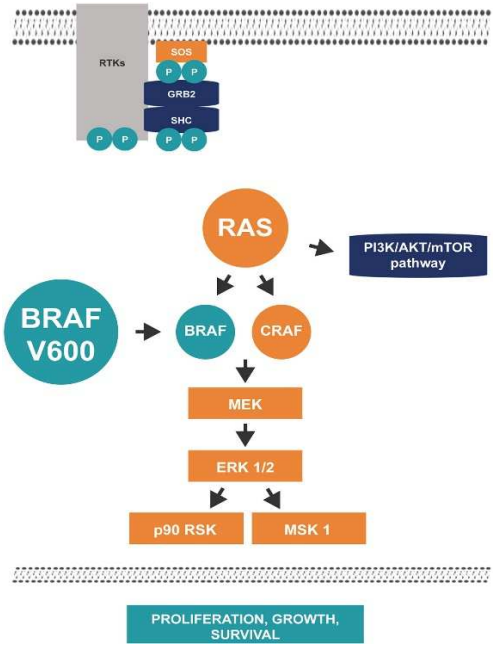
CENTRUM ONKOLOGII – INSTYTUT
IM. MARII SKŁODOWSKIEJ-CURIE

Status of targeted therapy in the treatment of advanced melanoma



Anna M. Czarnecka

Poznań, 15.03.2019

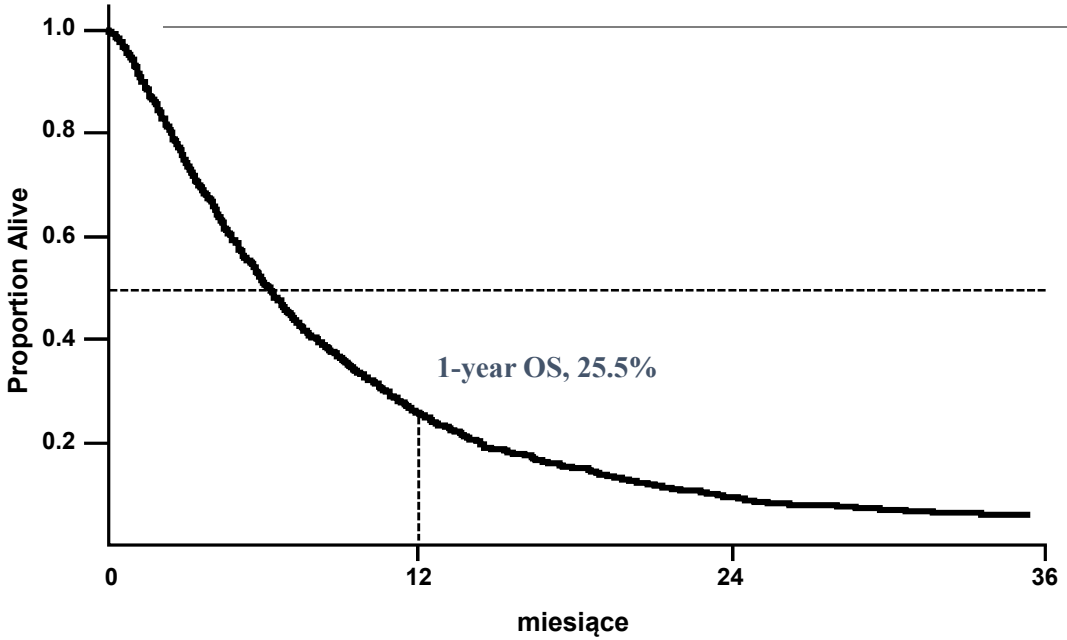
Conflict of interest

Pierre Fabre

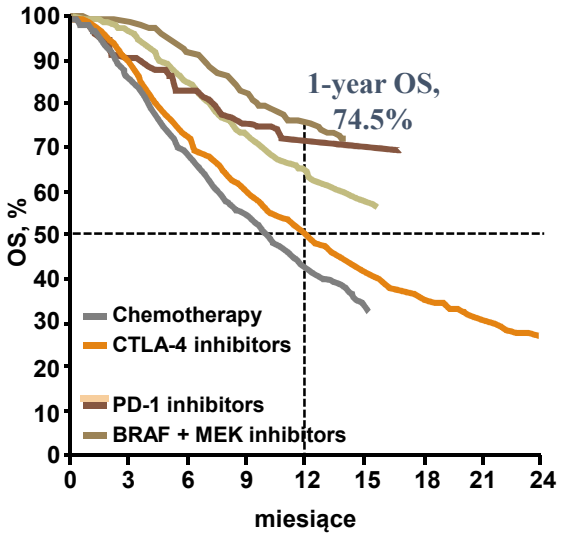
Metastatic melanoma historically and now….

Annual survival of patients with non-resectable or stage IV melanomas

Historical data OS[1]



New therapies OS



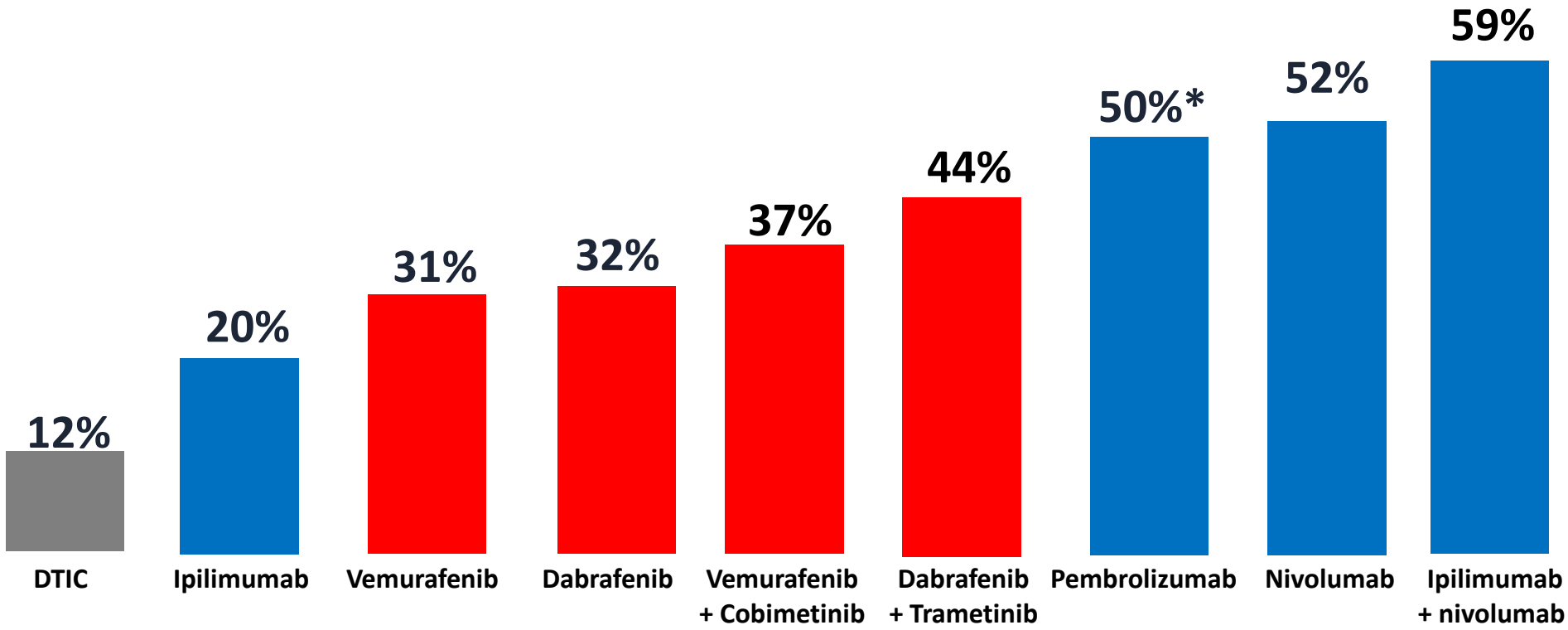
Korn EL, et al. *J Clin Oncol.* 2008;26:527-534

Ugurel S, et al. *Eur J Can*. 2016;53:125-134.

CTLA-4; cytotoxic T-lymphocyte–associated antigen 4; MEK, mitogen-activated protein kinase/extracellular sigr regulated kinase kinase; OS, overall survival; PD-1, programmed death 1.

Melanoma treatment efficacy

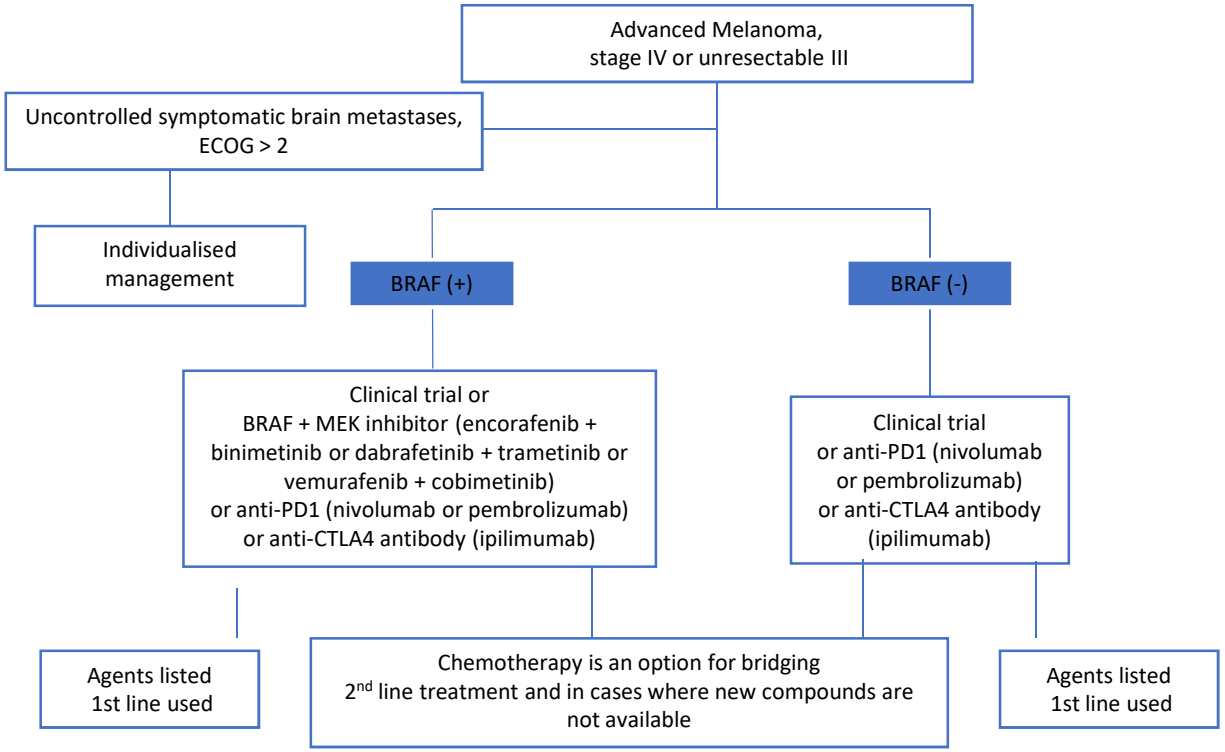
Targeted therapy and immunotherapy have improved
3 year OS of stage IV melanoma patients



*OS rate at 33 months

Hodi et al., NEJM 2010; Robert et al., NEJM 2011; COMBI-d ASCO 2016; COMBI-v ESMO 2016; Co-BRIM - SMR 2016, Keynote 006 - ASCO 2017; Wolchok et al NEJM 2017

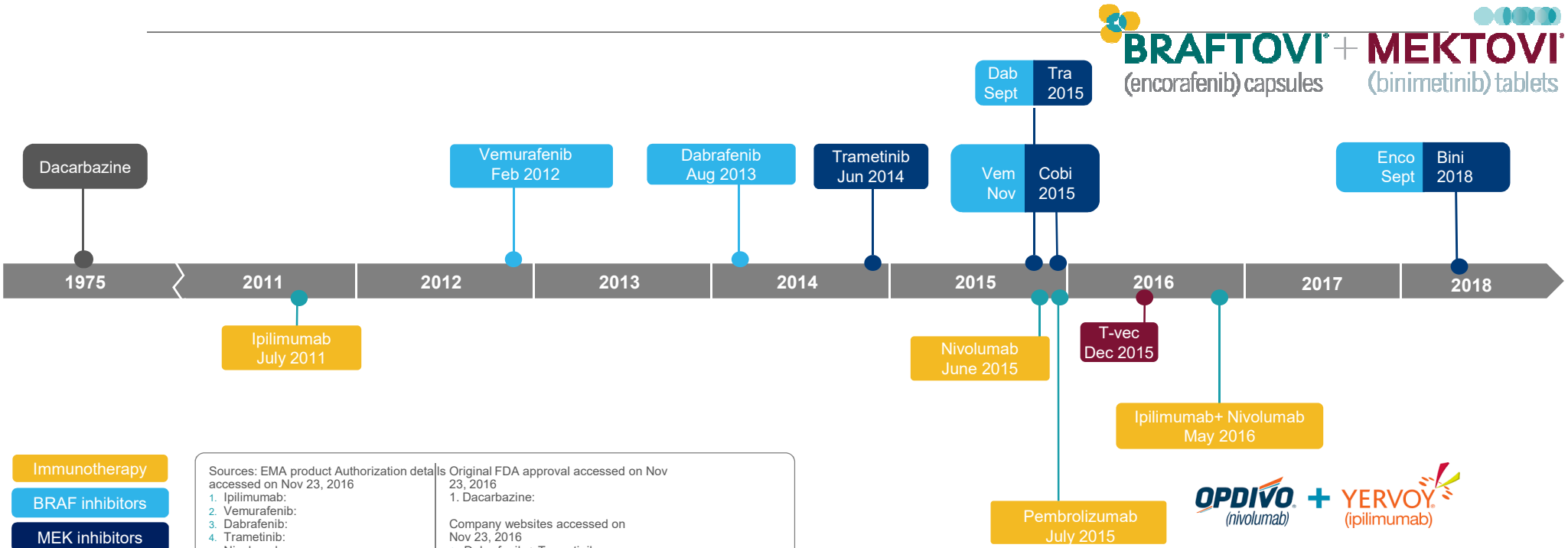
ESMO Guidelines?



- **For BRAF-V600-mutated melanoma, a combination of BRAFi and MEKi is a valid treatment option in first and second lines. It has a high chance for rapid response and offers improvements in quality of life.**
- **BRAFi/MEKi inhibitor combos offer high response rates (70%) and rapid response induction associated with symptom control, with a PFS of ~12 months.**
- Anti-PD1 therapy, and to a lesser extent ipilimumab, offer lower response rates in the range, but many responses are durable
- Anti-PD1 antibody therapy is the preferred first-line treatment of patients with BRAF-wt disease .
- Anti-PD1 therapies also demonstrate efficacy for patients with other BRAF mutations and are recommended as a second-line treatment, after ipilimumab failure
- In general, stage IV melanoma patients need to be treated and discussed in an interdisciplinary tumour board, within centres that have broad experience in this disease

Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Dummer R, et al. Ann Oncol (2015) 26 (suppl 5): v126-v132.

Key EU approvals in Melanoma

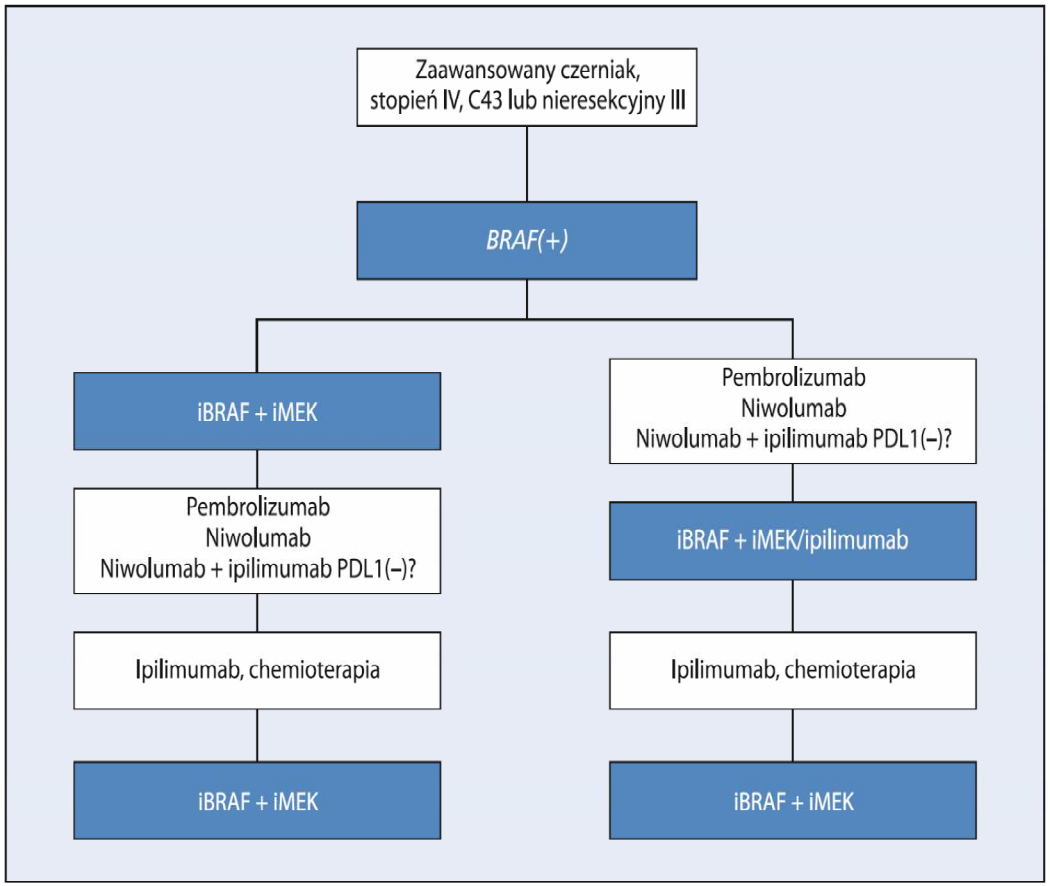


Sources: EMA product Authorization details accessed on Nov 23, 2016
1. Ipilimumab:
2. Vemurafenib:
3. Dabrafenib:
4. Trametinib:
5. Nivolumab:
6. Pembrolizumab:
7. T-vec:
8. Vemurafenib + Cobimetinib:
9. Encorafenib:
10. Binimetinib:

Original FDA approval accessed on Nov 23, 2016
1. Dacarbazine:

Company websites accessed on Nov 23, 2016
1. Dabrafenib + Trametinib:
2. Ipilimumab + Nivolumab:

Where do we stand in 2019?
In Poland?



Rycina 4. Schemat szczegółowy leczenia systemowego u chorych na zaawansowane czerniaki w stopniu IV lub nieresekcyjnym III z obecnością mutacji *BRAF*. iBRAF — inhibitor BRAF; iMEK — inhibitor MEK

VIA MEDICA

WYTYCZNE POSTĘPOWANIA DIAGNOSTYCZNO-TERAPEUTYCZNEGO

Czerniaki skóry

Cutaneous melanomas

Redakcja:
Piotr Rutkowski, Piotr J. Wysocki

Zespół autorski:
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Where do we stand in 2019? (stage IV disease)

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Cutaneous Melanoma

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE[1]

Metastatic or unresectable disease →

FIRST-LINE THERAPY[2]

- Preferred regimens
  - Anti PD-1 monotherapy[3,4]
    - Pembrolizumab (category 1)
    - Nivolumab (category 1)
  - Combination targeted therapy if *BRAF* V600-activating mutation;[6] preferred if clinically needed for early response[7,8,9,10]
    - Dabrafenib/trametinib (category 1)
    - Vemurafenib/cobimetinib (category 1)
    - Encorafenib/binimetinib (category 1
- Useful in certain circumstances
  - Nivolumab/ipilimumab (category 1)[3,4,5]

→ **Disease progression or Maximum clinical benefit from BRAF targeted therapy** →

SECOND-LINE OR SUBSEQUENT THERAPY[11]

- Systemic therapy
  - Preferred regimens
    - Anti PD-1 monotherapy[3,4]
      - Pembrolizumab
      - Nivolumab
    - Nivolumab/ipilimumab[3,4,5]
    - Combination targeted therapy if *BRAF* V600-activating mutation[8,9,10]
      - Dabrafenib/trametinib
      - Vemurafenib/cobimetinib
      - Encorafenib/binimetinib
  - Other regimens
    - Ipilimumab[3]
    - High-dose IL-2[12]
  - Useful in certain circumstances
    - Ipilimumab[3]/intralesional T-VEC (category 2B)
    - Cytotoxic agents[13]
    - Imatinib for tumors with activating mutations of *KIT*
    - Larotrectinib for *NTRK* gene fusion positive tumors
- Consider best supportive care for poor performance status (See NCCN Guidelines for Palliative Care)

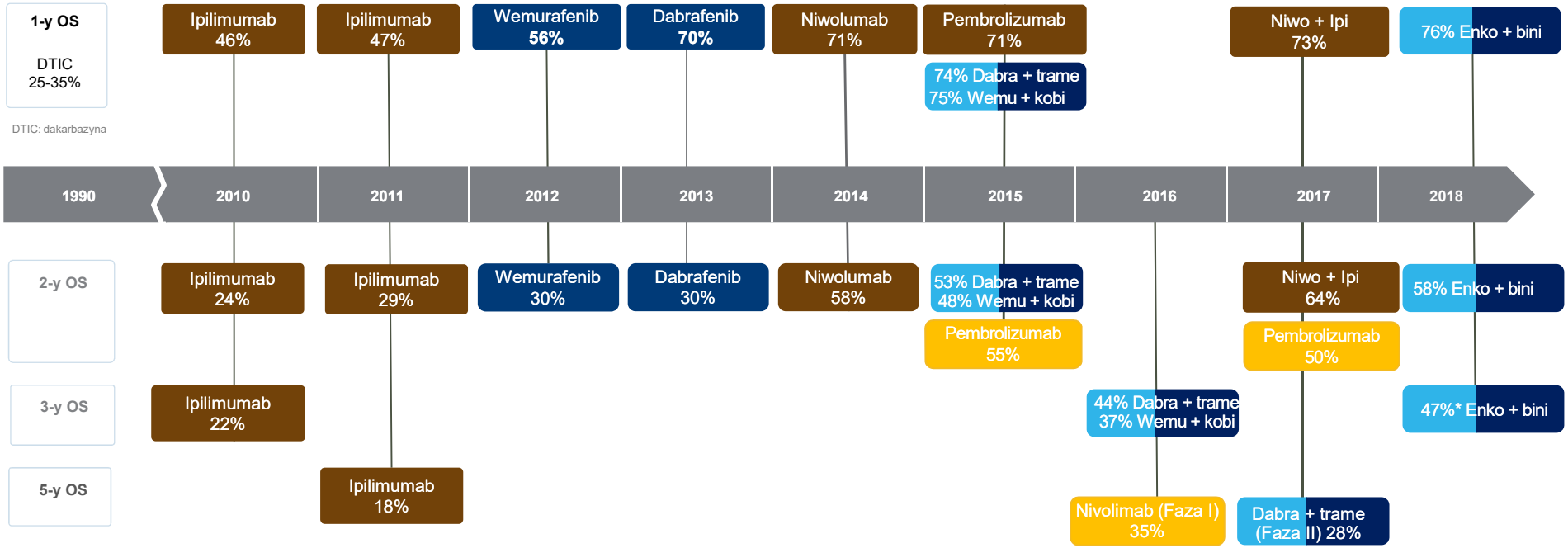
[1] See Principles of Imaging --Treatment Response Assessment (ME-D).
[2] The choice of a treatment is based on evaluation of the individual patient.
[3] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[4] The use of PD-L1 as a biomarker for selection of anti-PD-1 therapy and/or nivolumab/ipilimumab combination therapy is an emerging research issue with non-uniform application among the NCCN Member Institutions (category 2B).
[5] Nivolumab/ipilimumab combination therapy is associated with improved ORR, PFS, and OS compared with single-agent ipilimumab, at the expense of significantly increased toxicity. Compared to nivolumab, the impact of nivolumab/ipilimumab combination therapy on OS is not known. The phase III trial of nivolumab/ipilimumab or nivolumab monotherapy versus ipilimumab monotherapy was conducted in previously untreated patients with unresectable stage III or IV melanoma. Relative indications for combination nivolumab/ipilimumab in comparison to PD-1 monotherapy include: patient willingness to take on high risk of treatment-related toxicities (irAEs); absence of comorbidities or autoimmune processes that would elevate the risk of irAEs; patient social support and anticipated compliance with medical team to handle toxicities; and absent/low tissue PD-L1.
[6] Positive VE1 IHC results are sufficient for starting targeted therapy in patients who are symptomatic or have rapidly progressing disease. Due to the risk of false positives and false negatives, all VE1 IHC results should be confirmed by sequencing. See Principles of Molecular Testing (ME-C).
[7] Because BRAF/MEK inhibitors have a shorter time to response compared with checkpoint immunotherapies, they may be preferred in patients with rapidly progressing disease and/or symptoms.
[8] See Management of Toxicities Associated with Targeted Therapy (ME-J).
[9] In previously untreated patients with unresectable AJCC 7th Edition stage IIIC or stage IV disease, BRAF/MEK inhibitor combination therapy was associated with improved response rate, PFS, and OS compared to BRAF inhibitor monotherapy.
[10] If BRAF/MEK inhibitor combination therapy is contraindicated, BRAF-inhibitor monotherapy with dabrafenib or vemurafenib are recommended options, especially in patients who are not appropriate candidates for checkpoint immunotherapy.
[11] For patients who experience progression of melanoma during or shortly after first-line therapy, consider second-line agents if not used first line and not of same class. For patients who progressed on single-agent checkpoint immunotherapy, nivolumab/ipilimumab combination therapy is a reasonable treatment option. For patients who experience disease control (CR, PR, or SD) and have no residual toxicity, but subsequently experience disease progression/relapse >3 months after treatment discontinuation, re-induction with the same agent or same class of agents may be considered.
[12] High-dose IL-2 should not be used for patients with inadequate organ reserve, poor performance status, or untreated or active brain metastases. For patients with small brain metastases and without significant peritumoral edema, IL-2 therapy may be considered (category 2B). Therapy should be restricted to an institution with medical staff experienced in the administration and management of these regimens.
[13] For a list of cytotoxic regimens, see (ME-I 2 of 5).

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Currently available MM therapies and expected survial

The progress in pharmacology has translated into a significant improvement in OS (overall survival) among patients with metastatic melanoma

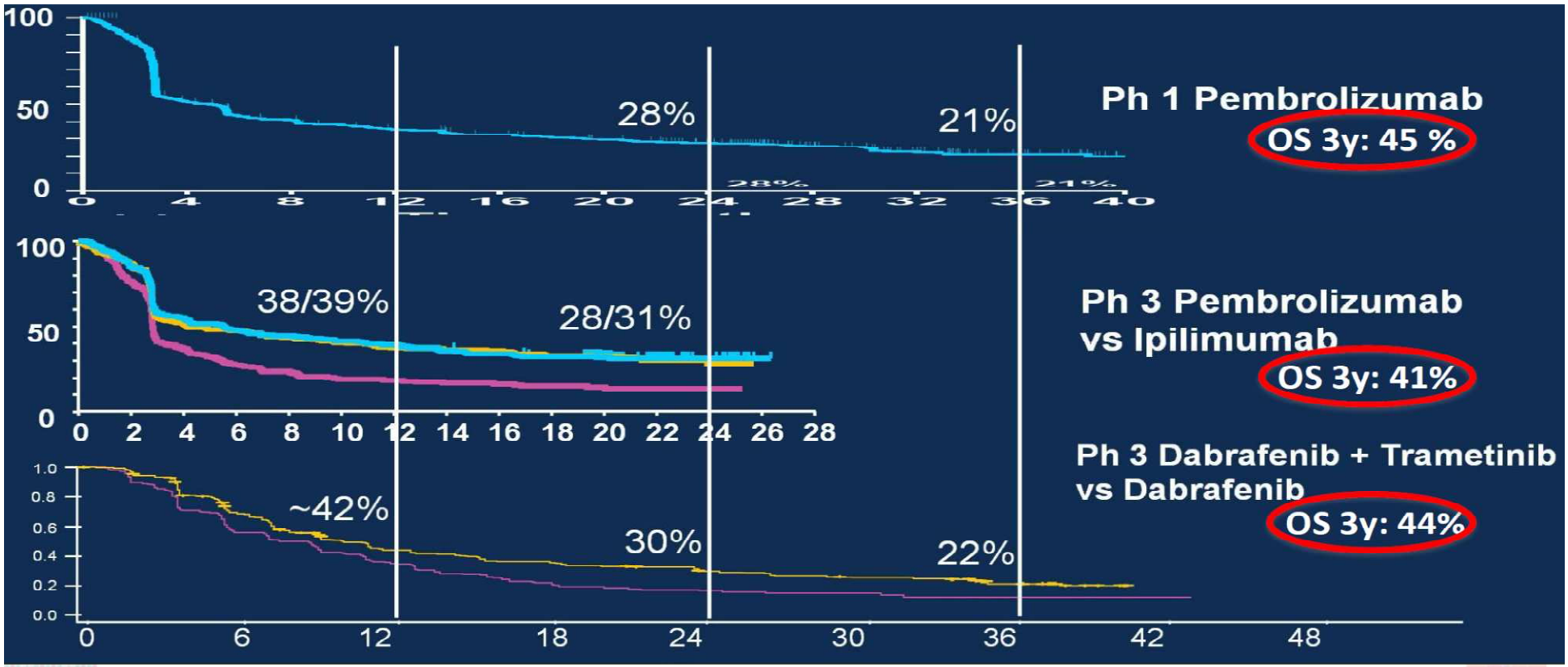


By: Georgina Long (ASCO Annual Meeting 2016 2017 & EADO 2017)

* Dane niedojrzałe

Is BRAFi/MEKi or ITH for 1LT?

BRAFi plus MEKi vs Immunotherapy



Presented By Georgina Long at 2016 ASCO Annual Meeting

Progression-free survival

Cochrane Community

Trusted evidence.
Informed decisions.
Better health.

- both combination of immune checkpoint inhibitors and combination of small-molecule targeted drugs were favoured compared to chemotherapy;
- both BRAF inhibitors and combination of small-molecule targeted drugs were favoured compared to anti-CTLA4 monoclonal antibodies;
- biochemotherapy led to less favourable results than BRAF inhibitors;
- the combination of small-molecule targeted drugs was favoured compared to anti-PD1 monoclonal antibodies;
- both biochemotherapy and MEK inhibitors led to less favourable results than the combination of small-molecule targeted drugs; and
- biochemotherapy led to less favourable results than the combination of immune checkpoint inhibitors

- combination of immune checkpoint inhibitors (anti-PD1 plus anti-CTLA4 monoclonal antibodies) performed better than anti-CTLA4 monoclonal antibodies alone (high-quality evidence), but anti-PD1 monoclonal antibodies performed better than anti-CTLA4 monoclonal antibodies (high-quality evidence).

- combination of small-molecule inhibitors (BRAF plus MEK inhibitors) lead to better results than BRAF inhibitors alone (moderate-quality evidence)

Ovearall survival

Cochrane Community

Trusted evidence.
Informed decisions.
Better health.

- Anti-PD1 monoclonal antibodies improved patients' overall survival compared with either standard chemotherapy (high-quality evidence) or anti-CTLA4 monoclonal antibodies (high-quality evidence).

- Compared to chemotherapy alone, both BRAF inhibitors (high-quality evidence), and anti-angiogenic agents combined with chemotherapy (moderate-quality evidence) also prolong overall survival,

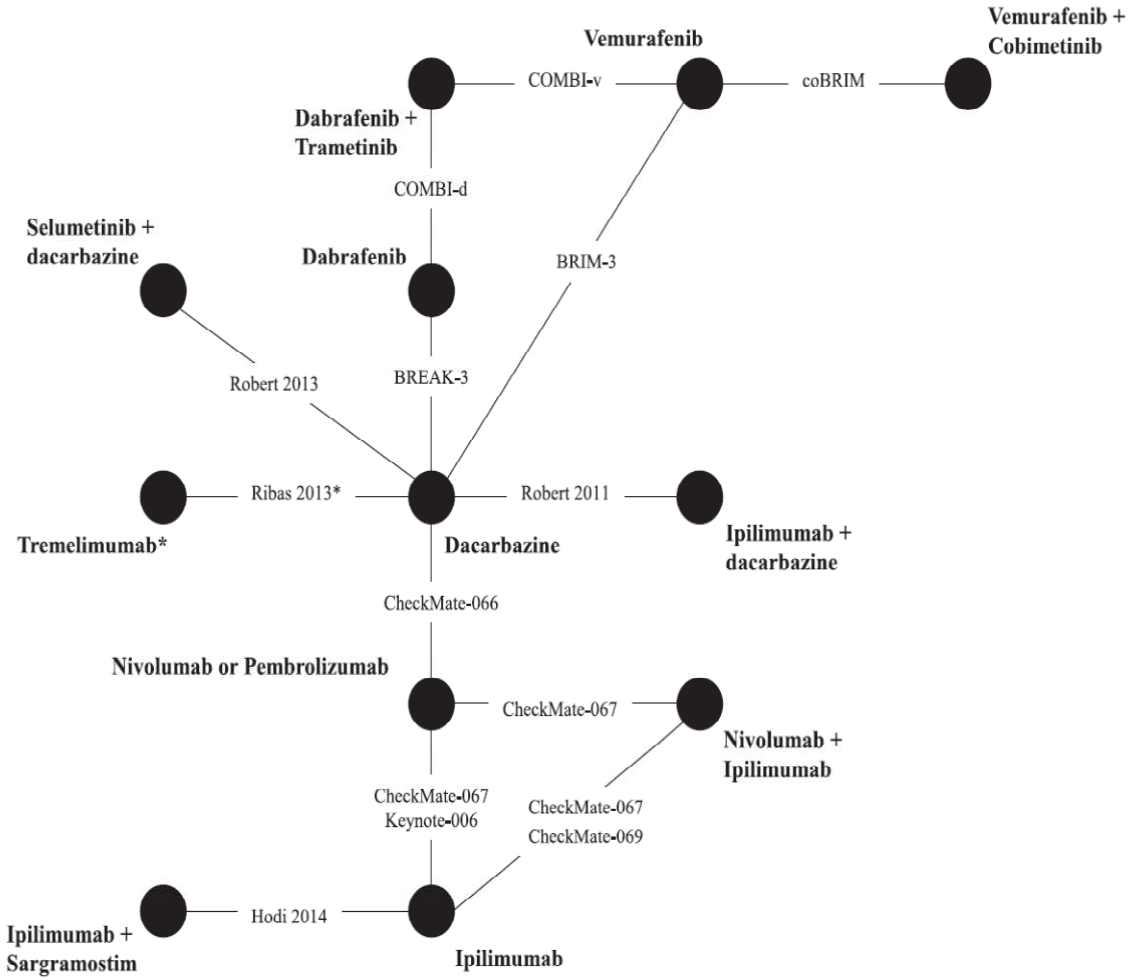
- Anti-CTLA4 monoclonal antibodies plus chemotherapy (low-quality evidence), MEK inhibitors (low-quality evidence), combined multiple chemotherapeutic agents (polychemotherapy) (high-quality evidence), or biochemotherapy (high-quality evidence) did not lead to significantly improved overall survival.

- Combination of small-molecule inhibitors performed better than BRAF inhibitors alone (high-quality evidence).

What is the status of targeted therapies in MM?

The spectrum of treatment options for patients with metastatic BRAF-mutated melanoma is broad, spanning multiple treatment classes.

There is a lack of head-to-head evidence comparing targeted and immunotherapies.



*Data only for OS

Fig. 1. Network of evidence for overall survival and progression-free survival outcomes.

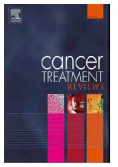
Cancer Treat Rev. 2019 Mar;74:43-48.

BRAFi/MEKi better? ITH better?

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv



Systematic or Meta-analysis Studies

Network meta-analysis of therapies for previously untreated advanced BRAF-mutated melanoma

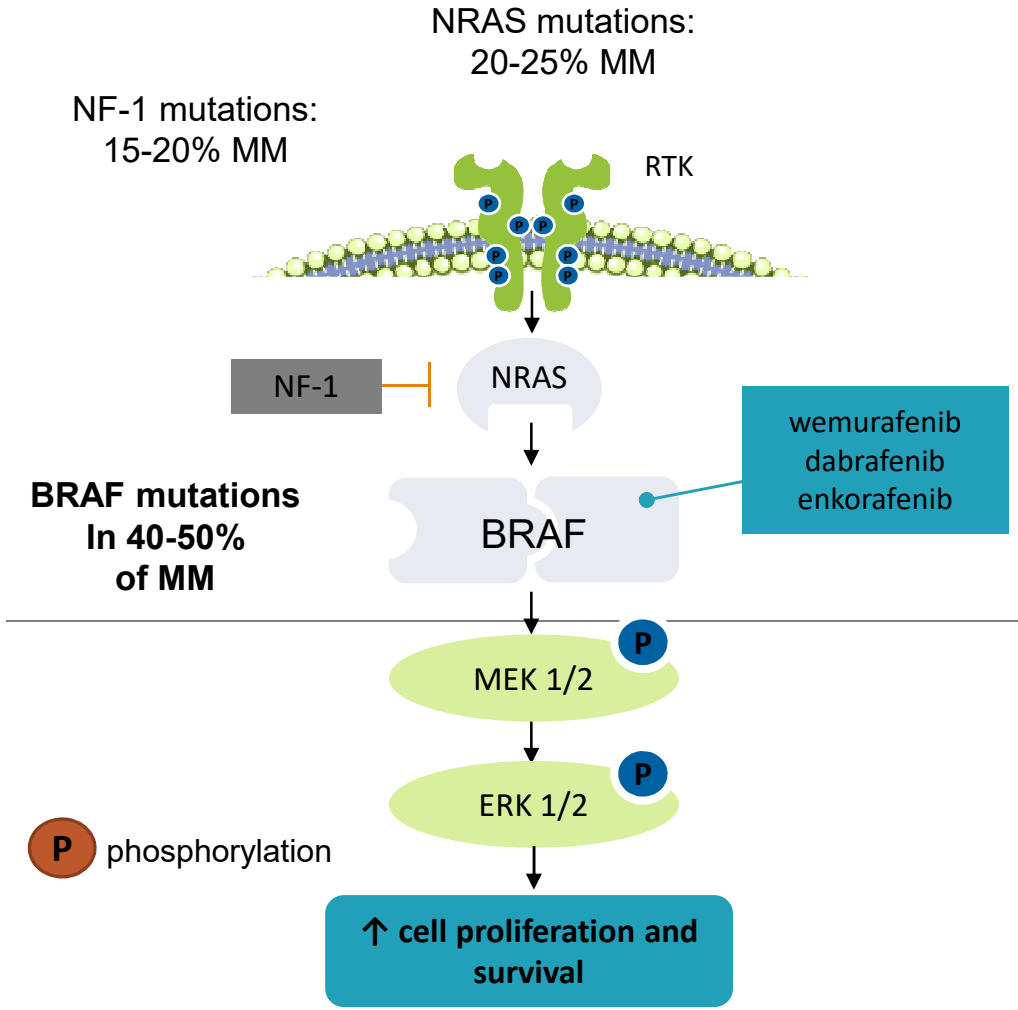
Michael J. Zoratti[a], Tahira Devji[a], Oren Levine[a,b], Lehana Thabane[a], Feng Xie[a,c,*]

Combination dabrafenib with trametinib (HR 0.22 [95% CrI 0.17, 0.28] vs dacarbazine) and combination vemurafenib with cobimetinib (HR 0.22 [95% CrI 0.17, 0.29] vs dacarbazine) were likely to rank as the most favorable treatment options for PFS.

Combination nivolumab with ipilimumab was likely to be the most efficacious in terms of OS (HR 0.33 [0.24, 0.47] vs dacarbazine).

Differences between treatments within the same treatment class (dabrafenib vs. vemurafenib; combination dabrafenib with trametinib vs. combination vemurafenib with cobimetinib) were not statistically important. Combination dabrafenib with trametinib was more efficacious than most treatments in the network, though the relative effects compared to combination vemurafenib with cobimetinib (HR 0.98, CrI 0.73, 1.31) and to combination nivolumab with ipilimumab (HR 0.83, CrI 0.58, 1.18) were not statistically important. All treatments, with the

MAPK signaling pathway and BRAF mutations



Functions	Genes	Significance
Cell growth and proliferation	58	6.48E-4 - 4.82E-2
Cell morphology	56	1.89E-4 - 4.96E-2
Cell death	50	2.14E-4 - 4.82E-2
Cell cycle	36	9.87E-5 - 4.82E-2
Cellular movement	33	3.28E-4 - 4.82E-2
Cell-to-cell signaling	32	3.49E-4 - 4.33E-2
Nervous system function	32	5.17E-5 - 4.82E-2
Gene expression	19	6.30E-4 - 4.25E-2
Immune response	8	1.68E-2 - 2.94E-2

The Ingenuity analysis tool was used to determine enriched biological function categories within the dataset for changes in BRAF-dependent gene expression. The top categories are shown, along with a p-value corrected for variations in category sizes.

Adapted from : Koeblinger et al. Future Oncology, 2017

Wemurafenib

BRIM-3

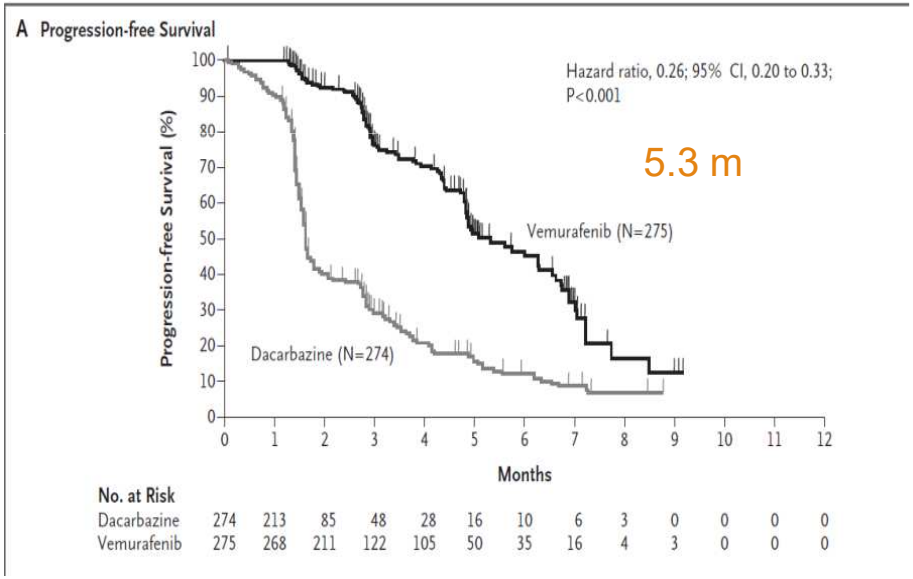
The BRIM-3 trial showed improved progression-free survival (PFS) and overall survival (OS) for vemurafenib compared with dacarbazine in treatment-naive patients with BRAFV600 mutation-positive metastatic melanoma.
675 patients were randomized to vemurafenib (n = 337) or dacarbazine (n = 338, of whom 84 crossed over to vemurafenib).
Median OS, censored at crossover, was significantly longer for vemurafenib than for dacarbazine {**13.6 months** [95% confidence interval (CI) 12.0-15.4] versus 9.7 months [95% CI 7.9-12.8; hazard ratio (HR) 0.81 [95% CI 0.67-0.98]; P = 0.03}.
Kaplan-Meier estimates of OS rates for vemurafenib versus dacarbazine were **56%** versus 46%, **30%** versus 24%, **21%** versus 19% and **17%** versus 16% at 1, 2, 3 and 4 years, respectively.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D., John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D., Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D., Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D., Celeste Lebbe, M.D., Thomas Jouary, M.D., Dirk Schadendorf, M.D., Antoni Ribas, M.D., Steven J. O'Day, M.D., Jeffrey A. Sosman, M.D., John M. Kirkwood, M.D., Alexander M.M. Eggermont, M.D., Ph.D., Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jiang Li, Ph.D., Betty Nelson, M.A., Jeannie Hou, M.D., Richard J. Lee, M.D., Keith T. Flaherty, M.D., and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group*

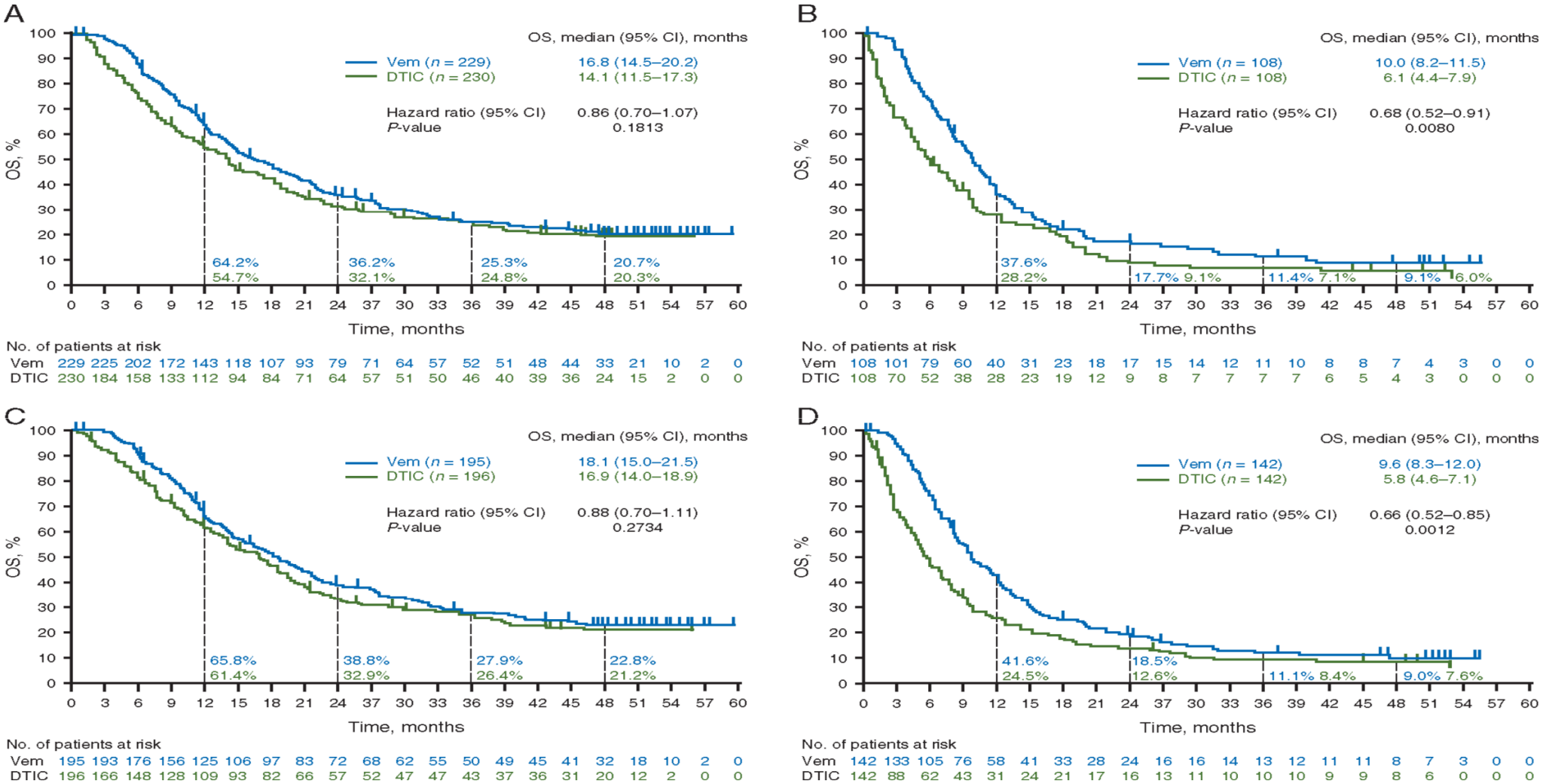


PFS HR=0.26

N Engl J Med. 2011 Jun 30;364(26):2507-16.

Wemurafenib

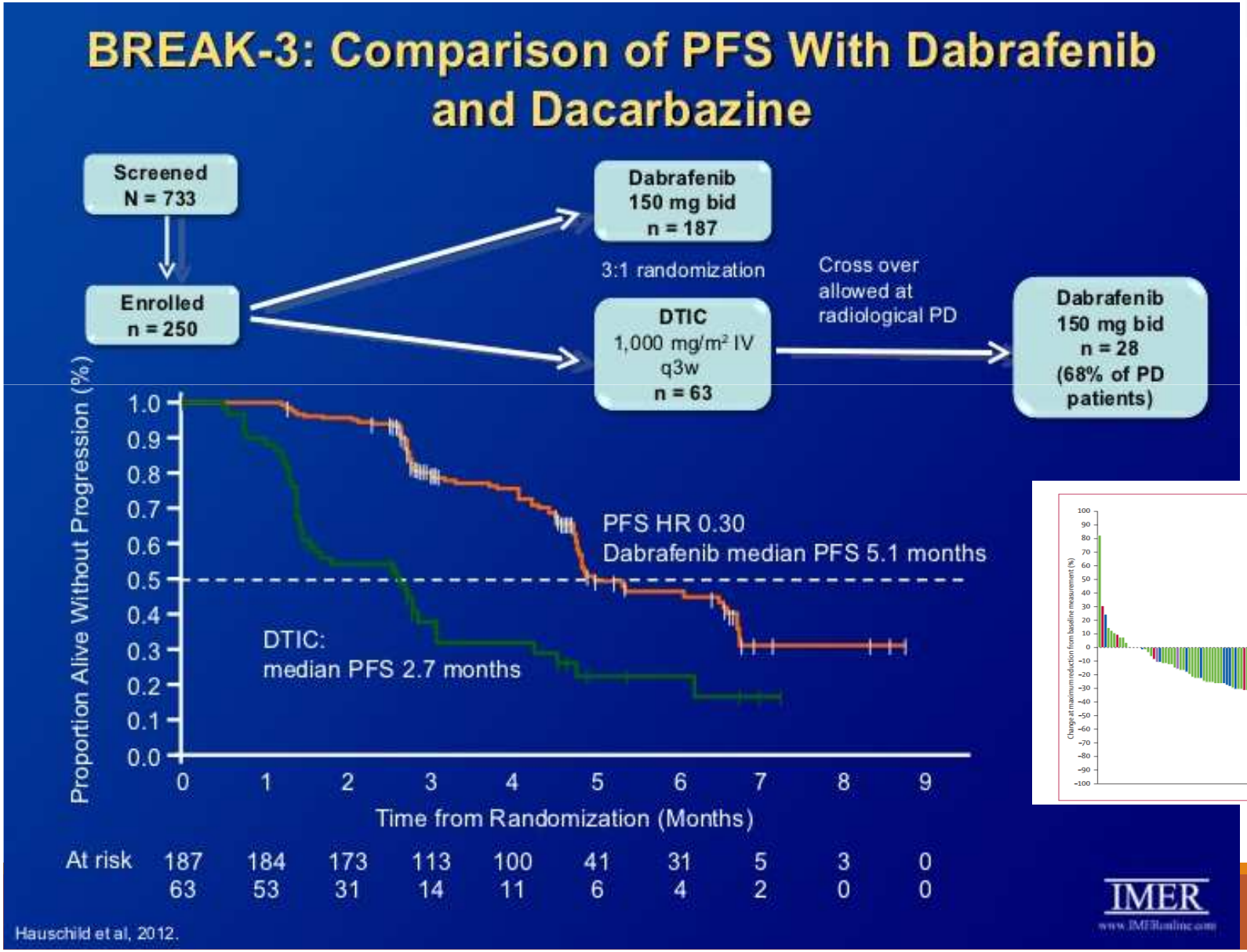
BRIM-3

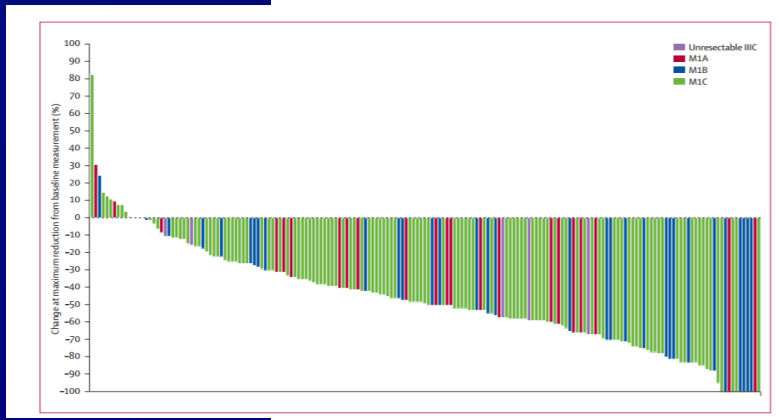


Kaplan–Meier curves for OS (without censoring at crossover) for patients with (A) ECOG PS 0, (B) ECOG PS 1, (C) LDH level normal and (D) LDH level elevated.

Annals of Oncology, Volume 28, Issue 10, 02 August 2017, Pages 2581–2587.

Dabrafenib





IMER
www.IMERonline.com

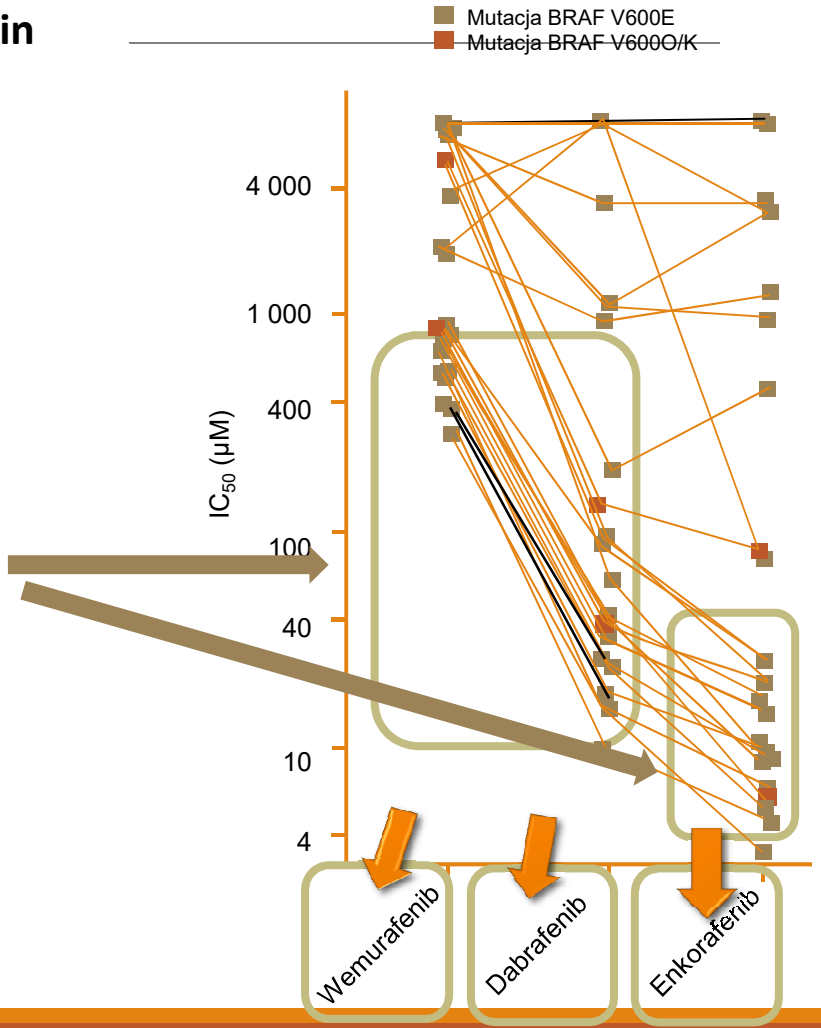
Enkorafenib

In vitro analysis of the effects of BRAFi on cell proliferation in various BRAF mutant cell lines:

- **IC50** – (*inhibitory concentration*) – medial inhibitor concentration that inhibits 50% biological and biochemical functions, here - cell proliferation

Enkorafenib exhibits a more potent inhibition of cell proliferation in vitro than other BRAF inhibitors

It can potentially show higher efficacy than other inhibitors



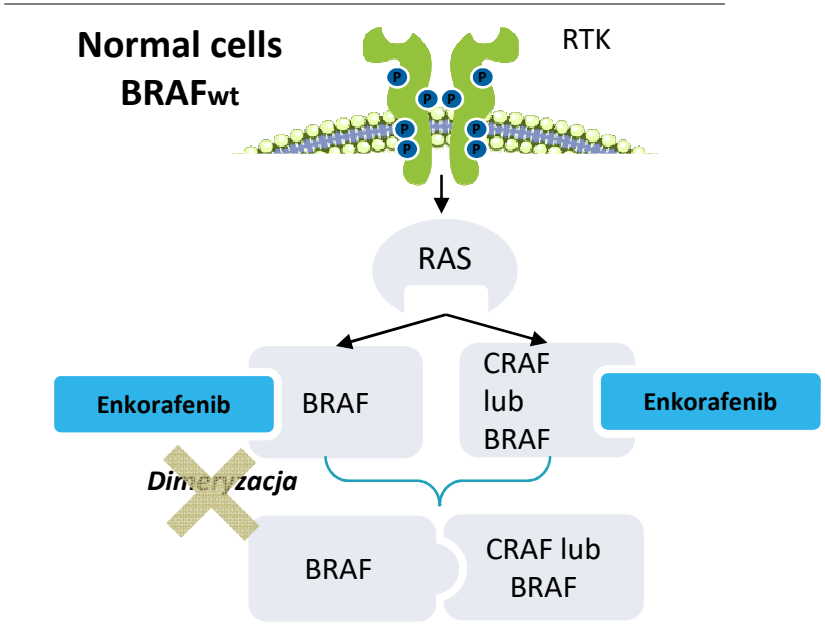
BRAFi: inhibitor BRAF

Stuart DD, et al. AACR. 2012: abstract 3790

BRAFi exhibit different kinase inhibitory activity

Inhibition of RAF kinases in vitro:
IC 50: 50% inhibitory concentration of kinase activity in vitro

Inhibitor	Biochemical parameter		
	BRAF IC_{50} (µM)	BRAFV600E IC_{50} (µM)	CRAF IC_{50} (µM)
Enkorafenib[1]	0.0005	0.0004	0.0003
Dabrafenib[2]	0.0032	0.0006	0.005
Wemurafenib[3]	0,11	0.035	0,048



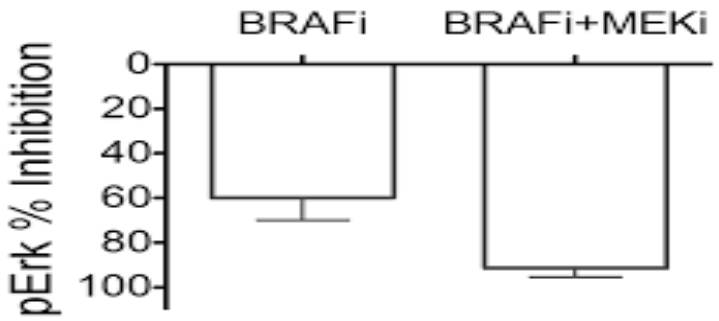
Enkorafenib inhibit $BRAF^{wt}$, $BRAF^{V600E}$ i CRAF with similar efficacy

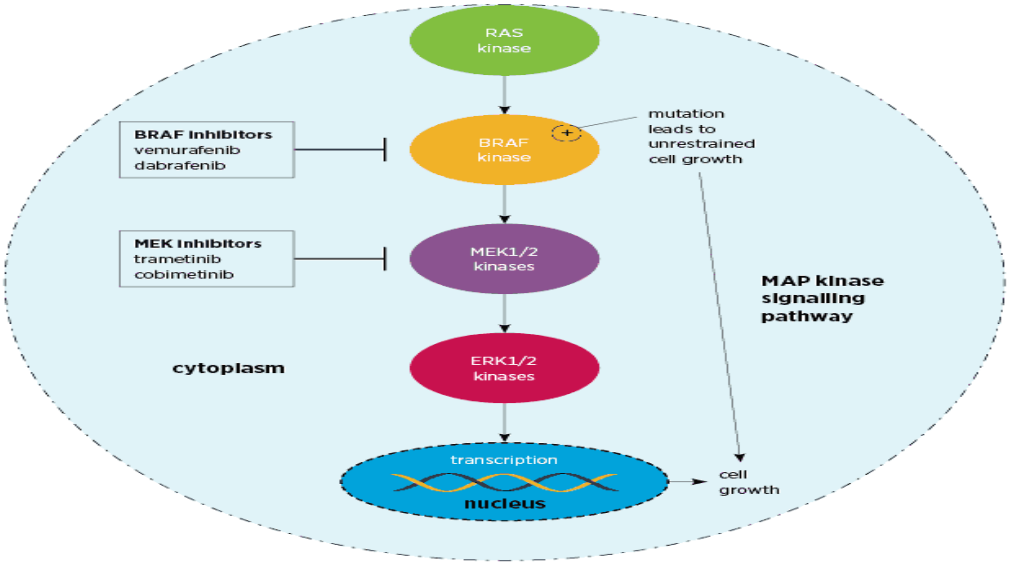
but at lower IC50 than othr BRAFi

The effectiveness of inhibition can have a significant impact on the low paradoxical activation of ERK

Stuart DD, et al. AACR. 2012: abstract 3790, King AJ, et al. PLoS ONE 8:e67583, Poulikakos et al. Nature, 2010

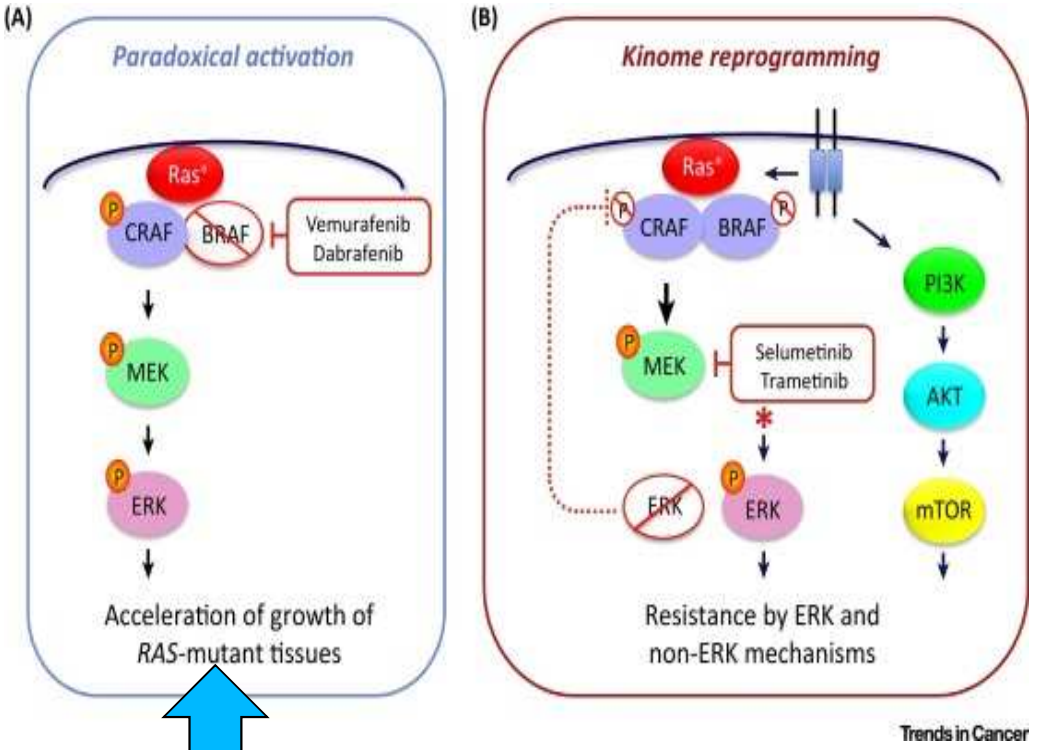
MEK inhibitors



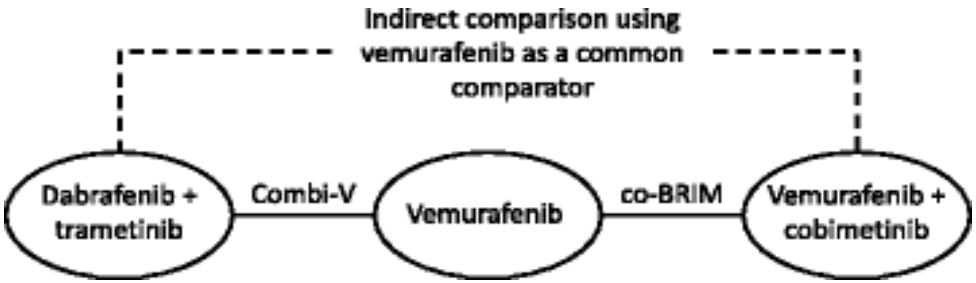


Mechanism of Action

- Cobimetinib is a reversible inhibitor of MAPK/MEK1 and MEK2
- Cobimetinib and vemurafenib target two different kinases in the RAS/RAF/ MEK/ERK pathway
- Compared to either drug alone, coadministration with vemurafenib led to increased apoptosis *in vitro* and reduced tumor growth in mouse implantation models of tumor cell lines harboring BRAF V600E mutations



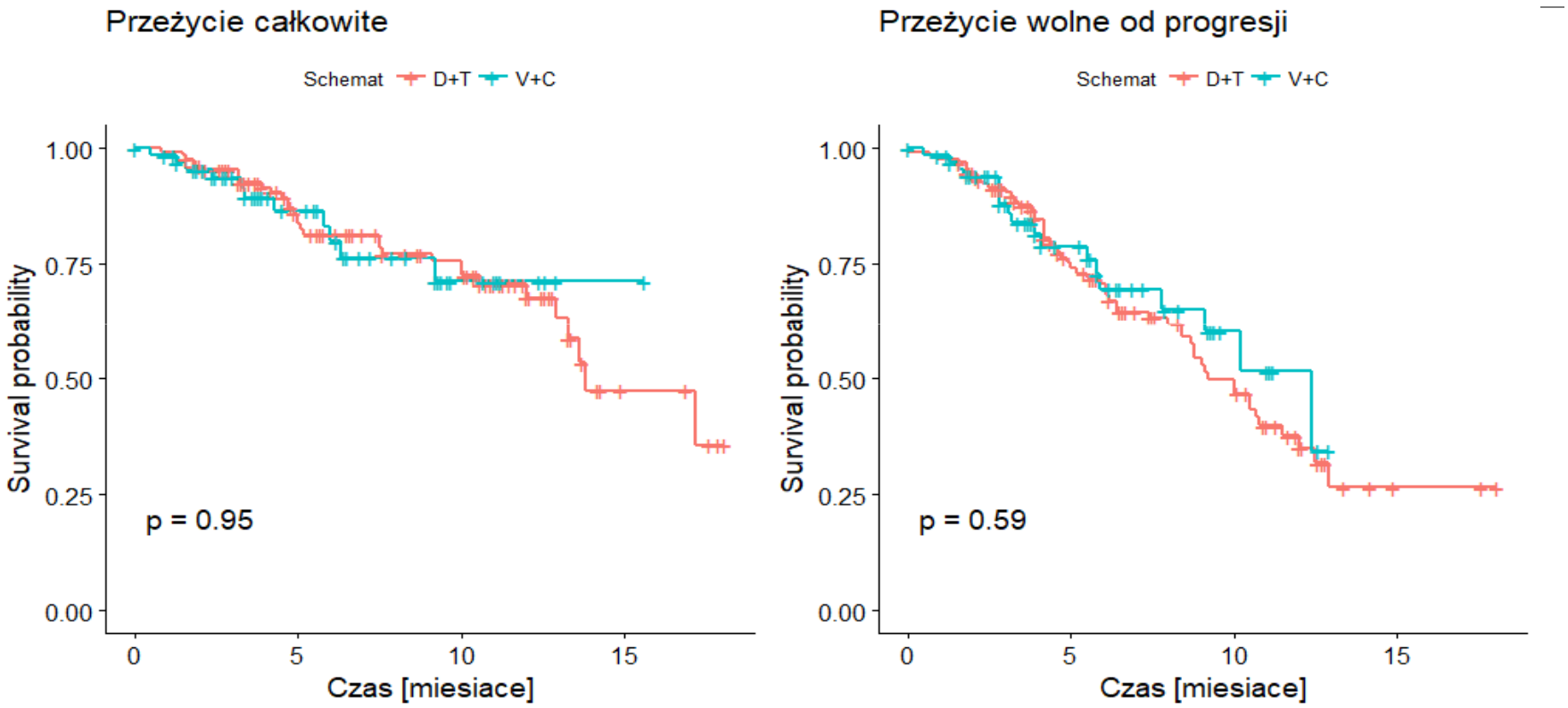
Comparison of doublets



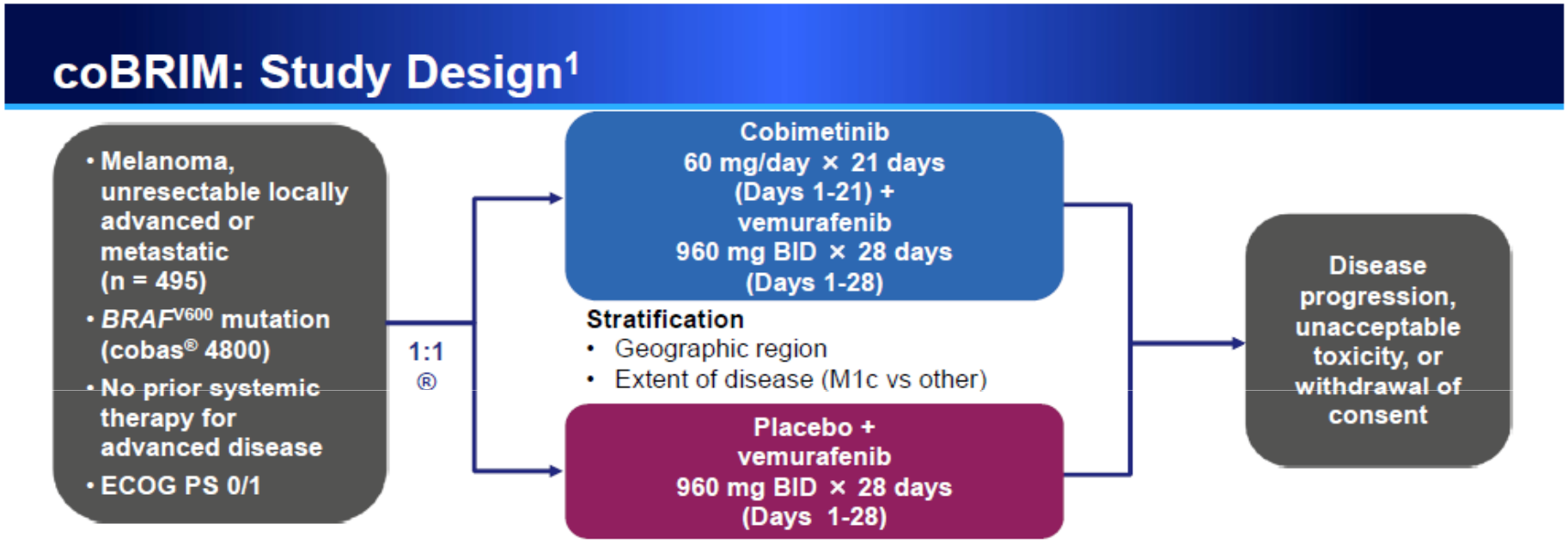
Outcome	COMBI-v		coBRIM		ITC results			
	D + T	V	V	V + C	HR/RR[a]	LCI	UCI	p value
Overall survival, median (95% CI), months	25.6 (22.6 – NR)	18.0 (15.6 – 20.7)	17.4 (15.0 – 19.8)	22.3 (20.3 – NR)	0.94	0.68	1.30	0.7227
Progression-free survival, median (95% CI), months	12.6 (10.7 – 15.5)	7.3 (5.8 – 7.8)	7.2 (5.6 – 7.5)	12.3 (9.5 – 13.4)	1.05	0.79	1.40	0.7300
Overall response rate, no./total no. (%)	226/352 (64%)	180/352 (51%)	124/248 (70%)	172/247 (50%)	0.90	0.74	1.10	0.3029

BRAF(+) treatment in COI

OS and PFS



Vemurafenib-Cobimetinib teratment



Primary end point
- PFS, investigator assessed[1]

Secondary end points
- OS, objective response rate, duration of response, PFS, IRC assessed, safety, pharmacokinetics, quality of life (QLQ-C30 and EQ-5D)

BID, twice daily; ECOG, Eastern Cooperative Oncology Group; EQ, EuroQoL; IRC, independent review committee; PS, performance status; QLQ, quality-of-life questionnaire.

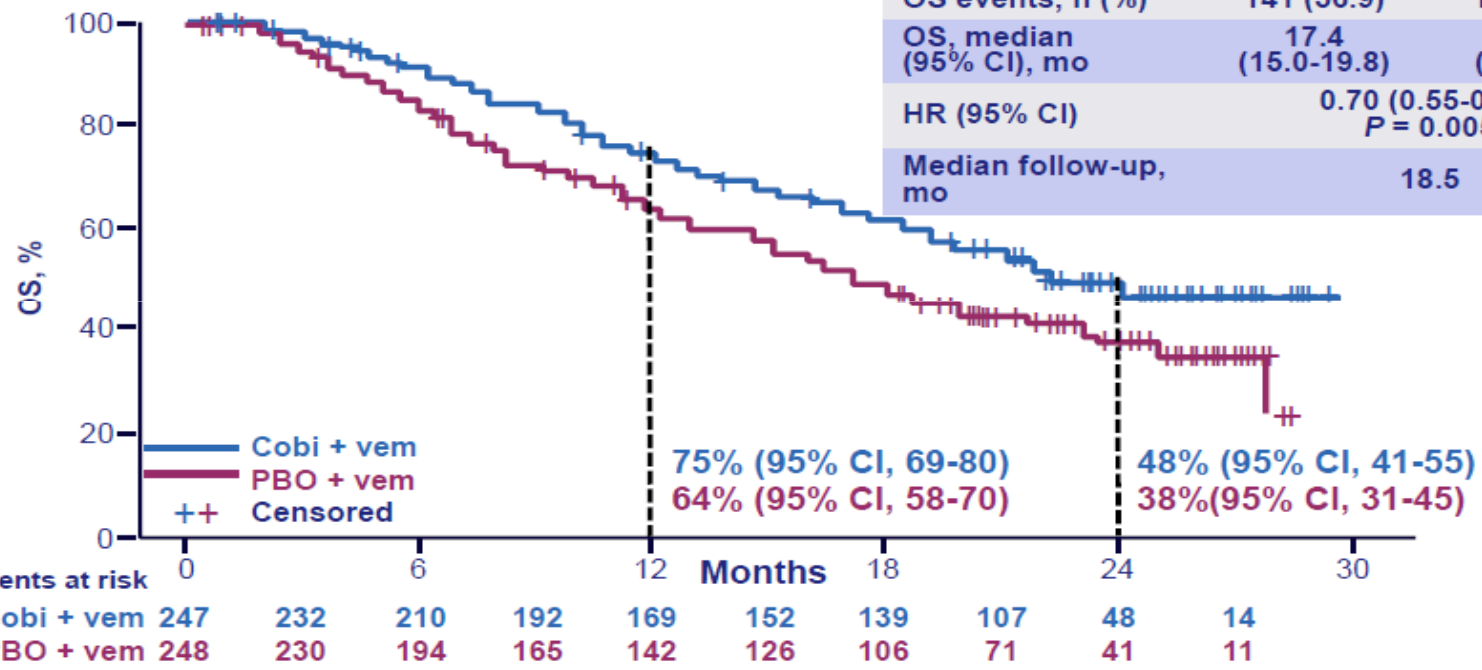
1. Larkin J et al. *N Engl J Med.* 2014;371:1867-1876.

4

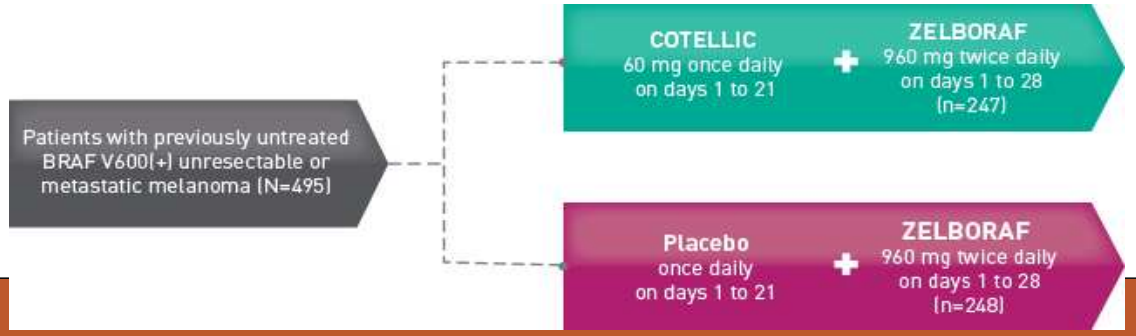
Vemurafenib-Cobimetinib teratment

coBRIM: Addition of Cobimetinib to Vemurafenib Resulted in Significant and Meaningful OS Benefit

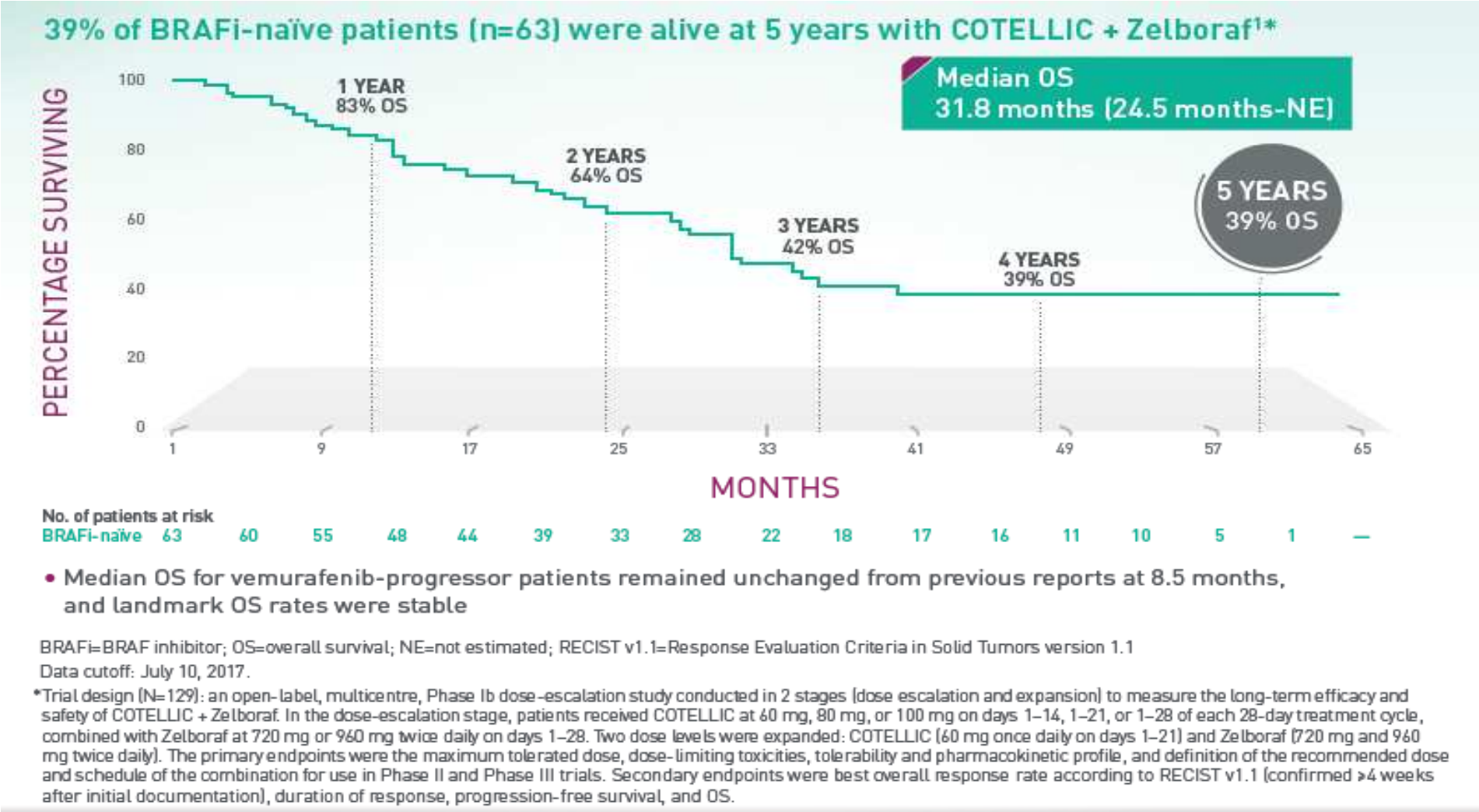
	PBO + Vem n = 248	Cobi + Vem n = 247
OS events, n (%)	141 (56.9)	114 (46.2)
OS, median (95% CI), mo	17.4 (15.0-19.8)	22.3 (20.3-NE)
HR (95% CI)	0.70 (0.55-0.90) *P* = 0.005	
Median follow-up, mo	18.5	



Data cutoff, August 28, 2015.



Vemurafenib-Cobimetinib teratment



- Median OS for vemurafenib-progressor patients remained unchanged from previous reports at 8.5 months, and landmark OS rates were stable

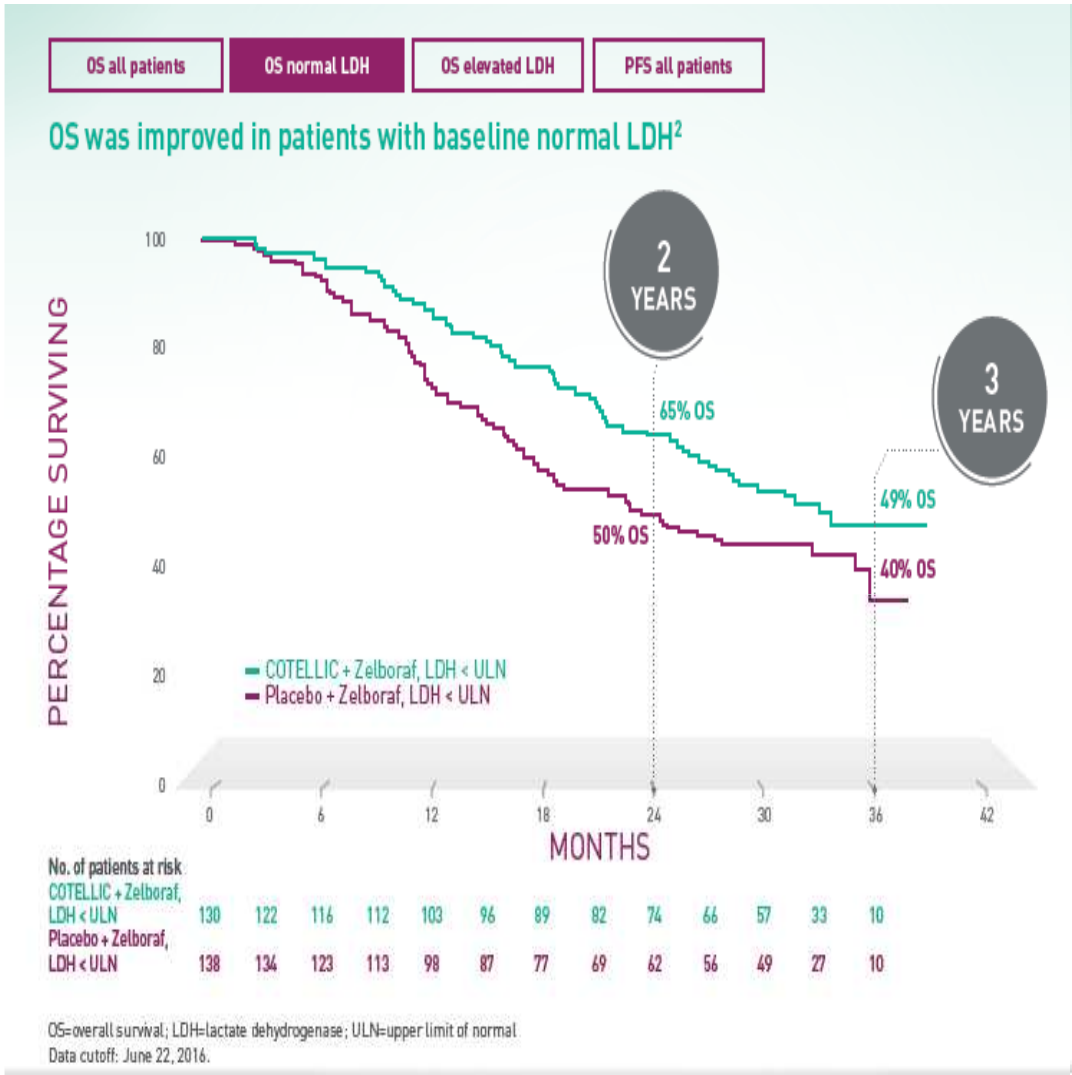
BRAFi=BRAF inhibitor; OS=overall survival; NE=not estimated; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1

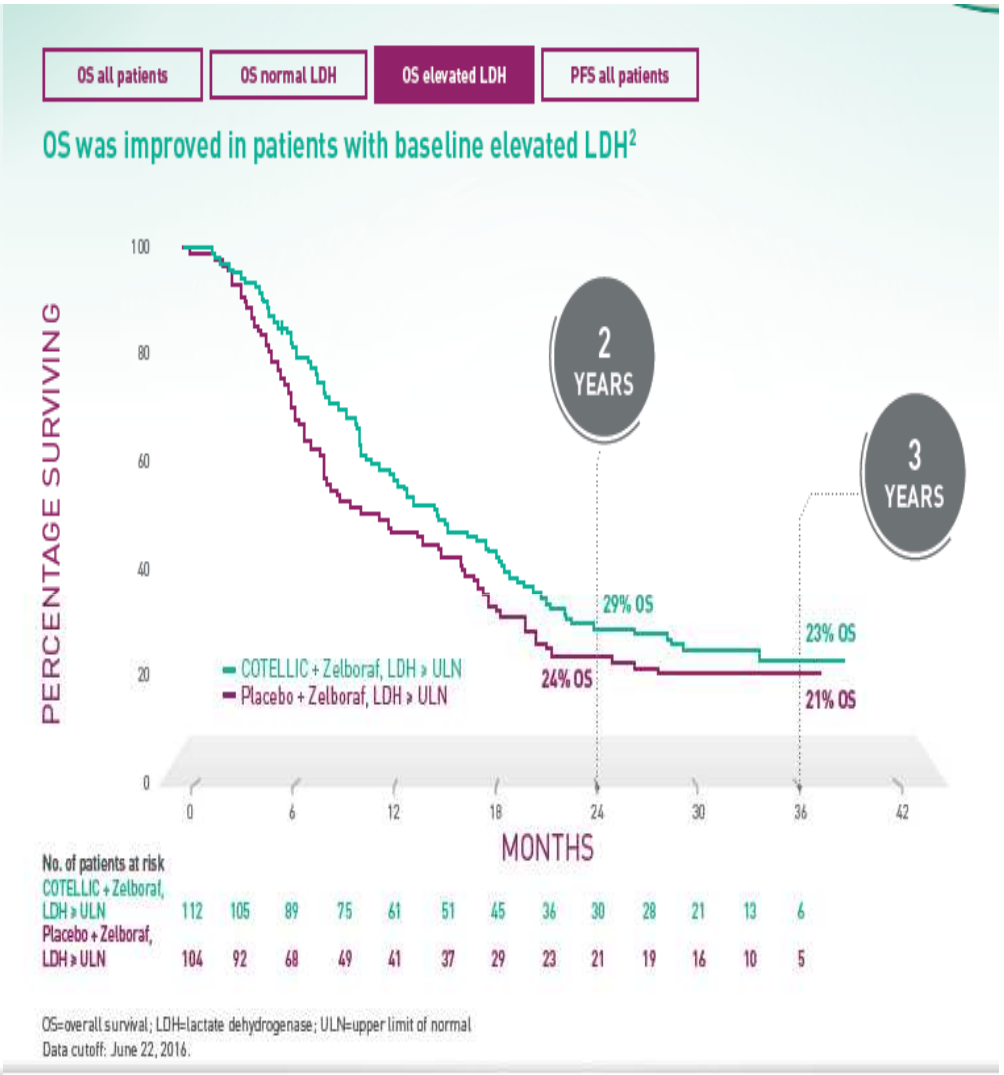
Data cutoff: July 10, 2017.

*Trial design (N=129): an open-label, multicentre, Phase Ib dose-escalation study conducted in 2 stages (dose escalation and expansion) to measure the long-term efficacy and safety of COTELLIC + Zelboraf. In the dose-escalation stage, patients received COTELLIC at 60 mg, 80 mg, or 100 mg on days 1–14, 1–21, or 1–28 of each 28-day treatment cycle, combined with Zelboraf at 720 mg or 960 mg twice daily on days 1–28. Two dose levels were expanded: COTELLIC (60 mg once daily on days 1–21) and Zelboraf (720 mg and 960 mg twice daily). The primary endpoints were the maximum tolerated dose, dose-limiting toxicities, tolerability and pharmacokinetic profile, and definition of the recommended dose and schedule of the combination for use in Phase II and Phase III trials. Secondary endpoints were best overall response rate according to RECIST v1.1 (confirmed >4 weeks after initial documentation), duration of response, progression-free survival, and OS.

Daud A, et al. Poster presented at: 2017 Society for Melanoma ResearchCongress; October 18–21, 2017; Brisbane, Australia.

Vemurafenib-Cobimetinib teratment

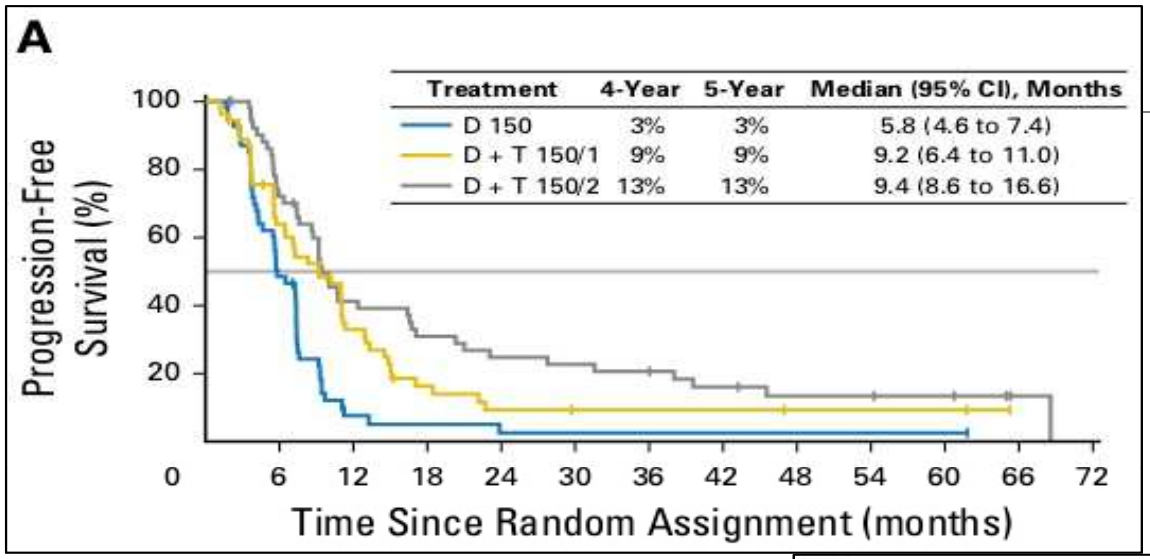




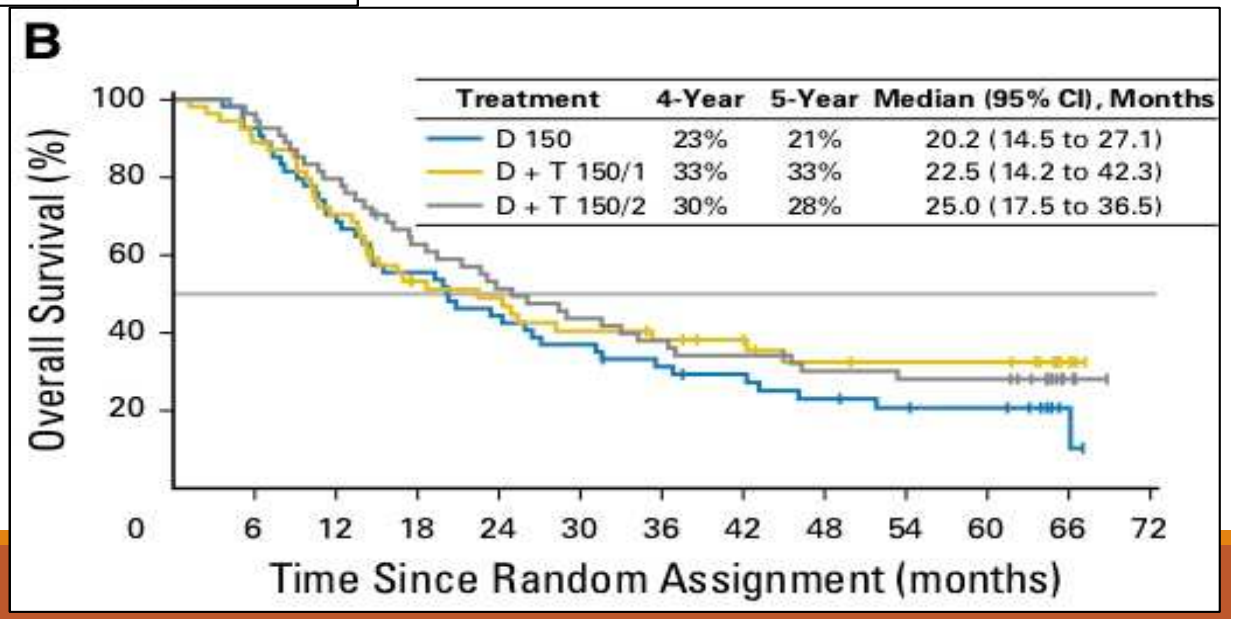
LDH < ULN

LDH > ULN

Long term effects of BRAFi/MEKi treatment?

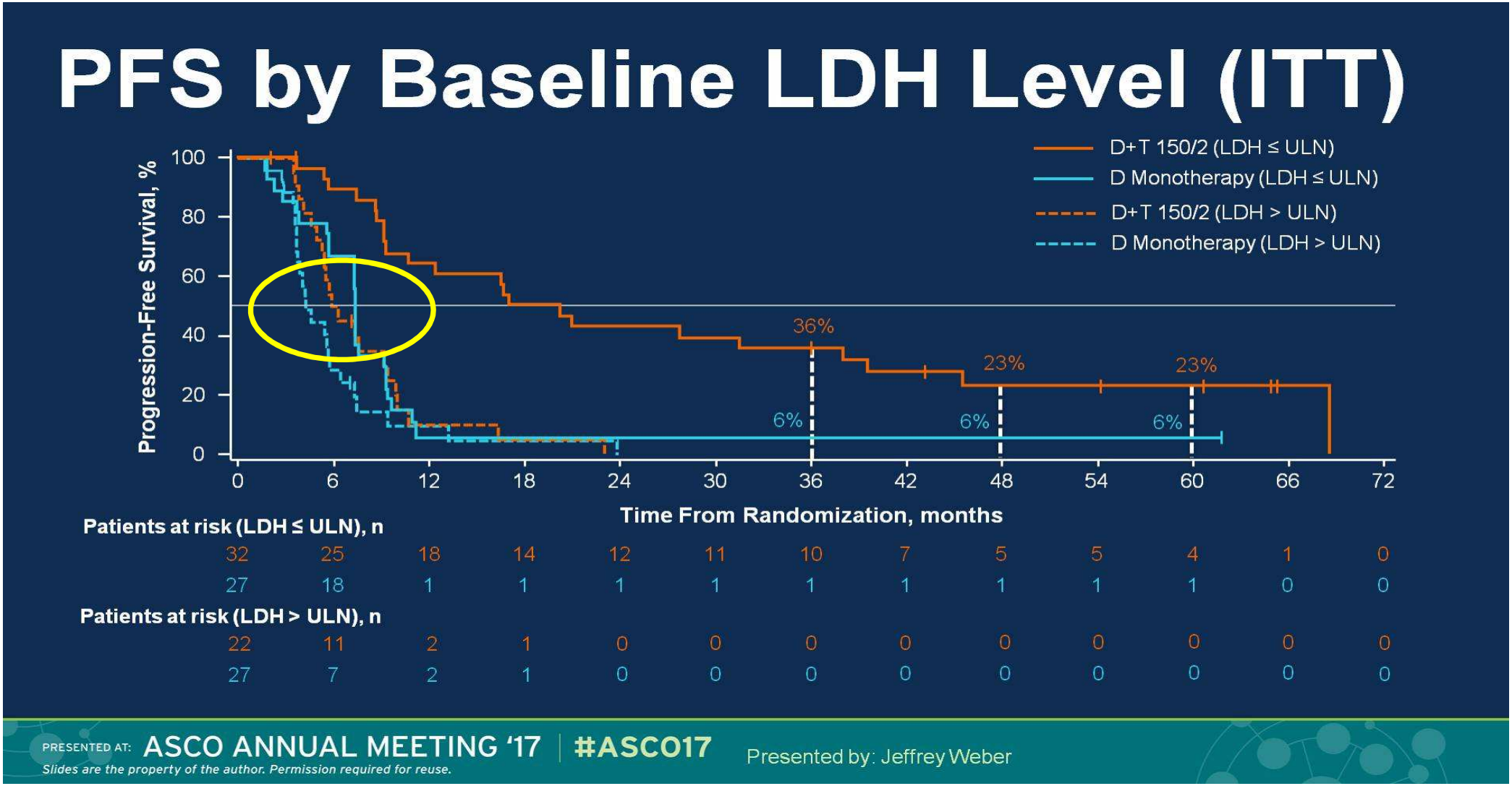


After 5 years:
PFS =13% OS= 28%



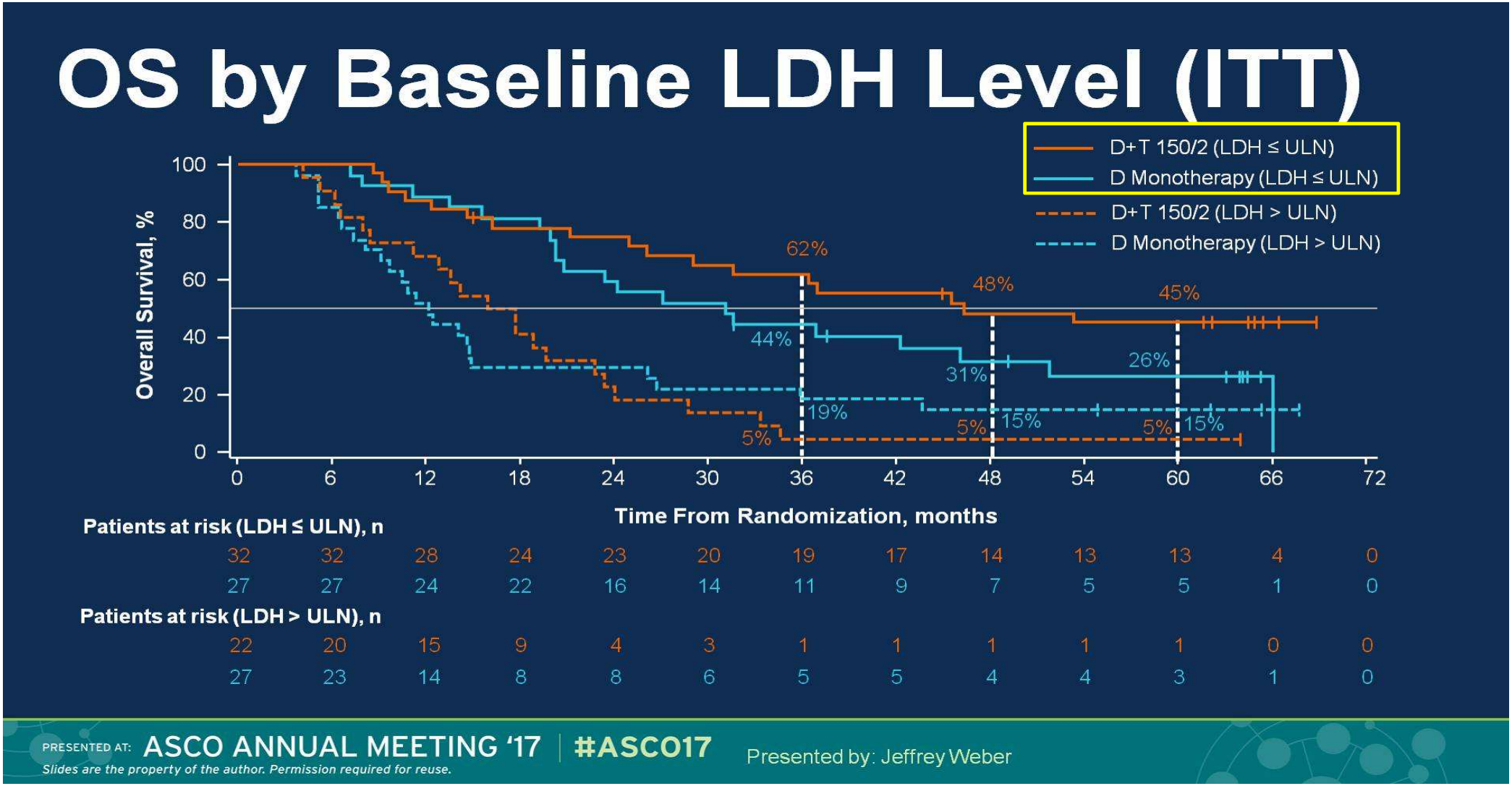
Long GV.et al. J Clin Oncol. 2018 36:667-673

Long term effects of BRAFi/MEKi treatment?



Presented By Georgina Long at 2017 ASCO Annual Meeting

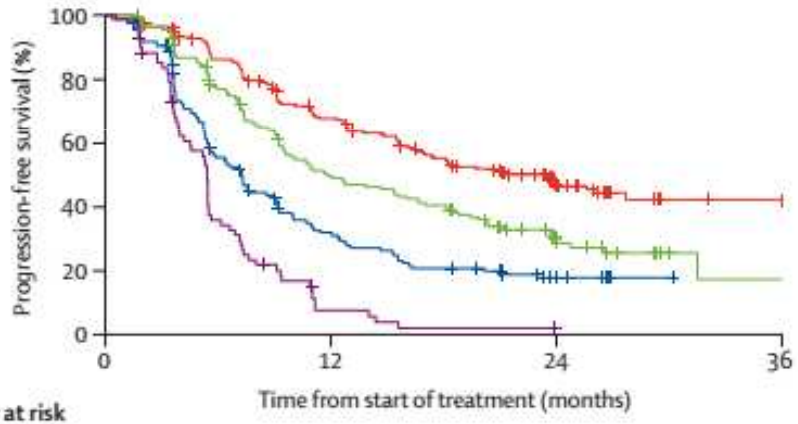
Long term effects of BRAFi/MEKi treatment?



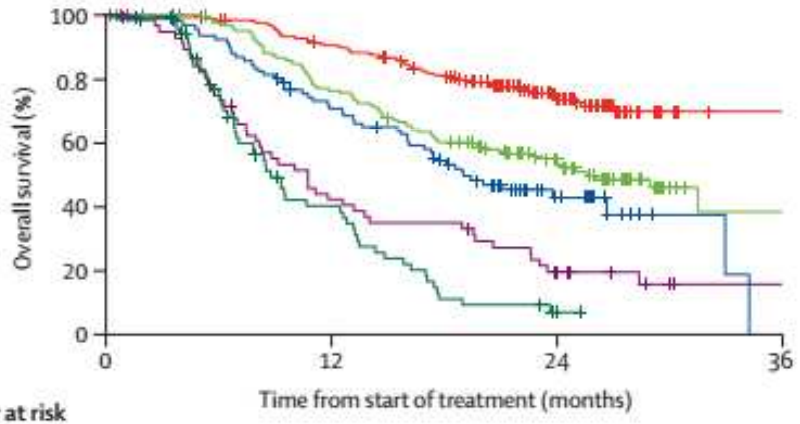
Long term benefit with BRAFi/MEKi?

Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination treatment: a pooled analysis of individual patient data from randomised trials

Georgina V Long, Jean-Jacques Grob, Paul Nathan, Antoni Ribas, Caroline Robert, Dirk Schadendorf, Stephen R Lane, Carmen Mak, Philippe Legenne, Keith T Flaherty, Michael A Davies



Number at risk (number censored)				
Normal LDH, <3 organ sites with metastasis	237 (0)	149 (15)	53 (53)	8 (42)
Normal LDH, ≥3 organ sites with metastasis	161 (0)	69 (20)	23 (19)	2 (18)
LDH: ≥1 to <2×ULN	149 (0)	40 (16)	9 (14)	0 (9)
LDH: ≥2×ULN	70 (0)	4 (7)	0 (1)	0 (0)



Number at risk (number censored)				
Normal LDH, <3 organ sites with metastasis	237 (0)	206 (9)	103 (70)	14 (84)
Normal LDH, ≥3 organ sites with metastasis	161 (0)	119 (5)	58 (29)	5 (45)
LDH: ≥1 to <2×ULN, ECOG PS=0	93 (0)	61 (6)	15 (24)	0 (12)
LDH: ≥1 to <2×ULN, ECOG PS ≥1	56 (0)	23 (1)	9 (2)	1 (7)
LDH: ≥2×ULN	70 (0)	22 (12)	1 (3)	0 (1)

igure 2: **Regression tree analysis of factors most associated with progression-free survival and overall survival**

Long term benefit with BRAFi/MEKi?

VOLUME 34 · NUMBER 8 · MARCH 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Overall Survival and Durable Responses in Patients With *BRAF* V600–Mutant Metastatic Melanoma Receiving Dabrafenib Combined With Trametinib

Georgina V. Long, Jeffrey S. Weber, Jeffrey R. Infante, Kevin B. Kim, Adil Daud, Rene Gonzalez, Jeffrey A. Sosman, Omid Hamid, Lynn Schuchter, Jonathan Cebon, Richard F. Kefford, Donald Lawrence, Ragini Kudchadkar, lageatte Ibrahim, Peng Sun, n Patel, and Keith T. Flaherty

Overall Survival in Melanoma With BRAF and MEK Inhibition

Table 2. Baseline Characteristics, Best Response, and OS in Patients Treated With a Combination of Dabrafenib 150 mg Twice Daily and Trametinib 2 mg Once Daily: Part C (n = 54)

Factor	No.	HR	Median OS, Months	1-Year OS, %	2-Year OS, %	3-Year OS, %
Overall population	54		25 (17.5 to 36.5)	80 (66 to 88)	51 (37 to 64)	38 (25 to 51)
LDH						
> ULN	22		16.6 (11.1 to 22.6)	68 (44.6 to 83.4)	18 (5.7 to 36.3)	5 (0.3 to 18.9)
≤ ULN	32	0.25 (0.12 to 0.53)	45.5 (29.0 to not reached)	88 (70.0 to 95.1)	75 (55.6 to 86.4)	62 (42.4 to 76.1)
No. of disease sites						
≥ 3	28		17.5 (12.7 to 23.8)	68 (47.3 to 81.8)	30 (14.5 to 47.9)	19 (7.0 to 35.5)
< 3	26	0.36 (0.18 to 0.69)	45.5 (28.4 to not reached)	92 (72.6 to 98.0)	73 (51.7 to 86.2)	58 (36.8 to 73.9)
Sex						
Male	34	1.13 (0.57 to 2.23)	23.8 (17.5 to 36.5)	88 (71.6 to 95.4)	49 (31.1 to 64.3)	37 (20.8 to 52.6)
Female	20		25.5 (9.1 to not reached)	65 (40.3 to 81.5)	55 (31.3 to 73.5)	40 (19.3 to 60.0)
Stage						
IIIC/M1a/M1b	16	0.36 (0.18 to 0.72)	— (34.3 to not reached)	88 (58.6 to 96.7)	74 (45.4 to 89.6)	68 (38.8 to 85.2)
M1c	38		21.9 (15.7 to 28.4)	76 (59.4 to 86.9)	42 (26.4 to 57.0)	26 (13.7 to 40.8)
Sum of diameters						
≥ Median	27		17.4 (10.7 to 29.0)	63 (42.1 to 78.1)	37 (19.6 to 54.6)	30 (14.1 to 47.0)
< Median	27	0.61 (0.31 to 1.18)	34.3 (22.6 to 45.5)	96 (76.5 to 99.5)	66 (44.2 to 80.4)	46 (26.8 to 63.8)
Age, years						
≥ 65	11		21.3 (12.4 to not reached)	82 (44.7 to 95.1)	36 (11.2 to 62.7)	27 (6.5 to 53.9)
< 65	43	0.81 (0.35 to 1.88)	28.4 (17.5 to 45.5)	79 (63.6 to 88.5)	55 (39.1 to 68.7)	41 (26.0 to 55.1)
Baseline ECOG PS						
≥ 1	19		22.6 (12.7 to not reached)	74 (47.9 to 88.1)	42 (20.4 to 62.5)	37 (16.5 to 57.5)
< 1	35	0.92 (0.46 to 1.86)	29.0 (18.6 to 37.0)	83 (65.8 to 91.9)	56 (38.3 to 70.9)	39 (22.5 to 54.3)
Prior immunotherapy						
No	34	1.27 (0.64 to 2.48)	24.0 (17.4 to 36.5)	79 (61.6 to 89.6)	50 (32.4 to 65.3)	35 (19.9 to 51.0)
Yes	20		31.6 (14.6 to not reached)	80 (55.1 to 92.0)	53 (29.4 to 72.4)	43 (20.8 to 63.0)
RECIST best response						
Stable disease	13		21.3 (8.6 to not reached)	69 (37.3 to 87.2)	35 (10.9 to 60.2)	35 (10.9 to 60.2)
Partial response	33	0.98 (0.44 to 2.19)	23.1 (16.2 to 34.3)	79 (60.6 to 89.3)	48 (30.8 to 64.1)	33 (18.2 to 49.3)
Complete response	8	0.38 (0.12 to 1.25)	— (29.0 to not reached)	100	88 (38.7 to 98.1)	63 (22.9 to 86.1)

Abbreviations: ECOG, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal.

What where when?

Figure. General Algorithm for Treatment of Patients With Metastatic Melanoma

Metastatic melanoma clinical status							
• Poor performance status (ECOG PS >1) related to melanoma[a] • High-volume disease (total volume ≥10 cm or involvement of >5 organ systems) • Rapid progression • Lactate dehydrogenase ≥2 x ULN		• CNS metastases[b]		• Good performance status (ECOG PS ≤1) • Low-volume disease (total volume <10 cm or involvement of <5 organ systems) • No CNS disease • Slow to moderate progression • Lactate dehydrogenase <2 x ULN		• Locoregional disease (IIIB through IVM1a) • Low visceral metastatic burden	
Molecular status (*BRAF* V600E or V600K mutation present [+] or absent [-])							
BRAF (+)	*BRAF* (-)	*BRAF* (+)	*BRAF* (-)	*BRAF* (+)	*BRAF* (-)	*BRAF* (+)	*BRAF* (-)
Treatment: 1st line							
IPI/NIVO or BRAF/MEK[c]	IPI/NIVO	IPI/NIVO or BRAF/MEK[d]	IPI/NIVO	Anti-PD-1	Anti-PD-1	Anti-PD-1 or T-VEC	Anti-PD-1 or T-VEC
2nd line							
BRAF/MEK or IPI/NIVO	Clinical trial or Palliative care or T-VEC[e]	BRAF/MEK or IPI/NIVO	IL-2[f] or Clinical trial or Palliative care	Ipilimumab or BRAF/MEK	Ipilimumab	T-VEC or Anti-PD-1	T-VEC or Anti-PD-1
3rd line							
Clinical trial or Palliative care or T-VEC[e]		IL-2[f] or Clinical trial or Palliative care		IL-2[f] or Clinical trial or Palliative care	IL-2[f] or Clinical trial or Palliative care	Ipilimumab or BRAF/MEK	Ipilimumab

Abbreviations: Anti-PD-1, anti-programmed cell death 1 monotherapy (pembrolizumab or nivolumab); BRAF/MEK, combination BRAF plus MEK inhibitors; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; IL-2, Interleukin 2; IPI/NIVO, combination ipilimumab plus nivolumab; T-VEC, talimogene laherparepvec; ULN, upper limit of normal.

[a]Patients with poor performance status due to comorbidities should not be treated with IPI/NIVO.

[b]Treatment of CNS metastasis may also include craniotomy and/or stereotactic radiosurgery.

[c]Preferred if imminent, life-threatening complications of melanoma.

[d]Preferred if symptomatic and unable to taper steroids or resect lesions, with risk of steroid dependency.

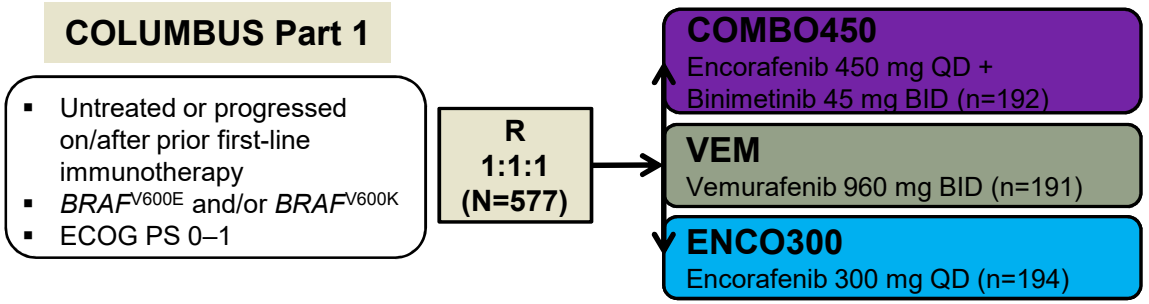
[e]If limited visceral disease burden.

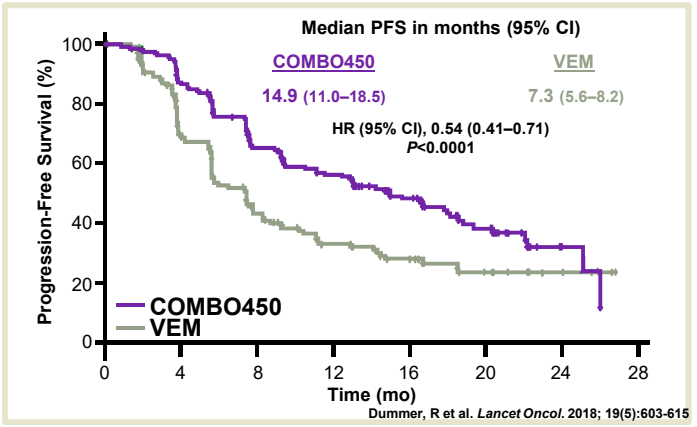
[f]IL-2 can be considered if all CNS disease is controlled and there is no cerebral edema or corticosteroid use.

JAMA Oncol. 2018;4(6):857-858.

What is new in BRAFi/MEKi treatment?

Study Design and Objectives





Efficacy update with additional follow-up of 18 months:

OS:

- Secondary endpoint†
- Planned after 232 events in the COMBO450 and VEM groups combined
- Median duration of follow-up‡: 36.8 months

PFS:

- Primary endpoint
- Median duration of follow-up‡: 32.1 months

COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; ECOG PS=Eastern Cooperative Oncology Group performance status; OS=overall survival; PFS=progression-free survival; R=randomization; VEM=vemurafenib 960 mg BID.
*Amendment requested by FDA.
†Included in hierarchical testing approach.
‡Median follow-up of patients assessed using reverse Kaplan-Meier approach (i.e. median potential follow-up).

New BRAFi/MEKi treatment – encorafenib + binimetinib

Baseline Characteristics

Characteristic	COMBO450 n=192	ENCO300 n=194	VEM n=191
Median age (range), years	57 (20–89)	54 (23–88)	56 (21–82)
Male sex	60%	56%	58%
ECOG performance status 0	71%	72%	73%
LDH > ULN	29%	24%	27%
LDH ≤ ULN	71%	76%	73%
***BRAF* mutation status (*BRAF*^{V600E}/*BRAF*^{V600K})**	89%/12%	89%/10%	88%/12%
Tumor stage at study entry			
IIIB/IIIC	5%	3%	6%
IVM1a	14%	15%	13%
IVM1b	18%	20%	16%
IVM1c	64%	62%	65%
Number of organs involved			
1	25%	29%	24%
2	30%	27%	31%
≥3	45%	44%	46%

New BRAFi/MEKi treatment – encorafenib + binimetinib

Previous Immunotherapy

Adjuvant/neoadjuvant settings	COMBO450 n=192	ENCO300 n=194	VEM n=191
Ipilimumab*	1%	1%	1%
Interferons/interleukins†			
Adjuvant	24%	24%	24%
Neoadjuvant	0	1%	1%

Advanced/metastatic settings	COMBO450 n=192	ENCO300 n=194	VEM n=191
Ipilimumab*	3%	5%	3%
Anti–PD-1 or anti–PD-L1*,‡	1%	1%	0
Interferons/interleukins§	2%	2%	3%

COMBO450=encorafenib 450 mg QD plus binimetinib 45 mg BID; ENCO300=encorafenib 300 mg QD; PD-1=programmed death 1; PD-L1=programmed death ligand 1; VEM=vemurafenib 960 mg BID.
*A patient may have received ipilimumab and anti–PD1/PD-L1 in combination.
†Includes interferon, interferon α, interferon α-2A, interferon α-2B, and interferon β.
‡Nivolumab.
§Includes interferon, interferon α-2B, and interleukin-2.

New BRAFi/MEKi treatment – encorafenib + binimetinib

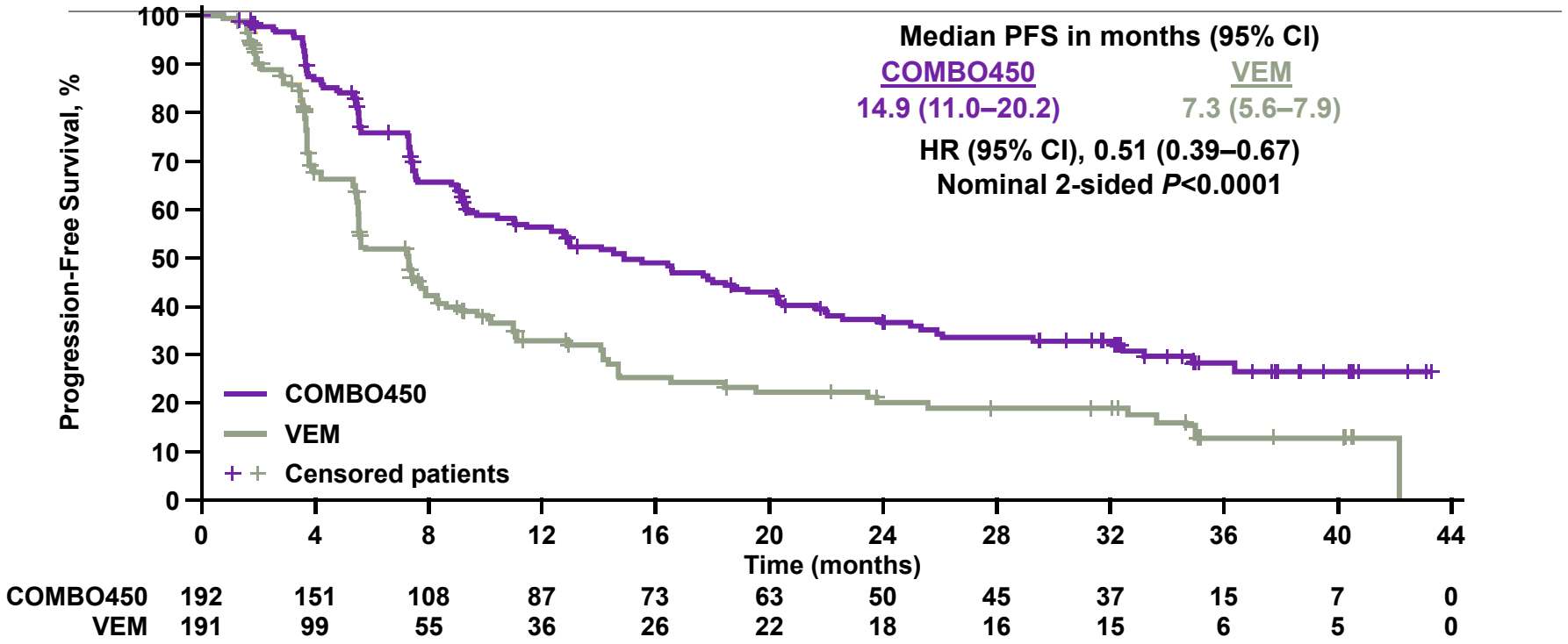
Patient Disposition

Variable, %	COMBO450 n=192	ENCO300 n=194	VEM n=191
Untreated	0	1%	3%
Discontinued treatment	78%	87%	91%
Progressive disease	52%	52%	57%
Adverse event	10%	13%	13%
Physician or patient decision*	10%	21%	18%
Death	4%	1%	2%
Other†	1%	1%	1%
Treatment ongoing‡	22%	12%	7%

COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; ENCO300=encorafenib 300 mg QD; VEM=vemurafenib 960 mg BID.
*Physician or patient/guardian decision.
†Includes protocol violation, lost to follow-up, and new therapy for study indication.
‡As of the data cutoff date of November 7, 2017.

New BRAFi/MEKi treatment – encorafenib + binimetinib

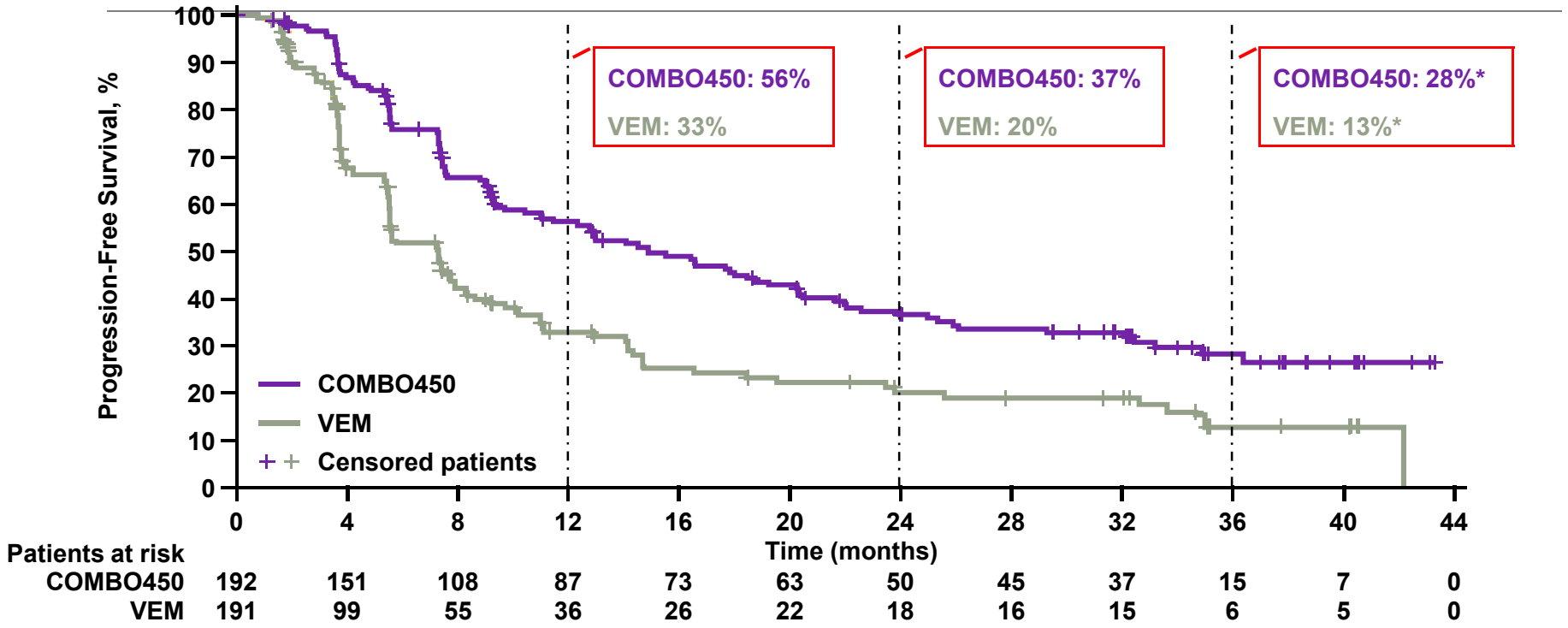
Updated Progression-Free Survival: COMBO450 vs VEM



COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; HR=hazard ratio; PFS=progression-free survival; VEM=vemurafenib 960 mg BID.

New BRAFi/MEKi treatment – encorafenib + binimetinib

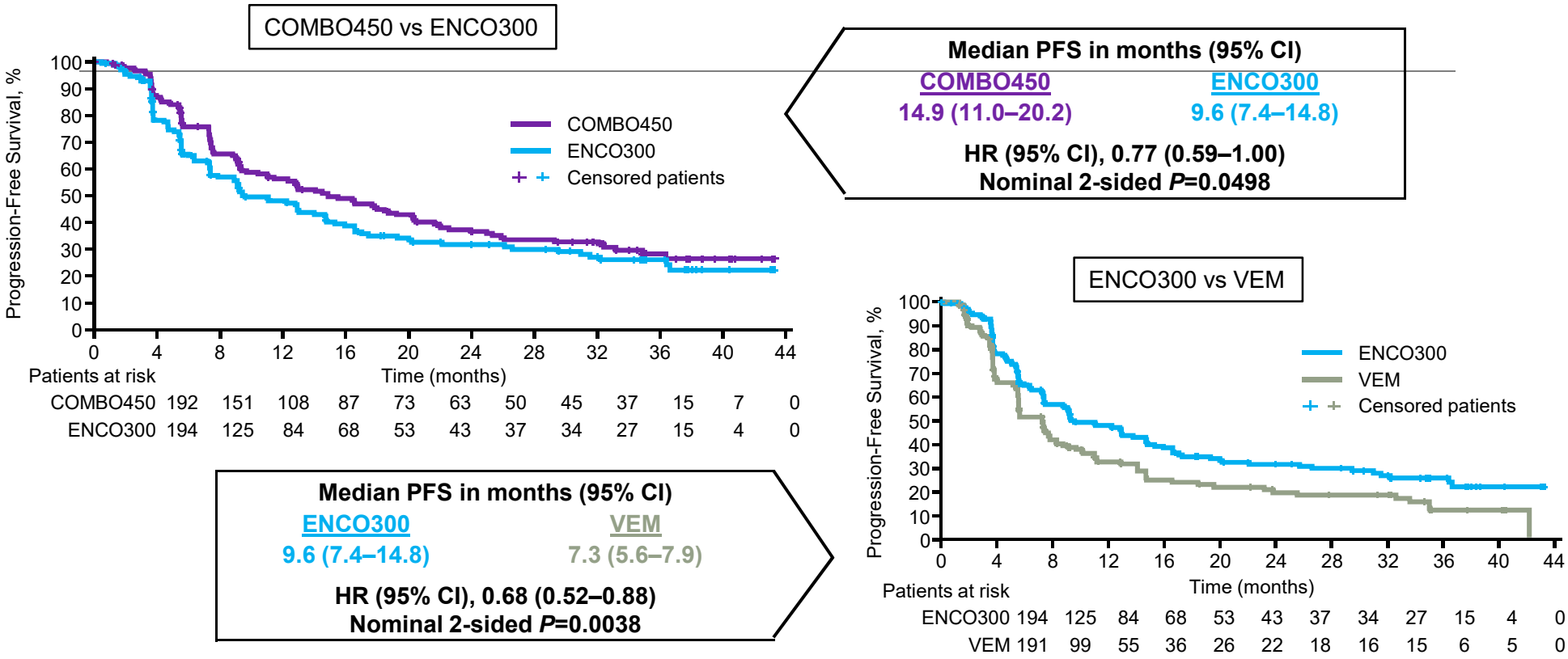
Updated Progression-Free Survival Landmark Data: COMBO450 vs VEM



COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; VEM=vemurafenib 960 mg BID.
*3-year rates are not fully mature and are based on small numbers of patients at risk.

New BRAFi/MEKi treatment – encorafenib + binimetinib

Updated Progression-Free Survival



COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; ENCO300=encorafenib 300 mg QD; HR=hazard ratio; PFS=progression-free survival; VEM=vemurafenib 960 mg BID.

New BRAFi/MEKi treatment – encorafenib + binimetinib

Confirmed Response Rates

Confirmed Response	COMBO450 n=192		ENCO300 n=194		VEM n=191	
	Central Review	Local Review	Central Review	Local Review	Central Review	Local Review
ORR (95% CI)*	**64% (57–70)**	**76% (69–81)**	**52% (44–59)**	58% (50–65)	**41% (34–48)**	49% (42–57)
CR	11%	19%	7%	10%	8%	8%
PR	52%	56%	44%	48%	32%	41%
Median DOR (95% CI), mo	18.6 (12.7–24.1)	16.2 (11.1–24.1)	15.2 (11.1–27.6)	14.8 (11.0–16.6)	12.3 (6.9–14.5)	7.7 (5.8–11.0)
SD†	29%	17%	32%	29%	40%	35%
PD‡	8%	7%	16%	13%	19%	16%
DCR (95% CI)§	92% (87–96)	93% (88–96)	84% (78–89)	87% (81–91)	81% (75–86)	84% (78–89)

COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; CR=complete response; DCR=disease control rate; DOR=duration of response; ENCO300=encorafenib 300 mg QD; ORR=overall response rate; PD=progressive disease; PR=partial response; SD=stable disease; VEM=vemurafenib 960 mg BID.

*ORR = CR + PR.

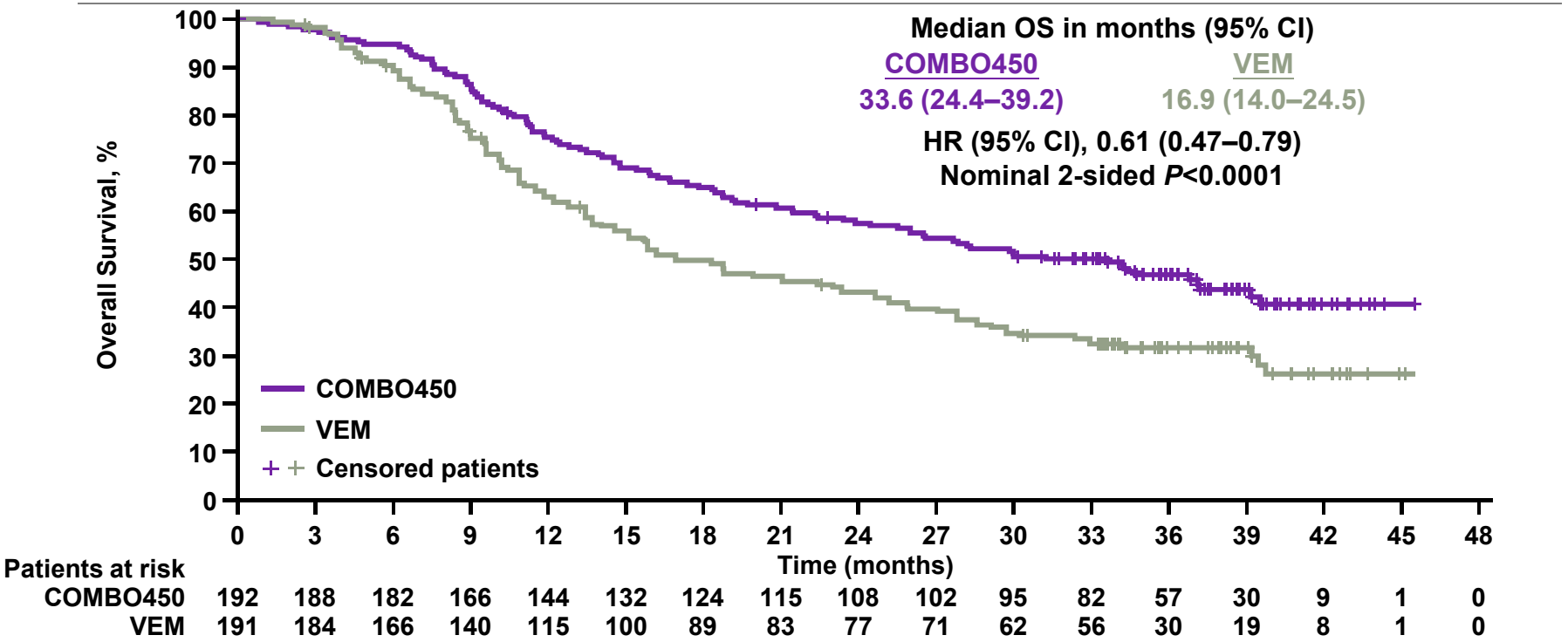
†Includes patients with only non-target lesions with best response of non-CR/non-PD.

‡Includes patients with best response of unknown or no assessment.

§DCR = CR + PR + SD.

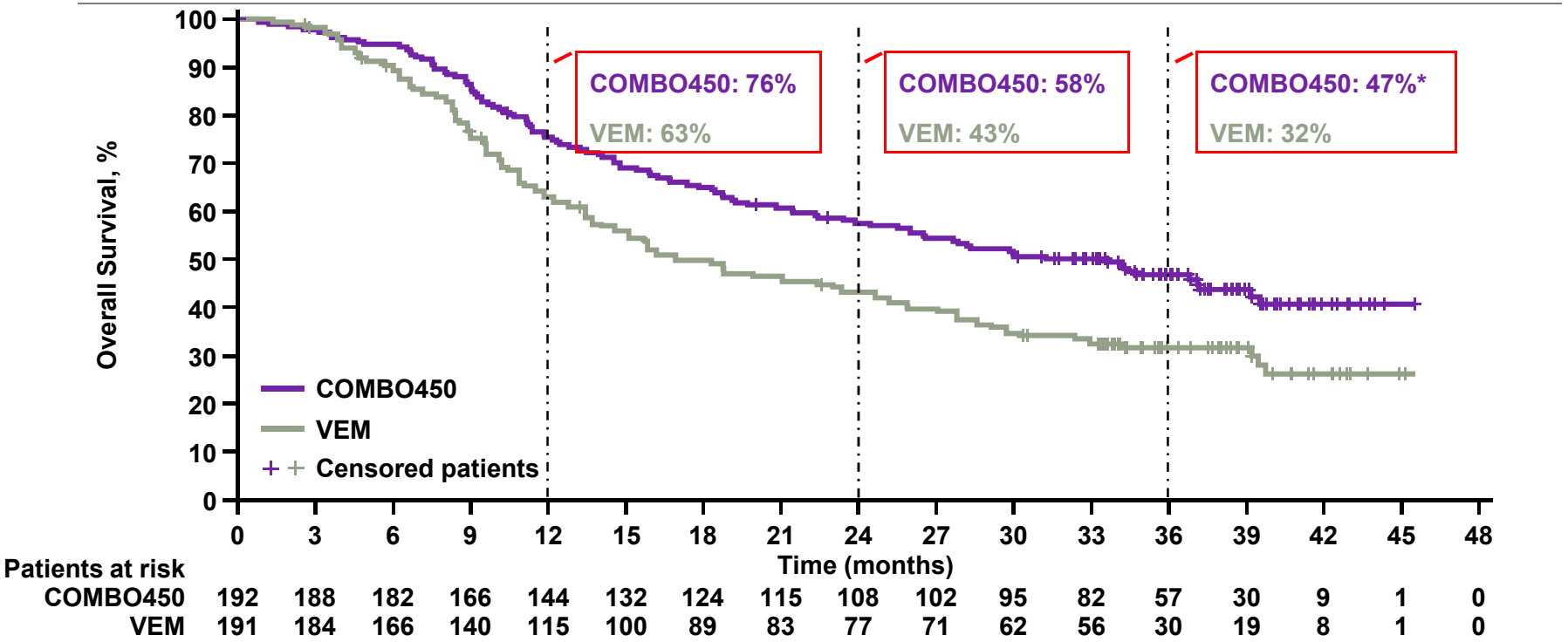
New BRAFi/MEKi treatment – encorafenib + binimetinib

Overall Survival: COMBO450 vs VEM



New BRAFi/MEKi treatment – encorafenib + binimetinib

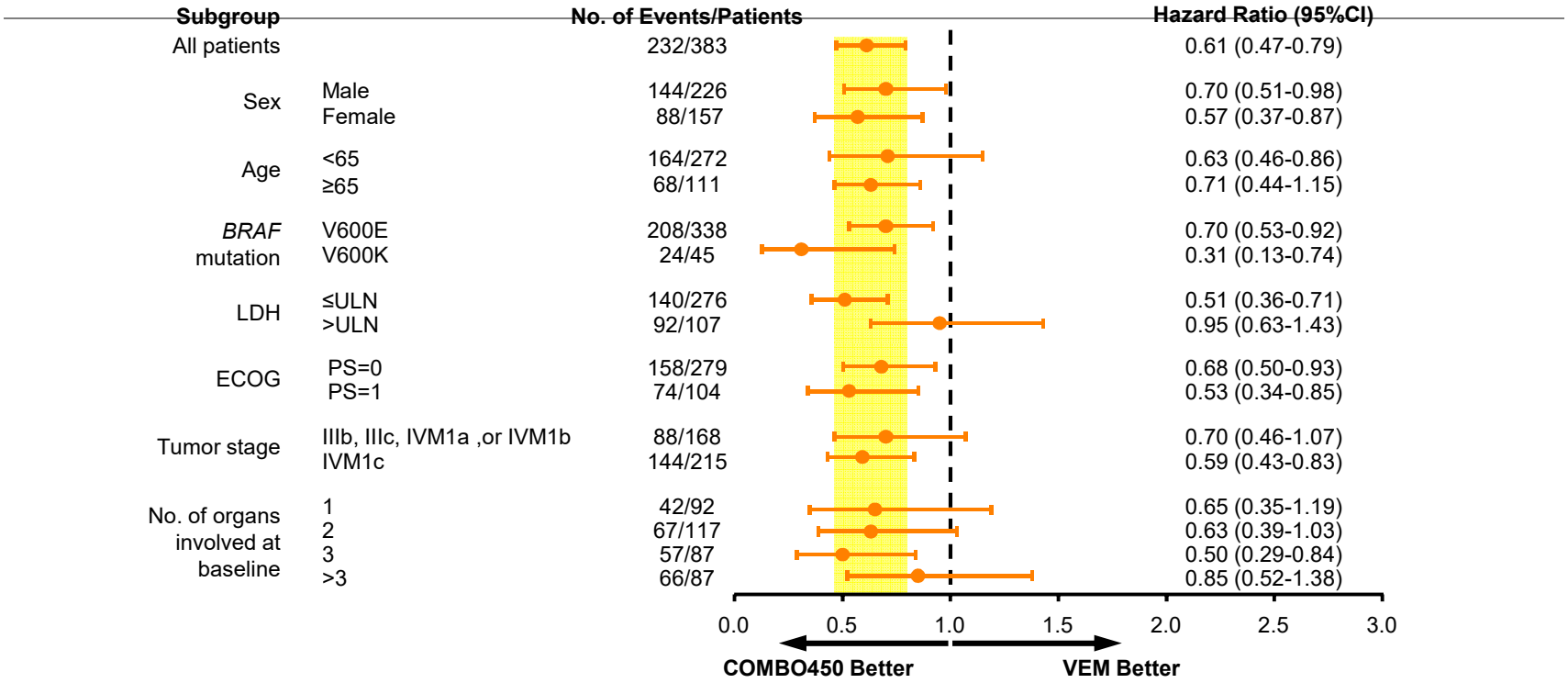
Overall Survival Landmark Data: COMBO450 vs VEM



COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; VEM=vemurafenib 960 mg BID.
*3-year rates are not fully mature.

New BRAFi/MEKi treatment – encorafenib + binimetinib

Overall Survival in Subgroups:COMBO450 vs VEM



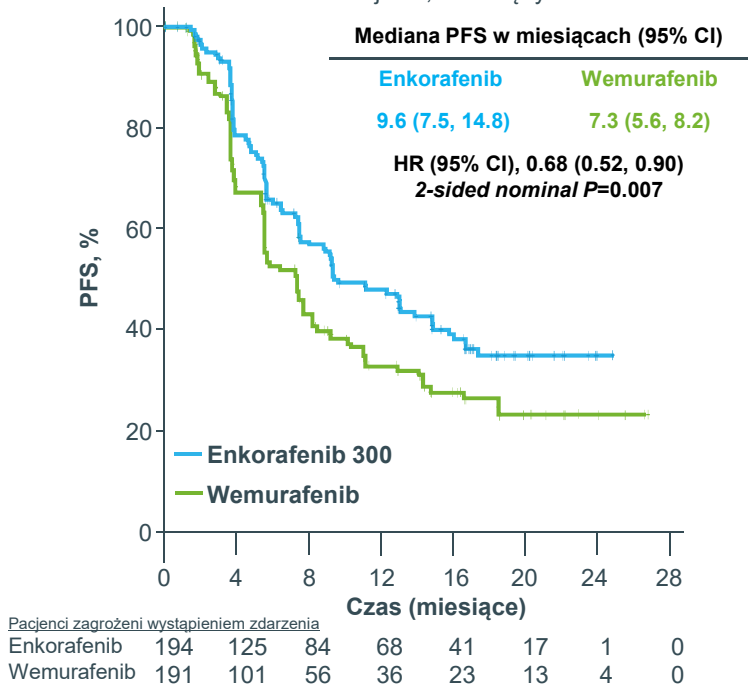
COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; PS=performance status; ULN=upper limit of normal; VEM=vemurafenib 960 mg BID.

New BRAFi/MEKi treatment – encorafenib + binimetinib

PFS: encorafenib 300 vs vemurafenib

Ocena centralna

Mediana czasu obserwacji: 16,6 miesięcy



Pacjenci zagrożeni wystąpieniem zdarzenia

Enkorafenib	194	125	84	68	41	17	1	0
Wemurafenib	191	101	56	36	23	13	4	0

CI, przedział ufności HR, współczynnik ryzyka; PFS, czas wolny od progresji

Drugorzędowy punkt końcowy: Ocena lokalna[1]

Mediana czasu obserwacji: 16,6 miesięcy

Mediana PFS w miesiącach (95% CI)	
Enkorafenib	Wemurafenib
9.2 (7.4, 12.9)	7.3 (5.7, 8.5)

HR (95% CI), 0.70 (0.54, 0.91)
P=0.0084**

*Nominal *P* value

Aktualizacja PFS: Ocena centralna[2]

Mediana czasu obserwacji : 32,1 miesiąca

Mediana PFS w miesiącach (95% CI)	
Enkorafenib	Wemurafenib
9.6 (7.4–14.8)	7.3 (5.6–7.9)

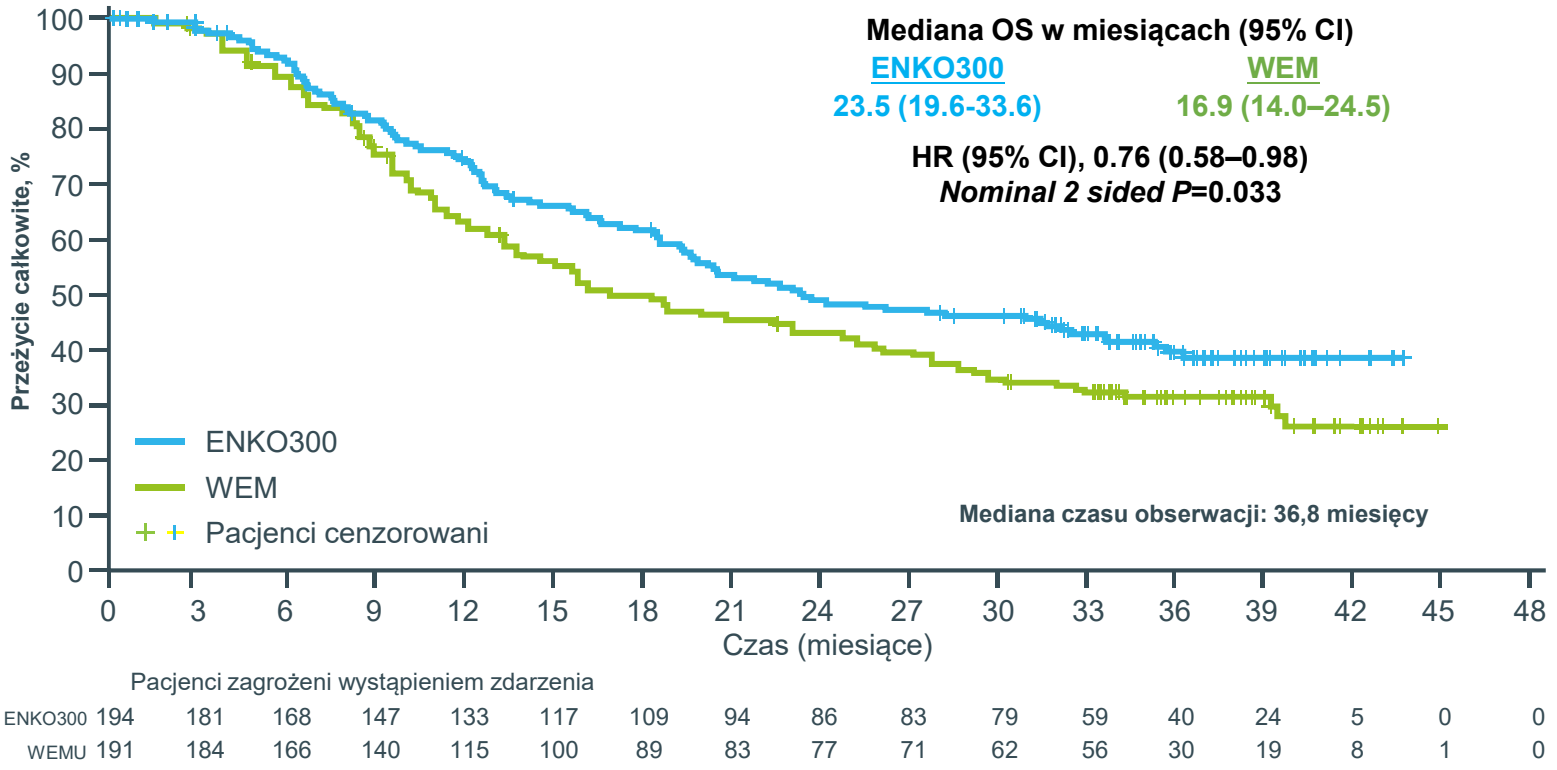
HR (95% CI), 0.68 (0.52–0.88)
Nominal 2-sided *P*=0.0038

[1]Dummer R et al .Lancet Oncol 2018: published on line March 21 2018

[2]Dummer R et al .Lancet Oncol 2018: published on line September 12 2018

New BRAFi/MEKi treatment – encorafenib + binimetinib

OS: encorafenib 300 vs vemurafenib

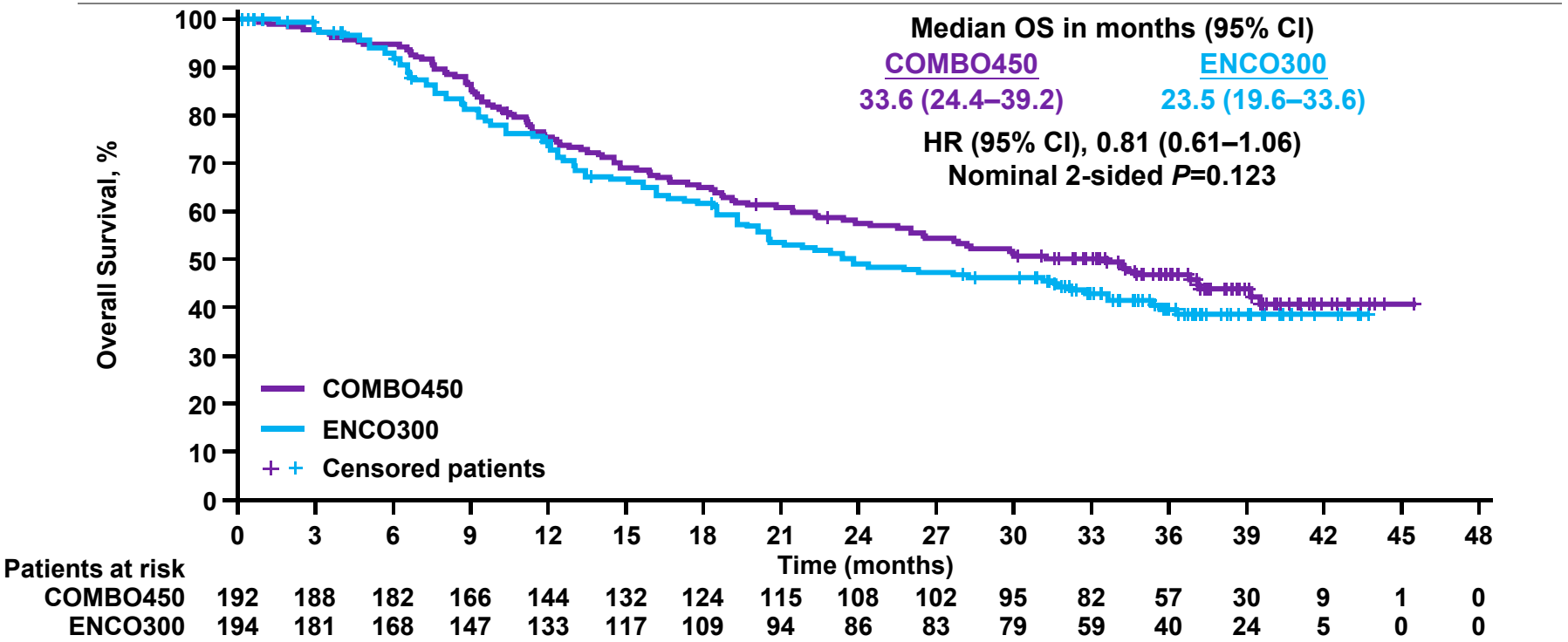


ENKO300=enkorafenib 300 mg 1x/d; OS=przeżycie całkowite; WEM=wemurafenib 960 mg 2x/d.

Dummer, et al. Overall Survival in COLUMBUS : ASCO 2018 oral presentation.

New BRAFi/MEKi treatment – encorafenib + binimetinib

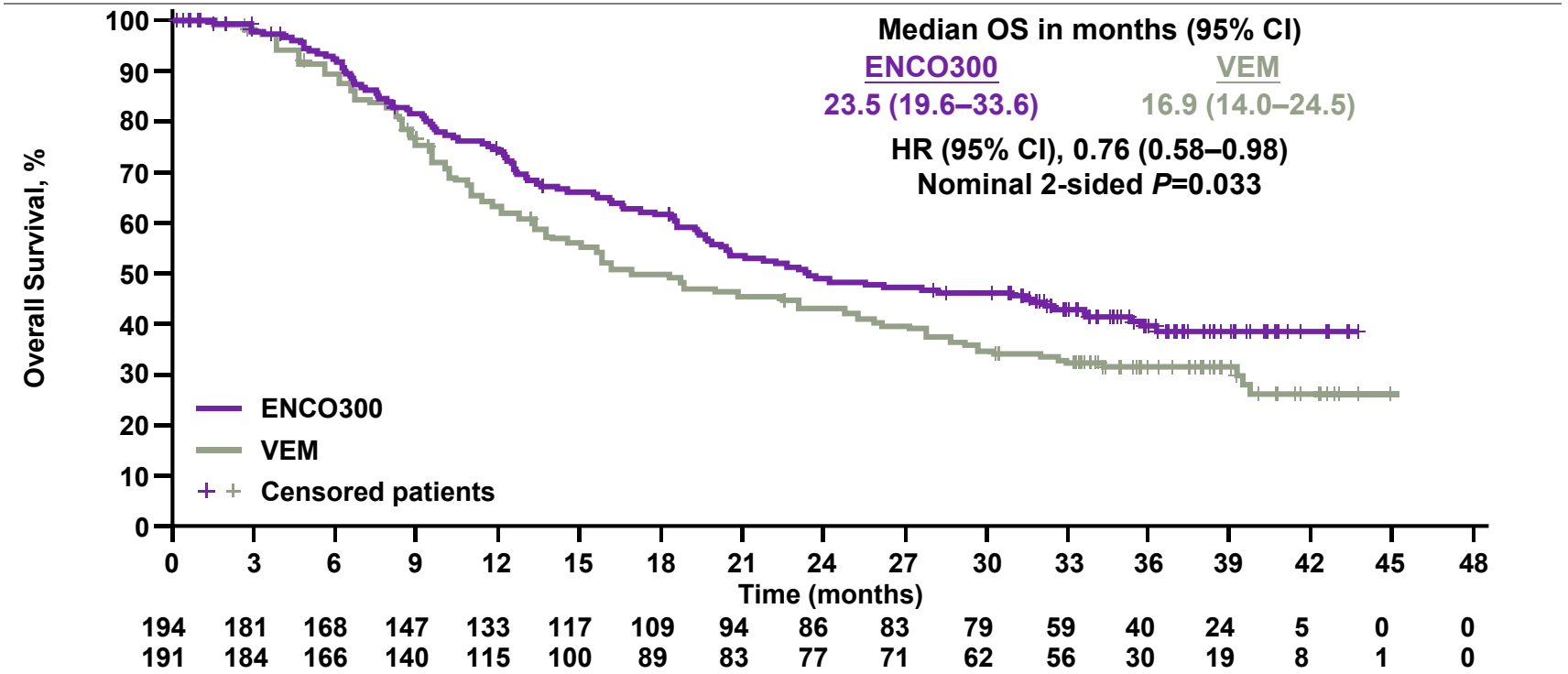
Overall Survival: COMBO450 vs ENCO300



COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; ENCO300=encorafenib 300 mg QD; HR=hazard ratio; OS=overall survival.

New BRAFi/MEKi treatment – encorafenib + binimetinib

Overall Survival: ENCO300 vs VEM



ENCO300=encorafenib 300 mg QD; HR=hazard ratio; OS=overall survival; VEM=vemurafenib 960 mg BID.

New BRAFi/MEKi treatment – encorafenib + binimetinib

Systemic Treatment Following Study Drug Discontinuation

Treatment received after study drug*	COMBO450 n=192	ENCO300 n=194	VEM n=191
Any treatment	42%	56%	62%
Anti–PD-1/anti–PD-L1	20%	21%	25%
Anti–CTLA-4	17%	16%	19%
Anti–CTLA-4 + anti–PD-1/anti–PD-L1	3%	2%	2%
BRAFi + MEKi	5%	14%	20%
BRAFi	6%	8%	13%
Chemotherapy	7%	12%	12%
Other	3%	2%	7%

New BRAFi/MEKi treatment – encorafenib + binimetinib

Use of Checkpoint Inhibitors as First Post-Study Treatment

Treatment received after study drug*	COMBO450 n=192	ENCO300 n=194	VEM n=191
Anti–PD-1/anti–PD-L1	20%	21%	25%
Used first after study drug	12%	14%	13%
Anti–CTLA-4	17%	16%	19%
Used first after study drug	15%	13%	15%
Anti–CTLA-4 + anti–PD-1/anti–PD-L1	3%	2%	2%
Used first after study drug	2%	0	1%

COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; CTLA-4=cytotoxic T-lymphocyte-associated protein 4; ENCO300=encorafenib 300 mg QD; PD-1=programmed death 1; PD-L1=programmed death ligand 1; VEM=vemurafenib 960 mg BID.
*Multiple uses of a therapy in a single patient were only counted once in the frequency for that category of therapy; patients who received multiple categories of therapy are counted in each respective row.

Toxicity of treatment with BRAF inhibitors

Table 4. Grade 2 and 3 adverse events from the BRIM-3 trial*[45]

Adverse event, n (%)	Vemurafenib (n = 336)†	DTIC (n = 282)
Cutaneous adverse events		
Rash	61 (18)	0
Cutaneous squamous cell carcinoma‡	40 (12)	1 (<1)
Keratoacanthoma§	27 (8)	0
Alopecia	26 (8)	0
Pruritus	24 (7)	0
Hyperkeratosis	21 (6)	0
Other adverse events		
Arthralgia	71 (21)	3 (1)
Fatigue	44 (13)	38 (14)
Diarrhea	18 (5)	5 (2)
Headache	17 (5)	5 (2)

*Most adverse events were mild to moderate. Those listed are of grade 2 or higher and were reported in more than 5% of patients in either study group.

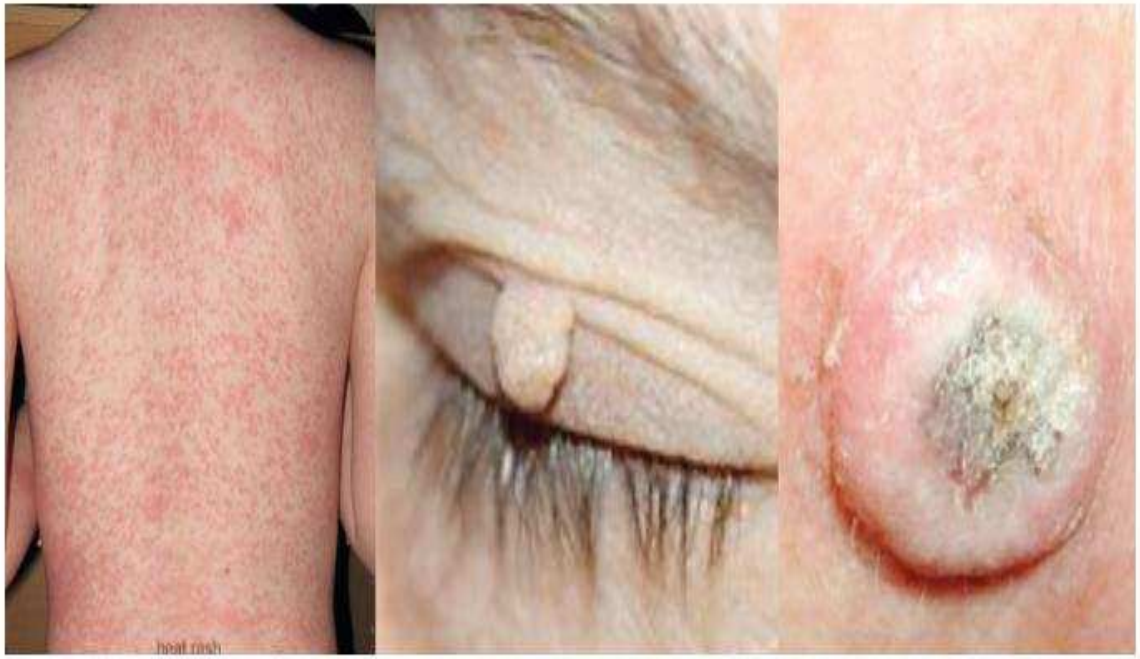
†One patient in the DTIC group who was treated with vemurafenib in error was included in the vemurafenib group for the assessment of adverse events.

‡The criteria for the diagnosis of cutaneous squamous-cell carcinoma were defined in the protocol and were reported as grade 3, according to the National Cancer Institute Common Terminology Criteria for Adverse Events. These events were evaluated by the investigators as grade 1 in one patient and grade 2 in one patient.

§Three patients with keratoacanthomas that were assessed by the investigator as grade 1 were included among the grade 2 keratoacanthomas.

DTIC = dacarbazine

BRAF-SPECIFIC SKIN REACTIONS

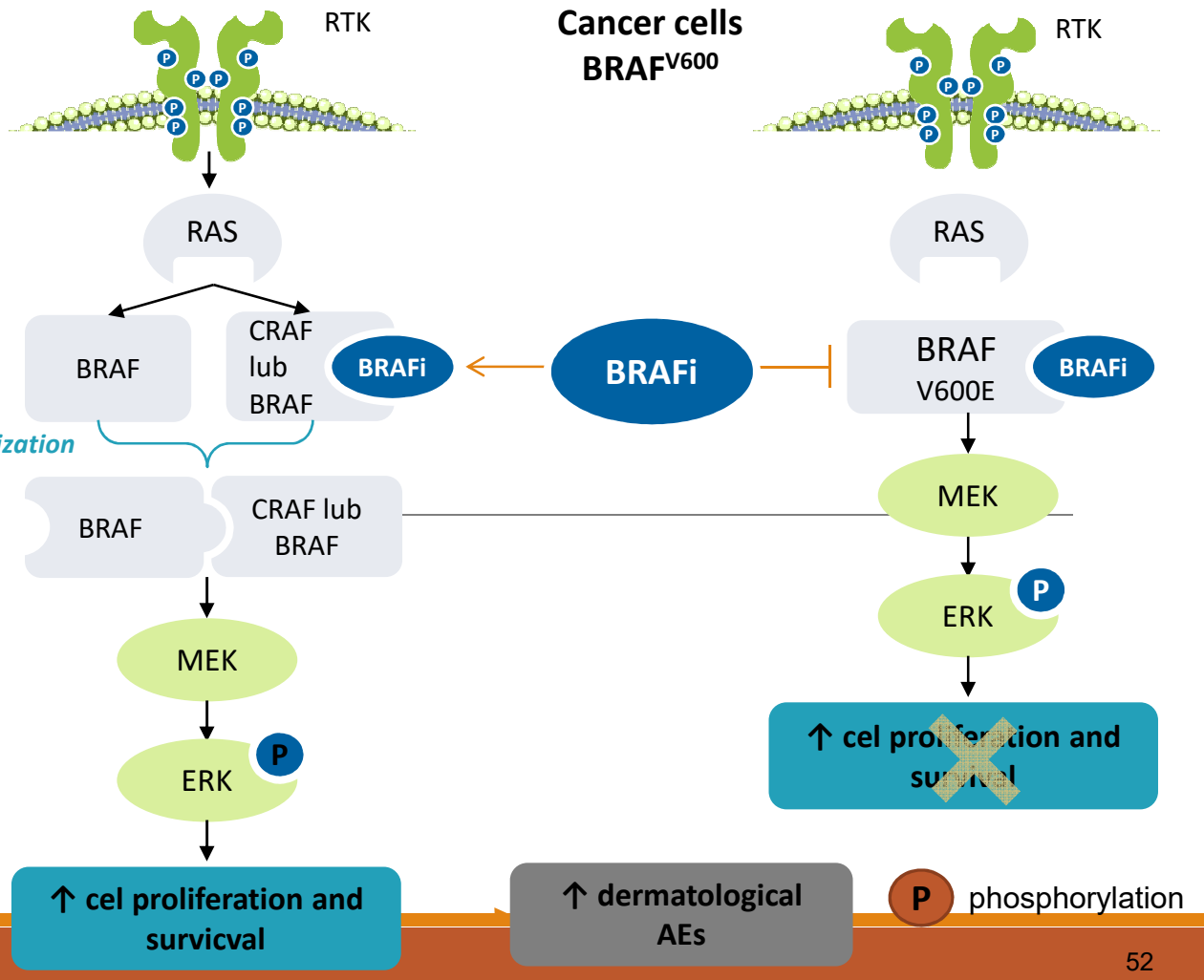


BRAF inhibitors cause a rash over the whole body (left), as well as stem warts (centre), which can be burnt with nitrogen, and squamous cell carcinoma (right), which must be excised.

Courtesy of the Netherlands Cancer Institute

Paradoxical ERK activation and BRAF inhibitors

- **BRAF inhibitors induce a change in the conformation of CRAF or BRAF monomers promoting their dimerization in healthy cells**
- **RAF Dimethylation - RAF leads to the activation of ERK in healthy cells**
- **BRAF inhibitors induce paradoxical activation of ERK in healthy cells**



Poulikakos et al. Nature, 2010
Adelmann et al., 2016, Oncotarget

AE of BRAFi/MEKi treatment?

coBRIM: Safety Profile of Cobimetinib and Vemurafenib Was Tolerable and Manageable

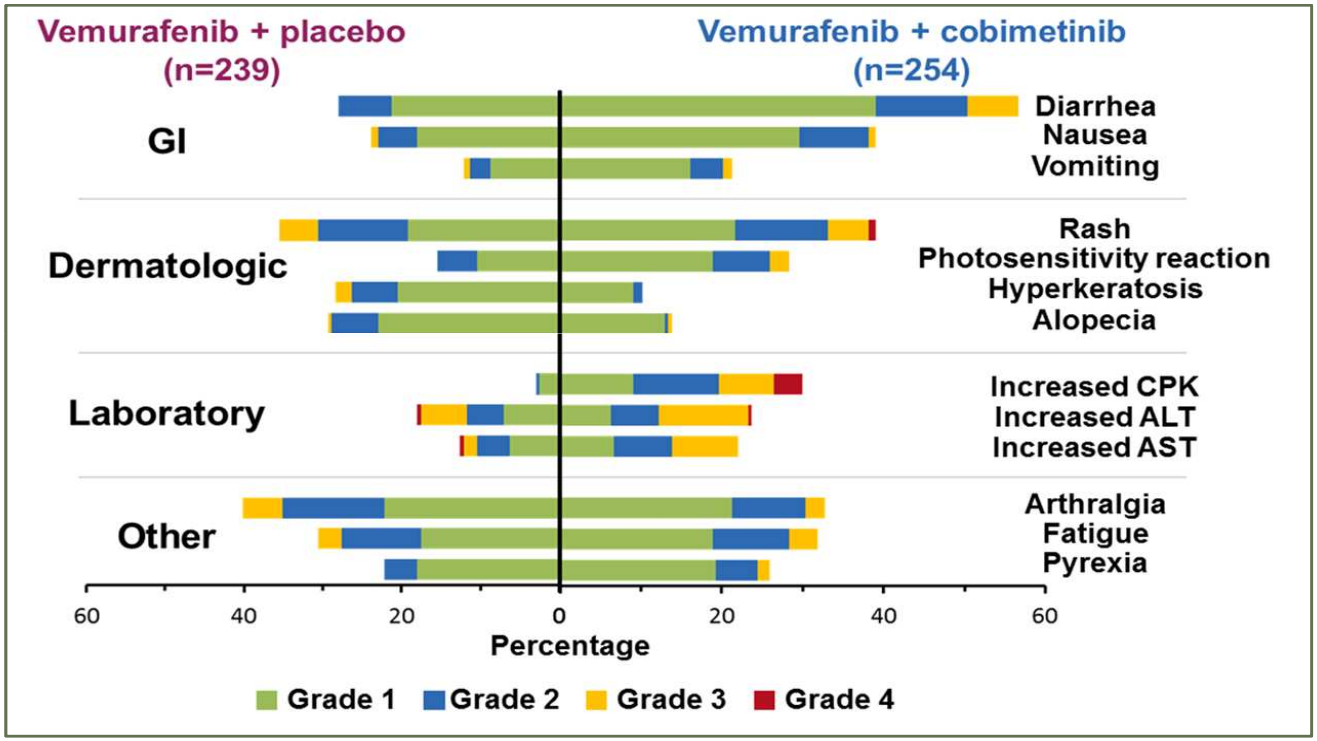
	PBO + Vem n = 246	Cobi + Vem n = 247
Median follow-up, months	10.3	11.2
Treatment-related AEs, n (%)	232 (94)	237 (96)
Treatment-related grade 3-4 AEs, n (%)	122 (50)	142 (57)
Treatment-related grade 5 AEs, n (%)	1 (0.4)	1 (0.4)
Treatment discontinuation for related AEs, n (%)	16 (7)	31 (13)

AE, adverse event.
Data cutoff, September 19, 2014.

McArthur GA et al. *Eur J Cancer*. 2015;51:S720-S723.

AEs of W+K vs W mono

coBRIM (GO28141; phase III): Adverse events occurring in ≥ 20% of patients

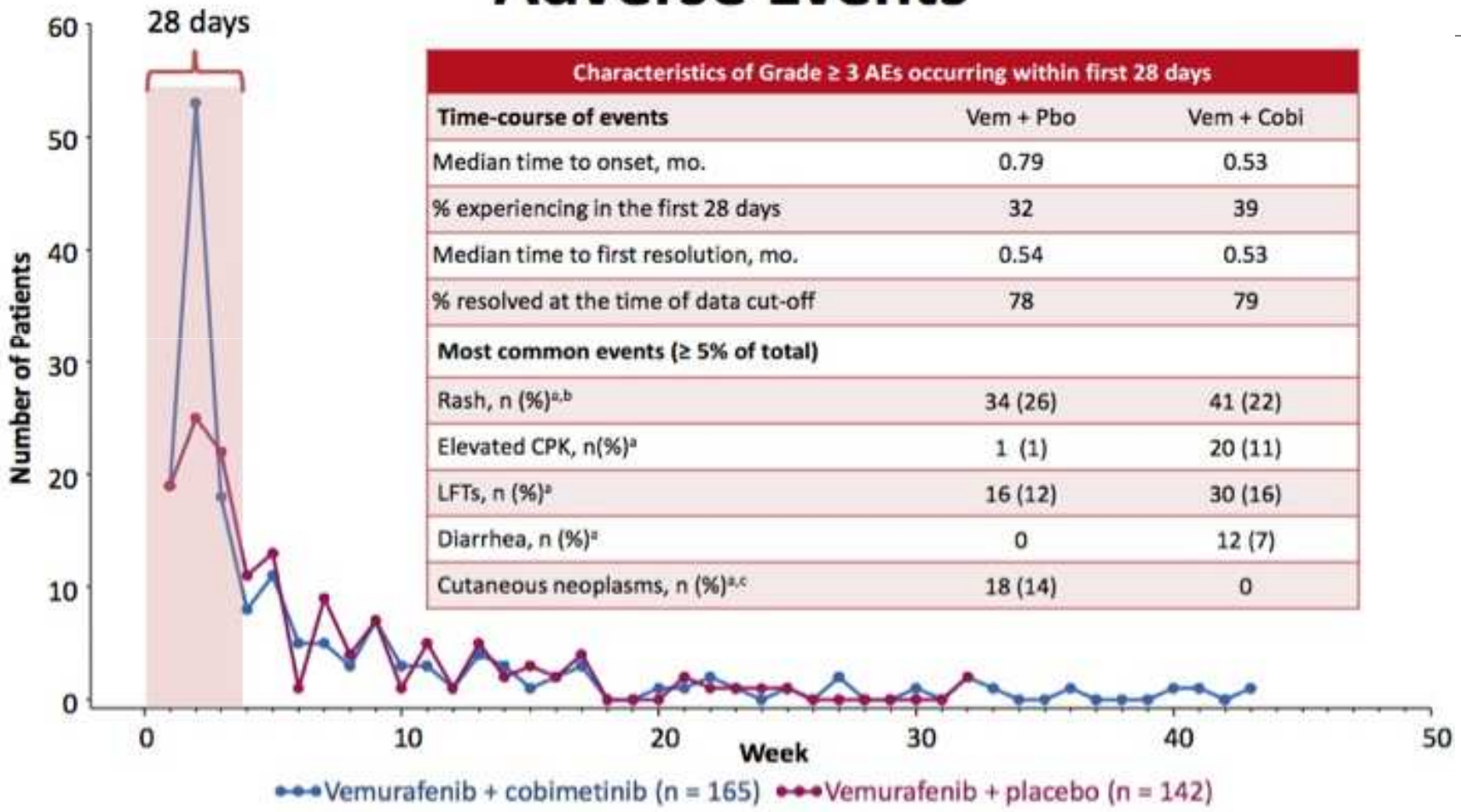


Multiple occurrences of a specific adverse event for a patient were counted once at the highest NCI CTCAE grade of the occurrence.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GI = gastrointestinal.

1. Larkin J, et al. N Engl J Med. 2014;371:1867–1876. 2. Dréno B, et al. Poster presented at 11th SMR Congress November 13–16, 2014; Zurich, Switzerland.

AE of BRAFi/MEKi - dynamics

coBRIM: Kinetics of First Onset For Grade ≥ 3 Adverse Events



Characteristics of Grade ≥ 3 AEs occurring within first 28 days		
Time-course of events	Vem + Pbo	Vem + Cobi
Median time to onset, mo.	0.79	0.53
% experiencing in the first 28 days	32	39
Median time to first resolution, mo.	0.54	0.53
% resolved at the time of data cut-off	78	79
Most common events (≥ 5% of total)		
Rash, n (%)[a,b]	34 (26)	41 (22)
Elevated CPK, n(%)[a]	1 (1)	20 (11)
LFTs, n (%)[a]	16 (12)	30 (16)
Diarrhea, n (%)[a]	0	12 (7)
Cutaneous neoplasms, n (%)[a,c]	18 (14)	0

AE of BRAFi/MEKi

Toksyczność iBRAF/iMEK

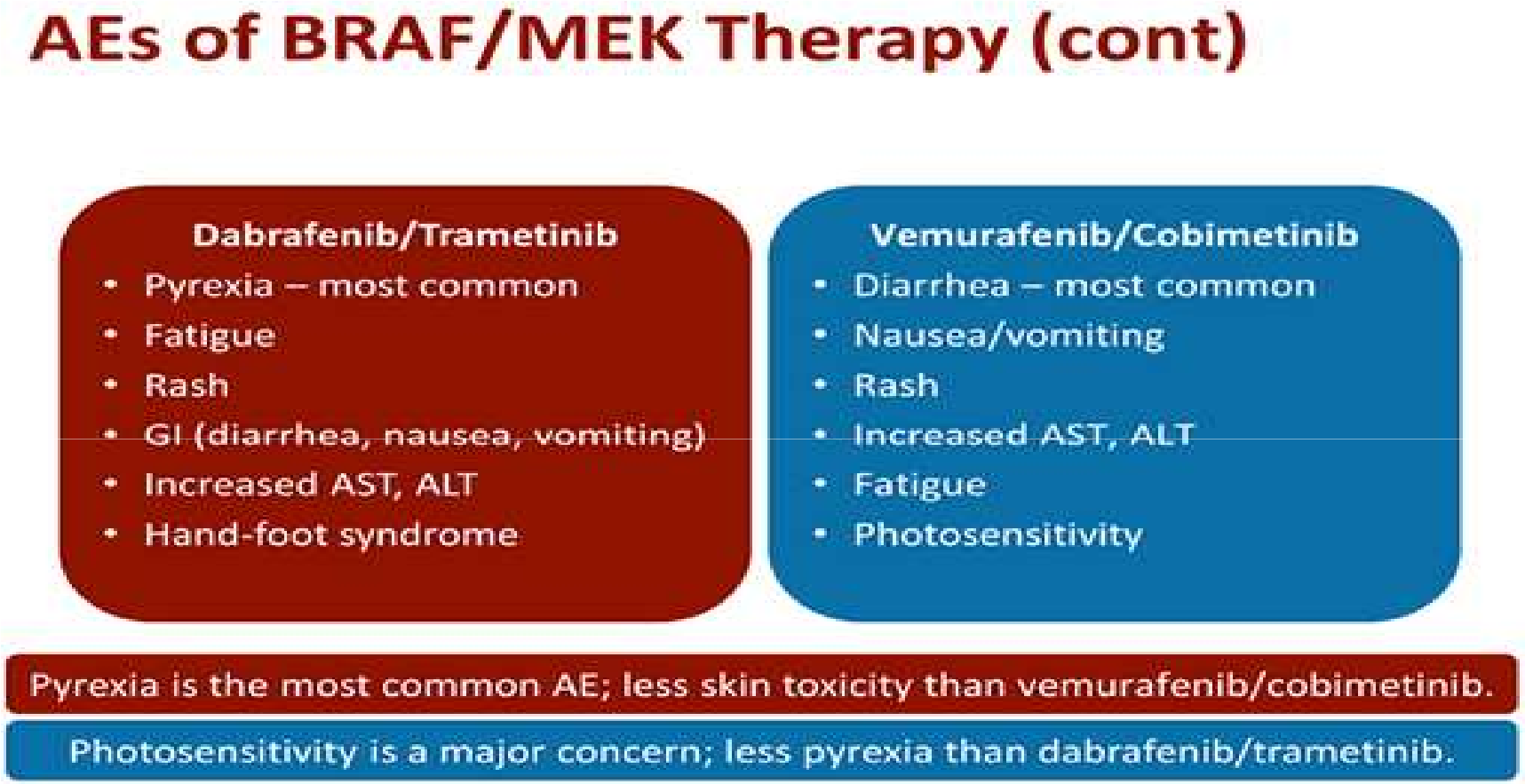
W badaniu BRIM-3 działania niepożądane wemurafenibu prowadziły do modyfikacji dawkowania/przerwania leczenia u 38% chorych

Częstość SCC wyniosła 19%, choć wymagały one głównie leczenia miejscowego

	Vemurafenib*$	Dabrafenib‡	Trametinib§	Dabrafenib + trametinib ‖¶#
Rash	41 (9)	30 (0)	57 (8)	27 (0)
Cutaneous SCC	19 (19)	10 (4)	0	7 (5)
Diarrhoea	25 (<1)	NR	43 (0)	36 (2)
Pyrexia	NR	16 (3)	NR	51 (6)
Arthralgia	56 (6)	19 (<1)	NR	24 (0)
Fatigue	46 (3)	18 (1)	26 (4)	53 (4)
Cardiac	NR	NR	7 (1)	9 (0)
ILD/pneumonitis	NR	NR	2 (2)	1
Ophthalmologic	NR	NR	9 (<1)	2 (2)
Hypertension	NR	4 (0)	15 (12)	9 (2)
Hyperglycaemia	NR	49 (2)#	NR	58 (5)
Liver laboratory abnormalities:	36 (11)	26 (2) #	24 (2)	60 (2)
Alkaline phosphatase		11 (0) #	39 (3)	42 (4)
Alanine aminotransferase		0 (0) #	NR	15 (0)
Bilirubin		60 (2)#	60 (2)	60 (5)
Aspartate aminotransferase				

Toxicities are expressed as percentage of all CTC grades (CTC grade 3/4). The data in this table are summarized from different trials and do not represent direct comparisons.
*Chapman *et al.* [2011].
$Larkin *et al.* [2014].
‡Hauschild *et al.* [2012, 2013].
§Flaherty *et al.* [2012b].
‖Flaherty *et al.* [2012a].
¶Long *et al.* [2014].
#Data are a composite of phase I/II and III trial data since limited data are available from the phase III trial.
SCC, squamous cell carcinoma; ILD, interstitial lung disease; NR, not reported.

AE of BRAFi/MEKi – is it important?



NCCN website. 2016; Long GV, et al. *Lancet*. 2015;386:444-451;
Larkin J, et al. *N Engl J Med*. 2014;371:1867-1876.

New BRAFi/MEKi treatment – encorafenib + binimetinib

Overall Summary of Safety

Event	COMBO450 n=192 Median Duration of Exposure: 51 weeks	ENCO300 n=192 Median Duration of Exposure: 31 weeks	VEM n=186 Median Duration of Exposure: 26 weeks
Adverse events	98%	99%	100%
Grade 3/4 adverse events	64%	67%	66%
Adverse events leading to discontinuation	15%	15%	17%
Adverse events leading to dose reduction/interruption	53%	71%	62%
On-treatment deaths*	12%	8%	11%

COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; ENCO300=encorafenib 300 mg QD; VEM=vemurafenib 960 mg BID.
*Includes on-treatment deaths and deaths within 30 days of stopping study treatment.

Toxicity of E+B treatment

Most Common Adverse Events Regardless of Assessed Causality*

Preferred Term, %	COMBO450 n=192 Median Duration of Exposure: 51 weeks		ENCO300 n=192 Median Duration of Exposure: 31 weeks		VEM n=186 Median Duration of Exposure: 27 weeks	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Total	98	58	>99	66	>99	63
Nausea	41	2	39	4	34	2
Diarrhea	36	3	14	2	34	2
Vomiting	30	2	27	5	15	1
Fatigue	29	2	25	1	31	2
Arthralgia	**26**	**1**	**44**	**9**	**45**	**6**
Blood CK increased	23	7	1	0	2	0
Headache	22	2	27	3	19	1
Pyrexia	**18**	**4**	**15**	**1**	**28**	**0**
GGT increased	15	9	11	5	11	3
Alopecia	**14**	**0**	**56**	**0**	**37**	**0**
Hyperkeratosis	**14**	**1**	**38**	**4**	**29**	**0**
Dry skin	**14**	**0**	**30**	**0**	**23**	**0**
Myalgia	14	0	28	10	18	1
Rash	**14**	**1**	**21**	**2**	**29**	**3**
Hypertension	11	6	6	3	11	3
Palmoplantar keratoderma	**9**	**0**	**26**	**2**	**16**	**1**
Palmar-plantar erythrodysesthesia syndrome	**7**	**0**	**51**	**14**	**14**	**1**

AE=adverse event; BID=twice daily; BINI=binimetinib; CK=creatine phosphokinase; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; ENCO=encorafenib; GGT=gamma-glutamyltransferase; QD=once daily; VEM=vemurafenib.
*All-cause AEs (>25% in any treatment group) or grade 3/4 AEs (>5% in any treatment group).

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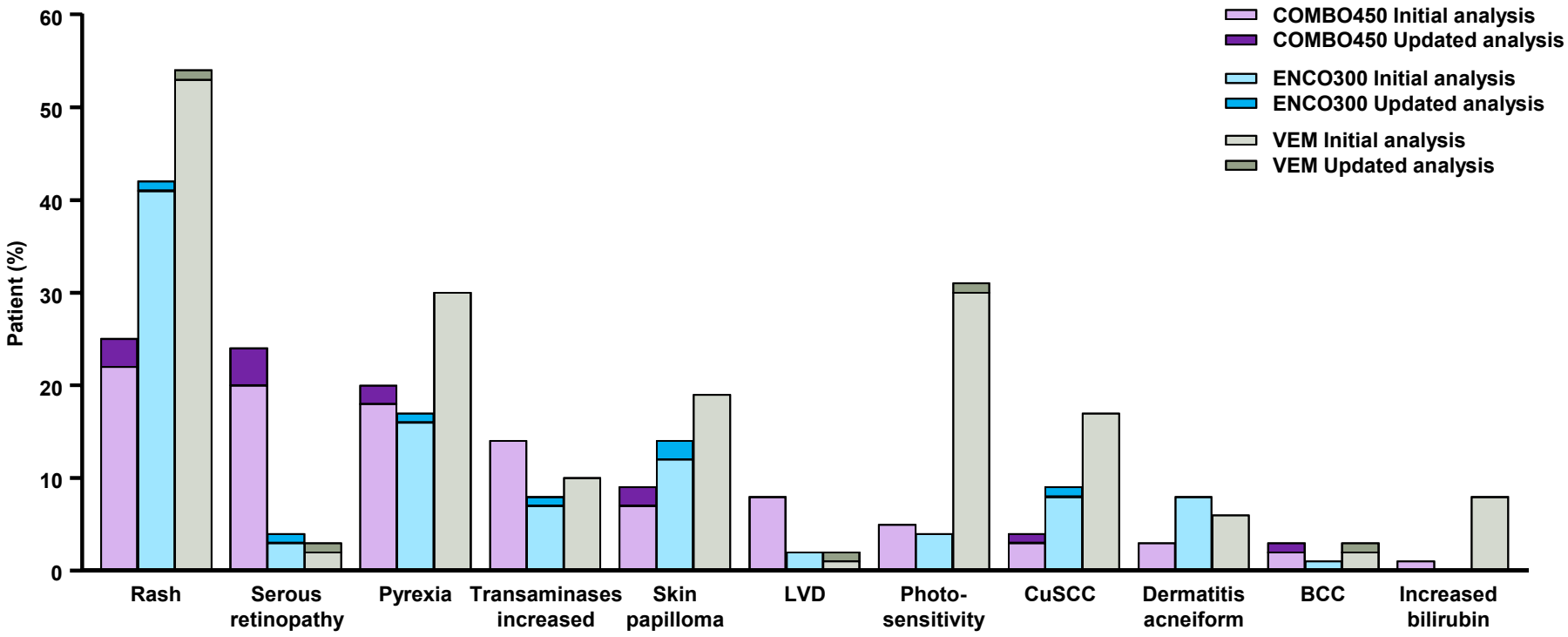
New BRAFi/MEKi treatment – encorafenib + binimetinib

Groupings of AEs Associated With BRAFi and MEKi

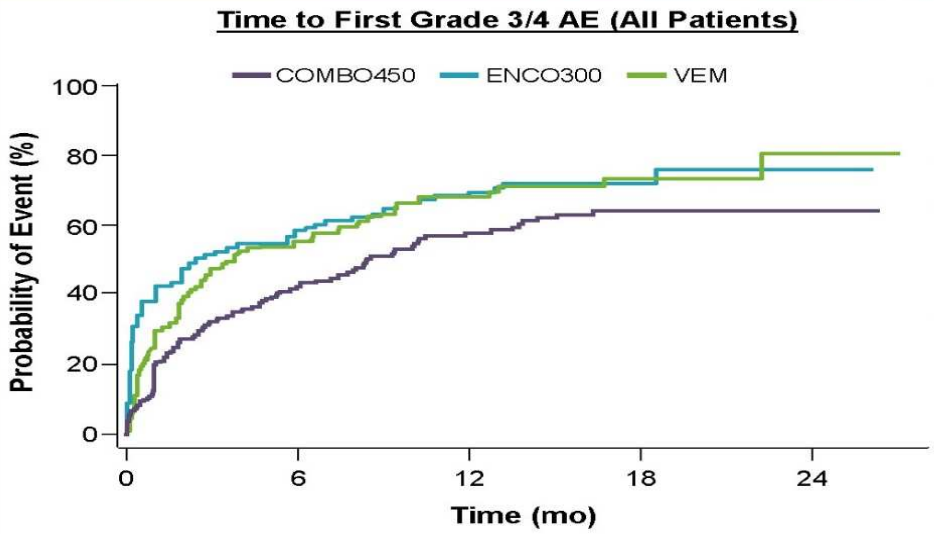


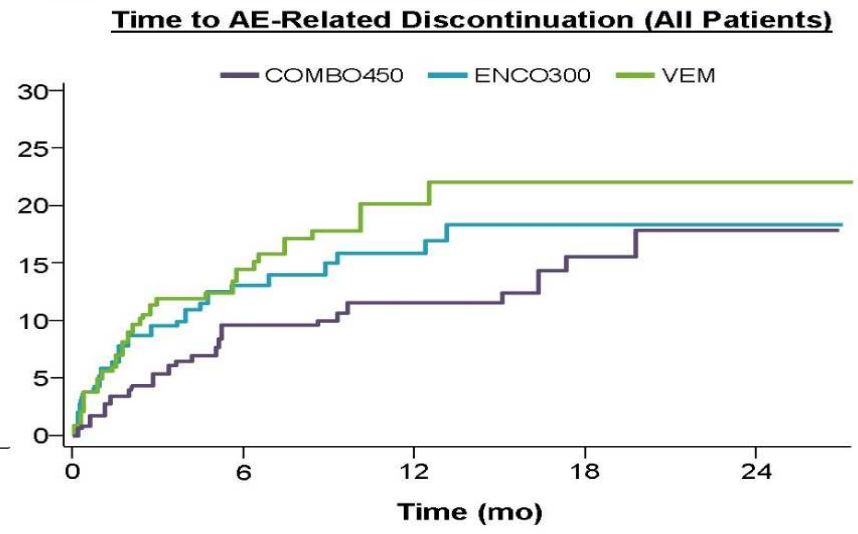
Terms represent groupings of similar or related adverse events.

BCC=basal cell carcinoma; BRAFi=BRAF inhibitor; COMBO450=encorafenib 450 mg QD + binimetinib 45 mg BID; CuSCC=cutaneous squamous cell carcinoma; ENCO300=encorafenib 300 mg QD; LVD=left ventricular dysfunction; MEKi=MEK inhibitor; VEM=vemurafenib 960 mg BID.

Toxicity of E+B treatment

Time to First Grade 3 or 4 Adverse Event and Discontinuation Due to Adverse Events





First Grade 3/4 AE Among Patients Having an Event	
Treatment	**Median months (95% CI)**
COMBO450	2.5 (1.4–3.7)
ENCO300	0.4 (0.2–0.9)
VEM	1.3 (0.9–1.8)

AE-Related Discontinuation Among Patients Having an Event	
Treatment	**Median months (95% CI)**
COMBO450	3.8 (1.8–5.6)
ENCO300	1.8 (0.9–4.0)
VEM	1.8 (1.0–2.9)

AE=adverse event; BID=twice daily; BINI=binimetinib; CI=confidence interval; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; ENCO=encorafenib; QD=once daily; VEM=vemurafenib.

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Different goals of treatment in patients with BRAF (+) metastatic MM - ??

Rapid target: remission of clinical symptoms in patients requiring rapid response, one might prefer inhibitors (BRAF + MEK)

- faster response (sometimes after 1-2 weeks of treatment)
- up to 70% objectiveresponses
- almost always resistance to treatment develops

Long-term goal: a long-term response to treatment

- slower response after ITH (especially after IPI)
- up to 45% of objective responses
- the use of immunotherapy more often leads to long-lasting responses

1. Long GV et al. JCO 2016; 34:871-878;
2. Long GV et al. Annals of Oncology 2017;28 1631-1637;
3. Wolchok JD et al. NEJM 2017;
4. Ribas A et al. JAMA. 2016;315(15):1600-1609;
5. https://www.nccn.org/professionals/physician_gls/categories_of_consensus.asp

More BRAF(+) MM treatment?

MADRID 2017 ESMO congress

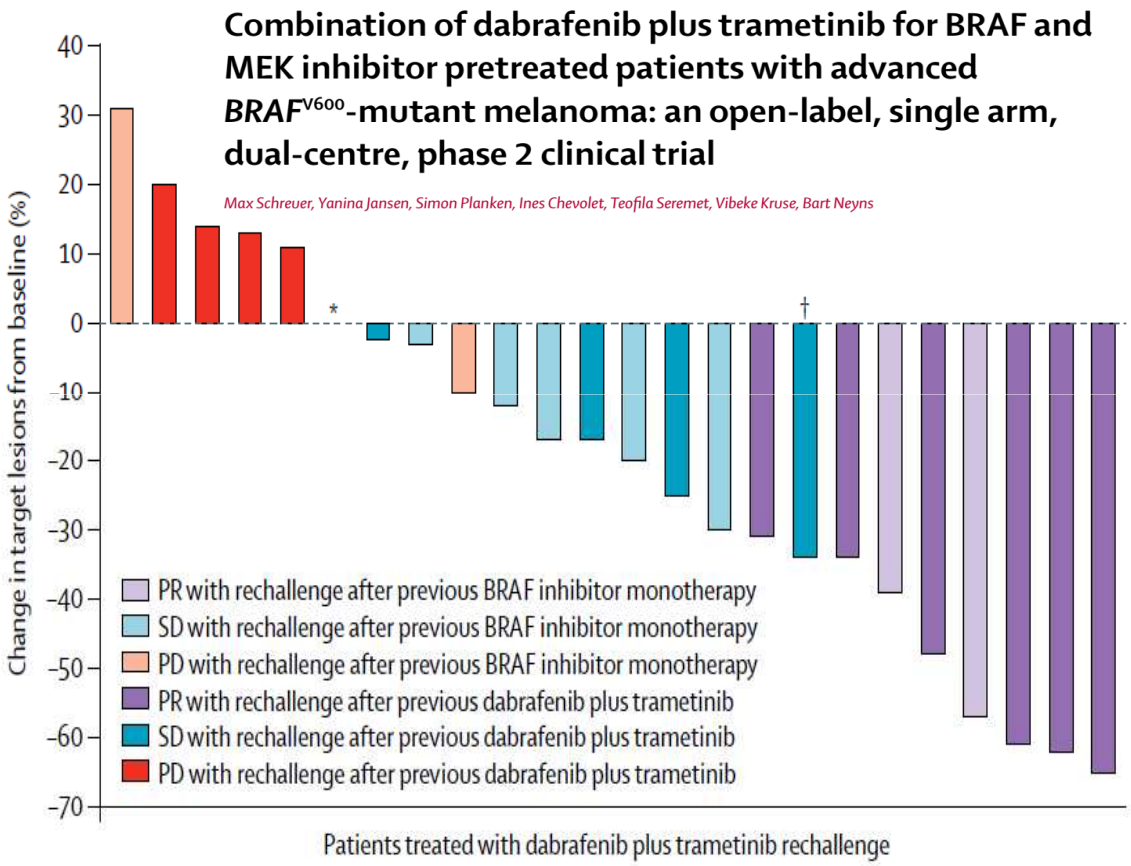
3L?

Rechallenge With Targeted Therapy

Patients who previously progressed on BRAFi and received subsequent immunotherapy were treated with dabrafenib + trametinib

PR was observed in 8/25 (32%) of patients and SD was noted in 10 (40%)

These data suggest that rechallenge may be an option for these patients



Schreuer M. et al. Lancet Oncol. 2017 [Epub].

More BRAF(+) MM treatment

RECHALLENGE WITH TARGETED THERAPY

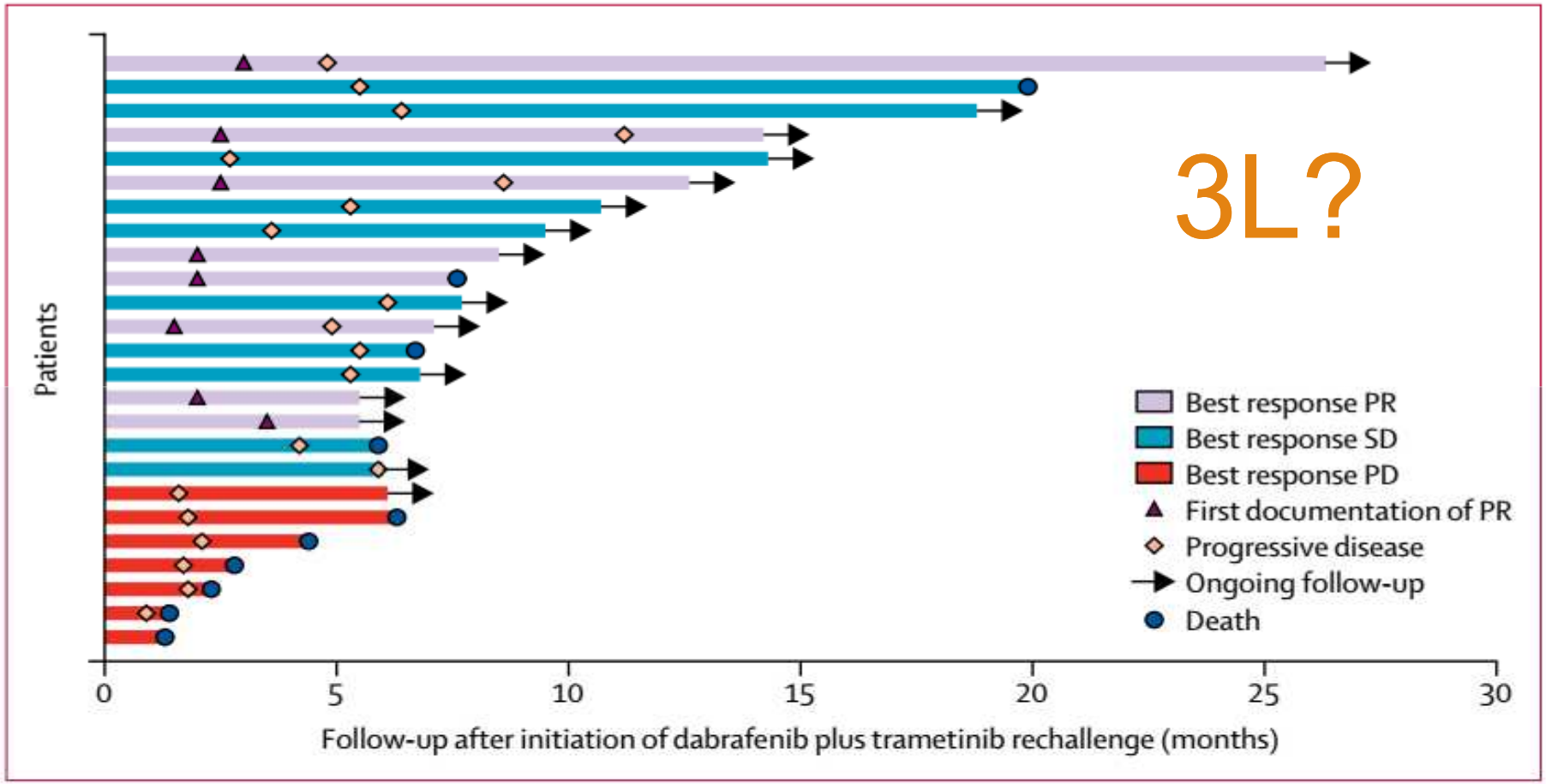


Figure 2: **Duration of response with dabrafenib plus trametinib rechallenge**
Assessed in 25 patients with *BRAF*^{V600}-mutant melanoma. Best response denotes best investigator-assessed confirmed response classified according to Response Evaluation Criteria in Solid Tumors version 1.1. PR=partial response. SD=stable disease. PD=progressive disease.

Toxicities of treatment

Table 2 Comparative toxicities of vemurafenib plus cobimetinib

	Vemurafenib + cobimetinib in patients previously treated with BRAF inhibitor[35]	Vemurafenib + cobimetinib in BRAF inhibitor-naïve patients[35]	Vemurafenib + cobimetinib in Phase III trial (vs dacarbazine)[34]	Vemurafenib (in extended safety study)[20]
Rash	33 (2)	87 (14)	39 (6)	49 (5)
Diarrhea	47 (3)	83 (8)	56 (6)	16 (<1)
Fatigue	27 (2)	70 (10)	32 (4)	34 (3)
Photosensitivity	15 (2)	67 (3)	28 (2)	31 (2)
Liver laboratory abnormality	33 (6)	67 (19)	<46 (<20)	13 (5)
Cutaneous SCC	2 (8)	11 (11)	<3 (2)	14 (12)
Elevated CPK	15 (2)	43 (3)	31 (11)	NR
Central serous retinopathy	0	3 (0)	<13 (<1)	NR
Decreased ejection fraction	NR	NR	8 (1)	NR
QTc prolongation	8 (3)	6 (2)	<4 (<1)	10 (2)

Note: Data shown as % total (% grade 3/4).
Abbreviations: SCC, squamous cell carcinoma; CPK, creatine phosphokinase; NR, not reported.

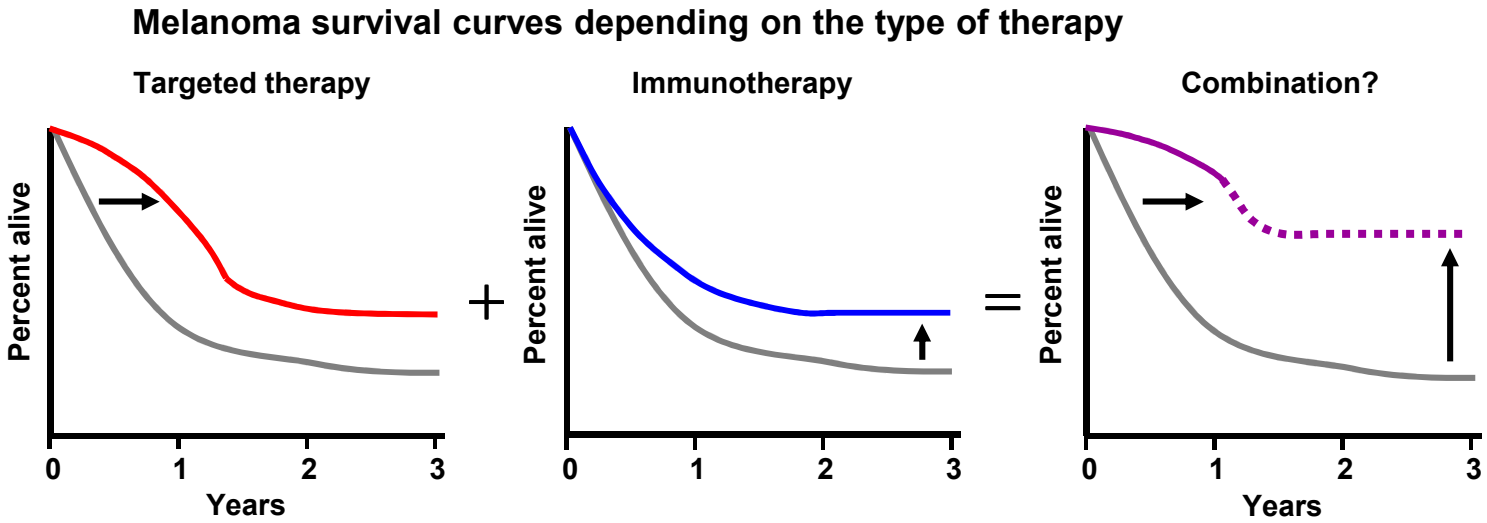
3L ?

Medina T,OncoTargets and Therapy, Volume 2016:9 Pages 3739—3752

WHAT IS THE FUTURE OF BRAFI/MEKI?

What is the right sequence of immunotherapy and targeted therapy?

- BRAF inhibitor alone or BRAF + MEK inhibitors → rapid and clinically significant responses
- Immunotherapy → less frequent objective responses, but clinically significant durability
- Combining targeted therapy with immunotherapy
  - Can harness and perpetuate the enhanced anti-tumor response following targeted inhibition
  - May lead to durable response and prolonged survival???

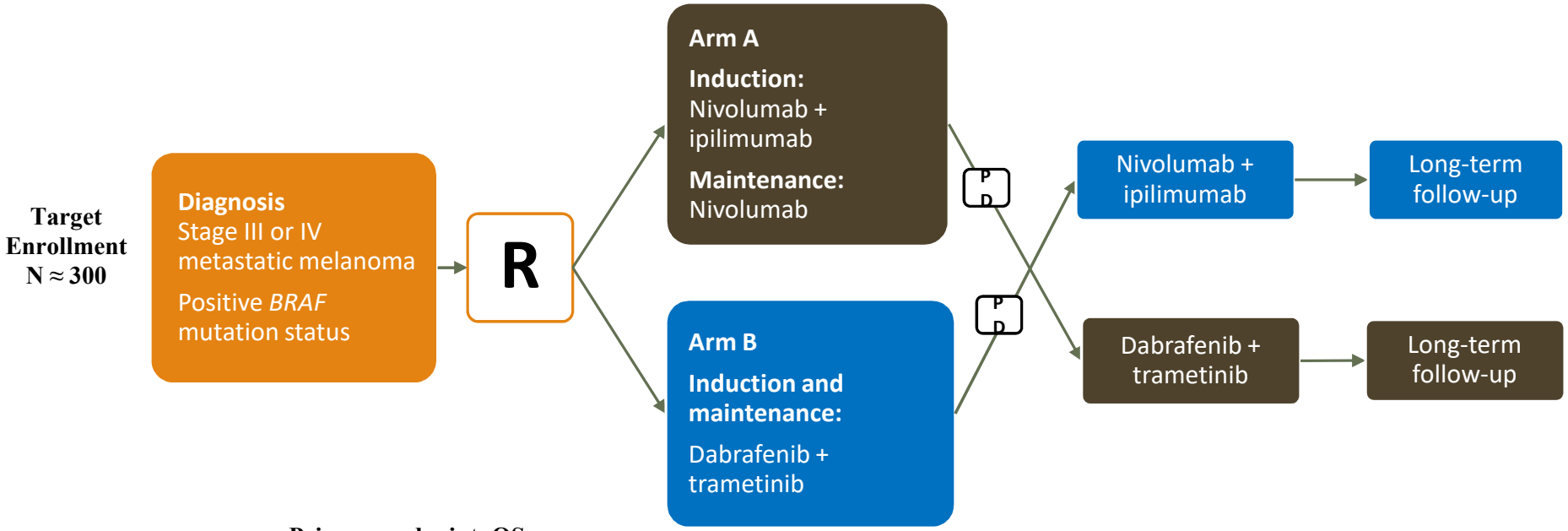


Ribas A et al. Clin Cancer Res 2012 and Hamid O et al. SMR 2015.

Sequencing immunotherapy and targeted therapy trial

ECOG-ACRIN SWITCH: Study Design – Phase 3 (EA6134)

Randomised, phase 3, crossover trial of nivolumab + ipilimumab followed by dabrafenib + trametinib vs dabrafenib + trametinib followed by nivolumab + ipilimumab in patients with unresectable or metastatic *BRAF* V600–mutant melanoma



- **Primary endpoint: OS**
- **Secondary endpoints: PFS, ORR, safety**

ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R, randomisation.

ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02224781. Accessed 2 February 2017.

Sequencing immunotherapy and targeted therapy trial

Sequential Combo Immuno and Target Therapy (**SECOMBIT**) – Phase 2

Randomised, phase 2, crossover trial of nivolumab + ipilimumab followed by encorafenib + binimetinib and vice versa in patients with *BRAF* V600–mutant unresectable or metastatic melanoma[a]

Key eligibility criteria

- Histologically confirmed stage III unresectable or stage IV metastatic melanoma
- Confirmed *BRAF* V600E/K mutation
- ECOG PS 0 or 1
- No active brain metastases

N ≈ 230 → R (RANDOM ASSIGNMENT)

- **ARM A: Combo T** Encorafenib 450 mg QD + binimetinib 45 mg BID → PD → Combo I until PD
- **ARM B: Combo I** Nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W for first 4 doses, then nivolumab 3 mg/kg Q2W → PD → Combo T until PD
- **ARM C: Sandwich** Encorafenib 450 mg QD + binimetinib 45 mg BID → Combo I until PD → Combo T until PD

- **Primary endpoint: OS**
- **Secondary endpoints: PFS, total PFS, time to second progression, percentage of patients alive at 2-3 years, BORR, DOR, toxicity, quality of life and general health, and 3-year PFS rate**

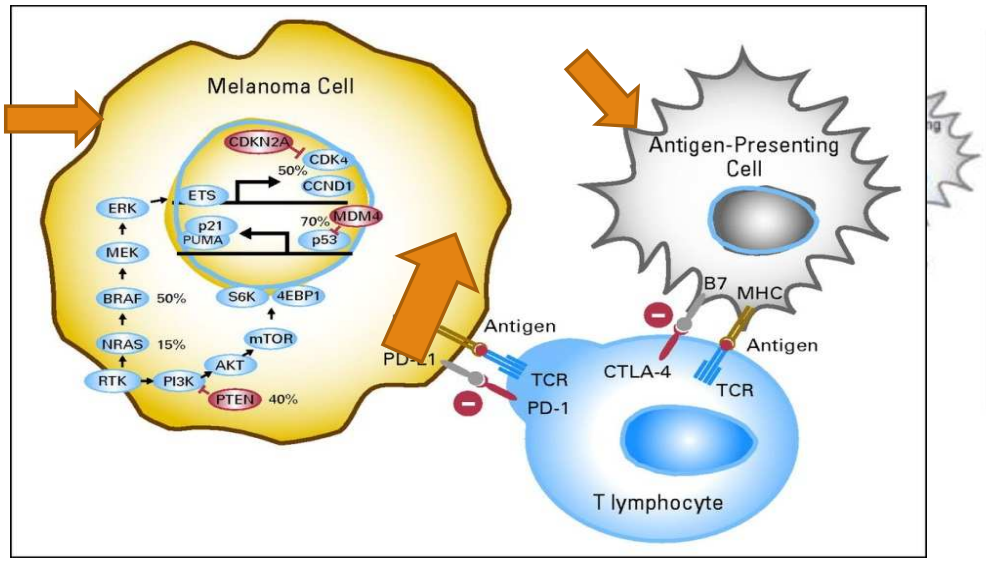
BID, twice daily; BORR, best overall response rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; Q2W, every 2 weeks; Q3W, every 3 weeks; QD, once daily.

[a] This study is designed as a phase 2 randomised trial with no formal comparative test. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02631447. Accessed 14 February 2017.

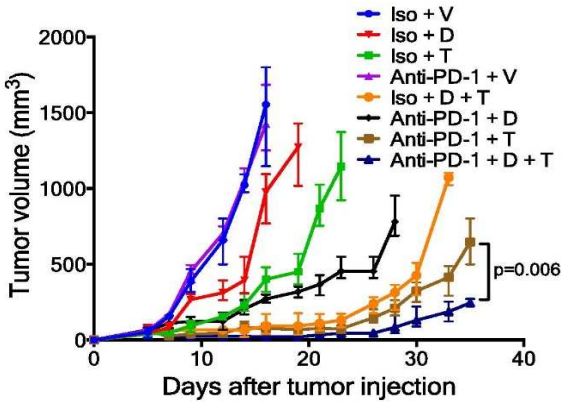
WHAT IS THE FUTURE OF BRAFI/MEKI WITH ITH?

New triplets are on the way….

Triple Combination Therapy for *BRAF*^{V600}-Mutant Melanoma



- BRAF + MEK + anti–PD-1 inhibitors demonstrated superior antitumor activity vs BRAF + MEK inhibitors in preclinical model[2]



1. McArthur GA, Ribas A. *J Clin Oncol.* 2013;31:499-506. 2. Hu-Lieskvoan S et al. *Sci Transl Med.* 2015;7:279ra41.

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Complementary action modes between BRAFi/MEKi and ITH

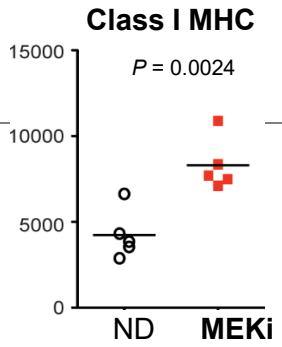
Cobimetinib alters tumor immunity:

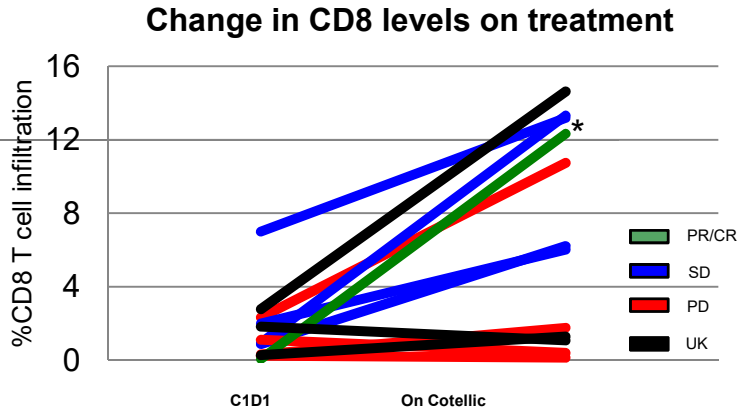
- **Increase CD8+ T cell infiltration** in tumors[1-5]
  - 75% biopsies on Cotellic have increased CD8+ T cell infiltration (66% > 4 fold increase)
  - prime naïve T cells without inhibiting previously activated T cells[1]
  - survival of intratumoral T cells[1]
- Increase tumor cell expression of MHC I and PD-L1[1-3, 5]
- Reduce tumor MDSCs[4]

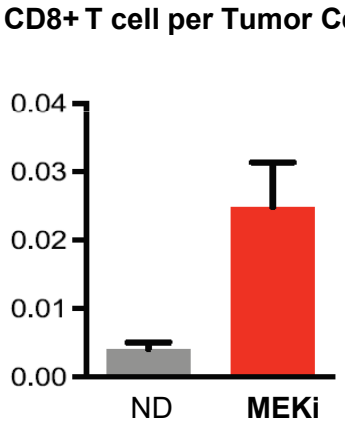
Therapeutic Hypothesis

- A more favorable tumor microenvironment resulting from MEK inhibition may help unlock the full anti-tumor potential of PD-L1 inhibition

MDSC (*myeloid-derived suppressor cells*)

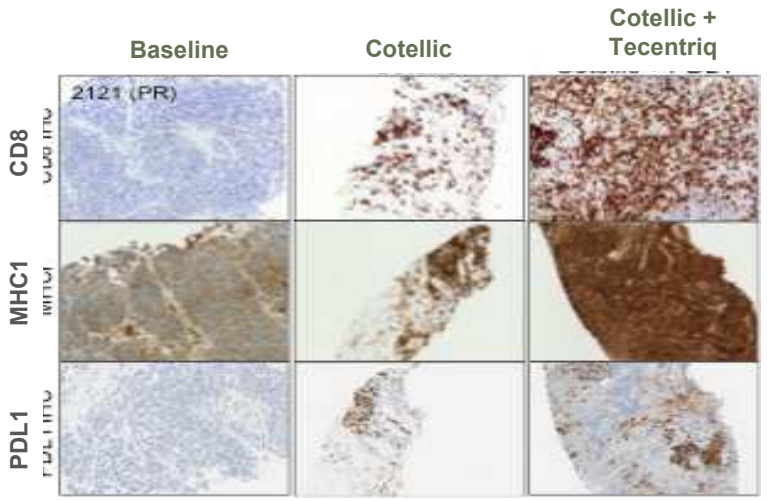






Intratumoral T cell accumulation

* Archival tissue

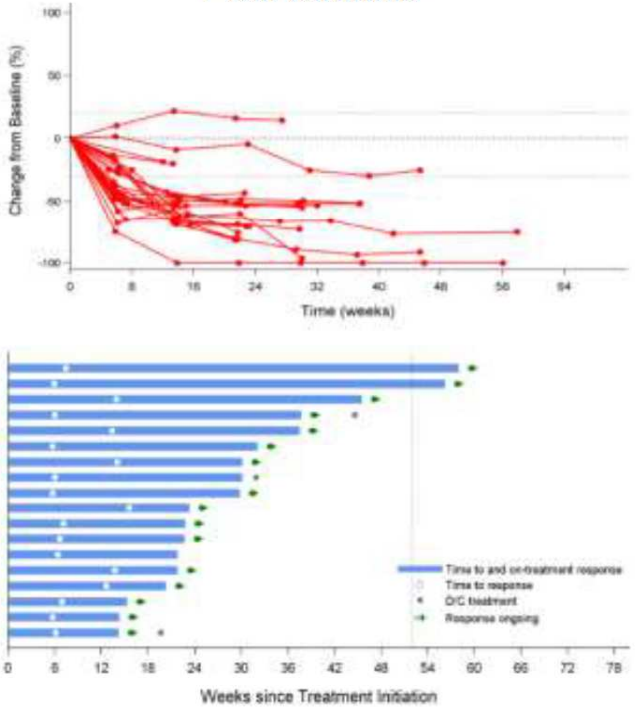


[1]Ebert P, et al, 2016; [2]Liu L, et al, 2015; [3]Loi S, et al. 2015; [4]Phan V, et al. 2013 [5]Study GP28363 - PhIb Cobimetinib + Atezolizumab biopsy cohort

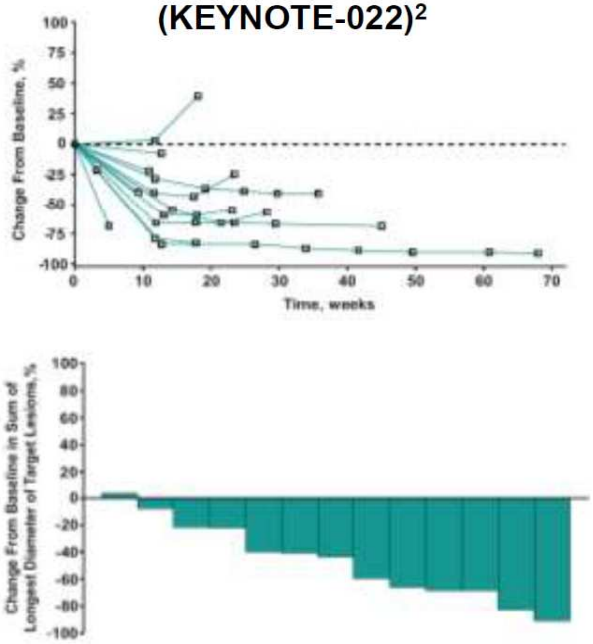
Are triplest active? (early phase data)

Previously Reported Phase 1 Clinical Trials of BRAFi + MEKi + Anti–PD-1/L1

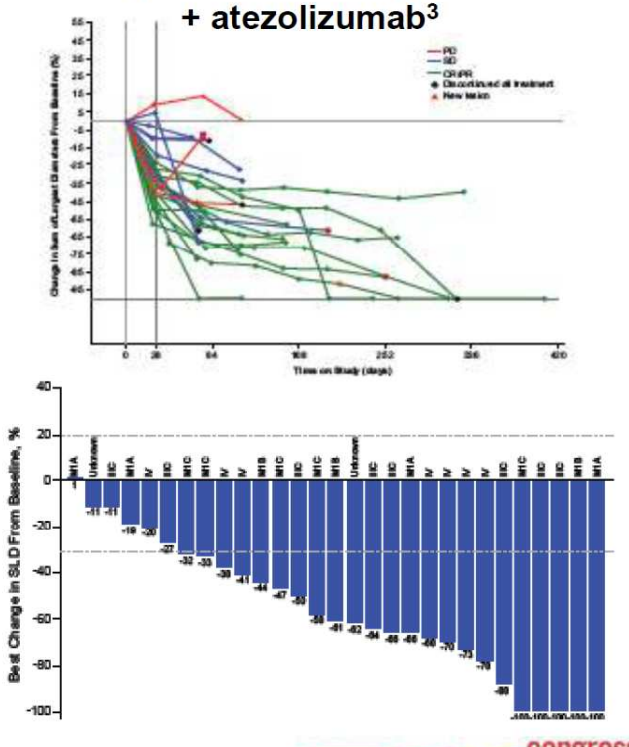
Dabrafenib + trametinib + durvalumab[1]



Dabrafenib + trametinib + pembrolizumab (KEYNOTE-022)[2]



Vemurafenib + cobimetinib + atezolizumab[3]



1. Ribas et al. *J Clin Oncol* 33, 2015 (suppl, abstr 3003 ASCO). 2. Ribas et al. *J Clin Oncol* 34, 2016 (suppl; abstr 3014 ASCO). 3. Hwu et al. *Annals of Oncology* 27; 2016 (supp 6; abstr 1109PD ESMO).

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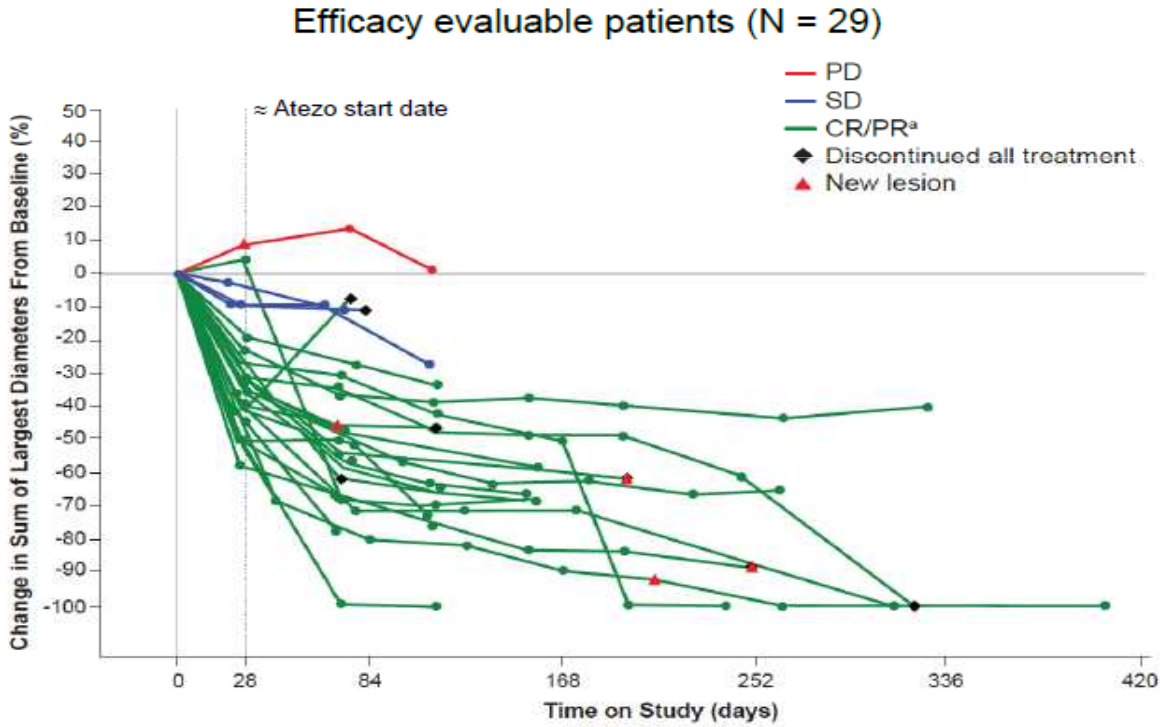
New triplets

Safety and Clinical Activity of Atezolizumab + Cobimetinib + Vemurafenib in *BRAF* V600 Mutant Metastatic Melanoma

Change in Tumor Burden Over Time

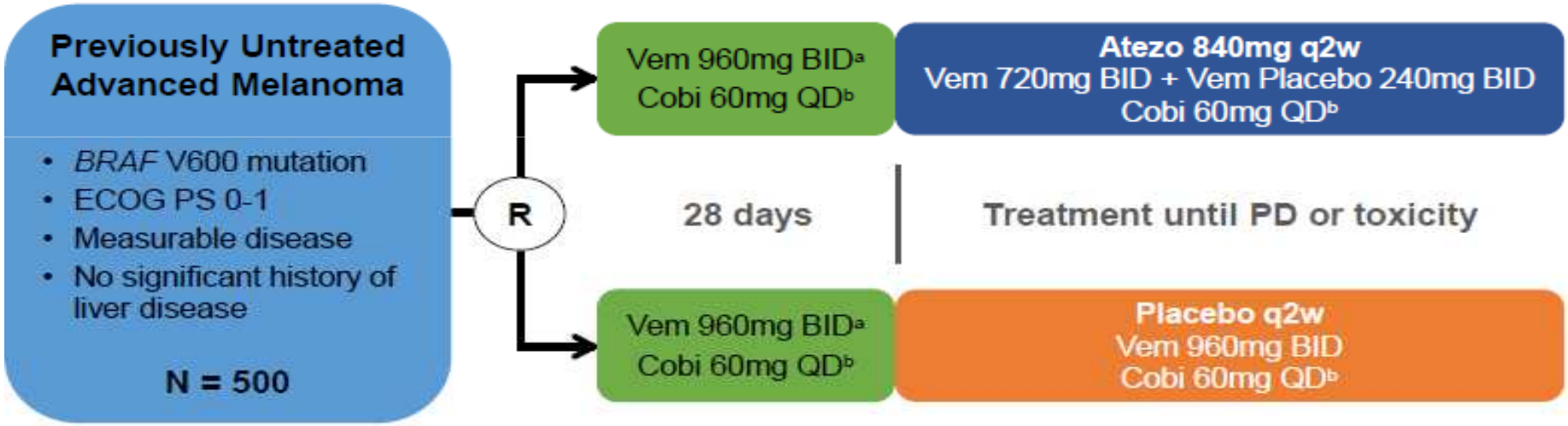


[a]Unconfirmed per RECIST v1.1

Phase III trial with a triplet

TRILOGY: A Phase III Study of Atezo + Cobi + Vem in *BRAF* V600 Mutant Melanoma (NCT02908672)

- A Phase III study evaluating atezo + cobi + vem vs placebo + cobi + vem in patients with ***BRAF* V600 mutant** advanced melanoma is planned



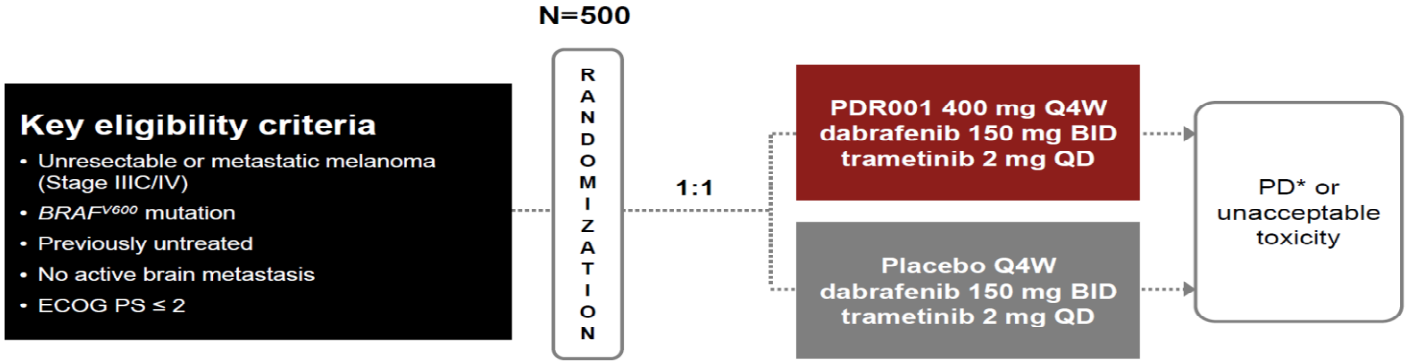
- **Key study objectives**
  - Primary: investigator-assessed PFS
  - Secondary: PFS (IRF-assessed), OS, ORR, DOR, Safety, PK

New triplets

New drugs (PDR001)

spartalizumab

Part 3, randomized portion: Study schema



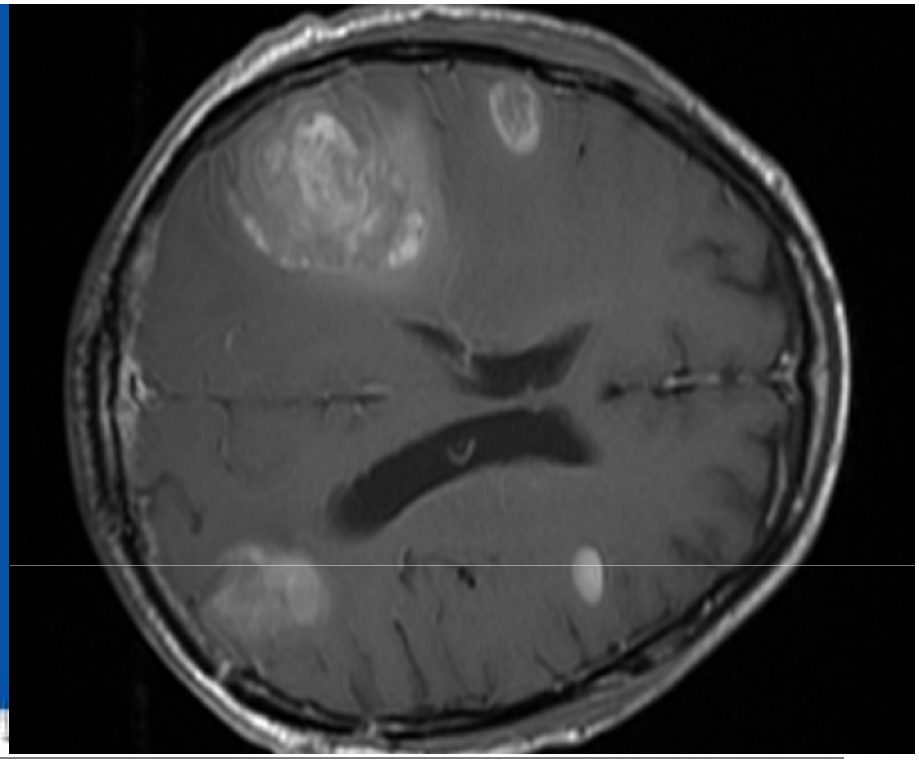
Randomization stratification:
- ECOG PS (0 vs 1 vs 2)
- LDH (<1 × ULN vs ≥1 to <2 × ULN vs ≥2 × ULN)

Primary endpoint: $PFS^{RECIST\ v1.1}$

Secondary endpoints: OS, ORR, DOR, DCR, Safety, PROs, PK

*Treatment beyond PD is permitted if protocol-specific criteria are met
BID, twice per day; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient-reported outcome; PS, performance status; QD, daily; Q4W, every 4 weeks; ULN, upper limit of normal.

Category	Endpoint
Primary	Investigator assessed PFS using RECIST 1.1
Key secondary	OS
Other secondary	• ORR, DOR, DCR • Safety and tolerability: ○ Incidence and severity of AEs and SAEs ○ Change in labs, ECOG PS, vital signs, liver, and cardiac assessments ○ Dose interruptions and reductions, dose intensity • PRO: changes in EORTC QLQ-C30, FACT-M, and EQ-5D • PK: Ctrough for PDR001, dabrafenib, and trametinib • Immunogenicity: ADA incidence • PFS and OS by PD-L1 status (cut-offs of 1, 5, and 10%)

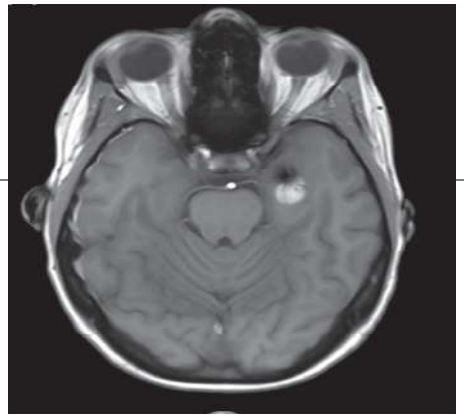


WHAT TO DO IN PTS WITH BRAIN METS?

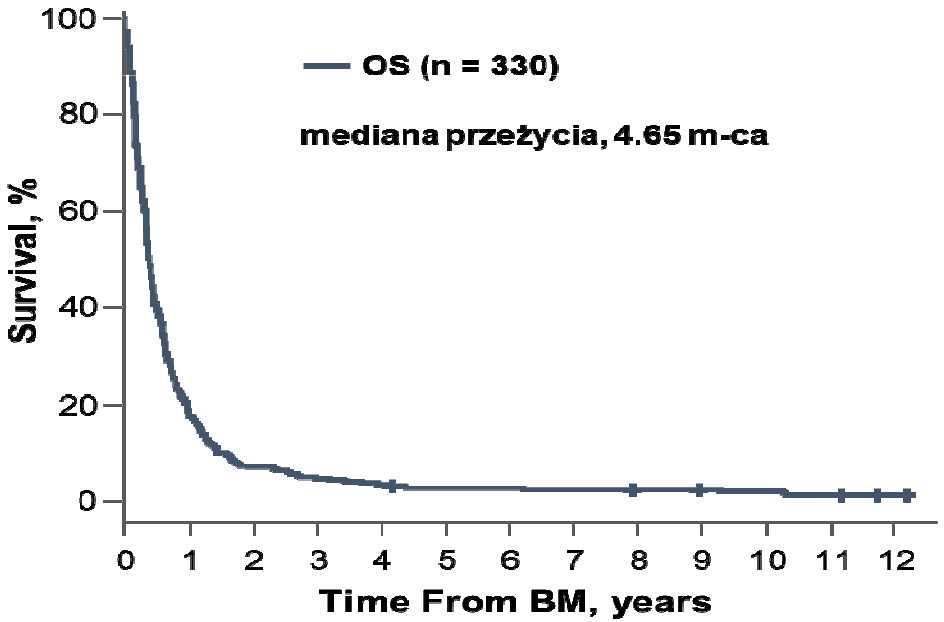
Why brain mets startegy is important?

- Melanoma often gives metastases to the CNS, the finding of changes in the brain is associated with poor prognosis
- The incidence of CNS metastases in melanoma:
- 13-20% at initial diagnosis (symptomatic changes in the CNS)
- About 50% in the course of the disease treatment
- Up to 75% in the autopsy material

CNS metastases are the cause of death in 20-50% of melanoma patients.



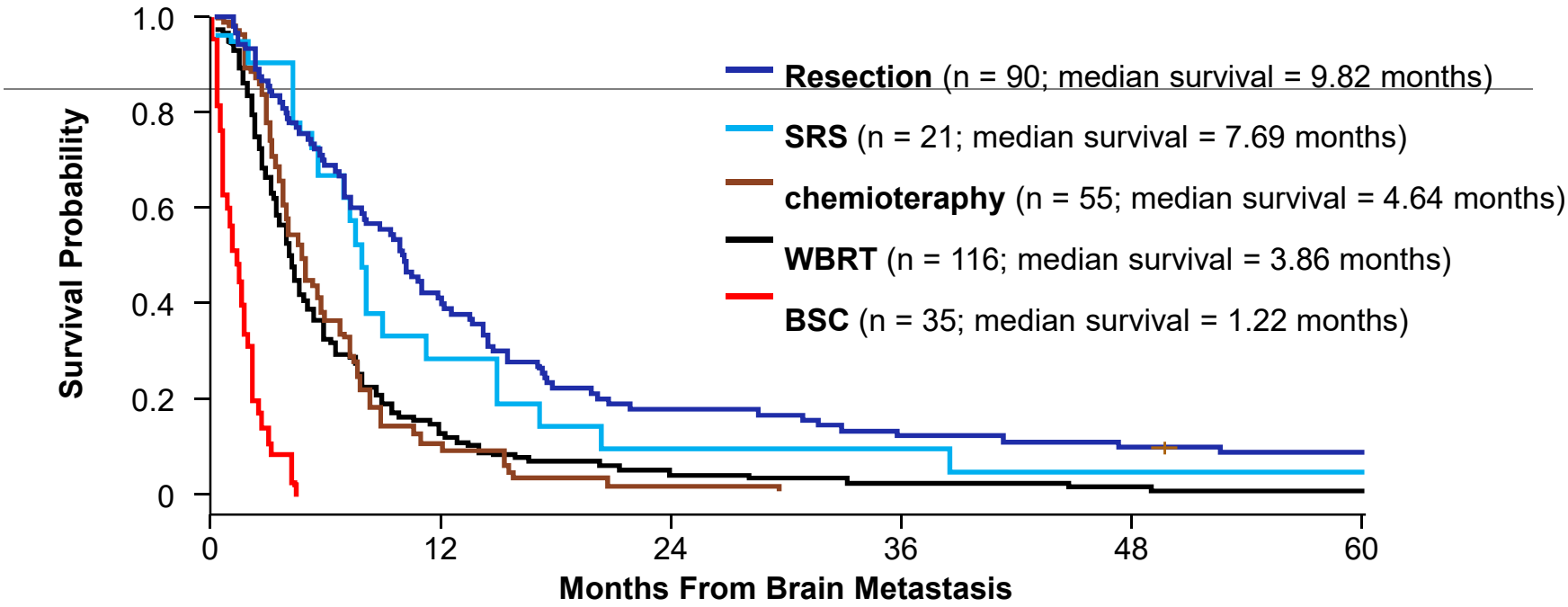
Pic: Dummer R, *et al*. *Pigment Cell Melanoma Res* 2012; 25:836–903.



1. Long GV, *et al. Lancet Oncol* 2012;13:1087–95.
2. BalchCM et. Al . Cuteneous Melanoma Quality Medical Pub. Inc, 1998 pp 347 , 379

What was the treatment before?

Overall survival curves with different treatment approach used (before the era of new therapies)



For patients with advanced melanoma enrolled in clinical trials between 1986 and 2004

- Median survival from diagnosis ranged from 1.22 to 9.82 months
- Administered at diagnosis, temozolomide was similar to other systemic therapies (4.67 vs 4.64 months); a longer median OS (7.79 vs 6.92 months) was observed when administered at any time

SRS = stereotactic radiosurgery; WBRT = whole-brain radiotherapy.

What is the treatment now?

Dabrafenib plus trametinib in patients with *BRAF*^{V600}-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial

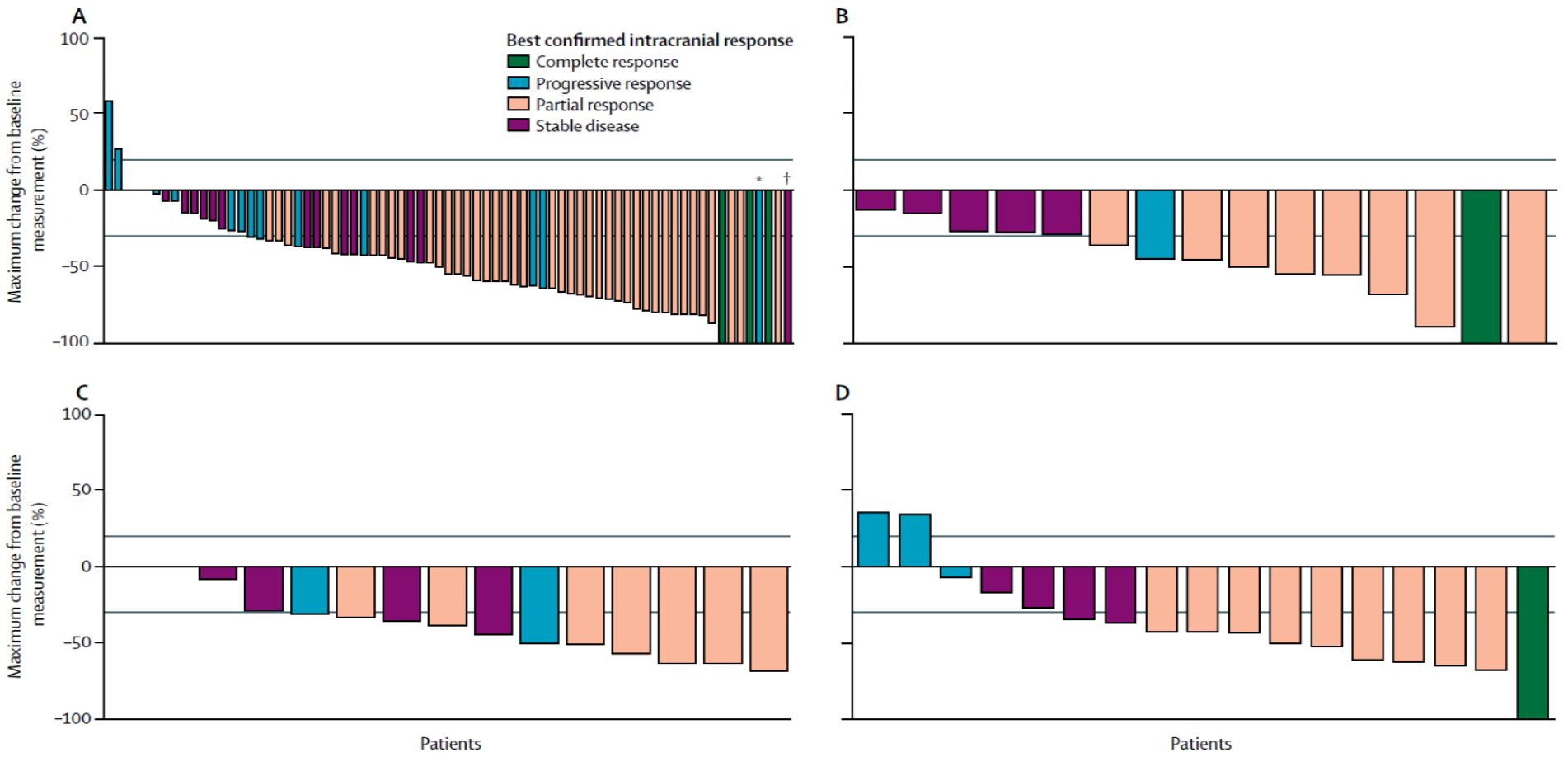


***Figure 2*: Confirmed maxiumum reduction in intracranial target lesion in cohort A (A), cohort B (B), cohort C (C), and cohort D (D)**

Grey lines at 20% represent threshold of progression and grey lines at −30% represent threshold of partial response. Cohort A=*BRAF*^{V600E}-mutant, asymptomatic melanoma brain metastases, without previous local brain-directed therapy, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Cohort B=*BRAF*^{V600E}-mutant, asymptomatic melanoma brain metastases, with previous local therapy, ECOG performance status of 0 or 1. Cohort C=*BRAF*$^{V600D/K/R}$-mutant, asymptomatic melanoma brain metastases, with or without previous local therapy, ECOG performance status of 0 or 1. Cohort D=*BRAF*$^{V600D/E/K/R}$-mutant, symptomatic melanoma brain metastases, with or without previous local therapy ECOG performance status of 0, 1, or 2. Three patients in cohort A were not assessable

Are (new) BRAFi/MEKi active in CNS mets pts?

Melanoma Res. 2019 Feb;29(1):65-69. doi: 10.1097/CMR.0000000000000527.

Clinical experience with combination BRAF/MEK inhibitors for melanoma with brain metastases: a real-life multicenter study.

Drago JZ[1], Lawrence D[1], Livingstone E[2], Zimmer L[2], Chen T[3], Giobbie-Hurder A[3], Amann VC[4,5], Mangana J[4], Siano M[6], Zippelius A[7], Dummer R[4], Goldinger SM[4], Sullivan RJ[1].

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7 Department of Biomedicine.

Abstract

BRAF and MEK kinase inhibitors can be highly effective in treating BRAF-mutant melanomas, but their safety and activity in patients with active/symptomatic brain metastases are unclear. We sought to shed light on this open clinical question. We conducted a multicenter retrospective study on real-life patients with melanoma and active brain metastases treated with combination BRAF/MEK inhibitors. A total of 65 patients were included (38 men and 27 women; median age: 49 years). Of them, 53 patients received dabrafenib/trametinib, 10 received vemurafenib/cobimetinib, one received encorafenib/binimetinib, and one received vemurafenib/trametinib. We did not observe any unexpected treatment-related safety signals in our cohort. Overall, 17 patients continued on therapy through the cutoff date. After initiation of therapy, steroid dose could be decreased in 22 of 33 patients (11 tapered off entirely), anticonvulsants were stopped in four of 21, and narcotics were stopped in four of 12. Median progression-free survival from the start of therapy was 5.3 months (95% confidence interval: 3.6-6.1), and median overall survival was 9.5 months (95% confidence interval: 7.7-13.5). A total of 20 patients were surviving at the cutoff date. Univariate analysis of age, sex, ulceration status, thickness, stage, location, or lactate dehydrogenase did not reveal significant predictors of progression-free survival or overall survival within our cohort, but multivariate analysis suggested that older age, lower risk location of original lesion, and nodular melanoma are poor prognostic indicators. Combination therapy with BRAF/MEK inhibitors is a viable treatment option for patients with BRAF-mutant melanoma and brain metastases, but further studies should help to define the optimal treatment approach in this population.

PMID: 30376465 DOI: 10.1097/CMR.0000000000000527

Should we combine BRAFi/MEKi with SRS?

Annals of Oncology 27: 2288–2294, 2016
doi:10.1093/annonc/mdw417
Published online 15 September 2016

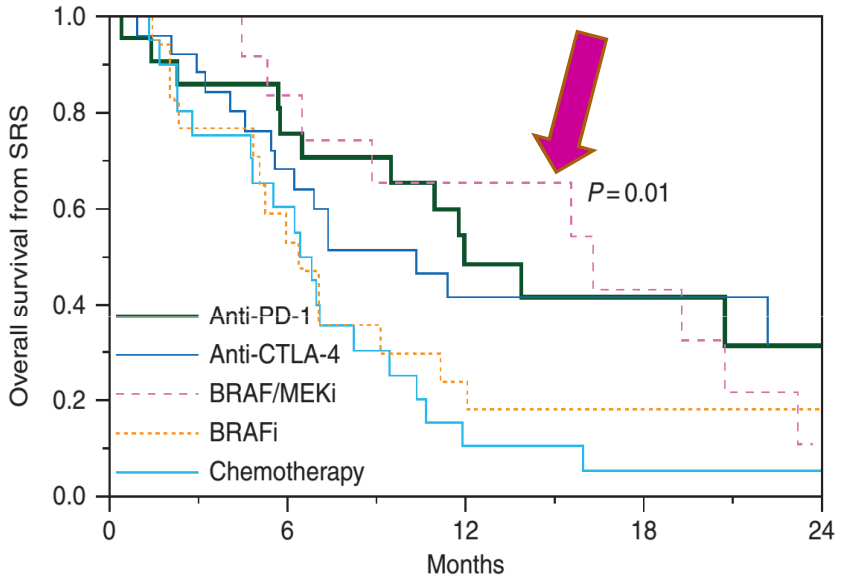
Clinical outcomes of melanoma brain metastases treated with stereotactic radiosurgery and anti-PD-1 therapy, anti-CTLA-4 therapy, BRAF/MEK inhibitors, BRAF inhibitor, or conventional chemotherapy

K. A. Ahmed[1], Y. A. Abuodeh[1], M. I. Echevarria[1], J. A. Arrington[2], D. G. Stallworth[2], C. Hogue[3], A. O. Naghavi[1], S. Kim[1], Y. Kim[4], B. G. Patel[5], S. Sarangkasiri[1], P. A. S. Johnstone[1], S. Sahebjam[6], N. I. Khushalani[7], P. A. Forsyth[6], L. B. Harrison[1], M. Yu[1], A. B. Etame[6] & J. J. Caudell[1*]

Departments of [1]Radiation Oncology; [2]Radiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa; [3]School of Medicine, University of Louisville, Louisville; [4]Biostatistics, H. Lee Moffitt Cancer Center and Research Institute, Tampa; [5]Morsani College of Medicine, University of South Florida, Tampa; [6]Neuro-Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa; [7]Cutaneous-Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, USA

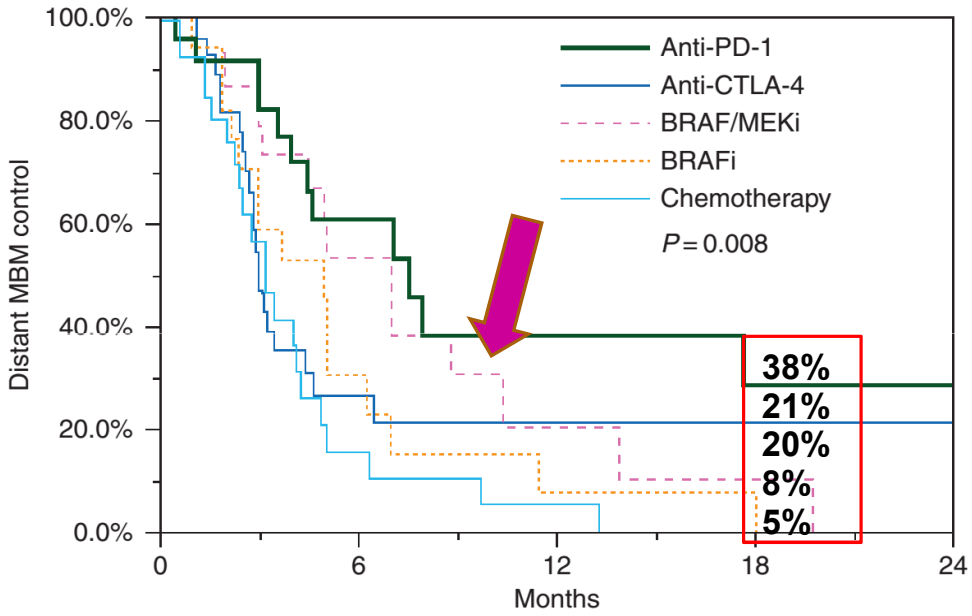
Why to we combine BRAFi/MEKi with SRS?

OS, 96 pts



No. at risk					
Anti-PD-1	21	16	10	5	4
Anti-CTLA-4	25	18	9	8	4
BRAF/MEKi	12	10	7	5	2
BRAFi	18	10	5	4	4
Chemotherapy	20	13	3	2	1

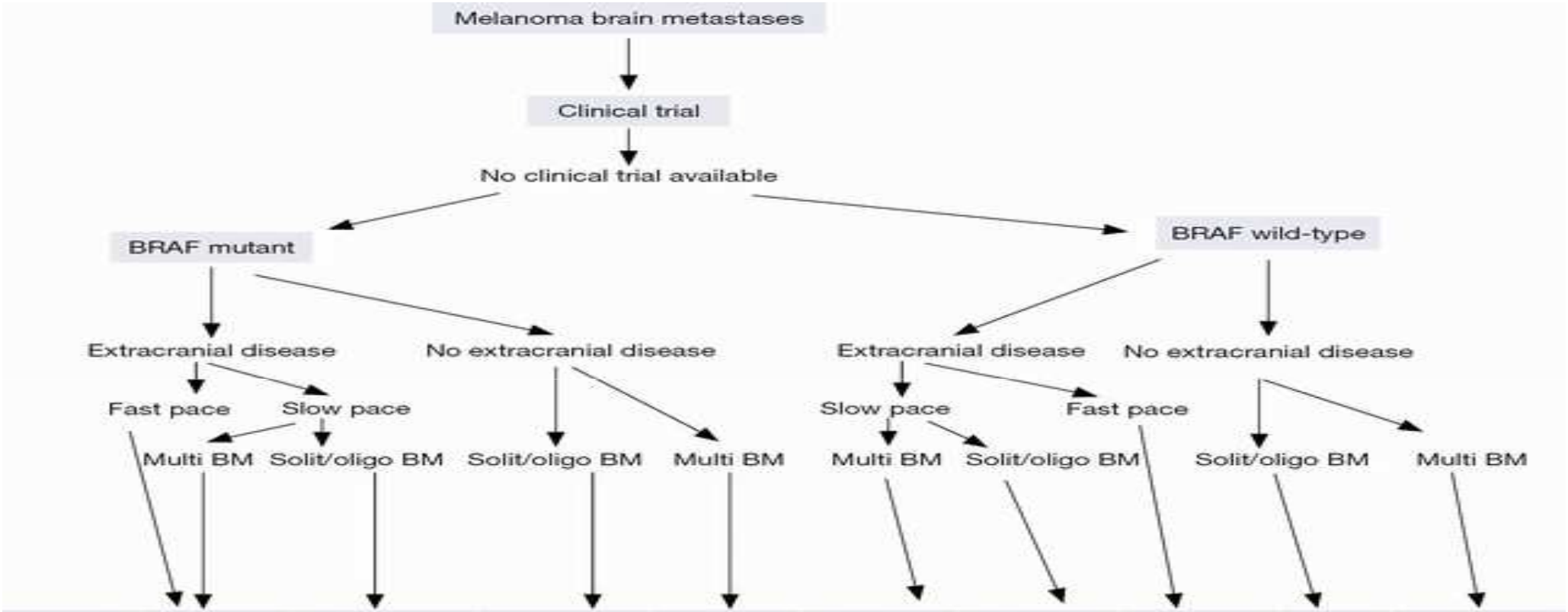
Non-CNS mets control rate, 96 pts



Anti-PD-1	25	11	6	4	4
Anti-CTLA-4	30	6	3	3	2
BRAF/MEKi	15	8	3	2	
BRAFi	22	6	2	2	
Chemotherapy	27	4	2		

no statistically significant differences in the control of CNS metastases between groups

Systemic therapies for melanoma brain metastases: which drug for whom and when?



Systemic therapy	BRAF inhibitor ± MEK inhibitor	BRAF inhibitor MEK inhibitor or checkpoint inhibitor	Neoadjuvant BRAF inhibitor ± MEK inhibitor	BRAF inhibitor ± MEK inhibitor	Checkpoint inhibitor	Checkpoint inhibitor	Checkpoint inhibitor	N/A	Checkpoint inhibitor may be considered
Local therapy	As needed	Surgery or SRS	Surgery or SRS	As needed	WBRT ± surgery or SRS	Surgery or SRS	As needed	Surgery or SRS	WBRT ± surgery or SRS

Chin Clin Oncol. 2015 Jun;4(2):25.

ADJUVANT TREATMENT IN MM?

BRAFi/MEKi not only in advanced disease

L. Eggermont AACR 2018

Introduction

Approved drugs for the adjuvant therapy of stage III melanoma

Old Era (1996–2009)

- High-Dose Interferon (IFN)-α2b (US, EU), Low-Dose IFN-α2a (EU), pegylated IFN-α2b (US)[1]

New Era (2015–2018)

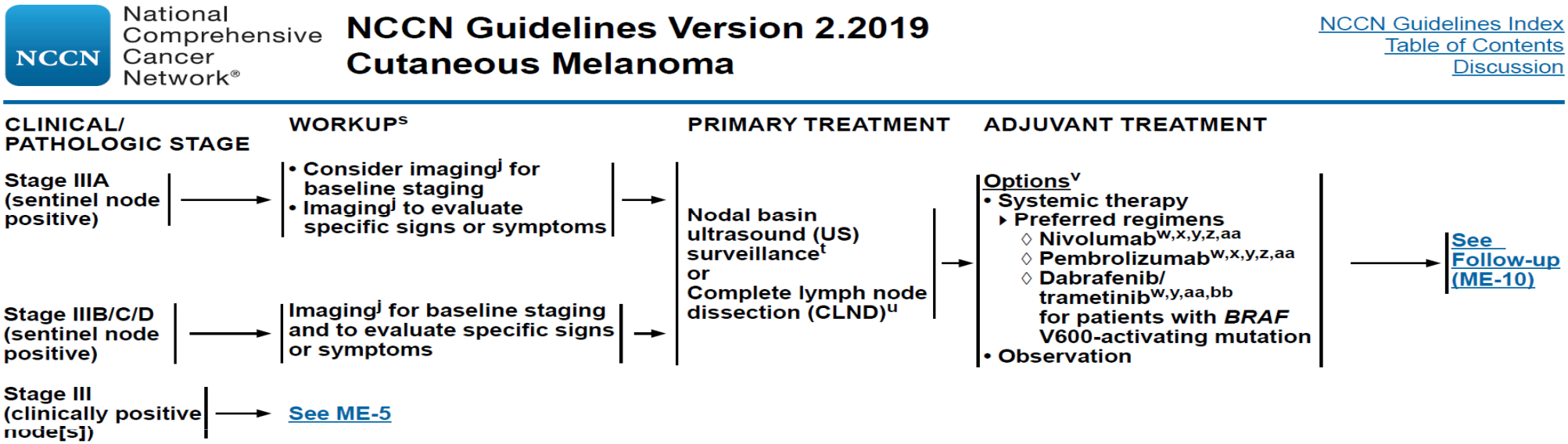
• ***Ipilimumab (US)**[2]	HR_{RFS}(Ipilimumab vs. Placebo)=0.75	(2015)
• **Nivolumab**[3]	HR_{RFS}(Nivolumab vs. Ipilimumab)=0.65	(2017)
• ***Dabrafenib plus Trametinib**[4]	HR_{RFS}(Dab+Tra vs. Placebo)=0.47	(2018)
• ***Pembrolizumab**[5]	HR_{RFS}(**Pembrolizumab** vs. **Placebo**)=0.57	(EXP/2018)

*** Trials performed in identical patient populations at high risk of relapse: IIIA >1mm; IIIB/C**

5-year relapse rates: stage IIIA, 37%; stage IIIB, 68%; stage IIIC, 89%[6]

[1]Eggermont AM, et al. *Lancet* 2014;383:816-27; [2]Eggermont AM, et al. *Lancet Oncology* 2015;16:522-30; [3]Weber J, et al. *N Engl J Med* 2017;377:1824-35; [4]Long GV, et al. *N Engl J Med* 2017;377:1813-23; [5]Eggermont AM, et al. *N Engl J Med* 2018;375:1845-55: 15 March; [6]Romano E, et al. *J Clin Oncol* 2010;28:3042-7.

Where do we stand in 2019? (sentinel node positive)



[j] See Principles of Imaging–Workup (ME-D).

[s] *BRAF* mutation testing is recommended for patients with stage III at high risk for recurrence for whom future BRAF-directed therapy may be an option. See Principles of Molecular Testing (ME-C).

[t] For patients with a positive SLNB who do not undergo CLND, it would be appropriate for the frequency of clinical exam and US surveillance to be consistent with the two prospective randomized trials (MSLT-II and DeCOG): at least every 4 months during the first 2 years, then every 6 months during years 3 through 5.

[u] For patients with a positive sentinel node, two prospective randomized phase III studies have demonstrated no improvement in melanoma-specific survival or OS in patients undergoing CLND compared to those who underwent nodal basin US surveillance. CLND did provide additional prognostic information as well as improvement in regional control/recurrence at the expense of increased morbidity, including wound complications and long-term lymphedema. Factors that predict non-SLN positivity include sentinel node tumor burden, number of positive nodes, and thickness/ulceration of the primary tumor. See Principles of Complete Lymph Node Dissection (ME-G).

[v] The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity.

[w] In patients with very-low-risk stage IIIA disease (non-ulcerated primary, SLN metastasis <1 mm), the toxicity of adjuvant therapy may outweigh the benefit.

[x] Nivolumab has shown a clinically significant improvement in RFS compared to high-dose ipilimumab, but its impact on OS has not yet been reported. Pembrolizumab has shown a clinically significant improvement in RFS compared to placebo, but its impact on OS has not yet been reported.

[y] Adjuvant dabrafenib/trametinib and pembrolizumab are category 1 options for patients with AJCC 7th Edition stage IIIA with SLN metastasis >1 mm or stage IIIB/C disease. Adjuvant nivolumab is a category 1 option for patients with AJCC 7th Edition stage IIIB/C disease.

[z] Randomized clinical trials testing adjuvant anti-PD-1 therapy included patients with sentinel node-positive disease at high risk: those with ulcerated primary (nivolumab, pembrolizumab) or an SLN metastasis >1 mm (pembrolizumab).

[aa] All patients in the clinical trials studying adjuvant anti-PD-1 or adjuvant dabrafenib/trametinib were required to undergo CLND prior to randomization. In the setting of two prospective trials demonstrating that CLND has no impact on DSS or OS, it is unclear whether CLND should be a factor in the decision to use either adjuvant therapy in sentinel node-positive patients.

[bb] The randomized clinical trial testing adjuvant dabrafenib/trametinib combination therapy for patients with *BRAF* V600E/K mutation included patients with sentinel node-positive disease at high risk: those with ulcerated primary and/or SLN metastasis >1 mm.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Where do we stand in 2019? (clinically + nodes)

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Cutaneous Melanoma

NCCN Guidelines Index
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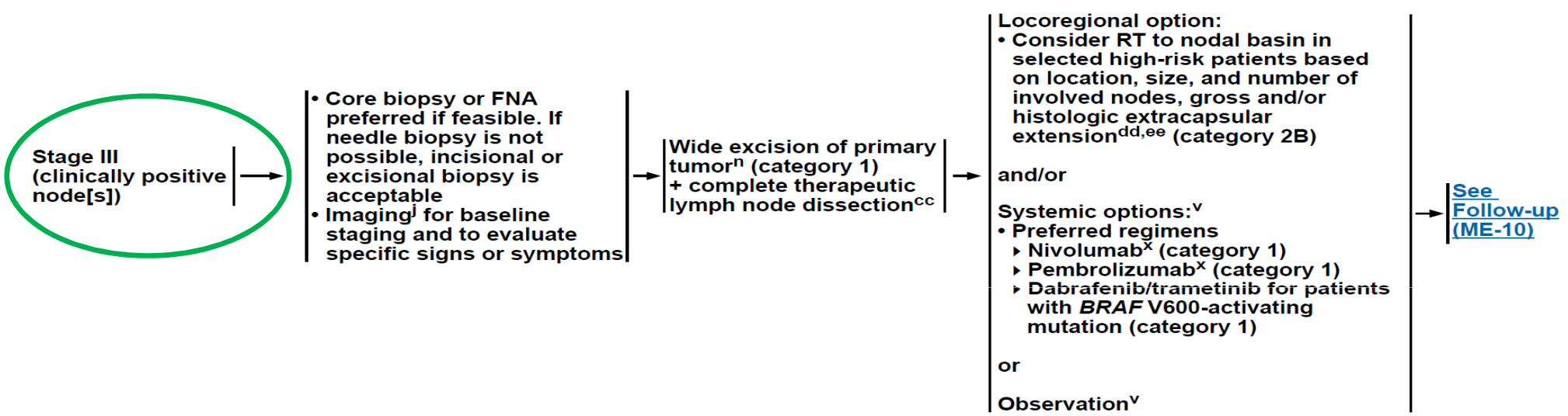
Discussion



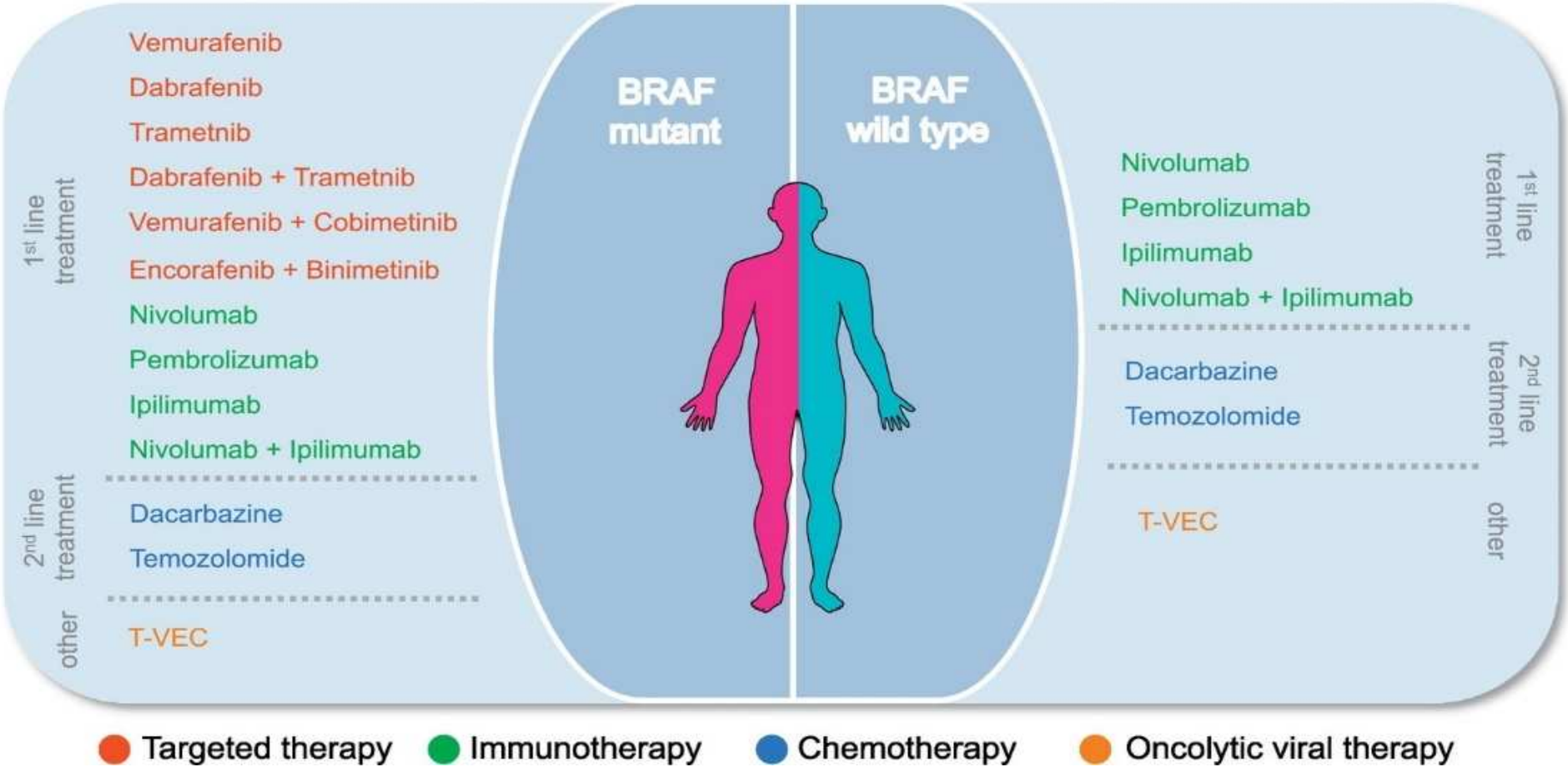
[j] See Principles of Imaging–Workup (ME-D).
[n] See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-E).
[s] *BRAF* mutation testing is recommended for patients with stage III at high risk for recurrence for whom future BRAF-directed therapy may be an option. See Principles of Molecular Testing (ME-C).
[v] The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity.
[x] Nivolumab has shown a clinically significant improvement in RFS compared to high-dose ipilimumab, but its impact on OS has not yet been reported. Pembrolizumab has shown a clinically significant improvement in RFS compared to placebo, but its impact on OS has not yet been reported.
[cc] In patients with borderline resectable lymphadenopathy or very high risk of recurrence after lymphadenectomy, consider a clinical trial of neoadjuvant systemic therapy.
[dd] Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has shown no improvement in RFS or OS. Its benefits must be weighed against potential toxicities such as lymphedema (limb) or oropharyngeal complications. The impact of these potential toxicities should be considered in the context of other adjuvant treatment options.
[ee] See Principles of Radiation Therapy for Melanoma (ME-H).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

And?

*Take home message

Summary (2019)



Biochim Biophys Acta Rev Cancer. 2019 Feb 15;1871(2):313-322.

Summary (2019)

Curr. Treat. Options in Oncol. (2016) 17: 52
DOI 10.1007/s11864-016-0427-z

Skin Cancer (BY Kwong, Section Editor)

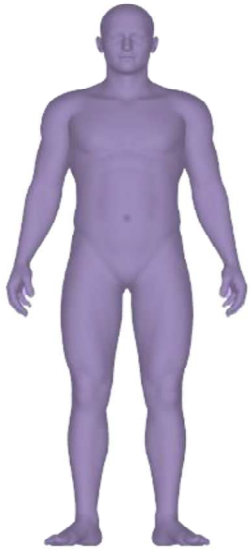
Sequencing of New and Old Therapies for Metastatic Melanoma

Table 1. Comparison of melanoma therapies

	Toxicity	Early response	Durable response
Immunotherapy			
Anti-PD1	+	++	+++
Anti-CTLA4	++	+	+++
Anti-CTLA4 and anti-PD1	+++	++	++++
Interleukin-2	++++	+	++
Targeted therapy			
Vemurafenib	+	+++++	+
Dabrafenib	+	+++++	+
Dabrafenib and trametinib	+	+++++	+/++
Vemurafenib and cometinib	+	+++++	+/++
Cytotoxic therapy			
Biochemotherapy	++++	+++	++
CVD	++	+++	+

In selecting therapies in each category, the likelihood of toxicity, early response, and durable response should be considered. Grading is based on published results as well as experience. Direct comparison in studies is not available. CVD is cisplatin, vinblastine, and dacarbazine. The number of "+" signs is indicative of the likelihood of developing toxicity, early response, or durable response

Selection of treatment in melanoma



BRAFi & MEKi treatment efficacy summary

	Chapman 2011	Hauschild 2012	Flaherty 2012	Long 2015/2016 COMBI-d		Robert 2014/Robert 2016 COMBI-v		McArthur 2014/Larkin 2015 CoBRIM	
Faza	III	III	III	III		III		III	
Lek	wemurafenib	dabrafenib	trametinib	dabrafenib	**dabrafenib + trametynib**	wemurafenib	**dabrafenib + trametynib**	wemurafenib	**wemurafenib + kobimetynib**
ORR	48%	50%	22%	53%	**69%**	51%	**64%**	50%	**70%**
PFS	6,9 m	6,9 m	4,8 m	8,8 m	**11 m**	7,3 m	**11,4 m**	7,2 m	**12,3 m**
OS	15 m	18 m	NR	18,7 m	**25,1 m**	18,0 m	**25,6 m**	17,4 m	**22,5 m**
3-l OS				32%	**44%**	31%	**45%**	31,1%	**37,4%**
LDH> N	**58%**	**36%**	**36%**	**33%**	**36%**	**32%**	**34%**	**43%**	**46%**

Targeted Therapy

	Dabrafenib + Trametinib COMBI-v	Dabrafenib + Trametinib COMBI-d	Vemurafenib + Cobimetanib CoBRIM	Encorafenib + Binimetanib Combo 450	Encorafenib + Binimetanib Combo 300
Median OS	25.6 (22.6-NR)	25.1 (18.7-NR)	22.3 (20.3-NR)	**33.6**	?
Median PFS	12.6 (10.7–15.5)	11.0 (8.0-13.9)	12.25 (9.6-13.37)	14.9 (11.0-18.5)	12.9 (10.1-14.0)
Response rate	66%	68%	69%	63%	66%

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THANK YOU FOR
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ANY QUESTIONS?
NO? GREAT!
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