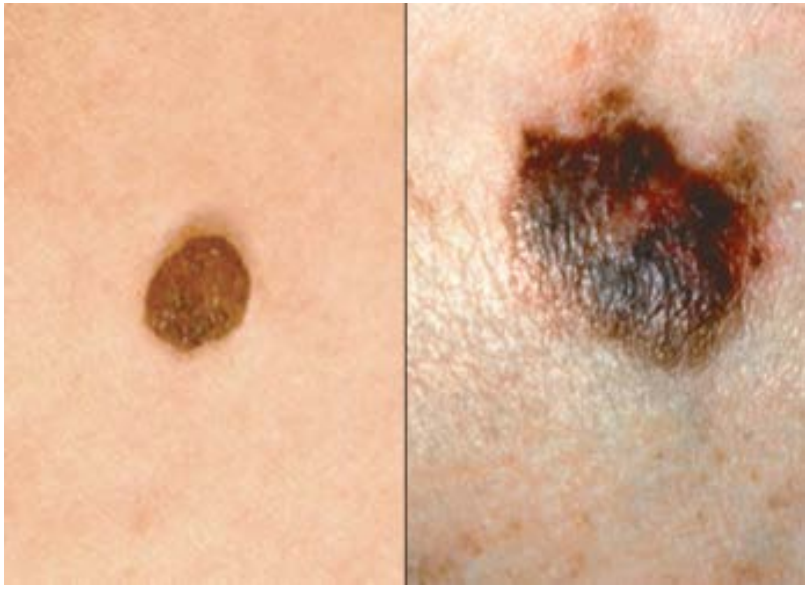
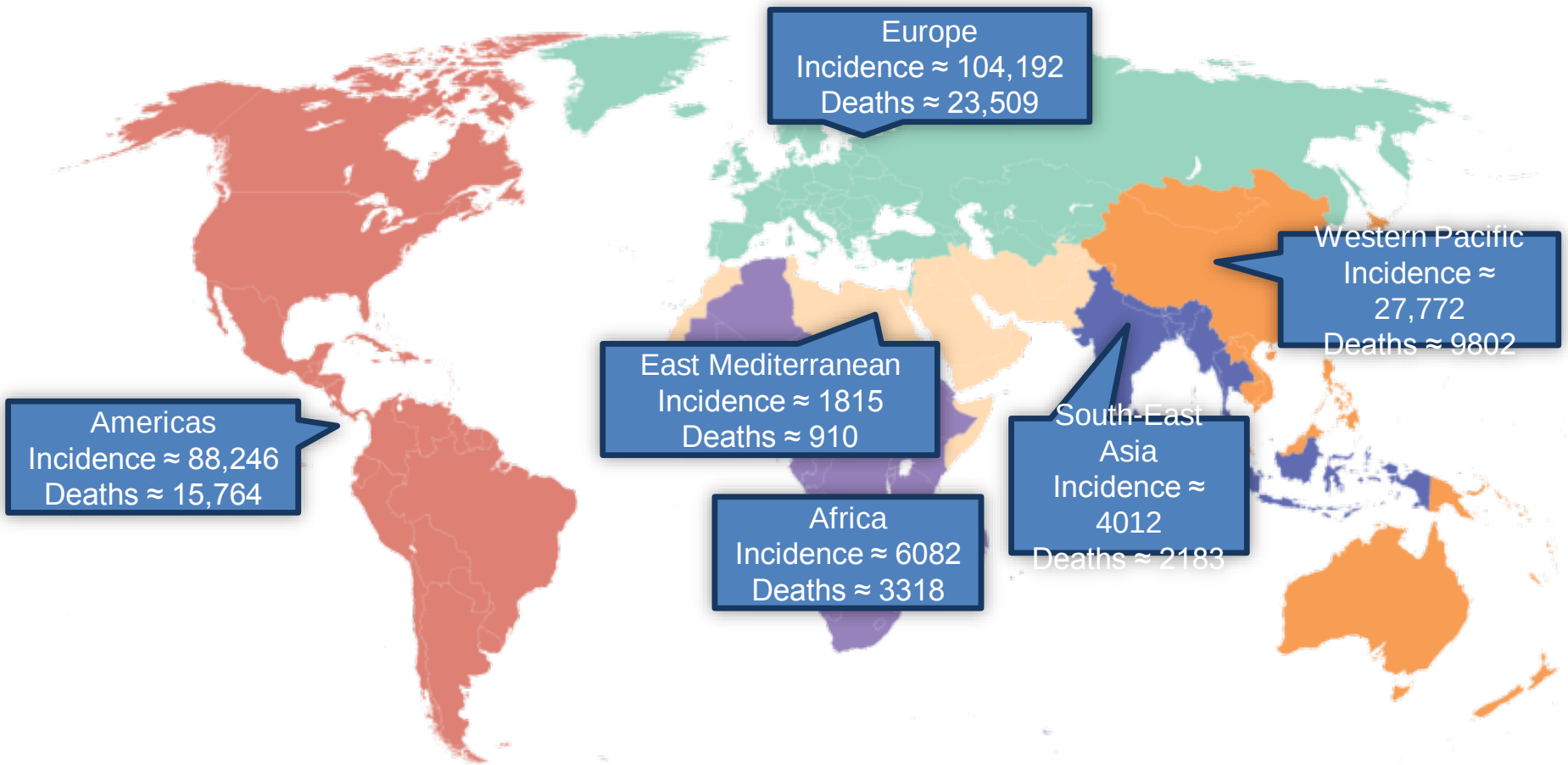
Malignant Melanoma, what's new ?

- Dr Daniel A Vorobiof
- Sandton Oncology Centre
- Johannesburg



Melanoma Epidemiology: Incidence and Mortality

Estimated 2012 Global Incidence and Mortality by WHO Region (all ages, both sexes)

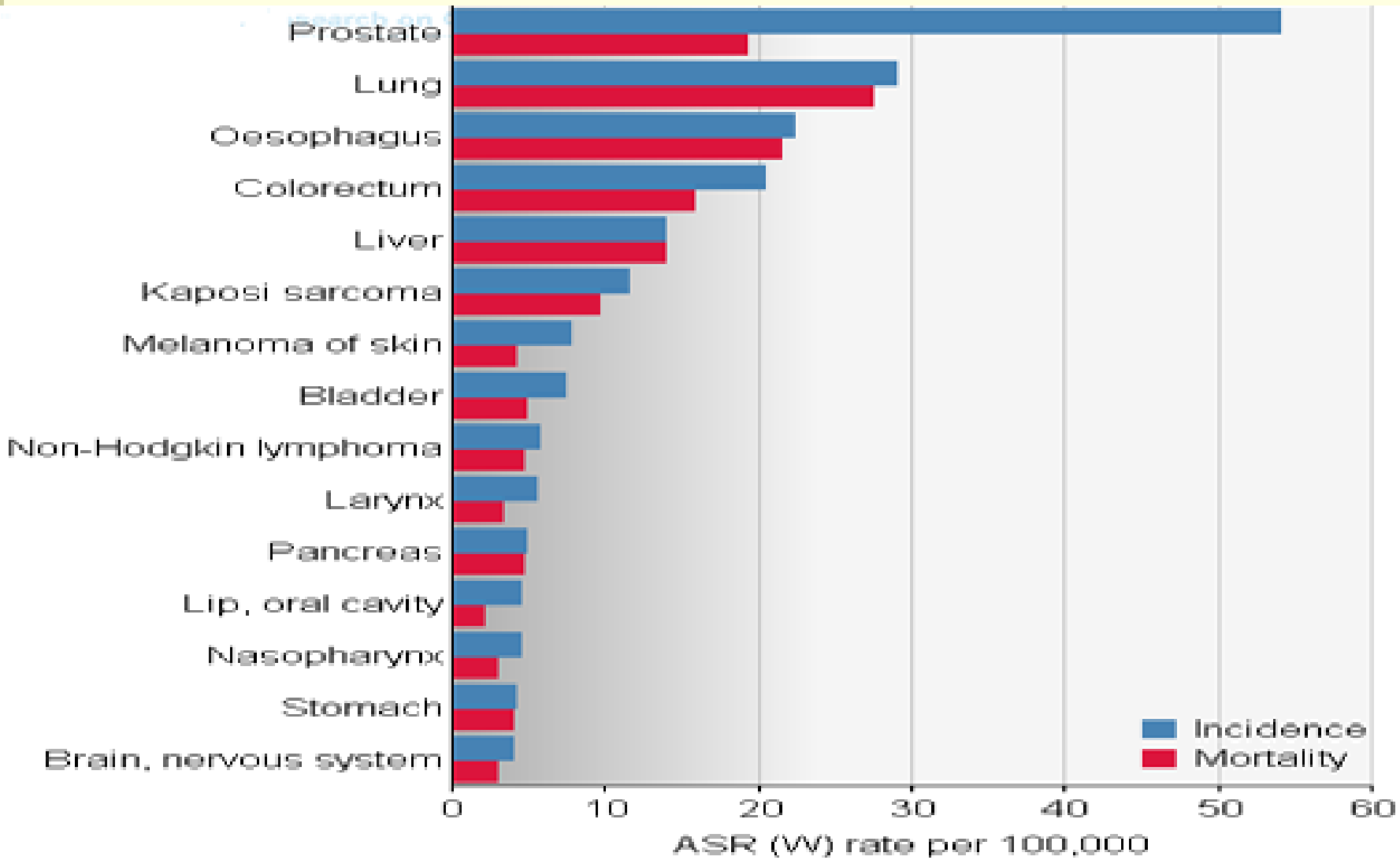


- In 2012, there were ≈ 232,130 cases of melanoma worldwide
  - There were ≈ 55,489 deaths due to melanoma worldwide

Globocan. http://globocan.iarc.fr/Pages/pie_site_sel.aspx. Accessed October 7, 2014.

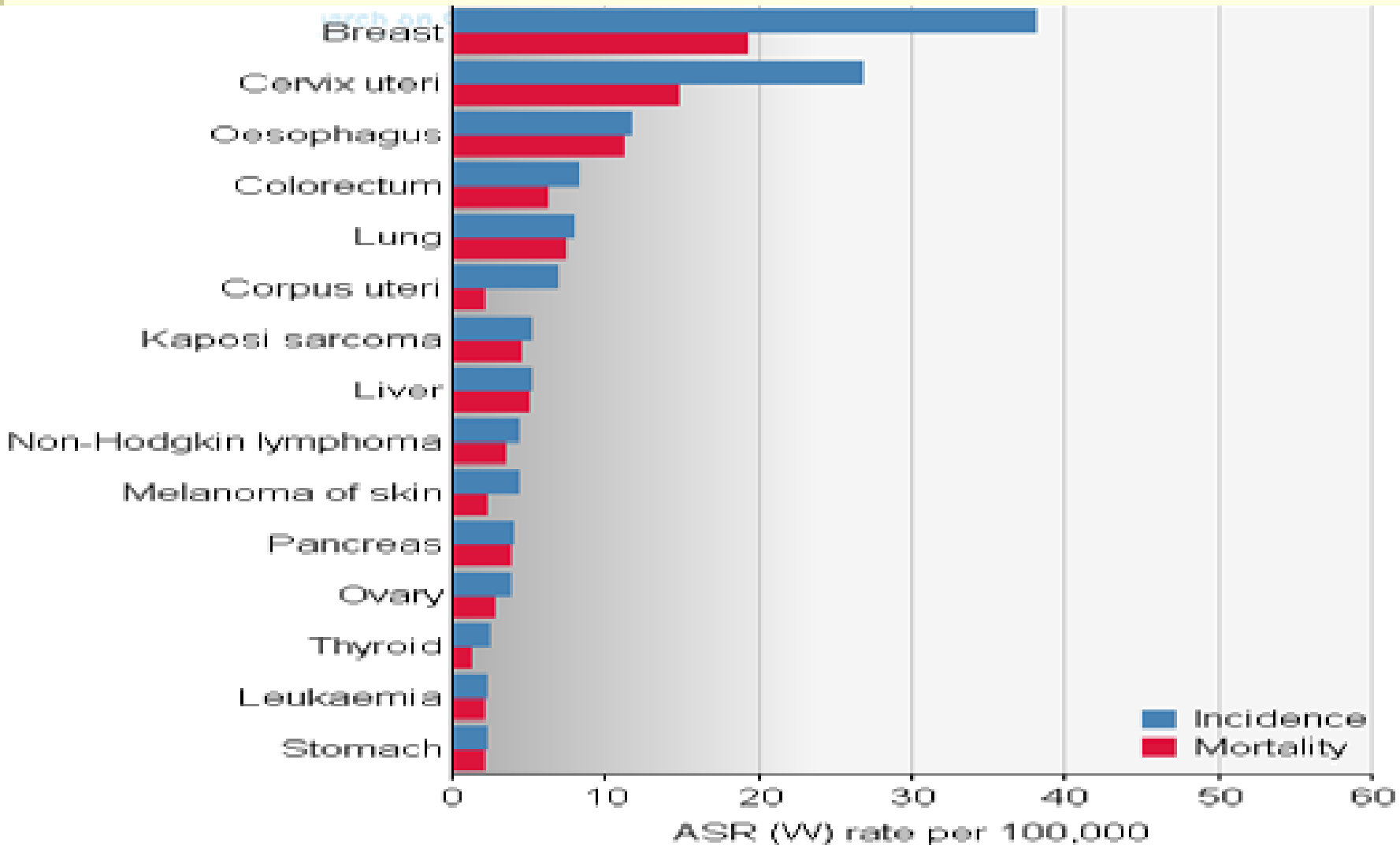
NOVARTIS

Southern Africa, 2008 – Estimated age-standardised incidence & mortality rates in men



Southern Africa, 2008 – Estimated age-standardised incidence & mortality rates

in women



Advanced Melanoma: Overview

- Accounts for ~ 1% of skin cancer diagnosed in the US[1,2]
  - New cases, 2016 (estimated): 76,380
  - Deaths, 2016 (estimated): 10,130
  - 5-yr survival rate for metastatic disease: 15% to 20%
- Multiple new therapeutic agents/regimens have been approved since 2011
  - Immune checkpoint inhibitors
  - BRAF and MEK inhibitors
  - Oncolytic virus therapy

1. Siegel RL, et al. CA Cancer. 2016;66:7-30.
2. Balch R, et al. J Clin Oncol. 2009;27:6199-6206.

THERAPY OF METASTATIC DISEASE

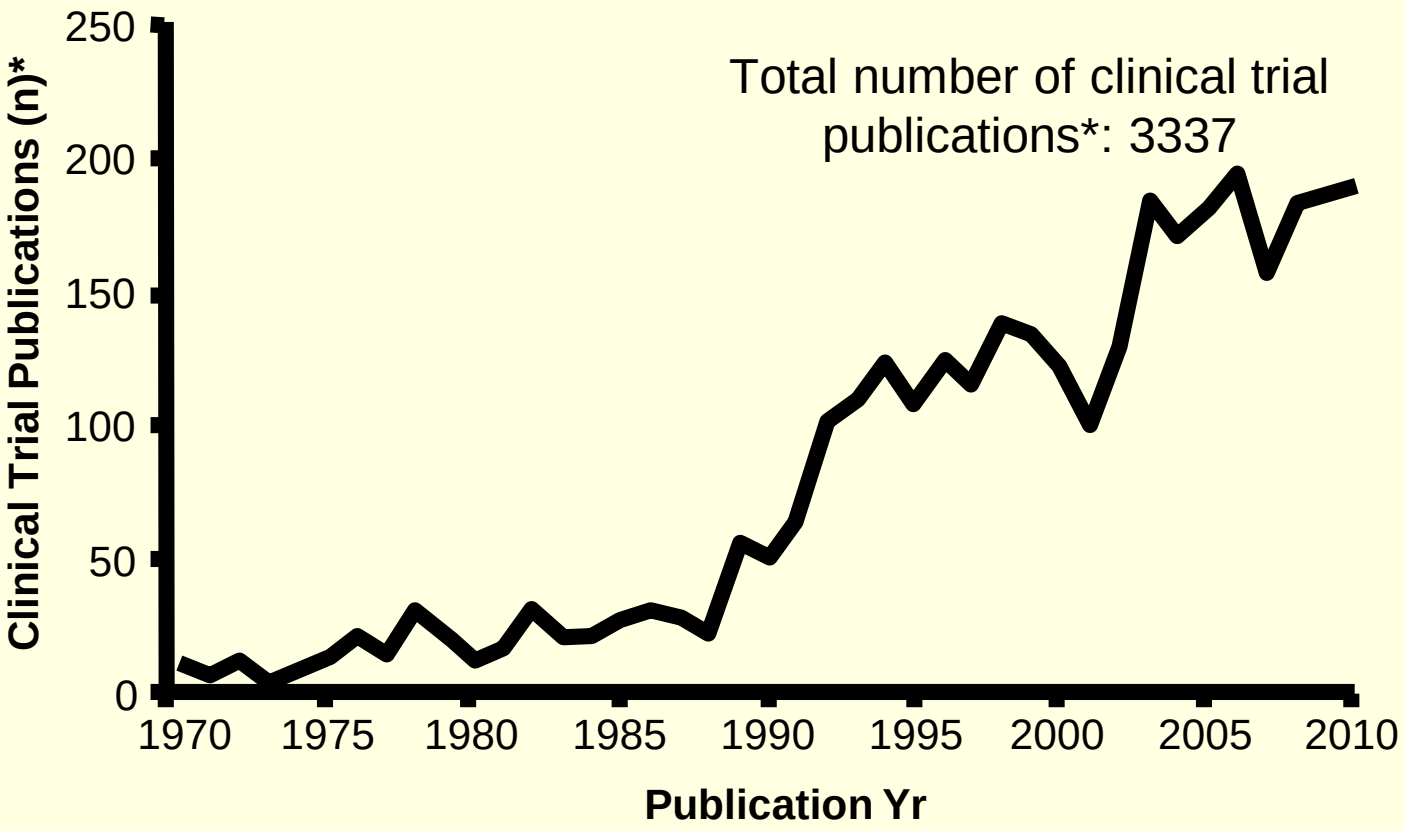
Monotherapy for the Treatment of Metastatic Melanoma

- Monotherapy with chemotherapy is relatively ineffective in treatment of metastatic melanoma

Chemotherapies	Response Rate
DTIC	**5.3%–28%**
Temozolomide	**13.5%–24%**
Fotemustine	**15.5%–24.2%**
Paclitaxel	**3.6%**
Vindesine	**12%–26%**

*

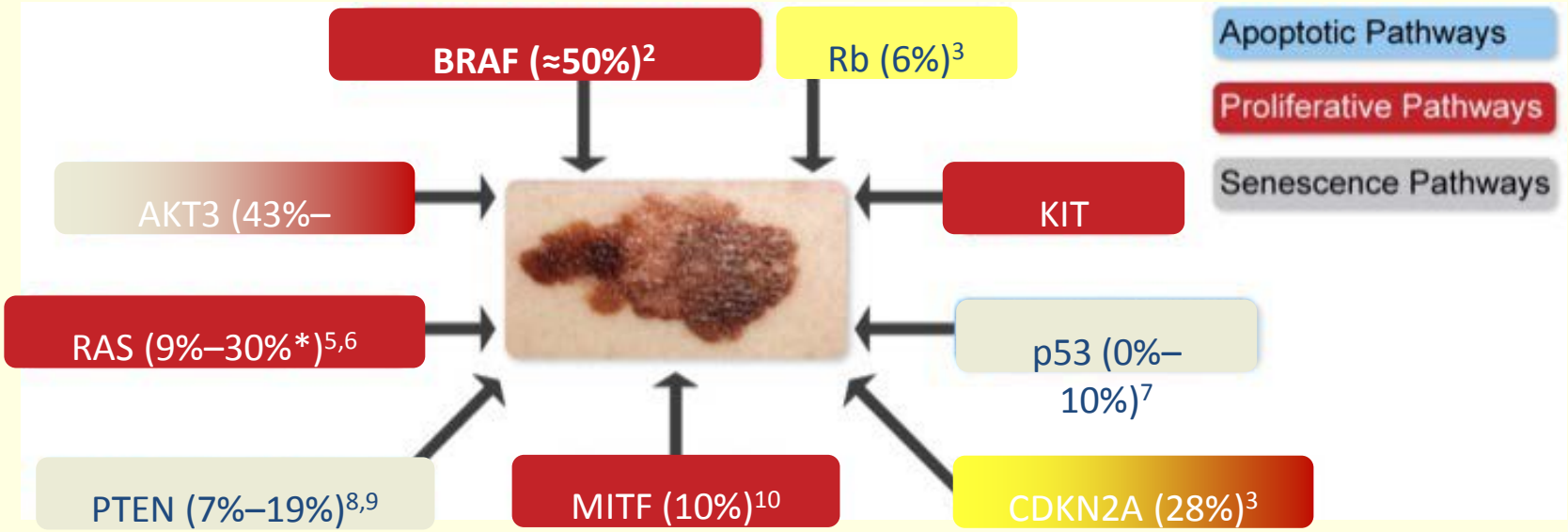
> 3000 Trials Between 1970 and 2010 Had No Real Clinical Impact



*Data collected using PubMed;
US National Library of Medicine and National Institutes of Health.

Molecular Pathways in Melanoma

- Key signalling pathways that are important in melanoma and that represent potential novel therapeutic targets have been identified[1]
- Alterations in several oncogenes, tumour suppressor genes, and their related pathways have been identified in melanoma, to varying extents



AKT = protein kinase B; BRAF = rapidly accelerated fibrosarcoma isoform B; CDKN2A = cyclin-dependent kinase inhibitor 2A; KIT = Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MITF = microphthalmia-associated transcription factor; p53 = protein 53; PTEN = phosphatase and tensin homolog; RAS = rat sarcoma; Rb = retinoblastoma.

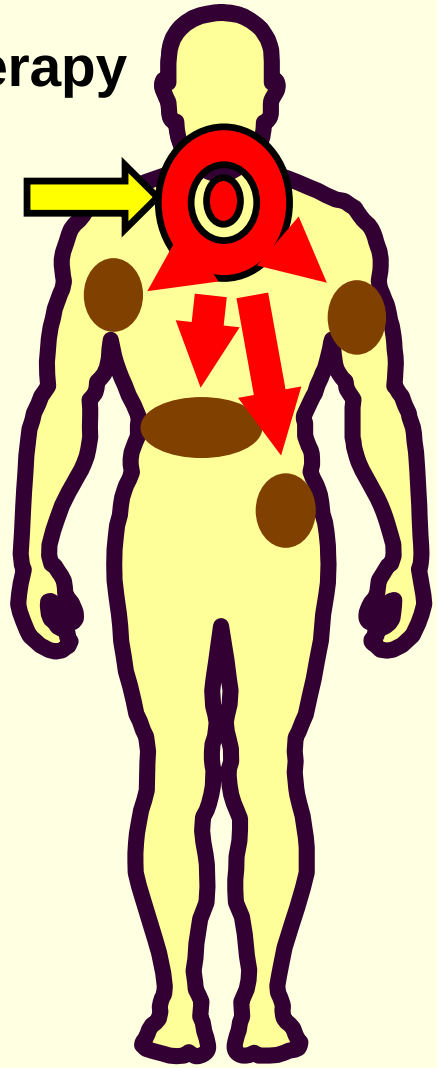
* The frequency of RAS mutation identified in melanoma is isoform-dependent.[5,6]

1. Sekulic A, *et al. Mayo Clin Proc* 2008;83:825–46.
2. Flaherty KT, *et al. Cancer* 2010;116:4902–13.
3. Forbes SA, *et al. Nucleic Acids Res* 2010;38:D652–7.
4. Stahl JM, *et al. Cancer Res* 2004;64:7002–10.
5. Davies H, *et al. Nature* 2002;417:949–54.
6. Omholt K, *et al. Clin Cancer Res* 2003;9:6483–8.
7. Box NF, *et al. Pigment Cell Melanoma Res* 2008;21:525–33.
8. Birck A, *et al. J Invest Dermatol* 2000;114:277–80.
9. Çelebi JT, *et al. J Med Genet* 2000;37:653–7.
10. Garraway LA, *et al. Nature* 2005;436:117–22.

Metastatic Melanoma: Treatment Advances

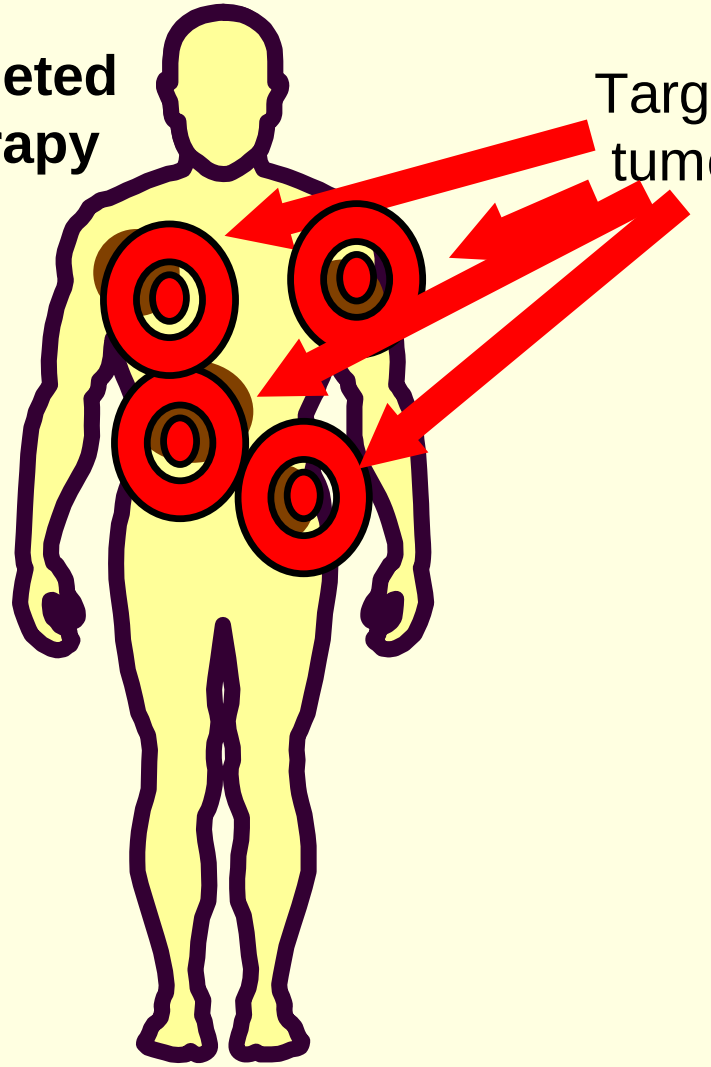
Immunotherapy

Target host



Targeted Therapy

Target tumor



Therapy of Metastatic Disease

1. **Molecular Targeted therapies (anti- BRAF and others).**
2. Immunotherapy (IL2, anti CTLA-4 and others)

Targeted Therapy

- Targeted cancer therapies are drugs or other molecules that block the growth and spread of cancer by interfering with specific changes or mutations in a pathway

- Many of these therapies focus on proteins that are involved in cell signaling pathways, which form a complex communication system that governs basic cellular functions and activities, such as cell division, cell movement, cell responses to specific external stimuli, and even cell death
  - By blocking signals that tell cancer cells to grow and divide uncontrollably, targeted cancer therapies can help stop cancer progression and may induce cancer cell death

Targeted therapy

The development of targeted therapies requires:

The identification of a target
The development of a therapy.

Most targeted therapies are either small-molecule drugs or monoclonal antibodies

By focusing on molecular and cellular changes that are specific to cancer, targeted cancer therapies may be more effective than other types of treatment, including chemotherapy and radiotherapy, and less harmful to normal cells

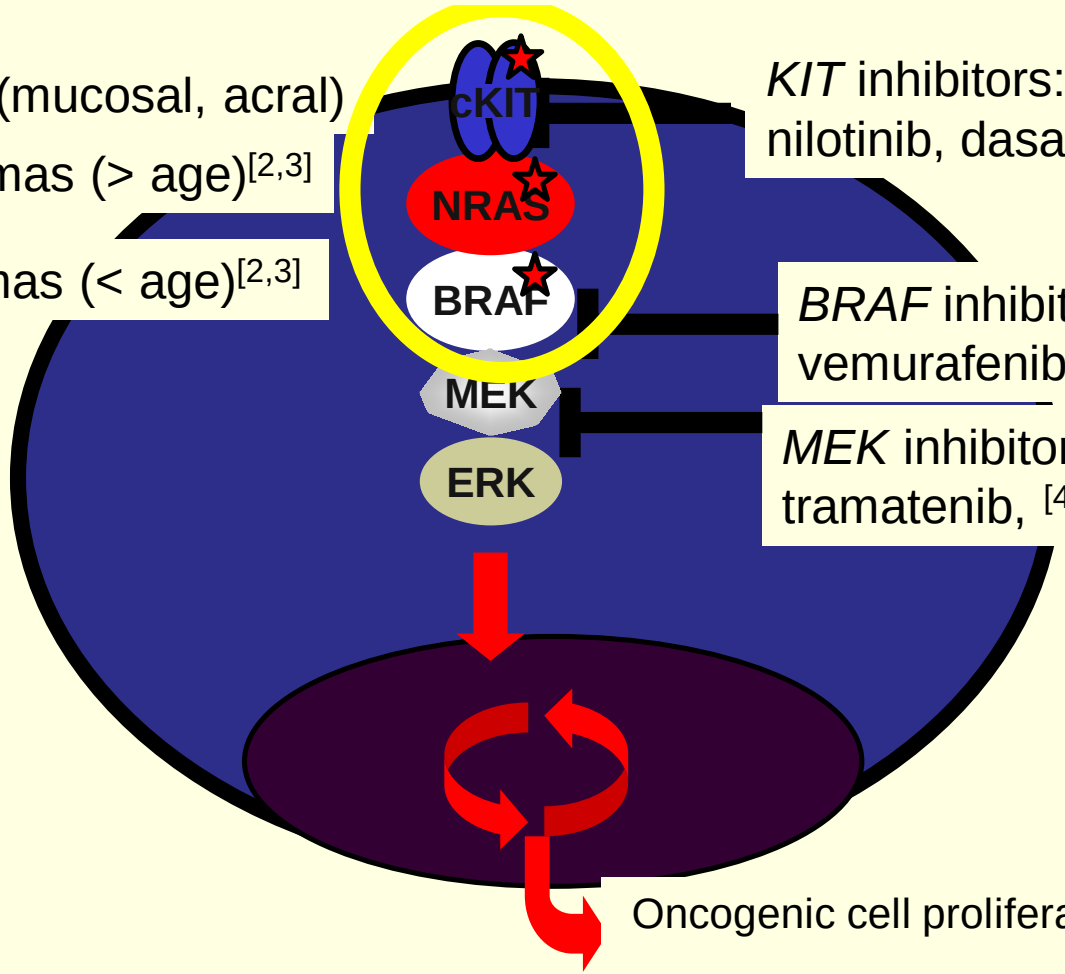
MAP Kinase Pathway Targeting in Melanoma

cKIT, NRAS, BRAF mutated in ~ 70% of melanomas, usually mutually exclusive[1]

< 5% melanomas (mucosal, acral)

~ 20% melanomas (> age)[2,3]

~ 50% melanomas (< age)[2,3]



KIT inhibitors: imatinib, nilotinib, dasatinib[4]

BRAF inhibitors: vemurafenib, dabrafenib[4

MEK inhibitors:cobimetinib tramatenib, [4]

Oncogenic cell proliferation and survival

1. Sosman JA, et al. ASCO 2011 Educational Book. 2. Arkenau HT, et al. Br J Cancer. 2011;104:392-398. 3. Thomas N, et al.
Cancer Epidemiol Biomarkers Prev. 2007;16:991-997. 4. Nikolaou VA, et al. J Invest Dermatol. 2012;132:854-863.

The NEW ENGLAND JOURNAL of MEDICINE

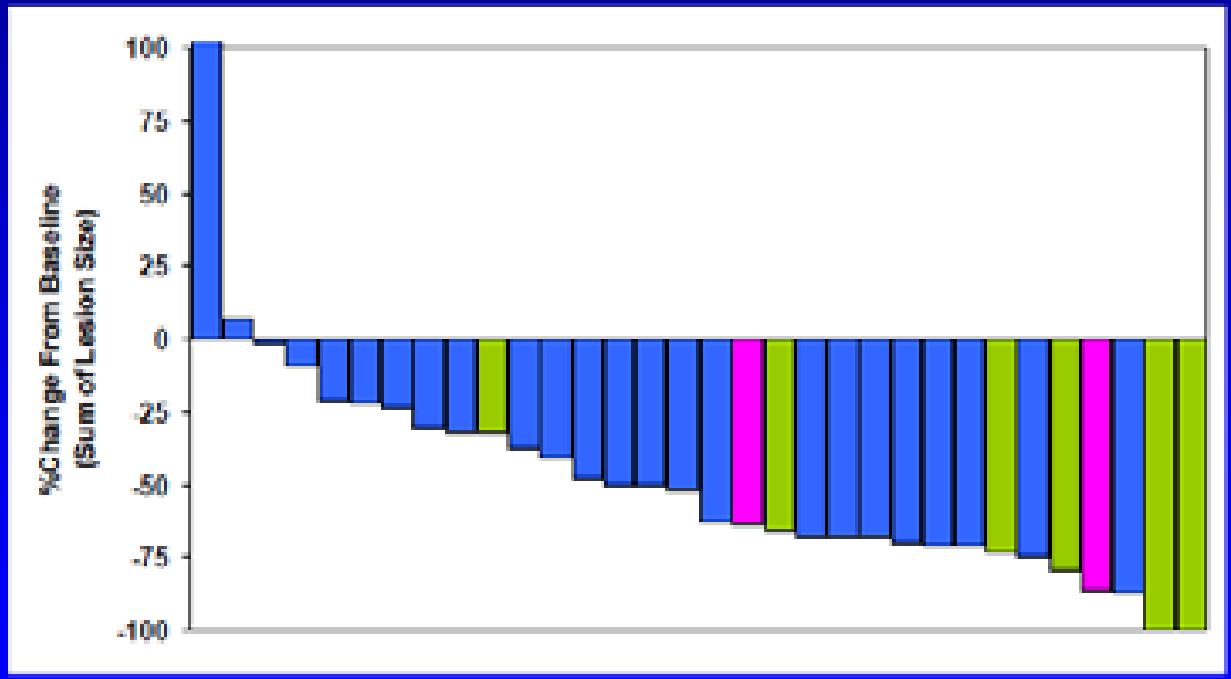
ESTABLISHED IN 1812 AUGUST 26, 2010 VOL. 363 NO. 9

Inhibition of Mutated, Activated BRAF in Metastatic Melanoma

Keith T. Flaherty, M.D., Igor Puzanov, M.D., Kevin B. Kim, M.D., Antoni Ribas, M.D., Grant A. McArthur, M.B., B.S., Ph.D., Jeffrey A. Sosman, M.D., Peter J. O'Dwyer, M.D., Richard J. Lee, M.D., Ph.D., Joseph F. Grippo, Ph.D., Keith Nolop, M.D., and Paul B. Chapman, M.D.

Phase I Trial:

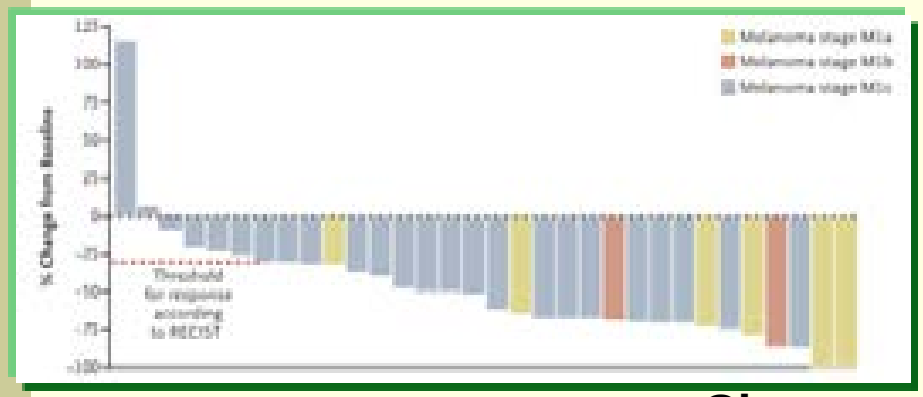
- Tumor responses occurred in majority (81%, 59% confirmed) of patients in V600E+ melanoma extension cohort (960 mg BID)
- V600K-2 pts (1 PR, 1 CR)
- PFS 7.6 months (vs. 1.8 months wt)
- Brain metastases excluded



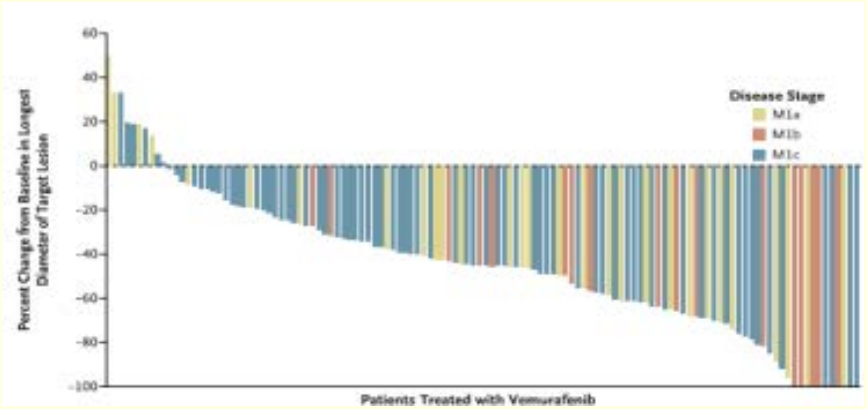
- Investigator assessments
- Includes confirmed & unconfirmed responses

Vemurafenib: Tumor Response by Metastatic Stage

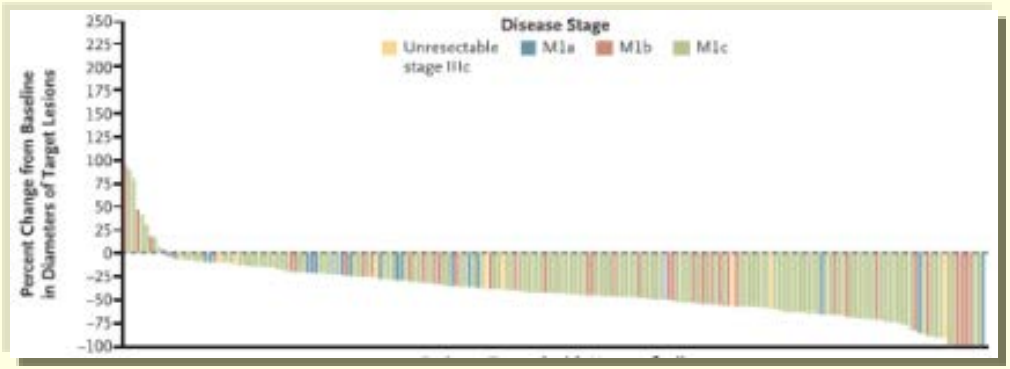
Flaherty 2010[1]



Sosman 2012 [2]

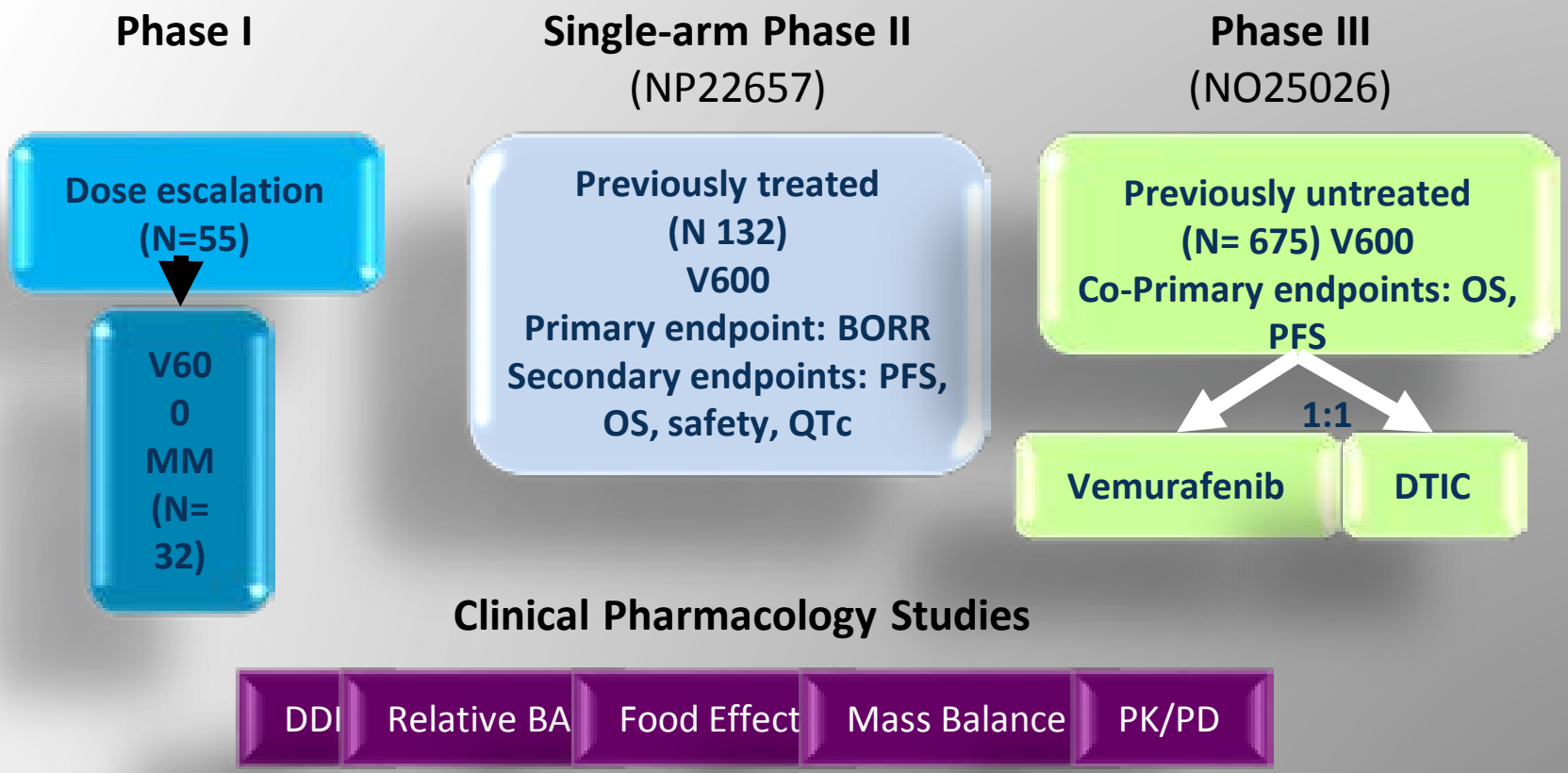


Chapman 2011[3]



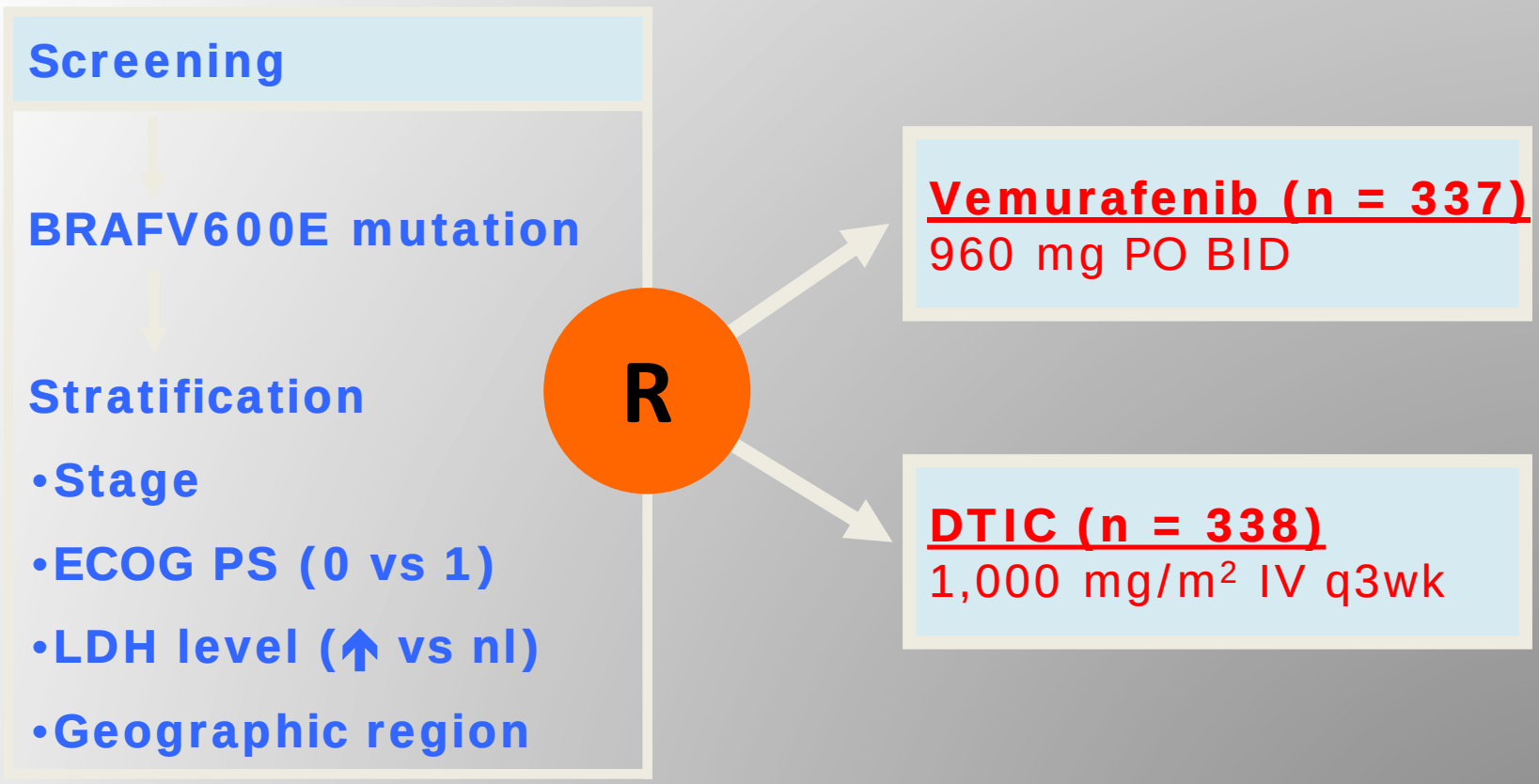
1. Flaherty KT, et al. N Engl J Med. 2010;363:809-819. 2. Sosman JA, et al. N Engl J Med. 2012;366:
707-714. 3. Chapman PB, et al. N Engl J Med. 2011;364:2507-2516.

Vemurafenib Development: The BRIM Program



BA=bioavailability; BORR=best overall RR; CRC=colorectal cancer; DDI=drug-drug interaction; PD=pharmacodynamics; PK=pharmacokinetics; QTc=corrected QT interval.

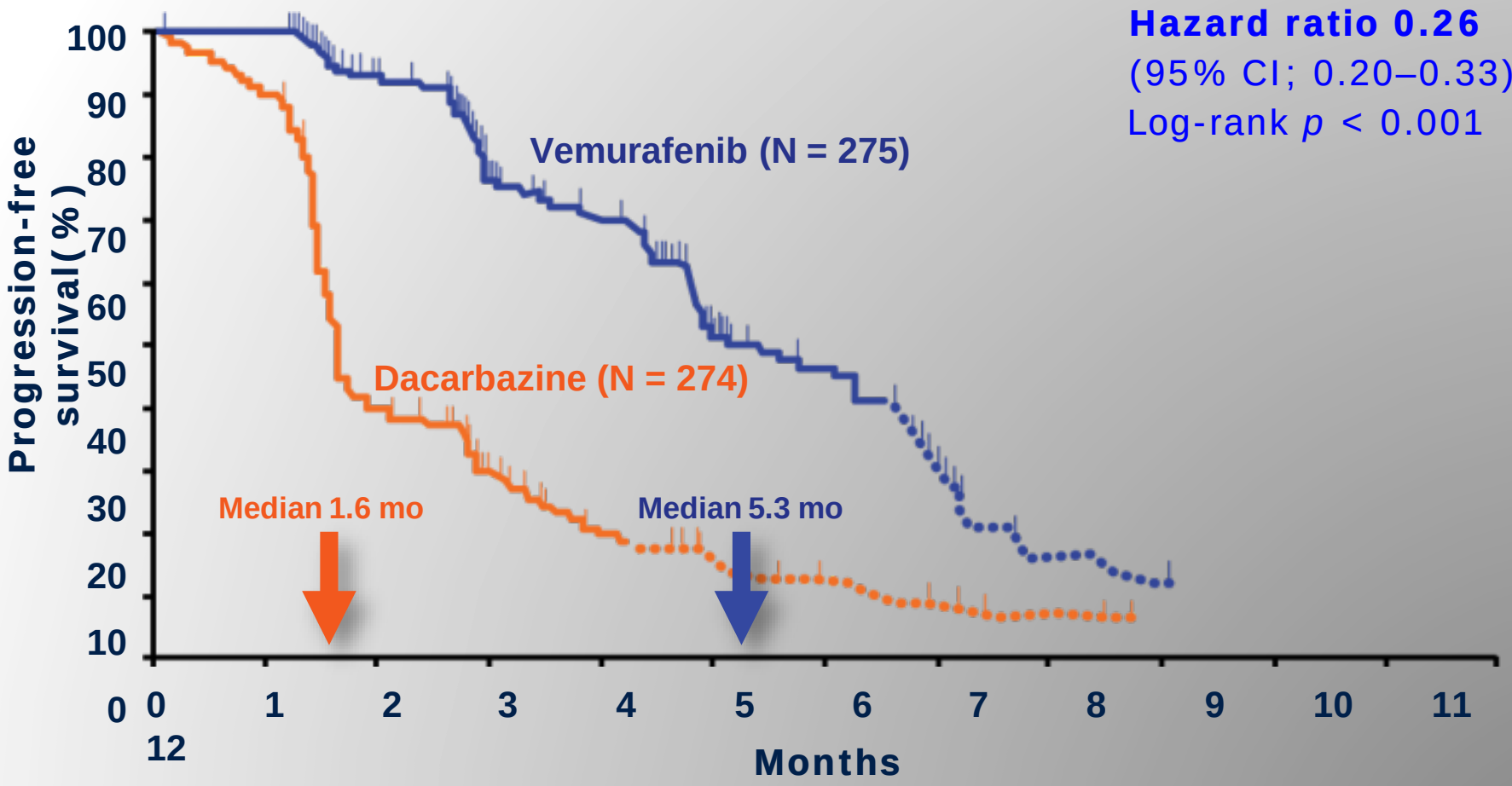
BRIM3: A Phase III Trial of Vemurafenib vs Dacarbazine (DTIC)



Coprimary endpoints: Overall and progression-free survival rates

Chapman PB et al. *N Engl J Med* 2011;364(26):2507-16.

Progression-Free Survival
(December 30, 2010 Cutoff)



THE LANCET Oncology

In an open-label, multicenter international study, patients with untreated or previously treated melanoma and a BRAF/600 mutation received oral Vemurafenib 960 mg twice a day. The primary endpoint was safety. All analyses were done on the safety population, which included all patients who received at least one dose of Vemurafenib. This study was approved by the local authorities. All patients signed an informed consent.

Larkin J. et al Lancet Oncol. 2014 Apr;15(4):436-44

South African Patients

	Global study (n=3222)	Global study %	SA subset (n=34)	SA subset %
Male	1823	57%	26	76,5%
Female	1399	43%	8	23,5%
Age: Median	55	NA	53,5	NA
Age: Range	13.0-95.0	NA	24 - 77	NA
Age <75	2965	92%	32	94,1%
Age >75	257	8%	2	5,9%
Time since metastatic diagnosis: Median	5,7	NA	5,3	NA
Time since metastatic diagnosis: Range	0-352.0	NA	0.2 - 151.1	NA
Time since metastatic diganosis: Mean	12,8	NA	12,8	NA
Time since metastatic diagnosis: SD	21,6	NA	27,7	NA
M1a	394	12%	6	17,6%
M1b	465	14%	5	14,7%

Proven Efficacy - BRIM Studies

- Phase I: 2nd line (previous systemic therapy, n=32 [with BRAF mutation])[1]
  - **RR = 56%**
  - **mPFS >7 months**
  - **mOS = 12.6 months**

BRIM1

- Phase II: 2nd line, n=132[2]
  - **RR = 53%**
  - **mPFS = 6.8 months**
  - **mOS = 15.9 months**

BRIM2

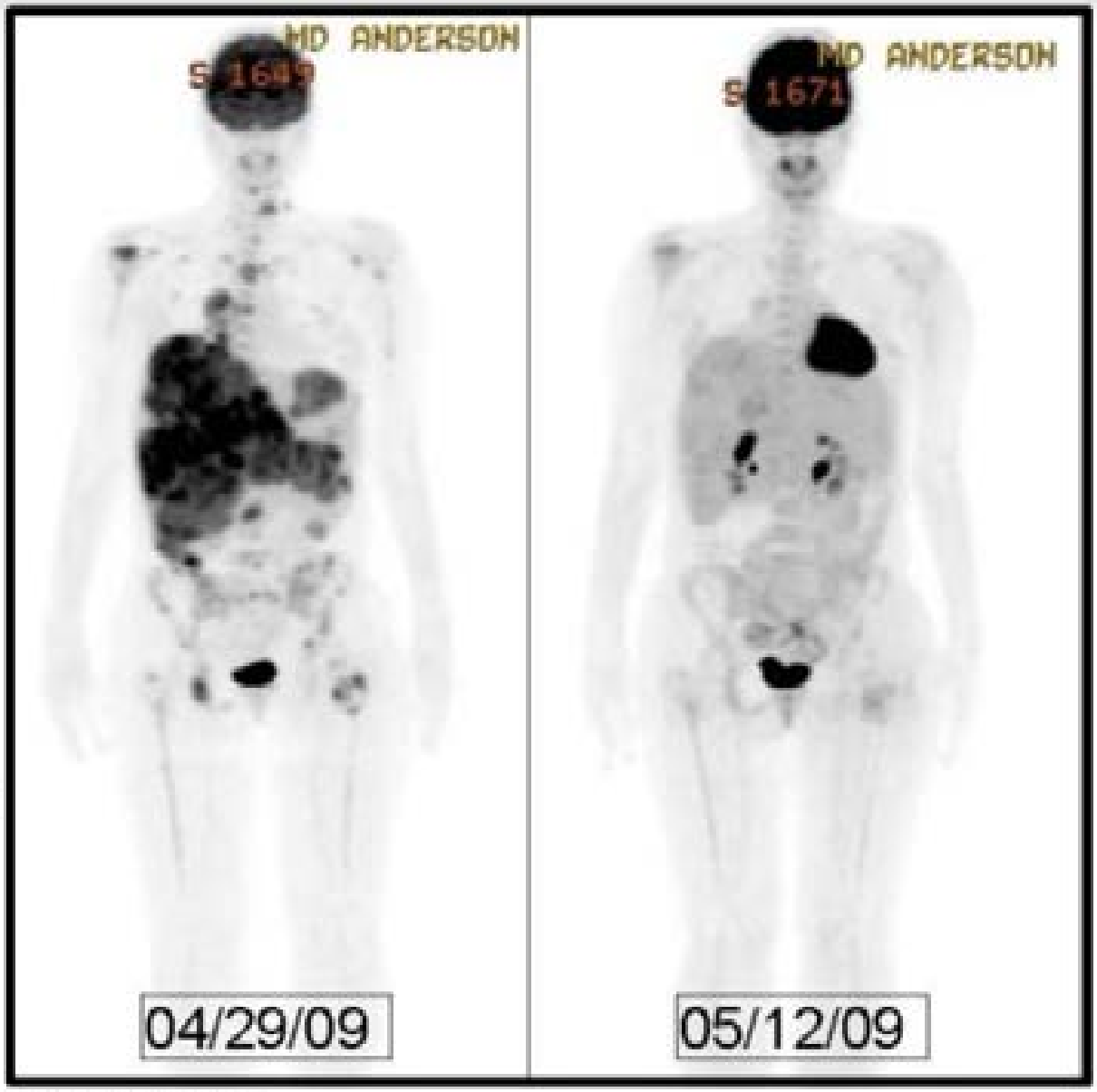
- Phase III: 1st line(no prior systemic therapy, n=337 treated with vemurafenib vs. n=338 treated with dacarbazine)[3,4]
  - **RR = 48%**
  - **mPFS = 6.9 months vs. 1.6 months (HR = 0.38)**
  - **mOS = 13.6 months vs. 9.7 months (HR = 0.70)**

BRIM3

1) Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. *N Engl J Med*. 2010;363: 809–819.
2) Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med*. 2012;366:707–714.
3) Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364:2507–2516.
4) Chapman PB, Hauschild A, Robert C, et al. Updated overall survival (OS) results for BRIM-3, a phase III randomized, openlabel, multicenter trial comparing BRAF inhibitor vemurafenib (vem) with dacarbazine (DTIC) in previously untreated patients with BRAFV600E-mutated melanoma. J Clin Oncol 30, 2012 (suppl; abstr 8502^). Presented at ASCO 2012, Chicago USA.

Clinical Trial Data for Vemurafenib

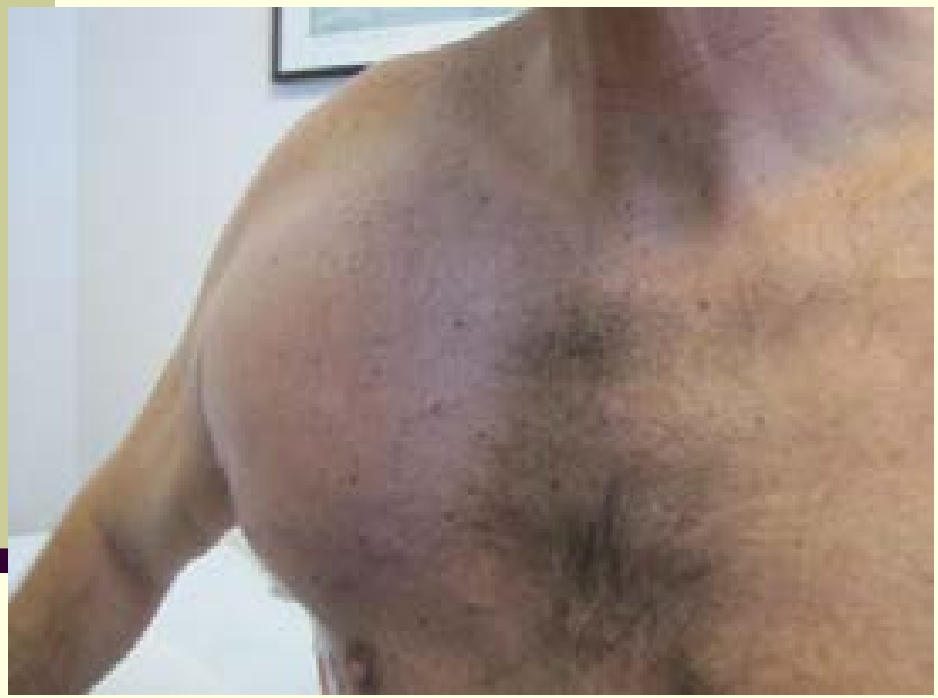
- > 50% response rate, with sustained responses
- Regression of lesions
- *BRAF*-positive patients not always responders



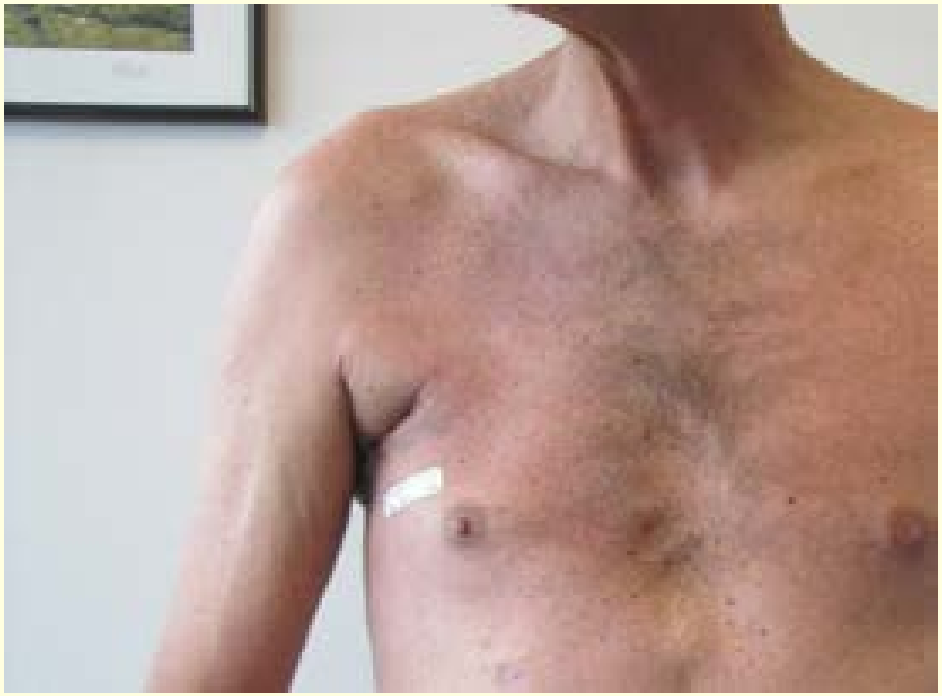
Sosman JA, et al. *N Engl J Med*. 2012;366:707-714.
Scans courtesy of Patrick Hwu, MD, and Robert W. Joseph, MD.

Tumor Response to Vemurafenib

Baseline, 3/15/2011



Cycle 4 Day 1, 6/8/2011



PLX4032 = RG7204 = vemurafenib

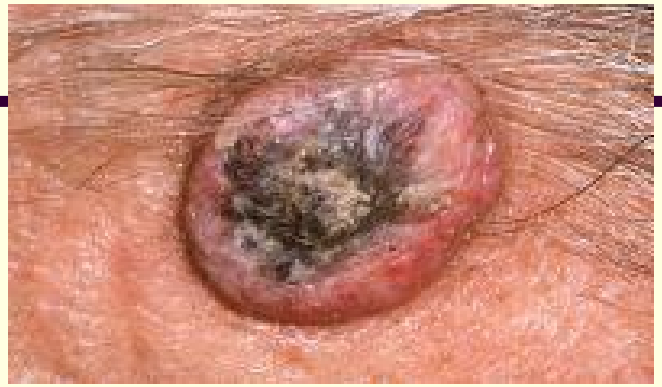
Vemurafenib: Toxicities

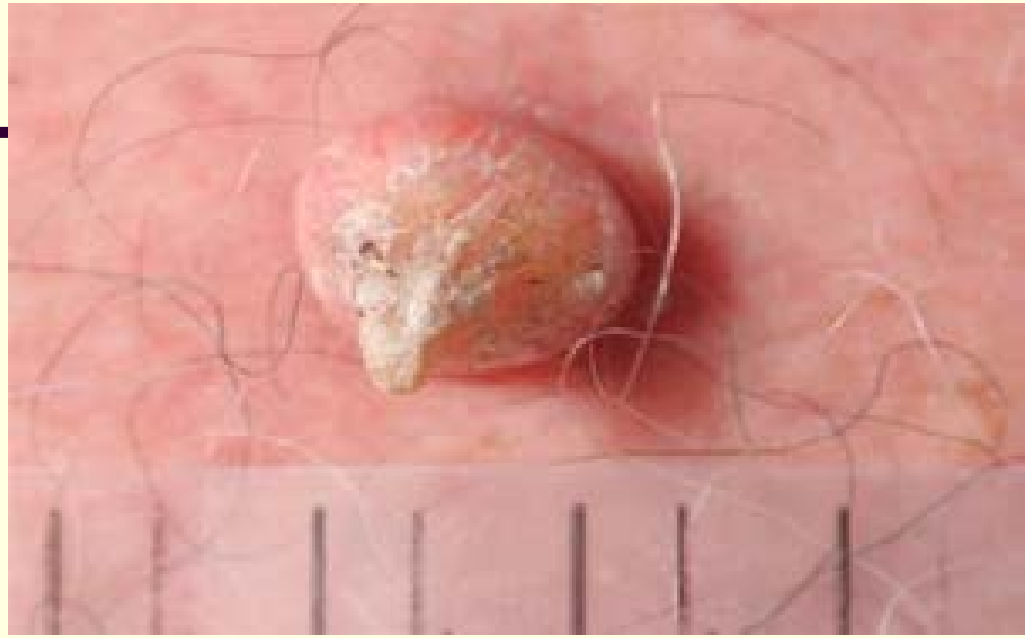
Adverse events reported from the BRIM-3 trial

- Skin toxicities
  - Rash: grade 2, 10%; grade 3, 8%
  - Cutaneous squamous-cell carcinoma (SCC): grade 3, 12%
  - Keratoacanthoma: grade 2, 2%; grade 3, 6%
- Photosensitivity, grades 2-3, 12%
- Arthralgias: grade 2, 18%; grade 3, 3%
- Fatigue: grade 2, 11%; grade 3, 2%
- Nausea: grade 2, 7%; grade 3, 1%
- Diarrhea: grade 2, 5%; grade 3, <1%
- Patients requiring dose interruption and modification: 38%

Chapman PB, et al. *N Engl J Med.* 2011;364:2507-2516.

Cutaneous SCC – Keratoacanthoma (KA) Subtype #8520 Lacouture et al.





Characteristics of KA subtype

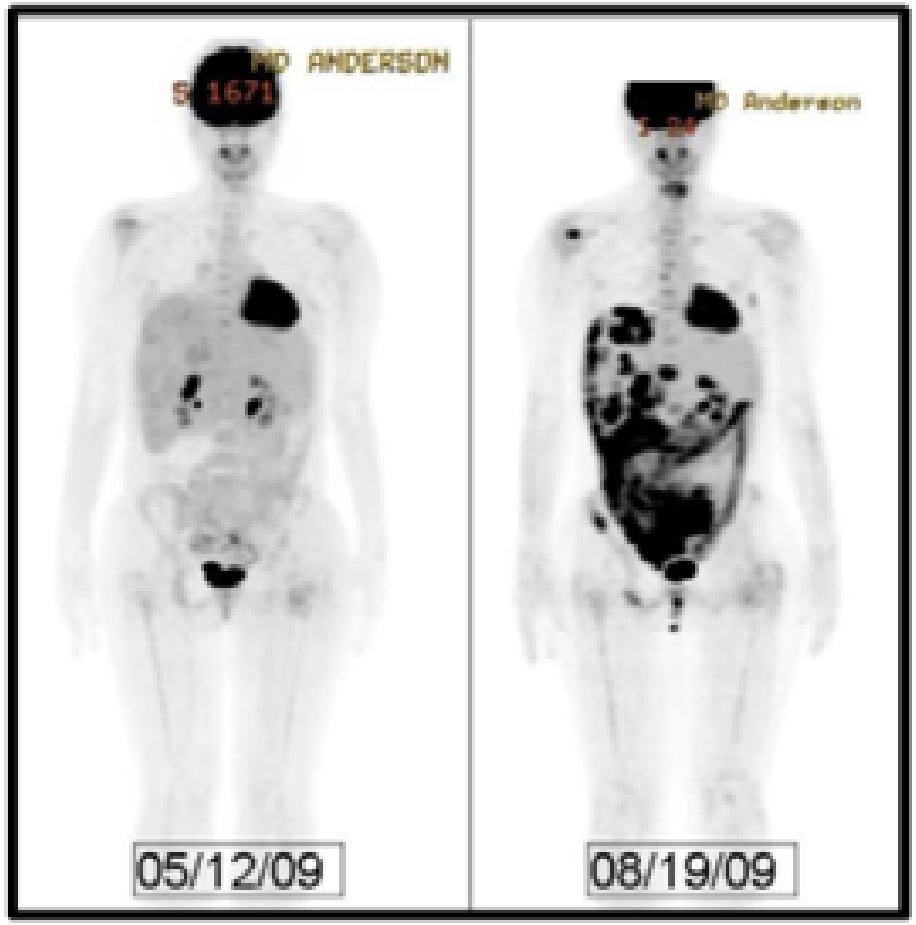
- **Raised button-like, central crater**
- **Well-differentiated neoplasm with low probability of invasion / metastasis**
- **Can grow rapidly; may involute and regress**
- **Typically treated by excision**
- **Did not result in treatment discontinuation**
- **Observed with RAF inhibitors**
- **Occurred on sun-exposed skin**
- **Association with HRAS (15 / 18) and NRAS (1 / 18) mutation in skin (higher then sporadic (6 / 53)**

Developing Resistance

- Patient treated with vemurafenib experiences disease regression at 2 weeks; progressive disease at 16 weeks.
- Pathways are reactivated in spite of ongoing treatment.

Molecular changes contributing to resistance

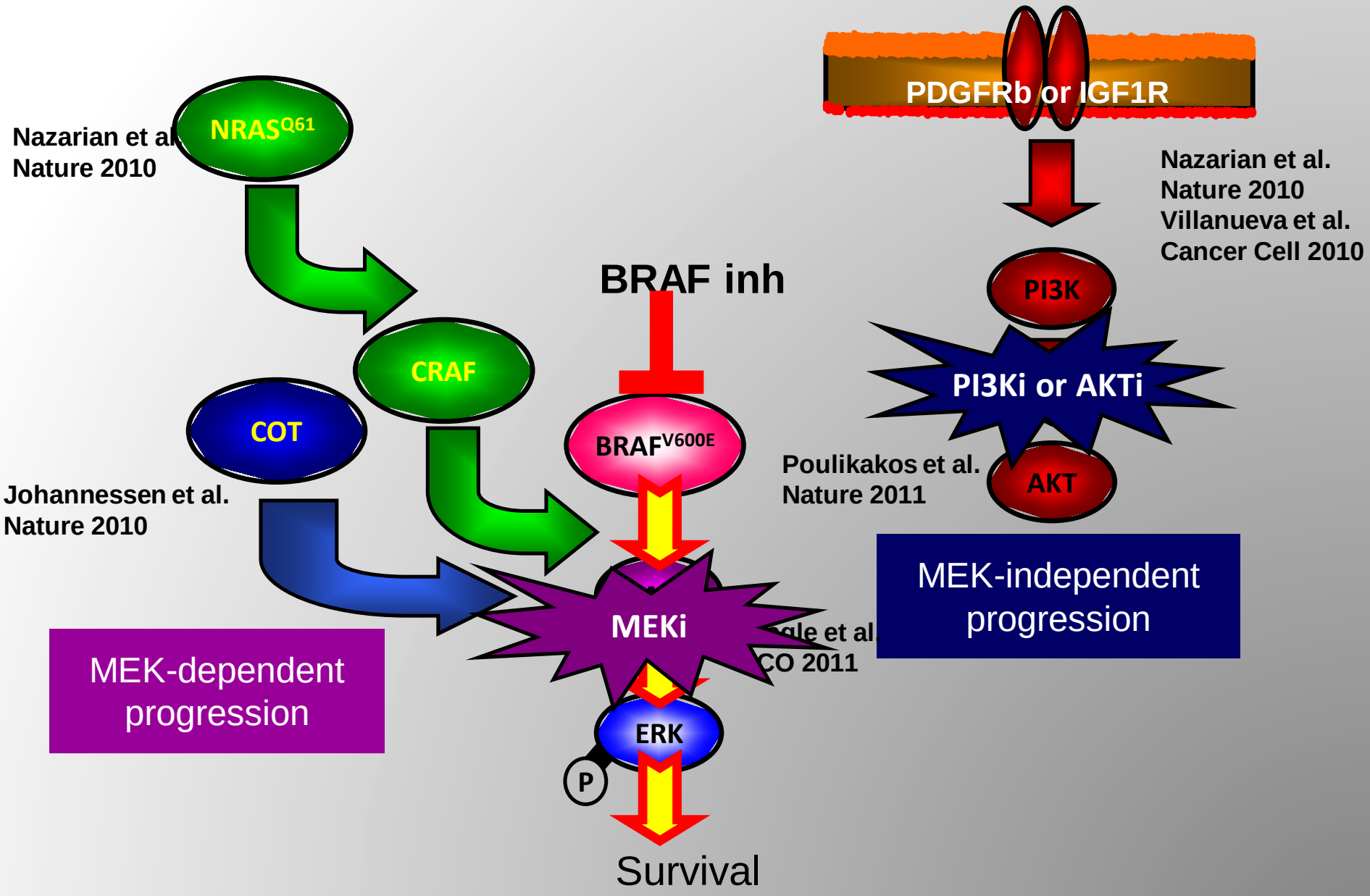
- *RAS* mutations
- Variant forms of RAF
- Alternate splicing of BRAF
- Amplification of BRAF
- Increased CRAF expression
- A-/B-/C- RAF heterodimers
- Increased expression of COT1 (2/3 increased with BRAFi; 1/1 at PD)
- *MEK1* mutations (1 patient, whole exome sequence)
- MEK-independent mechanisms
  - Activated: PDGRβ, IGF1R
  - Overexpressed: EGFR, c-MET, c-KIT
  - Loss of PTEN



2 weeks 16 weeks

Solit DB, et al. *N Engl J Med*. 2011;364:772-774.
Scans courtesy of Patrick Hwu, MD, and Robert W. Joseph, MD.

Mechanisms of Resistance to Vemurafenib



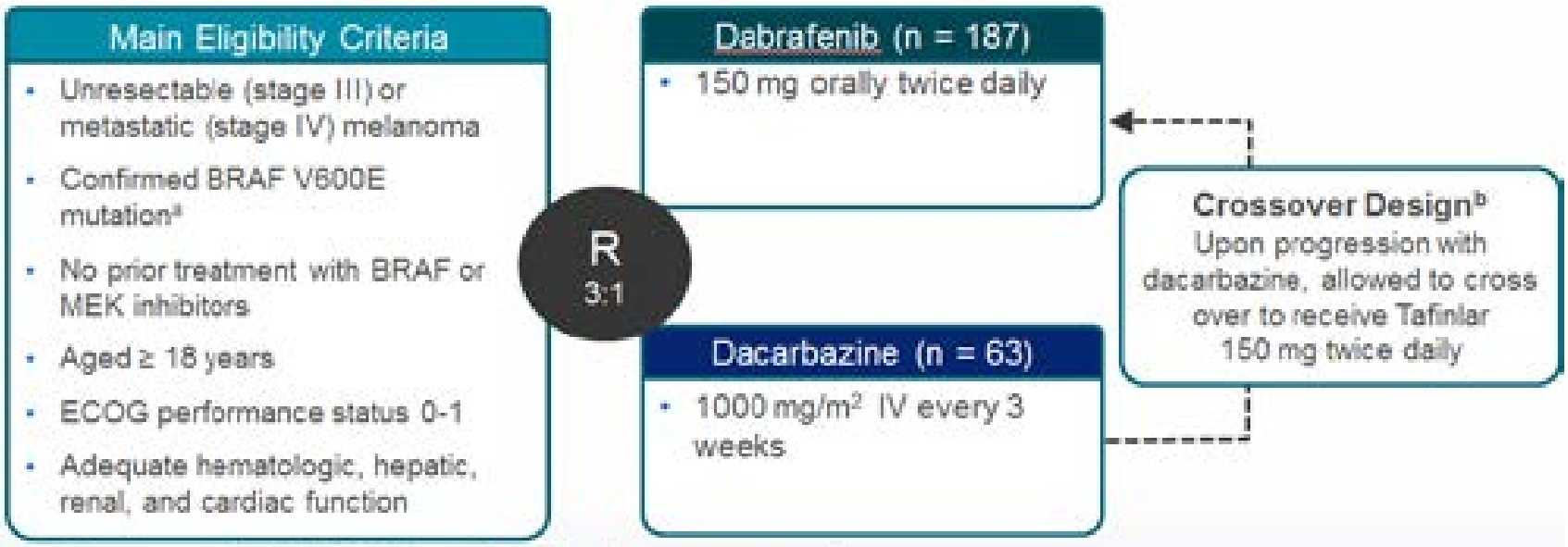
Conclusions

- Blockade of V600 mutated BRAF pathway is efficacious in advanced malignant melanoma
- Vemurafenib provides an OS benefit
- Rapid Responses, but resistance develops
- SCC and KA in a quarter of pts
- SA data follows the reported data in the multicentric international study

BREAK-3 Study Design

Pivotal first-line study for patients with advanced melanoma with a BRAF V600 mutation

- A multicenter, randomized, open-label, active-controlled phase 3 trial in previously untreated patients with BRAF V600E mutation–positive unresectable or metastatic melanoma



- Primary endpoint: PFS per investigator assessment
- Secondary endpoints: PFS as assessed by independent review committee; OS and ORR by both investigator and independent review committee; PFS after crossover; DOR; quality of life; safety and tolerability; and support of BRAF mutation assay validation

[a] BRAF V600E mutation status was determined by a clinical trial assay at a centralized testing site.
[b] Initial progression was confirmed by independent review.

Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2012;380(9839):358-365.

BREAK-3 Follow-Up Investigator PFS Analysis

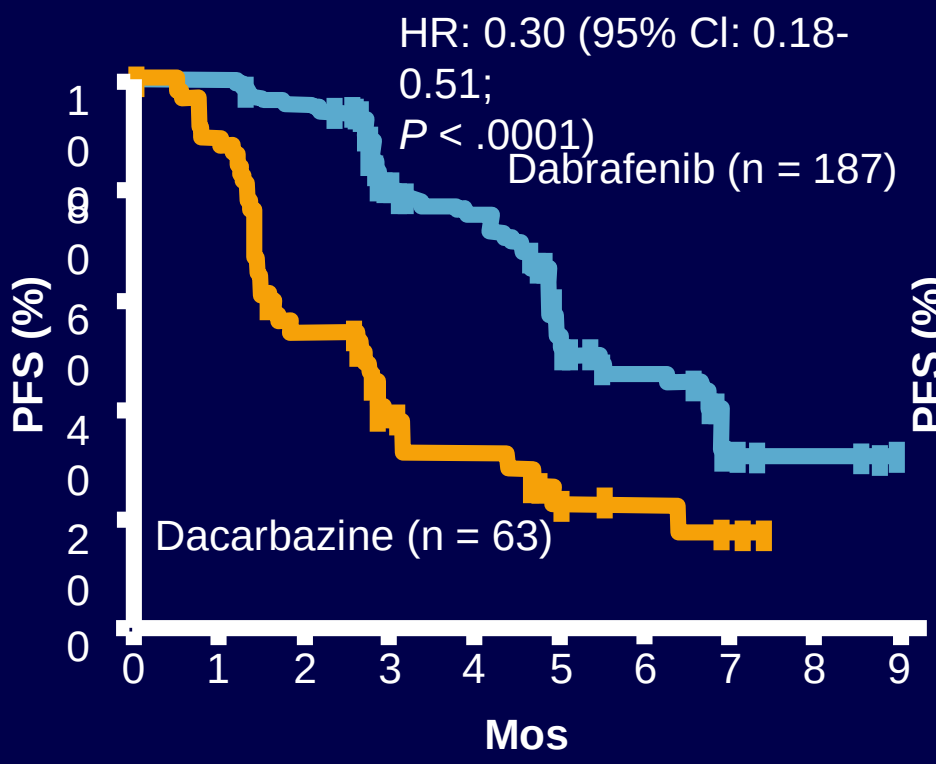
Subsequent PFS post hoc analysis results with 6 months additional follow-up were consistent with the initial prespecified results

- 63% reduction in relative risk of disease progression or death with Dabrafenib compared with dacarbazine ($P < .0001$)[5]
- 4.2-month increase in median PFS with Dabrafenib vs dacarbazine

NOVARTIS

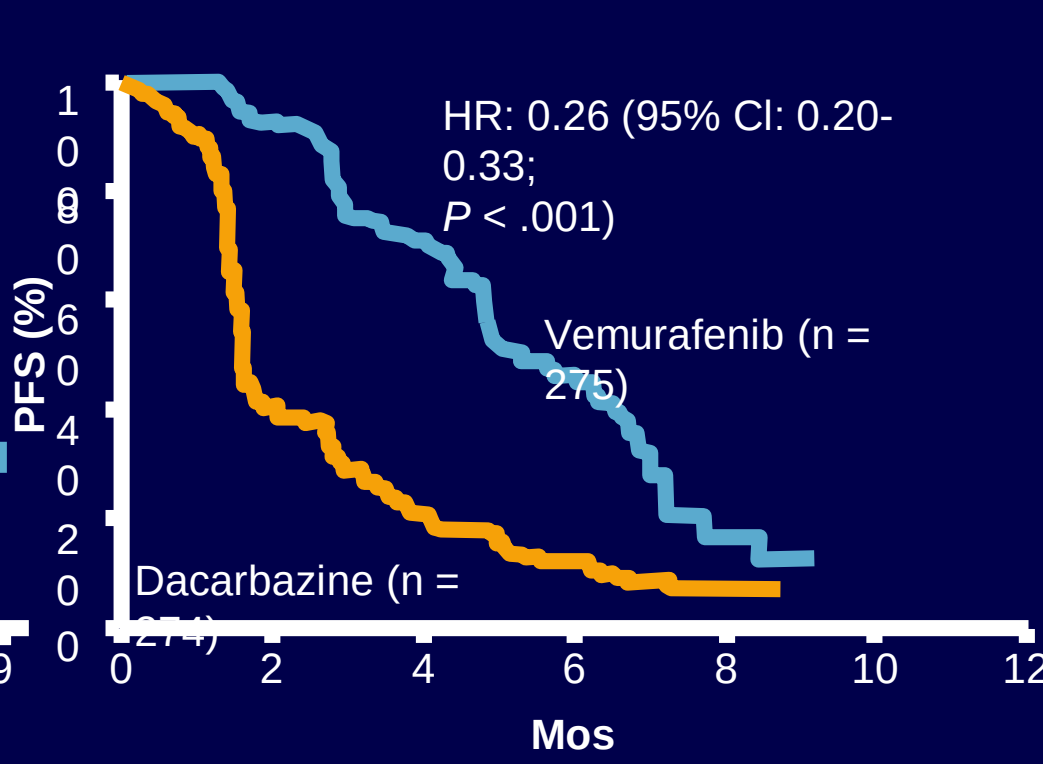
Single-Agent BRAF Inhibition vs Dacarbazine in Advanced Melanoma: PFS

Dabrafenib[1]



ORR: 50% vs 6% with dacarbazine

Vemurafenib[2]



ORR: 48% vs 5% with dacarbazine

1. Hauschild A, et al. Lancet Oncol. 2012;380:358-365.
2. Chapman PB, et al. N Engl J Med. 2011;364:2507-2516.

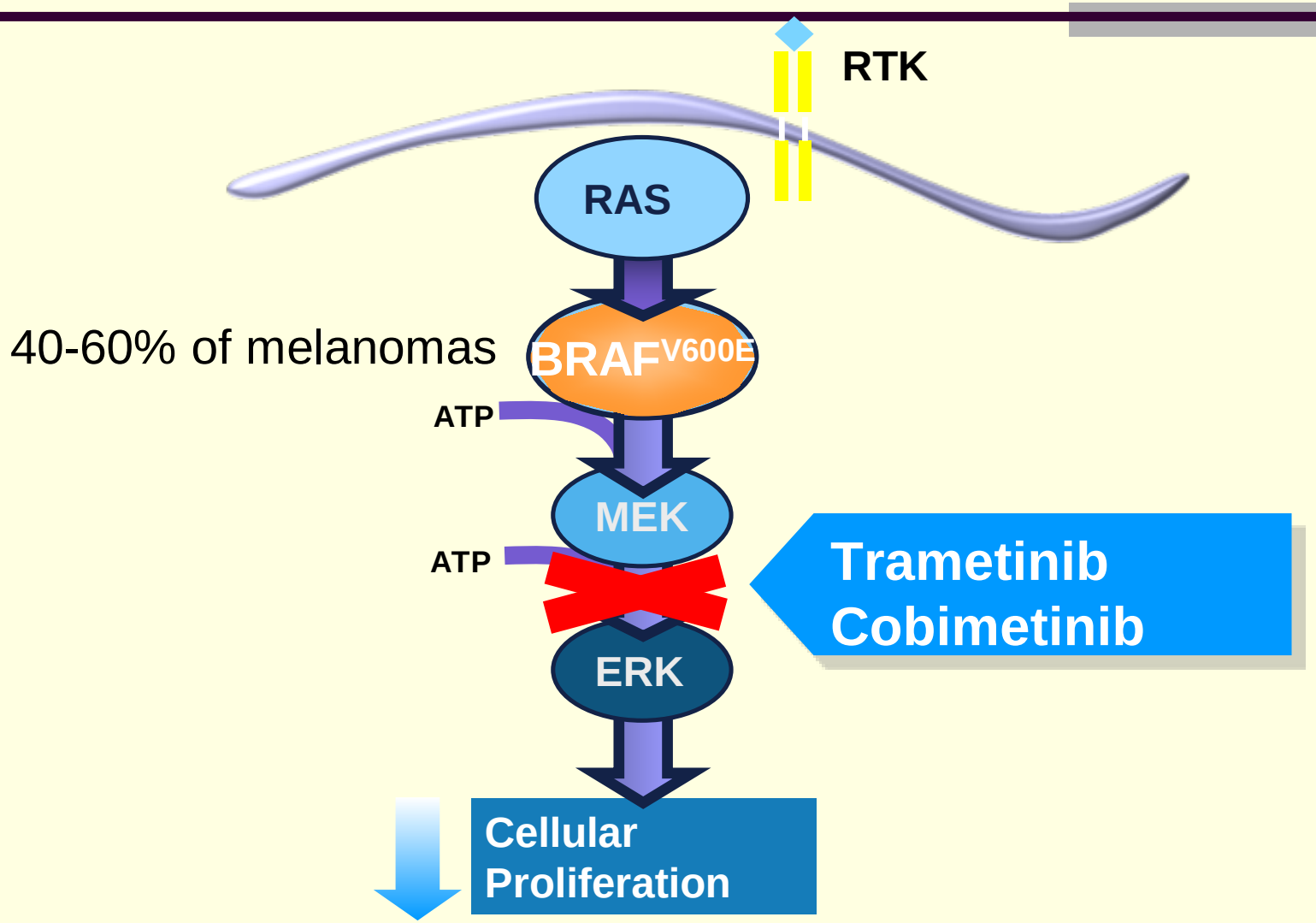
Slide credit: clinicaloptions.com

BRAF Inhibitors: Approved Indications in Advanced Melanoma

- Dabrafenib
  - Single agent (150 mg PO BID) for unresectable or metastatic melanoma with *BRAF* V600E mutation
  - In combination with trametinib (2 mg QD) for unresectable or metastatic melanoma with *BRAF* V600E/K mutation
- Vemurafenib
  - Single agent (960 mg PO BID) for unresectable or metastatic melanoma with *BRAF* V600E mutation
  - In combination with cobimetinib for unresectable or metastatic melanoma with *BRAF* V600E/K mutation

Dabrafenib [package insert]. November 2015.
Vemurafenib [package insert]. November 2015.

One step beyond: MEK inhibition



Rationale for combination of dabrafenib and trametinib in *BRAF*-mutant tumours

BRAF inhibitor (dabrafenib)
- OS: 20.1 months[1]
- PFS: 6.9 months[2]
- ORR: 59%[2]
- Hyperproliferative skin AEs[1,2]

MEK inhibitor (trametinib)
- OS: 15.6 months[3]
- PFS: 4.8 months[4]
- RR: 22%[4]
- Rash AE[3,4]

Preclinical _BRAF_i + MEKi[5]
- Delays *BRAF*i resistance
- Reduces hyperproliferative skin AEs

Goals of combination are to:
- **Suppress MAPK-dependent resistance mechanism**
  - Improve PFS, RR and OS
  - Prolong duration of response
- **Reduce the incidence of _BRAF_i-induced proliferative skin lesions**

1. Grob JJ, *et al.* Poster presented at SMR 2014;
2. Hauschild A, *et al.* Poster presented at ASCO 2013;
3. Schadendorf D, *et al.* Poster presented at SMR 2013;
4. Flaherty KT, *et al. N Engl J Med* 2012;367:107–14;
5. King AJ, *et al. PLoS ONE* 2013;8:e67583.

AE=adverse event; *BRAF*i=*BRAF* inhibitor; HR=hazard ratio; MAPK=mitogen-activated protein kinase; MEK=MAPK kinase; MEKi=MEK inhibitor; ORR=objective response rate; OS=overall survival; pERK=phosphorylated extracellular signal-regulated kinase; PFS=progression-free survival; RR=response rate.

Phase III evidence: COMBI-d study (MEK115306, NCT01584648)

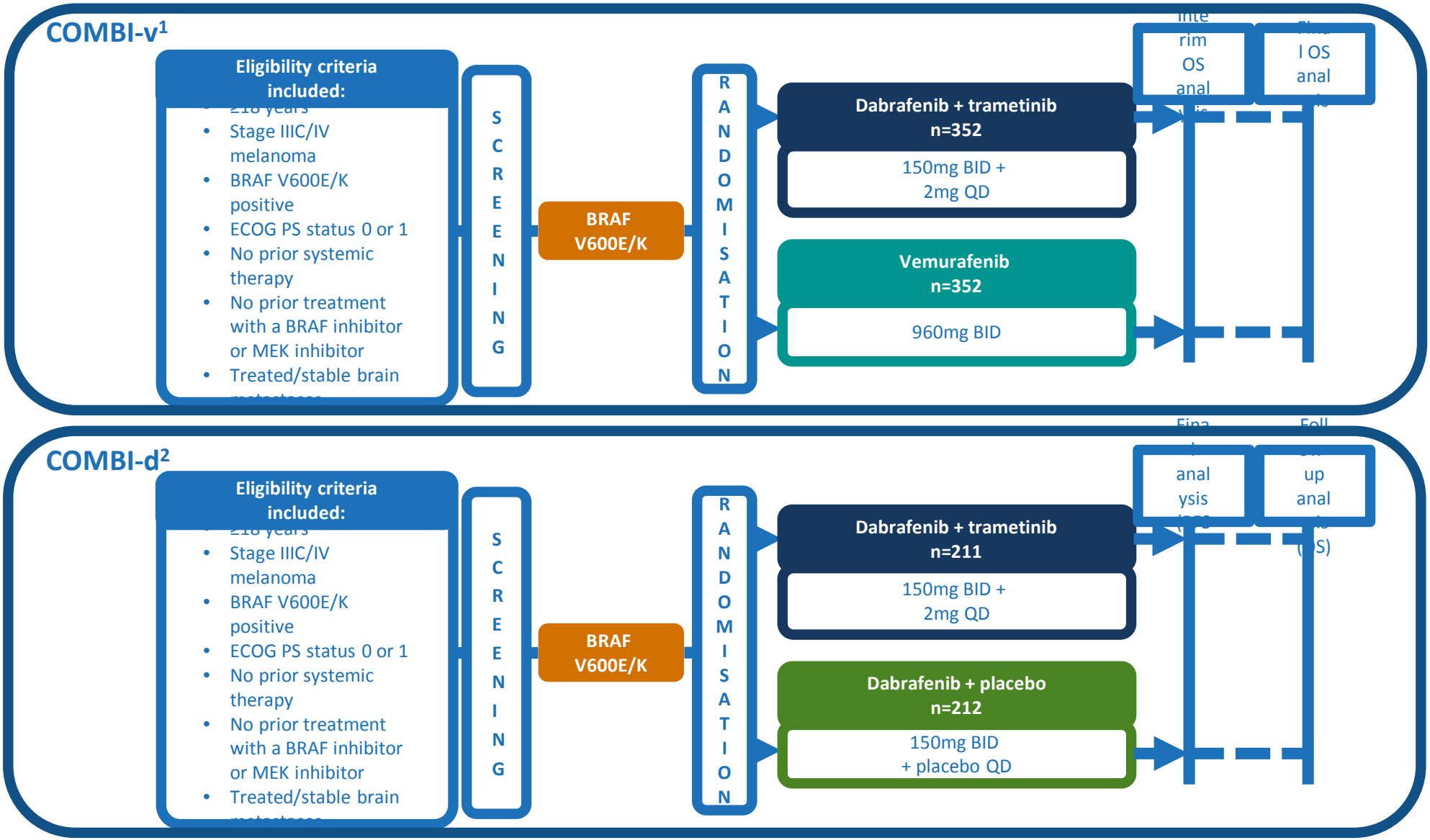
A Phase III, randomised, double-blind study comparing the combination of the *BRAF* inhibitor dabrafenib and the MEK inhibitor trametinib to the *BRAF* inhibitor dabrafenib in untreated patients with unresectable (stage IIIC) or metastatic (stage IV) *BRAF* V600E/K mutation-positive cutaneous melanoma – MEK115306 study (NCT01584648)

Phase III evidence: COMBI-v study (MEK116513, NCT01597908)

A Phase III, randomised, open-label study comparing the combination of the *BRAF* inhibitor dabrafenib and the MEK inhibitor trametinib to the *BRAF* inhibitor vemurafenib in subjects with unresectable (stage IIIC) or metastatic (stage IV) *BRAF* V600E/K mutation-positive cutaneous melanoma

COMBI-v and COMBI-d: Combination therapy

Study design

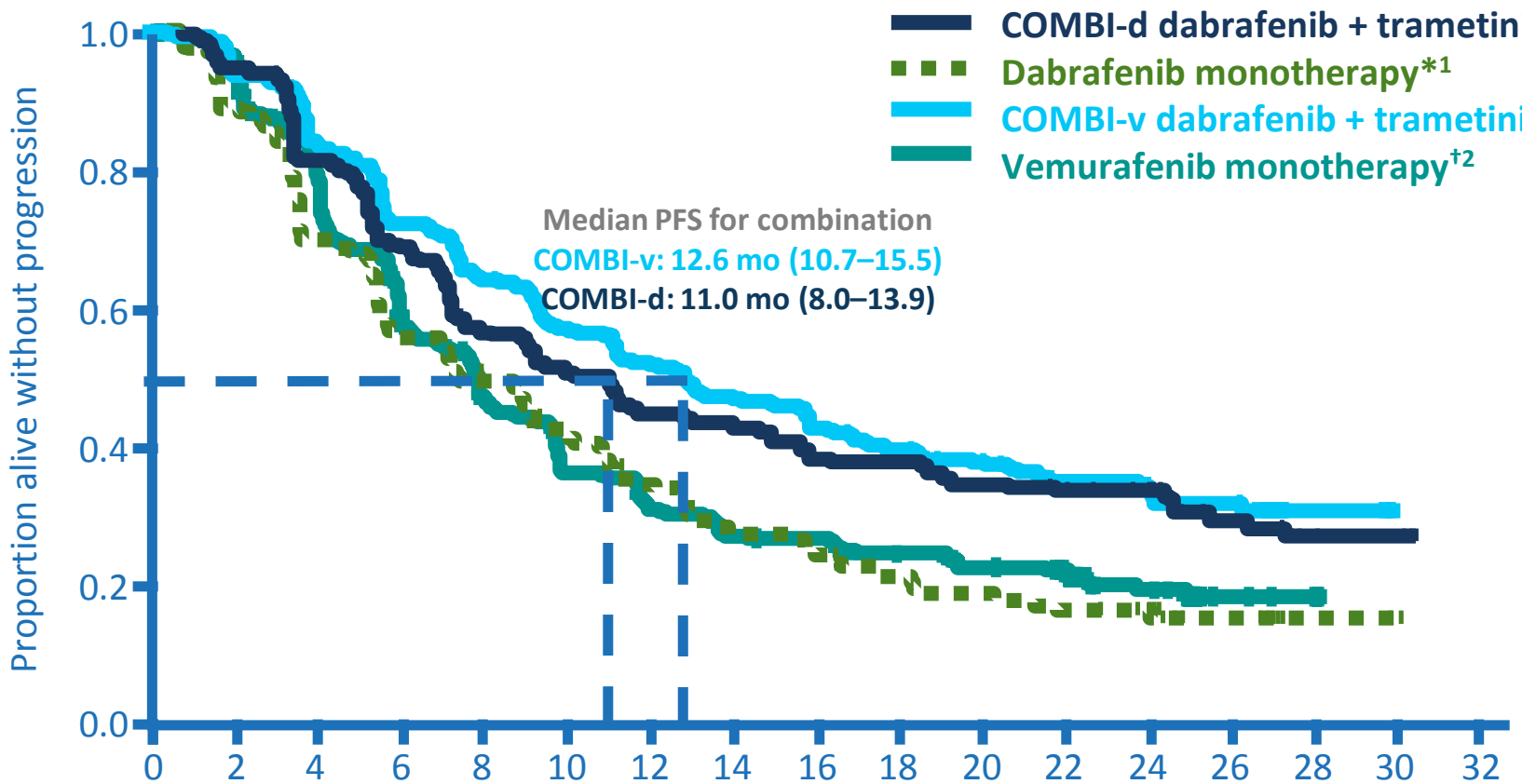


ECOG PS=Eastern Cooperative Group Performance Status.

1. Robert C *et al.* Oral presentation at ESMO 2014. Abstract LBA4_PR;
2. Long GV, *et al. Lancet* 2015;386:444–51.

COMBI-v and COMBI-d: Combination therapy

Consistent PFS benefit



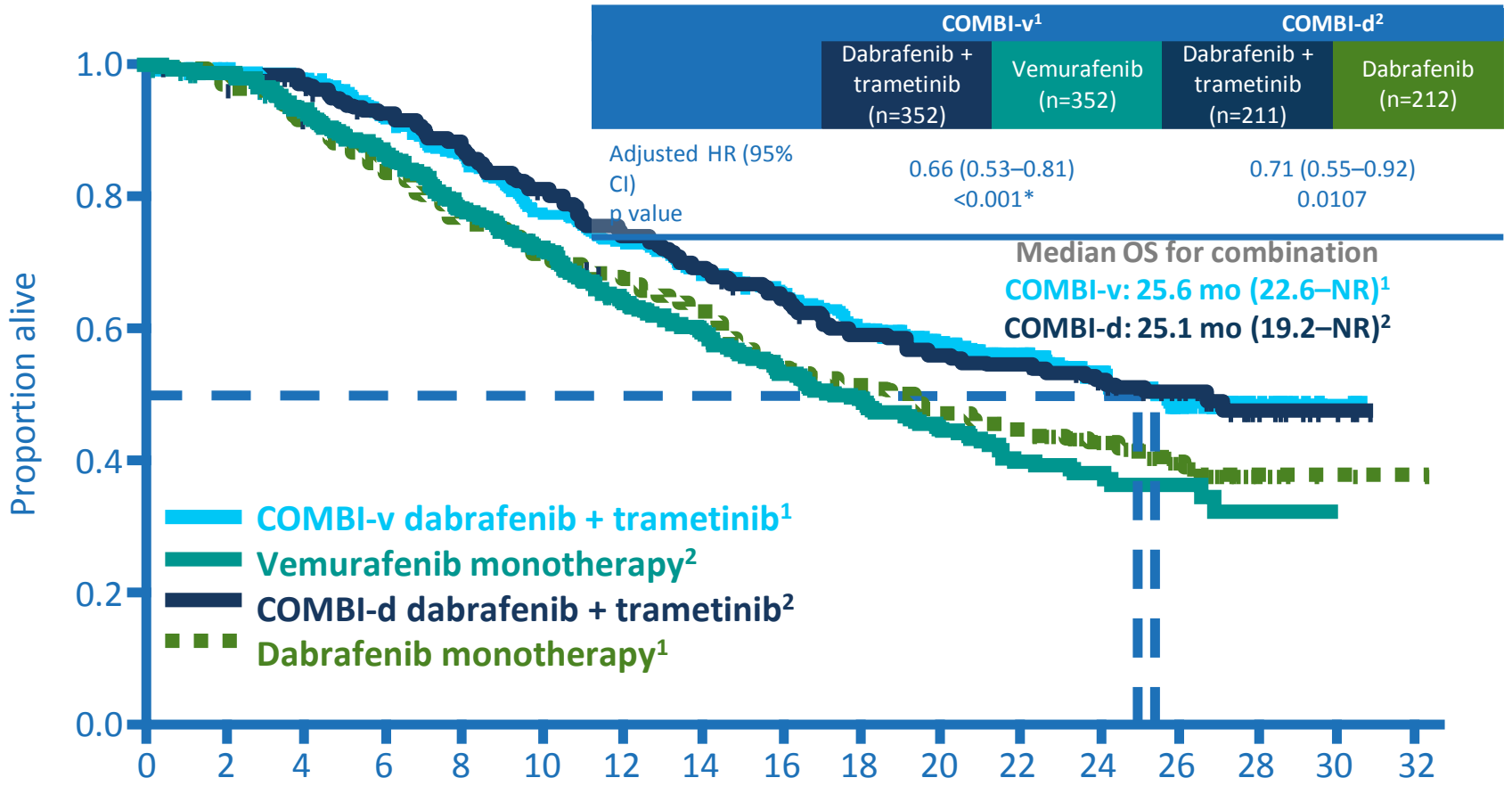
Number at risk																	
COMBI-d D + T[1]	211	196	164	137	125	96	84	80	71	70	65	61	38	26	6	0	0
Dabrafenib[1]	212	177	139	109	96	81	65	52	47	40	35	31	19	16	4	0	0
COMBI-v D + T[2]	352	310	270	229	202	175	158	140	125	115	98	56	30	26	4	0	0
Vemurafenib[2]	352	281	216	162	127	100	81	69	61	59	49	23	8	4	0	0	0

*Data cut-off: January 2015; †Data cut-off: March 2015.

1. Long GV, *et al. Lancet* 2015;386:444–51;
2. Robert C, *et al.* Oral presentation at ECC 2015, Abstract 3301.

COMBI-v and COMBI-d: Combination therapy

Consistent OS benefit



Number at risk																	
COMBI-d D + T[2]	211	208	200	187	174	159	144	135	124	112	106	103	88	53	21	3	0
Dabrafenib[1]	212	206	191	175	159	147	138	127	111	104	95	88	70	42	10	2	1
COMBI-v D + T[1]	352	342	336	311	286	260	245	230	217	198	173	128	68	38	16	5	0
Vemurafenib[2]	352	341	315	286	252	231	201	187	166	152	129	88	46	28	7	0	0

*Adjusted stopping boundaries: two-sided p<0.0214 for the efficacy analysis and p>0.2210 for the futility analysis.

1. Robert C, *et al.* Oral presentation at ECC 2015, Abstract 3301;
2. Long GV, *et al. Lancet* 2015;386:444–51.

Combined BRAF and MEK Inhibitors

COMBI-d: Dabrafenib/Trametinib vs Dabrafenib[a]

- ORR, 67% vs 51% (*P* = .0015); CR, 10% vs 9%
- Median PFS, 9.3 vs 8.8 mo (HR, 0.75; *P* = .035)
- OS favored combo: HR, 0.63 (95% CI, 0.42-0.94; *P* = .023)

COMBI-v: Dabrafenib/Trametinib vs Vemurafenib[b]

- ORR, 64% vs 51% (*P* < .001); CR, 13% vs 8%
- Median PFS, 11.4 vs 7.3 mo (HR, 0.56; *P* < .001)
- OS favored combo: HR, 0.69 (95% CI, 0.53-0.89; *P* = .005)

CoBRIM: Vemurafenib/Cobimetinib vs Vemurafenib[c]

- ORR, 68% vs 45% (*P* = .0015); CR/PR, 68% vs 45% (*P* <.001)
- Median PFS, 9.9 vs 6.2 mo (HR, 0.51; *P* < .001)
- OS favored combo: HR, 0.65 (95% CI, 0.42-1.00; *P* < .046)

a. Long GV, et al. *N Engl J Med*. 2014;371:1877-1888; b. Robert C, et al. *N Engl J Med*. 2015;372:30-39;
c. Larkin J, et al. *N Engl J Med*. 2014;371:1867-1876.

CONCERNS OVER PROMISE OF PERSONALIZED CANCER MEDICINE

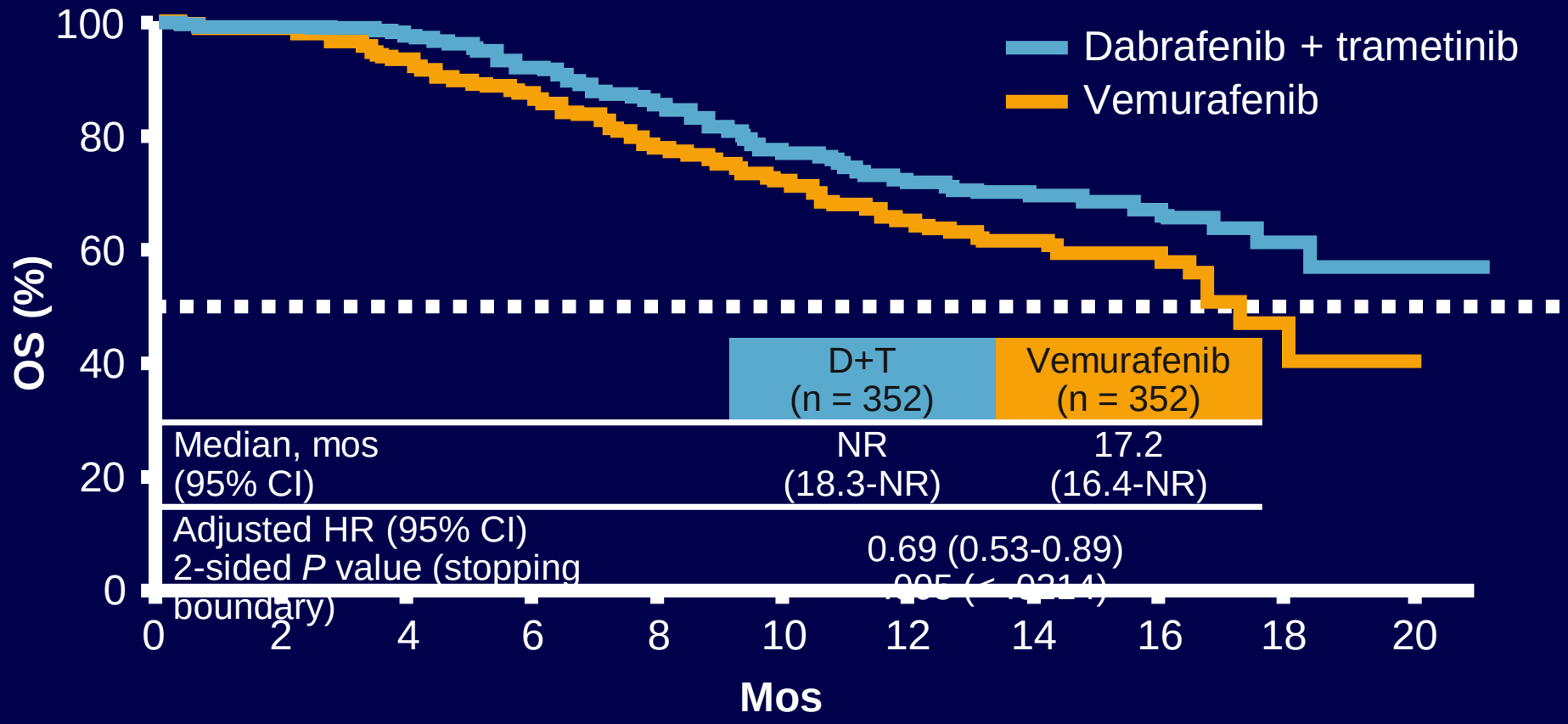
- Due to INTRATUMOR HETEROGENEITY (which appears early in cancer cells development), some mutations may be present in ALL sampled cancer cells ("clonal markers"), but other mutations are specific to subclones which appear during tumor growth and spread.
- Most of targeted therapies only partially inhibit signaling pathways.
- Intratumor heterogeneity is the major limitation to the main concept of personalized medicine treatment.


Oncology Centre
and
BRAF Positive
Clinic

‘THANK YOU’

SANDTON ONCOLOGY CENTRE

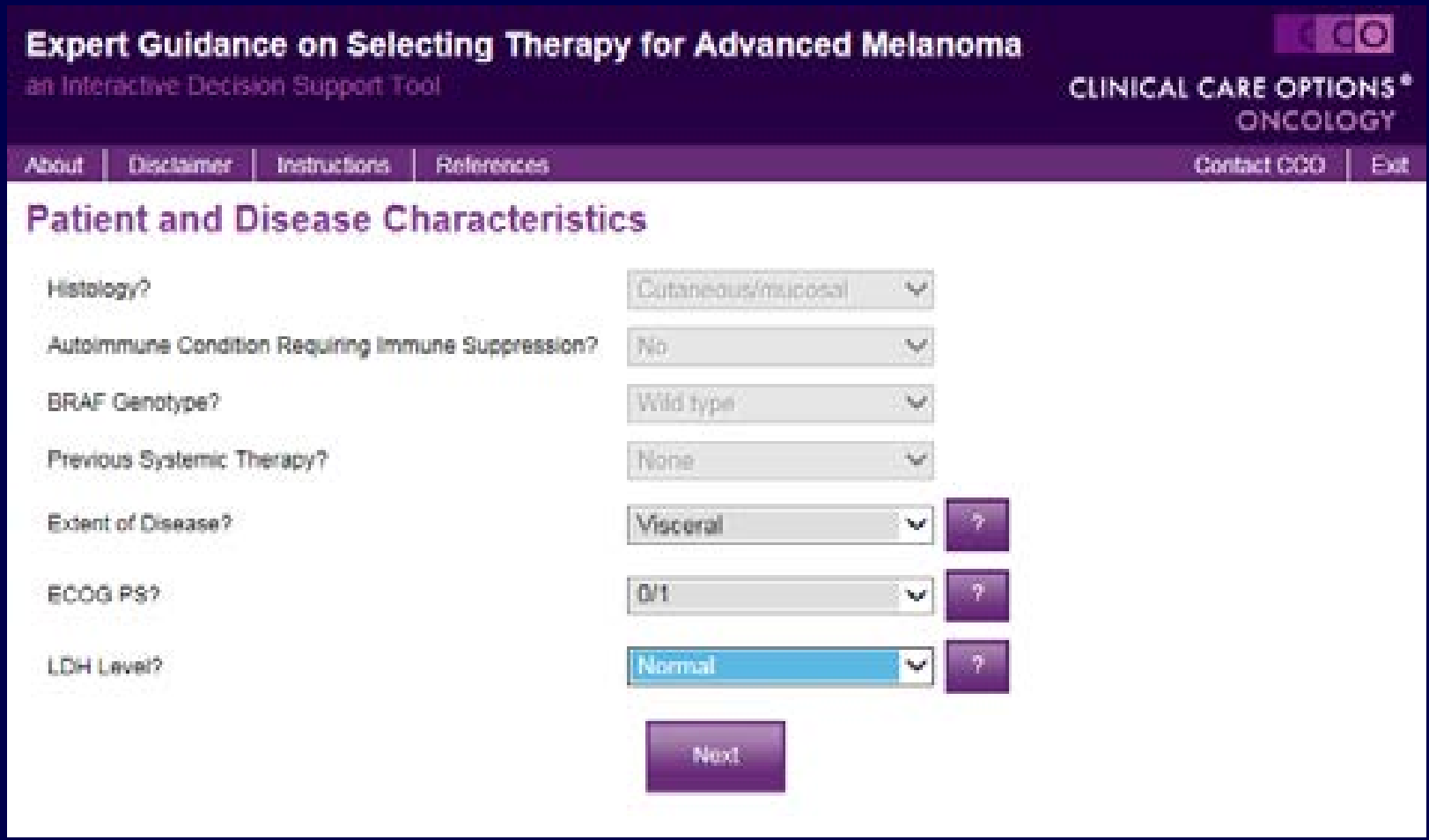
Combi-V Study of Dabrafenib + Trametinib vs Vemurafenib: OS



Robert C, et al. N Engl J Med. 2015;372:30-39.

Slide credit: clinicaloptions.com

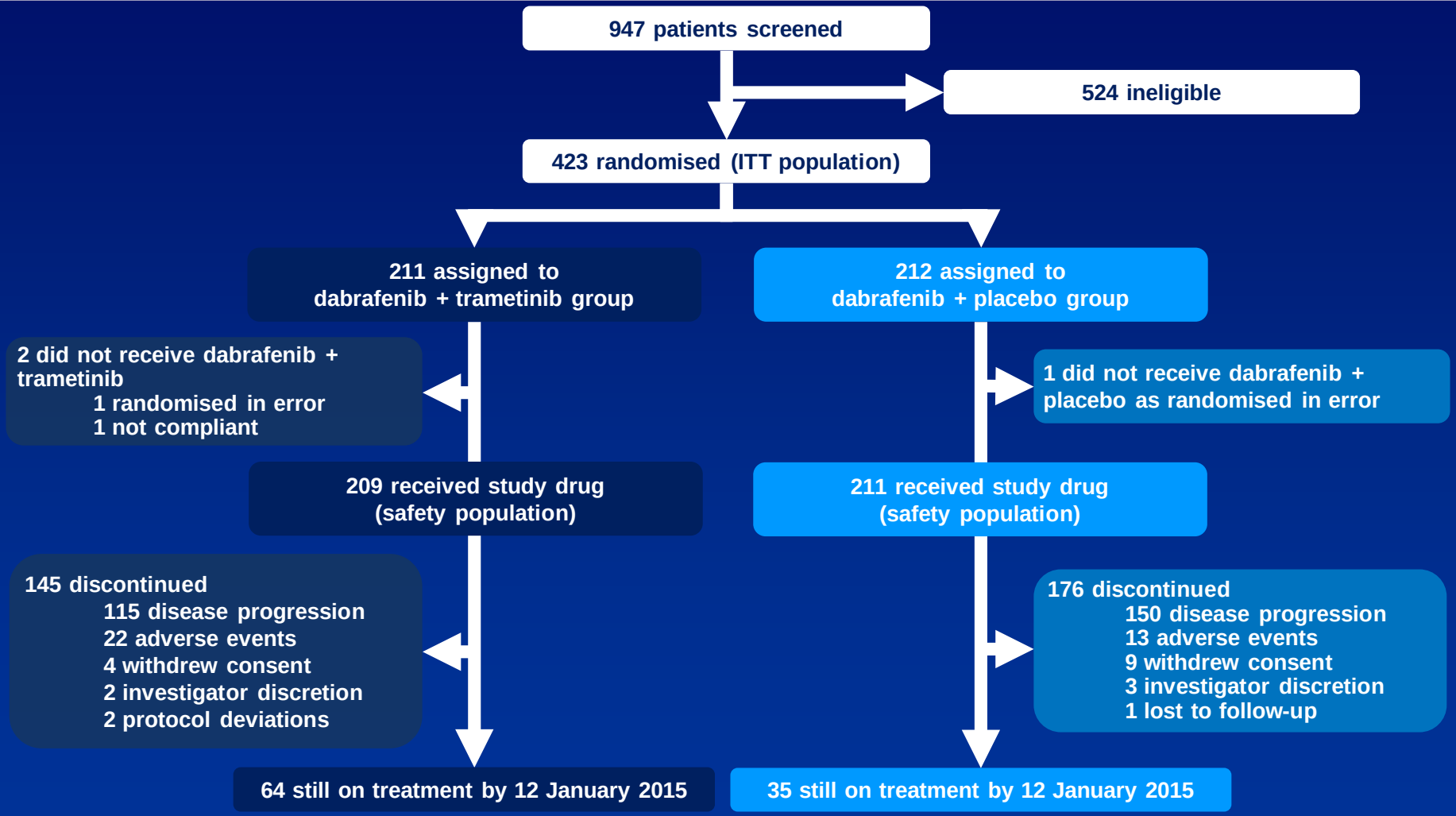
Therapeutic Decision Making in Advanced Melanoma: An Interactive Online Tool



The CCO Advanced Melanoma Interactive Decision Support Tool uses these 7 variables to make treatment recommendations. Available at: **clinicaloptions.com/Melanomatool**

Slide credit: clinicaloptions.com

COMBI-d: Consort diagram



Long GV, *et al*. *Lancet* 2015;386:444–51.

COMBI-d: Patient demographics, baseline characteristics, and stratification factors

	Dabrafenib + trametinib (n=211)	Dabrafenib (n=212)	Total (N=423)
Age, median (range)	55.0 (22–89)	56.5 (22–86)	56.0 (22–89)
Male sex, n (%)	111 (53)	114 (54)	225 (53)
ECOG PS, n (%)			
0	155 (73)	150 (71)	305 (72)
1	55 (26)	61 (29)	116 (27)
Disease stage, n (%)			
Stage IIIc, stage IV (M1a + M1b)	69 (33)	73 (34)	142 (34)
Stage IV (M1c)	142 (67)	138 (65)	280 (66)
Patient had visceral disease at baseline, n (%)	165 (78)	145 (68)	310 (73)
<3 disease sites at baseline, n (%)	109 (52)	119 (56)	228 (54)
No prior immunotherapy, n (%)	155 (73)	151 (71)	306 (72)
Stratification factors			
***BRAF* V600 mutation status, n (%)**			
V600E mutation-positive	179 (85)	181 (85)	360 (85)
V600K mutation-positive	32 (15)	30 (14)	62 (15)
LDH levels, n (%)			
≤ULN LDH	133 (63)	140 (66)	273 (65)
>ULN LDH	77 (36)	71 (33)	148 (35)

Data on file. ITT population

COMBI-d: Summary of results

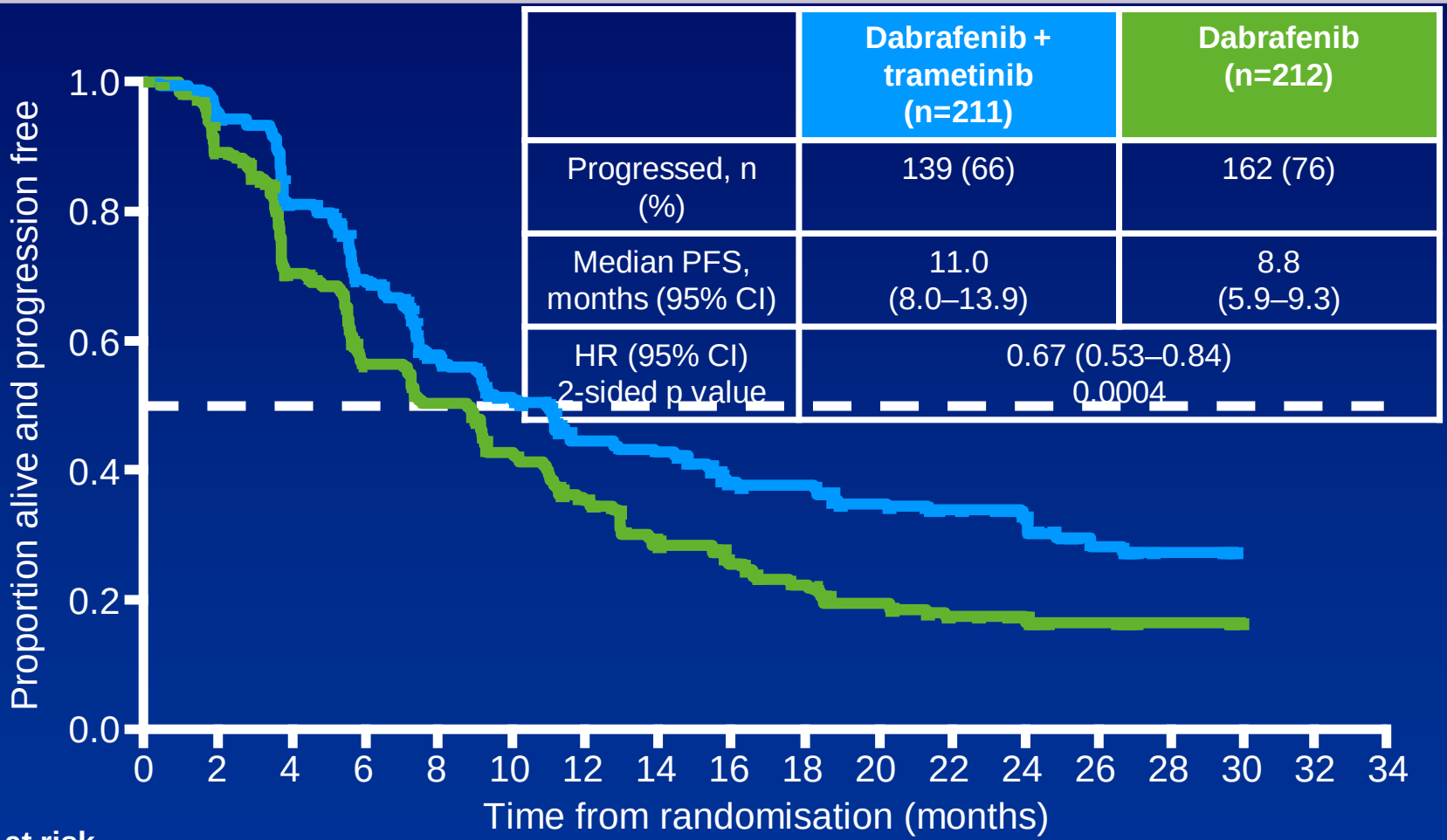
Summary of survival data	Dabrafenib + trametinib (n=211)	Dabrafenib (n=212)
Median PFS, months (95% CI)	11.0 (8.0–13.9)	8.8 (5.9–9.3)
Adjusted HR (95% CI) 2-sided p value	0.67 (0.53–0.84) 0.0004	
Median OS, months (95% CI)	25.1 (19.2–NR)	18.7 (15.2–23.7)
Adjusted HR (95% CI) 2-sided p value	0.71 (0.55–0.92) 0.011*	
Median follow-up, months	20	16

Summary of response data†	Dabrafenib + trametinib (n=210)	Dabrafenib (n=210)
CR, n (%)	33 (16)	28 (13)
PR, n (%)	111 (53)	84 (40)
ORR, n (%) 95% CI	144 (69) 62–75	112 (53) 46–60
Difference in ORR, % (95% CI), p value	15 (6.0–24.5) 0.0014	
Duration of response, months (95% CI)	12.9 (9.4–19.5)	10.6 (9.1–13.8)

Long GV, *et al*. *Lancet* 2015;386:444–51;
Data on file.

*Adjusted stopping boundaries: two-sided p<0.0214 for the efficacy analysis and p>0.2210 for the futility analysis; †Data are missing for one patient in the combination therapy group and two patients in the vemurafenib group because these patients did not have measurable disease at baseline.

COMBI-d (at January 2015): Updated PFS at final OS analysis



	Dabrafenib + trametinib (n=211)	Dabrafenib (n=212)
Progressed, n (%)	139 (66)	162 (76)
Median PFS, months (95% CI)	11.0 (8.0–13.9)	8.8 (5.9–9.3)
HR (95% CI) 2-sided p value	0.67 (0.53–0.84) 0.0004	

Number at risk

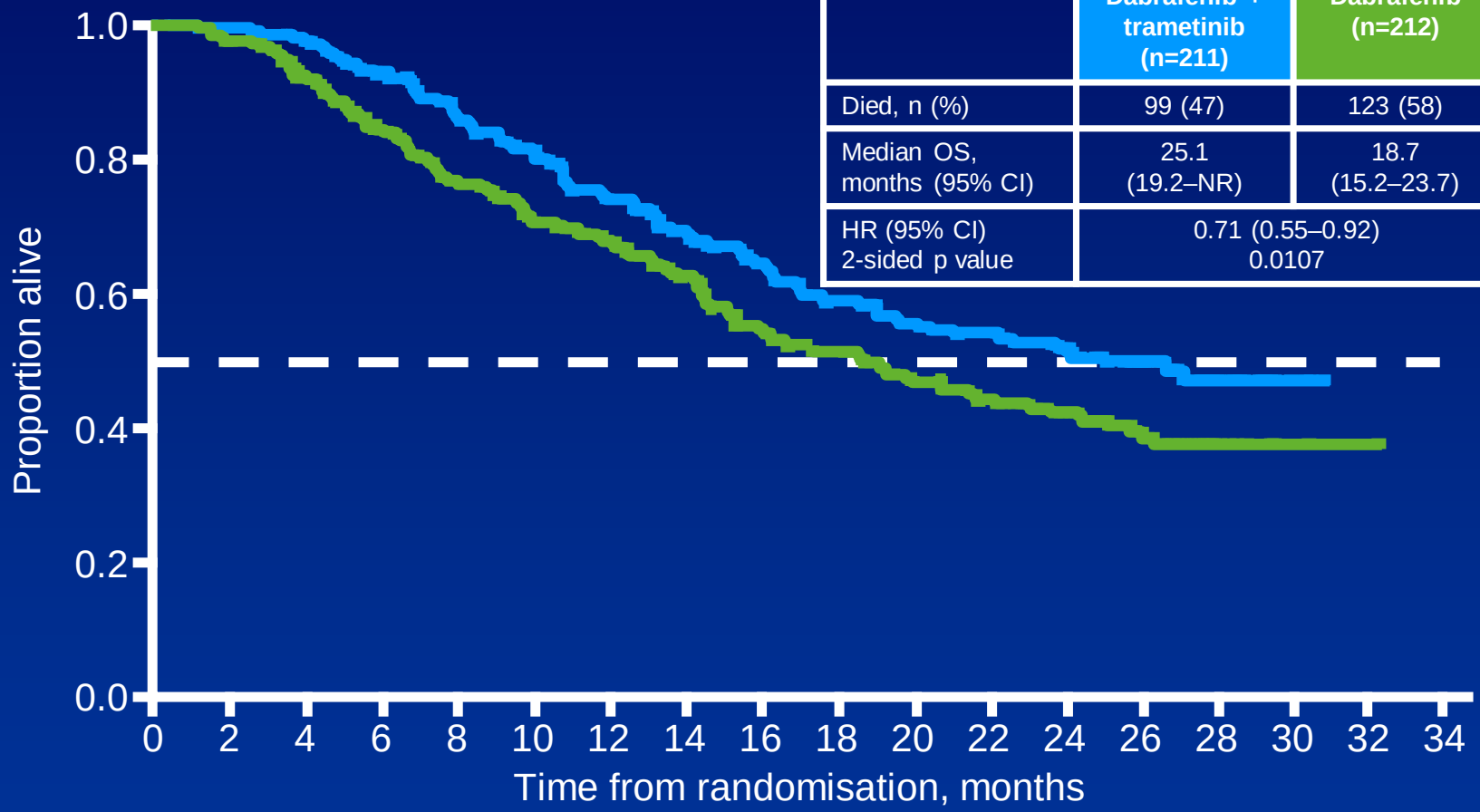
Dabrafenib + trametinib	211	196	164	137	125	96	84	80	71	70	65	61	38	26	6	0	0	0
Dabrafenib	212	177	139	109	96	81	65	52	47	40	35	31	19	16	4	0	0	0

Long GV, *et al. Lancet* 2015;386:444–51.

ITT population.

COMBI-d (at January 2015): OS at final OS analysis

	Dabrafenib + trametinib (n=211)	Dabrafenib (n=212)
Died, n (%)	99 (47)	123 (58)
Median OS, months (95% CI)	25.1 (19.2–NR)	18.7 (15.2–23.7)
HR (95% CI) 2-sided p value	0.71 (0.55–0.92) 0.0107	



Number at risk																	
	211	208	200	187	174	159	144	135	124	112	106	103	88	53	21	3	0	0
	212	206	191	175	159	147	138	127	111	104	95	88	70	42	10	2	1	0

Long GV, *et al. Lancet* 2015;386:444–51.

ITT population.

COMBI-d (at January 2015): OS landmarks at final OS analysis

	Dabrafenib + trametinib (n=211)	Dabrafenib (n=212)
OS landmarks, % (95% CI)		
1 year	74 (67–79)	68 (61–74)
2 years	51 (44–58)	42 (35–49)

Long GV, *et al. Lancet* 2015;386:444–51.

ITT population.

COMBI-d (at January 2015): Response at final OS analysis

	Investigator assessment	
	Dabrafenib + trametinib (n=210)	**Dabrafenib (n=210)**
Best response, n (%)		
CR	33 (16)	28 (13)
PR	111 (53)	84 (40)
SD	50 (24)	66 (31)
PD	13 (6)	19 (9)
Not evaluable	3 (1)	13 (6)
Response rate, n (%)		
CR + PR	144 (69)	112 (53)
95% CI	(62, 75)	(46, 60)
Difference in response rate, %		
CR + PR	15	
95% CI for difference	(6.0–24.5)	
p value	0.0014	

- Median duration of response for dabrafenib + trametinib was 12.9 months and for dabrafenib was 10.6 months

Long GV, *et al*. *Lancet* 2015;386:444–51;
Data on file.

ITT population.

COMBI-d: Conclusions

Updates from final OS analysis

- **Improved overall survival with dabrafenib + trametinib combination *vs* dabrafenib**
  - **HR 0.71; p=0.011**
  - **29% reduction in risk of death**
  - **Median OS of 25.1 months *vs* 18.7 months**
  - **2-year OS >50%**
- **Improved progression-free survival with combination *vs* dabrafenib**
  - **HR 0.67; p<0.001**
  - **33% reduction in risk of death**
  - **Median PFS of 11.0 months *vs* 8.8 months**
- **Efficacy data clinically relevant for patients with *BRAF* V600 mutation-positive metastatic melanoma, where an unmet medical need remains**
- **Safety profile consistent with previously reported results**
  - **No new safety concerns**
  - **Pyrexia most notable risk with combination *vs* dabrafenib**
  - **Fewer cutaneous hyperproliferative events with combination *vs* dabrafenib**
- **Additional landmark OS and safety analyses planned**

Long GV, *et al. Lancet* 2015;386:444–51.

COMBI-v: Summary of results

Summary of survival data[1]	Dabrafenib + trametinib (n=352)	Vemurafenib (n=352)
Median OS, months (95% CI)	25.6 (22.6–NR)	18.0 (15.6–20.7)
Adjusted HR (95% CI) 2-sided p value	0.66 (0.53–0.81) <0.001	
Median follow-up (months)[2]	19	15
Median PFS, months (95% CI)	12.6 (10.7–15.5)	7.3 (5.8–7.8)
Adjusted HR (95% CI) 2-sided p value	0.61 (0.51–0.73) <0.001	

Summary of response data[1]	Dabrafenib + trametinib (n=351)	Vemurafenib (n=350)
Complete response, n (%)	59 (17)	36 (10)
Partial response, n (%)	172 (49)	150 (43)
Stable disease, n (%)	87 (25)	102 (29)
Progressive disease, n (%)	22 (6)	39 (11)
ORR, n (%) 95% CI	231 (66) 60.4–70.6	186 (53) 47.5–58.2
Difference in ORR, % (95% CI)	13 (5.3–20.2)	
p value	0.0008	
Duration of response, months (95% CI)	13.8 (11.2–18.1)	8.5 (7.4–9.7)

1. Robert C, *et al*. Oral presentation at ECC 2015, Abstract 3301;
2. Data on file.

COMBI-d: Eligibility criteria

- ≥18 years
- Histologically confirmed cutaneous melanoma that is either stage IIIc (unresectable) or stage IV (metastatic)
- *BRAF* V600E/K mutation-positive as tested by a central reference laboratory
- ≥1 measurable lesion (based on RECIST 1.1)
- ECOG PS score 0 or 1
- No prior systemic therapy in the advanced or metastatic setting
  (but adjuvant setting is allowed)
  - Ipilimumab treatment must end at least 8 weeks prior to randomisation
- No prior treatment with a *BRAF* inhibitor or MEK inhibitor
- Treated and stable brain metastases

Long GV, *et al. N Engl J Med* 2014; 371:1877–88
+ supplementary appendix.

RECIST=Response Evaluation Criteria in Solid Tumors

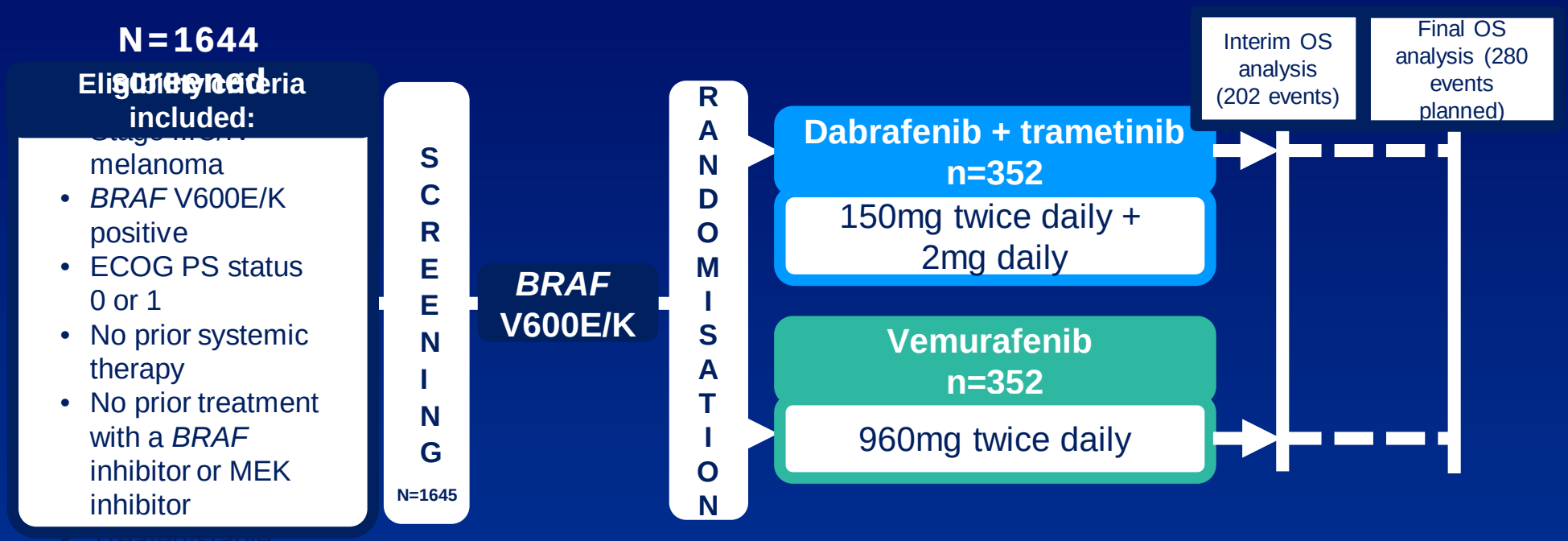
Part C: Conclusions

- **Combined dabrafenib 150mg + trametinib 2mg prolonged PFS, ORR, DoR and OS compared with dabrafenib alone in *BRAF* V600-mutant metastatic melanoma:[1–3]**
  - **Median PFS was 9.4 *vs* 5.8 months (HR: 0.39; p<0.001)[1,2]**
  - **ORR was 76% *vs* 54% (p=0.03)[1,2]**
  - **DoR was 10.5 *vs* 5.6 months[2]**
  - **Median OS was 25.0 *vs* 20.2 months – based on most recent data[3]**
    - **12-month OS: 80 *vs* 70%**
    - **24-month OS: 51 *vs* 44%**
    - **36-month OS: 38 *vs* 31%**
- **Combined dabrafenib + trametinib safety profile is tolerable and manageable[1–3]**
  - **Most common AEs were pyrexia, chills and fatigue**

1. Long GV, *et al.* Oral presented at ESMO 2012, Abstract LBA27;
2. Flaherty KT, *et al. N Engl J Med* 2012;367:1694–703;
3. Daud A, *et al. J Clin Oncol* 2015;33(Suppl):Abstract 9036.

COMBI-v: Study design

Combination of dabrafenib + trametinib vs vemurafenib



- **Stratification: LDH (>ULN *vs* ≤ULN) and *BRAF* mutation (V600E *vs* V600K)**
- **Primary endpoint: OS**
- **Secondary endpoints: PFS, ORR, DoR, safety**

Robert C, *et al. N Engl J Med* 2015;372:30–9;
Robert C, *et al.* Oral presentation at ESMO 2014, Abstract LBA4_PR;

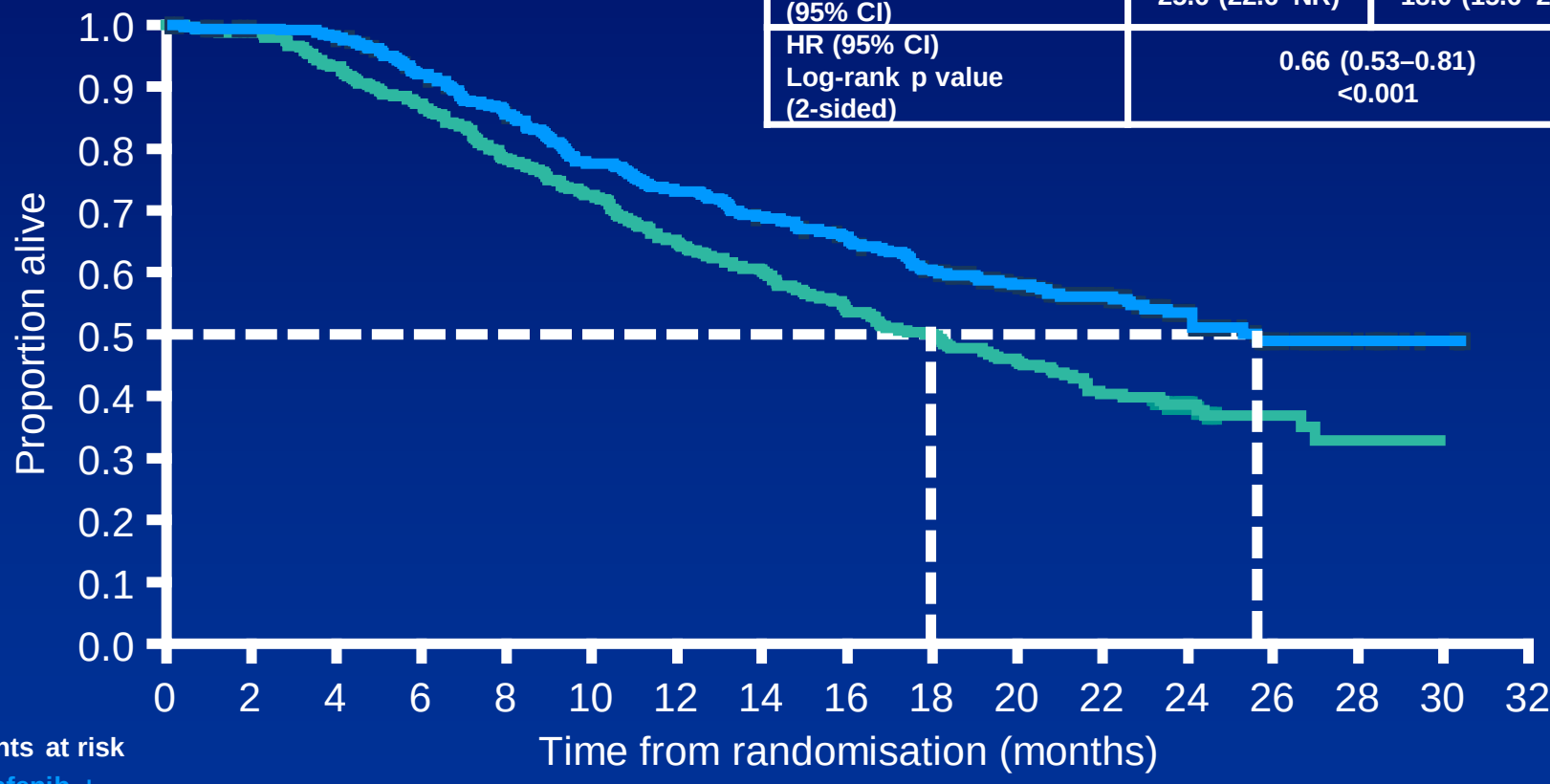
COMBI-v: Study population

	Dabrafenib + trametinib	Vemurafenib	Total
ITT, n			
All randomised patients whether or not treatment was administered	352	352	704
Safety, n			
All patients who received ≥1 dose of study treatment	350	349	699

Robert C, *et al*. *N Engl J Med* 2015;372:30–9.

COMBI-v (at March 2015): OS at final analysis

	Dabrafenib + trametinib (N=352)	Vemurafenib (N=352)
Median OS, months (95% CI)	25.6 (22.6–NR)	18.0 (15.6–20.7)
HR (95% CI) Log-rank p value (2-sided)	0.66 (0.53–0.81) <0.001	



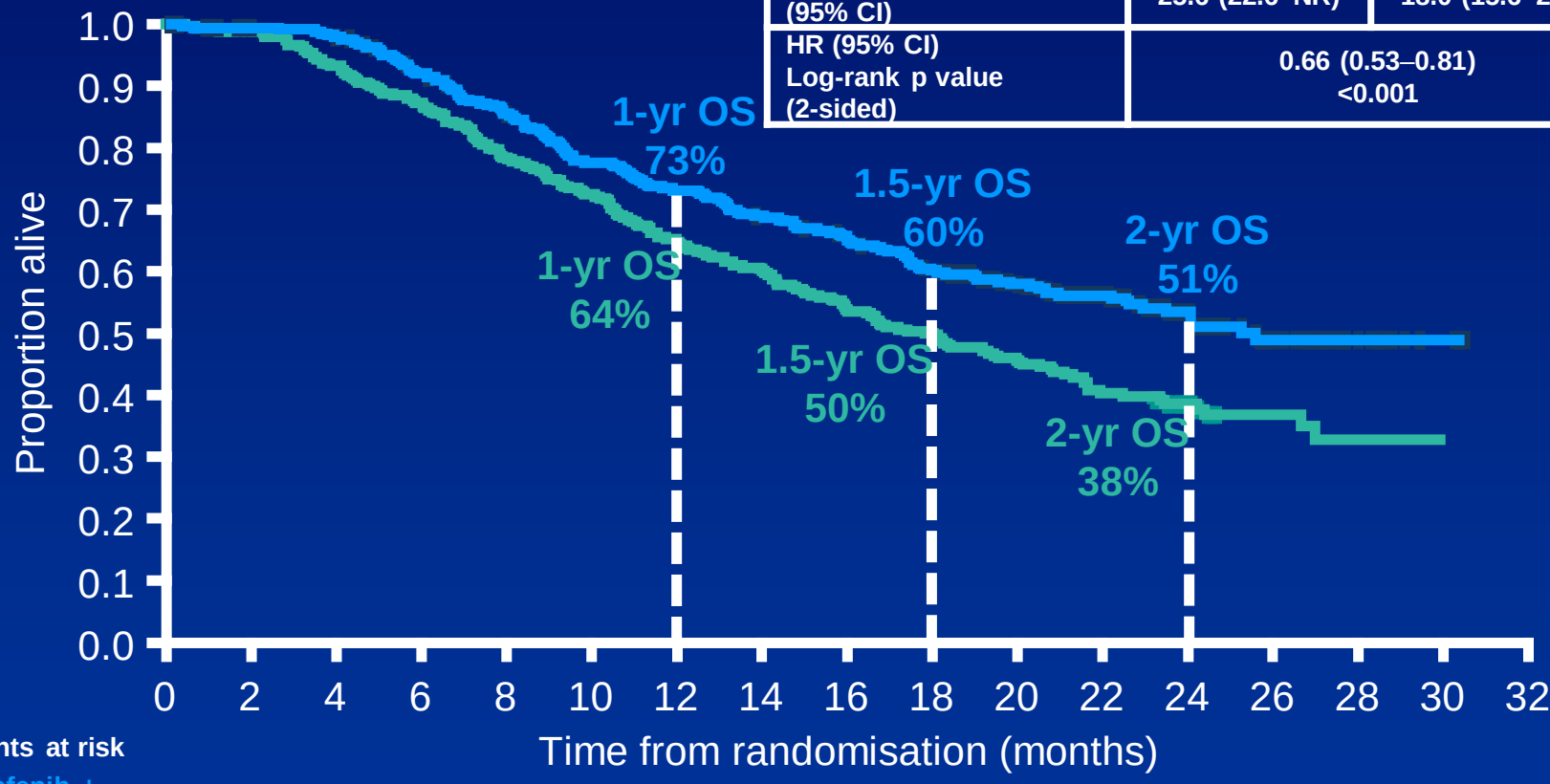
Patients at risk																	
Dabrafenib + trametinib	352	342	336	311	286	260	245	230	217	198	173	128	68	38	16	5	0
Vemurafenib	352	341	315	286	252	231	201	187	166	152	129	88	46	28	7	0	0

Robert C, et al. Oral presentation at ECC 2015, Abstract 3301.

NR=not reported

COMBI-v (at March 2015): Landmark OS analysis

	Dabrafenib + trametinib (N=352)	Vemurafenib (N=352)
Median OS, months (95% CI)	25.6 (22.6–NR)	18.0 (15.6–20.7)
HR (95% CI) Log-rank p value (2-sided)	0.66 (0.53–0.81) <0.001	



Patients at risk

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

Robert C, *et al*. Oral presentation at ECC 2015, Abstract 3301.

NR=not reported

COMBI-v (at March 2015): Response rates

Best confirmed response	Dabrafenib + trametinib (n=351)	Vemurafenib (n=350)
Complete response, n (%)	59 (17)	36 (10)
Partial response, n (%)	172 (49)	150 (43)
Stable disease, n (%)	87 (25)	102 (29)
Progressive disease, n (%)	22 (6)	39 (11)
Not evaluable, n (%)	12 (3)	25 (7)
ORR, n (%) 95% CI	231 (66) 60.4–70.6	186 (53) 47.5–58.2
Difference in ORR, % (95% CI)	13 (5.3–20.2)	
p value	0.0008	
Duration of response, months (95% CI)	13.8 (11.2–18.1)	8.5 (7.4–9.7)

Robert C, *et al.* Oral presentation at ECC 2015, Abstract 3301.

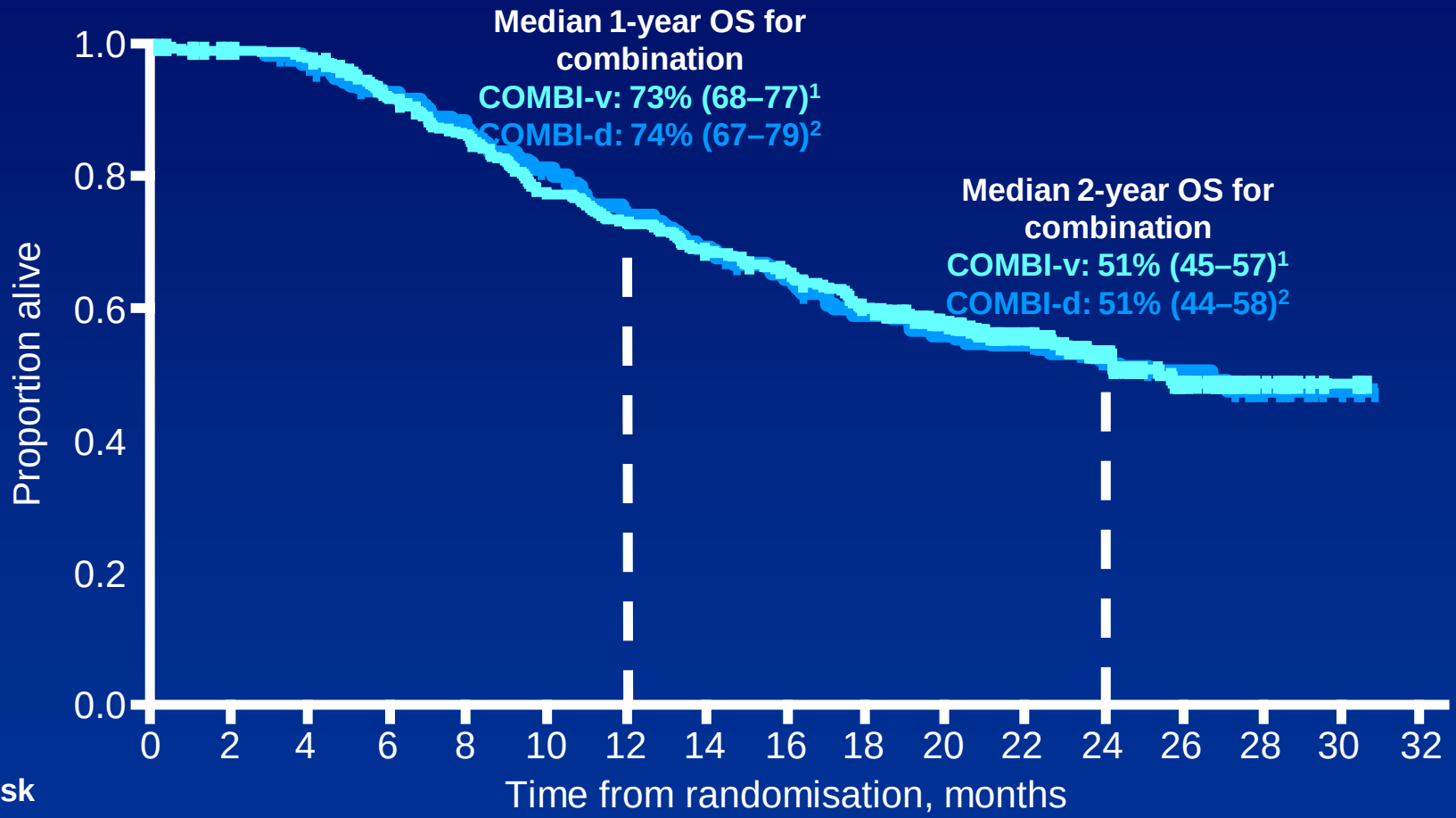
Data cut-off: March 2015.

COMBI-v: Summary

- **Dabrafenib + trametinib showed improved efficacy *vs* vemurafenib in *BRAF* V600-mutant melanoma**
  - **Improved median OS (25.6 *vs* 18.0 months)**
  - **34% reduction in risk of death (HR 0.66; 95% CI 0.53–0.81; p <0.001)**
  - **Improved 2-year survival (51% *vs* 38%)**
  - **Improved median PFS (12.6 *vs* 7.3 months; HR 0.61; p <0.001)**
  - **Improved ORR (66% *vs* 53%) and DOR (13.8 *vs* 8.5 months)**
- **Longest benefit in patients with LDH ≤ULN (2-year OS rate 66%)**
- **Manageable AE profile with no new safety signals**
  - **Higher incidence of pyrexia and ejection fraction decrease in combination arm**
  - **Lower incidence of cutaneous malignancies and hyperproliferative events in combination arm**
  - **Lower incidence and severity of photosensitivity in combination arm**
- **Overall results comparable to COMBI-d study**
  - **Improved OS and PFS shown with dabrafenib + trametinib combination therapy *vs* dabrafenib or vemurafenib monotherapy**

Robert C, *et al.* Oral presentation at ECC 2015, Abstract 3301; Data on file.

COMBI-d and COMBI-v: Landmark OS analysis

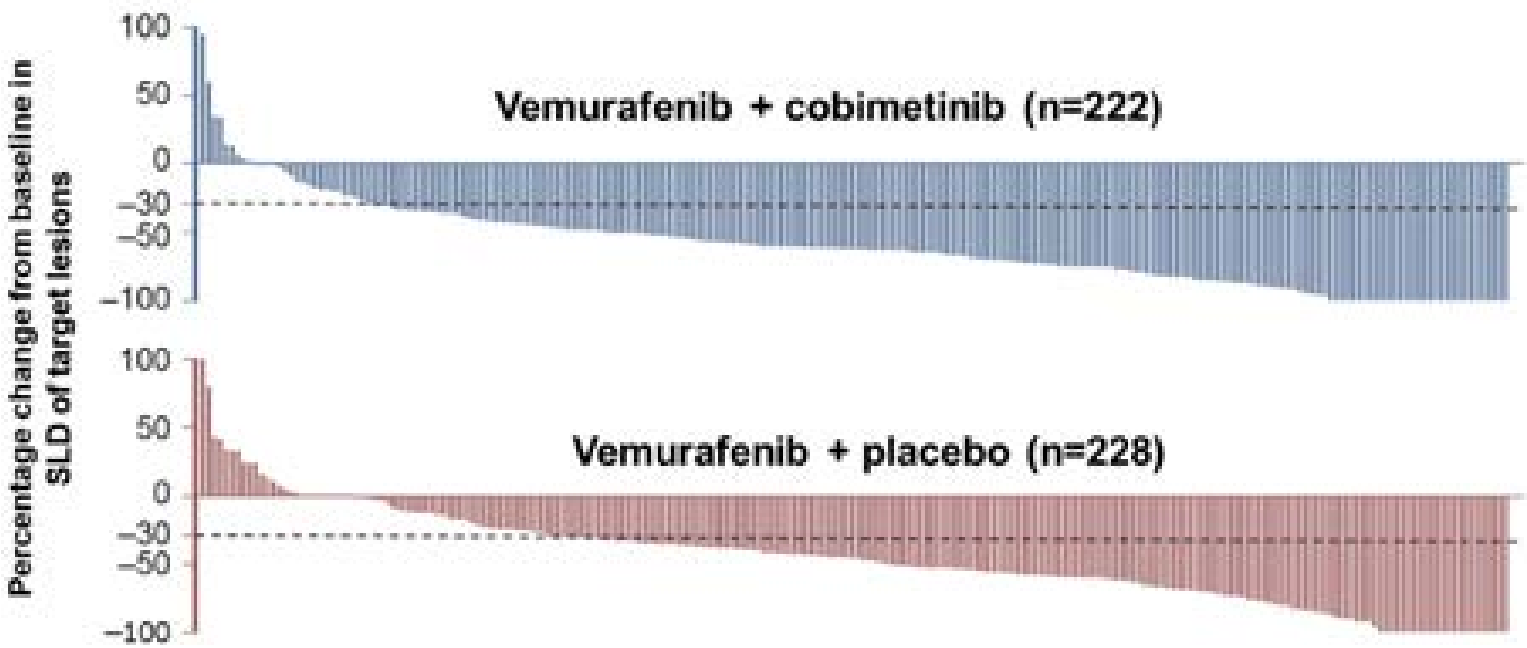


Number at risk

COMBI-d D + T[2]	211	208	200	187	174	159	144	135	124	112	106	103	88	53	21	3	0
COMBI-v D + T[1]	352	342	336	311	286	260	245	230	217	198	173	128	128	38	16	5	0

1. Robert C, *et al.* Oral presentation at ECC 2015, Abstract 3301;
2. Long GV, *et al. Lancet* 2015;386:444–51.

coBRIM (GO28141; phase III): Best tumour response



	Vemurafenib + placebo (n=248)	Cobimetinib + vemurafenib (n=247)
Patients with confirmed objective response % (95% CI)*	45 (38–51)	68 (61–73)
Complete response, n (%)	11 (4)	25 (10)
Partial response, n (%)	100 (40)	142 (57)
Stable disease, n (%)	105 (42)	49 (20)

*Only patients who had both pre and post tumour evaluations are included. CI = confidence interval; RECIST = Response Evaluation Criteria in Solid Tumours; SLD = the sum of the diameters of investigator identified target lesion per RECIST v 1.1. Data cutoff: May 9, 2014

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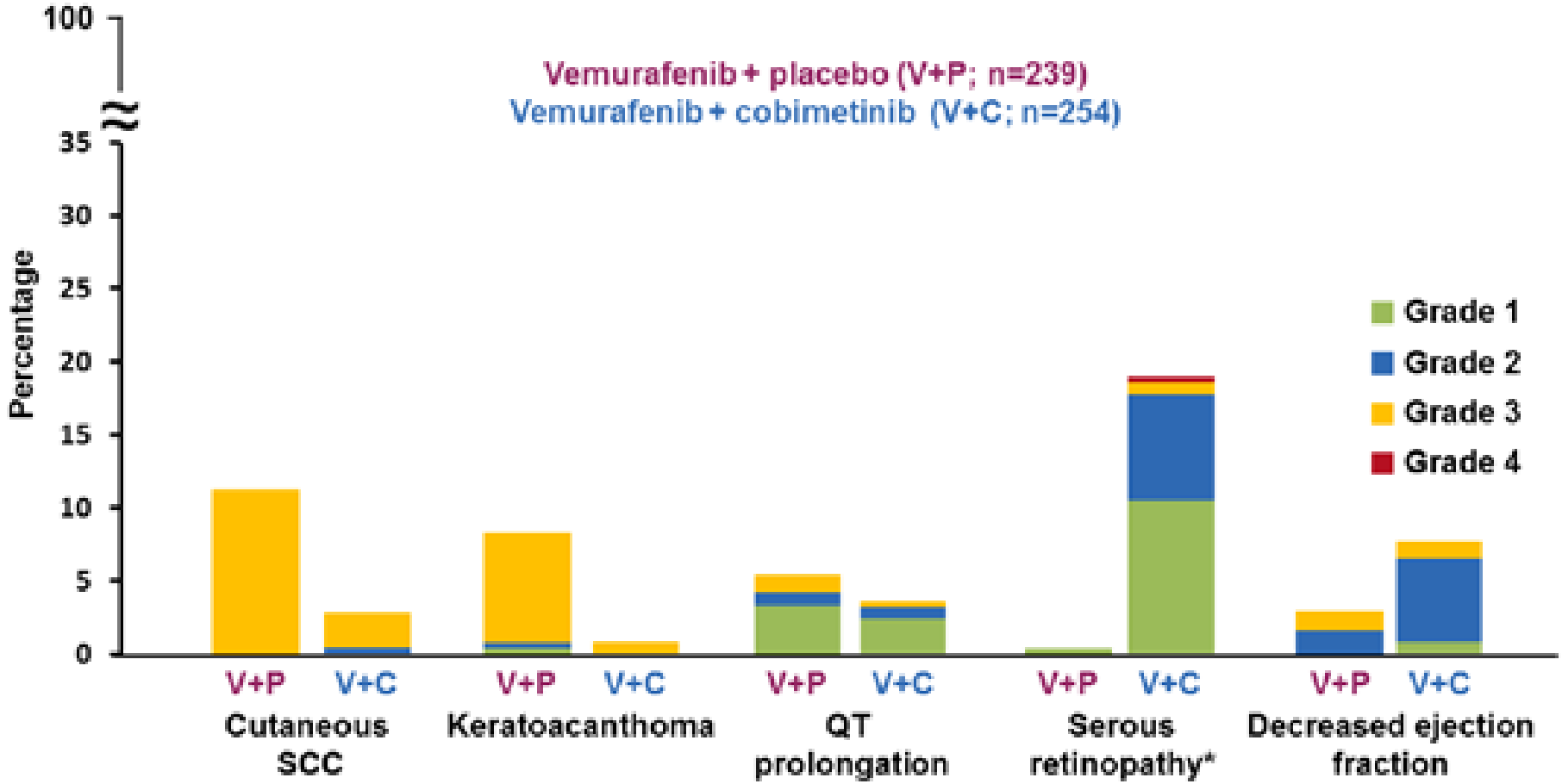
Larkin J, et al. N Engl J Med. 2014;371:1867–1876.

coBRIM: Summary of selected adverse events



*Includes specific terms chorioretinopathy and retinal detachment. No cases of retinal vein occlusion were reported.
SCC = squamous cell carcinoma.

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Larkin J, et al. N Engl J Med. 2014;371:1867–1876.

coBRIM: Summary

- coBRIM efficacy data confirmed clinical benefit of addition of cobimetinib to vemurafenib in *BRAF*^{V600} mutated melanoma
  - 12.25 months PFS for cobimetinib + vemurafenib
  - 7.2 months PFS for placebo + vemurafenib (HR 0.58; 95% CI, 0.46-0.72)
  - ORR 69.6% for cobimetinib + vemurafenib and 50% for placebo + vemurafenib
- Common AEs were usually grade 1 or 2
- Managed with dose modification and supportive care
- Permanent discontinuation of the combination due to AEs was relatively uncommon
- Rates of discontinuation were similar in the arms, indicating tolerability of the combination regimen
- Transient MEK inhibitor-related serous retinopathy was usually mild and resolved with no long-term sequelae

Larkin J, et al. Oral presentation at 51st ASCO Annual Meeting May 29– June 2, 2015; Chicago, Illinois.

NEMO: Conclusions

- Prolonged PFS, improved response rates achieved with binimetinib in pts with *NRAS*-mutant melanoma[1]
  - PFS (median): 2.8 vs 1.5 mos (HR: 0.62; 95% CI: 0.47-0.80; *P* < .001)
  - Benefit evident across subgroups, including those receiving prior immunotherapy (n = 85; 5.5 vs 1.6 mos for binimetinib vs dacarbazine)
- Binimetinib safety profile consistent with other MEK inhibitors[2,3]
- Investigators concluded that binimetinib is an effective new therapy for *NRAS*-mutant melanoma, a pt population with unmet clinical needs

1. Dummer R, et al. ASCO 2016. Abstract 9500. 2. Trametinib [package insert]. 3. Cobimetinib [package insert].

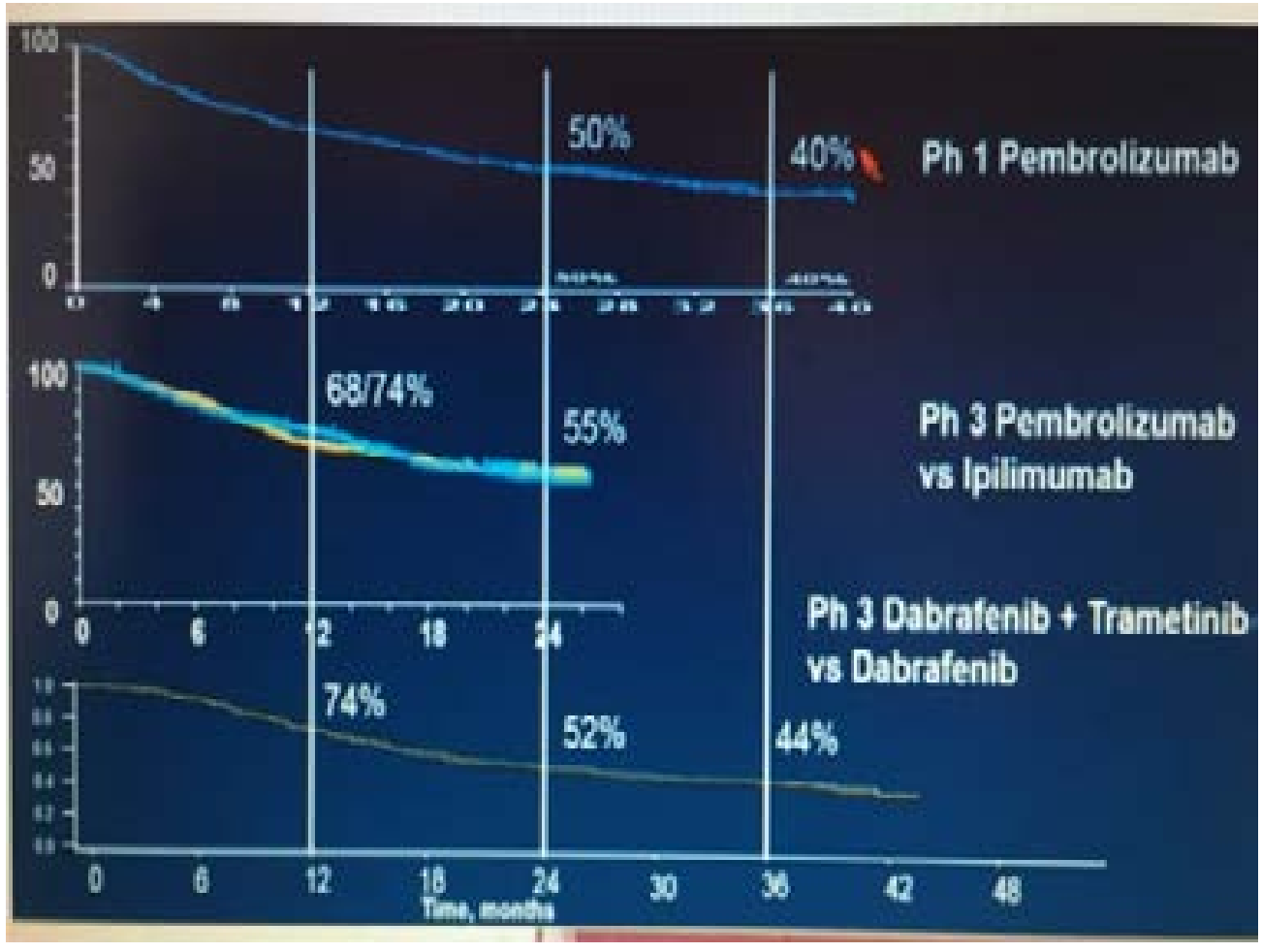
NEMO: Adverse Events

Selected AEs, %	Binimetinib (n = 269)		Dacarbazine (n = 114)	
	All Grades*	Grade 3/4†	All Grades*	Grade 3/4†
Total	100	68	91	46
Skin-related				
▪ Rash	36	4	1	0
▪ Dermatitis acneiform	35	3	1	0
Gastrointestinal				
▪ Diarrhea	40	1	11	1
▪ Nausea	29	1	32	1
▪ Vomiting	21	2	12	0
Muscle-related (blood CPK increase)	42	19	3	0
Other				
▪ Peripheral edema	36	< 1	3	0
▪ Fatigue	22	2	32	3
▪ Asthenia	18	3	17	4
▪ Hypertension	14	7	4	2
▪ AST increased	13	2	4	0
▪ Decreased appetite	12	1	16	1
▪ Ejection fraction decreased	11	4	2	1
▪ Neutropenia	1	1	18	9
▪ Thrombocytopenia	1	< 1	15	4

*> 15% of pts in any treatment group. †> 2 % of pts in any treatment group.
Other grade 3/4 AEs > 2%: binimetinib: general physical health deterioration (4%), ALT increase (3%); dacarbazine: anemia (10%), leukopenia (7%), decreased neutrophil count (7%), ALT increase (6%), lymphopenia (5%), GGT increase (5%).

Dummer R, et al. ASCO 2016. Abstract 9500.

Slide credit: clinicaloptions.com


100
50
0
50%
40%
Ph 1 Pembrolizumab
100
50
0
68/74%
55%
Ph 3 Pembrolizumab
vs Ipilimumab
0
6
12
18
24
Ph 3 Dabrafenib + Trametinib
vs Dabrafenib
74%
52%
44%
0
6
12
18
24
30
36
42
48
Time, months

coBRIM: Patient characteristics

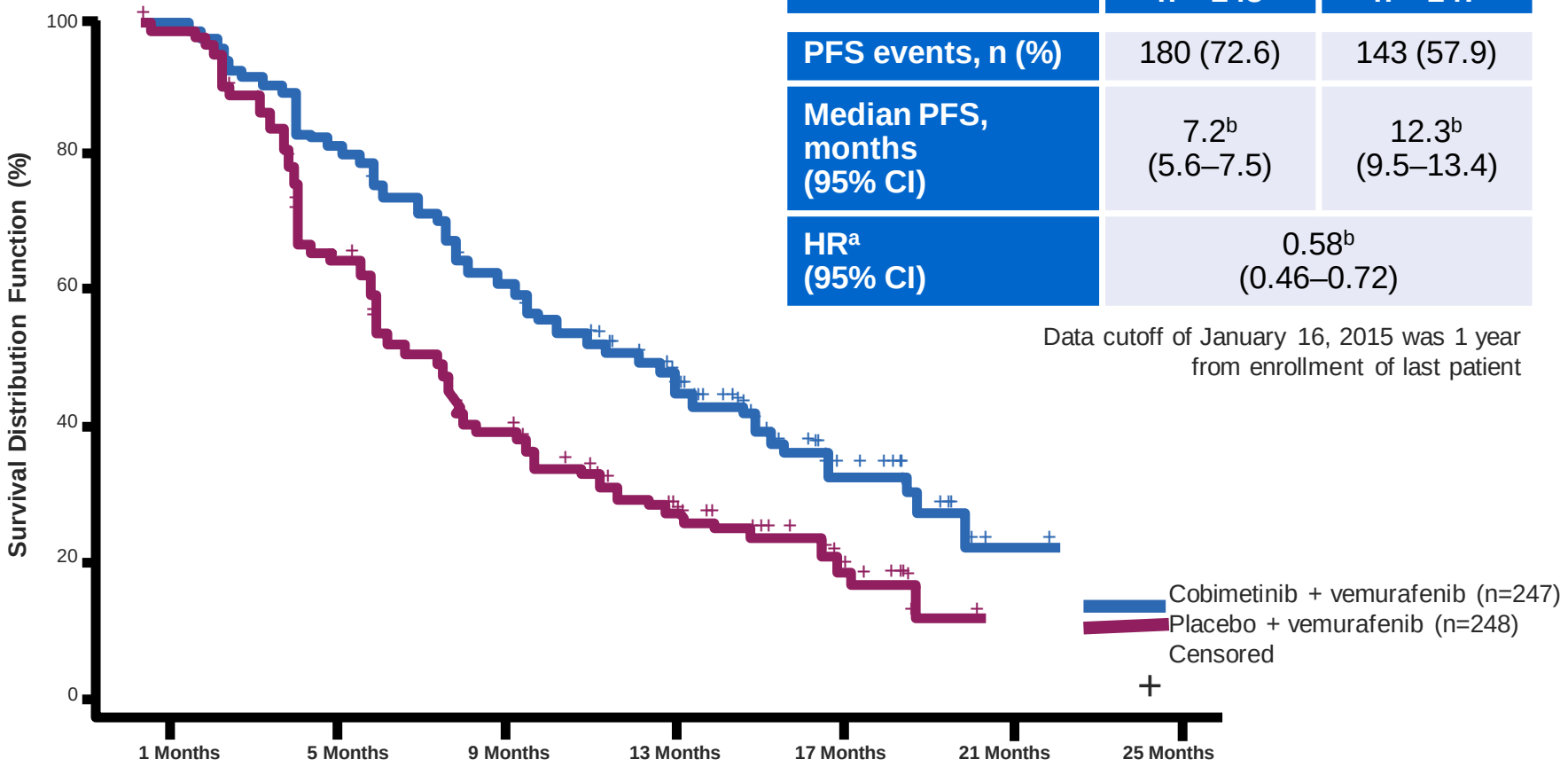
Characteristic	Vemurafenib + placebo (n=248)	Vemurafenib + cobimetinib (n=247)
Median age, years (range)	55 (25 – 85)	56 (23 – 88)
Sex, n (%)		
Male	140 (57)	146 (59)
Female	108 (44)	101 (41)
ECOG Performance Status, n (%)		
0	164 (67)	184 (76)
1	80 (33)	58 (24)
2	0 (0)	1 (<1)
Elevated LDH, n (%)	104 (43)	1 (<1)
History of brain metastases, n (%)	2 (0.8)	1 (<1)
Geographic region, n (%)		
Australia/New Zealand/Israel	38 (15)	40 (16)
Europe	184 (74)	182 (74)
North America	26 (11)	25 (10)
Melanoma stage at enrollment, n (%)		
Unresectable stage IIIC	13 (5)	21 (9)
Stage IV, M1a	40 (16)	40 (16)
Stage IV, M1b	42 (17)	40 (16)
Stage IV, M1c	153 (62)	146 (59)
Median follow-up (range), months	14.2 (0.5 – 24.8)	

LDH, lactate dehydrogenase. Data cutoff: Jan 16, 2015

Larkin J, et al. Oral presentation at 51st ASCO Annual Meeting May 29– June 2, 2015; Chicago, Illinois.

coBRIM : Updated investigator-assessed PFS

Kaplan-Meier Plot for PFS
Intent-to-Treat Population



ITT Population	Vem + Pbo n = 248	Cobi + Vem n = 247
PFS events, n (%)	180 (72.6)	143 (57.9)
Median PFS, months (95% CI)	7.2[b] (5.6–7.5)	12.3[b] (9.5–13.4)
HR[a] (95% CI)	0.58[b] (0.46–0.72)	

Data cutoff of January 16, 2015 was 1 year from enrollment of last patient

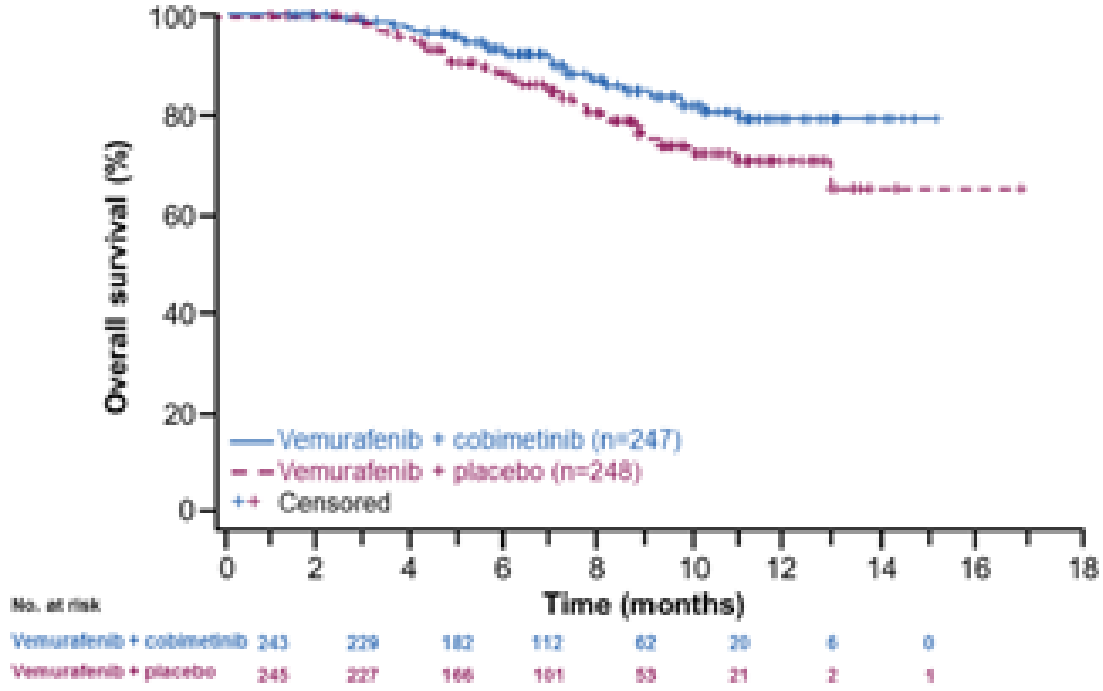
No. of patients at risk

Vemurafenib + cobimetinib	238	215	190	168	142	116	79	46	21	8	1
Vemurafenib + placebo	240	205	150	115	87	67	45	30	17	3	

[a]Stratified HR.

[b]The median PFS was 6.2 months in Pbo + Vem, and 9.9 months in Cobi + Vem (HR, 0.51; 95% CI, 0.39-0.68) at the May 9, 2014 data cutoff. Larkin J, et al. Oral presentation at 51st ASCO Annual Meeting May 29– June 2, 2015; Chicago, Illinois.

coBRIM: Overall survival



	Vemurafenib + placebo	Cobimetinib + vemurafenib
Overall survival events, n	51	34
Median overall survival	NE	NE
9-month overall survival (95% CI), %	72.5 (65.2–79.8)	81.1 (74.7–87.5)
HR (95% CI) p-value, two-sided	0.65 (0.42–1.00) p=0.046*	

*Descriptive p-value. Did not cross the pre-specified stopping boundary for the interim analysis (boundary p<0.0000037);
CI = confidence interval; HR = hazard ratio; NE = not estimable.
Data cutoff: May 9, 2014

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coBRIM: Updated response rates

	Vemurafenib + placebo n=248	Cobimetinib + vemurafenib n=247
Complete response (CR), n (%)	26 (10.5)	39 (15.8)
Partial response, n (%)	98 (39.5)	133 (53.8)
Objective response rate (ORR), n (%)	124 (50.0) (95% CI, 43.6–56.4)	172 (69.6) (95% CI, 63.5–75.3)
Difference in ORR, %	19.6[a] (95% CI, 11.0–28.3)	
Duration of response **Patients with event, n (%)** **Median (95% CI)** **Range**	 73 (58.9) 9.2 (7.5–12.8) 1.8–17.7	 84 (48.8) 13.0 (11.1–16.6) 2.9–20.1

At the primary analysis[2]:

- ORR was 45% (vem + placebo) and 68% (vem + cobi)
- CR was 4% (vem + placebo) and 10% (vem + cobi)

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1. Larkin J, et al. Oral presentation at 51st ASCO Annual Meeting May 29– June 2, 2015; Chicago, Illinois.
2. Larkin J et al. *N Engl J Med.* 2014;371:1867-1876.

Overall Survival
(December 30, 2010 Cutoff)