# “BRAF and MEK Inhibition in Melanoma”

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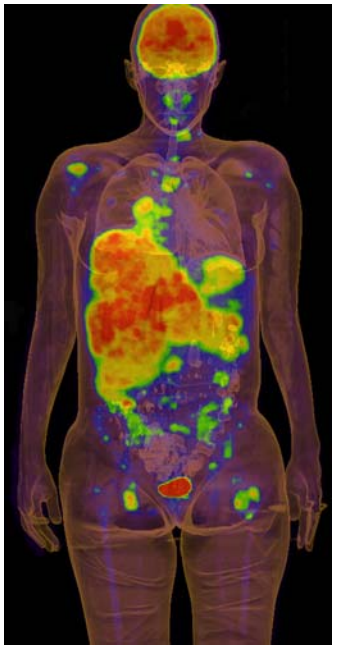

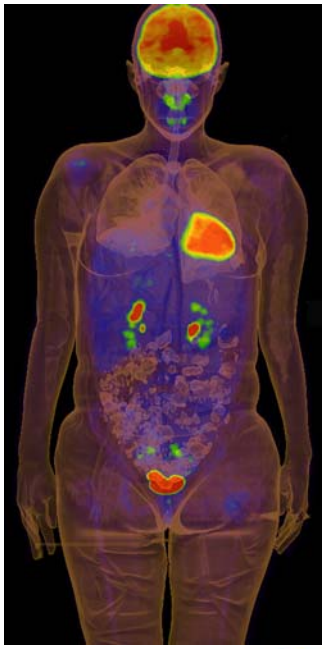

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# Disclosure Information

- **I have the following financial relationships to disclose**
  - **Research support from: Pfizer, Millennium & Novartis**

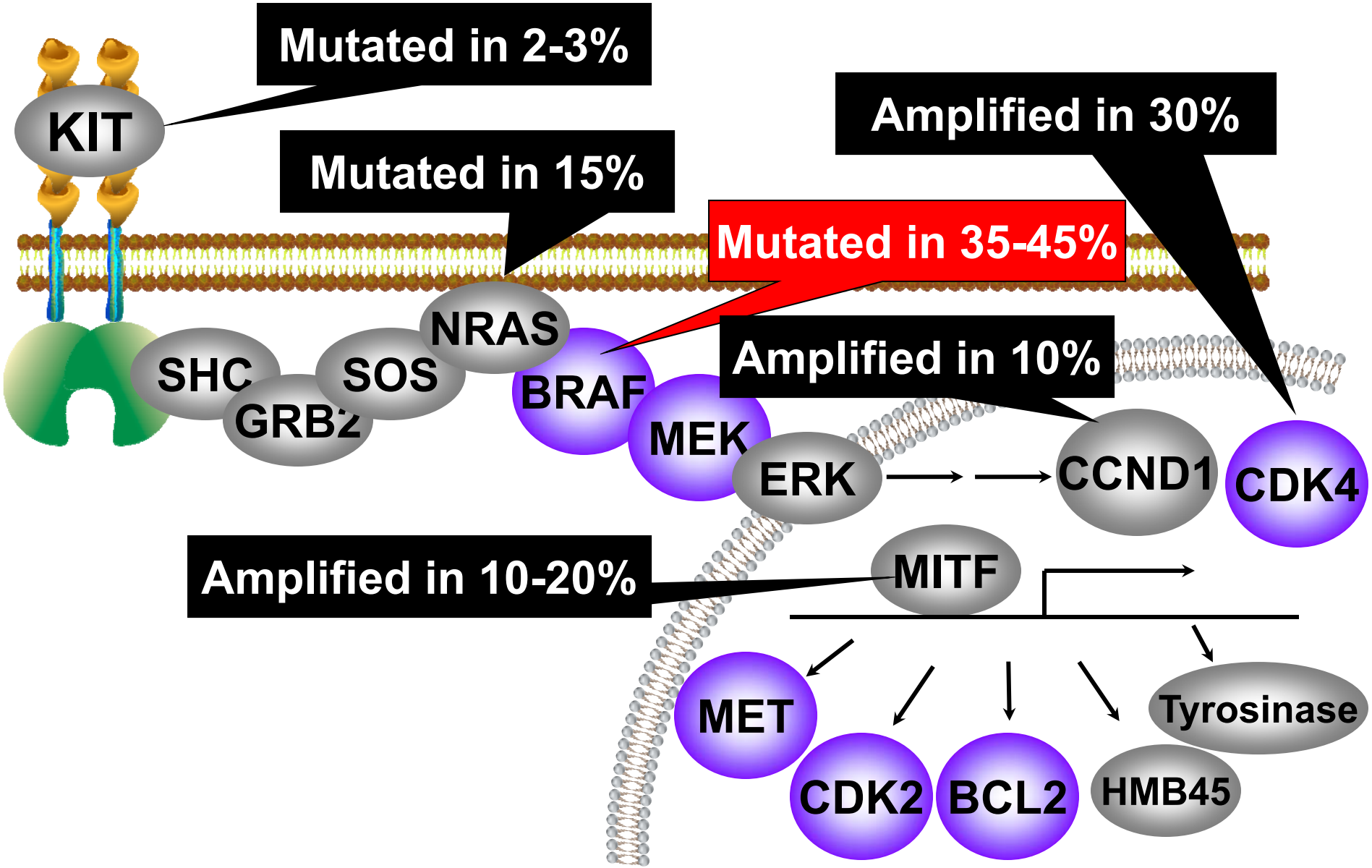
# Talk Overview

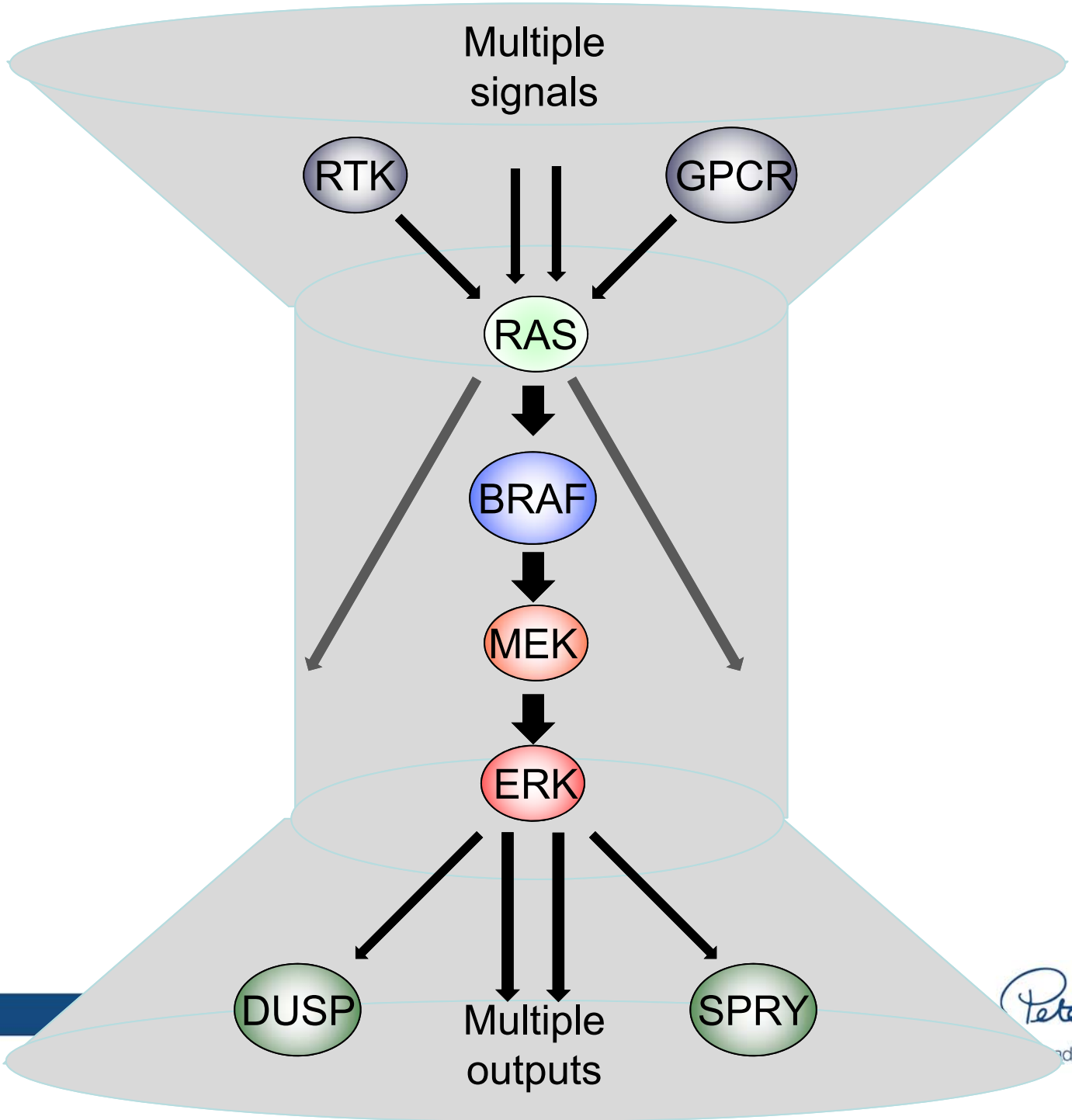
- Signaling by BRAF and MEK
- Clinical Efficacy of Inhibiting the BRAF/MEK pathway
- Toxicity of Inhibiting the BRAF/MEK pathway
- Resistance to BRAF inhibitors

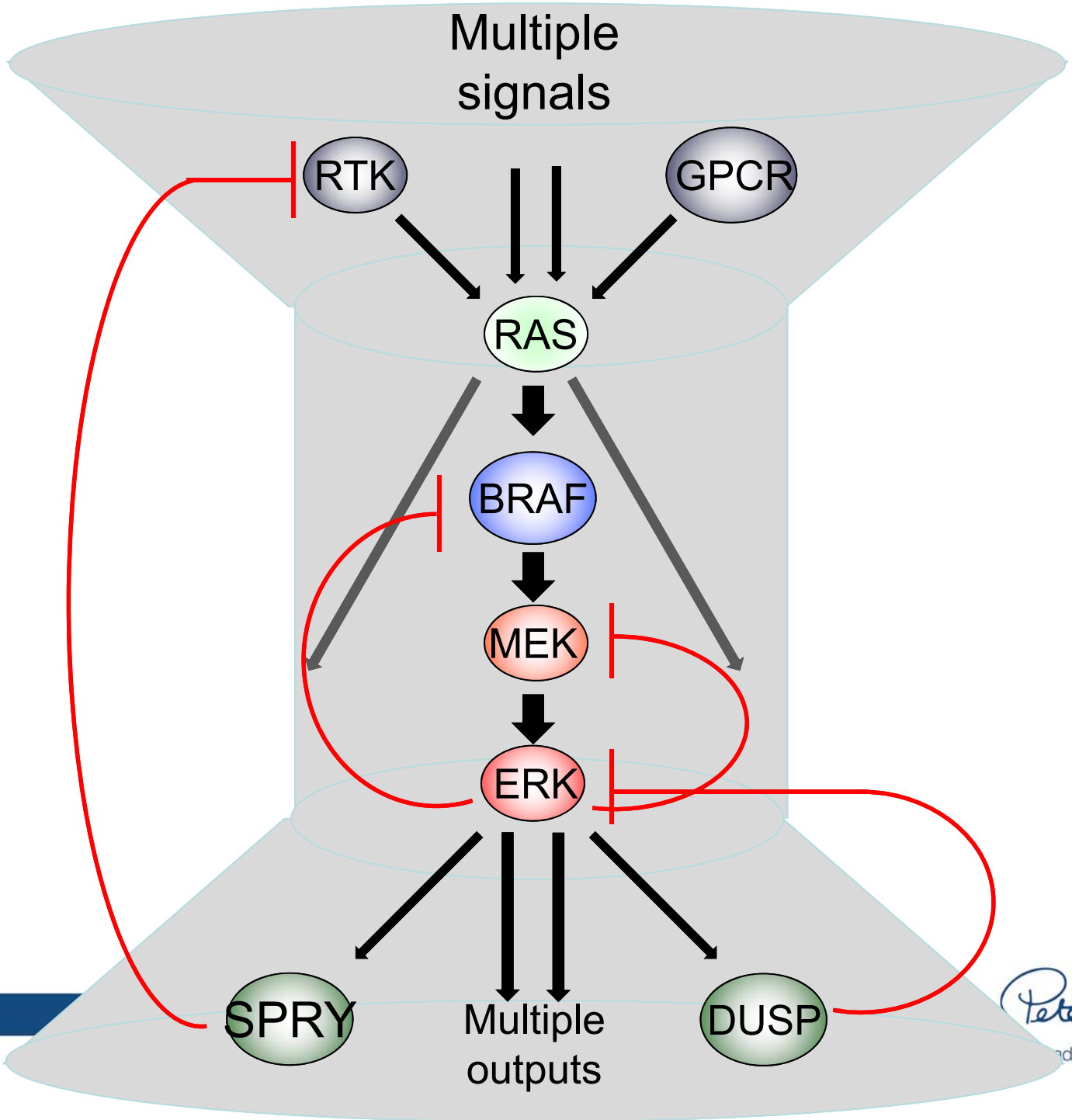
# Talk Overview

- **Signaling by BRAF and MEK**
- **Clinical Efficacy of Inhibiting the BRAF/MEK pathway**
- **Toxicity of Inhibiting the BRAF/MEK pathway**
- **Resistance to BRAF inhibitors**

# The KIT/RAS/RAF/ERK Pathway and Therapeutic Targets in Melanoma




Multiple
signals
RTK
GPCR
RAS
BRAF
MEK
ERK
DUSP
Multiple
outputs
SPRY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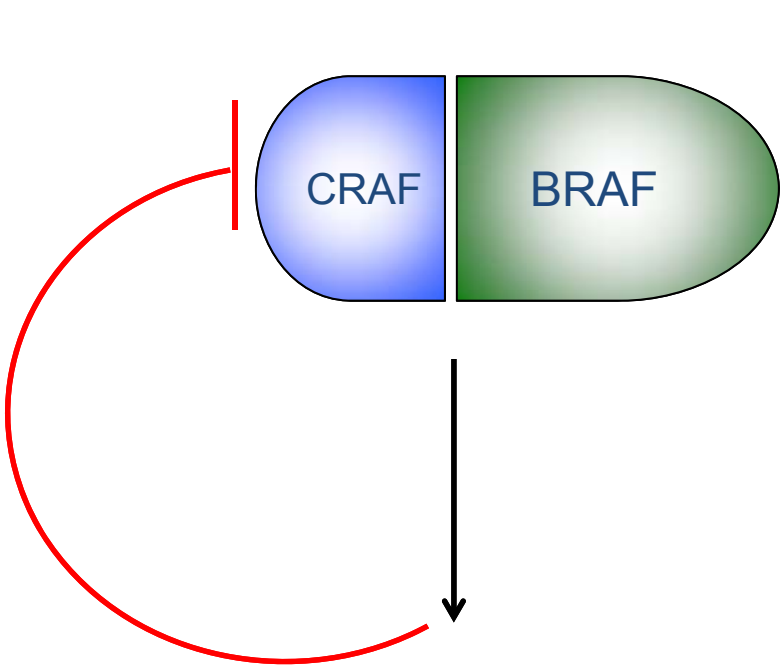
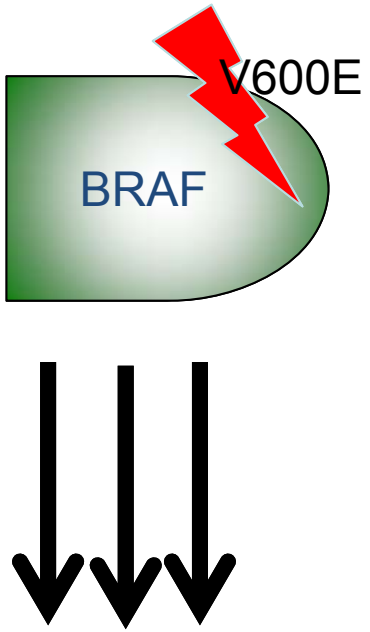



Proliferation
Survival




Proliferation
Survival

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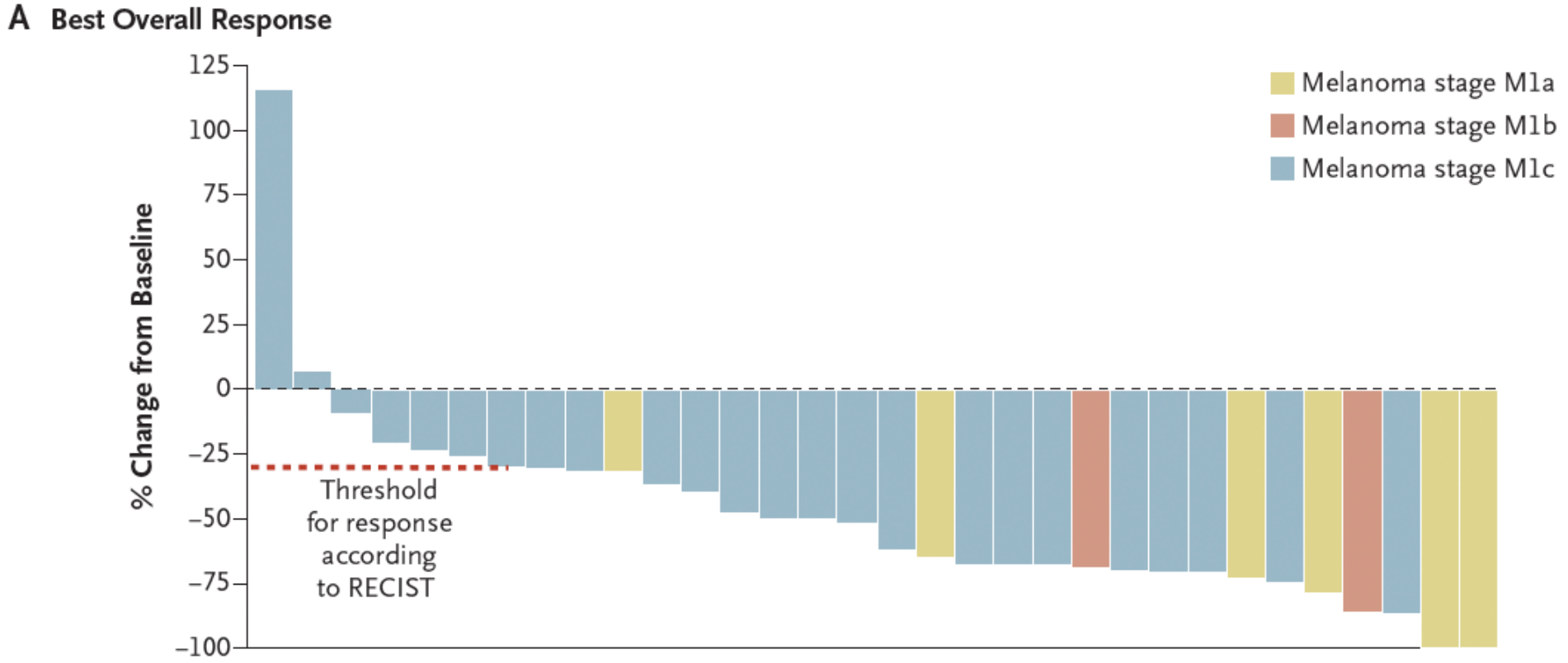
# CT Response to BRAF Inhibition- Phase 1 PLX06/02 Study of Vemurafenib




Flaherty et al, NEJM, 2010

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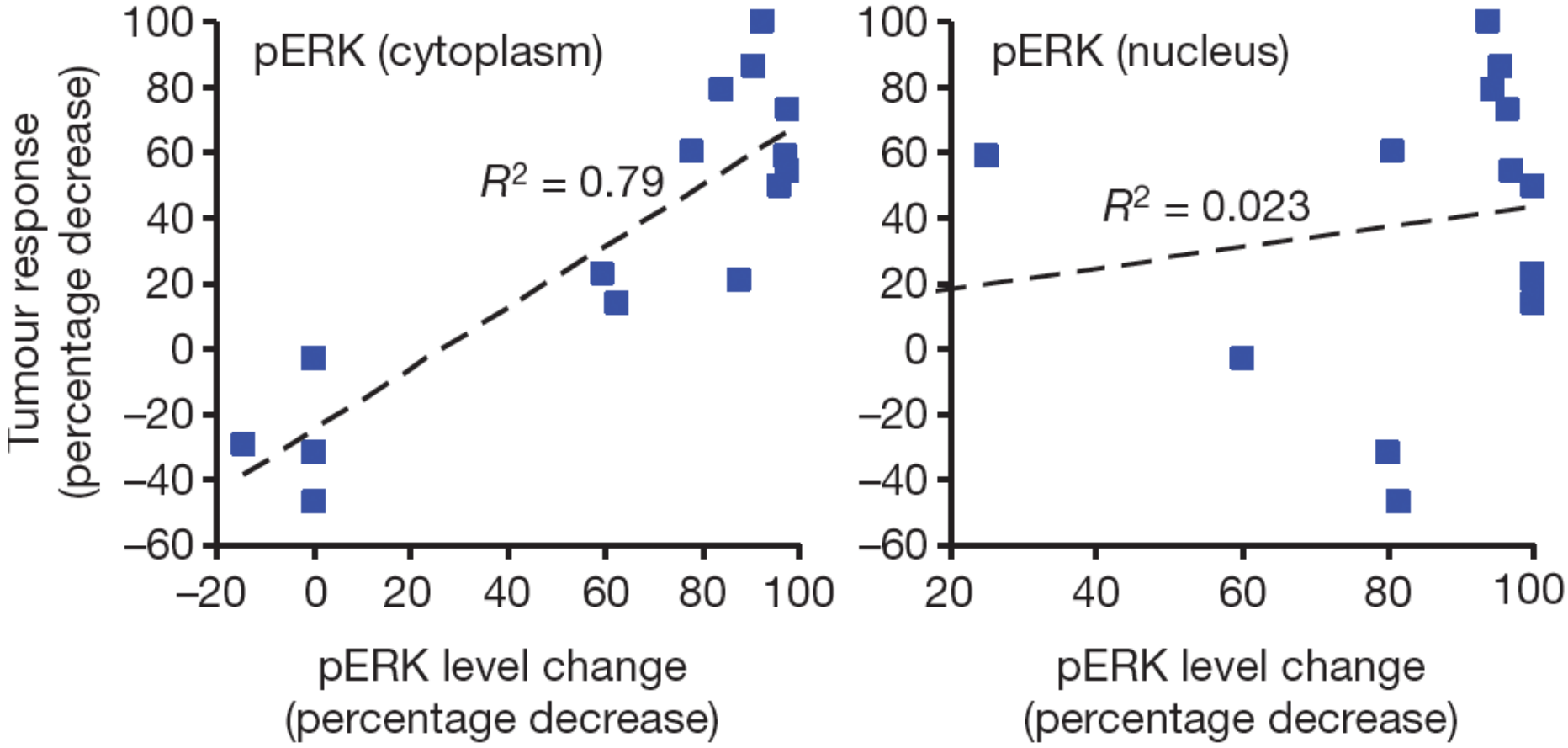
# Pharmacodynamic analyses suggest >90% inhibition of pERK is required for response in $BRAF^{V600E}$ melanoma patients




Bollag et al, Nature 2010

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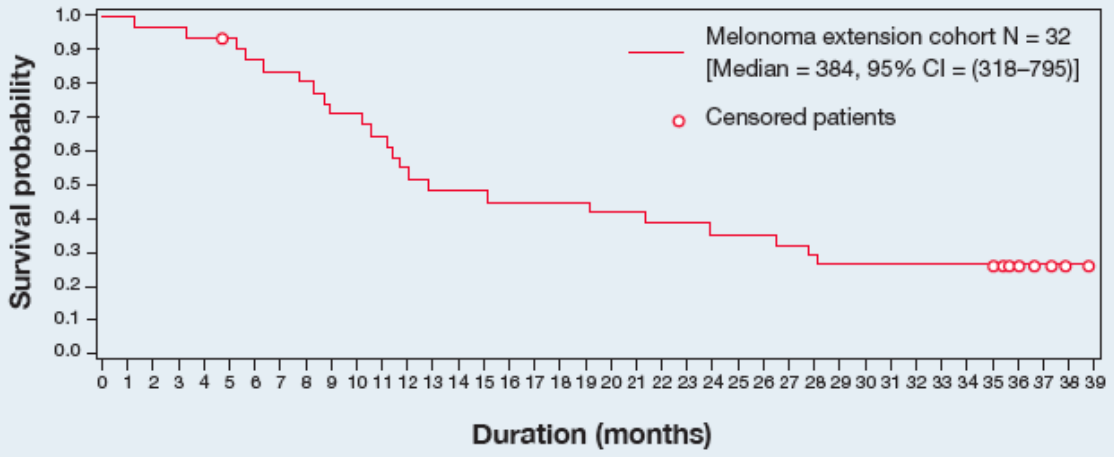
# Survival- Phase 1 PLX06/02 Study

**Figure 1.** Overall survival.




- Kaplan–Meier estimates of OS rate are presented in **Table 2.**

**Table 2.** Kaplan–Meier Analysis of Overall Survival

| Extension Cohort Time | Overall Survival Rate (%) | 95% CI |
|---|---|---|
| 6 months | 87.3 | 75.6–98.9 |
| 1 year | 55.0 | 37.4–72.5 |
| 2 years | 35.6 | 18.7–52.4 |
| 3 years | 25.9 | 10.4–41.3 |

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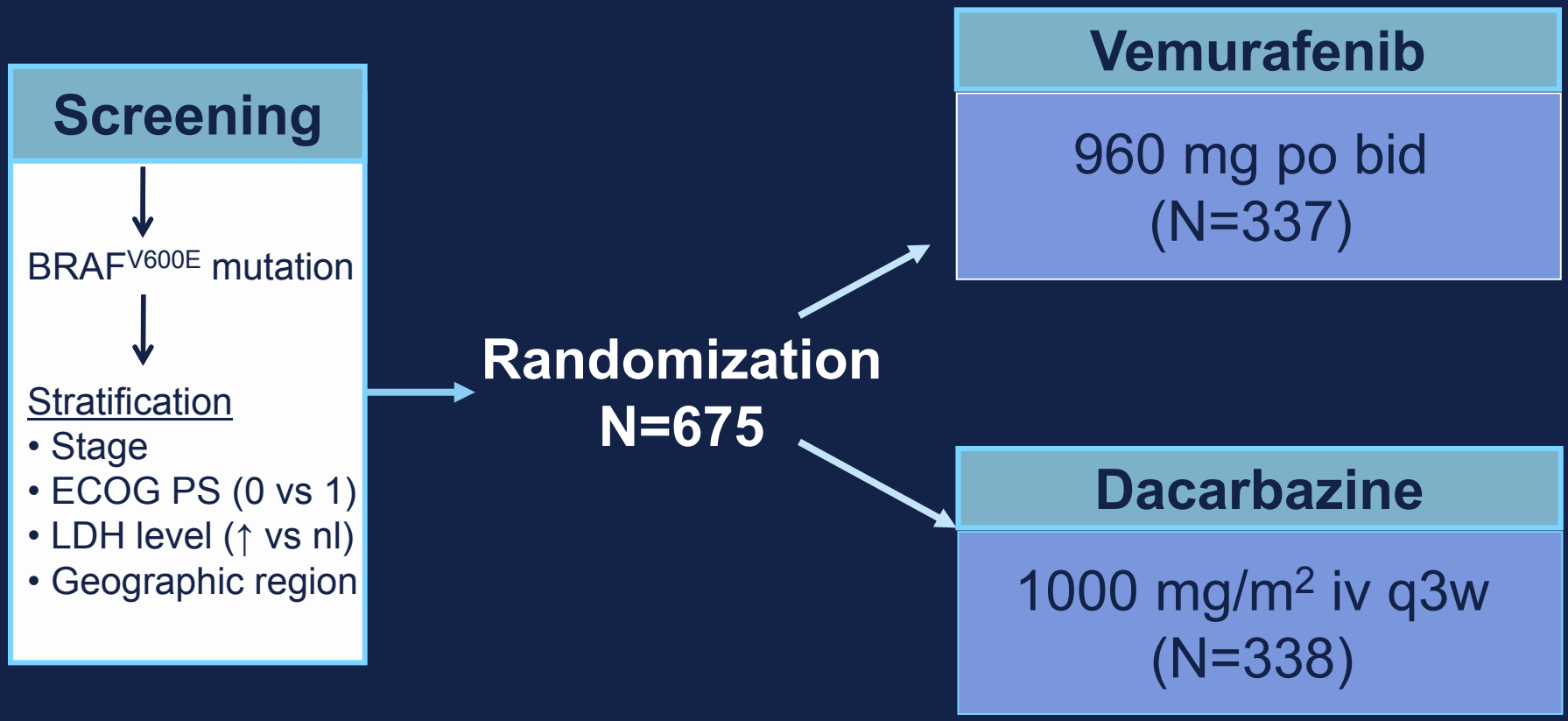
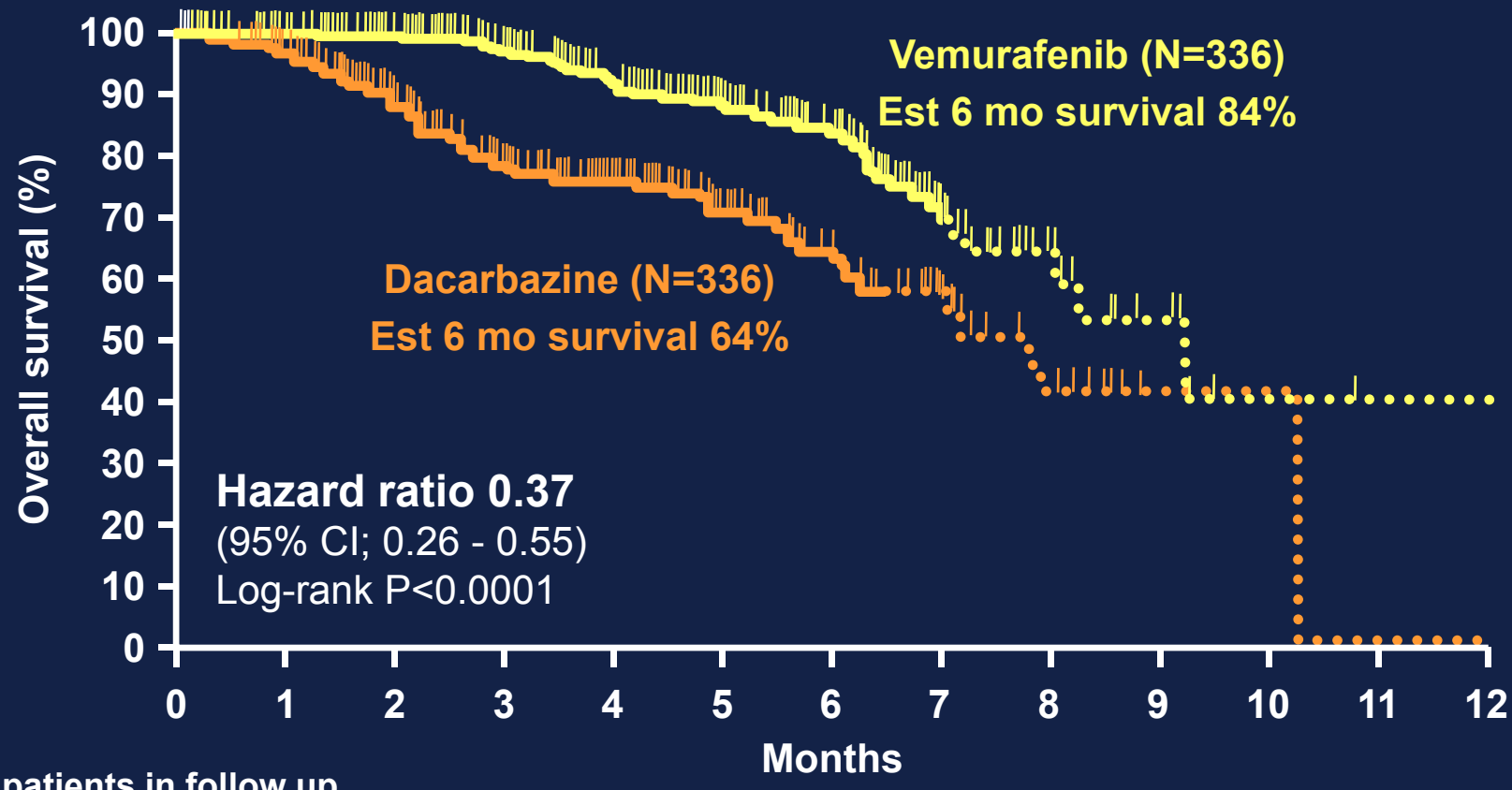
Kim et al, Society of Melanoma Research, 2012

# Phase III BRIM3 Study design




Chapman, NEJM, 2011

# Overall survival (Dec 30, 2010 cutoff)

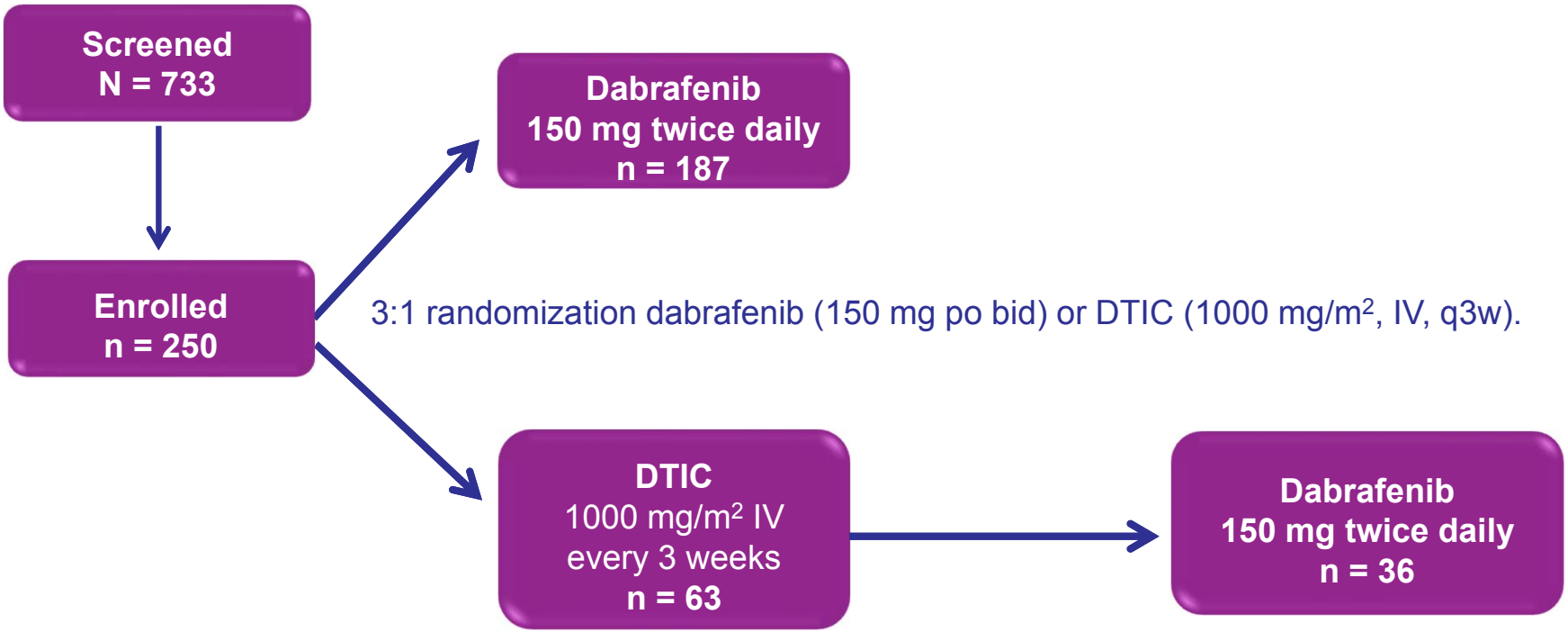



**No. of patients in follow up**

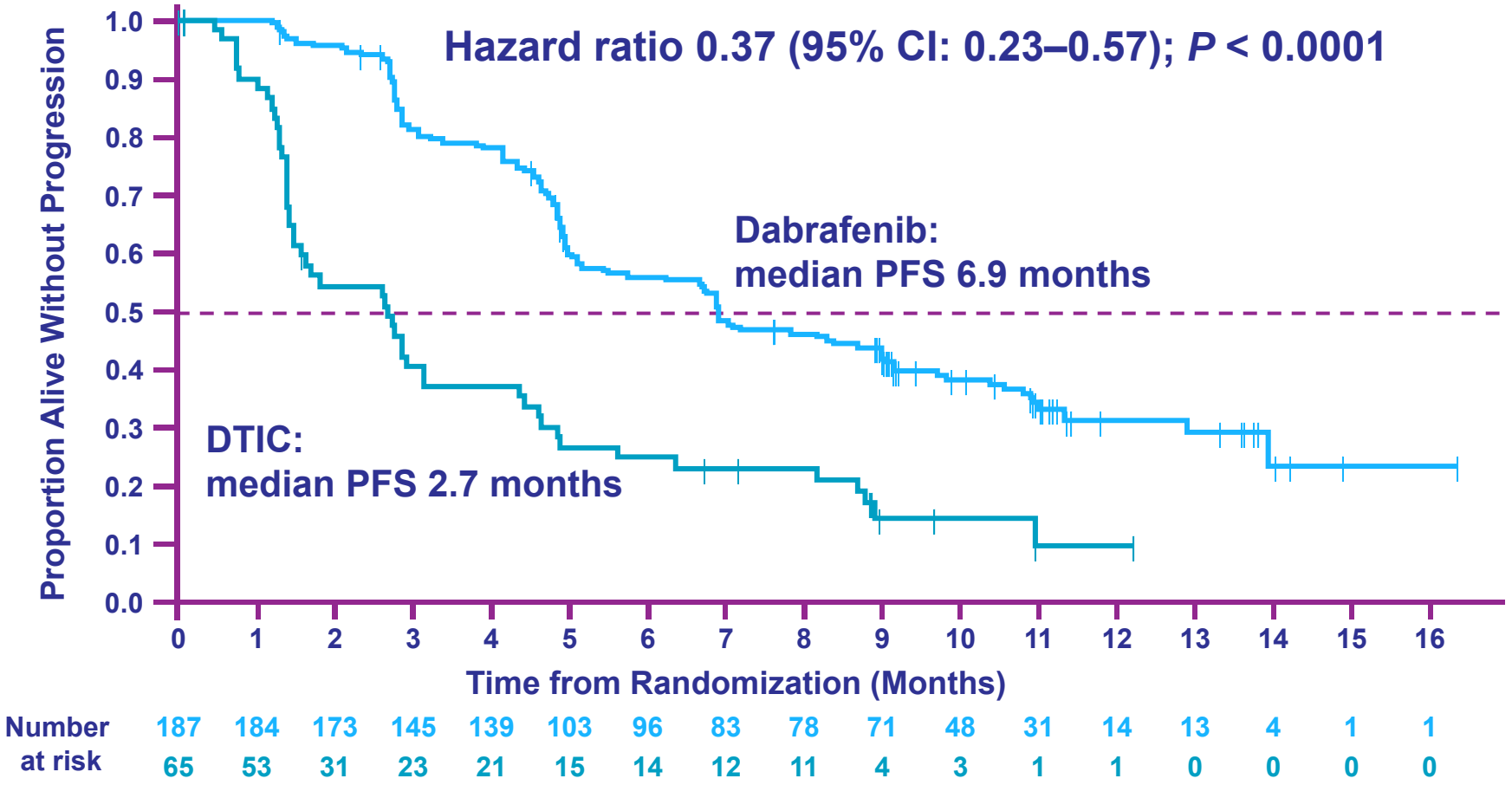
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dacarbazine | 336 | 283 | 192 | 137 | 98 | 64 | 39 | 20 | 9 | 1 | 1 |
| Vemurafenib | 336 | 320 | 266 | 210 | 162 | 111 | 80 | 35 | 14 | 6 | 1 |

Chapman, NEJM, 2011

# BREAK-3 study design

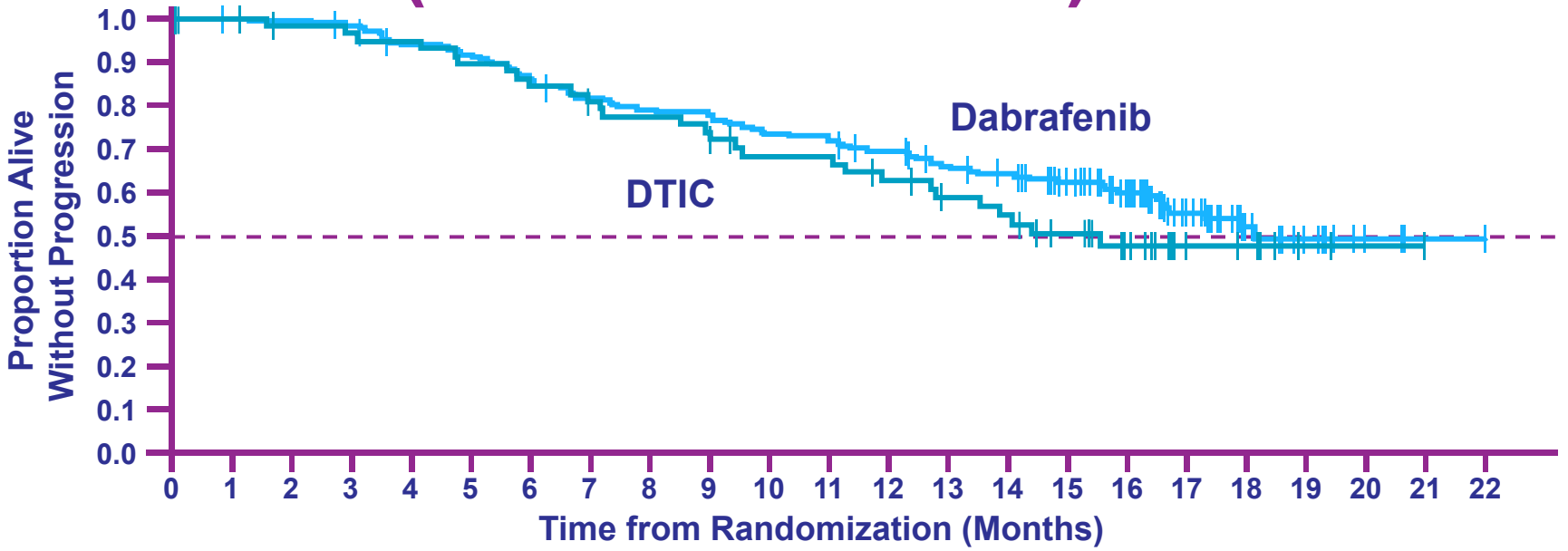


# Primary endpoint: PFS Investigator-Assessed (June 2012)




- On randomized study treatment at cut-off: dabrafenib 38%, DTIC 8%
- Median follow-up time: dabrafenib 10.5 months, and DTIC 9.9 months
- Median PFS following crossover was 4.4 months (n=35; 95% CI: 4.1, 6.3)

# Overall survival by randomized treatment (December 2012)

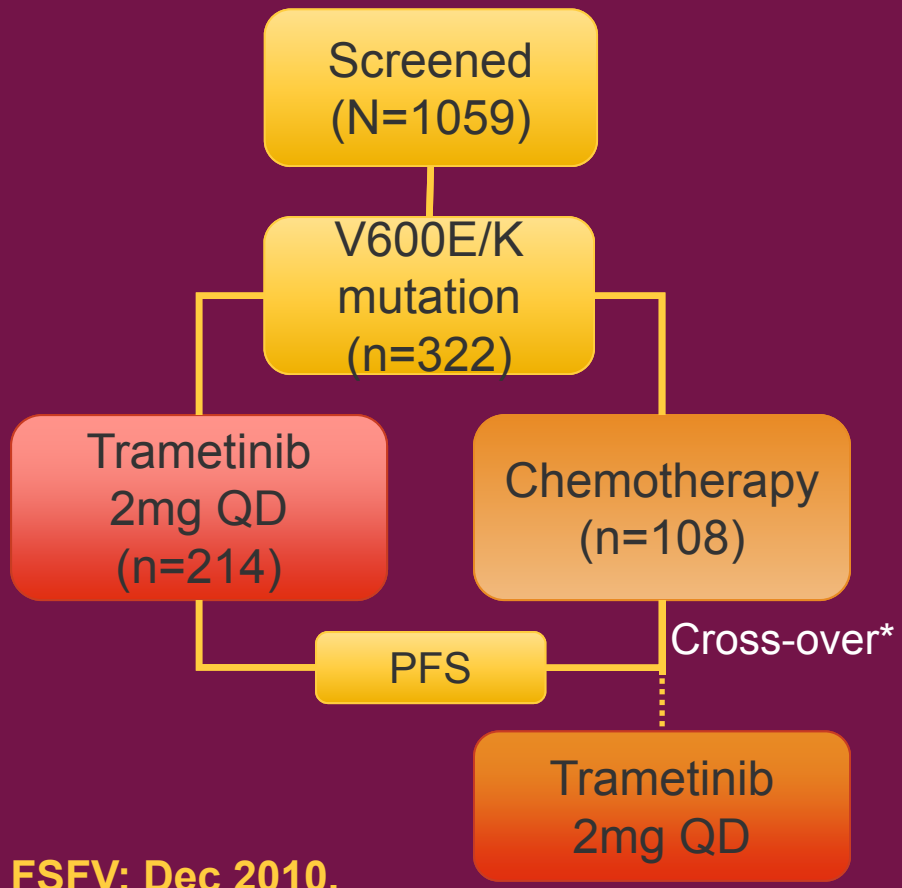



| Number at risk | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dabrafenib | 187 | 185 | 184 | 181 | 171 | 166 | 156 | 148 | 143 | 141 | 133 | 131 | 124 | 115 | 106 | 95 | 78 | 50 | 25 | 13 | 6 | 1 | 1 |
| DTIC | 63 | 60 | 57 | 56 | 55 | 52 | 49 | 46 | 44 | 42 | 37 | 37 | 33 | 29 | 27 | 22 | 16 | 8 | 6 | 2 | 1 | 1 | 0 |

| | Dabrafenib | DTIC |
|---|---|---|
| No. of death/No. of patients randomized (%) | 78/187 (42) | 28/63 (44) |
| Median (95% CI) | 18.2 (16.6, NR) | 15.6 (12.7, NR) |
| HR (95% CI) | 0.76 (0.48, 1.21) | |

- Percent alive at 15 months follow-up: dabrafenib 63%, DTIC 51%

# METRIC: Phase III Melanoma Study




**FSFV: Dec 2010,**
**LSFV: July 2011**

**BRAF mutation status**

Using allele-specific PCR at RGI

**Stratification factors**

LDH (> ULN vs. < ULN) and

Prior chemotherapy (Yes vs. No)

**Populations**

ITT (all randomized patients) n=322;

Primary efficacy (subset of ITT) n=273

**Primary endpoint**

Progression-Free Survival (PFS) in $BRAF^{V600E}$positive melanoma

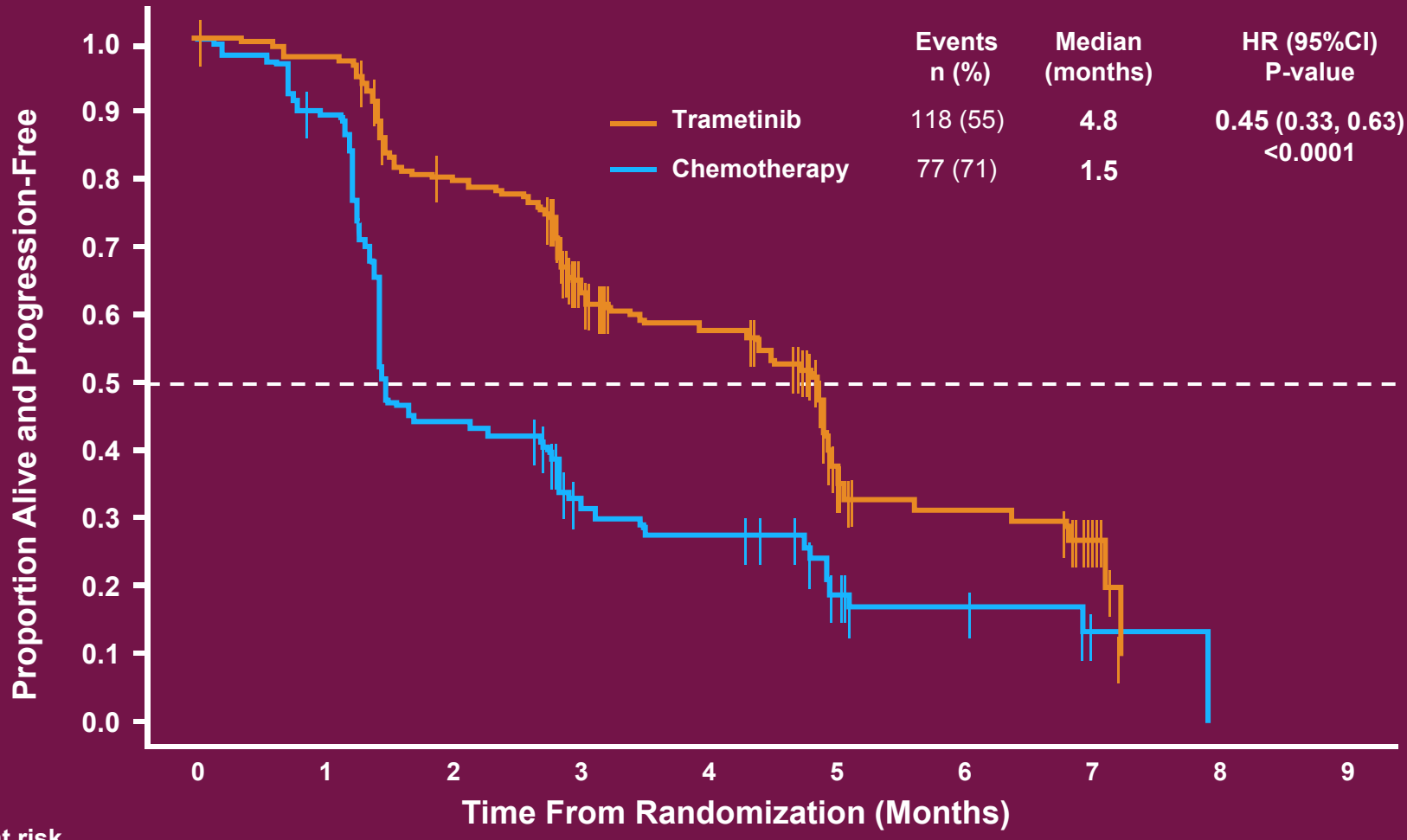
**Secondary endpoints**

PFS in ITT

Overall Survival, Response rate and Safety

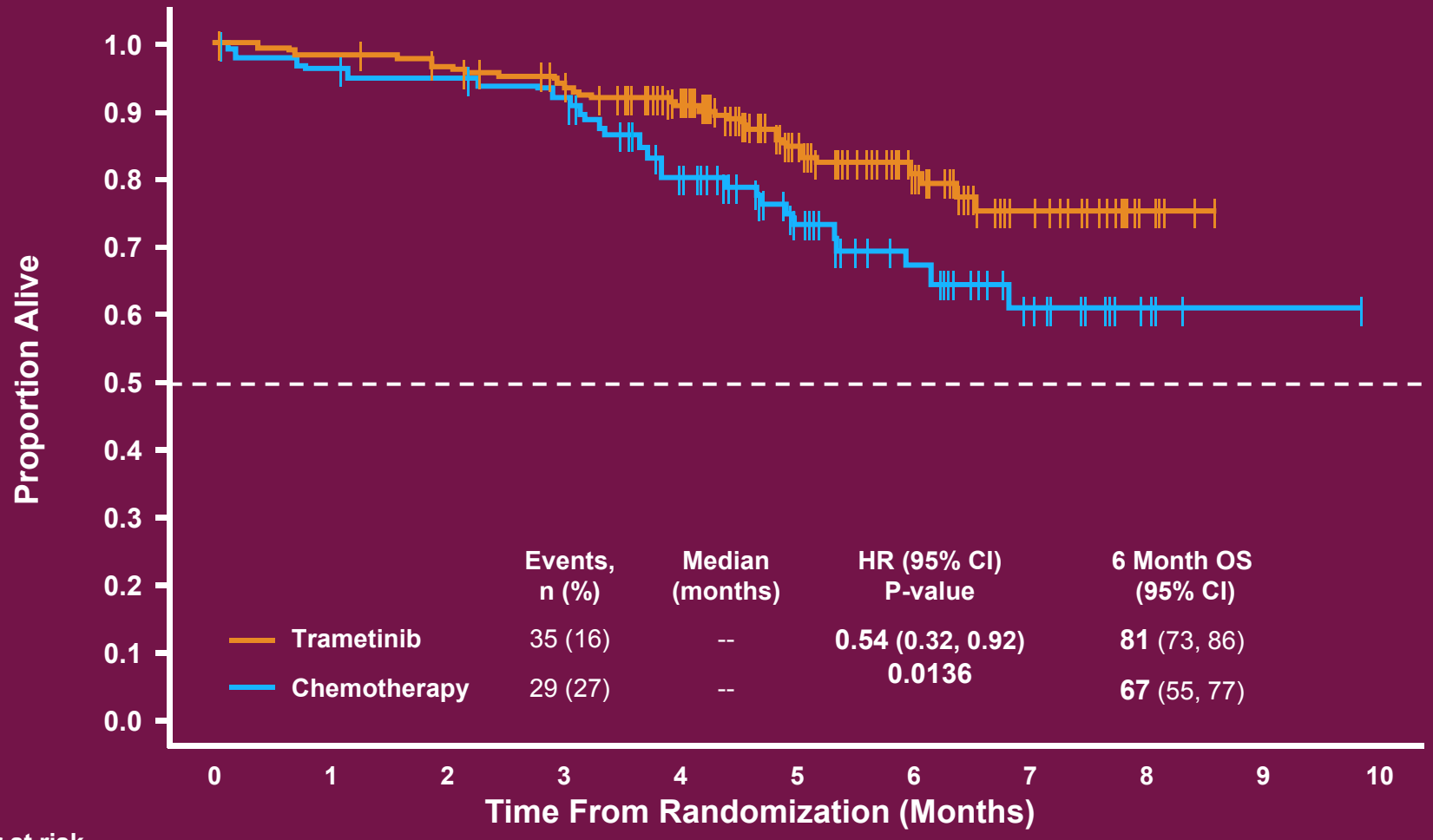
Chemotherapy = DTIC or paclitaxel
*Allowed after independent confirmation of progression

# METRIC Investigator-Assessed PFS – ITT




| Number at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Trametinib | 214 | 205 | 163 | 100 | 88 | 28 | 22 | 5 | 0 | 0 |
| Chemotherapy | 108 | 87 | 43 | 24 | 21 | 10 | 6 | 1 | 0 | 0 |

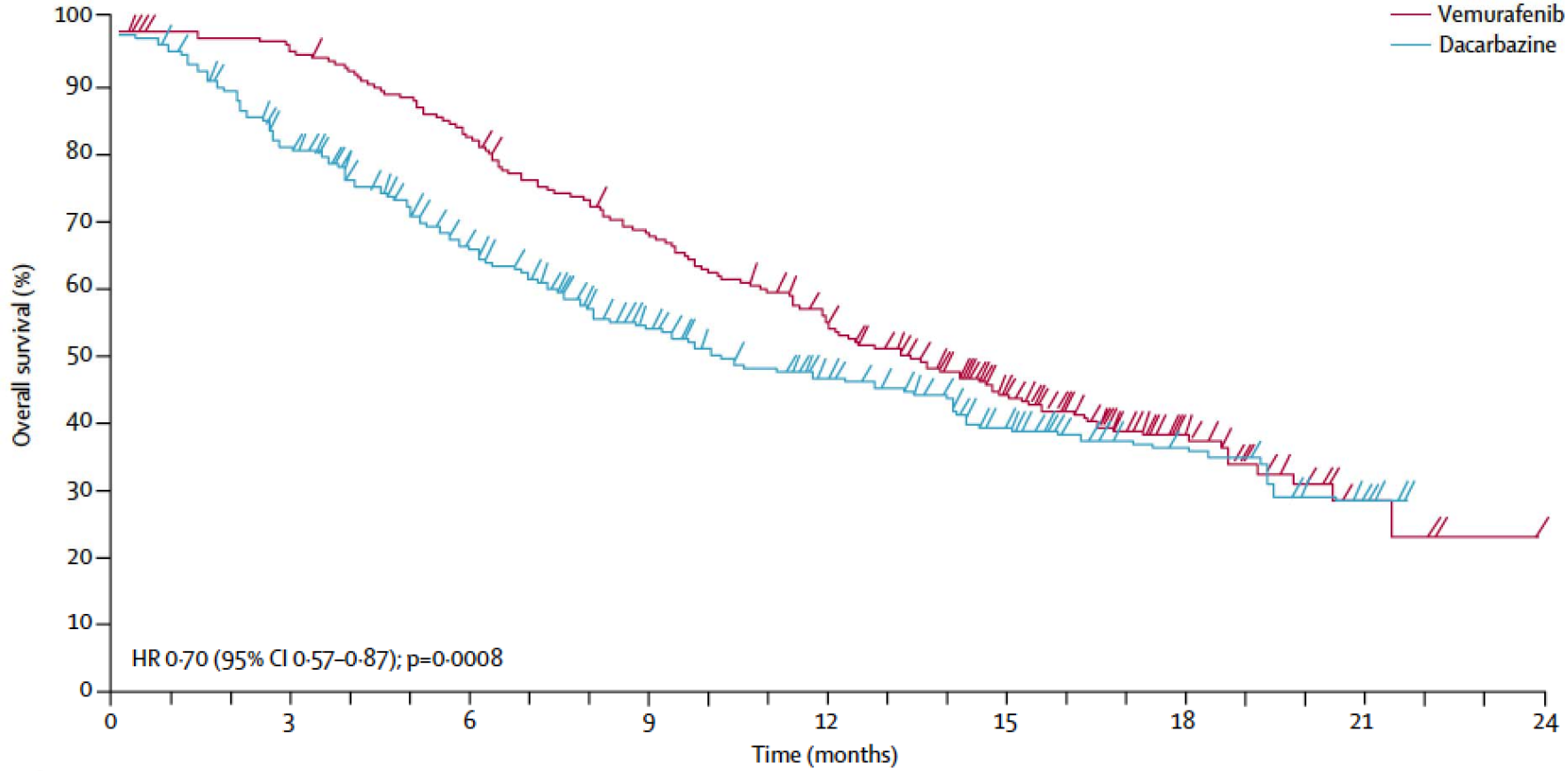
# METRIC Overall Survival – ITT




| Number at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Trametinib | 214 | 208 | 203 | 192 | 170 | 105 | 53 | 24 | 5 | 0 | 0 |
| Chemotherapy | 108 | 96 | 94 | 90 | 72 | 47 | 28 | 15 | 4 | 1 | 0 |

47% of the patients in the chemotherapy arm crossed over to trametinib

# Updated Overall Survival Data
# BRIM3 Studv




| Number at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Vemurafenib | 337 | 326 | 280 | 231 | 178 | 109 | 44 | 7 | 1 |
| Dacarbazine | 338 | 244 | 173 | 111 | 79 | 50 | 24 | 4 | 0 |

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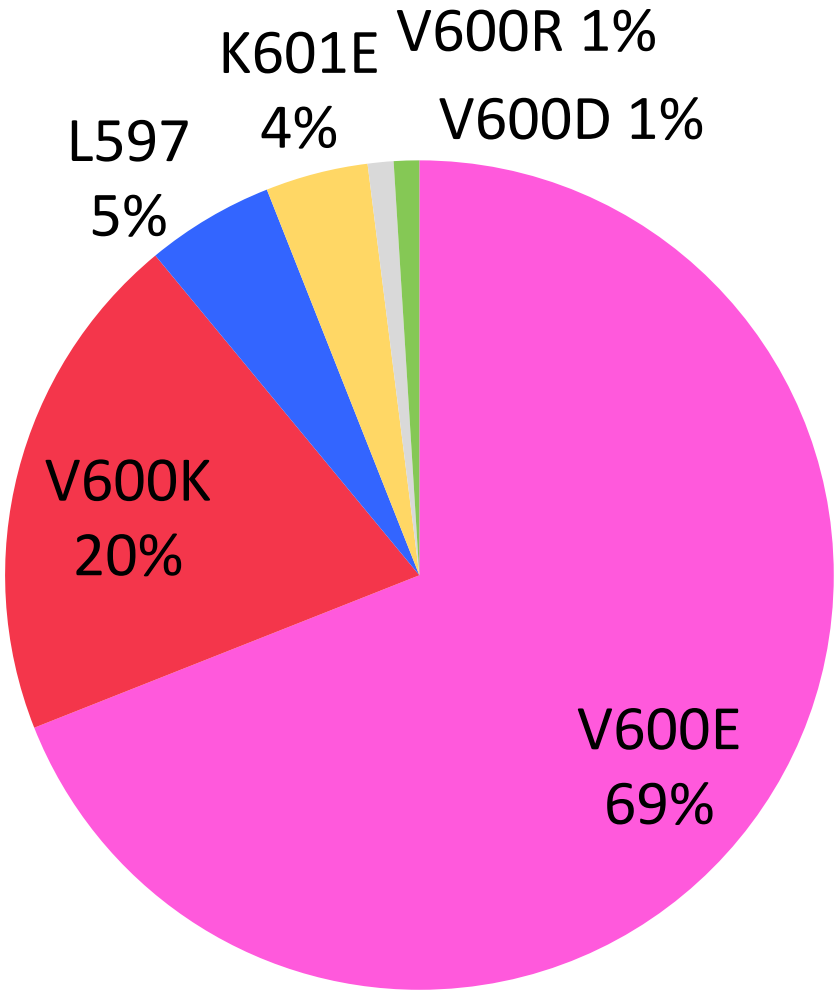
McArthur et al, Lancet Oncology, 2014

# Frequency of non-V600E BRAF mutations- Primary melanoma, Victoria, Australia n=234

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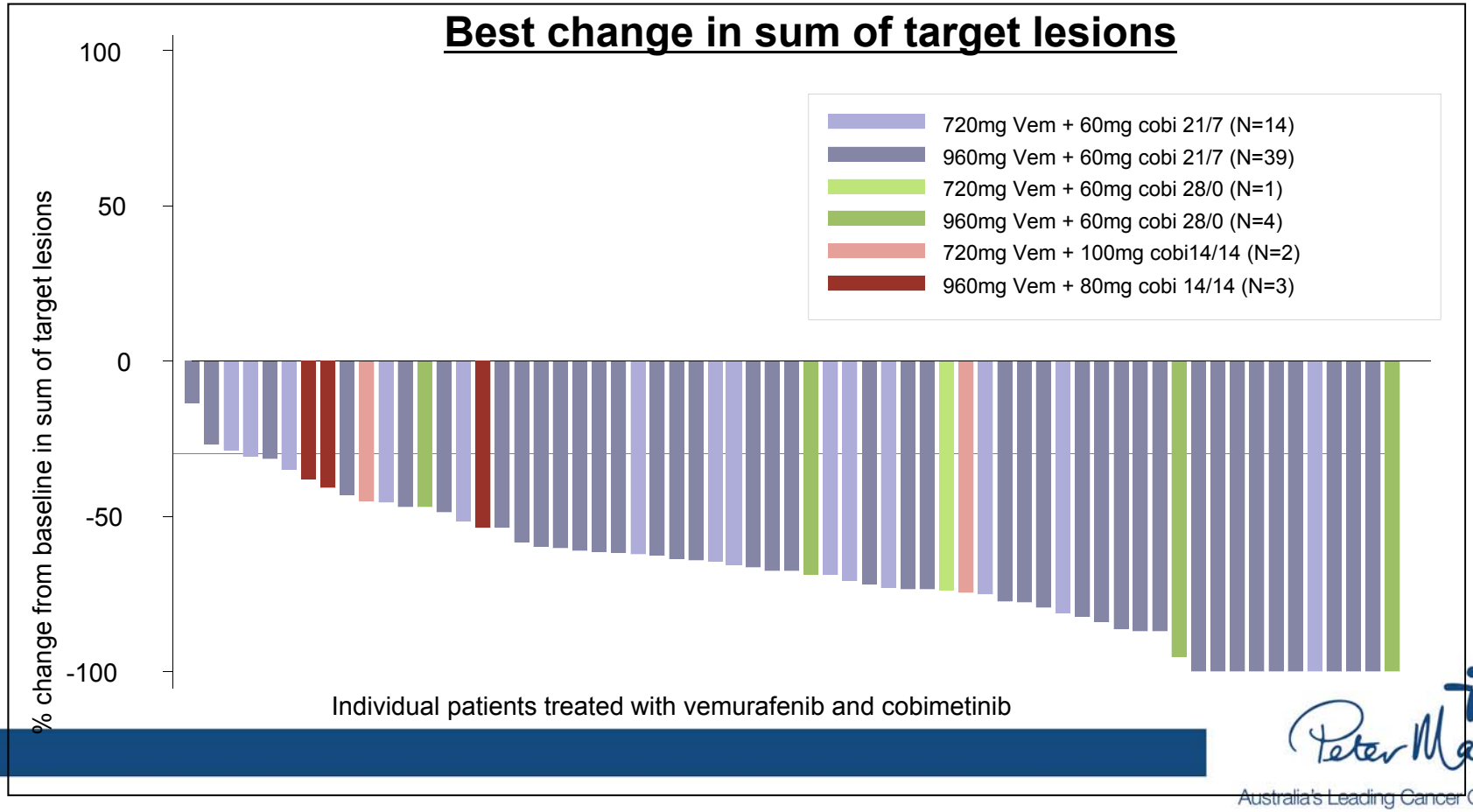
M. Voskoboynik, C.Hewitt A. Dobrovic, A. Rynska, S. Wong, V. Mar

# BRAF V600 Mutant melanoma- Precision Medicine

## Melanoma BRAF Mutation: BRAF inhibitor + MEK-inhibitor

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McArthur et al, ESMO 2013

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- Signaling by BRAF and MEK
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- Toxicity of Inhibiting the BRAF/MEK pathway
- Resistance to BRAF inhibitors

# Selected adverse events (% of patients) Vemurafenib

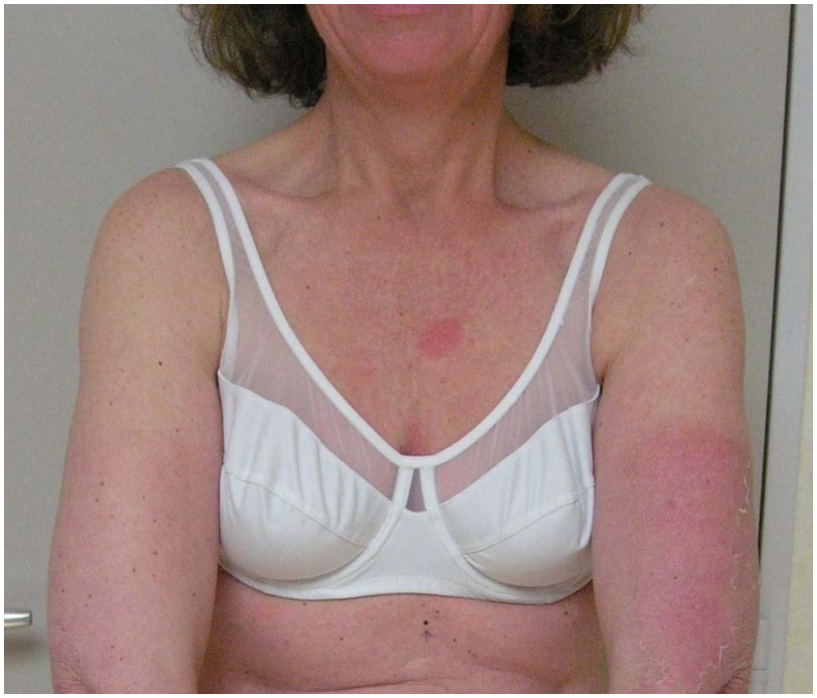
Median length of time on vemurafenib treatment: 4.2 months

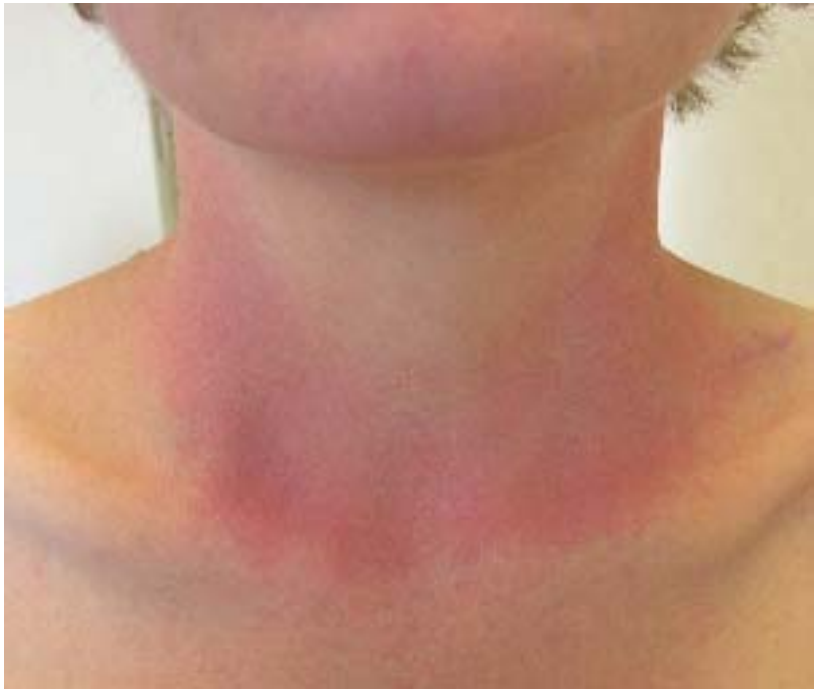
| | Vemurafenib, n=336 | | | Dacarbazine, n=287 | | |
|---|---|---|---|---|---|---|
| Adverse events | All | Grade 3 | Grade≥ 4 | All | Grade 3 | Grade ≥4 |
| Arthralgia | 53 | 4 | - | 3 | <1 | - |
| Rash | 37 | 8 | - | 2 | - | - |
| Fatigue | 38 | 2 | - | 33 | 2 | <1 |
| Photosensitivity | 33 | 3 | - | 4 | - | - |
| ↑LFTs | 22 | 8 | <1 | 5* | 1* | -* |
| Cutaneous SCC | 17 | 16 | - | <1 | <1 | - |
| Keratoacanthoma | 9 | 9 | - | - | - | - |
| Skin papilloma | 21 | <1 | - | - | - | - |
| Nausea | 35 | 2 | - | 43 | 2 | - |
| Neutropenia | <1 | - | <1 | 12 | 6 | 3 |
| Uveitis** | 3 | <1 | - | - | - | - |

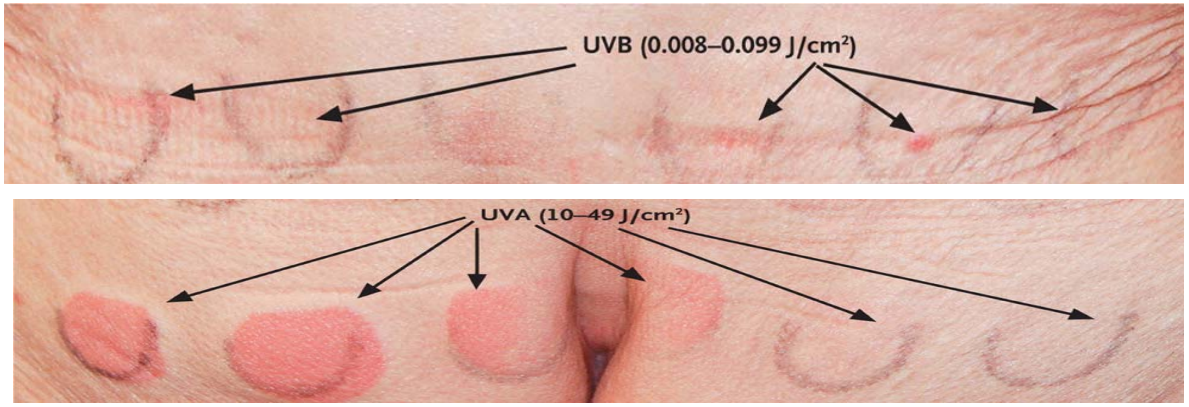
Discontinuations due to AE: 7% vemurafenib; 4% dacarbazine

*Data from OS IA Dec 30, 2010, not updated for March 1, 2011 cutoff. **Data obtained from a manual count rather than a statistical output.

# Photosensitivity








Dummer et al. *N Engl J Med*. 2012;366:480-481.

# Treatment-Related AEs in ≥ 10% of Dabrafenib Patients (June 2012)

| | | Dabrafenib n (%) | | | DTIC n (%) | | |
|---|---|---|---|---|---|---|---|
| | AE | All | Grade 3 | Grade 4 | All | Grade 3 | Grade 4 |
| Skin | Hyperkeratosis | 67 (36) | 2 (1) | 1 (<1) | 1 (2) | 0 | 0 |
| | Alopecia | 50 (27) | 1 (<1) | 0 | 2 (3) | 0 | 0 |
| | Skin papilloma | 42 (22) | 0 | 0 | 0 | 0 | 0 |
| | Palmar-plantar hyperkeratosis | 36 (19) | 4 (2) | 0 | 1 (2) | 0 | 0 |
| | Rash | 56 (30) | 0 | 0 | 0 | 0 | 0 |
| | SCC/KA | 18 (10) | 14 (7) | 0 | 0 | 0 | 0 |
| Gastrointestinal | Nausea | 26 (14) | 0 | 0 | 23 (39) | 0 | 0 |
| Other | Arthralgia | 36 (19) | 2 (1) | 0 | 0 | 0 | 0 |
| | Fatigue | 33 (18) | 2 (1) | 0 | 13 (22) | 0 | 0 |
| | Headache | 34 (18) | 0 | 0 | 2 (3) | 0 | 0 |
| | Pyrexia | 30 (16) | 5 (3) | 0 | 0 | 0 | 0 |
| | Asthenia | 27 (14) | 0 | 0 | 7 (12) | 0 | 0 |

Photosensitivity: dabrafenib 4 (2%), DTIC 2 (4%)
KA, keratoacanthoma; SCC, sqamous cell carcinoma

# Trametinib – Adverse Events (≥15% of patients)

| Preferred Term (≥15% of subjects) | Trametinib n=211 | Chemotherapy n=99 |
|---|---|---|
| **Rash** | **121 (57%)** | **10 (10%)** |
| Diarrhoea | 91 (43%) | 16 (16%) |
| Oedema peripheral | 54 (26%) | 3 (3%) |
| Fatigue | 54 (26%) | 27 (27%) |
| Dermatitis acneiform | 40 (19%) | 1 (1%) |
| Nausea | 38 (18%) | 37 (37%) |
| Alopecia | 36 (17%) | 19 (19%) |
| **Hypertension** | **32 (15%)** | **7 (7%)** |
| Constipation | 30 (14%) | 23 (23%) |
| Vomiting | 27 (13%) | 19 (19%) |

**MEKi known events with Trametinib:**

- Decreased Ejection Fraction / Ventricular dysfunction = 14 (7%)
- Chorioretinopathy = 1 (<1%)

**No reported case of cutaneous SCC or hyperproliferative skin lesions**

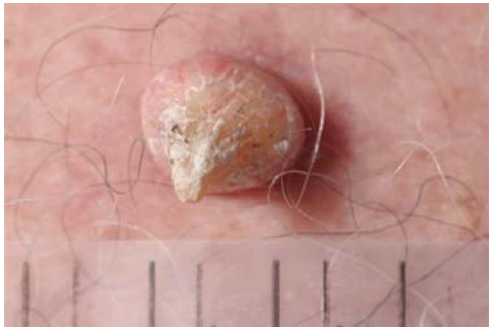
# Trametinib – Grade 3/4 AEs (> 1% of patients)

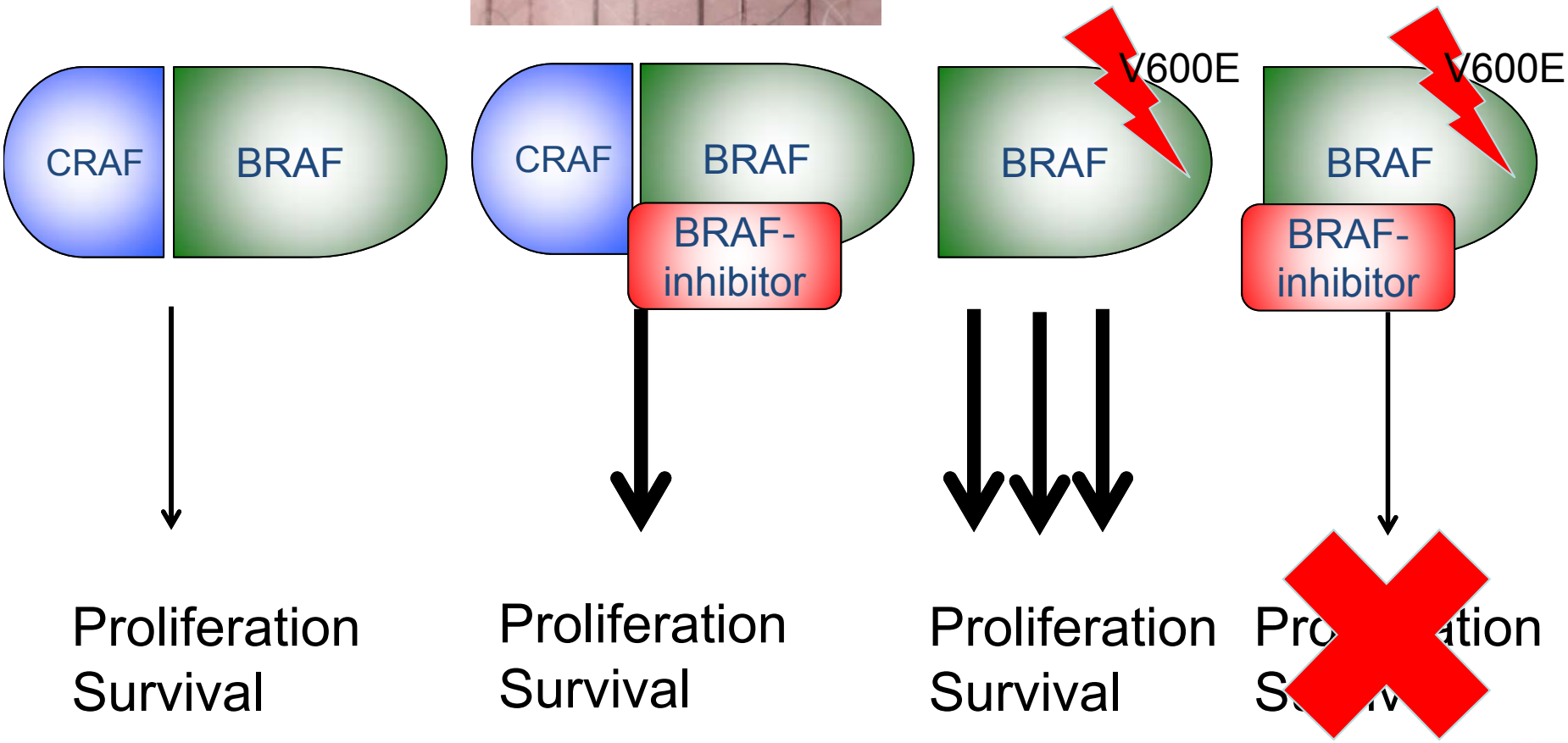
| | Trametinib | | Chemotherapy | |
|---|---|---|---|---|
| Preferred Term | Grade 3 | Grade 4 | Grade 3 | Grade 4 |
| **Hypertension** | **26 (12%)** | **0** | **3 (3%)** | **0** |
| **Rash** | **15 (7%)** | **1 (<1%)** | **0** | **0** |
| Fatigue | 8 (4%) | 0 | 3 (3%) | 0 |
| Pruritus | 4 (2%) | 0 | 0 | 0 |
| Alanine aminotransferases increased | 4 (2%) | 0 | 0 | 0 |
| Anaemia | 4 (2%) | 0 | 0 | 0 |
| Vomiting | 2 (<1%) | 0 | 2 (2%) | 0 |
| Pain in extremity | 1 (<1%) | 0 | 2 (2%) | 0 |
| Neutrophil count decreased | 0 | 0 | 4 (4%) | 0 |
| Neutropenia | 0 | 0 | 1 (1%) | 2 (2%) |
| Diarrhoea | 0 | 0 | 1 (1%) | 1 (1%) |
| Peripheral sensory neuropathy | 0 | 0 | 2 (2%) | 0 |
| Cholecystitis | 0 | 0 | 2 (2%) | 0 |

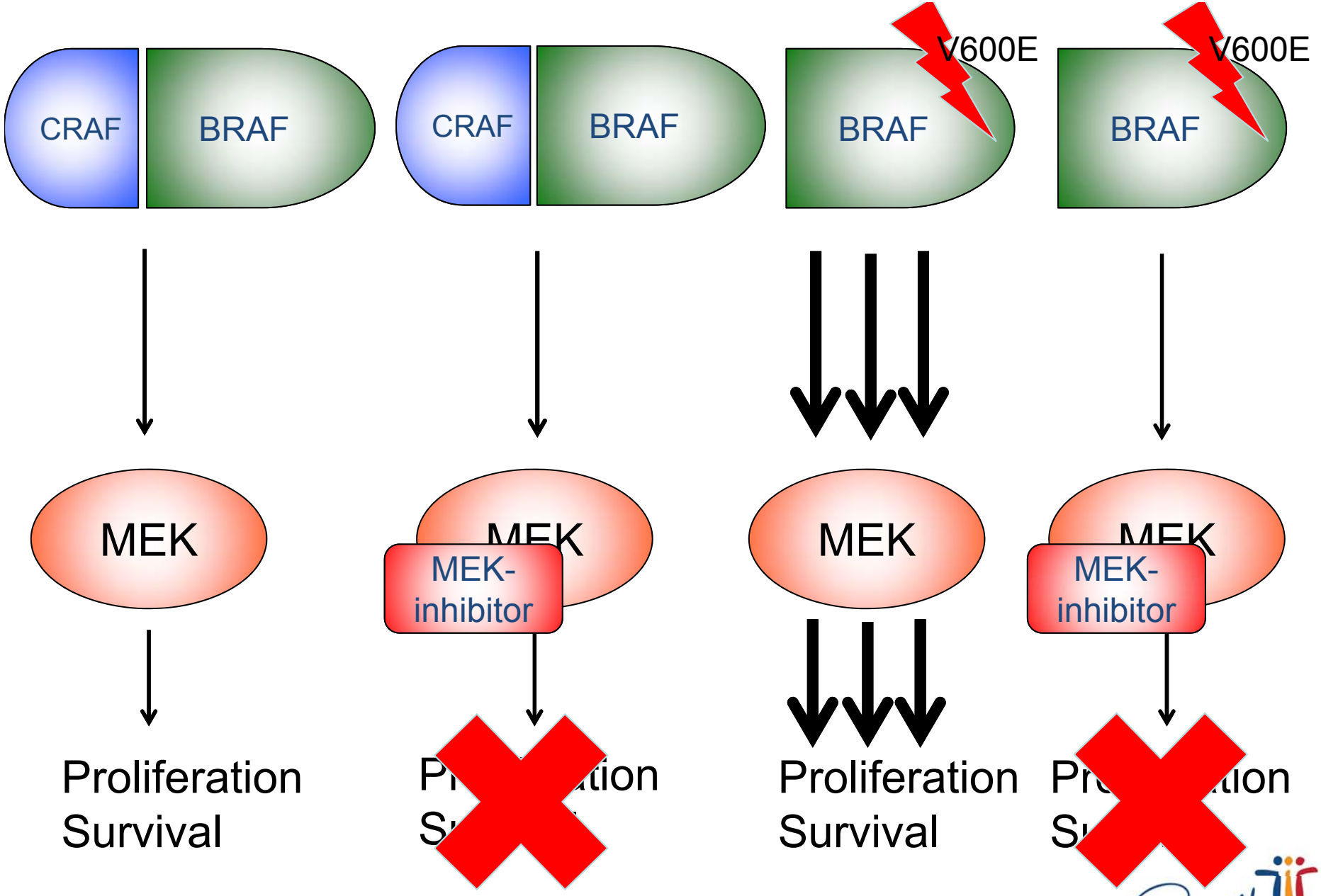
# Dabrafenib + Trametinib: Key Treatment-Related Skin Toxicities

| | All Part B Patients (N = 135) | |
|---|---|---|
| | Grade ≥ 3, n (%) | Any grade event, n (%) |
| Rash/Skin toxicities[1] | 3 (2%) | 61(45%) |
| Skin papilloma | 0 (0%) | 3 (2%) |
| Squamous cell carcinoma | 4 (3%) | 4 (3%) |
| Actinic keratosis | 0 (0%) | 7 (5%) |
| Hyperkeratosis | 0 (0%) | 5 (4%) |

[1]Skin toxicities include multiple terms




CRAF
BRAF
CRAF
BRAF
BRAF-
inhibitor
BRAF
V600E
BRAF
V600E
BRAF-
inhibitor
Proliferation
Survival
Proliferation
Survival
Proliferation
Survival

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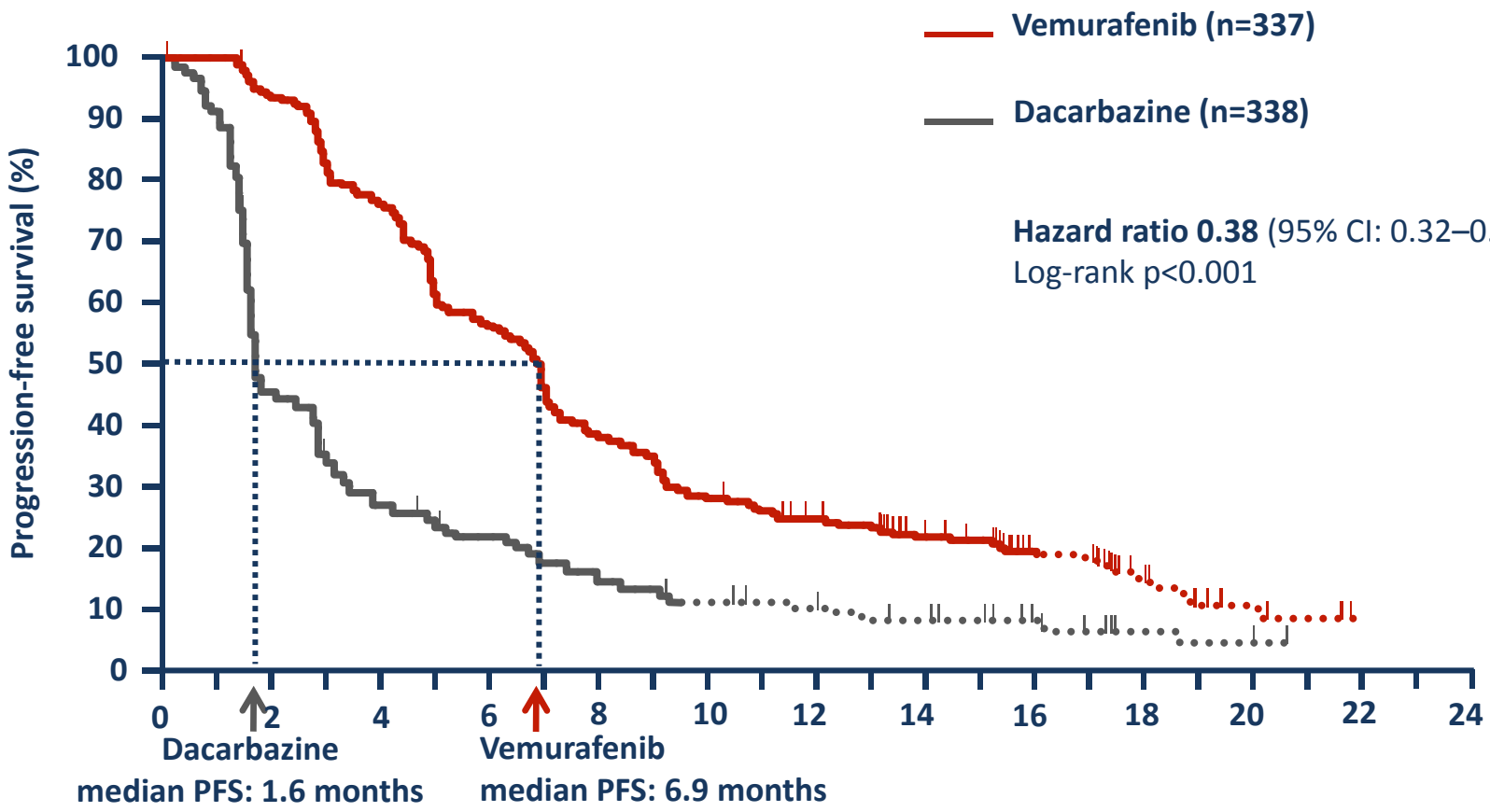
# Progression-free Survival BRIM3

## (Censored at Crossover; February 2012 Survival Update)



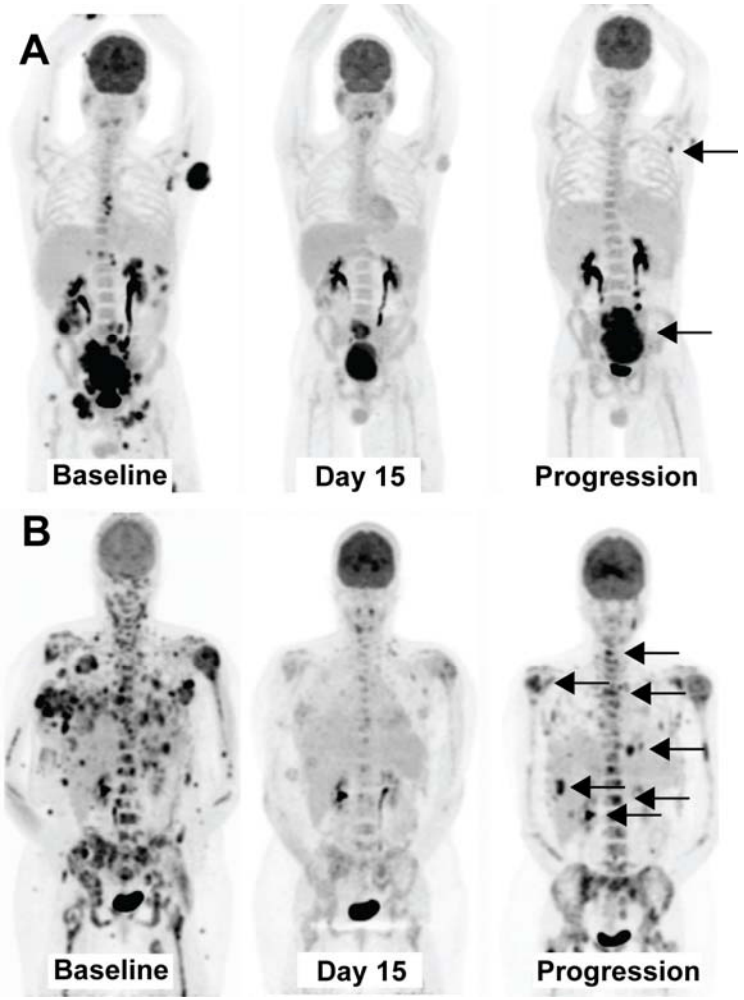

**No. of patients at risk**

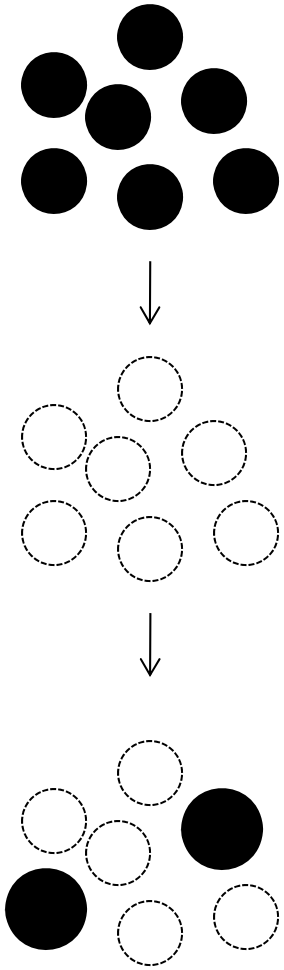
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Dacarbazine | 338 | 100 | 63 | 37 | 22 | 14 | 3 | 0 | 0 |
| Zelboraf | 337 | 269 | 186 | 113 | 77 | 49 | 16 | 3 | 0 |

CI = confidence interval; PFS = progression-free survival.

Figure from Chapman PB, *et al.* Presented at ASCO 2012. Oral Presentation 8502.

# Vemurafenib: Response is Homogeneous Progression is not



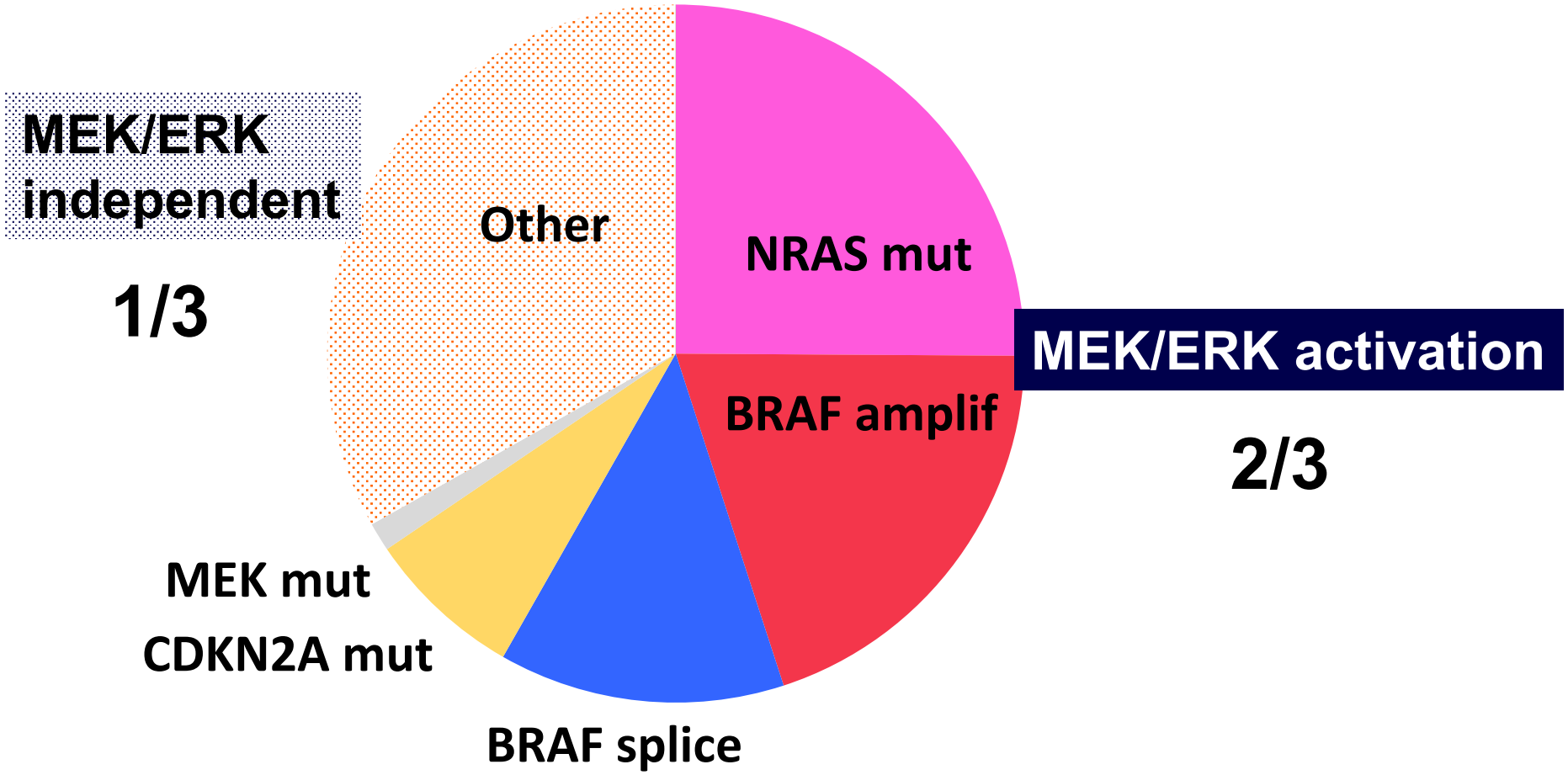



Baseline

Response

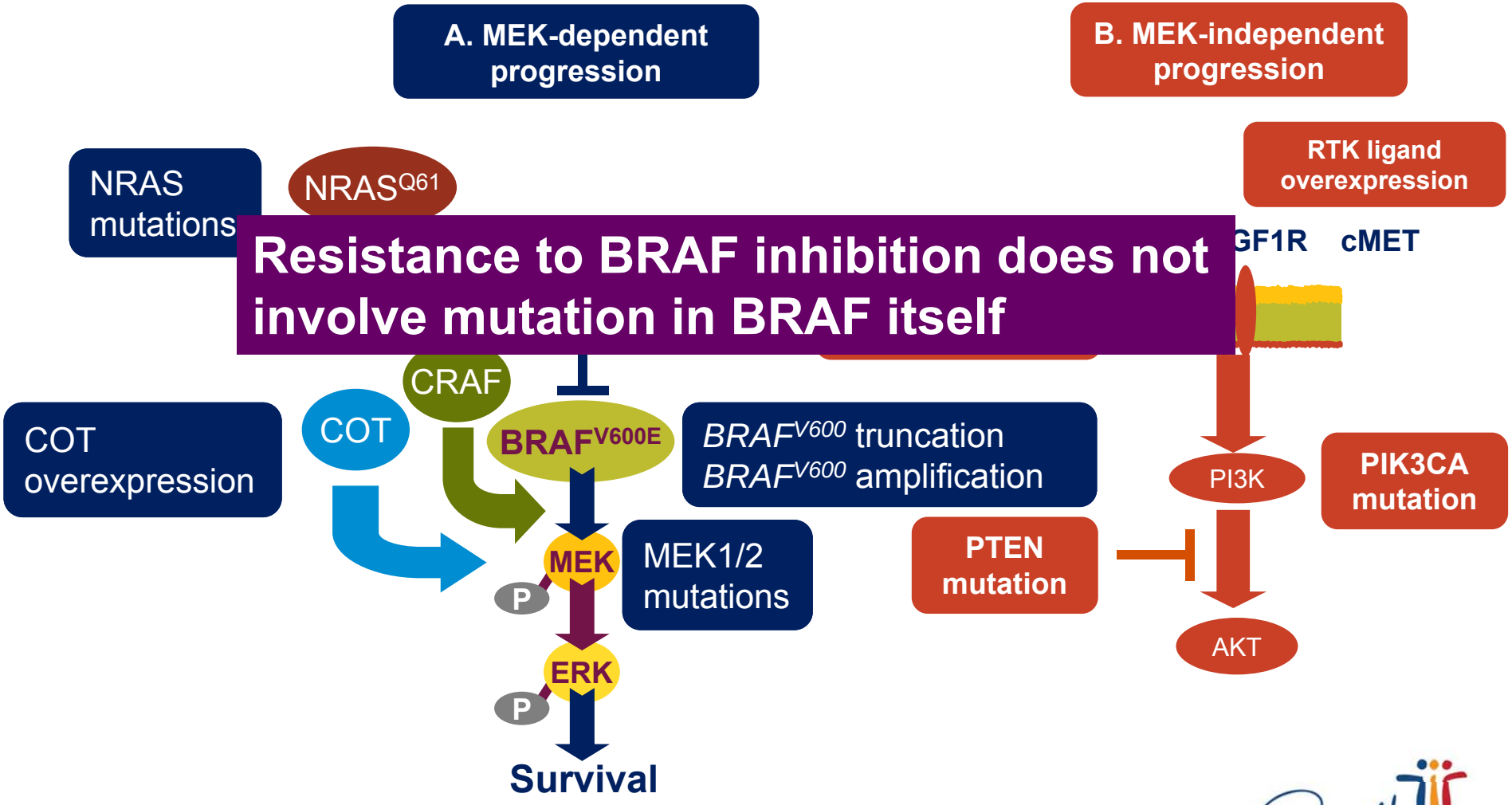
Progression

# Testing on progression- multiple mechanisms of resistance



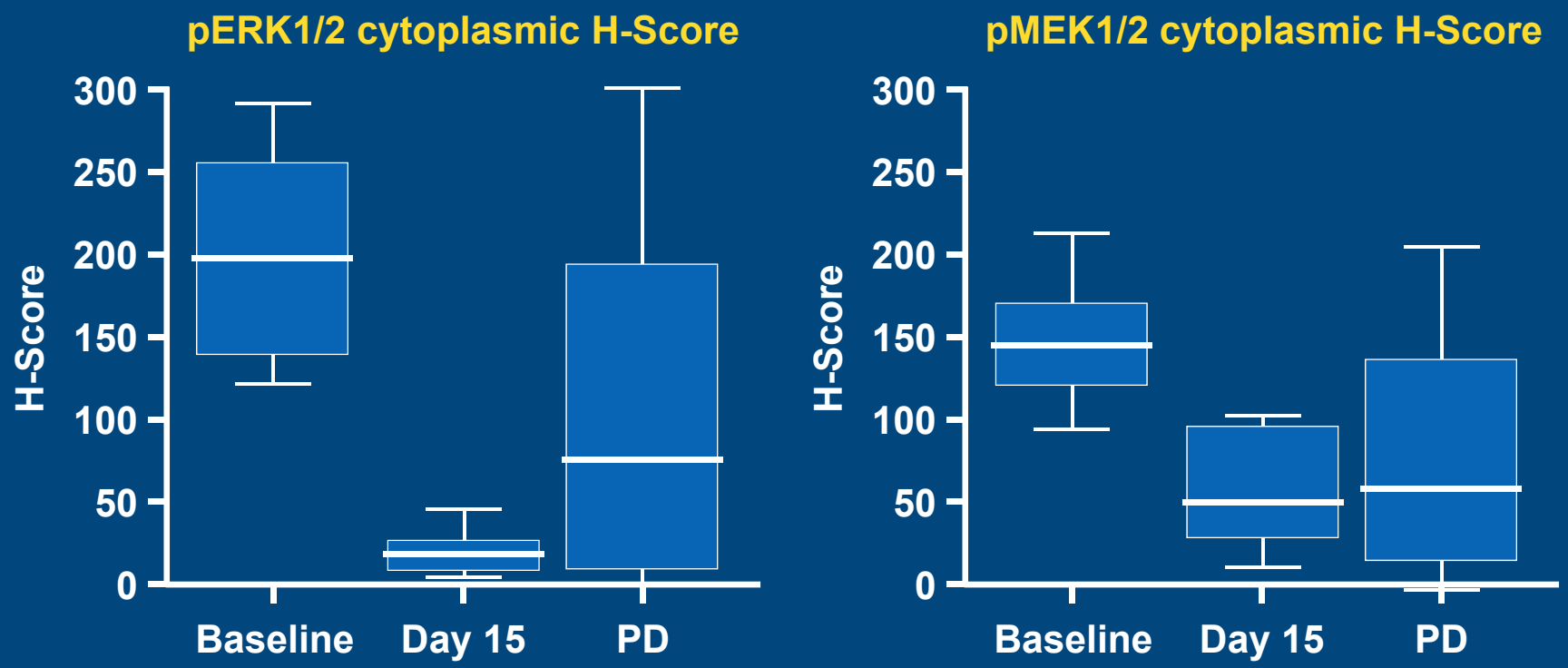

Adapted from Poulikakos….Rosen, Nature 2010; Nazarian…..Lo, Nature 2010; Johannessen…..Garraway, Nature 2010; Villanueva…..Herlyn, Cancer Cell, 2010; Wagle…..Garraway, JCO, 2011, Poulikakos….Solit, Nature 2011, Shi….Lo, Nature Comm, 2012, Trunzer…Ribas, JCO, 2013

# Resistance to BRAF inhibition




Nazarian et al. *Nature* 2010; Johannessen et al. *Nature* 2010; Poulikakos et al. *Nature* 2011; Shi et al. *Nature Com* 2012; Villanueva et al. *Cancer Cell* 2010; Wagle et al. *JCO* 2011, Strausman et al. *Nature* 2012; Wilsonet al. *Nature* 2012; Van Allen et al. *Cancer Disc* 2013

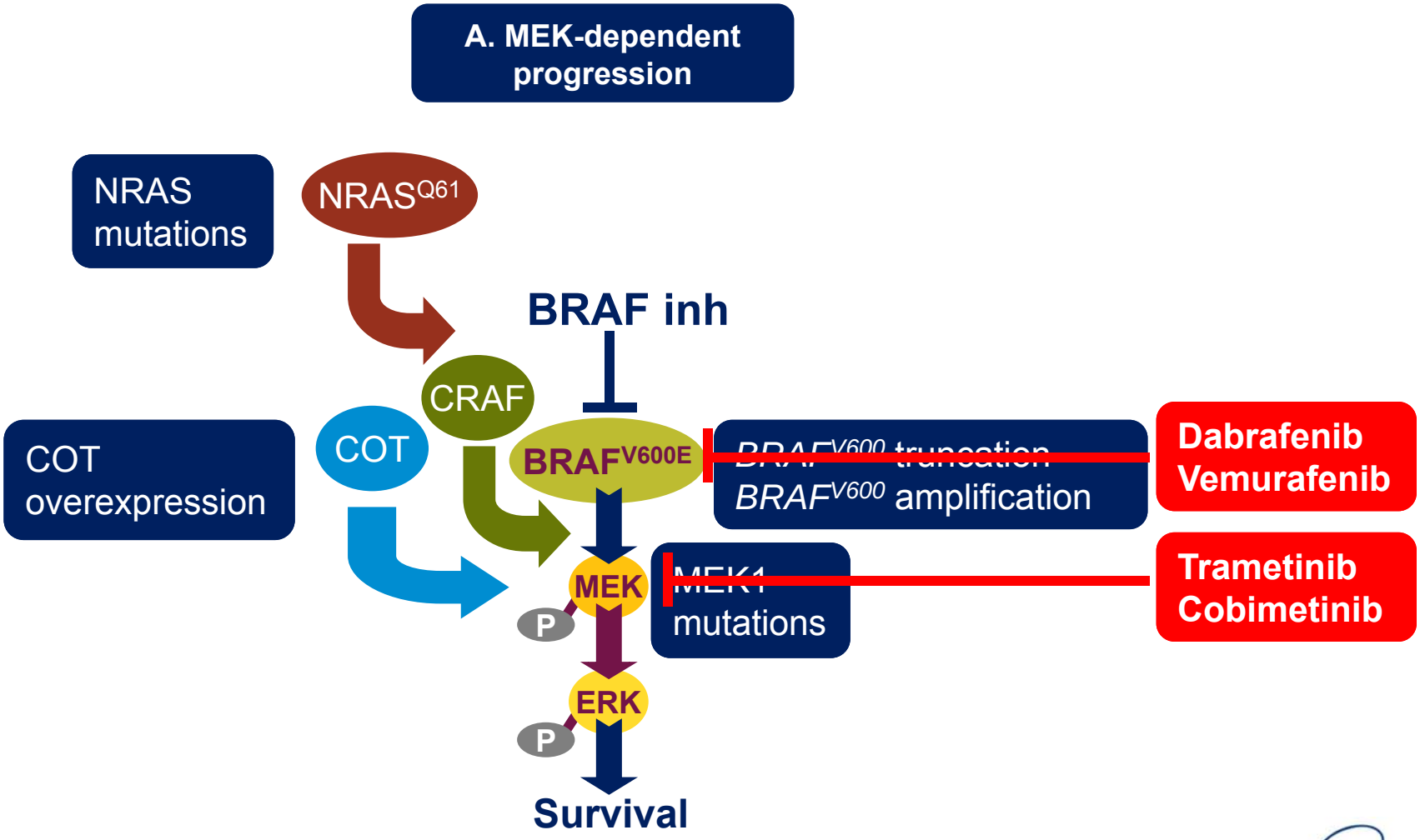
# Heterogeneity of ERK phosphorylation at progression




- Recovery of ERK and MEK phosphorylation at disease progression was observed in some but not all patients

McArthur ASCO, 2011

# Overcoming Resistance to BRAF inhibition




Nazarian et al. *Nature* 2010; Johannessen et al. *Nature* 2010; Poulikakos et al. *Nature* 2011; Shi et al. *Nature Com* 2012; Villanueva et al. *Cancer Cell* 2010; Wagle et al. *JCO* 2011, Strausman et al. *AACR* 2012

Peter Mac
Australia's Leading Cancer Centre

# Acknowledgements


**Keith Flaherty**

**Paul Chapman**

**Keith Nolop**

**Axel Hauschild**

**Nick Choong**

**Antoni Ribas**

Jeff Sosman

Kevin Kim

Igor Puzanov

Joe Grippo

Gideon Bollag

Richard Lee

Rene Gonzalez

**Study Coordinators**

**Patients & their families**

Australian Government
National Health and Medical Research Council
NHMRC

Linking research and patient care
Victorian Cancer Agency

The Cancer Council Victoria

# PD-1 and ipilimumab in sequence

Antoni Ribas, M.D., Ph.D.
Professor of Medicine
Professor of Surgery
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University of California Los Angeles (UCLA)
Chair, Melanoma Committee at SWOG

# PD-1/PD-L1 inhibiting reagents in clinical development

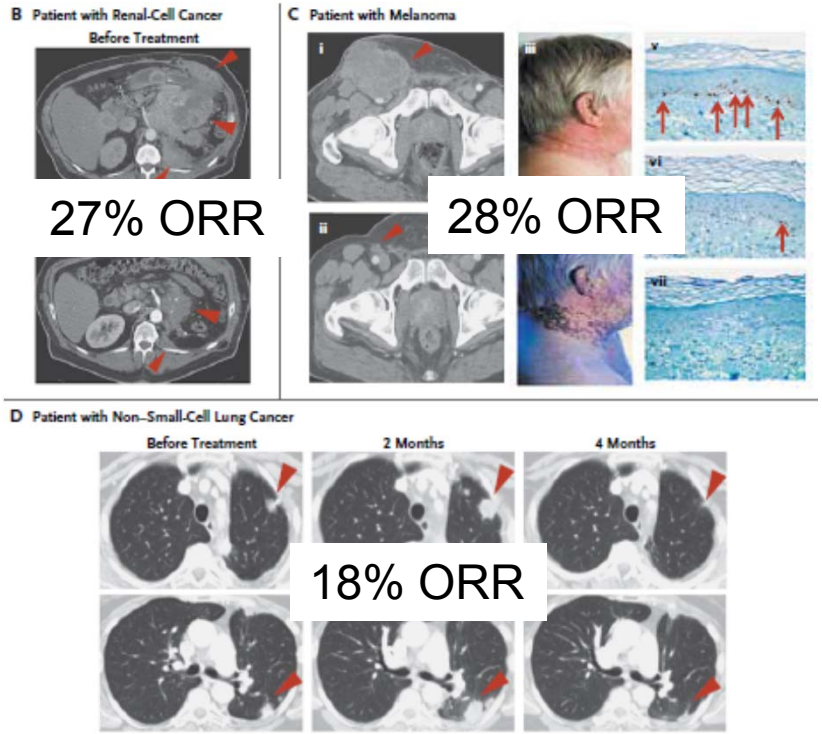
| Target | Agent | Class | $K_D$ |
|---|---|---|---|
| PD-1 | Nivolumab (MDX1106, BMS936558, BMS-ONO) | IgG4 fully human antibody | 3 nM |
| | MK-3475 (lambrolizumab, Merck) | IgG4 engineered humanized antibody | 29 pM |
| | Pidilizumab (CT-011, CureTech-Teva) | IgG1 humanized antibody | - |
| | AMP-224 (Amplimmune-GSK) | Fc-PD-L2 fusion protein | - |
| PD-L1 | BMS935559 (MDX-1105, BMS-ONO) | IgG4 fully human antibody | - |
| | MPDL3280A (Genentech) | IgG1 engineered fully human antibody | - |
| | MEDI4736 (MedImmune, AZ) | IgG1 engineered fully human antibody | - |
| | MSB0010718C (Merck-Serono) | NA | - |

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.




27% ORR

28% ORR

18% ORR

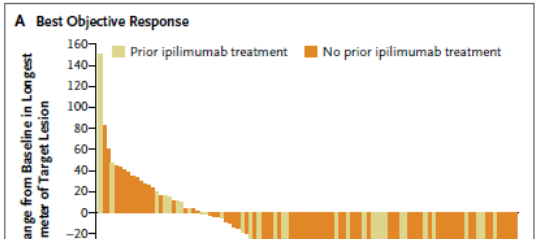
Nivolumab

The NEW ENGLAND JOURNAL of MEDICINE

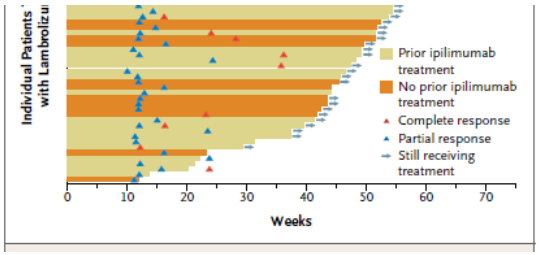
ORIGINAL ARTICLE

# Safety and Tumor Responses with MK-3475 (Anti–PD-1) in Melanoma

Omid Hamid, M.D., Caroline Robert, M.D., Ph.D., Adil Daud, M.D., F. Stephen Hodi, M.D., Wen-Jen Hwu, M.D., Ph.D., Richard Kefford, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., Peter Hersey, M.D., Ph.D., Richard W. Joseph, M.D., Jeffrey S. Weber, M.D., Ph.D., Roxana Dronca, M.D., Tara C. Gangadhar, M.D., Amita Patnaik, M.D., Hassane Zarour, M.D., Anthony M. Joshua, M.B., B.S., Ph.D., Kevin Gergich, M.A., Jeroen Elassaiss-Schaap, Ph.D., Alain Algazi, M.D., Christine Mateus, M.D., Peter Boasberg, M.D., Paul C. Tumeh, M.D., Bartosz Chmielowski, M.D., Ph.D., Scot W. Ebbinghaus, M.D., Xiaoyun Nicole Li, Ph.D., S. Peter Kang, M.D., and Antoni Ribas, M.D., Ph.D.




ORR: 38%
Highest dose ORR: 52%
(by RECIST 1.1 with confirmation assessed by ICR)

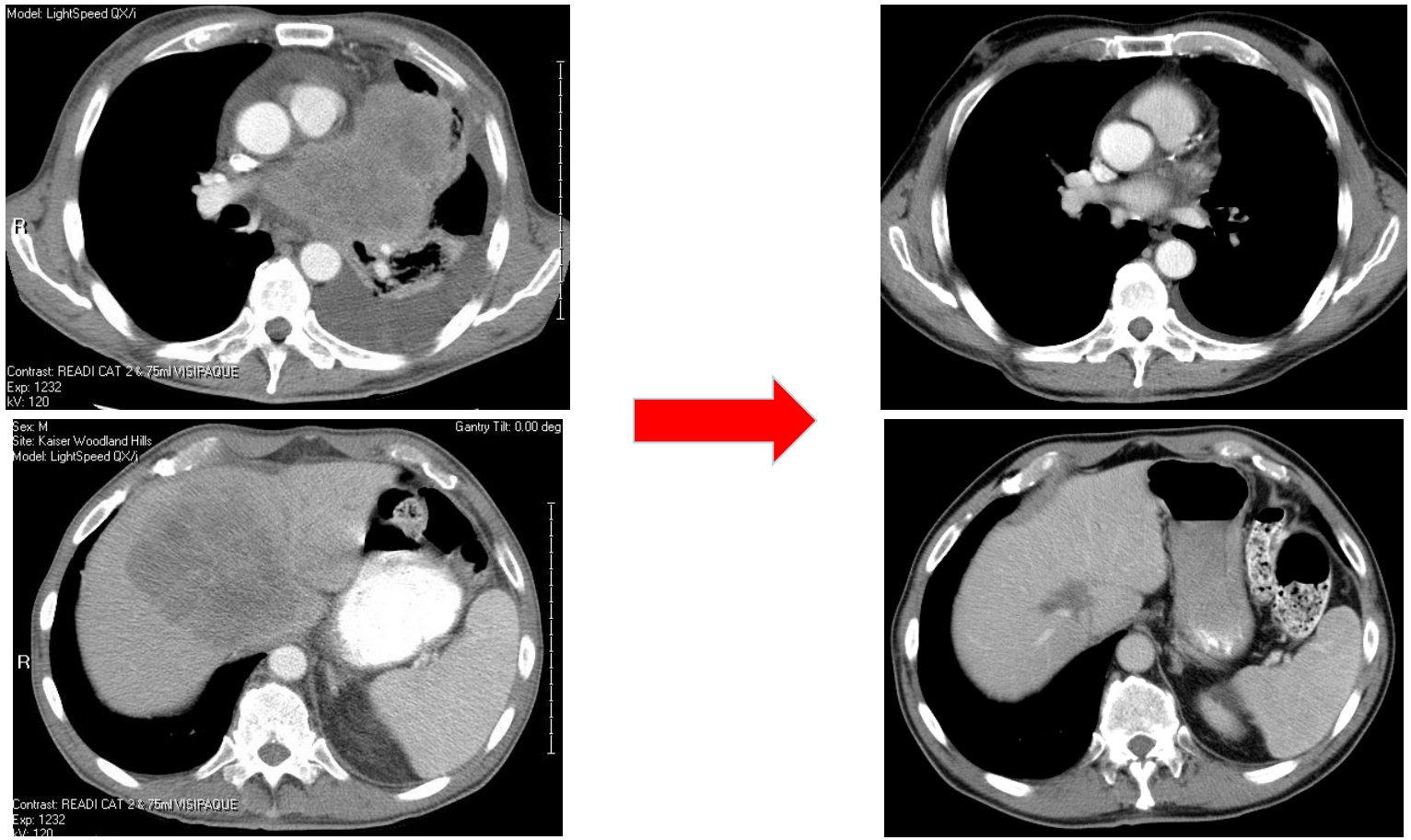



MK-3475

# Clinical activity of MK-3475 in a patient progressing to 3 prior lines of therapy

Baseline: April 13, 2012

April 9, 2013



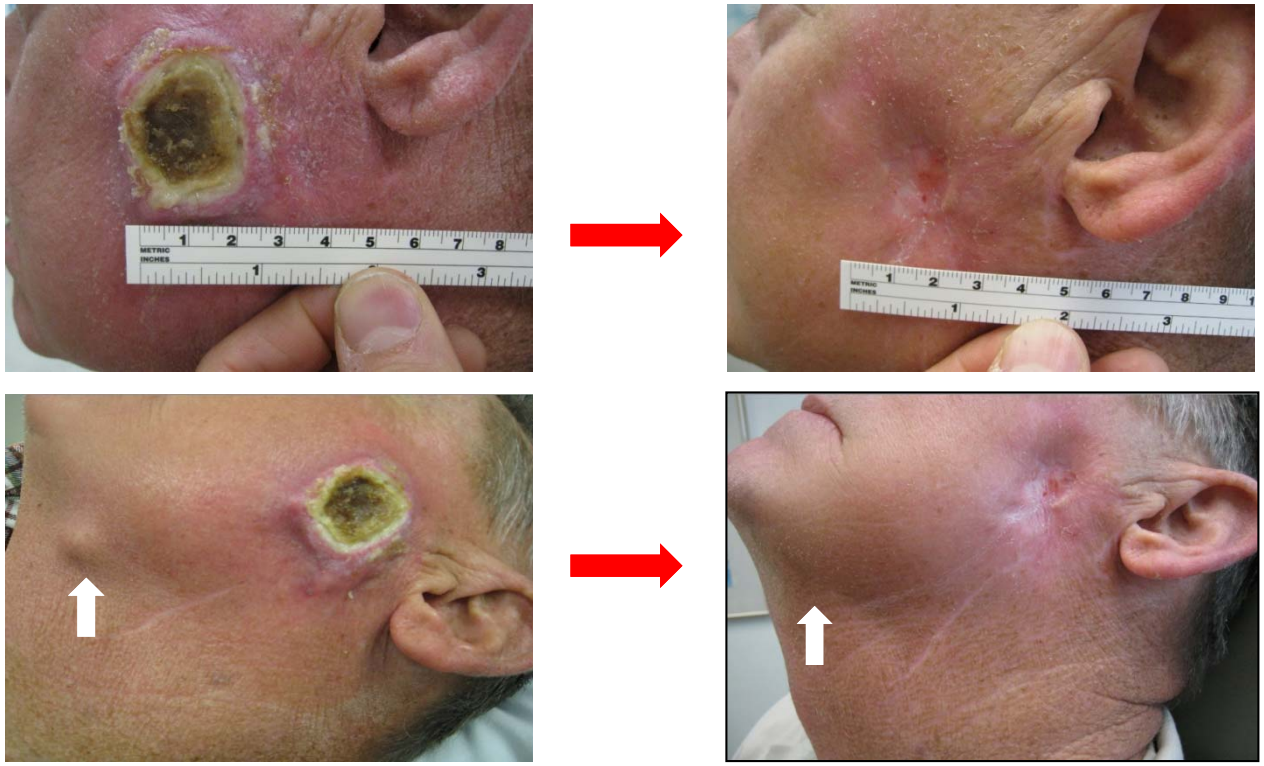

72-year-old male with symptomatic progression after bio-chemotherapy, HD IL-2, and ipilimumab

A. Ribas, ASCO 2013

# Clinical activity in a patient with a metastatic desmoplastic melanoma

Baseline Jan/2012

Apr/2012



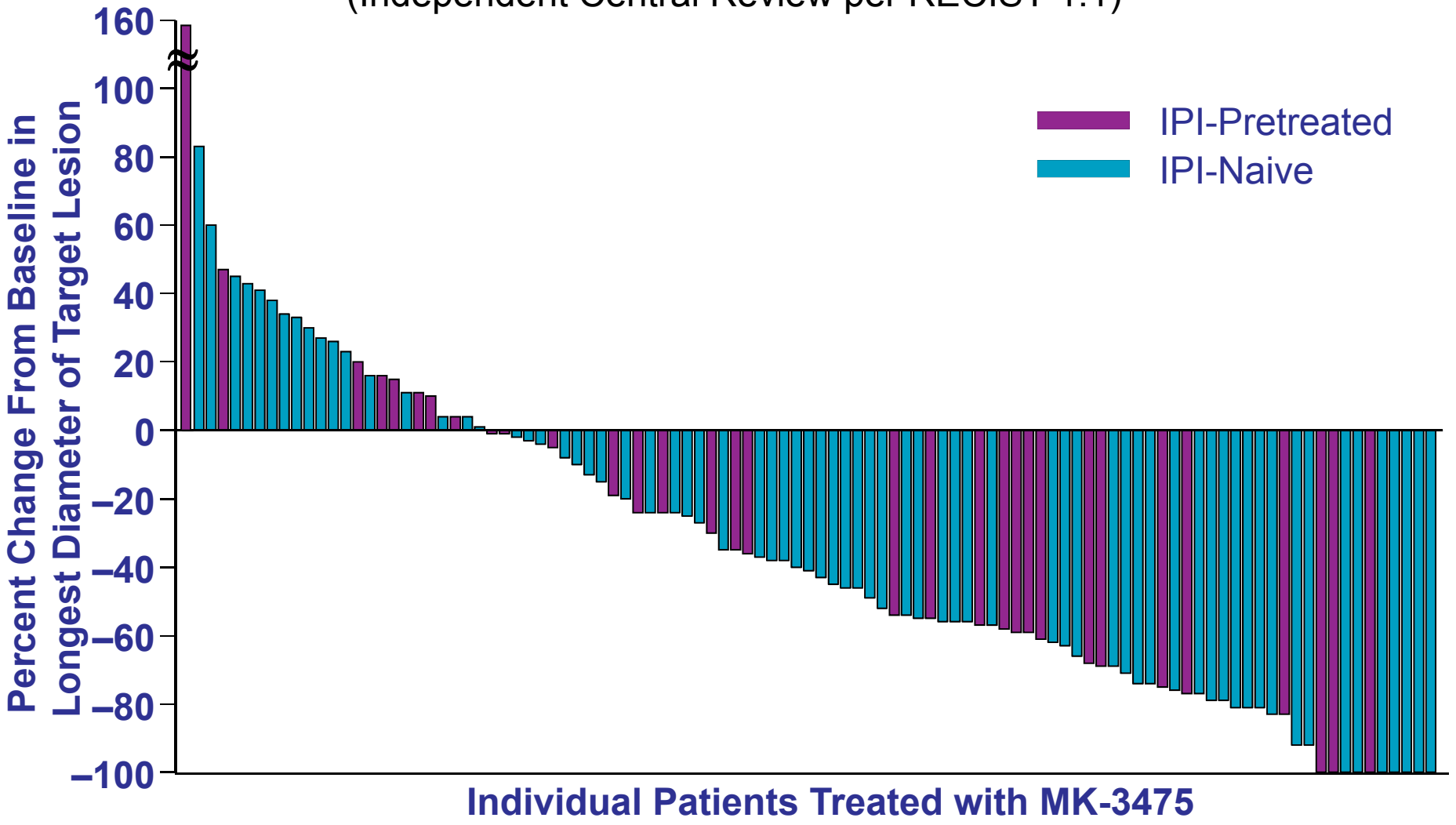
54 yrs old male with desmoplastic melanoma after progressing on ipilimumab

A. Ribas, ASCO 2013

B. Chmielowski M.D., Ph.D.
Paul Tumeh M.D.

# MK-3475 (lambrolizumab) single agent therapy: Maximum Change From Baseline in Tumor Size

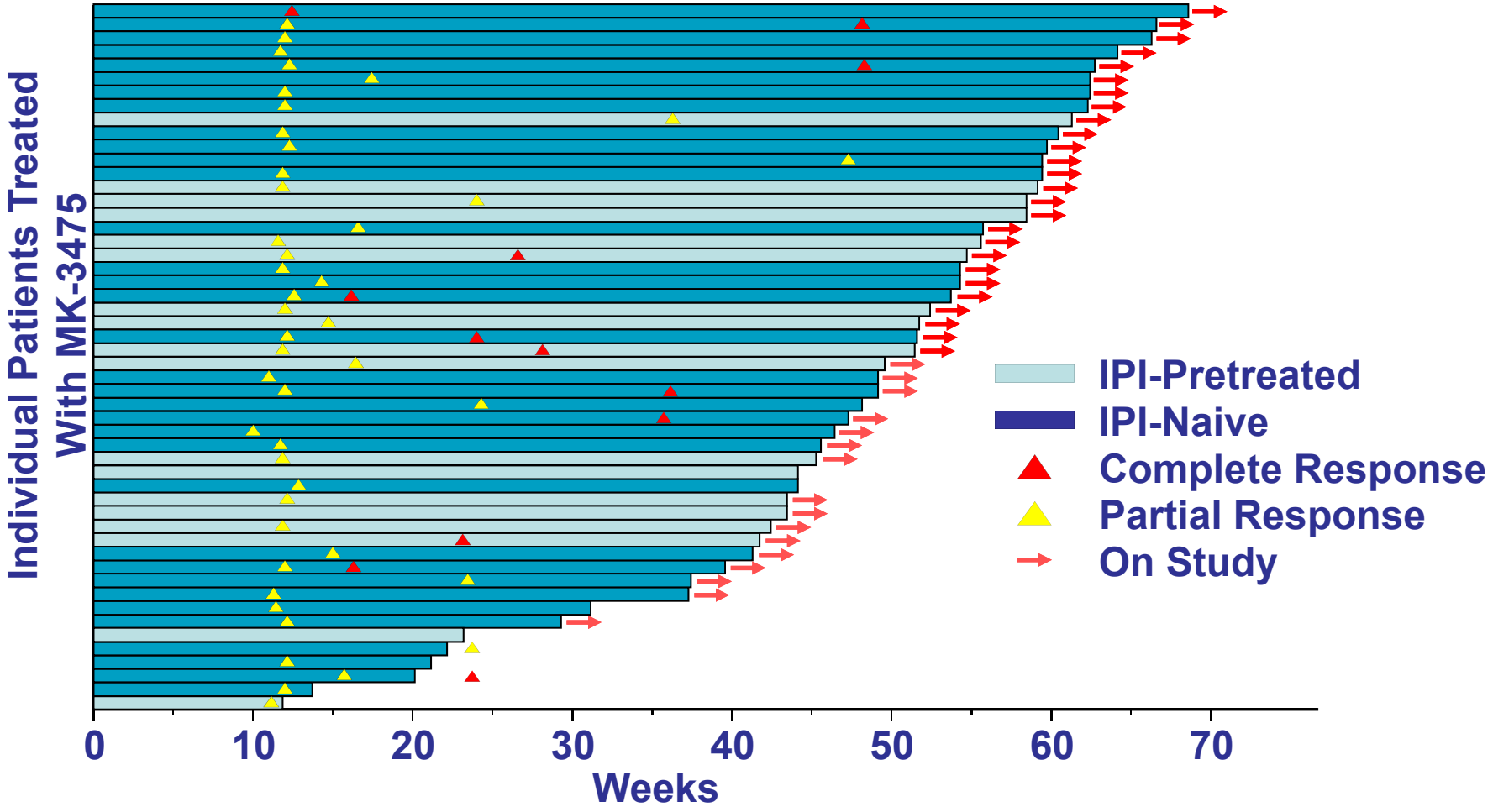
(Independent Central Review per RECIST 1.1)




Ribas *et al*. ASCO 2013

# Time to Response and On-Study Duration

## (Independent Central Review per RECIST 1.1)




The median duration of response had not been reached at the time of analysis, with median follow-up time of 11 months.

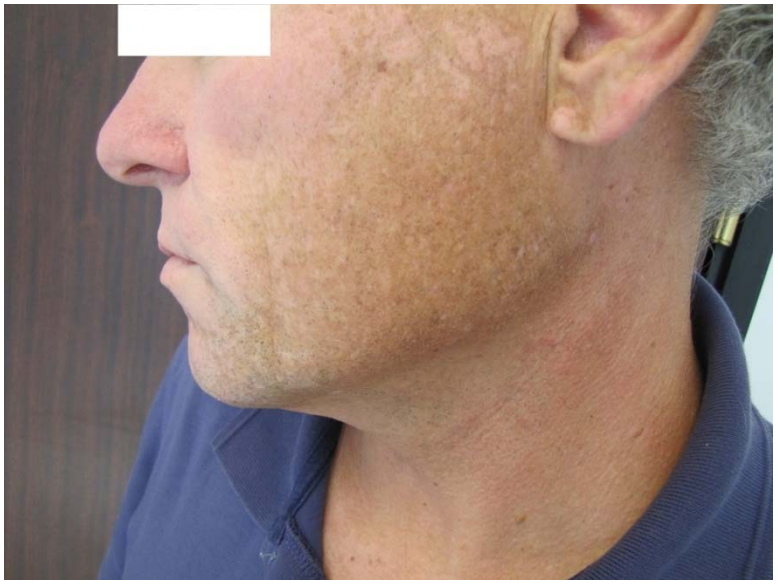
Ribas *et al*. ASCO 2013

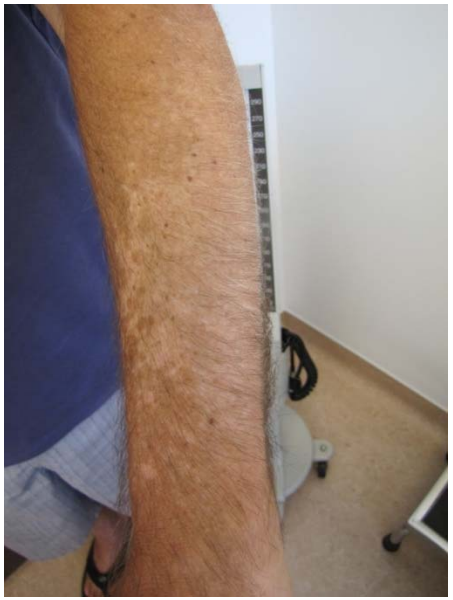
# Drug-Related Adverse Events

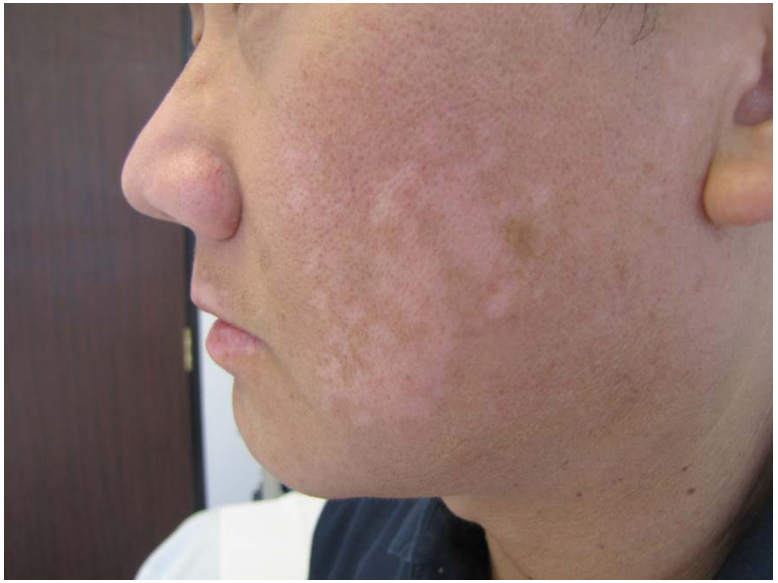
Observed in >5% of Patients (N = 135)

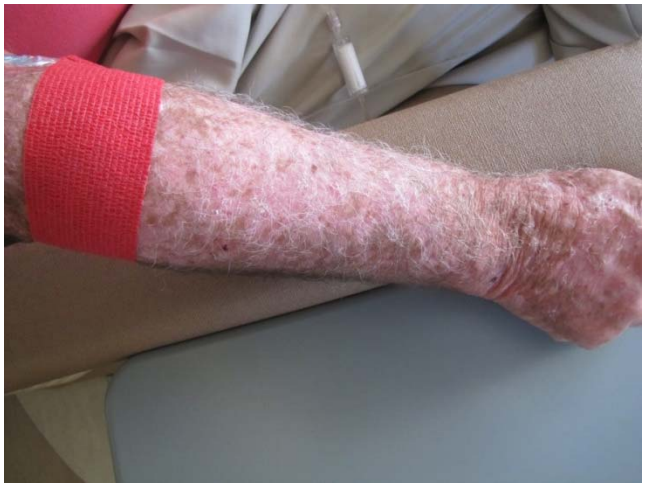
| Adverse Event | All Grades, n (%) | Grade 3-4, n (%) |
|---|---|---|
| Any | 107 (79.3) | 17 (12.6) |
| Fatigue | 41 (30.4) | 2 (1.5) |
| Rash | 28 (20.7) | 3 (2.2) |
| Pruritus | 28 (20.7) | 1 (0.7) |
| Diarrhea | 27 (20.0) | 1 (0.7) |
| Myalgia | 16 (11.9) | 0 |
| Headache | 14 (10.4) | 0 |
| Increased AST | 13 (9.6) | 2 (1.5) |
| Asthenia | 13 (9.6) | 0 |
| Nausea | 13 (9.6) | 0 |
| Vitiligo | 12 (8.9) | 0 |
| Hypothyroidism | 11 (8.1) | 1 (0.7) |
| Increased ALT | 11 (8.1) | 0 |
| Cough | 11 (8.1) | 0 |
| Pyrexia | 10 (7.4) | 0 |
| Chills | 9 (6.7) | 0 |
| Abdominal pain | 7 (5.2) | 1 (0.7) |

# Frequent development of vitiligo (skin depigmentation) in responding patients



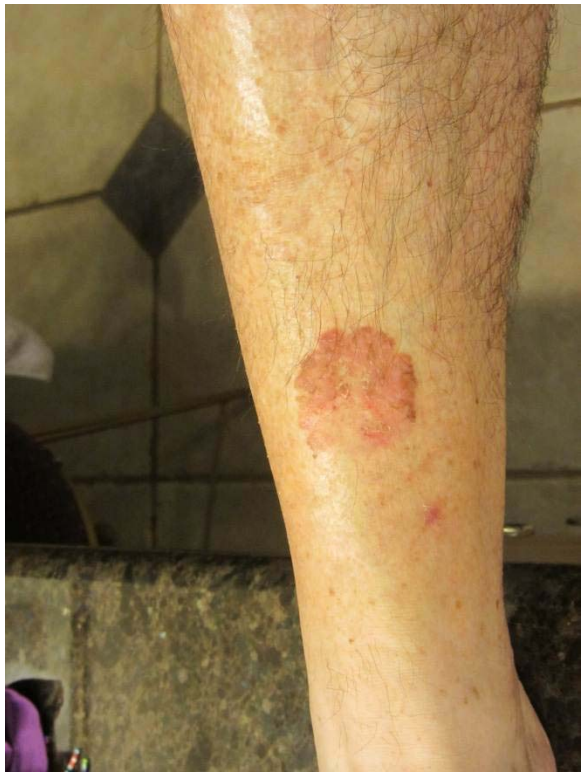




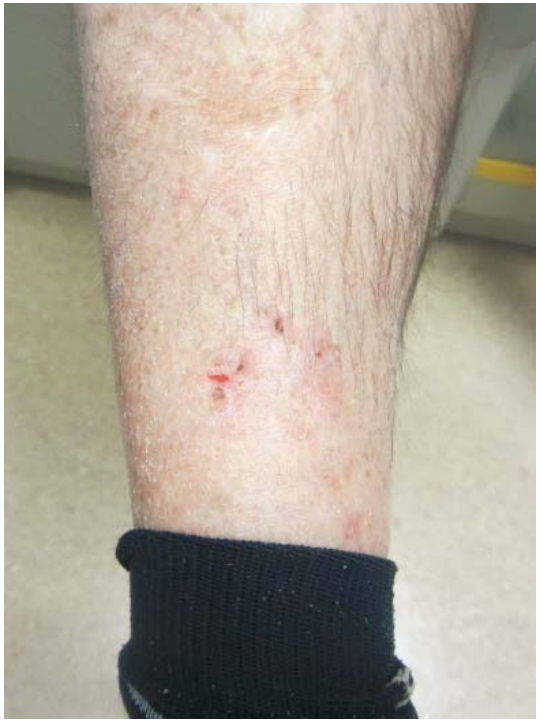


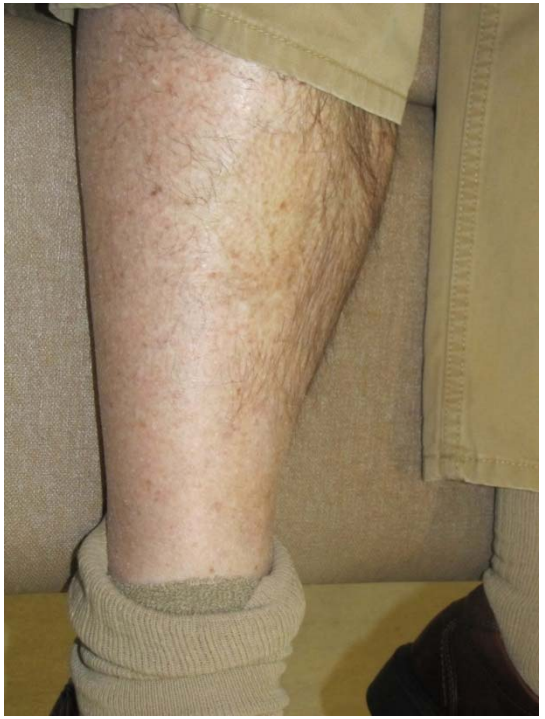
# PD-1 blockade with single agent MK-3475 improving other skin conditions

Before



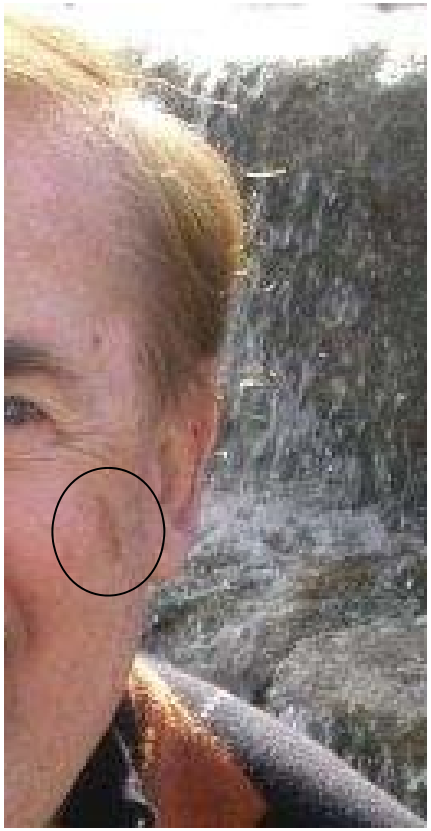
After



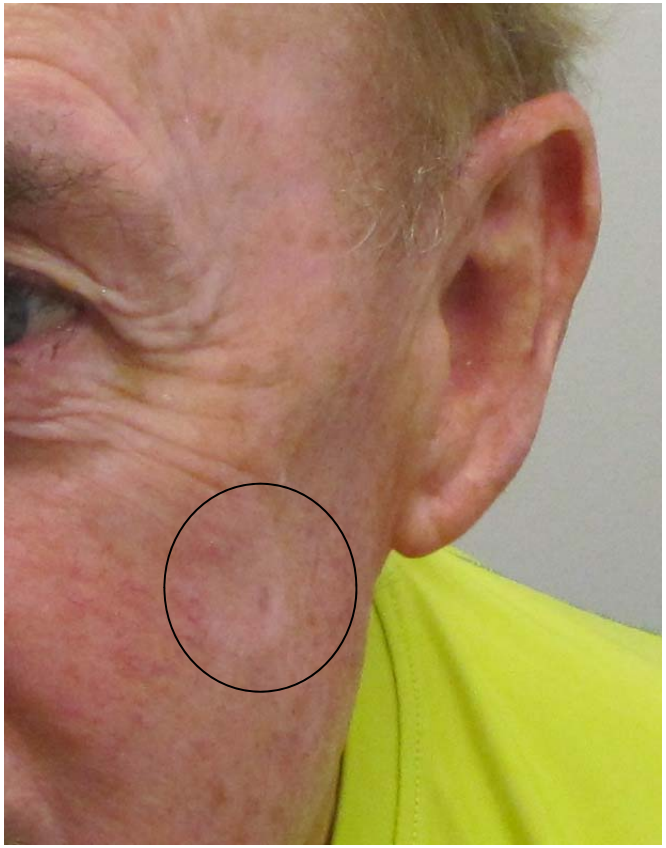


# PD-1 blockade with single agent MK-3475 leading to the disappearance of a pigmented birth mark

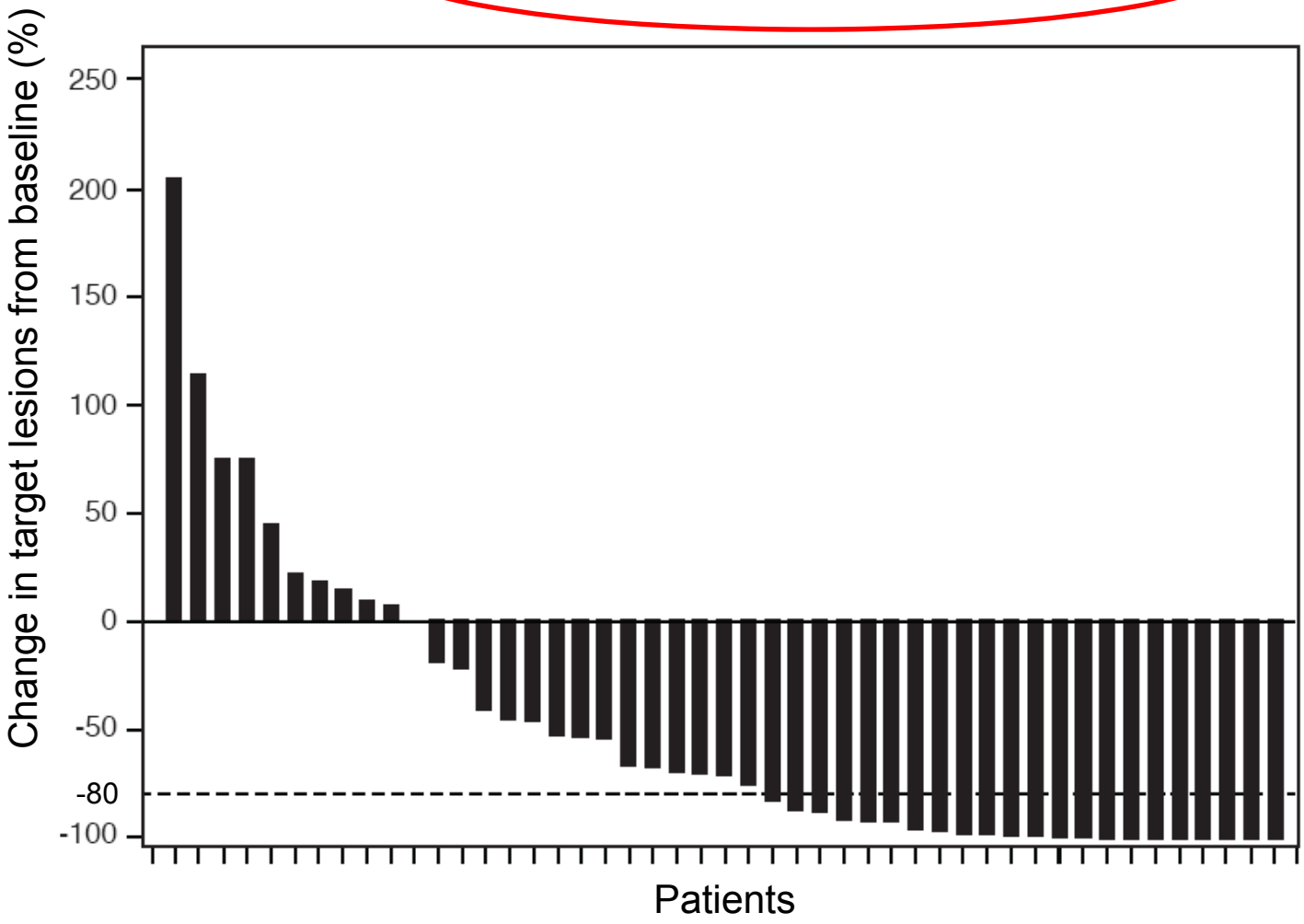
Before



After



# Nivolumab + Ipilimumab combination therapy: Best Responses in Concurrent Cohorts (WHO response criteria)

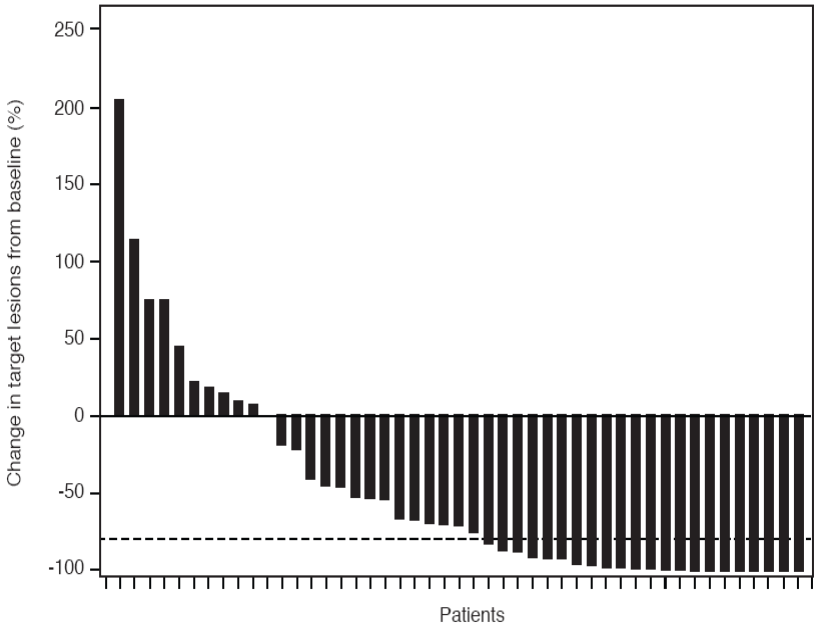



After ~13 months of follow-up, for all concurrent cohorts, 90% of all responding patients continue to respond as of Feb 2013.

Wolchok *et al*. ASCO 2013

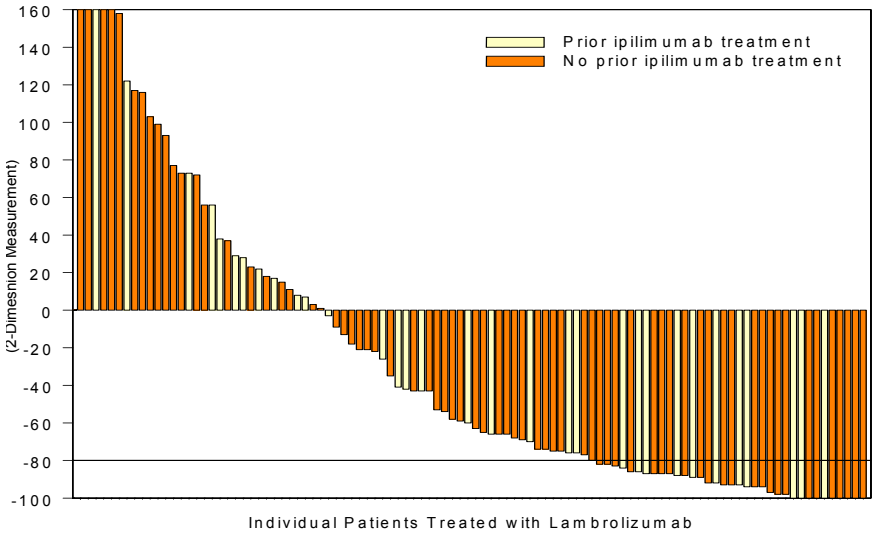
# WHO waterfalls with combination nivolumab + ipilimumab or single agent MK-3475

Nivolumab + Ipilimumab




Change from baseline using WHO measurements

MK-3475



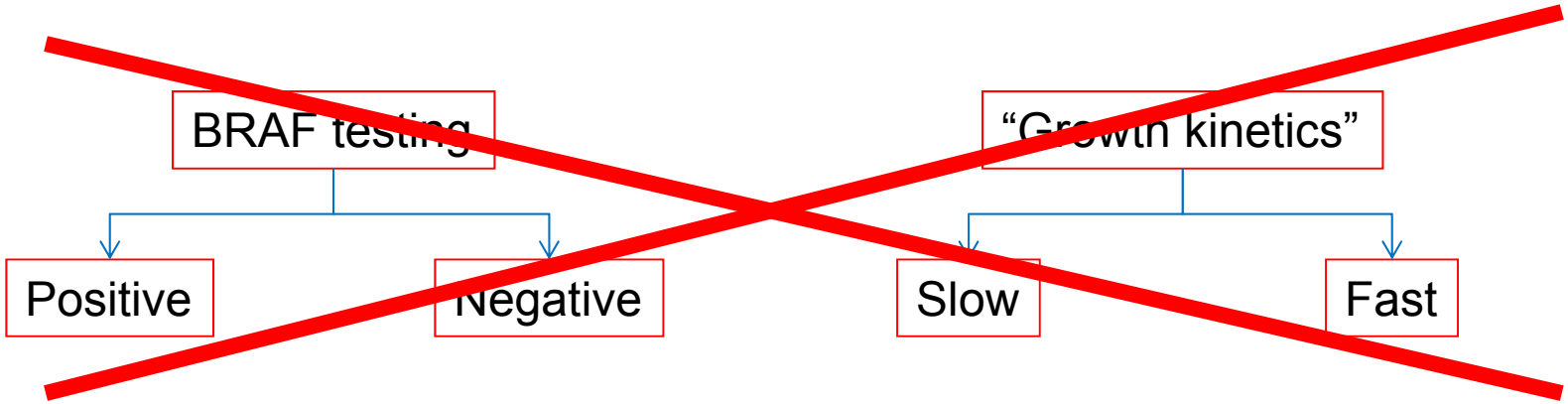

The “depth of the response” is in part an artifact of how the data is presented when using WHO (bidimensional measurements) in a waterfall plot

# Treatment-Related Adverse Events (≥10% of all patients)

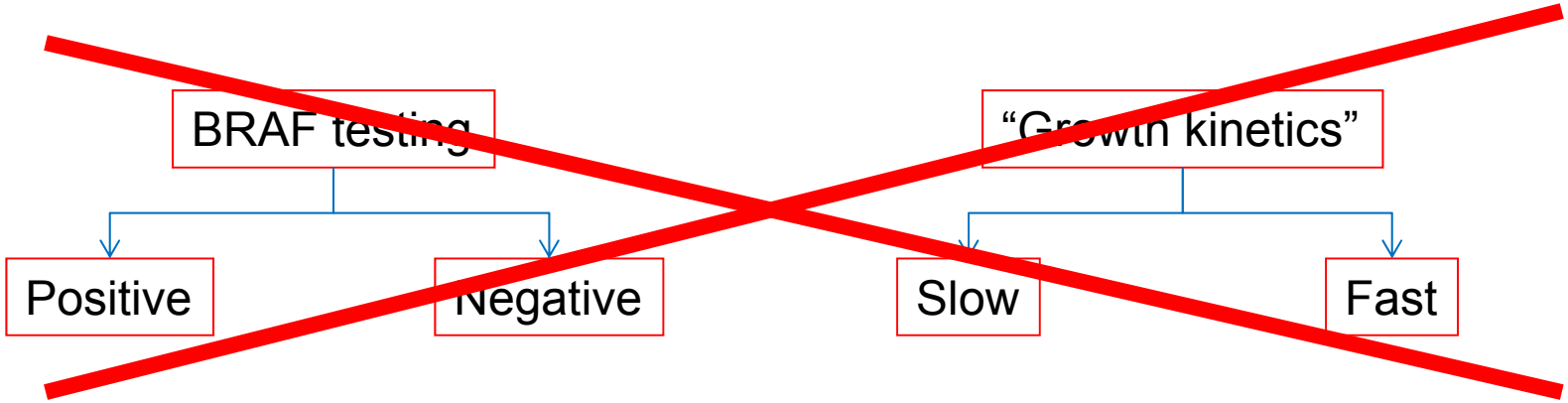
| Treatment-Related Adverse Event<br>Number of Patients (%) | Concurrent All Cohorts (n=53) | | Sequenced All Cohorts (n=33) | |
|---|---|---|---|---|
| | All Gr | Gr 3-4 | Al Gr | Gr 3-4 |
| Any adverse event | 49 (93) | 28 (53) | 24 (73) | 6 (18) |
| Rash | 29 (55) | 2 (4) | 3 (9) | 0 |
| Pruritus | 25 (47) | 0 | 6 (18) | 0 |
| Fatigue | 20 (38) | 0 | 3 (9) | 0 |
| Diarrhea | 18 (34) | 3 (6) | 3 (9) | 0 |
| Nausea | 11 (21) | 0 | 1 (3) | 0 |
| Pyrexia | 11 (21) | 0 | 1 (3) | 0 |
| AST | 11 (21) | 7 (13) | 0 | 0 |
| ALT | 11 (21) | 6 (11) | 1 (3) | 0 |
| Lipase | 10 (19) | 7 (13) | 4 (12) | 2 (6) |
| Amylase | 8 (15) | 3 (6) | 1 (3) | 1 (3) |
| Cough | 7 (13) | 0 | 2 (6) | 0 |
| Vomiting | 6 (11) | 1 (2) | 0 | 0 |
| Vitiligo | 6 (11) | 0 | 0 | 0 |
| Headache | 6 (11) | 0 | 0 | 0 |

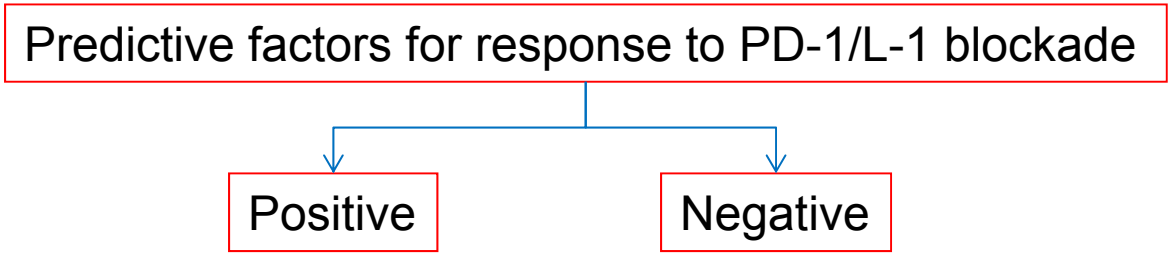
Presented by J. Wolchok, ASCO 2013

# What is the decision making for 1st line treatment of advanced melanoma?



# What is the decision making for 1st line treatment of advanced melanoma?



# Conclusions

- PD-1/PD-L1 blockade therapy should be used as single agent in patients who have a chance of responding to this therapy

- Combination therapies with PD-1/PD-L1 blockade should only be used in patients with a low likelihood of a tumor response to single agent therapy

Memorial Sloan Kettering Cancer Center

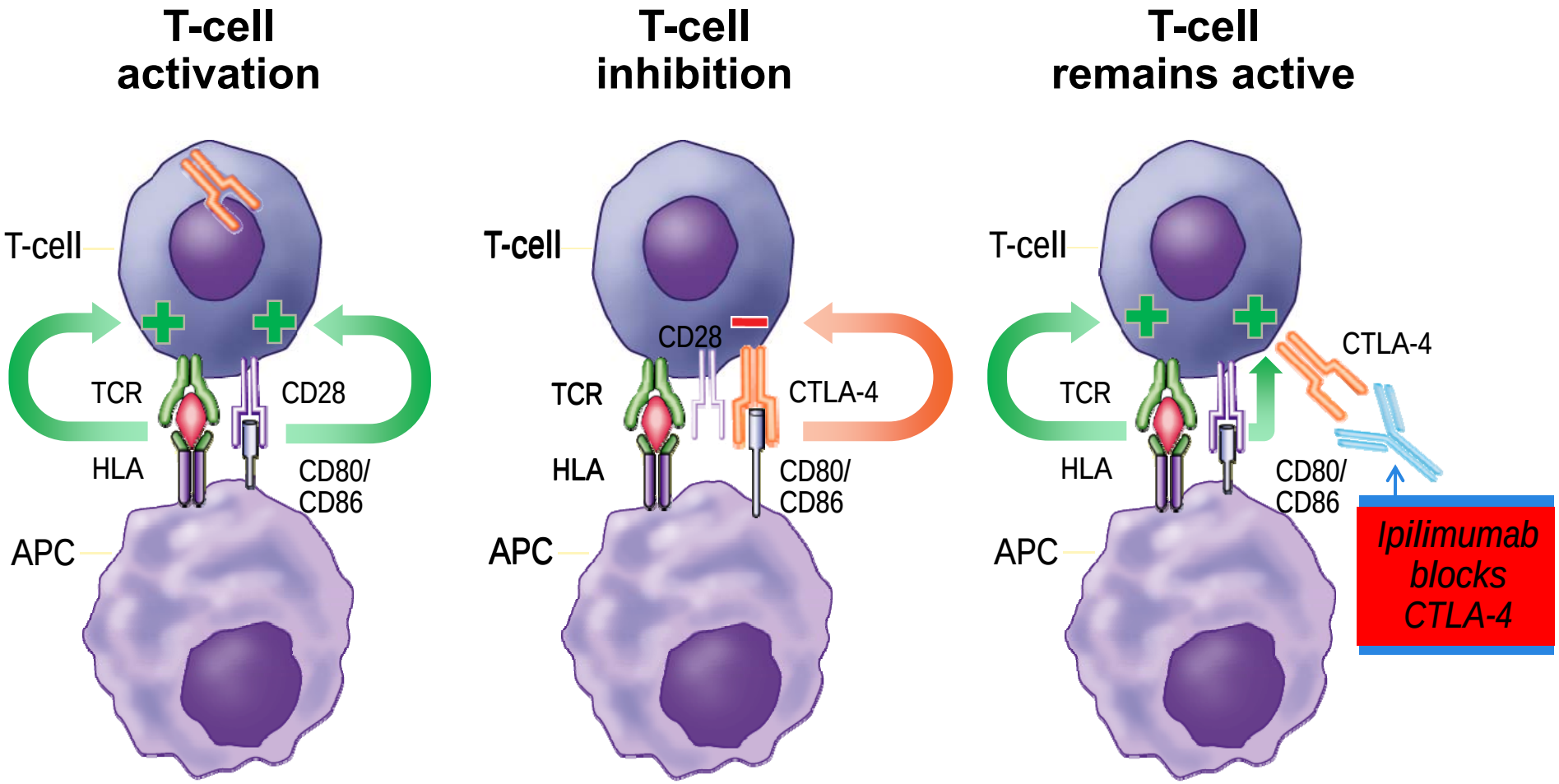
LUDWIG CANCER RESEARCH

# Combination Checkpoint Blockade Therapy for Melanoma

Jedd Wolchok

Ludwig Center at Memorial Sloan-Kettering Cancer Center, New York

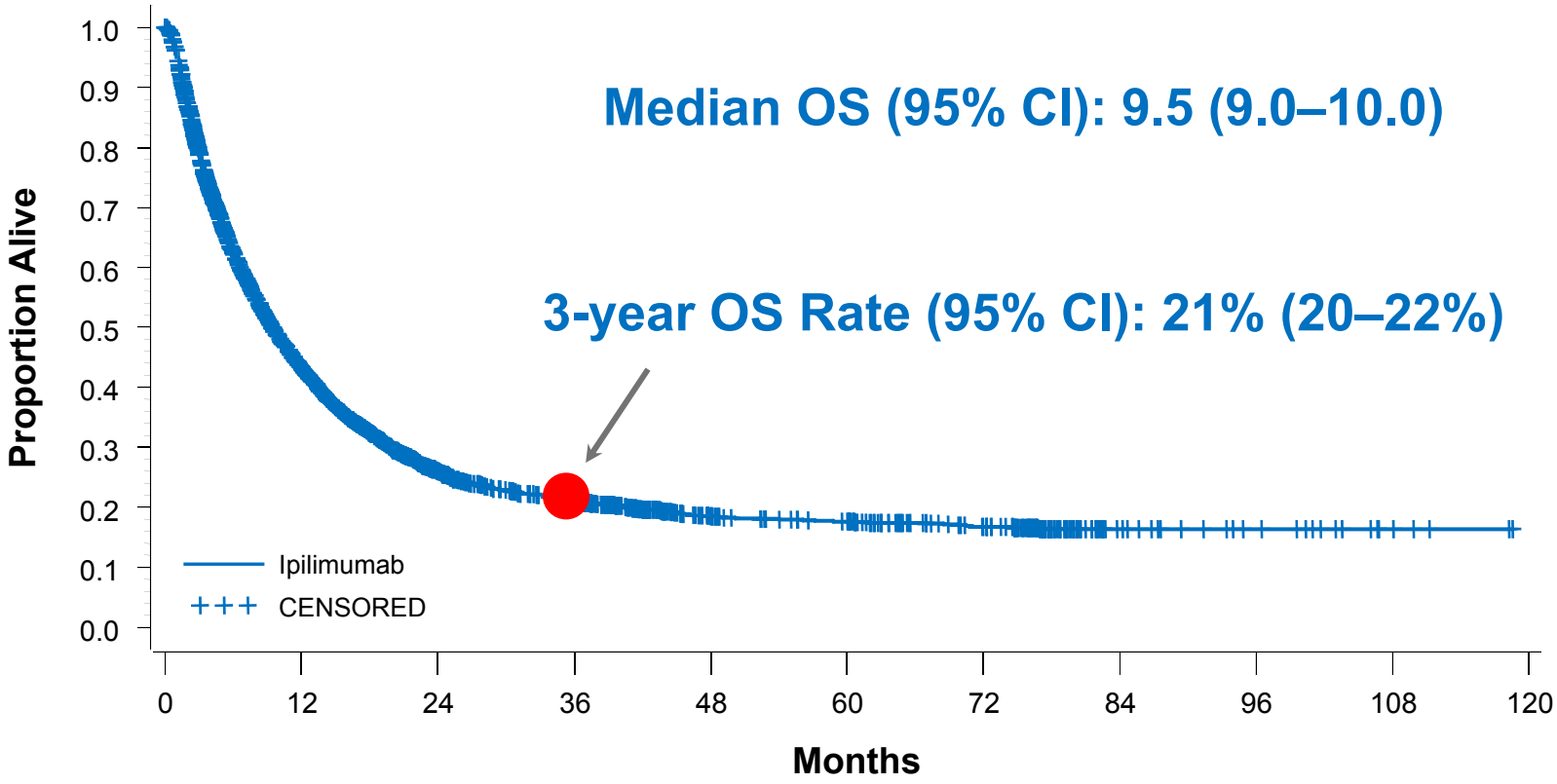
# Ipilimumab Augments T-Cell Activation and Proliferation




Adapted from O'Day et al. Plenary session presentation, abstract #4, ASCO 2010.

Memorial Sloan Kettering Cancer Center

# Pooled OS Analysis Including EAP Data: 4846 Patients




Hodi et al., ESMO, 2013

Memorial Sloan Kettering Cancer Center

# Immune-Related Adverse Events

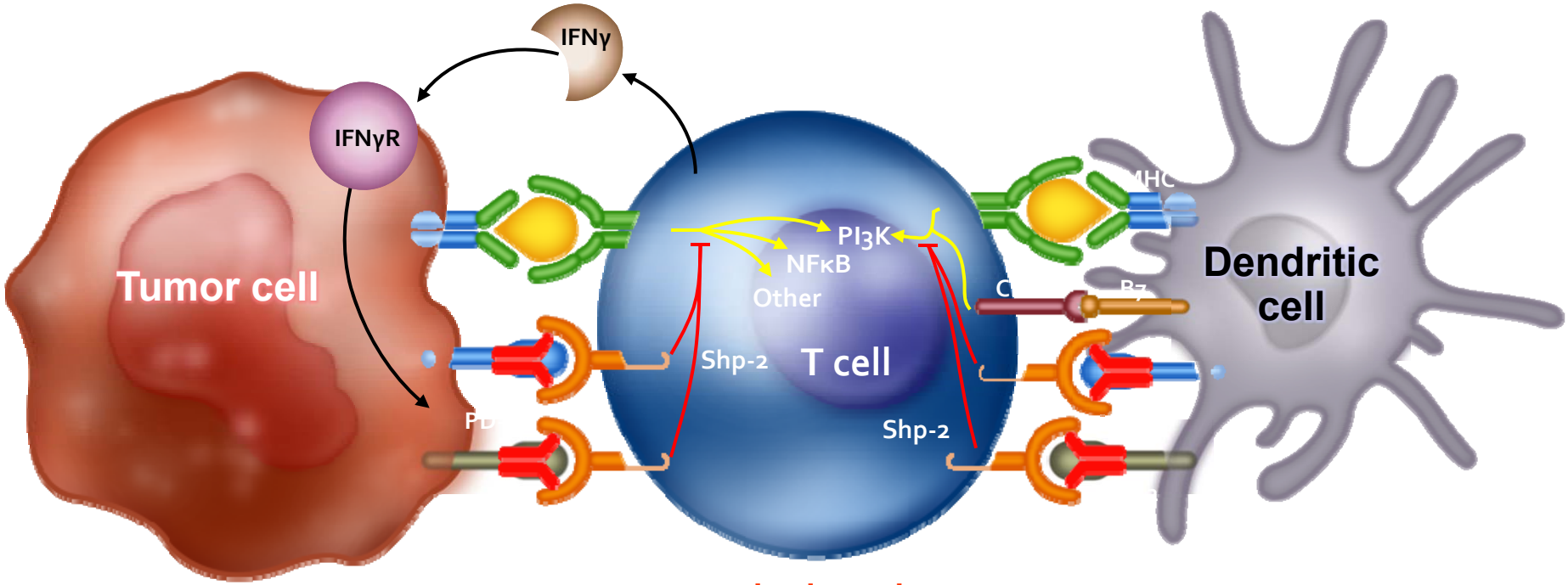
- Rash
- Colitis/enteritis
- Elevated AST/ALT
- Thyroiditis
- Adrenal insufficiency
- Hypophysitis

*Severity is inversely related to vigilance of surveillance.*
*If detected early, most are easily treated and reversible.*

# Role of PD-1 Pathway in Suppressing Anti-tumor Immunity

**Recognition of tumor by T cell through MHC/antigen interaction mediates IFNγ release and PD-L1/2 up-regulation on tumor**

**Priming and activation of T cells through MHC/antigen & CD28/B7 interactions with antigen-presenting cells**

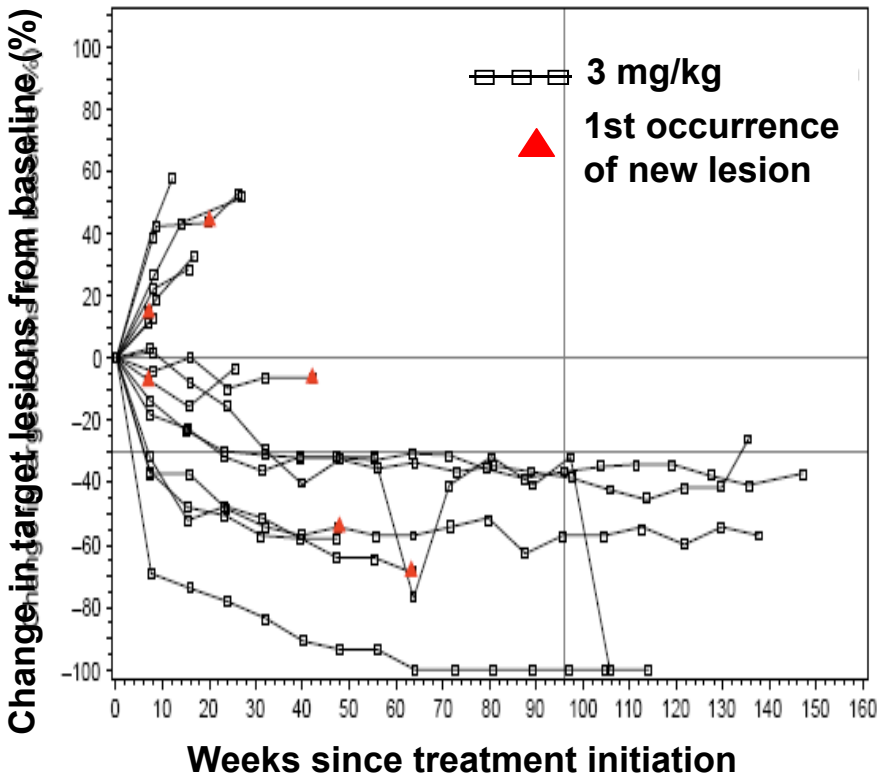


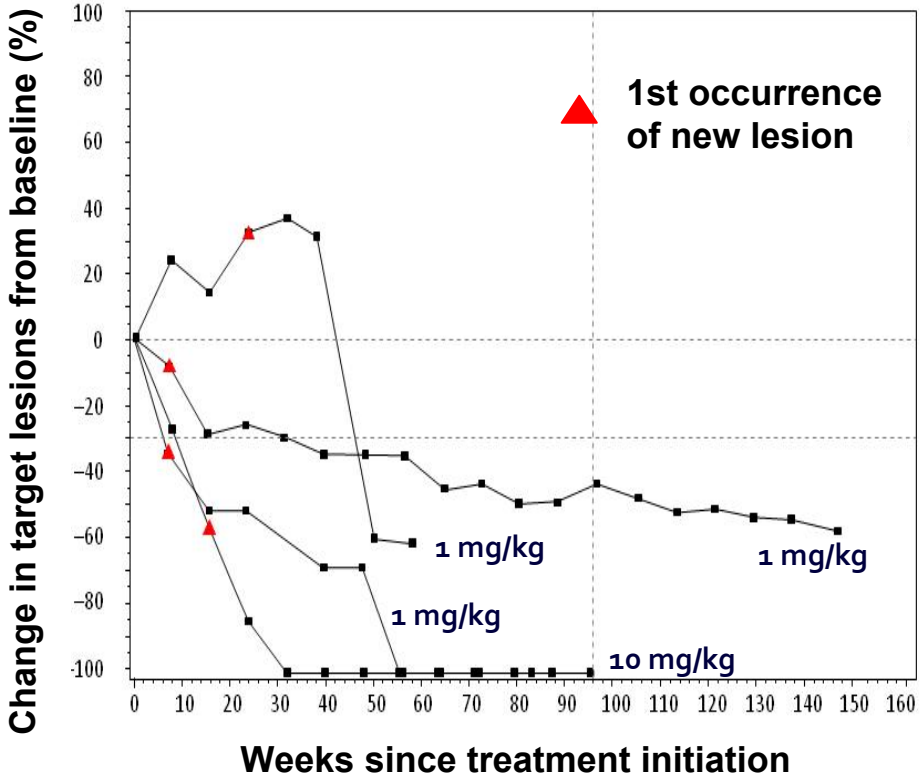

**Nivolumab**
**PD-1 Receptor Blocking Ab**

Sznol et al., ASCO, 2013

Memorial Sloan Kettering Cancer Center

# Tumor Burden in Patients with Melanoma Receiving Nivolumab 3 mg/kg




Sznol et al., ASCO, 2013

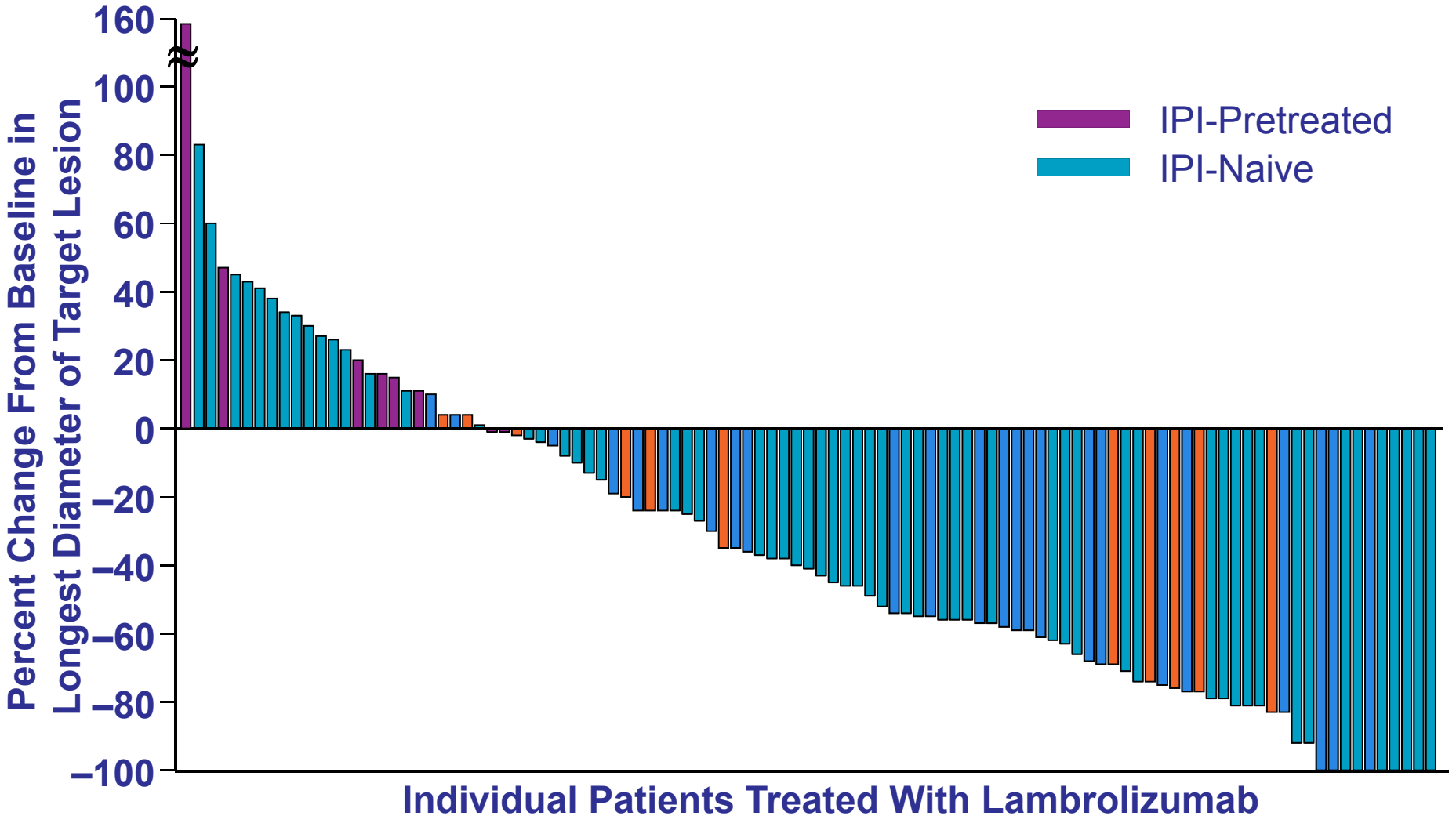
Memorial Sloan Kettering Cancer Center

# Select Drug-Related Adverse Events (≥1%) Occurring in Melanoma Patients Treated with Nivolumab

- Select AE: AE with potential immunologic etiologies that require more frequent monitoring and/or unique intervention

| Category | Any Grade % (n) | Grade 3-4 % (n) |
|---|---|---|
| Any select AE | 54 (58) | 5 (5) |
| Skin | 36 (38) | 2 (2) |
| Gastrointestinal | 18 (19) | 2 (2) |
| Endocrinopathies | 13 (14) | 2 (2) |
| Hepatic | 7 (7) | 1 (1) |
| Infusion reaction | 6 (6) | 0 |
| Pulmonary | 4 (4) | 0 |
| Renal | 2 (2) | 1 (1) |

# MK-3475: Maximum Change From Baseline in Tumor

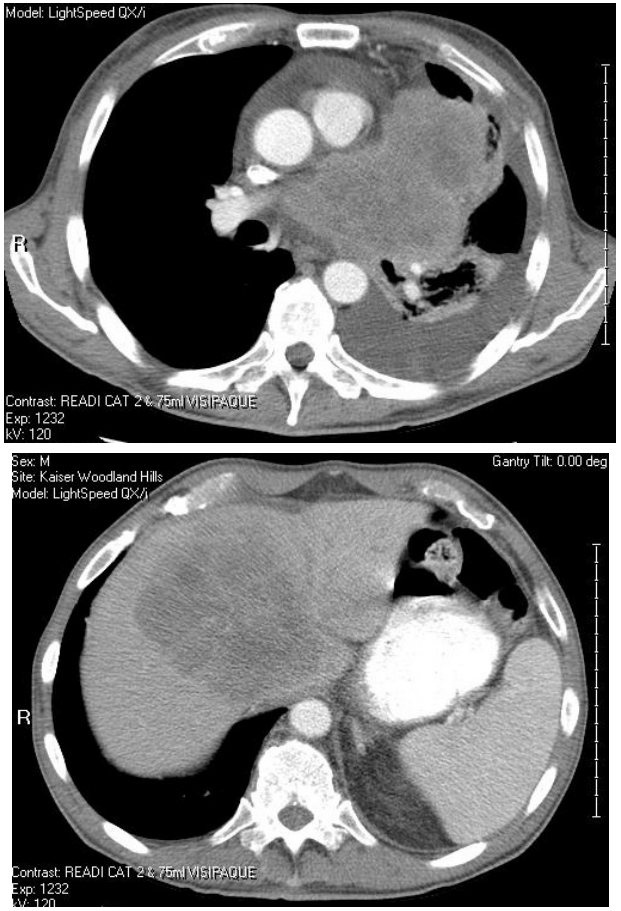



Ribas et al., ASCO, 2013

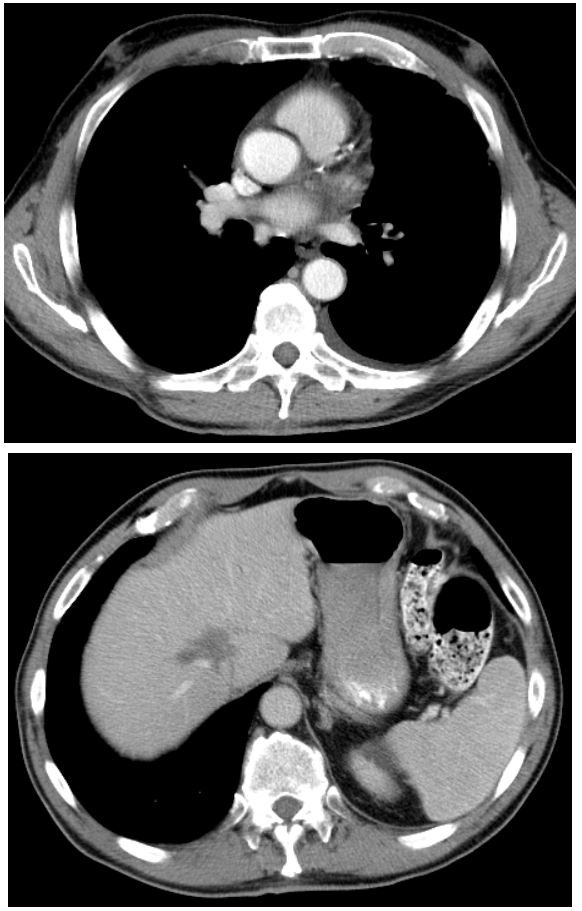
Memorial Sloan Kettering Cancer Center

# Clinical Activity, MK-3475

**Baseline: April 13, 2012**




**April 9, 2013**



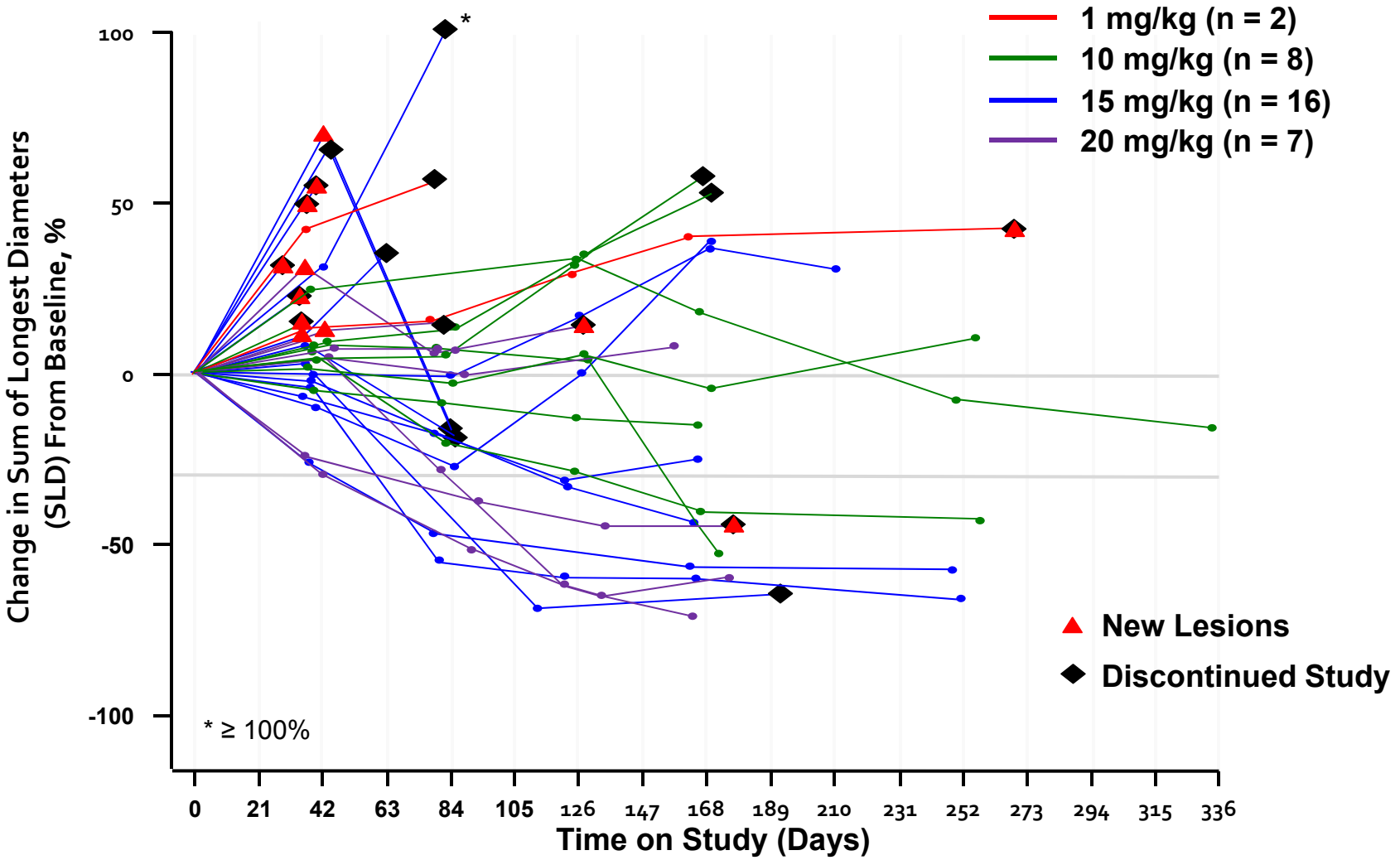
**72-year-old male with symptomatic progression after bio-chemotherapy, HD IL-2, and ipilimumab**

Images courtesy of A. Ribas, UCLA.

Ribas et al., ASCO, 2013

Memorial Sloan Kettering Cancer Center

# MPDL3280A Phase Ia: Tumor Burden Over Time (Melanoma)




Patients first dosed at 1-20 mg/kg prior to Aug 1, 2012 with at least 1 post-baseline evaluable tumor assessment; data cutoff Feb 1, 2013.



Hamid et al., ASCO, 2013

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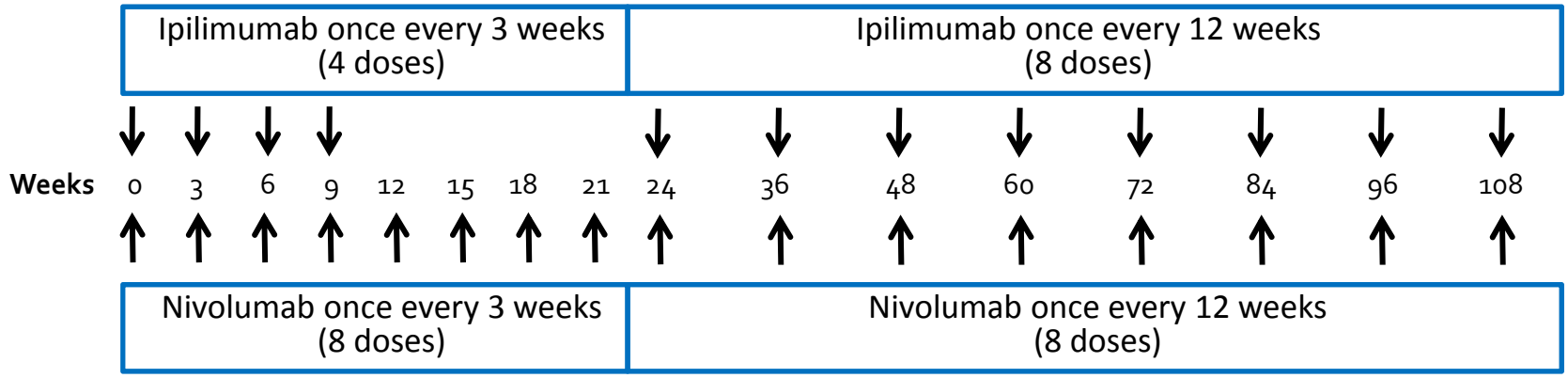
# Phase I Study: Schedule

## Concurrent Cohorts




- First tumor assessment at 12 weeks

## Sequenced Cohorts

- Following prior ipilimumab, patients received nivolumab every 2 weeks for a maximum of 48 doses
- First tumor assessment at 8 weeks

- **Tumor assessments by mWHO and immune-related response criteria**
- **Data as of Feb 2013 for 86 patients**

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# Treatment-Related Select Adverse Events

| Select Adverse Event<br>Number of Patients (%) | Concurrent Regimen All Cohorts (n=53) | | Sequenced Regimen All Cohorts (n=33) | |
|---|---|---|---|---|
| | All Gr | Gr 3-4 | All Gr | Gr 3-4 |
| Pulmonary | 3 (6) | 1 (2) | 1 (3 ) | 0 |
| Renal | 3 (6) | 3 (6) | 0 | 0 |
| Endocrinopathies | 7 (13) | 1 (2) | 3 (9) | 2 (6) |
| Uveitis | 3 (6) | 2 (4) | 0 | 0 |
| Skin | 37 (70) | 2 (4) | 8 (24) | 0 |
| Gastrointestinal | 20 (38) | 5 (9) | 3 (9) | 0 |
| Hepatic | 12 (23) | 8 (15) | 1 (3) | 0 |
| Infusion reaction | 1 (2) | 0 | 0 | 0 |
| Lipase | 10 (19) | 7 (13) | 4 (12) | 2 (6) |
| Amylase | 8 (15) | 3 (6) | 1 (3) | 1 (3) |

# Clinical Activity: Sequenced Regimen

| Nivolumab (mg/kg) | Response Evaluable Patients n | CR n | PR n | Objective Response Rate % [95% CI] | Aggregate Clinical Activity Rate % [95% CI] | ≥80% Tumor Reduction at 8 wk n (%) |
|---|---|---|---|---|---|---|
| 1 | 16 | 1 | 5 | 38 [15-65] | 69 [41-89] | 4 (25) |
| 3 | 14 | 0 | 0 | 0 | 14 [2-43] | 0 |
| Sequenced | 30 | 1 | 5 | 20 [8-39] | 43 [26-63] | 4 (13) |

- With sequenced nivolumab after prior ipilimumab, 20% of patients had confirmed objective responses
- 13% of patients had ≥80% tumor reduction at their first scheduled 8-week tumor assessment (rapid and deep responses)

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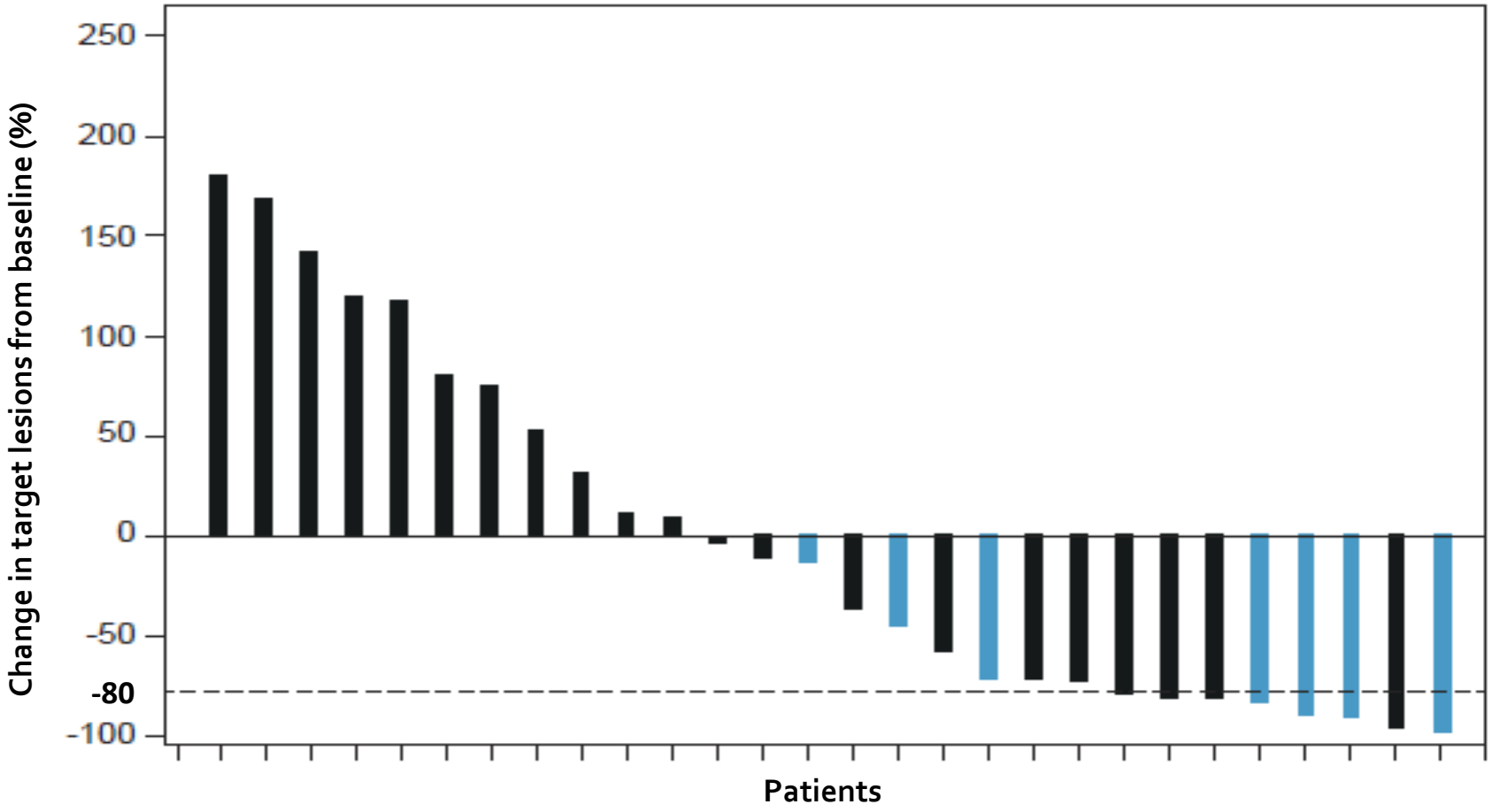
# Best Responses in All Evaluable Patients in Sequenced Cohorts




■ Patients who had radiographic progression with prior ipilimumab treatment.

■ Patients who had stable disease with prior ipilimumab treatment.

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# Clinical Activity: Concurrent Regimen

| Dose (mg/kg) | | Response Evaluable Patients n | CR n | PR n | Objective Response Rate % [95% CI] | Aggregate Clinical Activity Rate % [95% CI] | ≥80% Tumor Reduction at 12 wk n (%) |
|---|---|---|---|---|---|---|---|
| Nivolumab | Ipilimumab | | | | | | |
| 0.3 | 3 | 14 | 1 | 2 | 21 [5-51] | 50 [23-77] | 4 (29) |
| 1 | 3 | 17 | 3 | 6 | 53 [28-77] | 65 [38-86] | 7 (41) |
| 3 | 1 | 15 | 1 | 5 | 40 [16-68] | 73 [45-92] | 5 (33) |
| 3 | 3 | 6 | 0 | 3 | 50 [12-88] | 83 [36-100] | 0 |
| Concurrent | | 52 | 5 | 16 | 40 [27-55] | 65 [51-78] | 16 (31) |

- With 1 mg/kg nivolumab + 3 mg/kb ipilimumab, 53% of patients had confirmed objective responses (3 CRs and 6 PRs)
- All 9 of these had ≥80% tumor reduction, 7 at 12 weeks and 2 at their first assessment, which was after week 12
- ≥80% tumor reductions appear infrequently (<10%) in the nivolumab and ipilimumab monotherapy experiences

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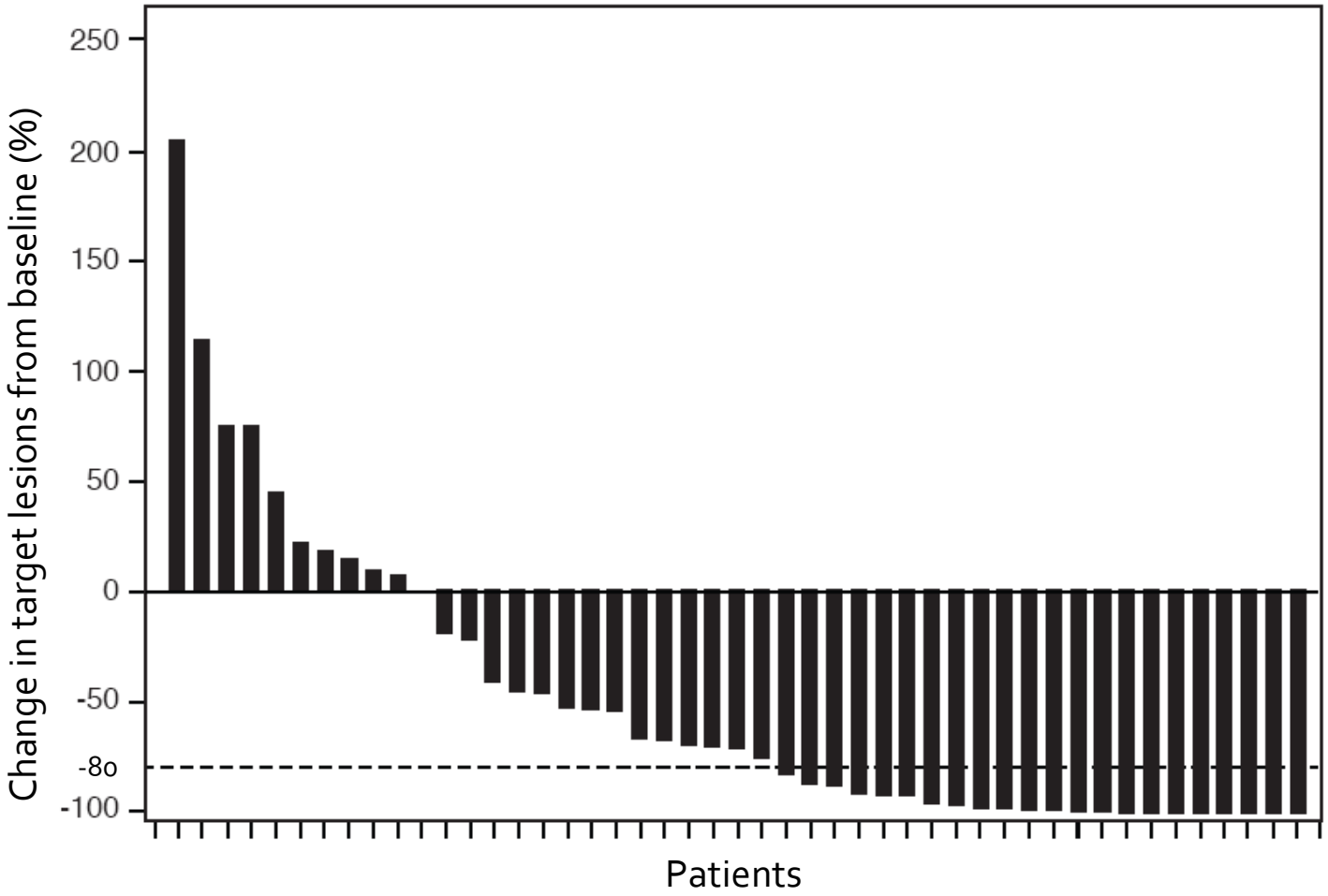
# Best Responses in All Evaluable Patients in Concurrent Cohorts

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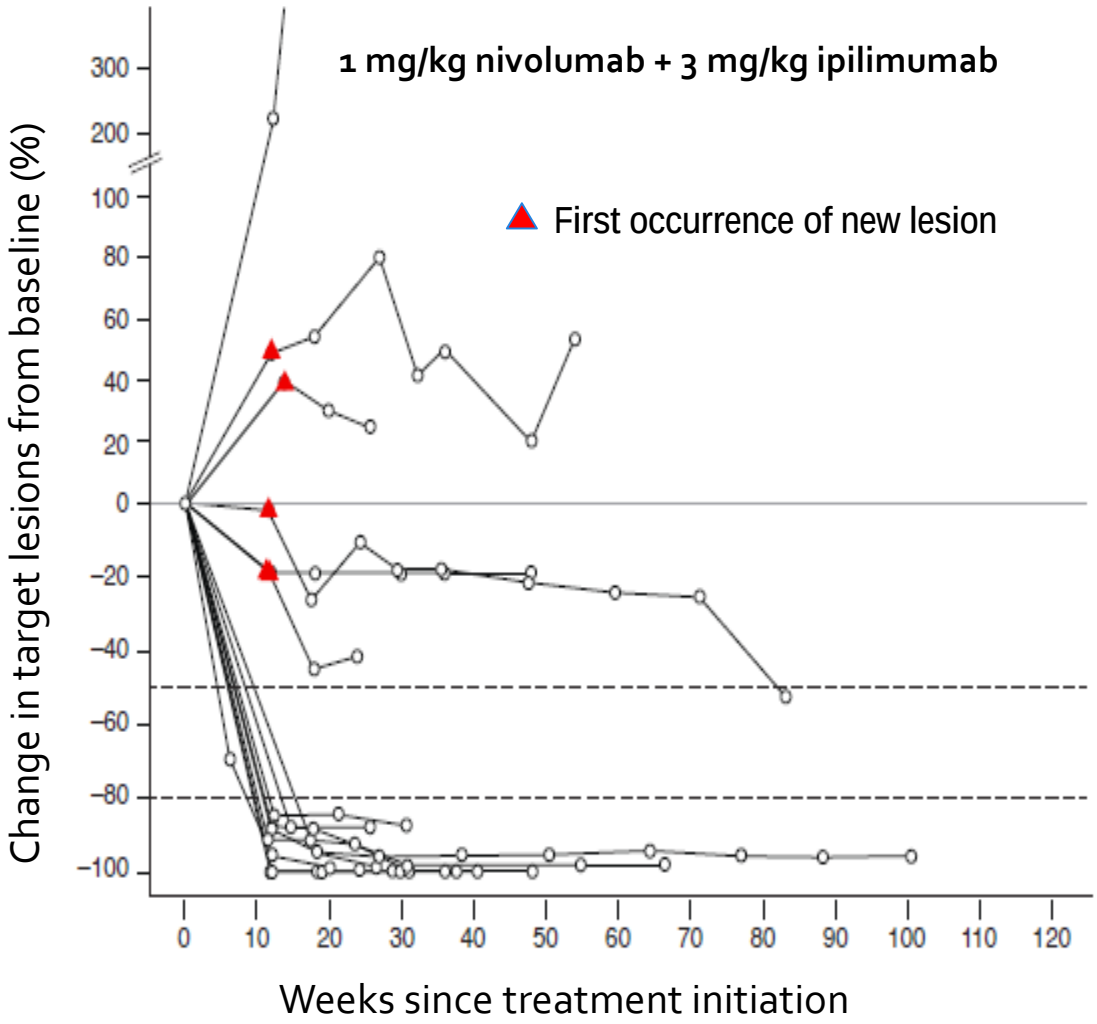
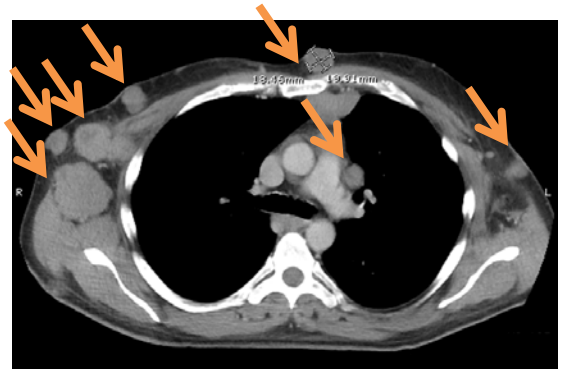
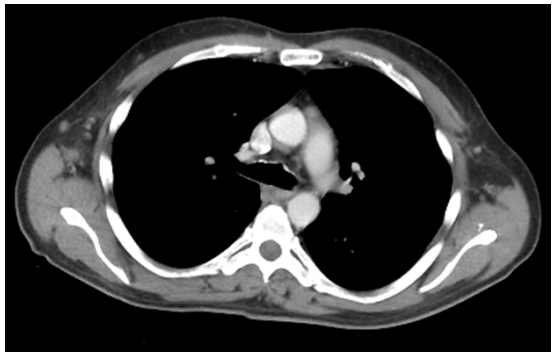
# Rapid and Durable Changes in Target Lesions



Pre-treatment



12 weeks

- A 52-year-old patient presented with extensive nodal and visceral disease
- Baseline LDH was elevated (2.3 x ULN); symptoms included nausea and vomiting
- Within 4 wk, LDH normalized and symptoms resolved
- At 12 wk, there was marked reduction in all areas of disease as shown

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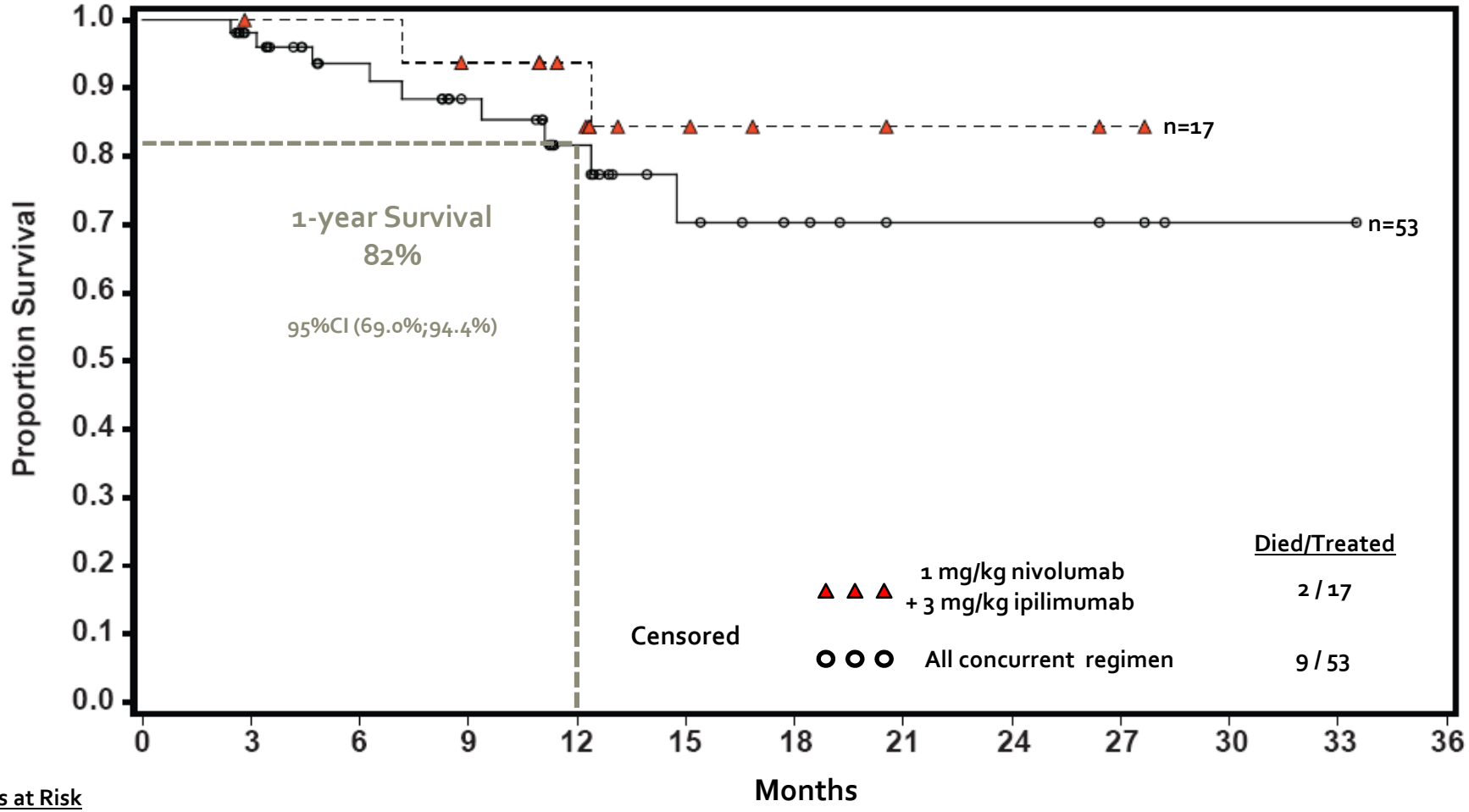
# Preliminary Survival of Patients Treated With Concurrent Regimen




**Patients at Risk**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 mg + 3 mg | 17 | 16 | 16 | 14 | 10 | 5 | 3 | 2 | 2 | 1 | 0 | 0 | 0 |
| All concurrent | 53 | 47 | 36 | 29 | 19 | 10 | 7 | 4 | 4 | 3 | 1 | 1 | 0 |

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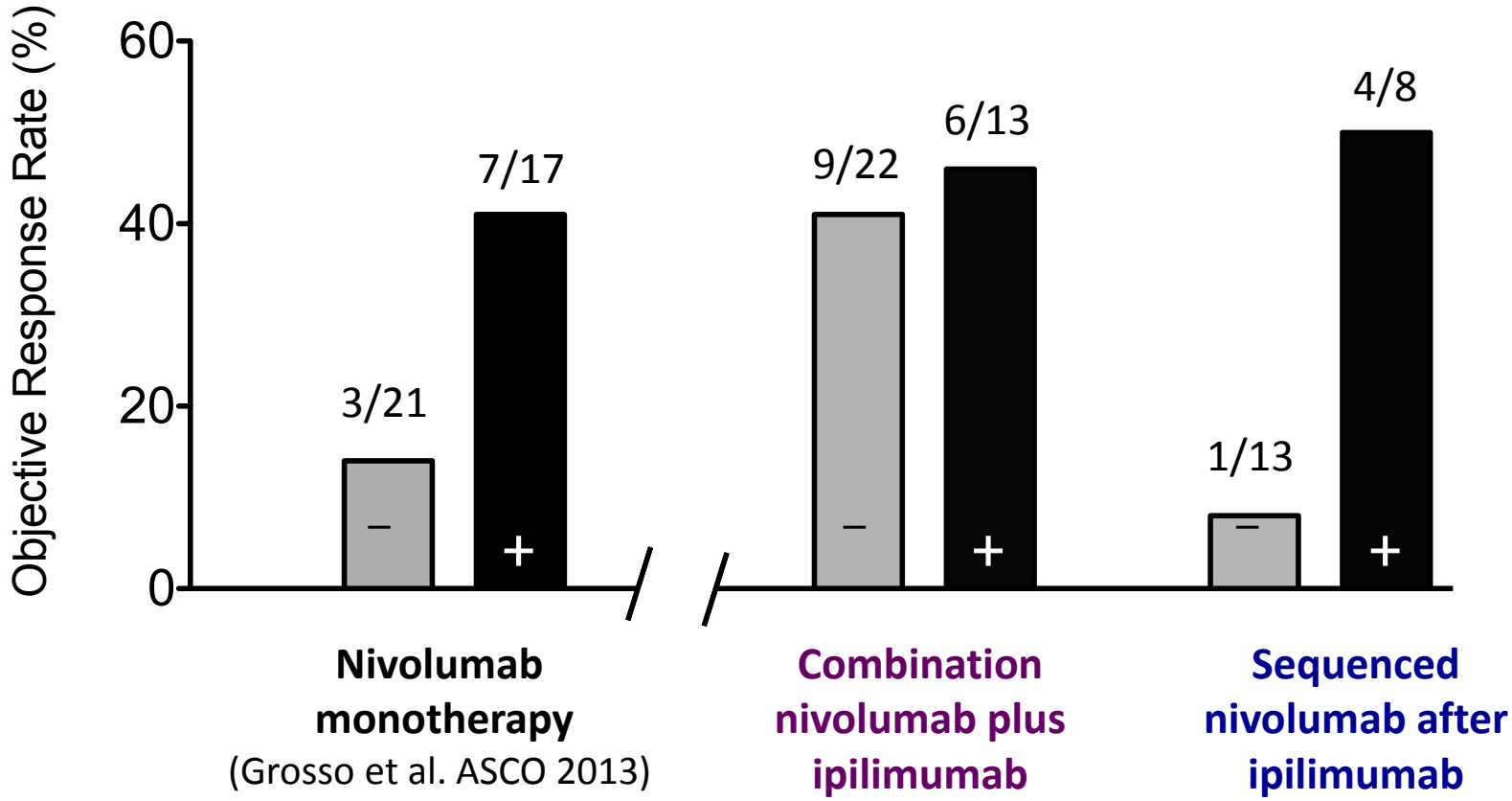
# Evaluating PD-L1 status as a candidate biomarker

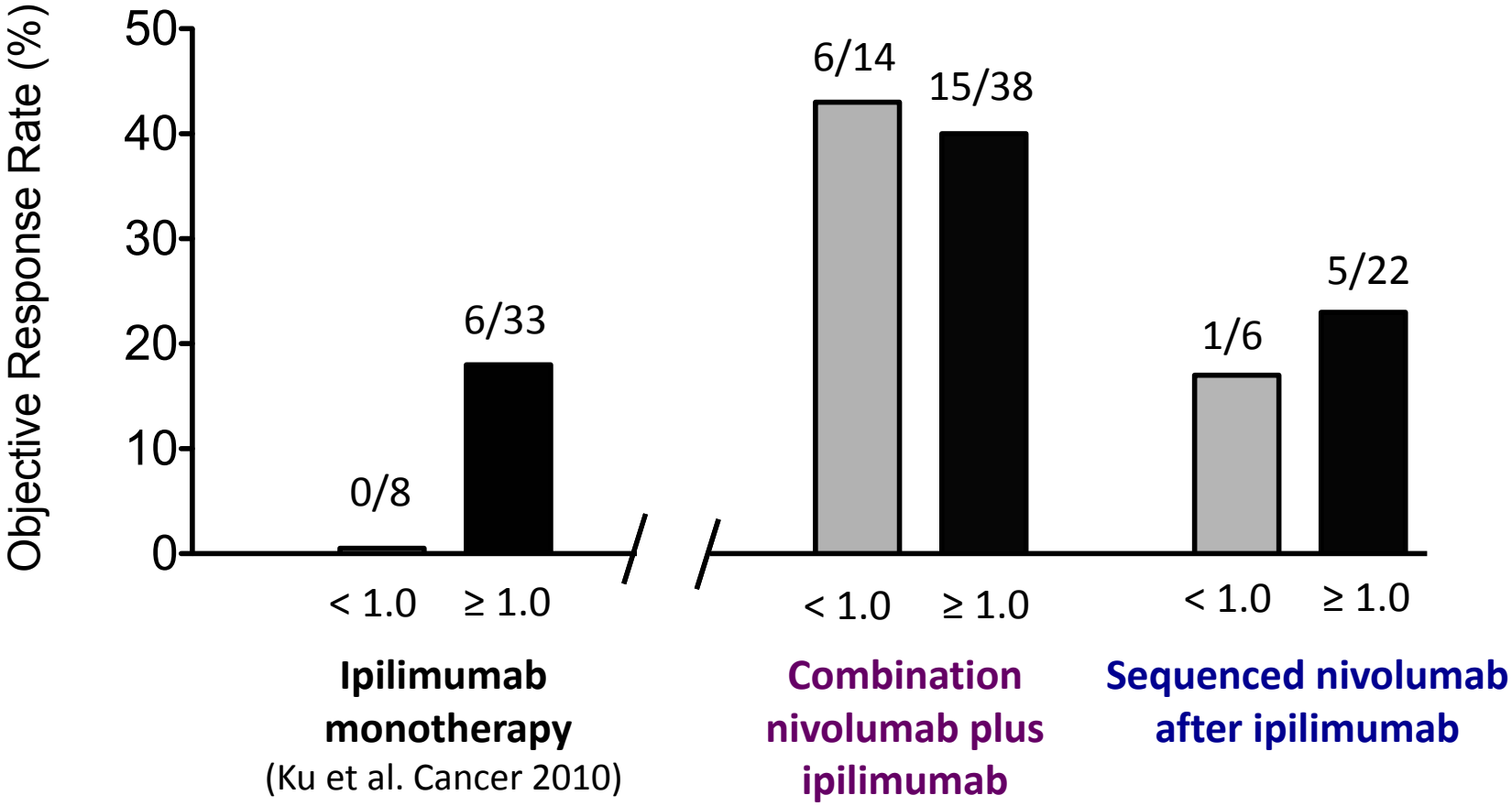



Positivity rate = 45% (17/38, monotherapy), 37% (13/35, combination therapy), and 38% (8/21, sequenced therapy)



Callahan et al., ASCO, 2013

# Evaluating ALC as a candidate biomarker

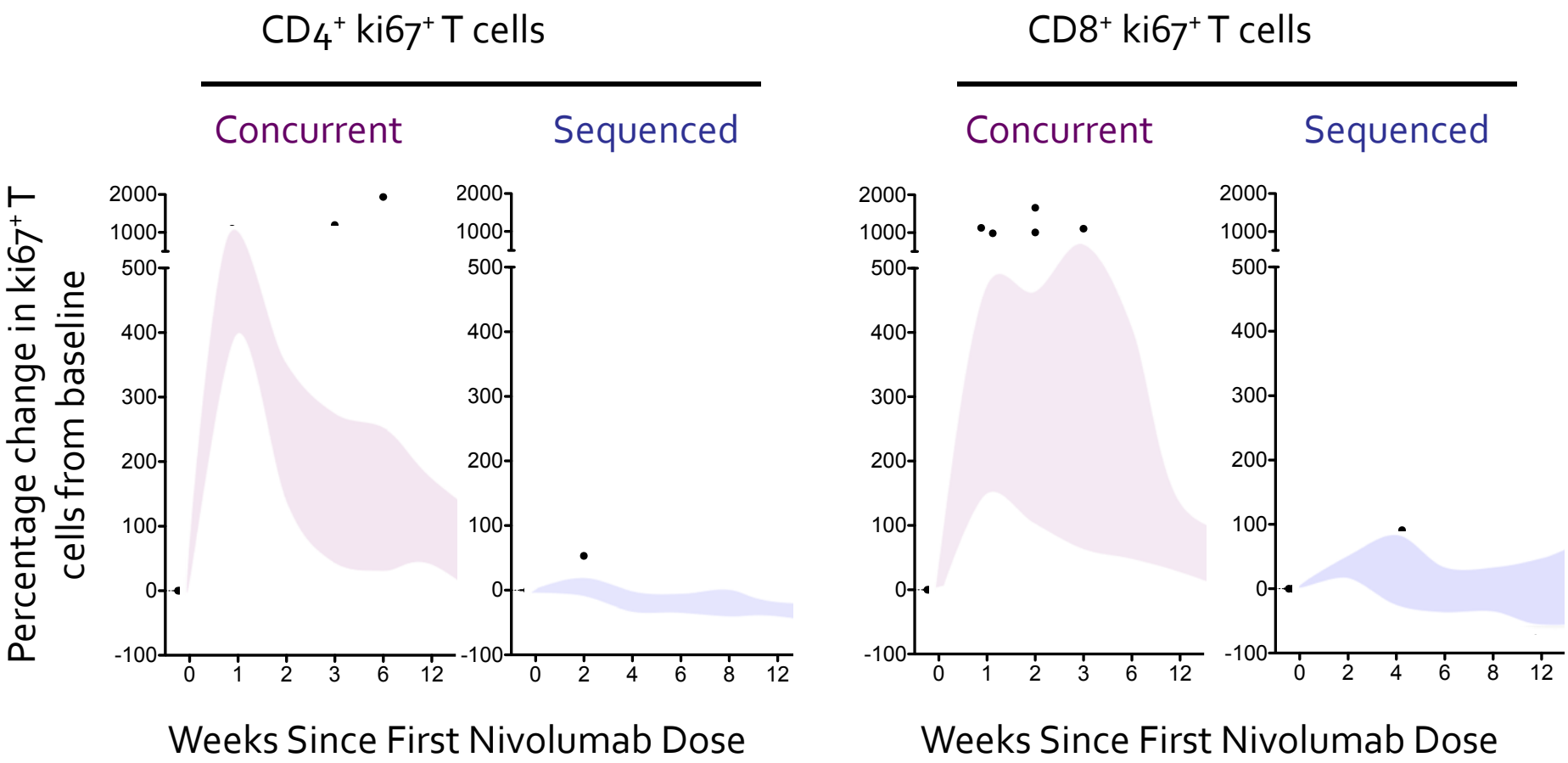



Low ALC rate = 20% (8/41, monotherapy), 27% (14/52, combination therapy), and 21% (6/28, sequenced therapy)



Callahan et al., ASCO, 2013

# Increased frequency of activated **(ki67$^+$)** CD4$^+$ and CD8$^+$ T cells with concurrent nivolumab + ipilimumab




Median with interquartile range



Callahan et al., ASCO, 2013

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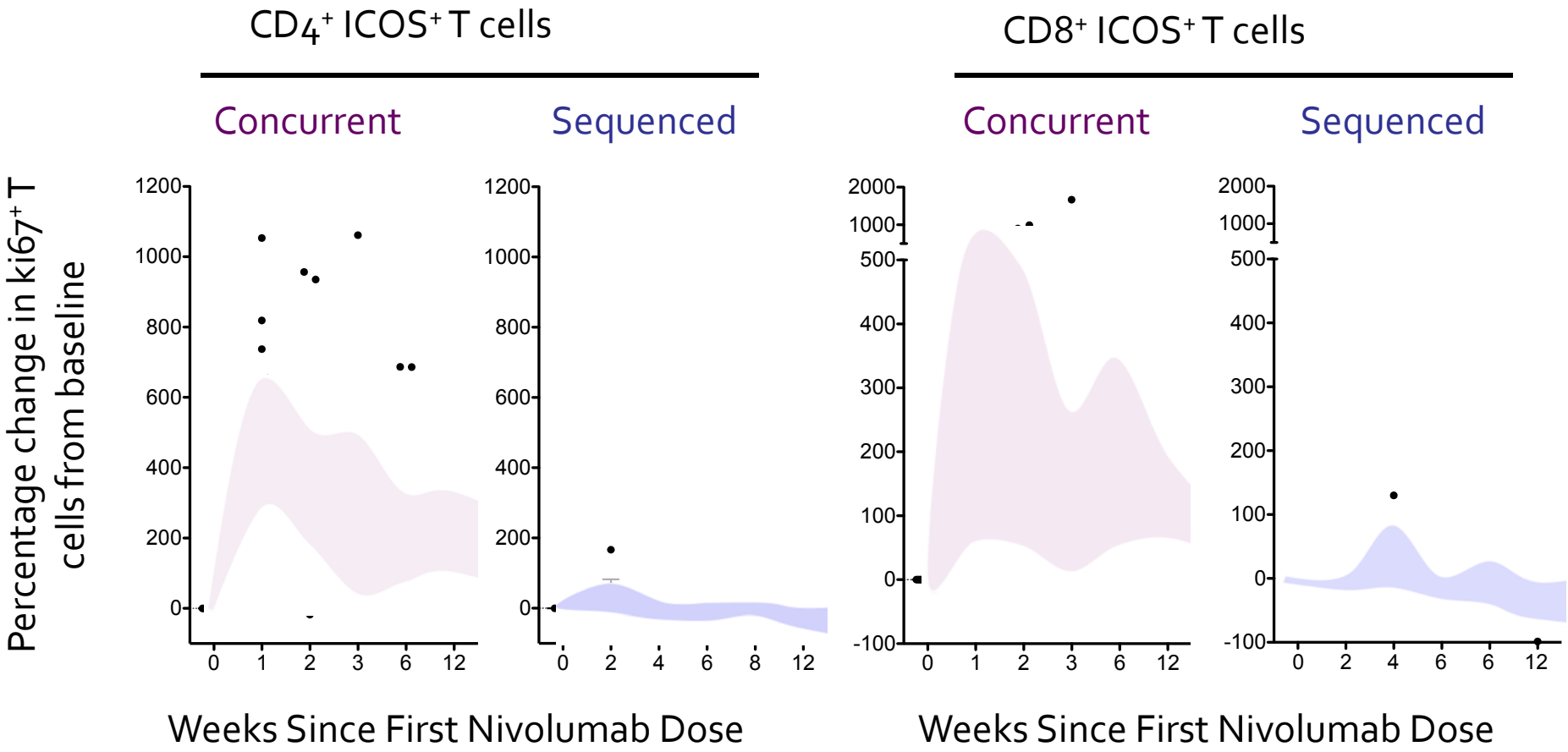
# Increased frequency of activated **(ICOS$^+$)** $CD4^+$ and $CD8^+$ T cells with concurrent nivolumab + ipilimumab




Callahan et al., ASCO, 2013

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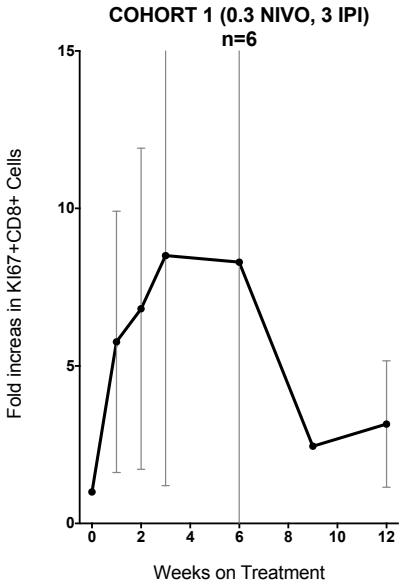
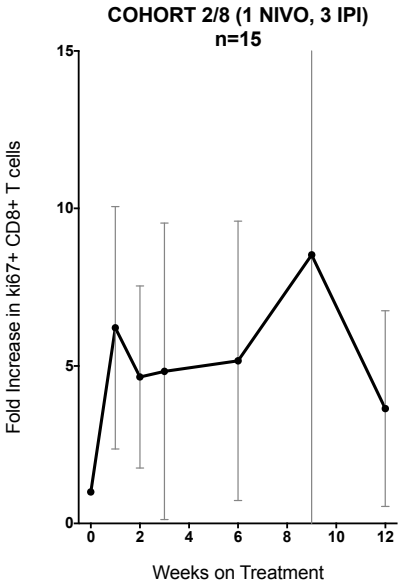
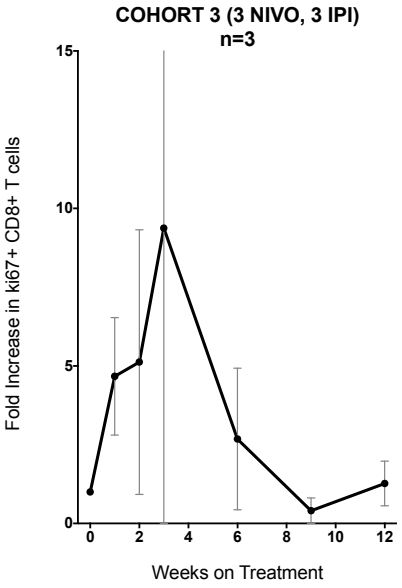
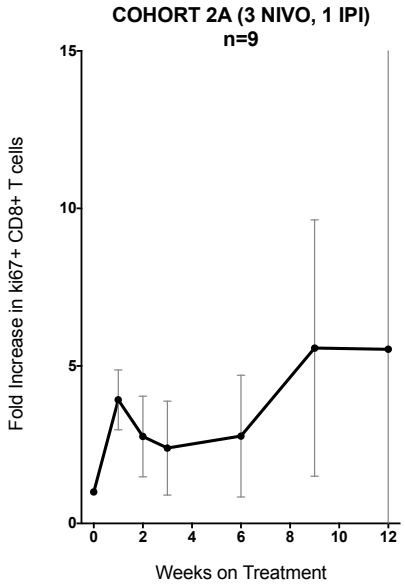
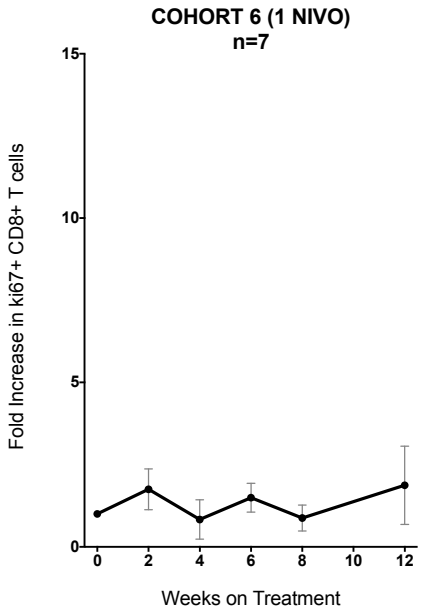
# Ki67 staining of CD8+ T cells

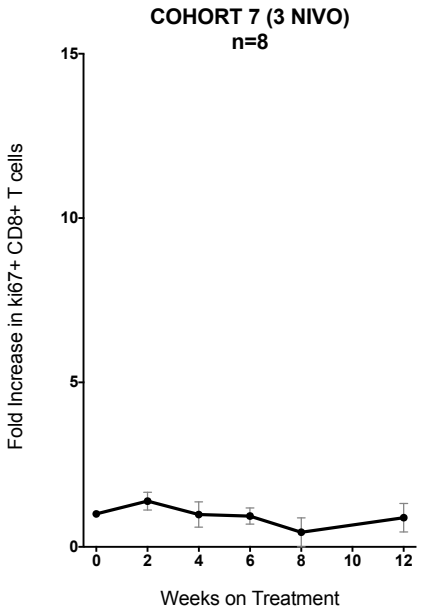
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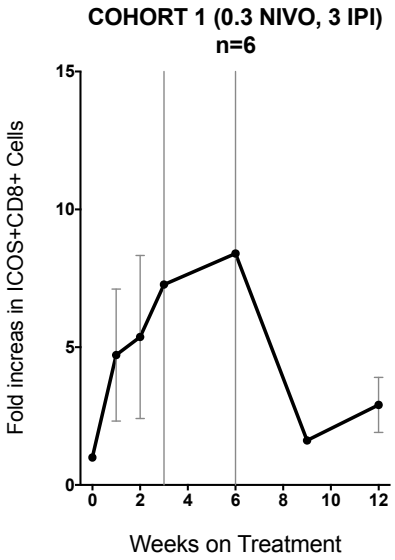
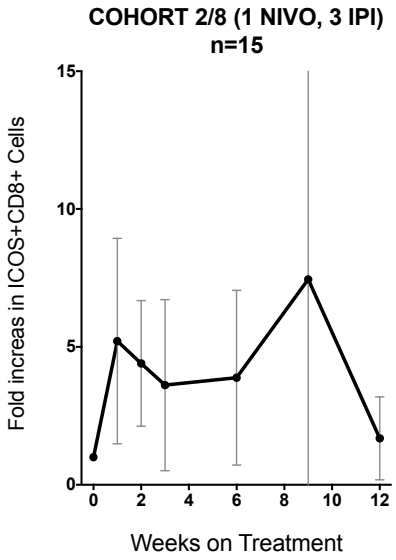
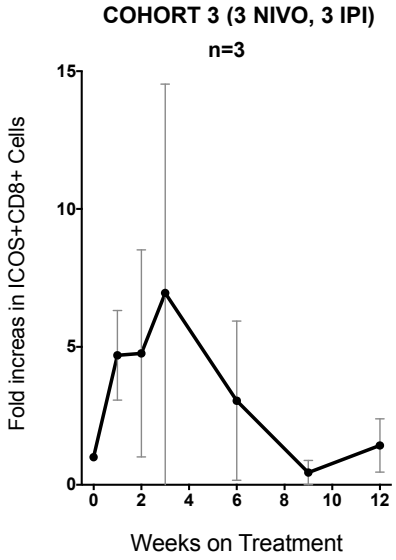
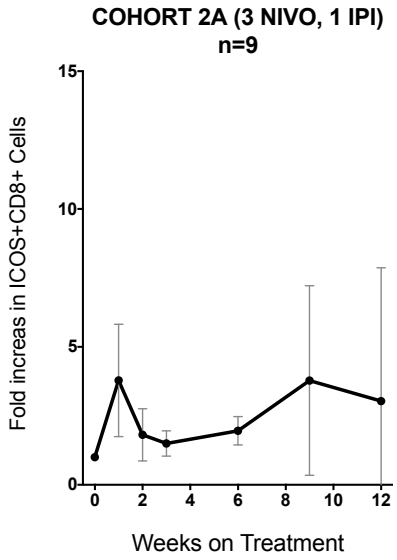
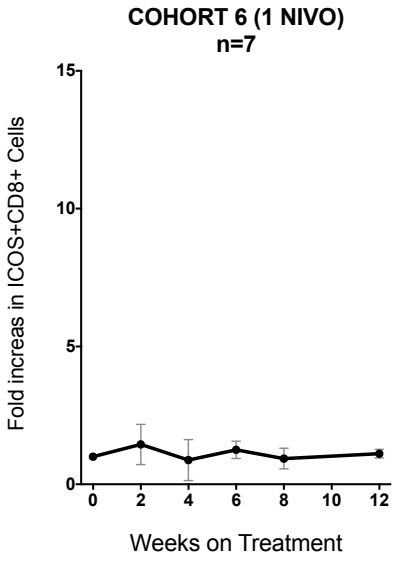
# ICOS Staining of CD8+ T cells by Cohort

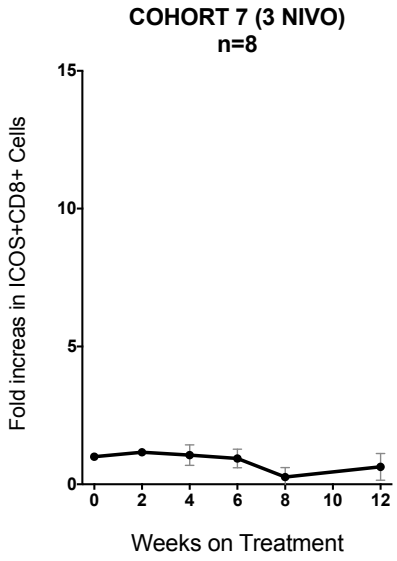
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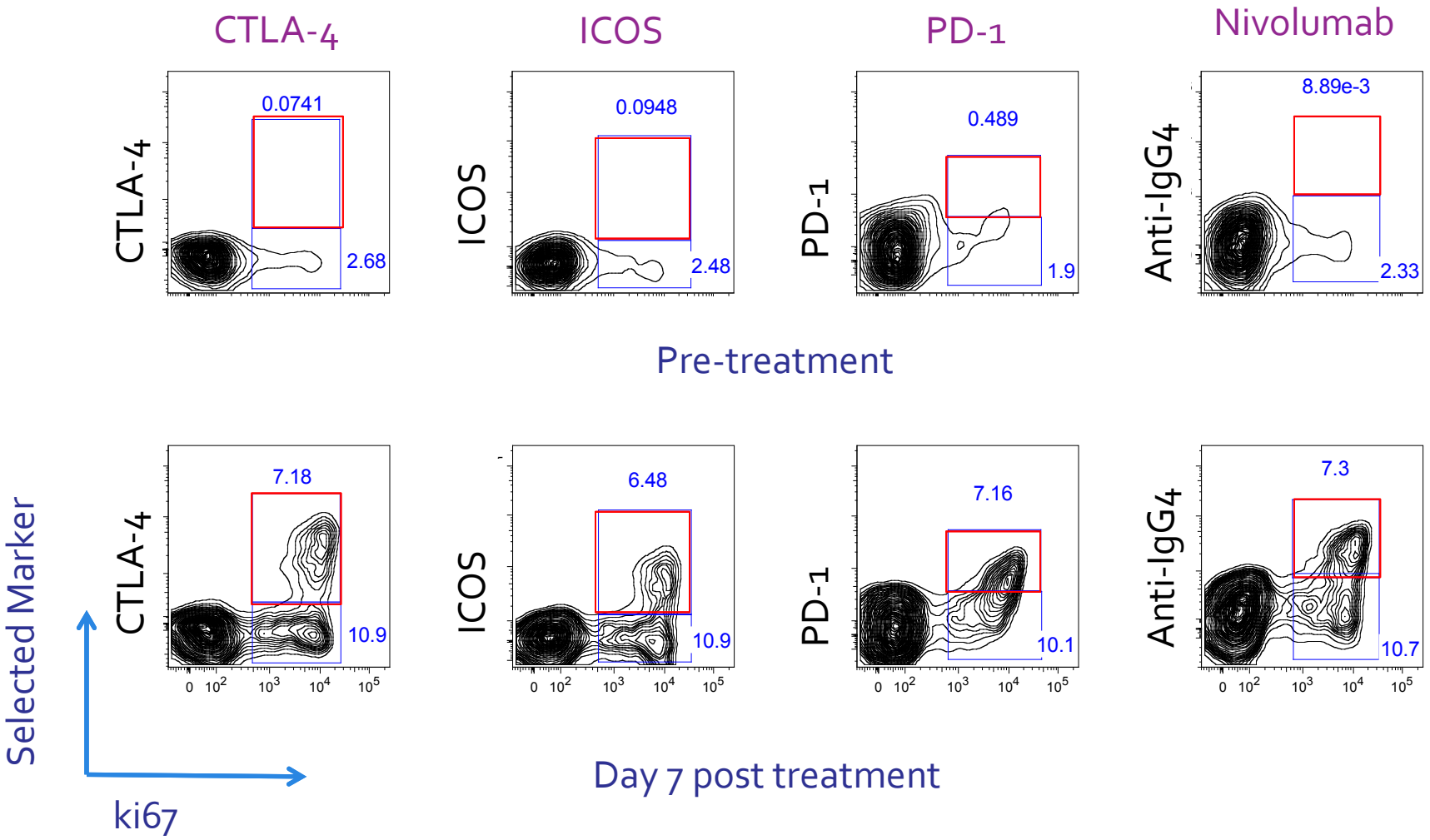
# Phenotype of activated peripheral blood CD8+ T cells after combination




Callahan et al., ASCO, 2013

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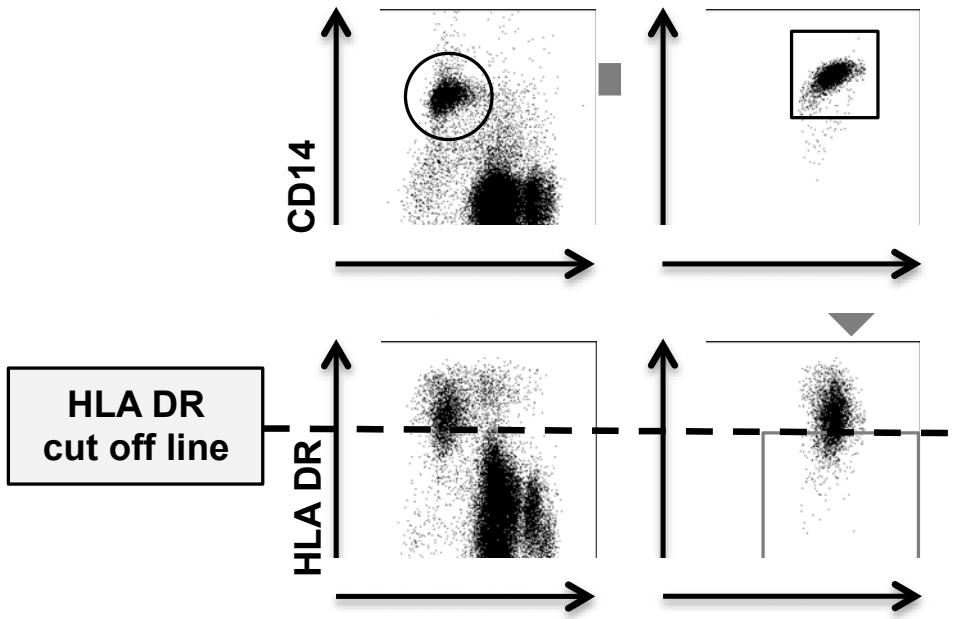
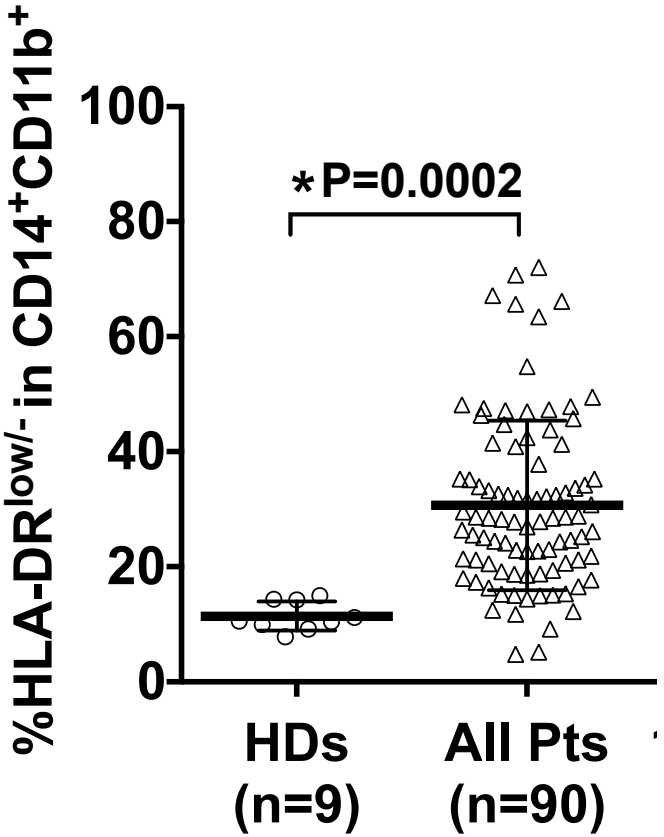
# Metastatic Melanoma Patients Have Increased MDSC




Kitano S, Postow M, et al. ASCO 2012

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# Summary

- Checkpoint blockade is an effective treatment with durable responses in melanoma
- Intense study of both predictive and pharmacodynamic biomarkers of response and toxicity will allow for more intelligent patient selection and novel target discovery.
- Combination therapy will be necessary for immunotherapy to achieve full potential (other immune modulators, vaccines, radiation, chemotherapy, targeted therapy, anti-angiogenic therapy).
- Combined checkpoint blockade may allow contraints for monotherapy to be overcome and is now being studied in phase 2 and phase 3 trials for melanoma.