

# Melanoma: highlights from the oral presentation session & clinical science symposium at ASCO 2009

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# Abstracts to be discussed

9006	Clinical relevance of miRNA expression in metastatic melanoma	Segura M
CRA9011	A phase III multi-institutional randomized study of immunization with the gp100 peptide followed by high-dose IL-2 compared with high-dose IL-2 alone in patients with metastatic melanoma	Schwartzentruber D
9033	Effect of ipilimumab treatment on 18-month survival: Update of patients with advanced melanoma treated with 10 mg/kg ipilimumab in three phase II clinical trials	O'Day S
9034	Association between immune-related adverse events and disease control or overall survival in melanoma patients treated with 10 mg/kg ipilimumab in 3 phase II clinical trials	Lutzky J
9055	A phase II trial of carboplatin and nab-paclitaxel in patients with unresectable stage IV melanoma: Final data from N057E	Markovic S
9061	Nab-paclitaxel and bevacizumab as first-line therapy in patients with unresectable stage III and IV melanoma	Boasberg P
LBA9012	Phase III, randomized, double-blind study of elesclomol and paclitaxel versus paclitaxel in stage IV metastatic melanoma	Hauschild A

# Abstracts to be discussed

9028	Phase II study of aflibercept (VEGF trap) in recurrent inoperable stage III or stage IV melanoma of cutaneous or ocular origin.	Tarhini A
9001	A phase II study of imatinib mesylate (IM) for patients with advanced melanoma harboring somatic alterations of <i>KIT</i> .	Carvajal R
9000	Phase I study of PLX4032: Proof of concept for V600E BRAF mutation as a therapeutic target in human cancer.	Flaherty K

## Clinical relevance of miRNA expression in metastatic melanoma

Segura M (NYU)

- Total RNA was extracted from formalin-fixed paraffin embedded (FFPE) tissue samples from 61 metastatic melanoma specimens
- RNA was hybridized into miRNA arrays containing probes for more than 600 miRNA sequences
- Significance Analysis of Microarrays (SAM) was used to identify miRNAs significantly associated with survival
- identified a signature of 18 miRNAs, whose up-regulation significantly associates with better prognosis (increased overall survival)
- Using cross-validation, miRNA signature consisting of 10 of these significant miRNAs with lowest misclassification error in predicting 1.5-year post-recurrence survival

# A phase III multi-institutional randomized study of immunization with the gp100 peptide followed by high-dose IL-2 compared with high-dose IL-2 alone in patients with metastatic melanoma

## Schwartzentruber D

- In a phase II study, 13 (42%) of 31 patients with metastatic melanoma receiving high-dose (HD) IL-2 plus gp100:209-217(210M) peptide experienced objective responses
- 185 patients with stage IV or locally advanced stage III cutaneous melanoma, HLA A0201, no brain metastases, eligible for HD IL-2
- Received Arm 1: HD IL-2 alone (720,000 IU/kg/dose) or Arm 2: gp100:209-217(210M) peptide + Montanide ISA followed by HD IL-2
- Primary objective was clinical response.
- Toxicities were consistent with HD IL-2 ± vaccine.
- Investigator assessed RR showed significant improvement in overall RR for Arm 2=22.1% vs Arm 1 = 9.7% (P=0.02)
- PFS Arm 2 = 2.9 months vs Arm 1 = 1.6 (P=0.01)
- Median overall survival favors Arm 2 = 17.6 mos vs 12.8 mos. (P=0.10)

# Central Response Assessment

Response	IL-2 N (%)	IL-2 + gp100 N (%)	P Value
CR + PR	6 (6.5)	16 (18.6)	0.013
SD + PD	87 (93.5)	70 (81.4)	

# Effect of ipilimumab treatment on 18-month survival: Update of patients with advanced melanoma treated with 10 mg/kg ipilimumab in three phase II clinical trials

O'Day S

- Retrospective analysis of two, mature phase II trials with ipilimumab administered to a large subset of previously treated patients
- CA184008 was an open-label, single-arm study of ipilimumab 10 mg/kg. Study CA184022 was a randomized, dose-ranging study of ipilimumab 0.3, 3, or 10 mg/kg

<b>Study (N)</b>	<b>12-month OS rate</b>	<b>18-month OS rate</b>
CA184008 (N=155)	47.2%	39.4%
CA184022 (N=214)	48.6%	34.5%
Korn analysis (N=2100)	25%	15%

Association between immune-related adverse events (irAEs) and disease control or overall survival in melanoma patients treated with 10 mg/kg ipilimumab in 3 phase II clinical trials  
Lutzky J

- Across 3 Phase II studies ipilimumab 10 mg/kg was given every 3 weeks (Q3W) x 4 (induction); Q12W starting at week 24 (maintenance)
- The rate of DC by mWHO in pts with grade 0/1 irAEs was 20-24% and in pts with grade  $\geq 2$  irAEs was 34-43% (p=NS)
- For pts who lived up to Day 81, median OS (95% CI) from Day 81 was 14.8 mo (10.0-21.7) for any irAE vs. 8.21 mo (5.29-13.7) for no irAE within 12 weeks
- But, median OS was 13.6 mo (5.78-NR) for any grade  $\geq 2$  irAE and 11.3 mo (7.95-15.8) for no grade  $\geq 2$  irAE within 12 weeks for all patients (p=NS)

# A phase II trial of carboplatin and nab-paclitaxel in patients with unresectable stage IV melanoma: Final data from N057E

Markovic S

- Phase II trial in stage IV melanoma, who were either chemotherapy naïve (CN) or were previously treated (PT)
- *nab-P* (100 mg/m<sup>2</sup>) and carboplatin (AUC 2) was administered on days 1, 8, and 15 of a 28 day cycle
- The primary aim of this study was to assess whether tumor response rate (CR + PR by RECIST) was  $\leq 15\%$  vs  $\geq 35\%$  in the CN group and  $\leq 5\%$  vs  $\geq 20\%$  in the PT cohort.
- 76 pts (41-CN and 35 PT)
- 1 CR and 10 PRs (28%) in the CN cohort (90% CI: 16.7-42.3%)
- 3 PRs (9%) in the PT cohort (90% CI: 2.5-21.3%)
- Median PFS was 4.5 months (CN) and 4.1 months (PT)
- Median OS was 11.1 months (CN) and 10.9 months (PT)

Abstract 9055

# Nab-paclitaxel and bevacizumab as first-line therapy in patients with unresectable stage III and IV melanoma

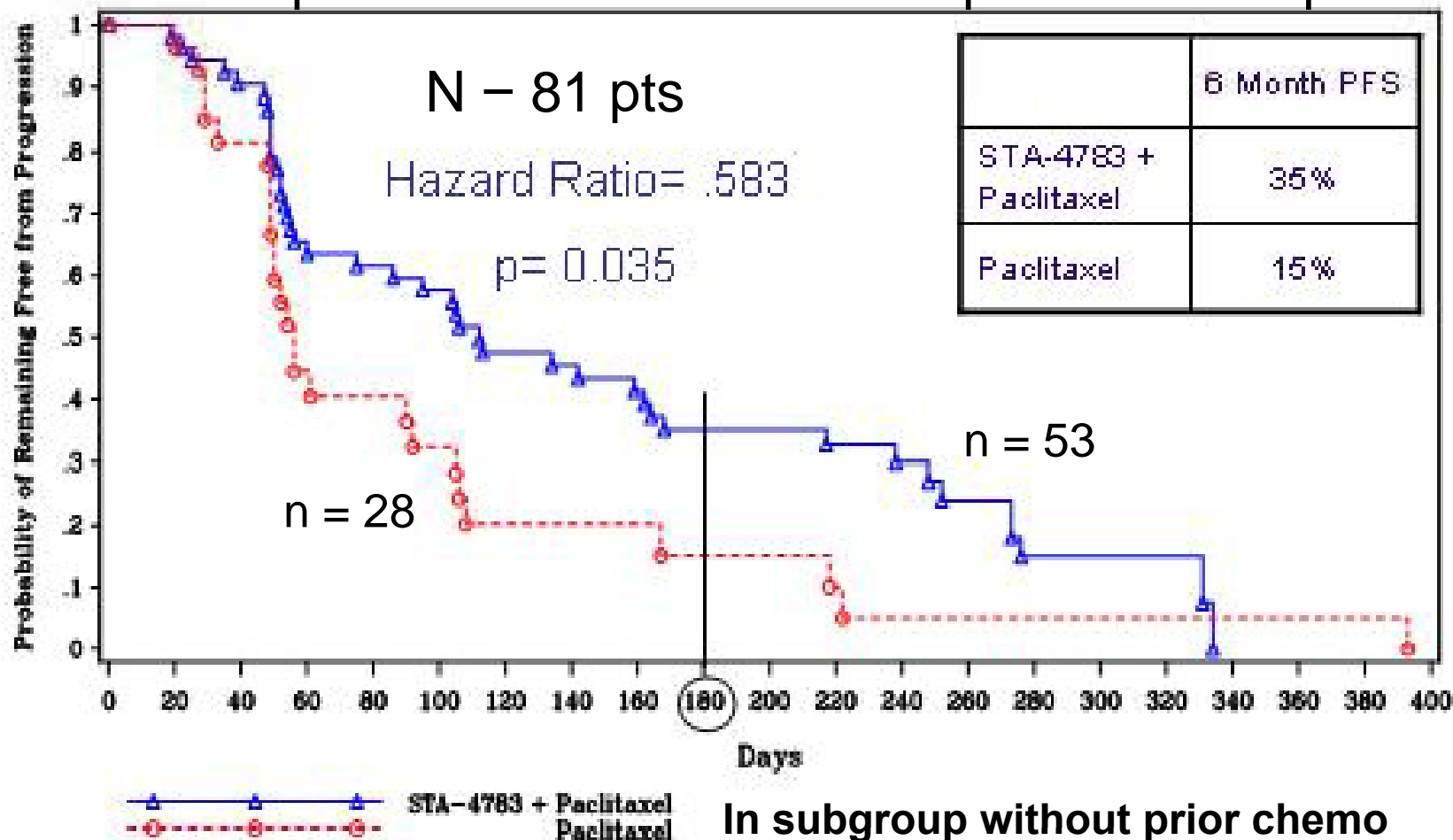
Boasberg P

- 41 chemotherapy-naïve patients (>50% M1c) received nab-paclitaxel 150 mg/m<sup>2</sup> on days 1, 8, and 15 and bevacizumab 10mg/kg on days 1 and 15 until disease progression or DLT
- Median follow-up: PFS 5.3 mos. & OS 4.7 mos.
- PFS at 4 months is 83% (95% CI 69%-97%)
- Median PFS is 6.25 months (95% CI 5.6-9.4)
- 6 month survival rate is 91% (95% CI 79%-100%)
- 12 month survival rate is 83% (95% CI 65%-100%)
- Median duration of overall survival has not been reached yet

Abstract 9061

# Kaplan-Meier Plot of Progression-Free Survival

Randomized phase II trial of STA-4783+paclitaxel vs. paclitaxel



Note: The p-value is from a 2-sided log-rank test.

In subgroup without prior chemo  
(n = 23 vs. 9)  
Median PFS 8.3 mo. vs. 2.4 mo.

Abstract 9032

# Phase III, randomized, double-blind study of elesclomol and paclitaxel versus paclitaxel in stage IV metastatic melanoma

## Hauschild A

- 651 pts with Stage IV melanoma, no prior chemotherapy, LDH < 2x ULN were randomized (1:1) to either 213 mg/m<sup>2</sup> elesclomol in combination with 80 mg/m<sup>2</sup> paclitaxel (ELPAC) or 80 mg/m<sup>2</sup> paclitaxel alone (P); both were given weekly x3 followed by 1 week rest until disease progression.
- Primary endpoint was PFS with >90% power to detect a 2-month improvement.
- Median PFS was 3.5 m (95% CI 2.7-3.7) in ELPAC and 1.9 m (95% CI 1.9-3.3) in P [HR 0.88; 95% CI 0.67-1.16, p=0.3695].
- Safety analysis showed increased overall deaths (80 vs 53); increased ≥Gr 3 AEs (N=405, 33% vs. 24%), increased AEs leading to death (N=405, 3.5% vs <1%)

# Overall Survival: Not Yet Mature Currently Favors PAC Arm

<b>ITT Population (N=651)</b>			
<b>Data Cut</b>	<b>% censored</b>	<b>HR (CI)</b>	<b>p-value</b>
<b>Feb 2009</b>	<b>80%</b>	<b>1.62*</b> (1.14 - 2.31)	<b>0.0068</b>
<b>April 2009</b>	<b>72%</b>	<b>1.31</b> (0.98 - 1.76)	<b>0.0719</b>

<b>Pts enrolled as of Sep 1, 2008 (N=300)</b>			
<b>Data Cut</b>	<b>% censored</b>	<b>HR (CI)</b>	<b>p-value</b>
<b>Feb 2009</b>	<b>63%</b>	<b>1.28</b> (0.88 - 1.87)	<b>0.1930</b>
<b>April 2009</b>	<b>54%</b>	<b>1.22</b> (0.87 - 1.71)	<b>0.2552</b>

\* There were 80 OS events in the ELPAC arm vs. 53 OS events in the PAC arm

Abstract LBA9012

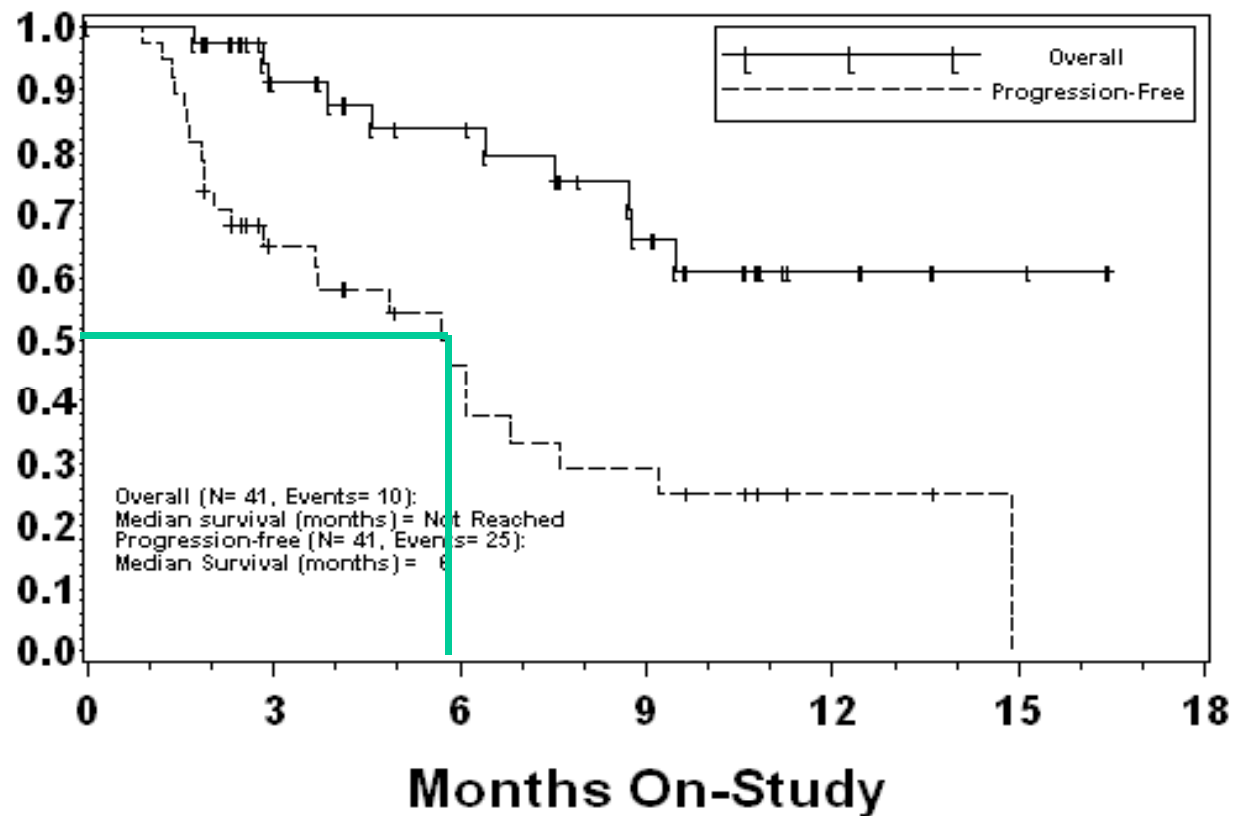
## Phase II study of aflibercept (VEGF trap) in recurrent inoperable stage III or stage IV melanoma of cutaneous or ocular origin

Tarhini A (Pittsburgh)

- Phase II study of aflibercept in patients with inoperable stage III or IV melanoma who had received no prior chemotherapy
- 2-stage design was adopted focusing upon response rate (RECIST) and 4-month PFS rate. First stage accrual of 21 patients was specified, while final accrual of 41 is planned, with adequate response/4 month PFSR. Aflibercept was given at 4 mg/kg IV every 2 weeks.
- Eight (1 M1a, 1M1b, 6M1c; 4 ocular, 3 cutaneous, 1 unknown primary) of the first 21 patients had at least 4 months of PFS
- 41 pts: 28 cutaneous primary, 10 ocular
- 68% M1c

Phase II study of aflibercept (VEGF trap) in recurrent inoperable stage III or stage IV melanoma of cutaneous or ocular origin  
Tarhini A (Pittsburgh)

**Probability of Survival**



## Abstract 9001

A phase II study of imatinib mesylate (IM) for patients with advanced melanoma harboring somatic alterations of *KIT*

Carvajal R

# Distinct Melanoma Subtypes



Arising from Skin  
Without Chronic  
Sun Damage



60% BRAF  
20% NRAS

0% KIT



Arising from Skin  
With Chronic  
Sun Damage



10% BRAF  
10% NRAS

28% KIT



Arising from  
Mucosal  
Surfaces



10% BRAF  
5% NRAS

39% KIT



Arising from  
Acral  
Surfaces



20% BRAF  
10% NRAS

36% KIT

# KIT Alterations by Melanoma Subtype

	Amp Only	Mutation Only	Both Amp AND Mutation	Either Amp OR Mutation
CSD (n = 33)	3% (1/34)	9% (3/34)	0% (0/34)	<b>12%</b> (4/34)
Mucosal (n = 59)	5% (3/59)	15% (9/59)	3% (2/59)	<b>24%</b> (14/59)
Acral (n = 43)	0% (0/43)	19% (8/43)	12% (5/43)	<b>30%</b> (13/43)
Unknown (n = 10)	0% (0/9)	0% (0/9)	0% (0/9)	<b>0%</b> (0/9)
<b>Total</b> (n = 146)	<b>3%</b> (4/146)	<b>14%</b> (20/146)	<b>5%</b> (7/146)	<b>21%</b> (31/146)

## Response Data (n = 12)

	<b>n</b>	<b>%</b>
Complete Response	<b>2</b>	<b>17%</b>
Partial Response	<b>2</b>	<b>17%</b>
Stable Disease	<b>6</b>	<b>50%</b>
Progression	<b>2</b>	<b>17%</b>
<b>Overall RECIST RR</b>	<b>4/12</b>	<b>33%</b>

# KIT Alteration and Response

#	Melanoma Subtype	KIT Mutation	KIT Amp	Best Response	Cycles	Wks
1	<b>Mucosal</b>	<b>Exon 11 L576P</b>	<b>Yes</b>	<b>CR</b>	<b>7</b>	<b>37+</b>
2	<b>Acral</b>	<b>Exon 11 L576P</b>	<b>Yes</b>	<b>CR</b>	<b>4</b>	<b>18+</b>
3	<b>Mucosal</b>	<b>Exon 11 L576P</b>	<b>No</b>	<b>PR</b>	<b>7</b>	<b>40+</b>
4	<b>Acral</b>	<b>Exon 13 K642E</b>	<b>No</b>	<b>PR</b>	<b>3</b>	<b>13+</b>
5	Mucosal	<b>Exon 13 K642E</b>	No	SD	3	18
6	Mucosal	<b>Exon 11 L576P</b>	No	SD	2	12
7	Mucosal	None	<b>Yes</b>	SD	2	11
8	Mucosal	None	<b>Yes</b>	SD	2	11
9	<b>Acral</b>	<b>Exon 13 K642E</b>	<b>No</b>	<b>SD</b>	<b>2</b>	<b>8+</b>
10	<b>Acral</b>	<b>Exon 13 K643X</b>	<b>Yes</b>	<b>SD</b>	<b>2</b>	<b>6+</b>
11	Mucosal	<b>Exon 13 V654A</b>	No	POD	1	6
12	Mucosal	<b>Exon 9 N463S</b> <b>Exon13 N655S</b>	No	POD	1	4

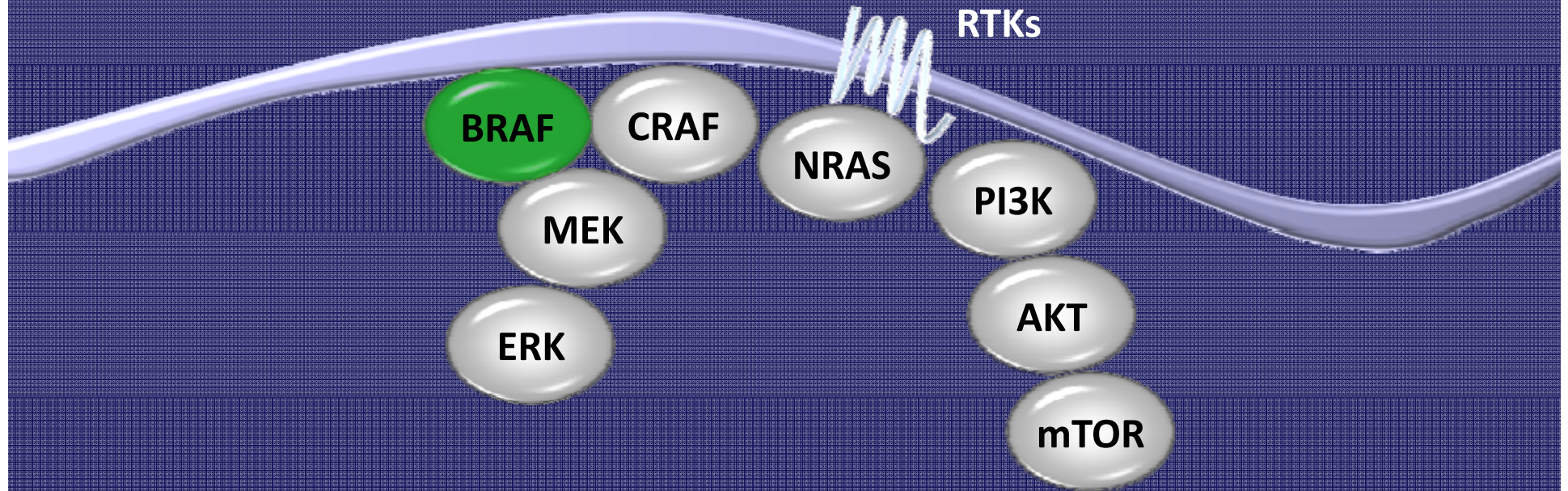
**Red** – on study; **Blue** – off study

Abstract 9001

Abstract 9000

Phase I study of PLX4032: Proof  
of concept for V600E BRAF  
mutation as a therapeutic target  
in human cancer  
Flaherty K

Curtin et al. JCO 2007



90% of all BRAF mutations in BRAF are V600E substitution

& transform 50-60% of melanomaocytes (Wellbrock Cancer Res 2004)

10% of colorectal cancer

BRAF<sup>V600E</sup> siRNA inhibits proliferation &

6-8% of all cancers (Davies H, Nature 2002; COSMIC database

induces apoptosis (Karasarides M, Oncogene 2004)

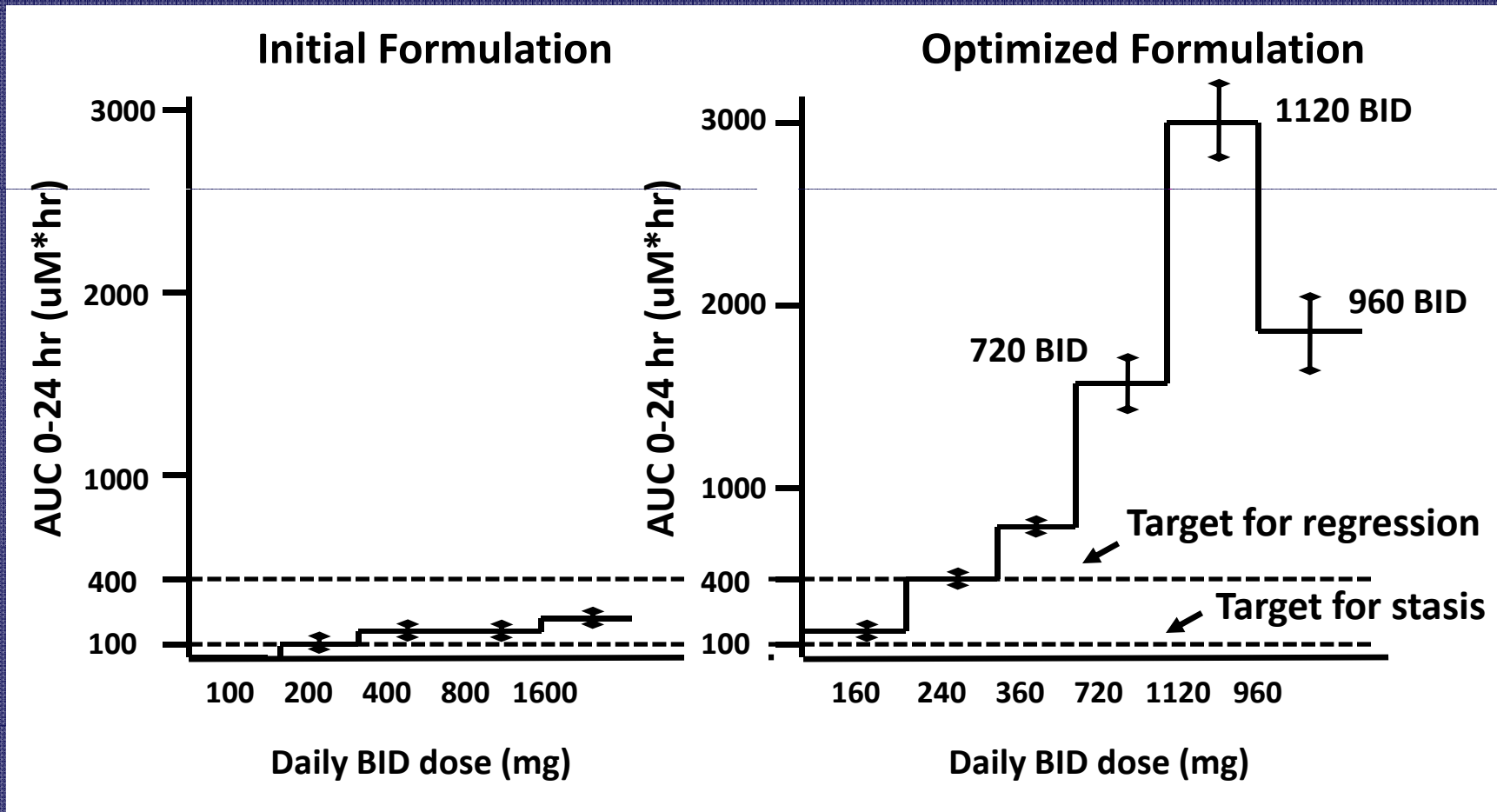
<http://www.sanger.ac.uk/genetics/CGP/cosmic/>

# Phase I dose escalation study of PLX4032 baseline characteristics (n=55 patients)

<b>Median age</b>	<b>years</b>	<b>ECOG PS</b>	<b>No. of pts</b>
(M) 25-89 years	63	0	28
(F) 30-90 years	64	1	27
<b>Gender</b>	<b>no. of pts</b>	<b>Prior lines of treatment</b>	
Male	34	0	5
Female	21	1	7
		2	11
<b>Tumor type</b>		3+	32
Melanoma	49	<b>AJCC stage</b>	
Thyroid	3	(n=49 melanoma)	
Rectal	1	M1a	7
Ovarian	1	M1b	6
Germ cell	1	M1c	36

Abstract 9000

# PLX4032 optimized formulation achieves preclinical target exposure for tumor regression



# PLX4032 safety summary (n=55 patients)

- Nearly all AEs mild and transient up to and including 720 mg BID
- Most frequent drug attributable AEs through 1120 mg BID:
  - Gr 1 and 2 rash (n=17); fatigue (n=9); photosensitivity (n=7)
  - Cutaneous SCC following chronic dosing (n=6)
- Dose-limiting toxicities:
  - 1 DLT out of 5 patients at 720 mg BID
    - Gr 4 pancytopenia resolved with dose reduction
  - 4 DLTs out of 6 patients at 1120 mg BID
    - Gr 3 rash ± grade 3 fatigue (n= 3); Gr 3 arthralgia (n= 1)
- 960 mg BID is under evaluation as MTD

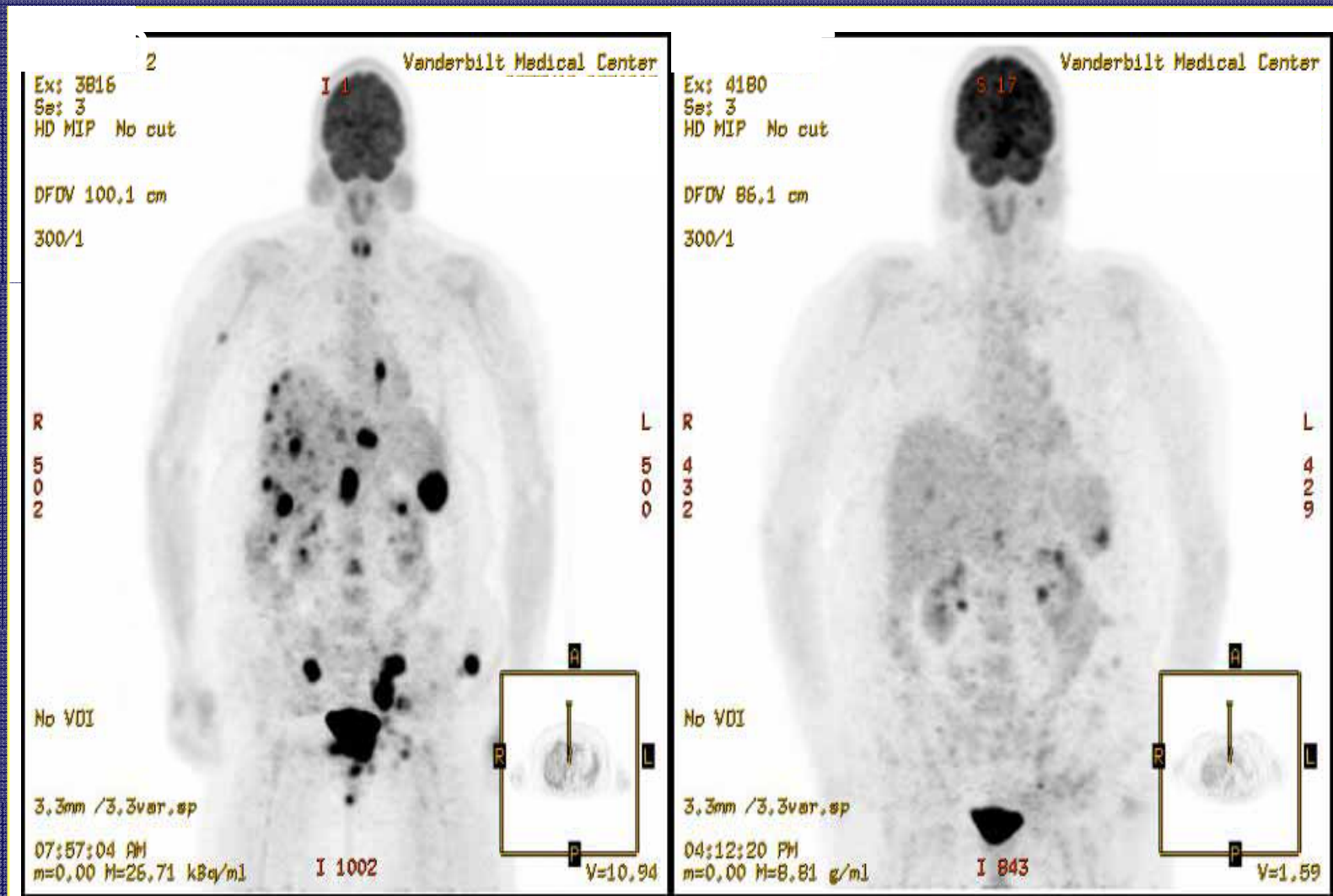
# BRAF<sup>V600E</sup> melanoma patient demographics enrolled at $\geq 240$ mg BID

	<u>N</u>
Melanoma patients at $\geq 240$ mg BID	21
- V600E present	16
- V600E absent	5

## BRAF<sup>V600E</sup> melanoma patients at $\geq 240$ mg BID (N)

	<u>AJCC stage</u>	<u>Prior treatments</u>	<u>ECOG PS</u>
M1a	4	0 3	0 7
M1b	1	1 6	1 9
M1c	11	$\geq 2$ 7	

# BRAF<sup>V600E</sup> melanoma patient PET scan at baseline and day +15 after PLX4032 treatment at 720 mg BID



Abstract 9000

# BRAF<sup>V600E</sup> melanoma patient on 720 mg BID 85% tumor shrinkage in visceral lesions

Liver

Baseline



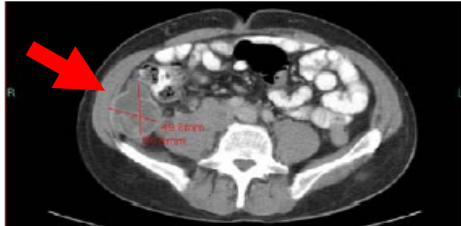
End of cycle 2



End of cycle 3



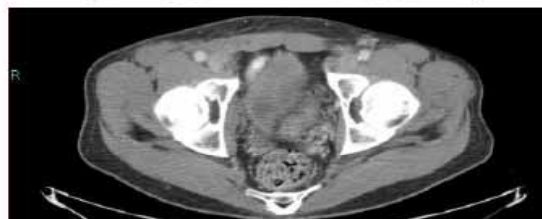
Bowel



Bone

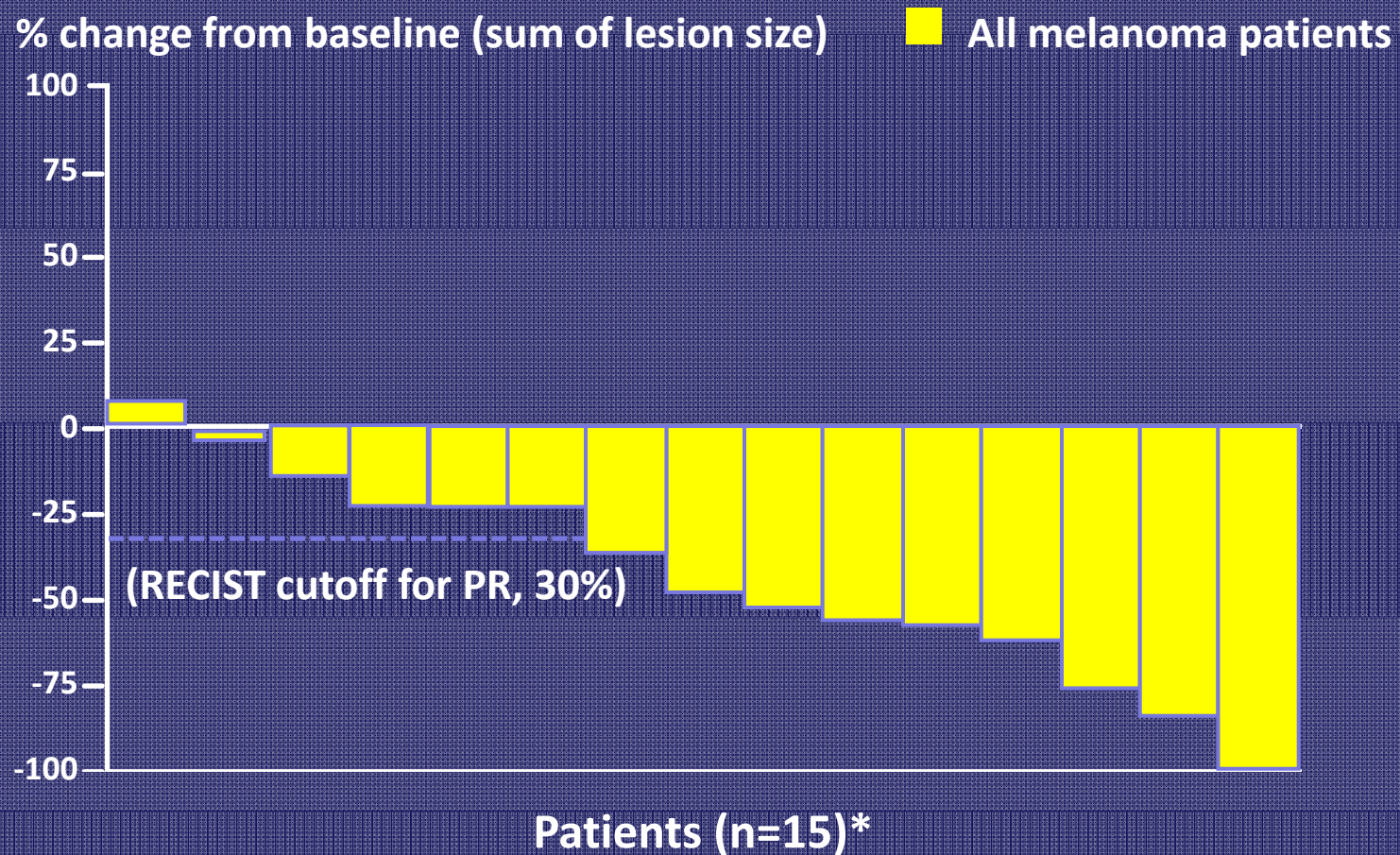


LN



Abstract 9000

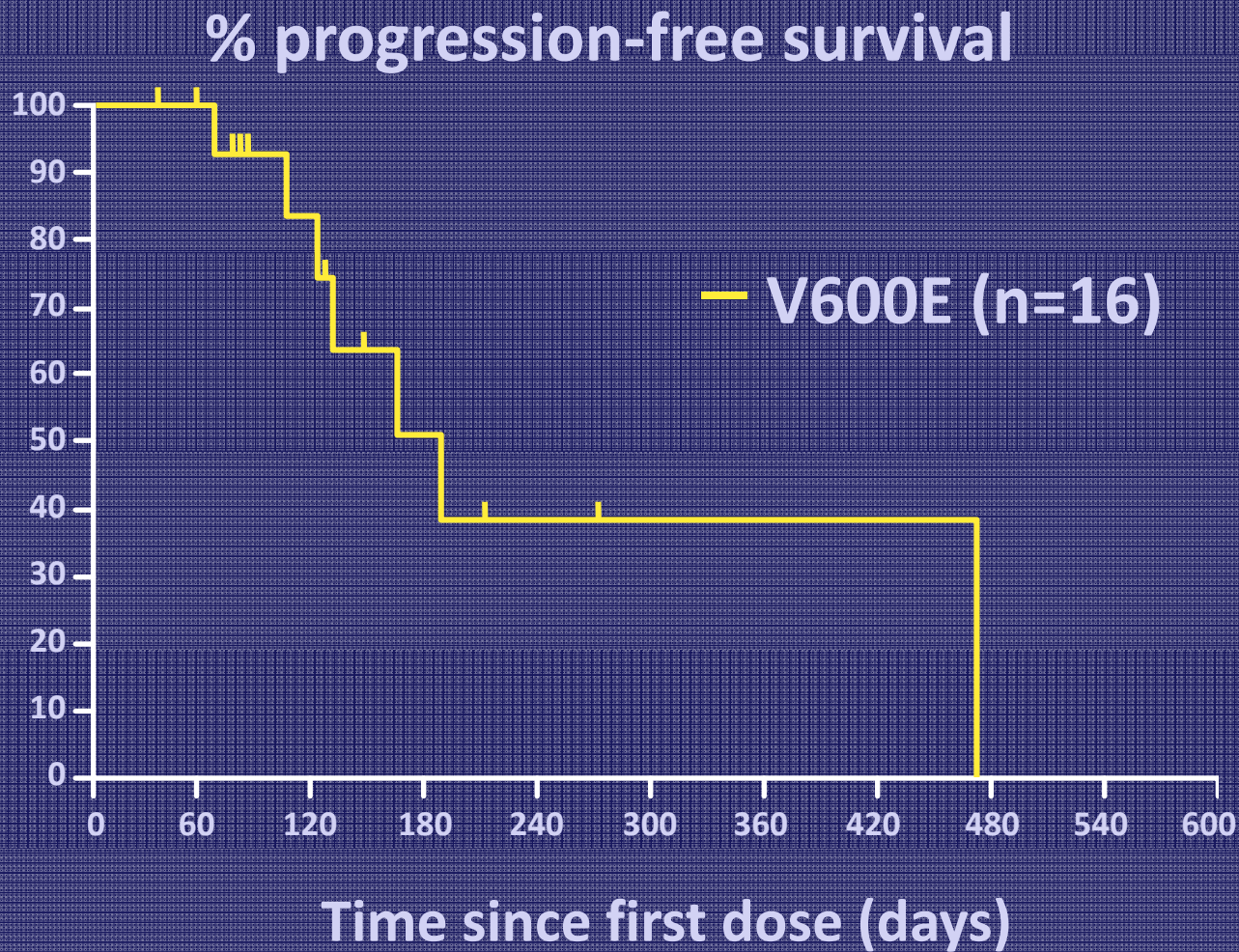
# BRAF<sup>V600E</sup> melanoma patients treated with PLX4032 $\geq$ 240 mg BID



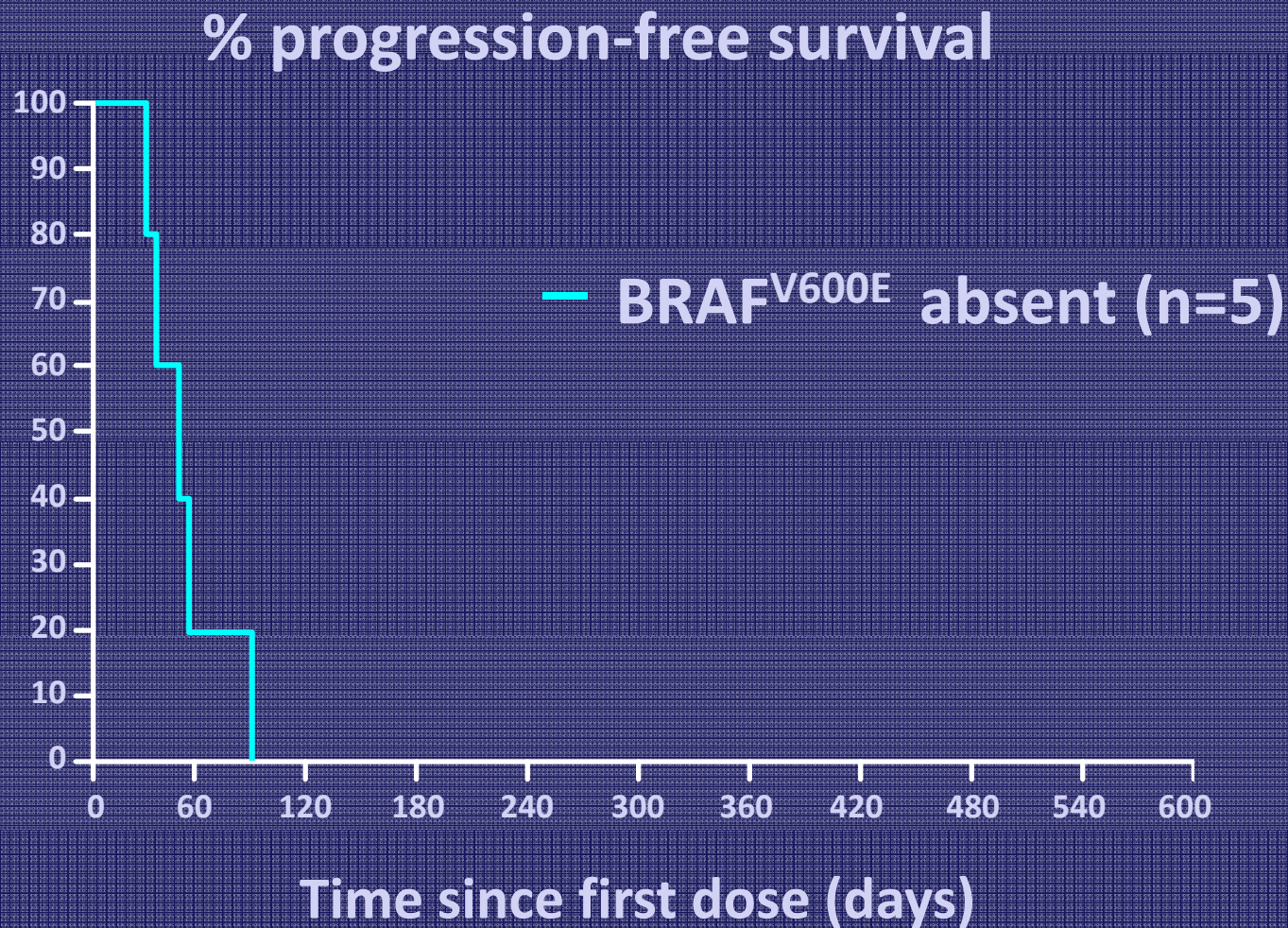
\* One M1c patient had 55% reduction in target lesions, but PD in non-target lesions; died before end C2 (not included above)

Abstract 9000

# Interim PLX4032 phase I Kaplan-Meier plot: BRAF<sup>V600E</sup> melanoma patients ( $\geq 240\text{mg BID}$ )



# Interim PLX4032 phase I Kaplan-Meier plot: non- BRAF<sup>V600E</sup> melanoma patients (≥ 240mg BID)



# Conclusions

- Vaccines may not be so harmful
- Platinum/taxane combinations continue to accumulate data in support of standard use
- Still no benefit demonstrated for the addition of new agents to standard chemotherapy
- Ipilimumab (and tremilimumab) clearly benefit a subset of patients
- Targeted therapies showing increasing promise
  - VEGF targeted therapies of unproven value
  - Kinase inhibitors for mutated kinases appear to be a promising new direction