse Events, Possibly Related and Occurring in ≥ 15% Subjects

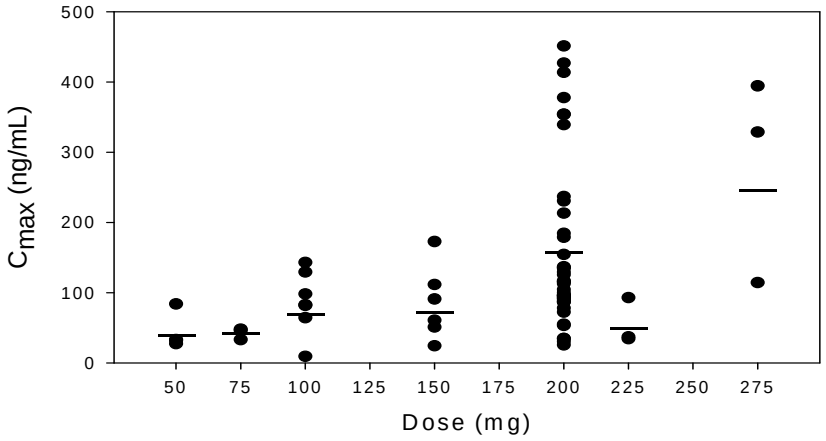
Event	Grade 1	Grade 2	Grade 3	Grade 4	All Grades (N=75)
Diarrhea	21 (28%)	13 (17%)	5 (7%)	0 (0%)	39 (52%)
Nausea	18 (24%)	2 (3%)	4 (5%)	0 (0%)	24 (32%)
Fatigue	7 (9%)	5 (7%)	4 (5%)	0 (0%)	16 (21%)
Vomiting	11 (15%)	4 (5%)	1 (1%)	0 (0%)	16 (21%)
Neutropenia	1 (1%)	8 (11%)	5 (7%)	0 (0%)	14 (19%)

LY2835219 administered continuously (Days 1-28 of a 28-day cycle)

PK of LY2835219 after a single dose

Dose (mg)	N	C_{max} (ng/mL) Geomean (CV)		T_{max} (hr) Median (range)		$AUC_{0\text{-}72hr}$ (ng.hr/mL) Geomean (CV)		$T_{1/2}$ (hr) Geomean (CV)		CL/F (L/hr) Geomean (CV)		Vz/F (L) Geomean (CV)	
50	4	39.6	(54)	4	(2-4)	1062	(68)	25.8	(40)	39.5	(88)	1473	(43)
75	3	41.9	(21)	4	(2-4)	878	(64)	17.4	(8)	79.5	(64)	1996	(67)
100	7	68.8	(117)	6	(4-10)	1692	(95)	20.8	(31)	53.3	(96)	1599	(92)
150	6	71.4	(77)	6	(4-71)	2462	(53)	28.8	(47)	42.9	(46)	1706	(60)
200	49	157.1	(115)	8	(2-25)	4738	(119)	20.5	(34)	39	(124)	1160	(118)
225	3	49.1	(60)	6	(6-6)	1816	(39)	38.1	(92)	83.4	(17)	4583	(83)
275	3	245.6	(75)	6	(6-8)	6237	(39)	25.0	(102)	34.9	(5)	1257	(111)



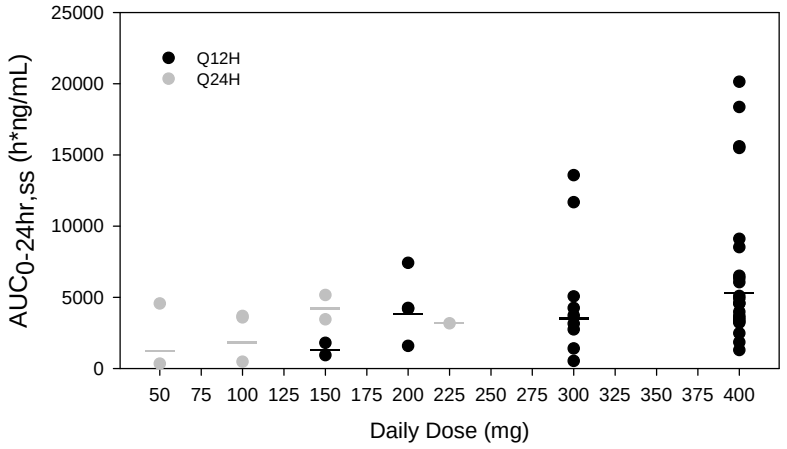


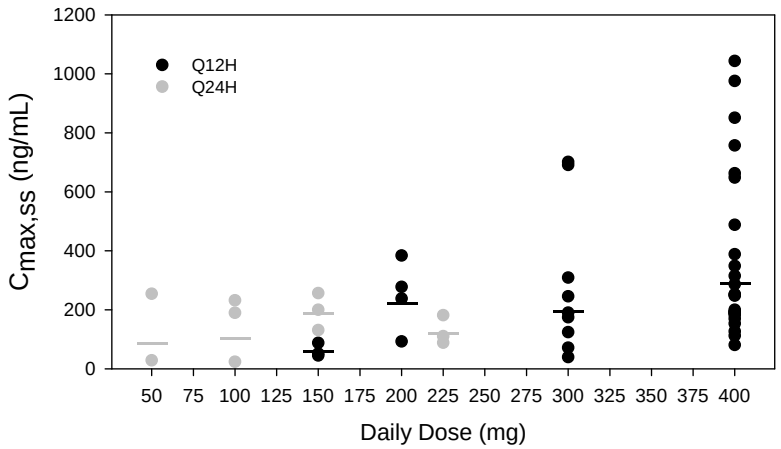
*2 pts had $_{AUC0\text{-}72hr}$ >25000 ng*hr/mL and were not included in the plot

LY2835219 demonstrates acceptable human exposures at steady state

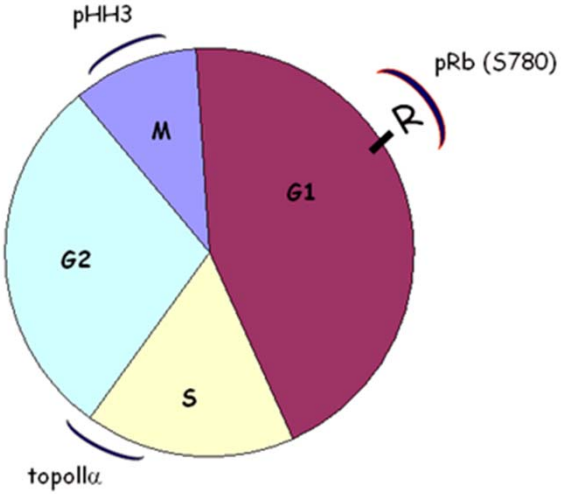
Dose (mg)	N	$C_{max,ss}$ (ng/mL) Geomean (CV)		$AUC_{0\text{-}tau,ss}$ (ng.hr/mL) Geomean (CV)		$AUC_{0\text{-}24hr,ss}$ (ng.hr/mL) Geomean (CV)	
50 QD	2	28.6, 254.2[a]	---	334, 4557[a]	---	334, 4557[a]	---
100 QD	3	102	(198)	1844	(172)	1844	(172)
150 QD	3	189	(35)	3448, 5159[a]	---	3448, 5159[a]	---
225 QD	3	121	(38)	3164[a]	---	3164[a]	---
75 BID	3	59	(37)	546	(43)	1092	(43)
100 BID	4	221	(67)	2171	(71)	4342	(71)
150 BID	9	196	(121)	1847	(135)	3694	(135)
200 BID	25	291	(80)	2899	(78)	5798	(78)

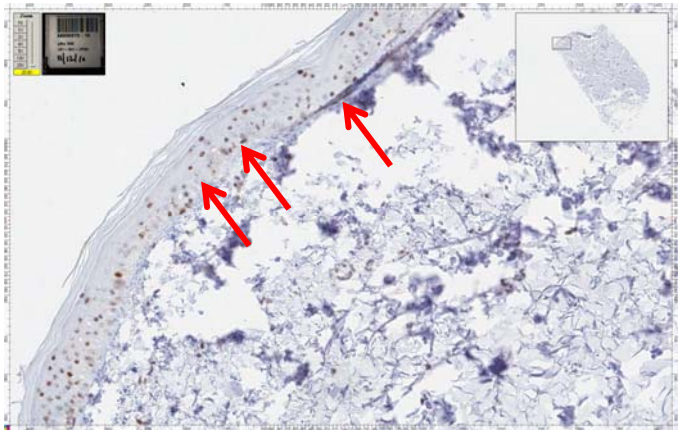
[a]: individual values are presented when n < 3



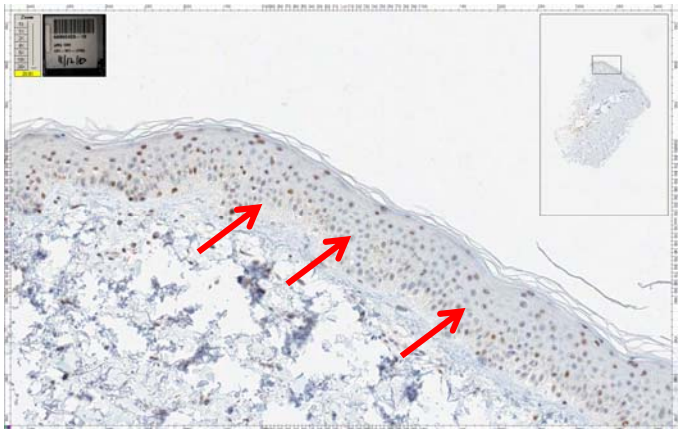


LY2835219 Inhibits p-Rb in Skin

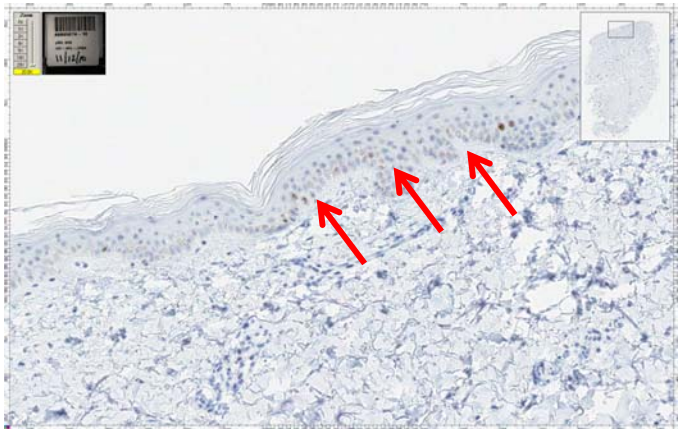




Steady State (Day 15) – Pre Dose



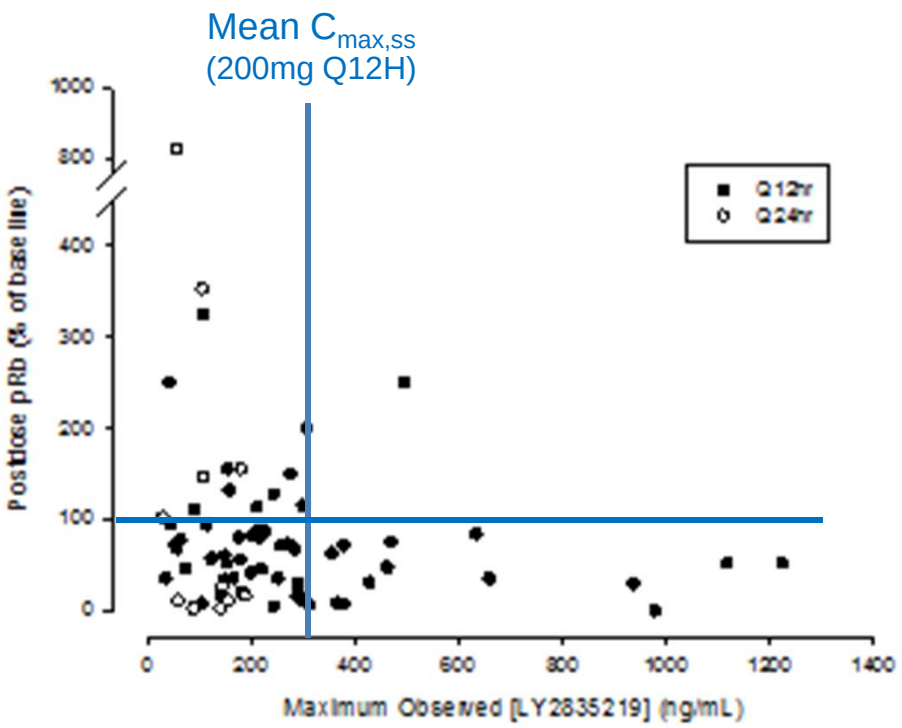
Baseline – Before LY



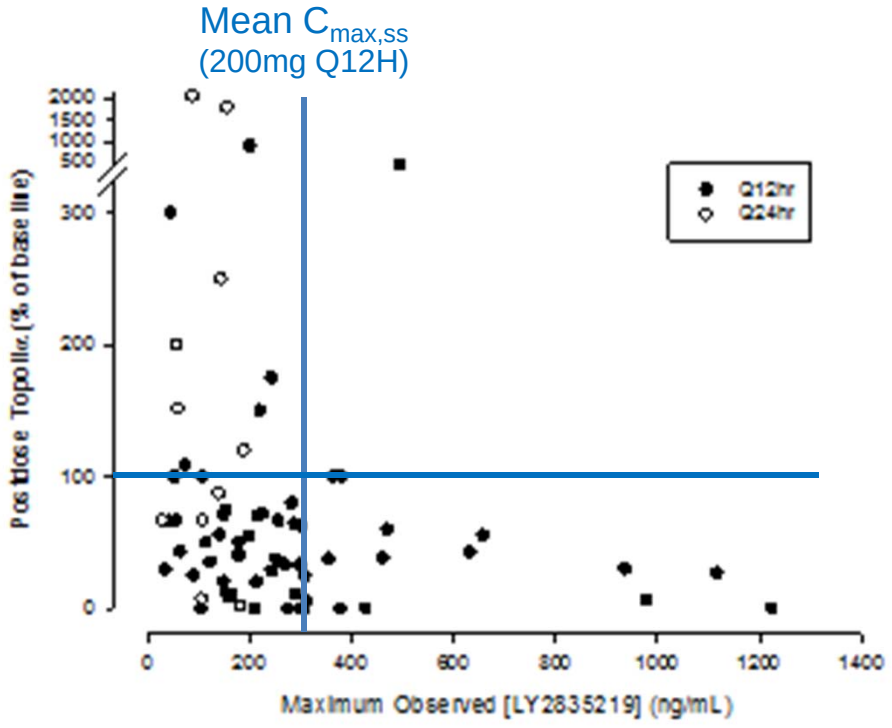
Steady State (Day 15) – Post Dose

Skin biopsies from a patient who received LY2835219 every 24 hours

Pharmacodynamic Biomarkers: p-Rb and Topoisomerase II α in Skin

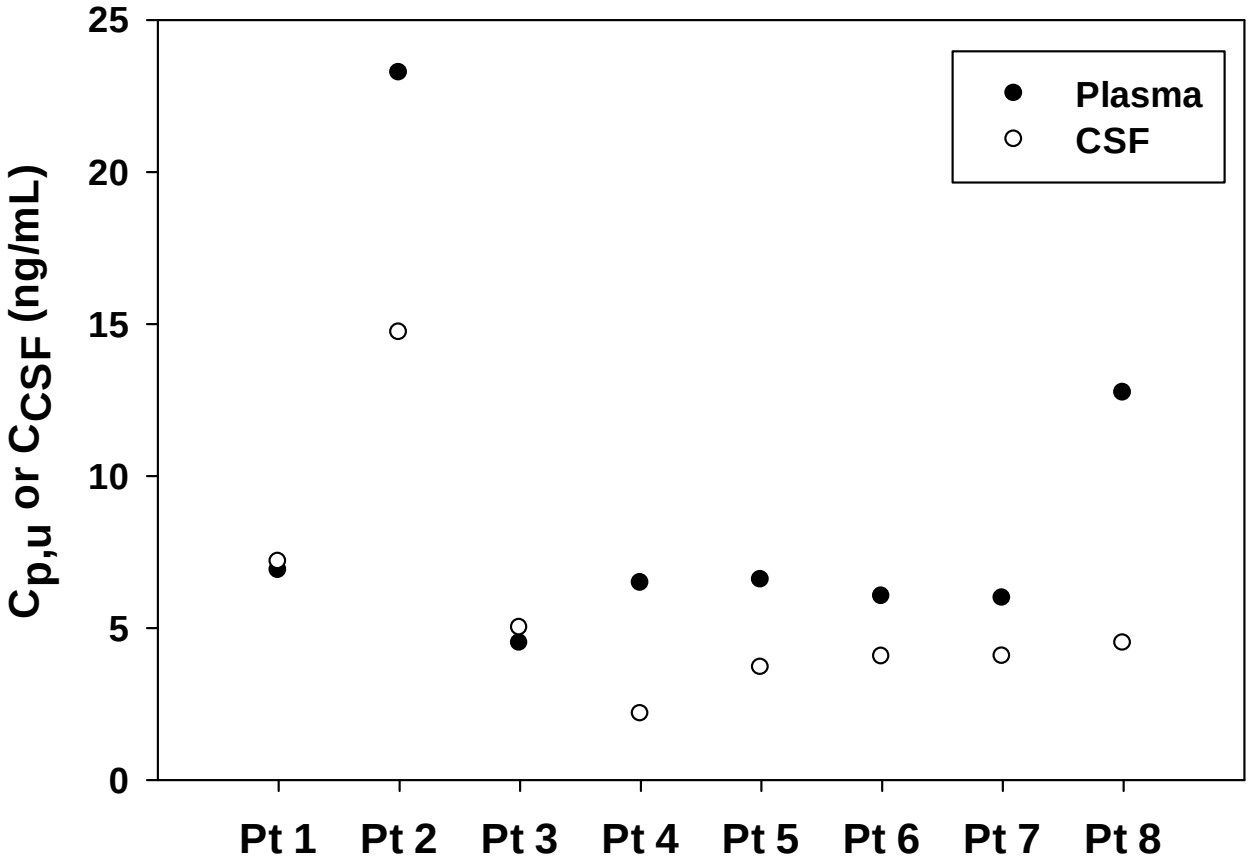


Post-dose p-Rb (% baseline)



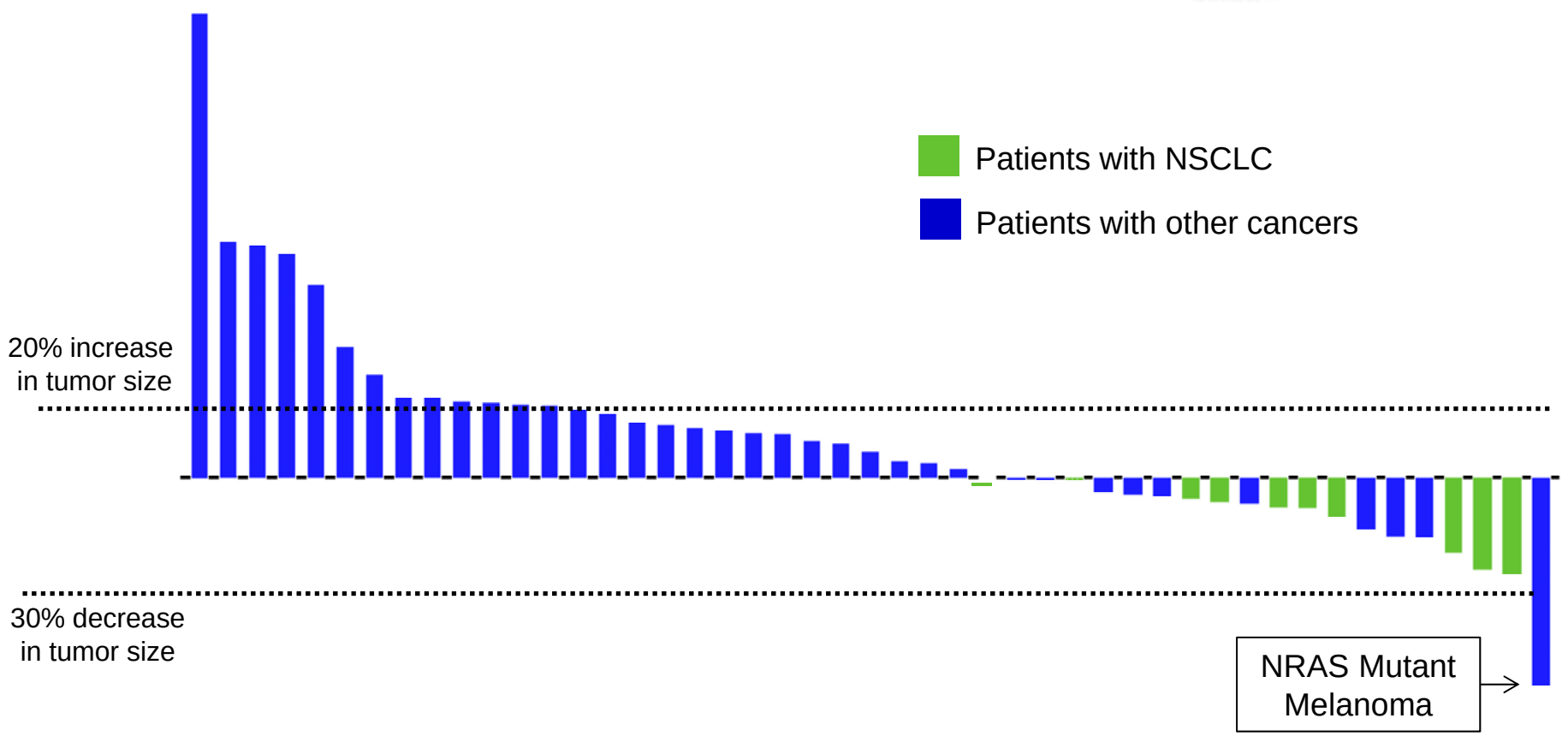
Post-dose Topo II α (% baseline)

LY2835219 is detectable in cerebrospinal fluid from patients



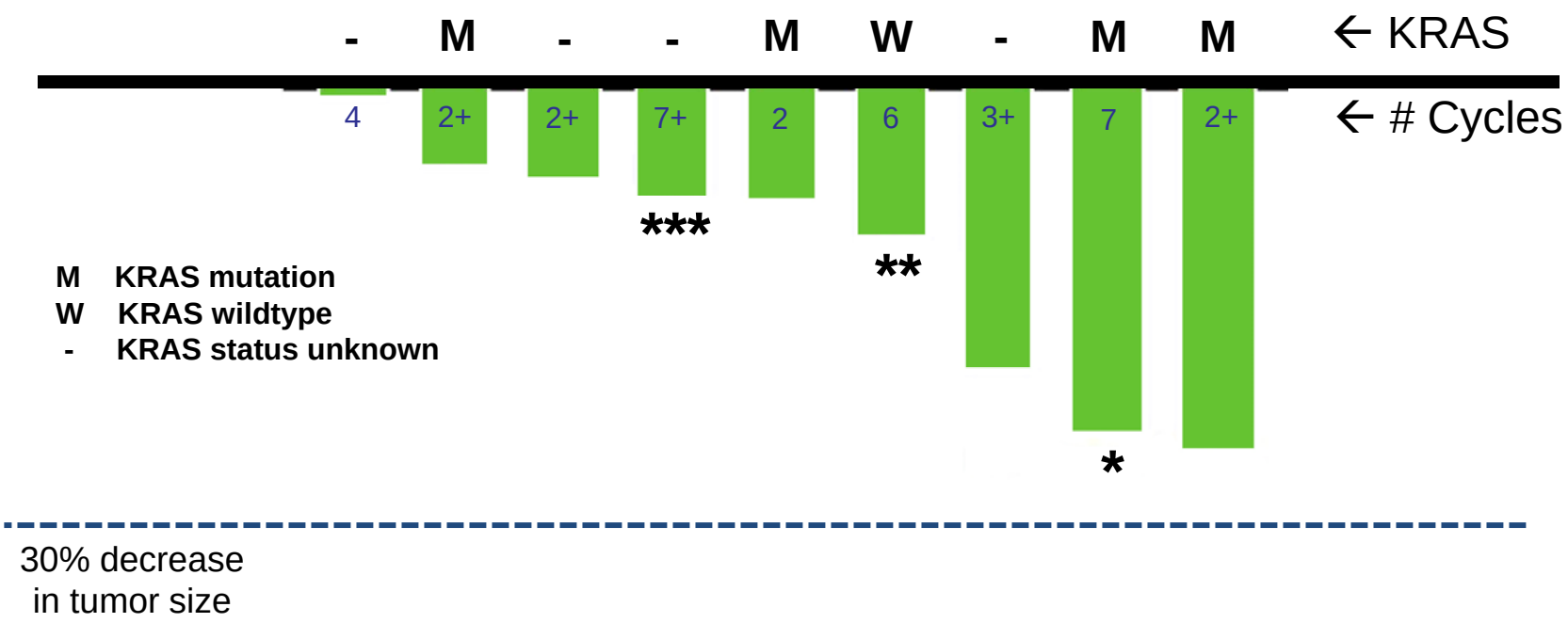
Plasma and CSF concentrations from patients were obtained after reaching steady state with < 2.5 hours between plasma and CSF sampling

Change in Tumor Size at Best Response



75 patients received LY2835219 across dose escalation and tumor-specific expansions. Of the 47 patients with pre- and post-treatment lesion measurements at the time of the interim analysis, 34 patients had SD or PR.

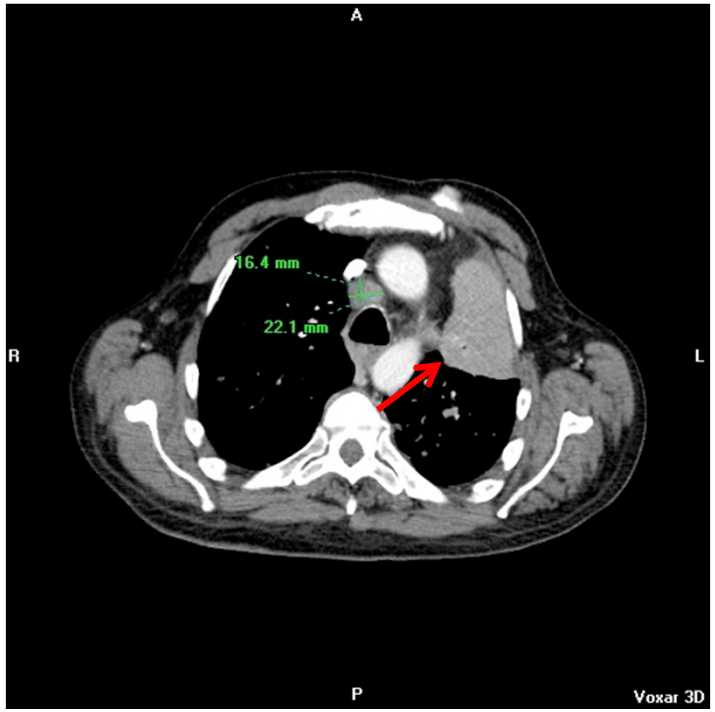
Change in Tumor Size at Best Response for NSCLC



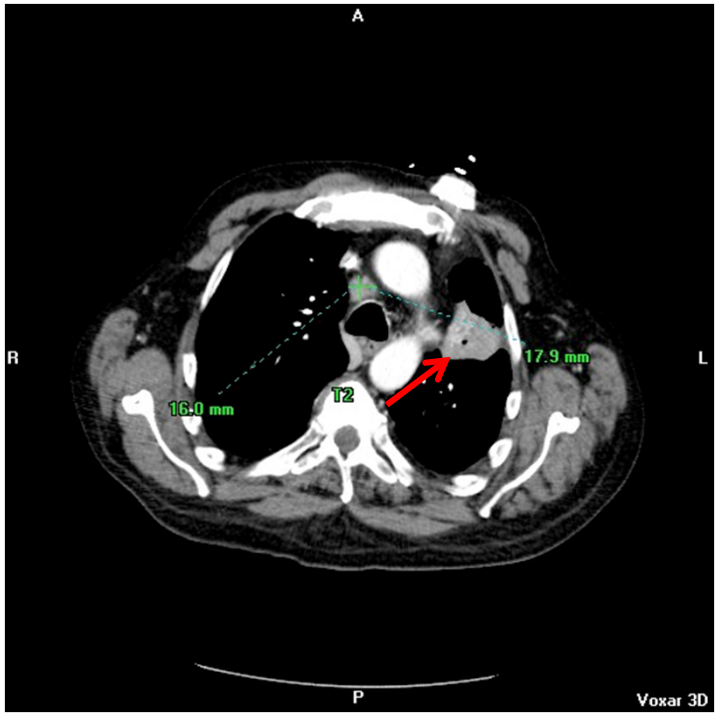
Prior therapies for patients reaching ≥6 cycles of LY2835219 therapy
***(1) paclitaxel + carboplatin, (2) pemetrexed**
****(1) paclitaxel + cisplatin, (2) gemcitabine + carboplatin + bevacizumab, (3) pemetrexed, (4) erlotinib**
*****(1) pemetrexed + cisplatin, (2) docetaxel, (3) everolimus + investigational drug**

L2835219 in KRAS Mutant NSCLC

Before treatment



After 4 cycles

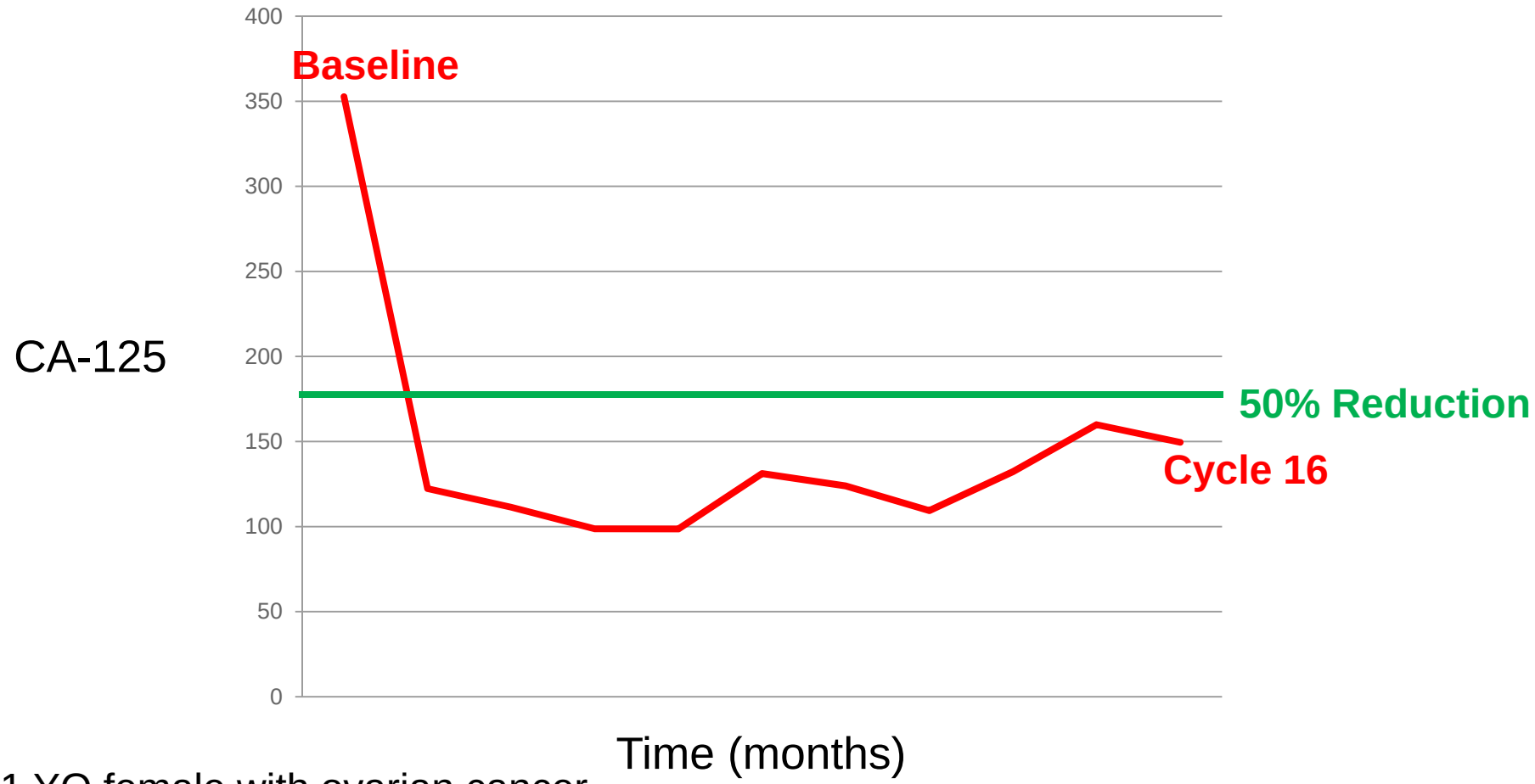


54 YO male with KRAS mutant NSCLC received prior therapy with:

- paclitaxel + carboplatin
- pemetrexed

LY 200 mg PO Q12H

CA-125 Response to LY2835219 in Ovarian Cancer



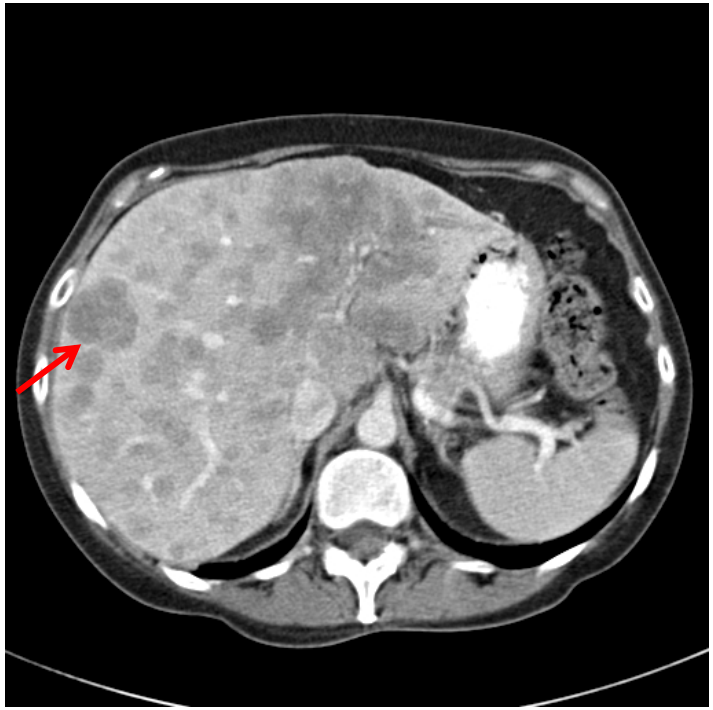
71 YO female with ovarian cancer

- paclitaxel + carboplatin (x2)
- topotecan

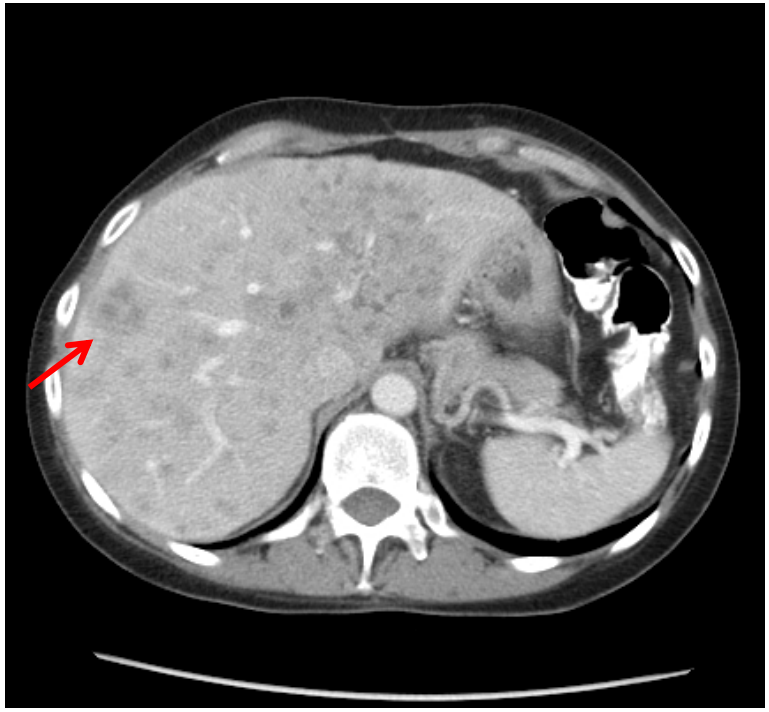
LY 150 mg PO Q24H

LY2835219 in ER+ HER2+ Breast Cancer

Before treatment



After 2 cycles



41 YO female with ER+ HER2+ breast cancer received prior therapy with:

- Adjuvant radiotherapy, hormonal therapy, and chemotherapy
- After relapse: vinorelbine, trastuzumab, gemcitabine, lapatinib + capecitabine, liposomal doxorubicin, and eribulin

LY 200 mg PO Q12H

Conclusions

- The safety profile for LY2835219 enables continuous dosing
- DLT for the twice-daily schedule is fatigue
- Tumor-specific expansions initiated at MTD of 200 mg every 12 hours
- Most common possibly related adverse events include diarrhea, nausea, fatigue, vomiting, and neutropenia
- Oral dosing of LY2835219 achieves acceptable human exposures
- LY2835219 demonstrates pharmacodynamic effect in skin as indicated by inhibition of Rb phosphorylation and topoisomerase II α
- LY2835219 is detectable in cerebrospinal fluid from patients
- Early clinical activity has been observed in multiple tumor types including NSCLC, melanoma, ovarian cancer, and breast cancer