”Sequencing and Combinations of Targeted Therpies and Immunotherapies”

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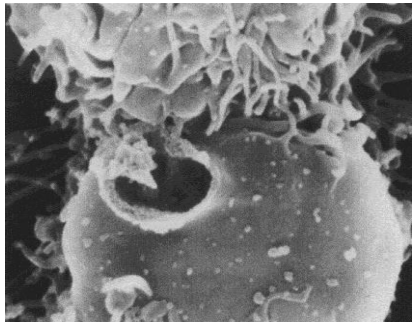

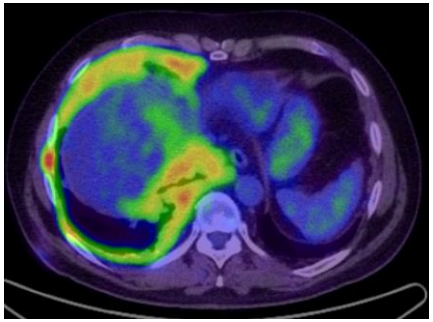

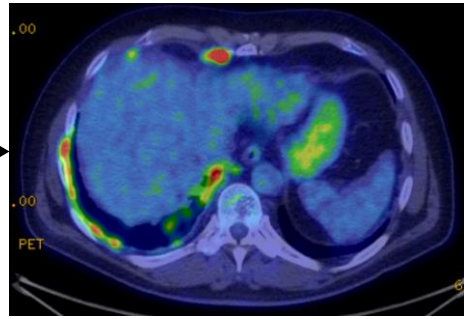

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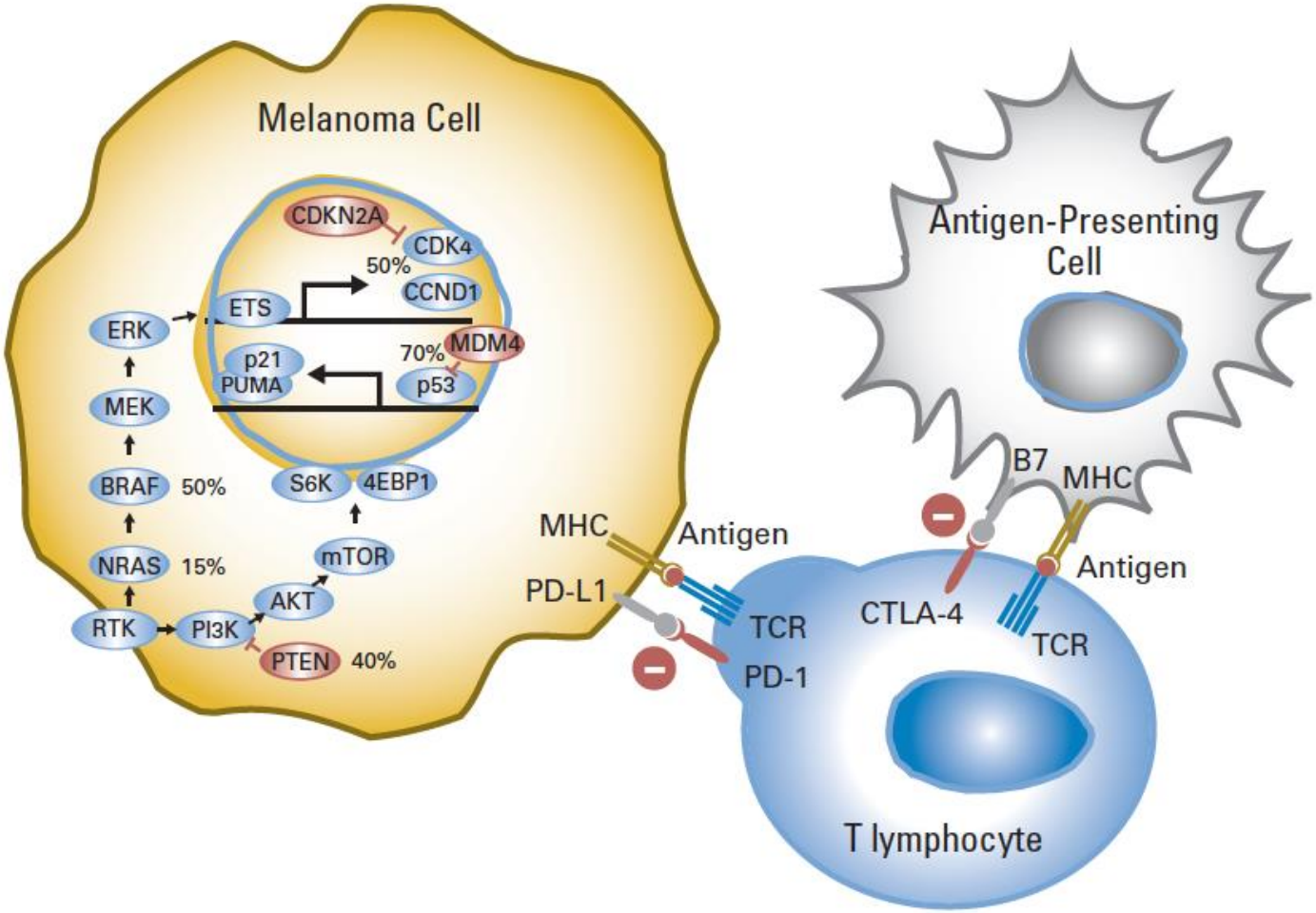
Disclosure Information

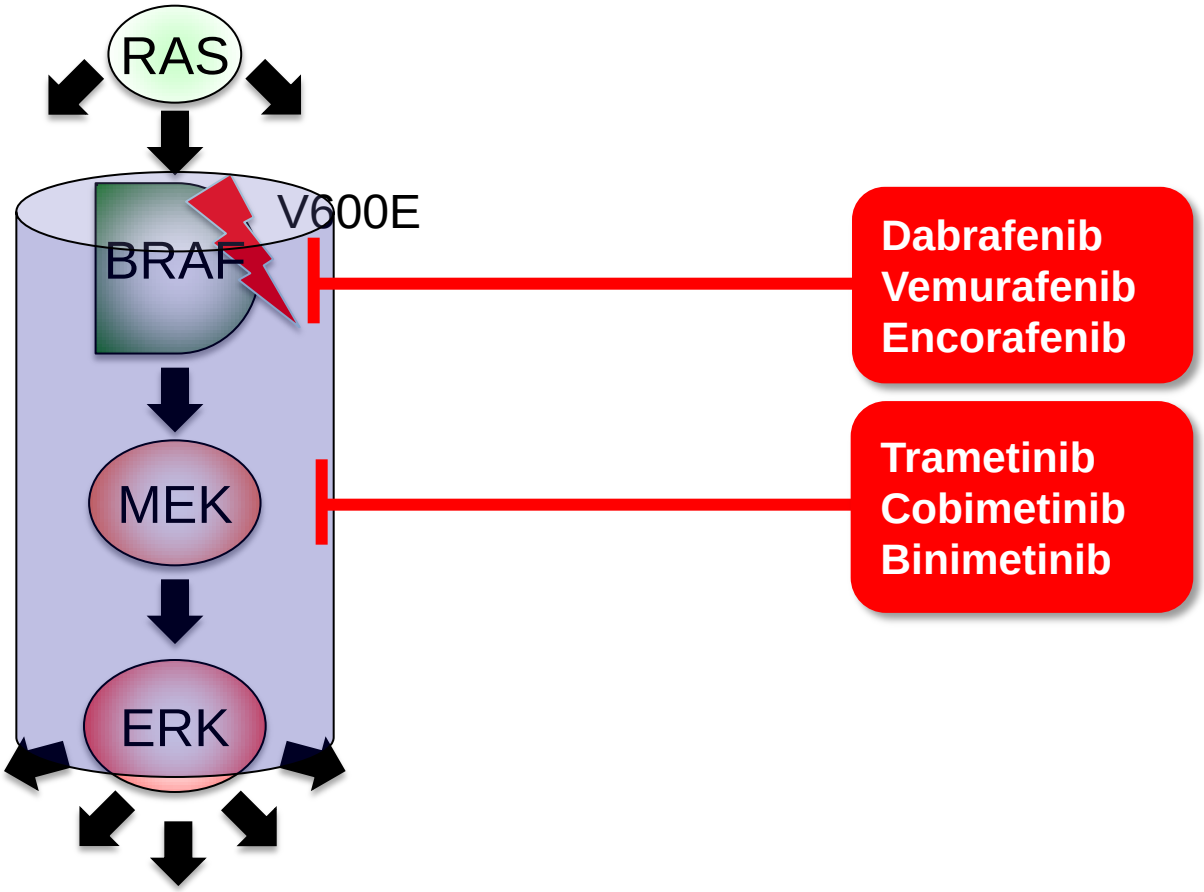
- I have the following financial relationships to disclose
  - Research support from: Pfizer, Celgene & Ventana
  - Consultant: Provectus

Melanoma an Immunogenic Oncogene-driven Cancer.



McArthur & Ribas, *J Clinical Oncology*, 2013

Therapies targeting the BRAF/MEK/ERK pathway



COMBI-v Study Design

N = 1645 screened

Key inclusion criteria

- *BRAF* V600E/K mutation
- Stage IIIC or IV cutaneous melanoma
- Treatment naive advanced or metastatic melanoma
- ECOG PS 0 or 1
- No brain metastases, unless:
  - Treated
  - Stable ≥ 12 weeks

Stratification

- *BRAF* mutant V600E vs K
- LDH (> ULN vs ≤ ULN)

N = 704

Dabrafenib + Trametinib
150 mg BID + 2 mg QD
n = 352

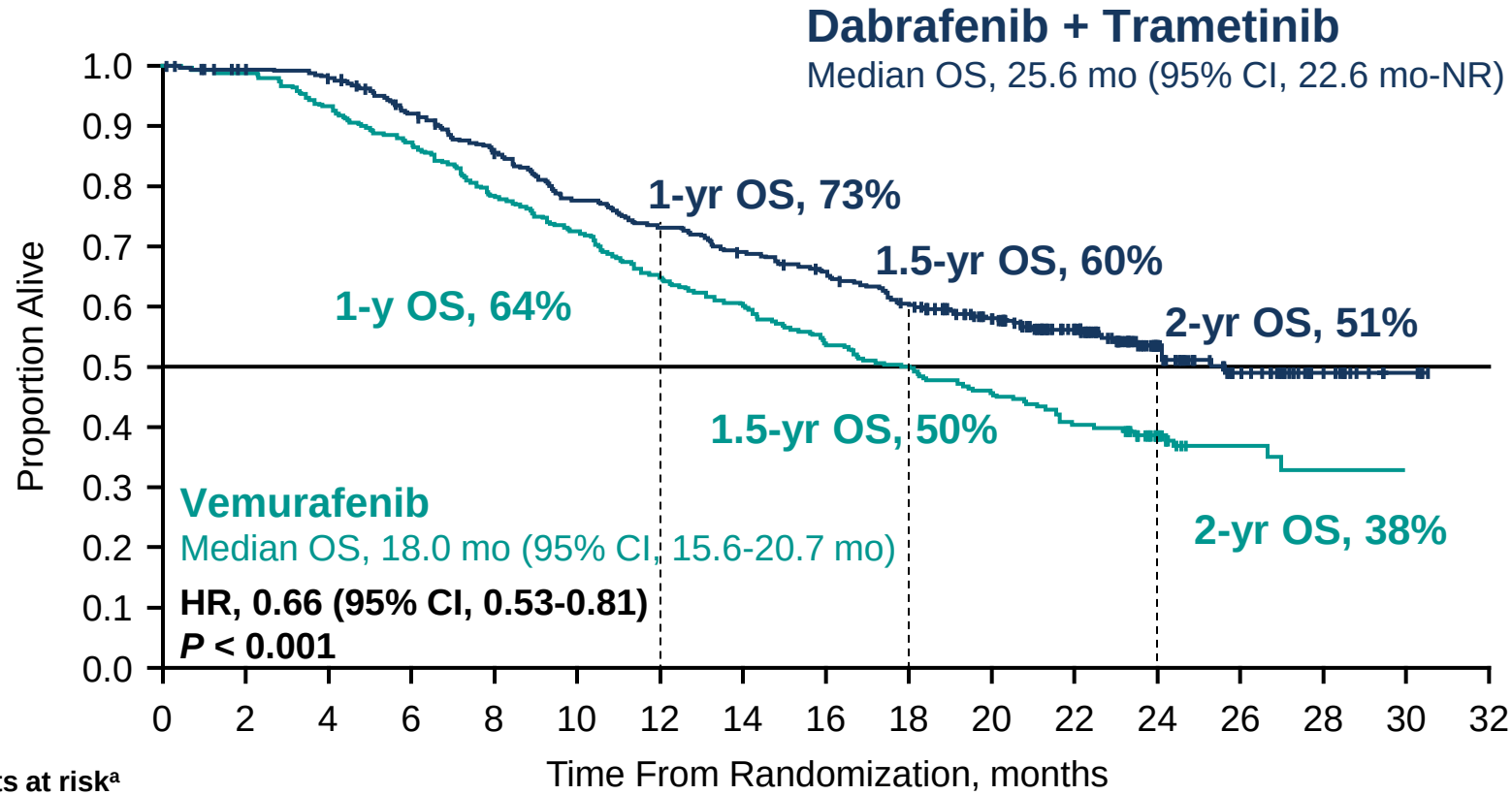
Vemurafenib
960 mg BID
n = 352

Interim OS Analysis (202 events)

Primary OS Analysis (280 events planned)

- **Primary Endpoint:** OS
- **Secondary Endpoints:** PFS, ORR, DOR, safety

COMBI-v: Overall Survival



Patients at risk[a]

Dabrafenib + trametinib	352	342	336	311	286	260	245	230	217	198	173	128	68	38	16	5	0
Vemurafenib	352	341	315	286	252	231	201	187	166	152	129	88	46	28	7	0	0

[a] Data cutoff: March 2015.

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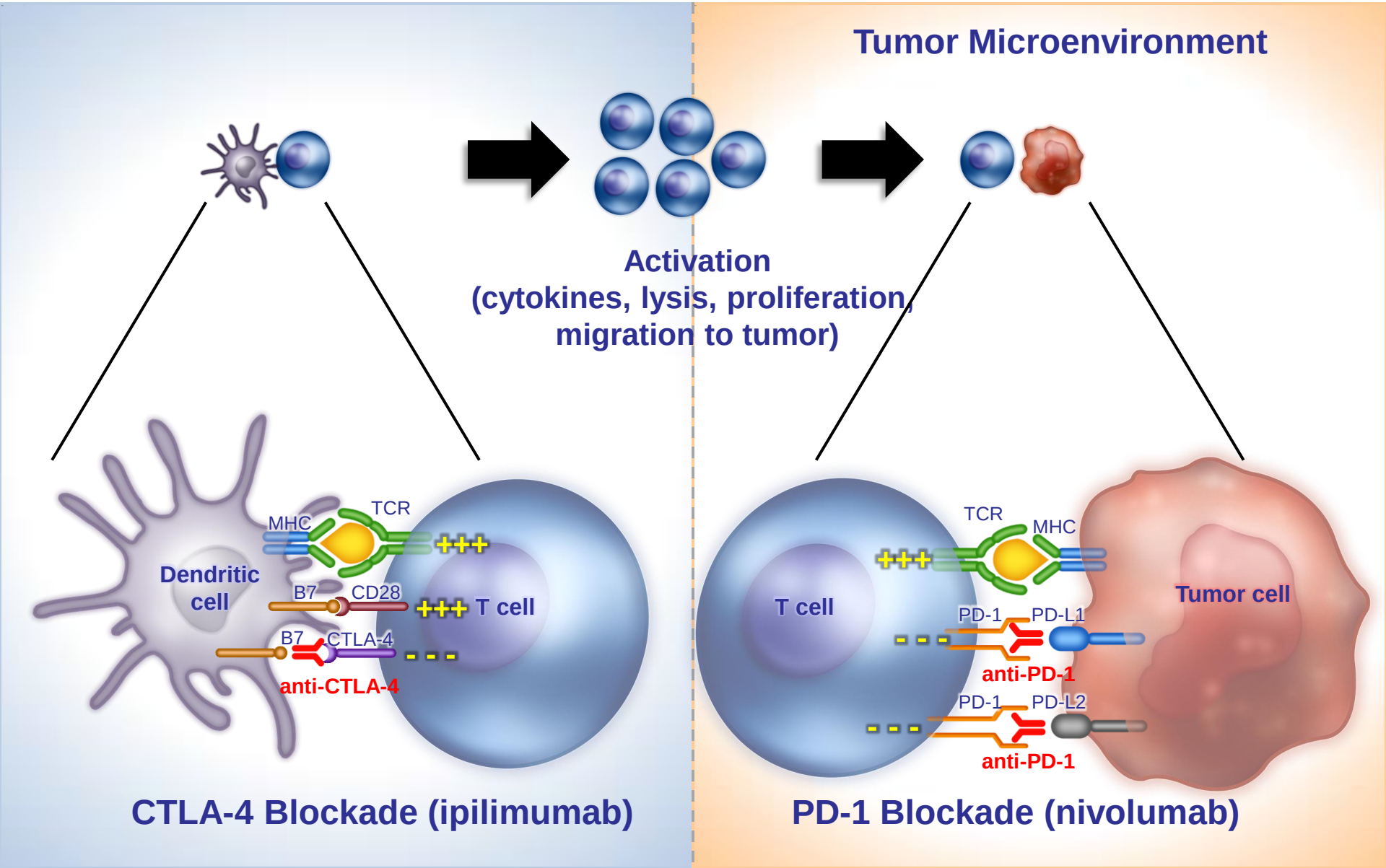
Immune checkpoint antibodies



KEYNOTE-006 (NCT01866319): International,[a] Randomized, Phase III Study

Patients

- Unresectable, stage III or IV melanoma
- ≤1 prior therapy, excluding anti–CTLA-4, PD-1, or PD-L1 agents
- Known *BRAF* status[b]
- ECOG PS 0-1
- No active brain metastases
- No serious autoimmune disease

R 1:1:1

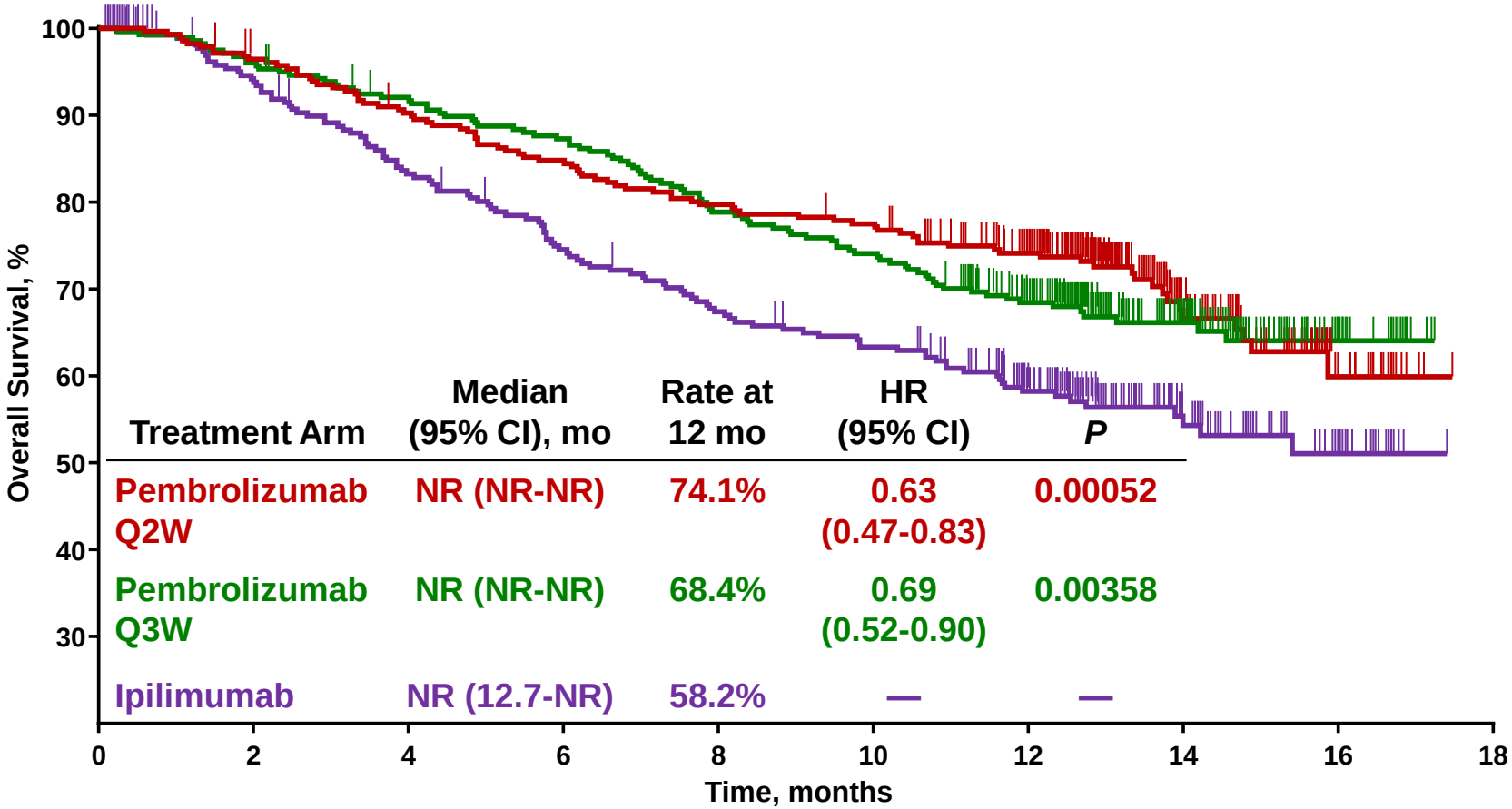
- Pembrolizumab 10 mg/kg IV Q2W
- Pembrolizumab 10 mg/kg IV Q3W
- Ipilimumab 3 mg/kg IV Q3W x 4 doses

Stratification factors:

- ECOG PS (0 vs 1)
- Line of therapy (first vs second)
- PD-L1 status (positive[c] vs negative)

- Primary end points: PFS and OS
- Secondary end points: ORR, duration of response, safety

OS at the Second Interim Analysis (IA2)



Treatment Arm	Median (95% CI), mo	Rate at 12 mo	HR (95% CI)	*P*
Pembrolizumab Q2W	NR (NR-NR)	74.1%	0.63 (0.47-0.83)	0.00052
Pembrolizumab Q3W	NR (NR-NR)	68.4%	0.69 (0.52-0.90)	0.00358
Ipilimumab	NR (12.7-NR)	58.2%	—	—

No. at risk

279	266	248	233	219	212	177	67	19	0
277	266	251	238	215	202	158	71	18	0
278	242	212	188	169	157	117	51	17	0

Analysis cut-off date: March 3, 2015.

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Ribas et al, AACR, 2015

CA209-067: Study Design

Randomized, double-blind, phase III study to compare NIVO + IPI or NIVO alone to IPI alone

Unresectable or Metatastic Melanoma

- **Previously untreated**
- **945 patients**

Randomize 1:1:1

Stratify by:

- **PD-L1 expression ***
- **BRAF status**
- **AJCC M stage**

N=314 → **NIVO 1 mg/kg + IPI 3 mg/kg Q3W for 4 doses then NIVO 3 mg/kg Q2W**

N=316 → **NIVO 3 mg/kg Q2W + IPI-matched placebo**

N=315 → **IPI 3 mg/kg Q3W for 4 doses + NIVO-matched placebo**

***Treat until progression** or unacceptable toxicity*

**Patients could have been treated beyond progression under protocol-defined circumstances.

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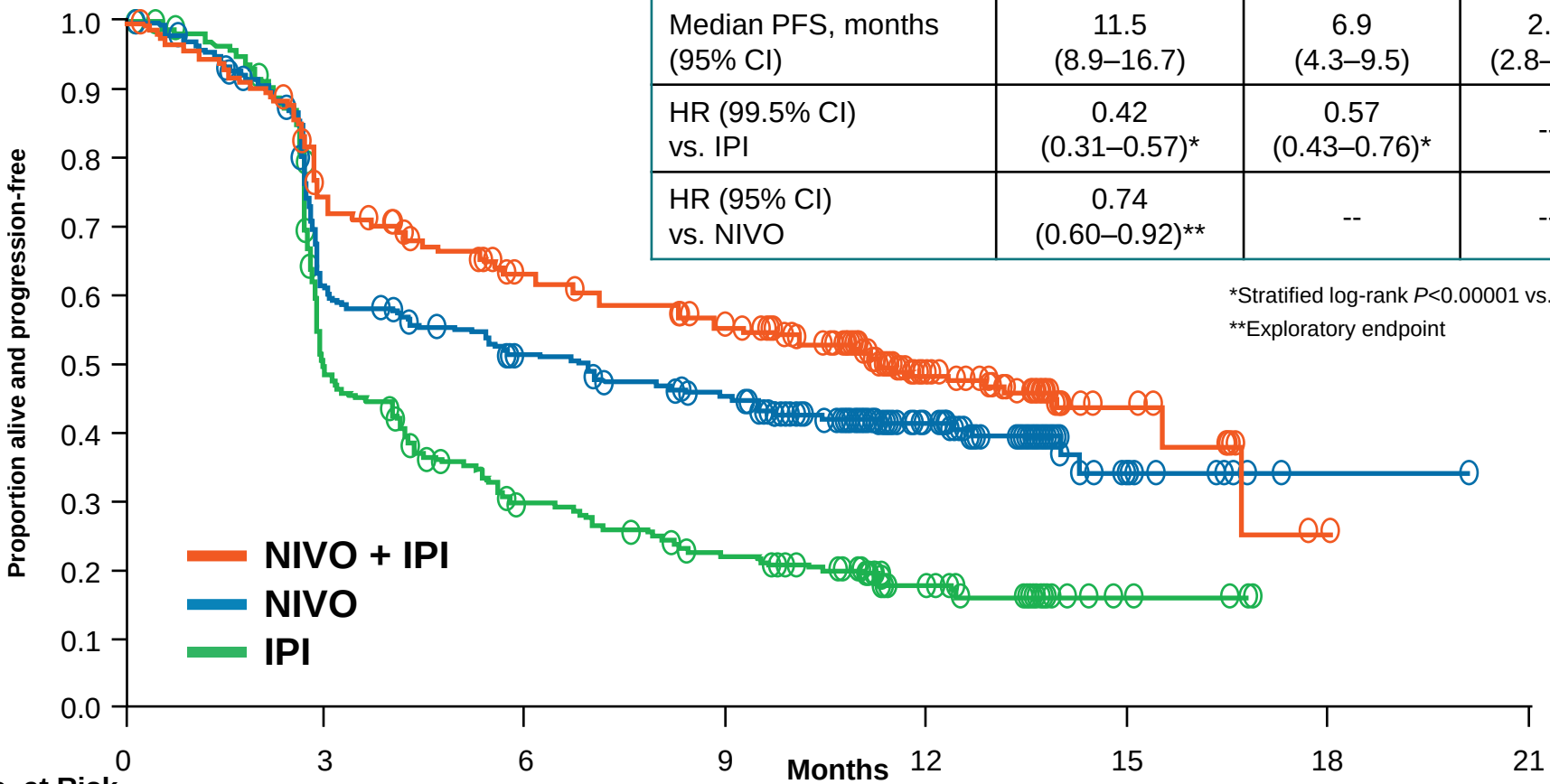
Wolchok, ASCO, 2015

PFS (Intent-to-Treat)

	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.74 (0.60–0.92)**	--	--

*Stratified log-rank *P*<0.00001 vs. IPI

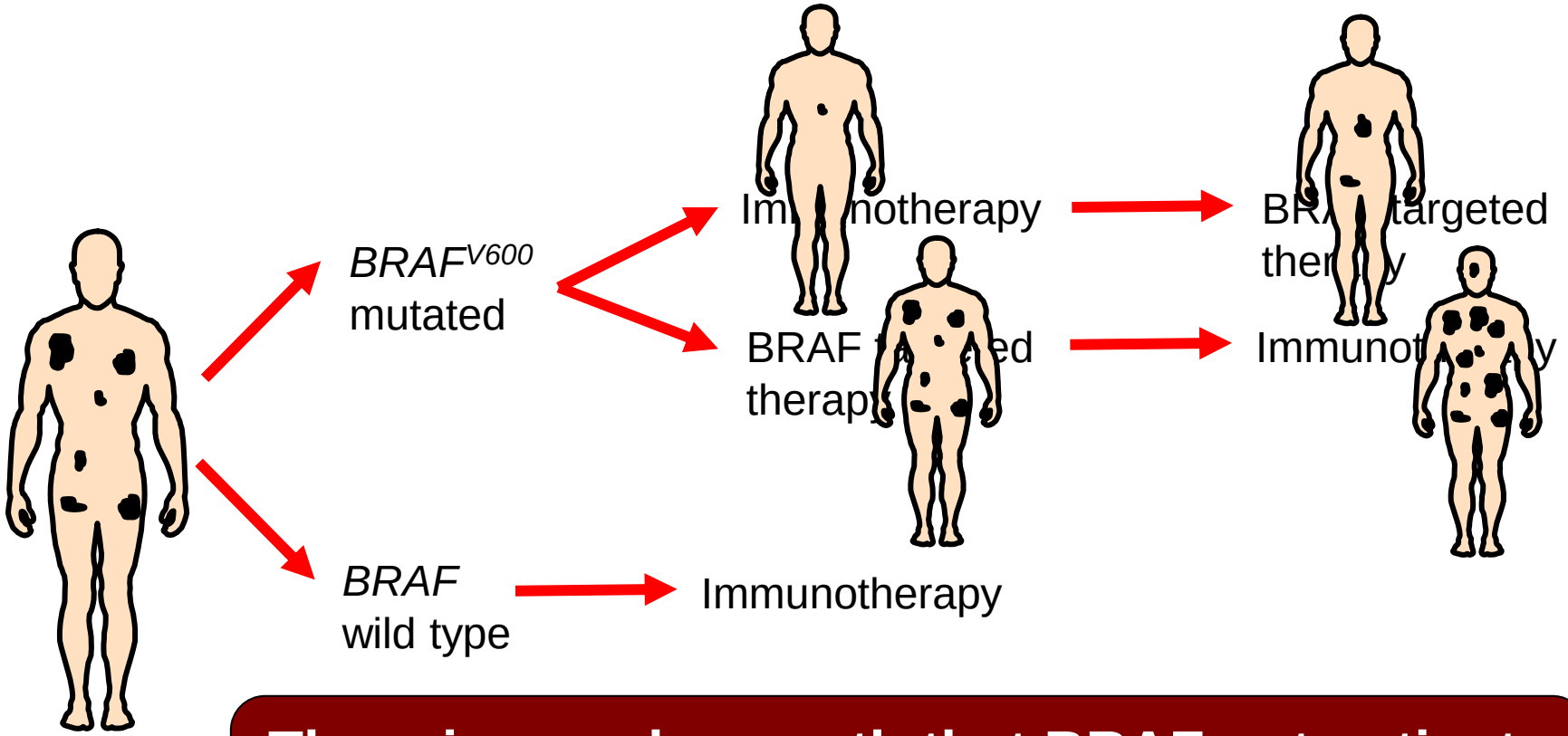
**Exploratory endpoint



No. at Risk								
NIVO + IPI	314	219	173	151	65	11	1	0
NIVO	316	177	147	124	50	9	1	0
IPI	315	137	77	54	24	4	0	0

Wolchok et al, ASCO, 2015

Treatment pathways for a patient with metastatic melanoma



There is an urban myth that BRAFmut patients do badly on immunotherapy in the second line

Slide courtesy of A. Ribas

EA6134: Ipi/Nivo to D/T vs D/T to Ipi/Nivo

ECOG PS
1. 0
2. 1

LDH
1. Normal
2. Elevated

→ **RANDOMIZE**

Arm 1:

Ipi 3/Nivo 1 mg/kg/ q 3wks x 4 + Maint Nivo → **Dabra 150 BID / Trame 2 mg Qd** → PD

Arm 2:

Dabra 150 BID / Trame 2 mg Qd → **Ipi 3/Nivo 1 mg/kg q 3wks x 4**

+ Maint Nivo → PD

PIs: Michael Atkins (ECOG), Bartosz Chmielowski (SWOG)
Open to accrual

Slide courtesy of A. Ribas

SEquential COMBo Immuno and Target therapy (SECOMBIT) Study

- Prospective randomized phase II study to evaluate the best sequential approach with combo immunotherapy (ipilimumab/nivolumab) followed by combo target therapy (dabrafenib/ trametinib) and vice-versa
- Patients affected by metastatic melanoma BRAF V600 mutated
- Sample size 230 pts

ARM A
Combo T
LGX 450 mg
MEK 162 45 mg
→ **PD** → **Combo I until PD**

ARM B
Combo I
Ipilimumab 3 mg/Kg
Nivolumab 1mg /Kg
→ **PD** → **Combo T until PD**

ARM C
Sandwich
LGX 450 mg
MEK 162 45 mg for 8 weeks
→ **Combo I until PD** → **Combo T until PD**

This study is designed as a phase II randomized trial with no formal comparative test.

Endpoints:

Primary – OS

Secondary – PFS, Total PFS (TPFS): the time to the second progression, % patients alive at 2-3 years, BORR;
Duration of Response, Toxicity, Biomarkers study

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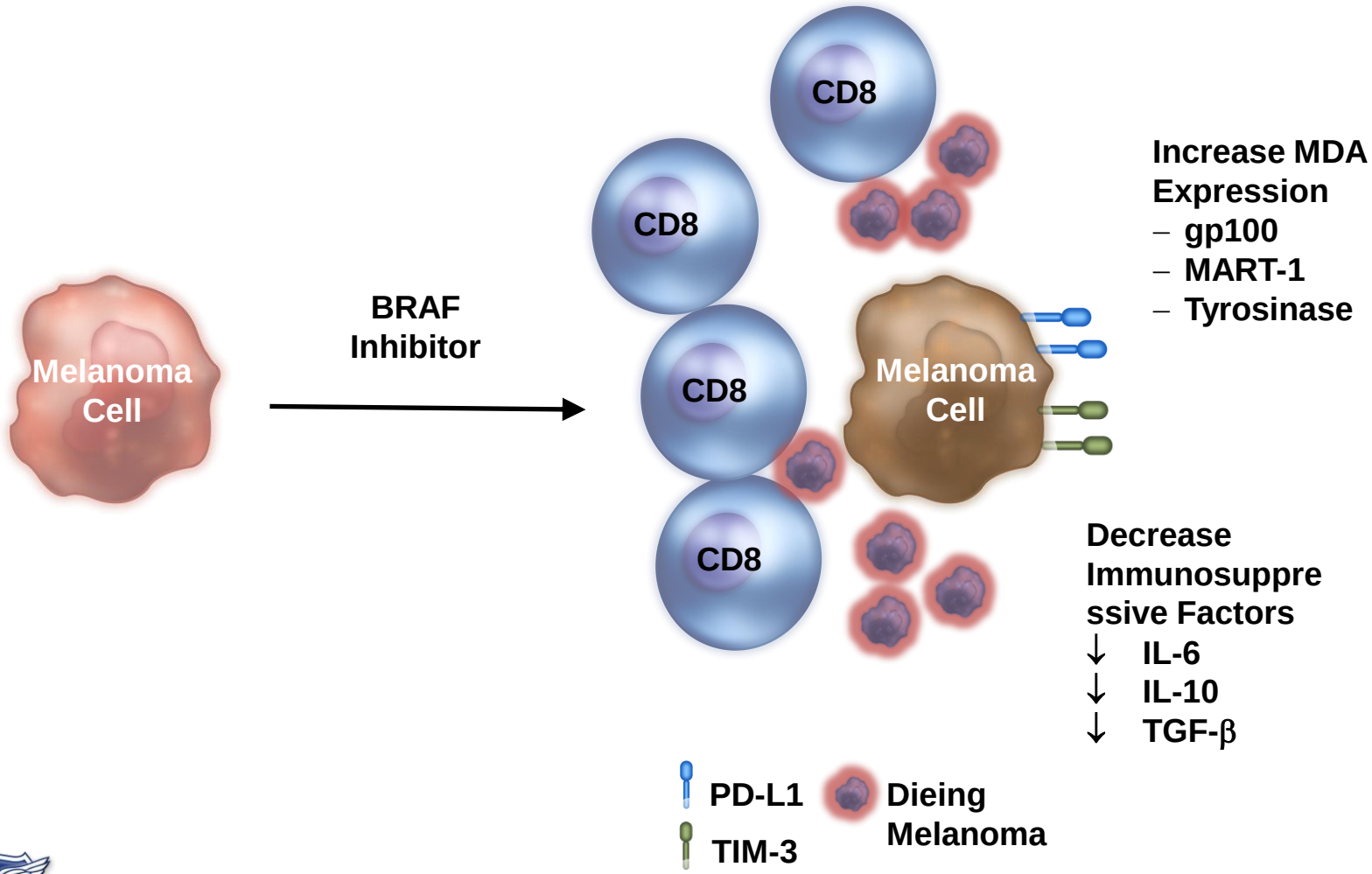
Response to BRAF-inhibition



Lau, Ascierto and McArthur, Curr Opinion in Immunol, in press

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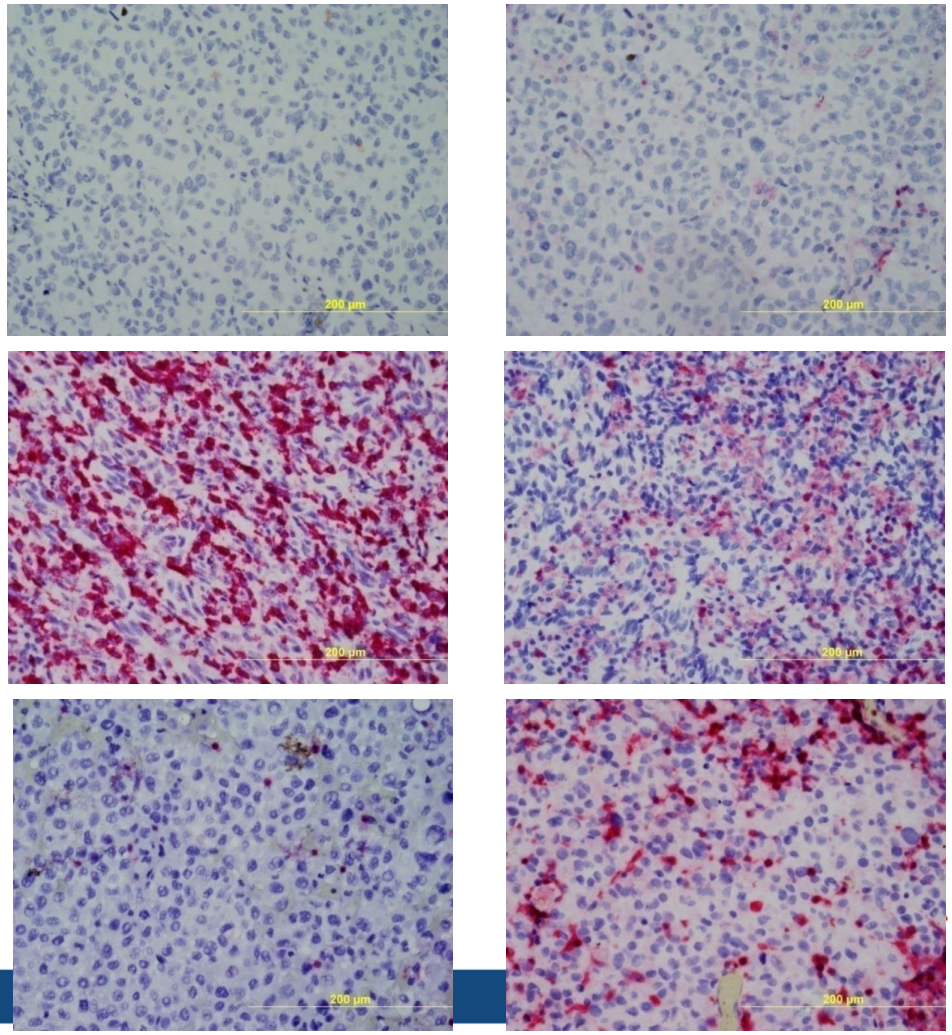
Response to BRAF-inhibition -Lymphocytes

CD8 CD4

Baseline

Responding Day 7

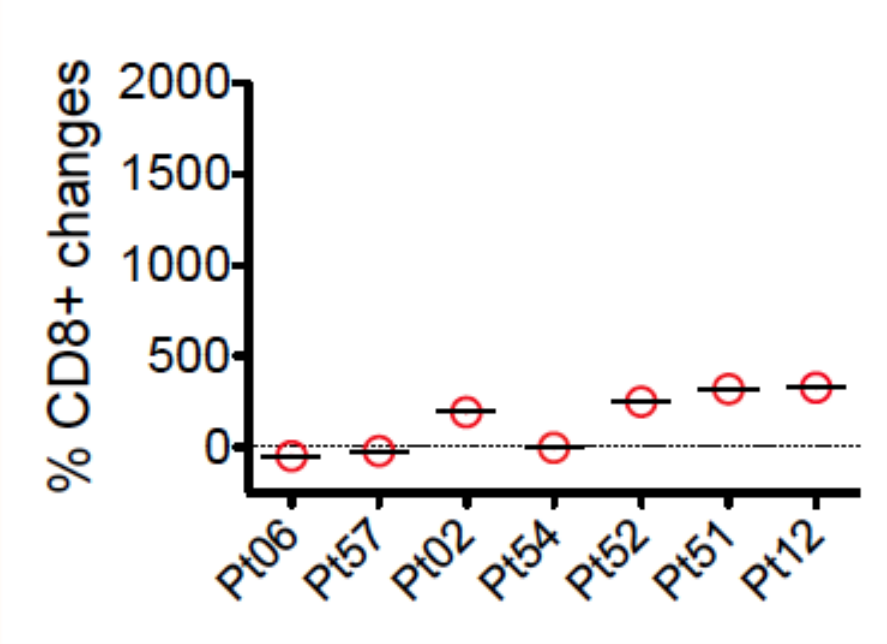
Progression



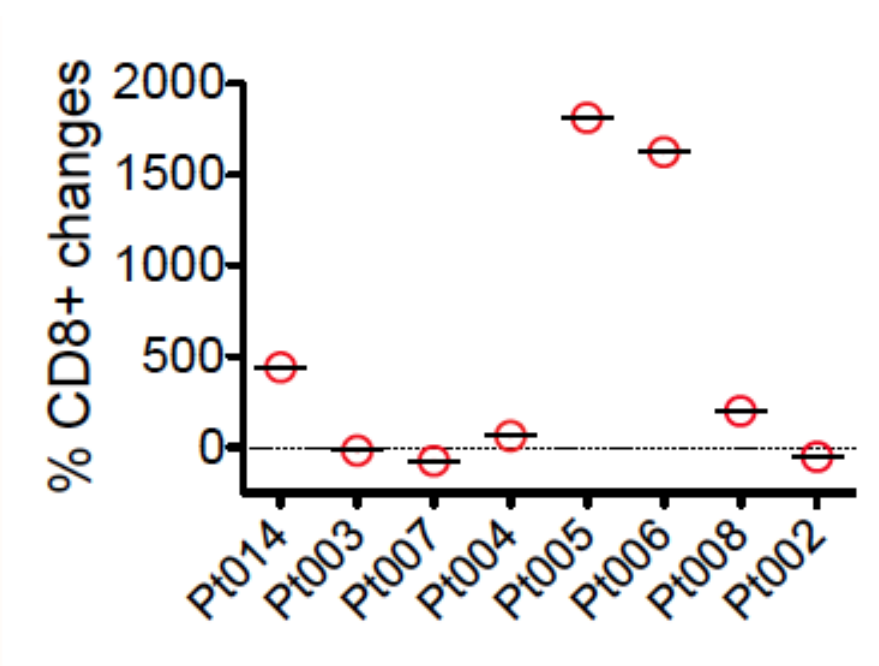
Wilmott, Long et al and Scolyer **CCR 2011**

A role for the host in the response to a therapy targeting BRAF?

Vemurafenib + Cobimetinib



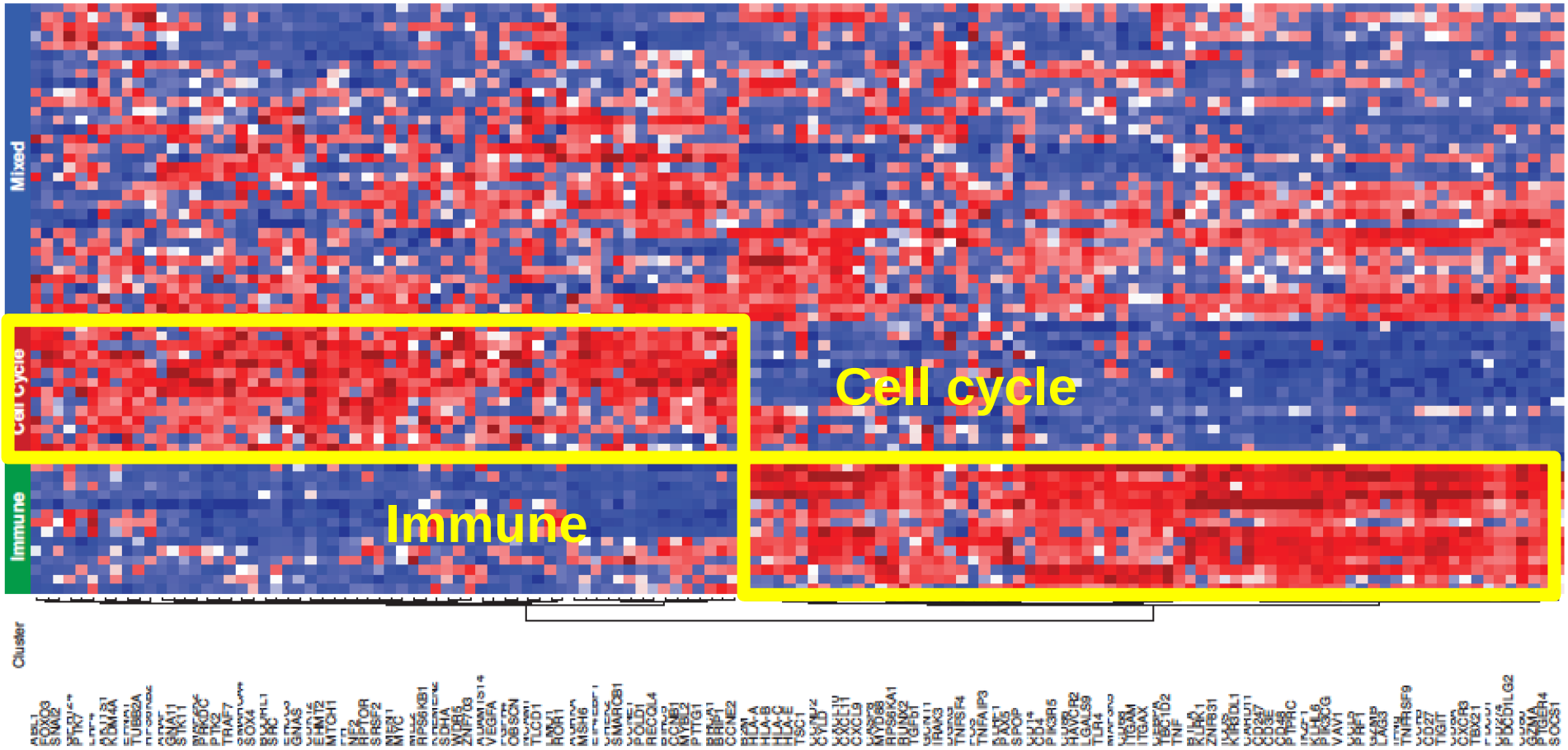
Vemurafenib



pairwise on-treatment/baseline comparison

Yang, McArthur. …Ribas, **Melanoma Bridge Meeting Dec 2013**

Gene expression profiling of melanoma tissue from patients enrolled in clinical trials targeting BRAF



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Wongchenko, McArthur. …Ribas, **Society for Melanoma Research, Nov 2015**

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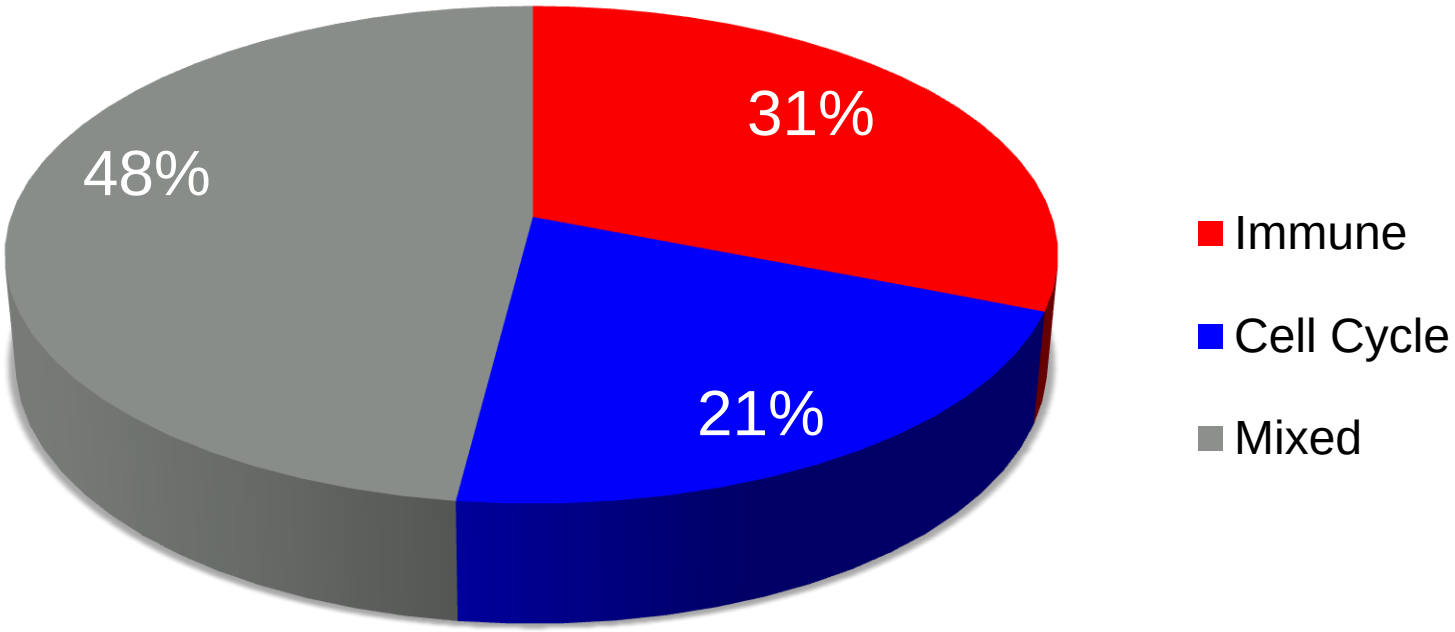

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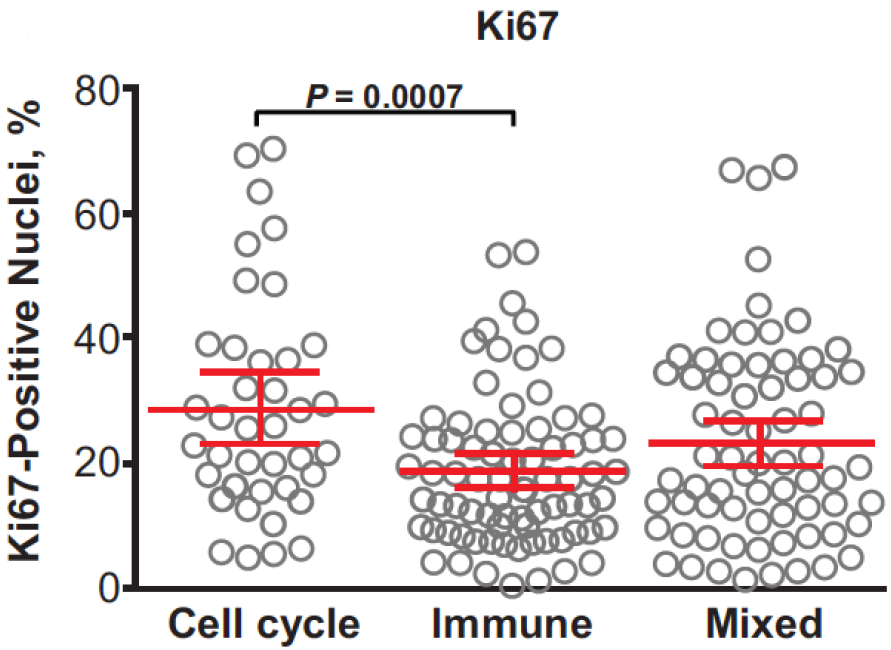

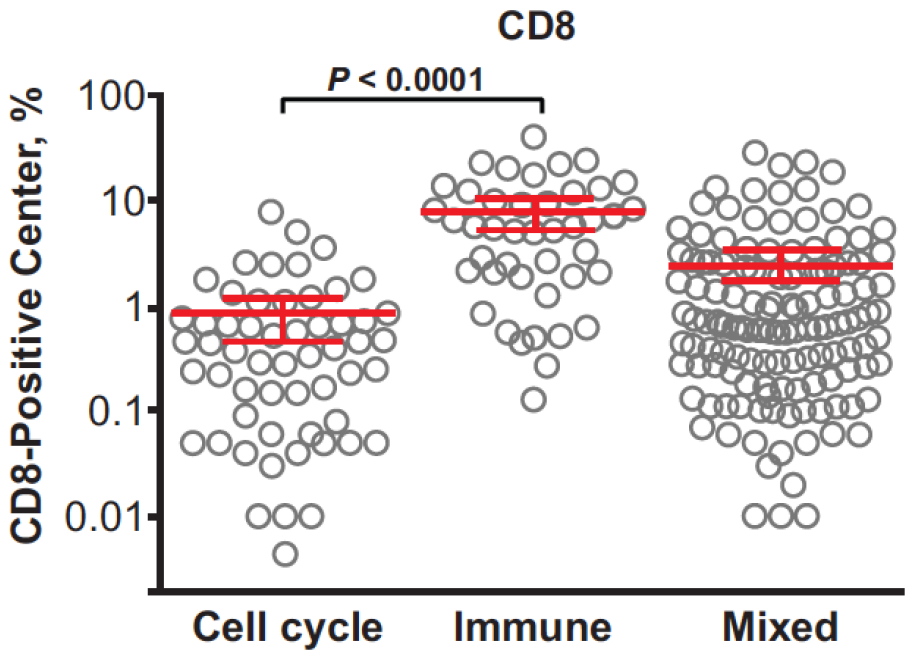

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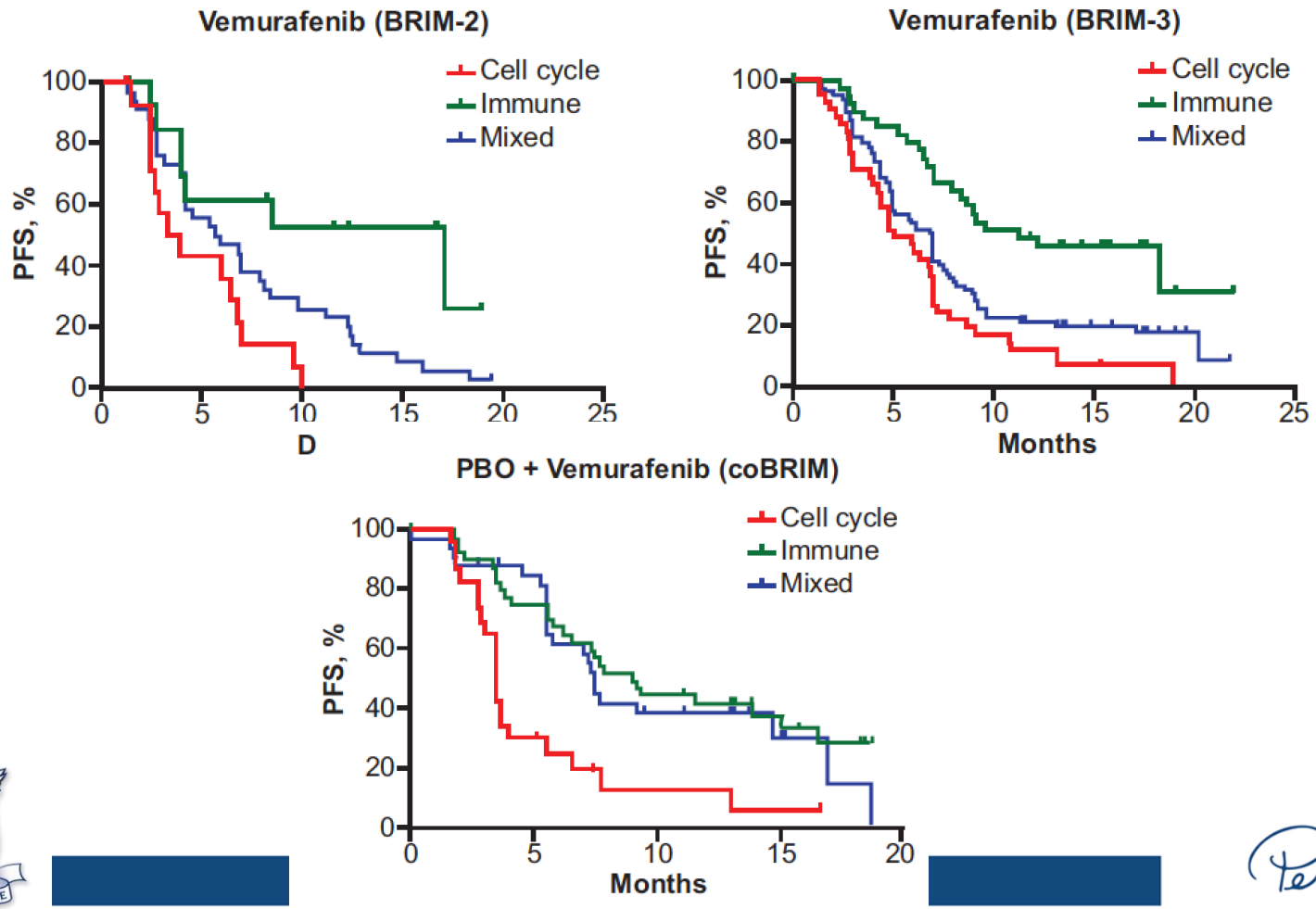
Wongchenko, McArthur. …Ribas, **Society for Melanoma Research, Nov 2015**

Gene expression profiling of melanoma tissue reveals an immune activation signature predicts outcome in patients treated with BRAFi



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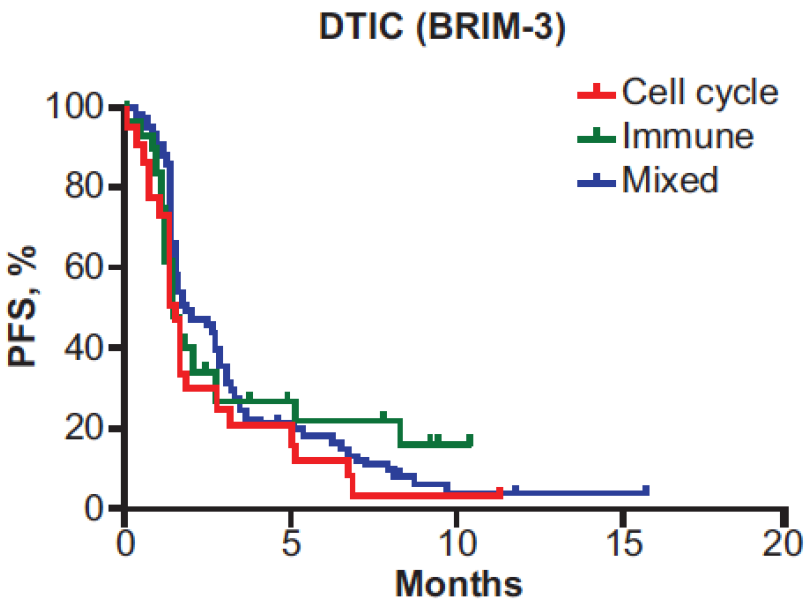

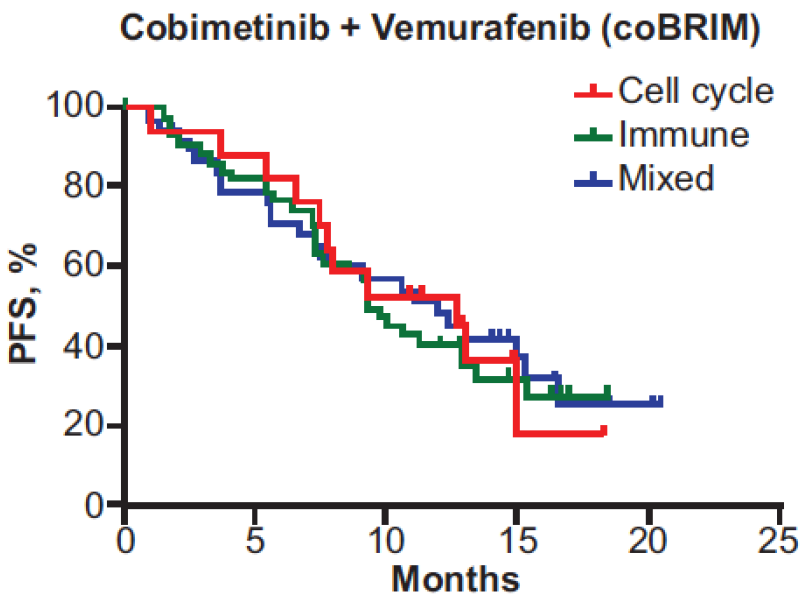

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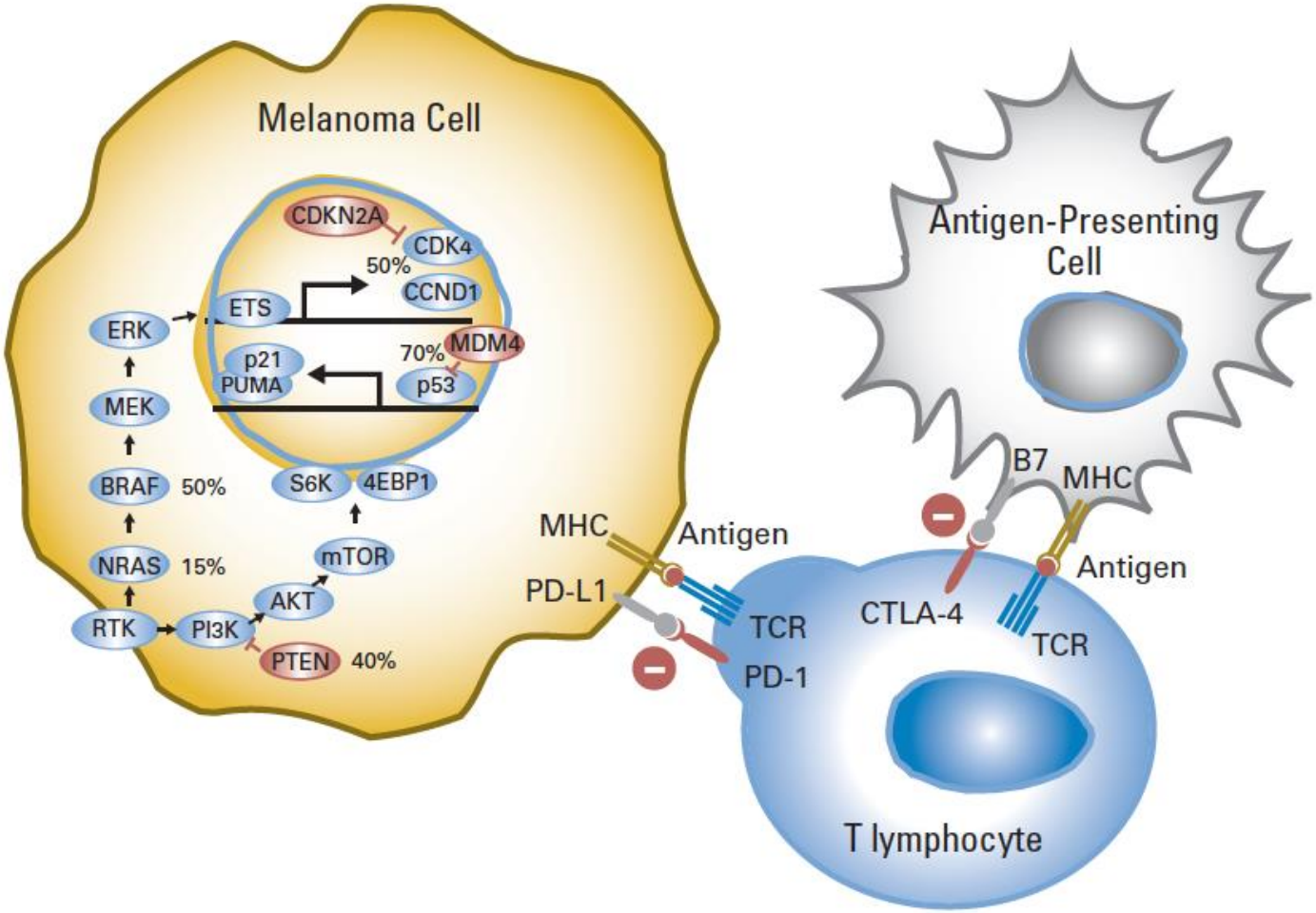

McArthur & Ribas, *J Clinical Oncology*, 2013

Acknowledgements

Karen Sheppard
Carleen Cullinane
Nicole Haynes
Laura Kirby
Claire Martin
Allen Foo
Richard Young
Kelly Waldeck
Stephen Fox

Andreas Behren
Stephen Wong
Victoria Mar
Alex Dobrovic
Jonathan Cebon
John Kelly
Richard Scolyer
Jason Li

Matthew Wongchenko
Yibing Yang
James Larkin
Paolo Ascierto
Nicholas Choong
Victoria Atkinson
Paul Chapman
Axel Hauschild
Jeff Sosman
Ming Yin
Kerstin Trunzer
Brigitte Dréno
Ilsung Chang
Antoni Ribas
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