Melanoma in 2017
Immunotherapy versus targeted therapy

Assoc. Prof Victoria Atkinson

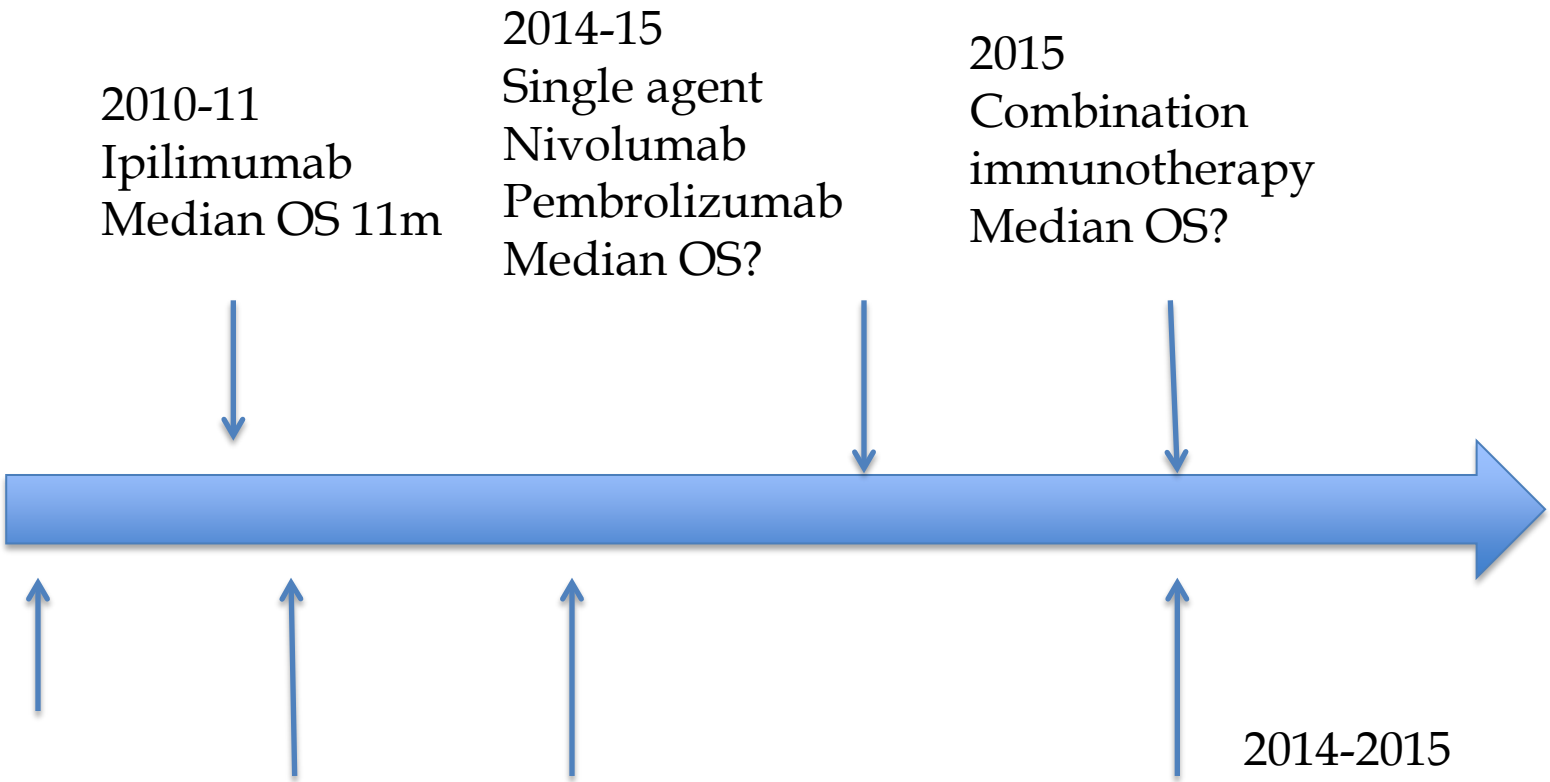
Disclosures

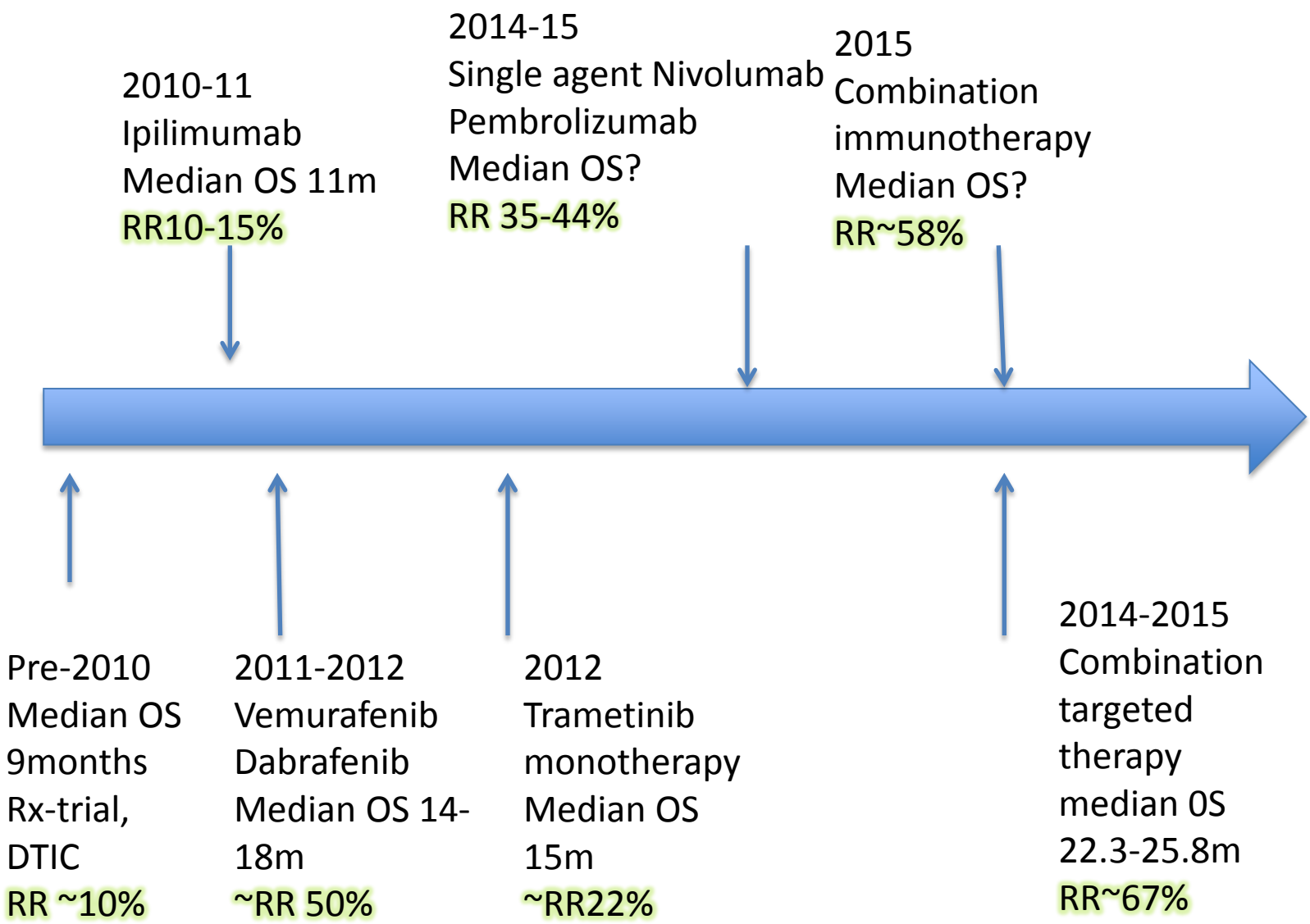
- Advisory Board- BMS, MSD, Novartis, Pierre Fabre
- Speakers Fees- BMS, MSD, Novartis, Roche
- Travel Support-BMS

Where we came from

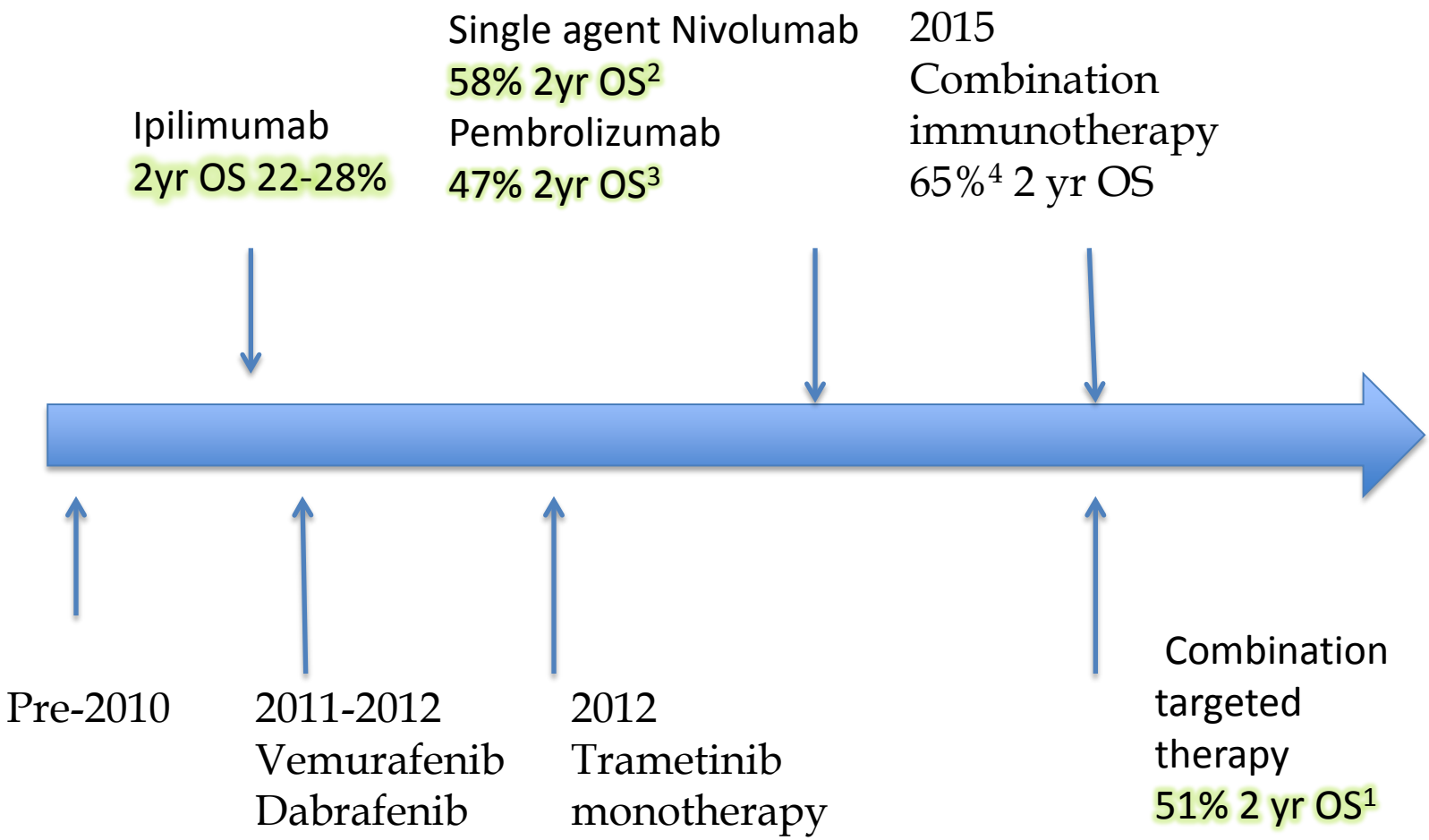
MEDIAN OVERALL SURVIVAL 9 MONTHS
UNCHANGED UNTIL 2010

TIMELINE


2010-11
Ipilimumab
Median OS 11m
2014-15
Single agent
Nivolumab
Pembrolizumab
Median OS?
2015
Combination
immunotherapy
Median OS?
Pre-2010
Median
OS
9months
Rx-trial,
DTIC
2011-2012
Vemurafenib
Dabrafenib
Median OS
14-18m
2012
Trametinib
monotherapy
Median OS
15m
2014-2015
Combination
targeted
therapy
median 0S
22.3-25.8m


2010-11
Ipilimumab
Median OS 11m
RR10-15%
2014-15
Single agent Nivolumab
Pembrolizumab
Median OS?
RR 35-44%
2015
Combination
immunotherapy
Median OS?
RR~58%
Pre-2010
Median OS
9months
Rx-trial,
DTIC
RR ~10%
2011-2012
Vemurafenib
Dabrafenib
Median OS 14-
18m
~RR 50%
2012
Trametinib
monotherapy
Median OS
15m
~RR22%
2014-2015
Combination
targeted
therapy
median 0S
22.3-25.8m
RR~67%

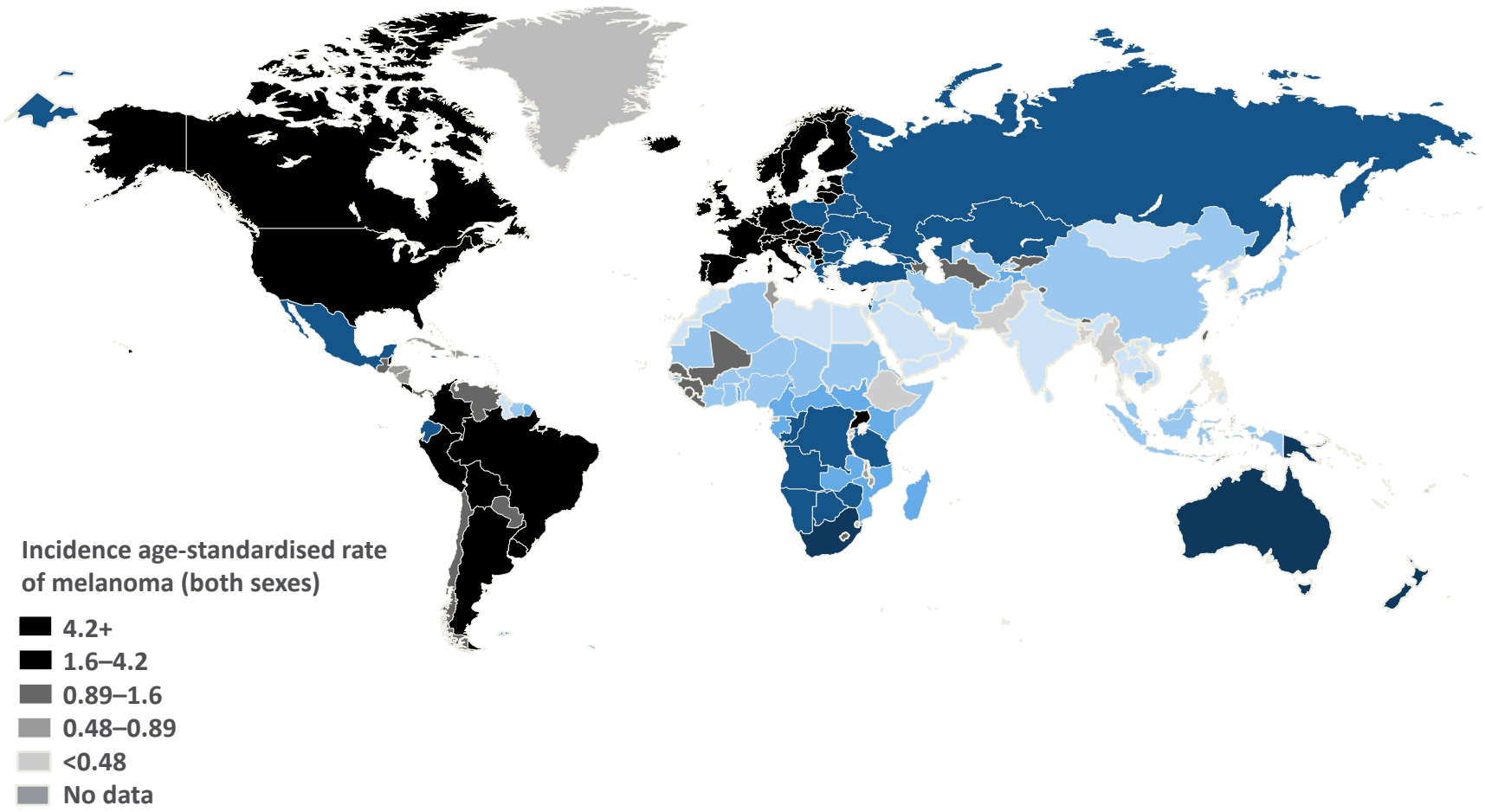
2 YEAR OVERALL SURVIVAL



3=Ipi naïve KEYNOTE 001 2=CA209-066 BRAF wt only
1=COMBI-D and COMBI-V 4=CA209-067

TARGETED THERAPY

Global incidence rates of melanoma

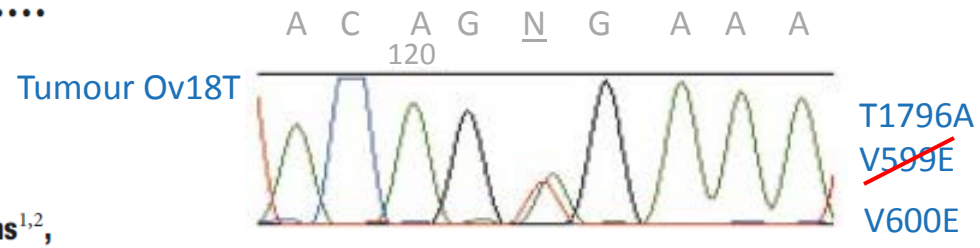


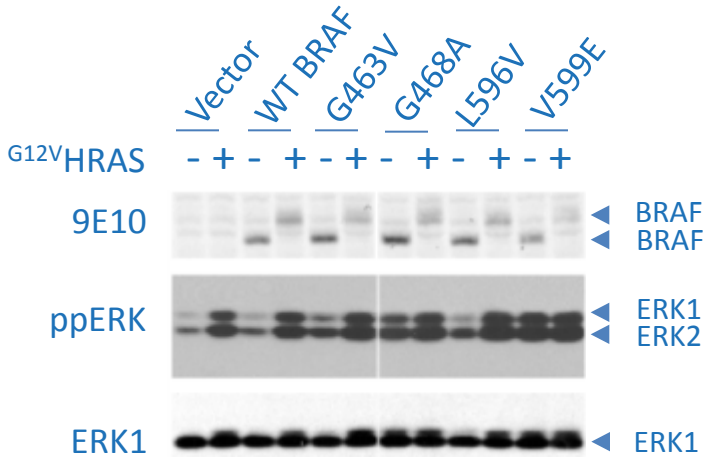
Globocan 2012. Available from: globocan.iarc.fr/. Accessed Sept 2015.

BRAF mutation in melanoma

Mutations of the *BRAF* gene in human cancer

Helen Davies[1,2], Graham R. Bignell[1,2], Charles Cox[1,2], Philip Stephens[1,2], Sarah Edkins[1], Sheila Clegg[1], Jon Teague[1], Hayley Woffendin[1], Mathew J. Garnett[3], William Bottomley[1], Neil Davis[1], Ed Dicks[1], Rebecca Ewing[1], Yvonne Floyd[1], Kristian Gray[1], Sarah Hall[1], Rachel Hawes[1], Jaime Hughes[1], Vivian Kosmidou[1], Andrew Menzies[1], Catherine Mould[1], Adrian Parker[1], Claire Stevens[1], Stephen Watt[1], Steven Hooper[3], Rebecca Wilson[3], Hiran Jayatilake[4], Barry A. Gusterson[5], Colin Cooper[6], Janet Shipley[6], Darren Hargrave[7], Katherine Pritchard-Jones[7], Norman Maitland[8], Georgia Chenevix-Trench[9], Gregory J. Riggins[10], Darell D. Bigner[10], Giuseppe Palmieri[11], Antonio Cossu[12], Adrienne Flanagan[13], Andrew Nicholson[14] Judy W. C. Ho[15], Suet Y. Leung[16], Siu T. Yuen[16], Barbara L. Weber[17], Hilliard F. Seigler[18], Timothy L. Darrow[18], Hugh Paterson[3], Richard Marais[3], Christopher J. Marshall[3], Richard Wooster[1,6], Michael R. Stratton[1,4] & P. Andrew Futreal[1]



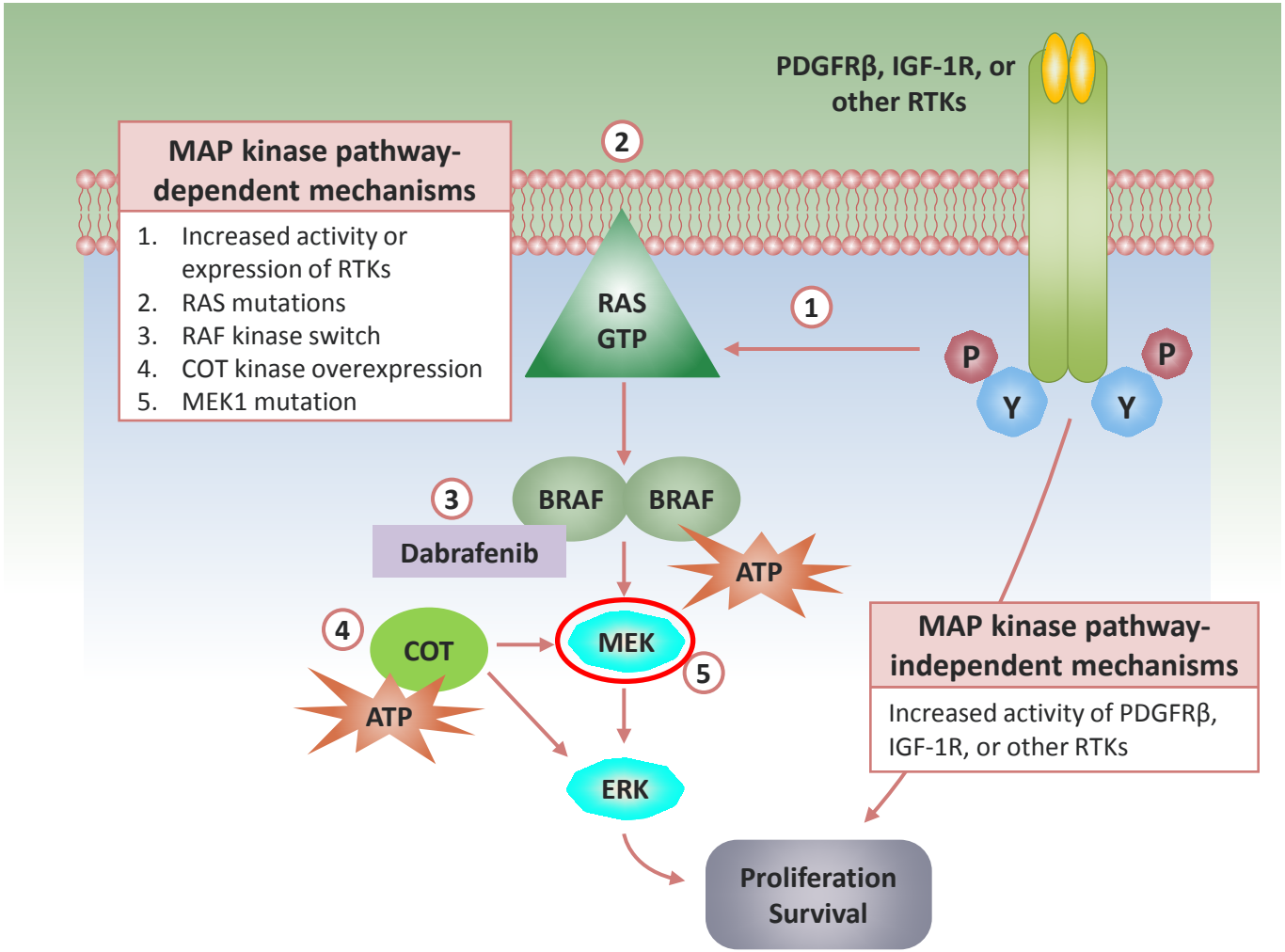


BRAF mutations		Cancer cell lines								Primary tumours						
Nucleotide	Amino acid	(1) Mel.	(2) Colo. ca	(3) Glioma	(4) Lung ca.	(5) Sarcoma	(6) Breast	(7) Ovarian	(8) Other	(1) Mel. STC	(2) Mel.	(3) Colo. ca	(4) Ovarian	(5) Sarcoma	(6) Other	Total
T1796A	V599E	19	5	4		5	1		1	11	5	2	3	1	0	57
TG1796-97AT	V599D	1														1
	Total	20	7	4	4	5	1	1	1	12	6	4	5	1	0	71
No. samples screened		34	40	38	131	59	45	26	172	15	9	22	35	182	104	923
Percent (%)		59	18	11	3	9	2	4	0.6	80	67	12	14	0.5	0	8

Mel.=melanoma; Colo.=colorectal; Ca.=cancer; STC=soft tissue cancer.

Davies H, *et al*. *Nature* 2002;417:494–54.

Opportunities to bypass BRAF inhibitor blockade



RTKs=receptor tyrosine kinases; ATP=adenosine triphosphate; GTP=guanosine triphosphate

Adapted from Alcalá AM, *et al. Clin Cancer Res* 2012;18:33–9.

BRAF by age and BMI

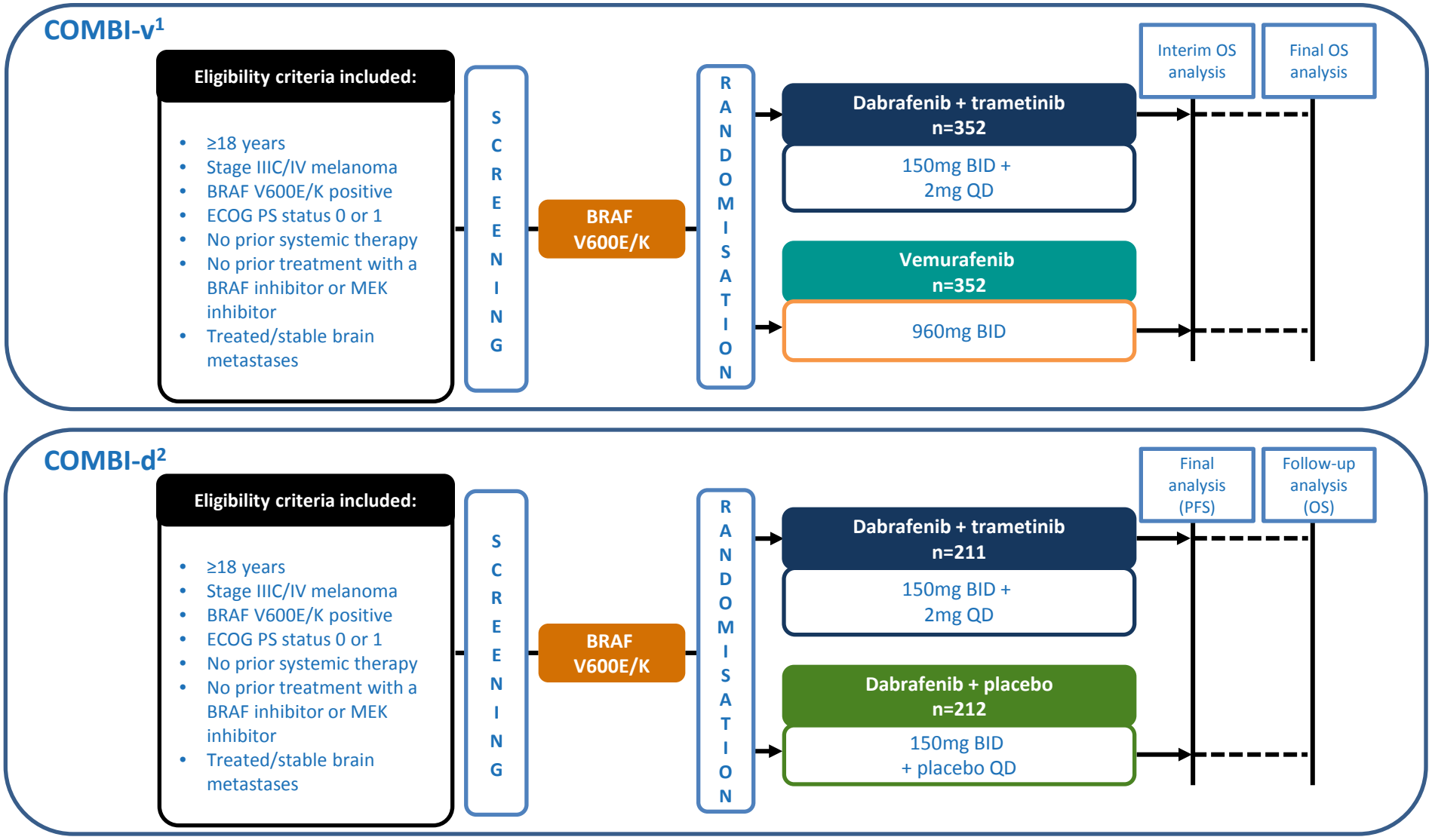
Menzies et al ASCO abstract 2011

- 312 consecutive Stage IIIC and IV patients were analysed
- 46% were BRAF mutant, 73% V600E, 19% V600K, 8% other

Age	Number	BRAF mt	V600E	V600K
20-30	14	86%	83%	0%
31-40	30	80%	92%	8%
41-50	42	50%	76%	14%
51-60	58	41%	67%	29%
61-70	103	48%	71%	24%
>70	65	22%	50%	21%

COMBI-v and COMBI-d: Combination therapy

Study design



ECOG PS=Eastern Cooperative Group Performance Status.

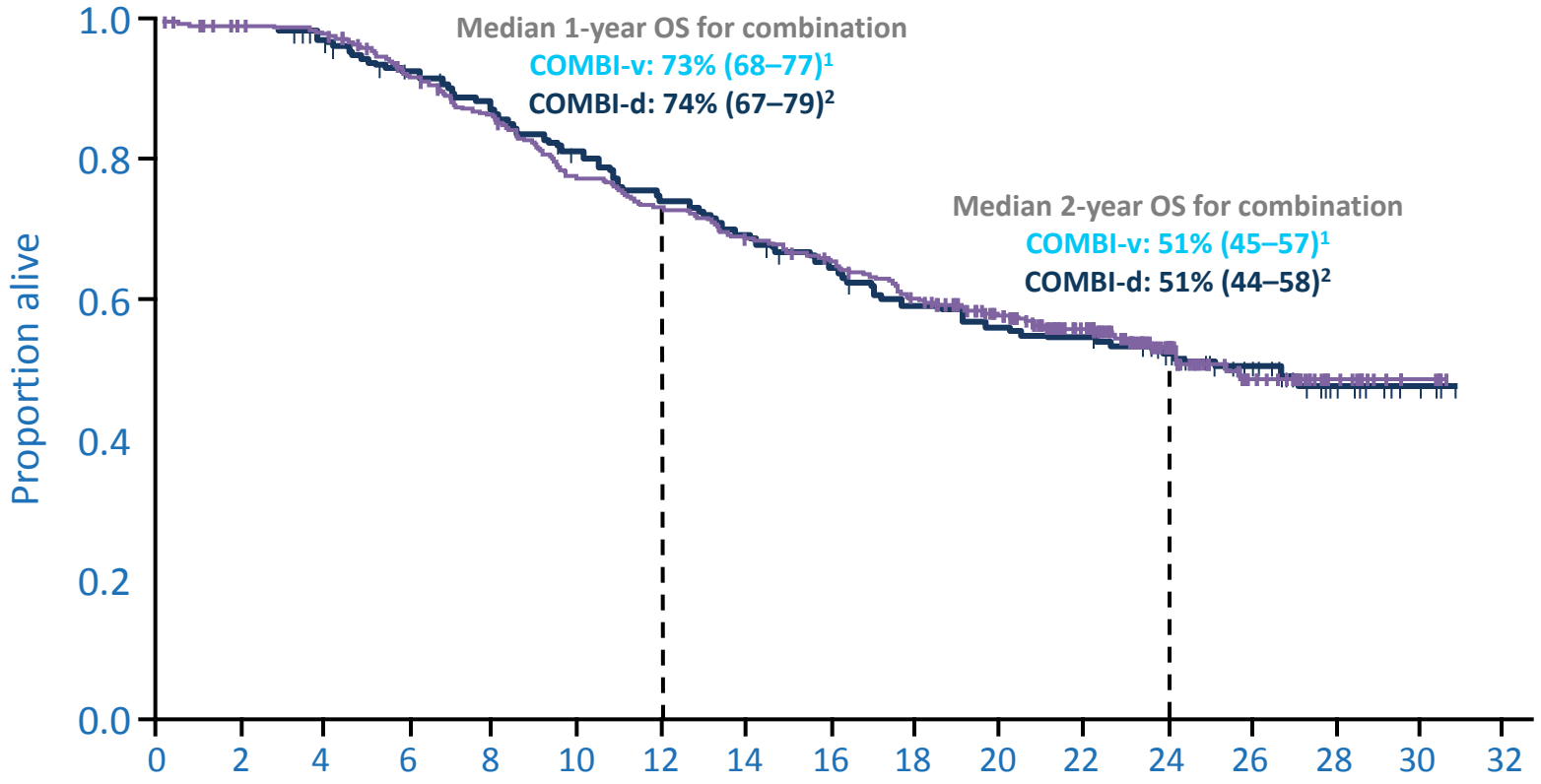
COMBI-v and COMBI-d: Combination therapy

Response

	COMBI-d[1,2]		COMBI-v[3]	
	Dabrafenib + trametinib (n=210)	Dabrafenib (n=210)	Dabrafenib + trametinib (n=351)	Vemurafenib (n=350)
Best response, %				
CR	16	13	17	10
PR	53	40	49	43
SD	24	31	25	29
PD	6	9	6	11
Not evaluable	1	6	3	7
Response rate, %				
CR + PR	69	53	66	53
95% CI	62–75	46–60	60.4–70.6	47.5–58.2
Difference in response rate, %				
CR + PR (95% CI)	15 (6.0–24.5)		13 (5.3–20.2)	
p value	0.0014		0.0008	
DoR (95% CI), months	12.9 (9.4–19.5)	10.6 (9.1–13.8)	13.8 (11.2–18.1)	8.5 (7.4–9.7)

ITT population.
SD=stable disease; PD=progressive disease; ITT=intention to treat.

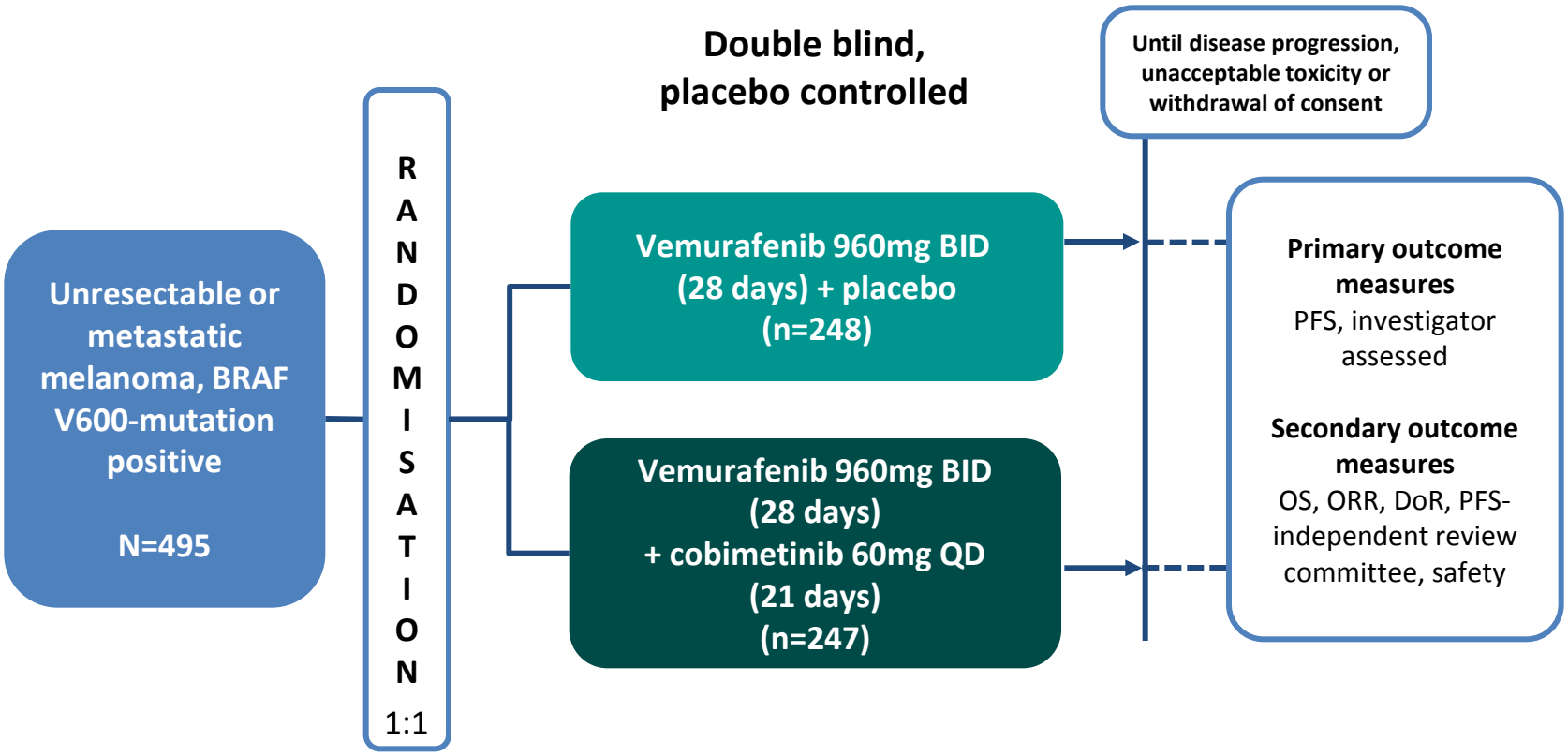
COMBI-v and COMBI-d: Combination therapy
Landmark OS analysis



Number at risk

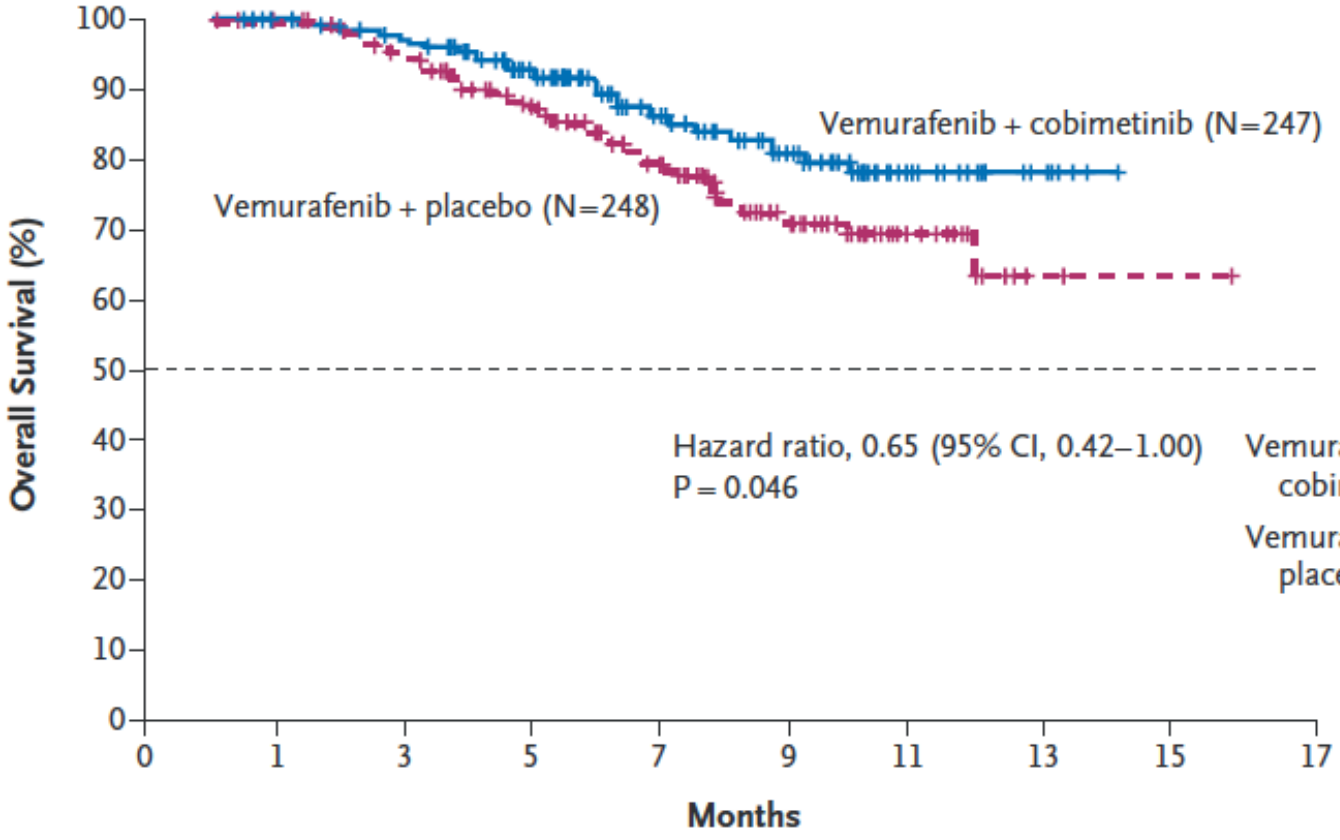
COMBI-d D + T[2]	**211**	**208**	**200**	**187**	**174**	**159**	**144**	**135**	**124**	**112**	**106**	**103**	**88**	**53**	**21**	**3**	**0**
COMBI-v D + T[1]	**352**	**342**	**336**	**311**	**286**	**260**	**245**	**230**	**217**	**198**	**173**	**128**	**128**	**38**	**16**	**5**	**0**

coBRIM: Vemurafenib + cobimetinib



BID=twice daily; QD=once daily; DoR=duration of response.

Larkin J, *et al*. *N Engl J Med* 2014;371:1867–76.



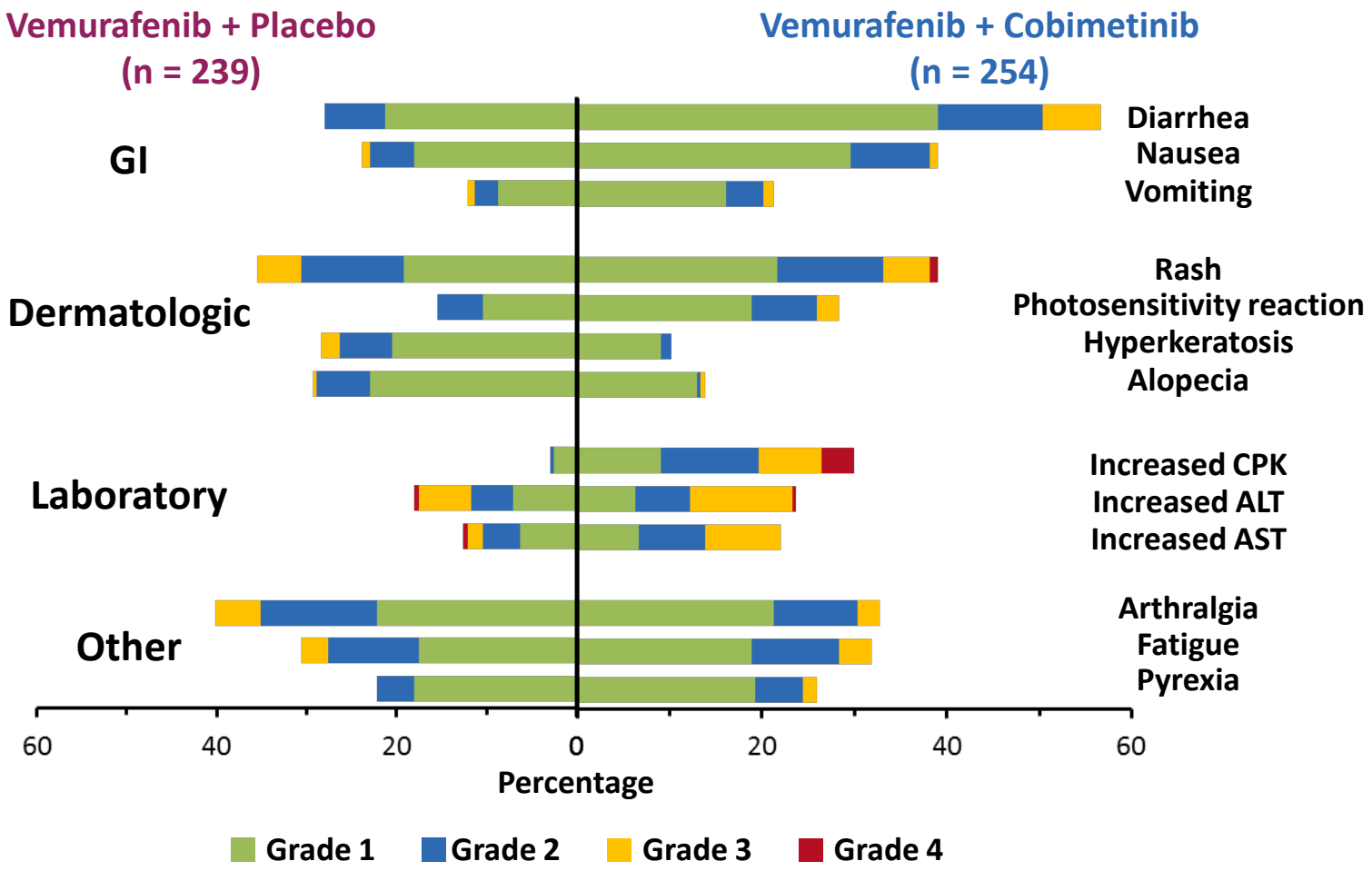
No. at Risk

Vemurafenib + cobimetinib	243	229	182	112	62	20	6	
Vemurafenib + placebo	245	227	166	101	53	21	2	1

Figure 2. Kaplan–Meier Estimates of Overall Survival in the Intention-to-Treat Population.

The tick marks indicate censored data, and the dashed line 50% survival.

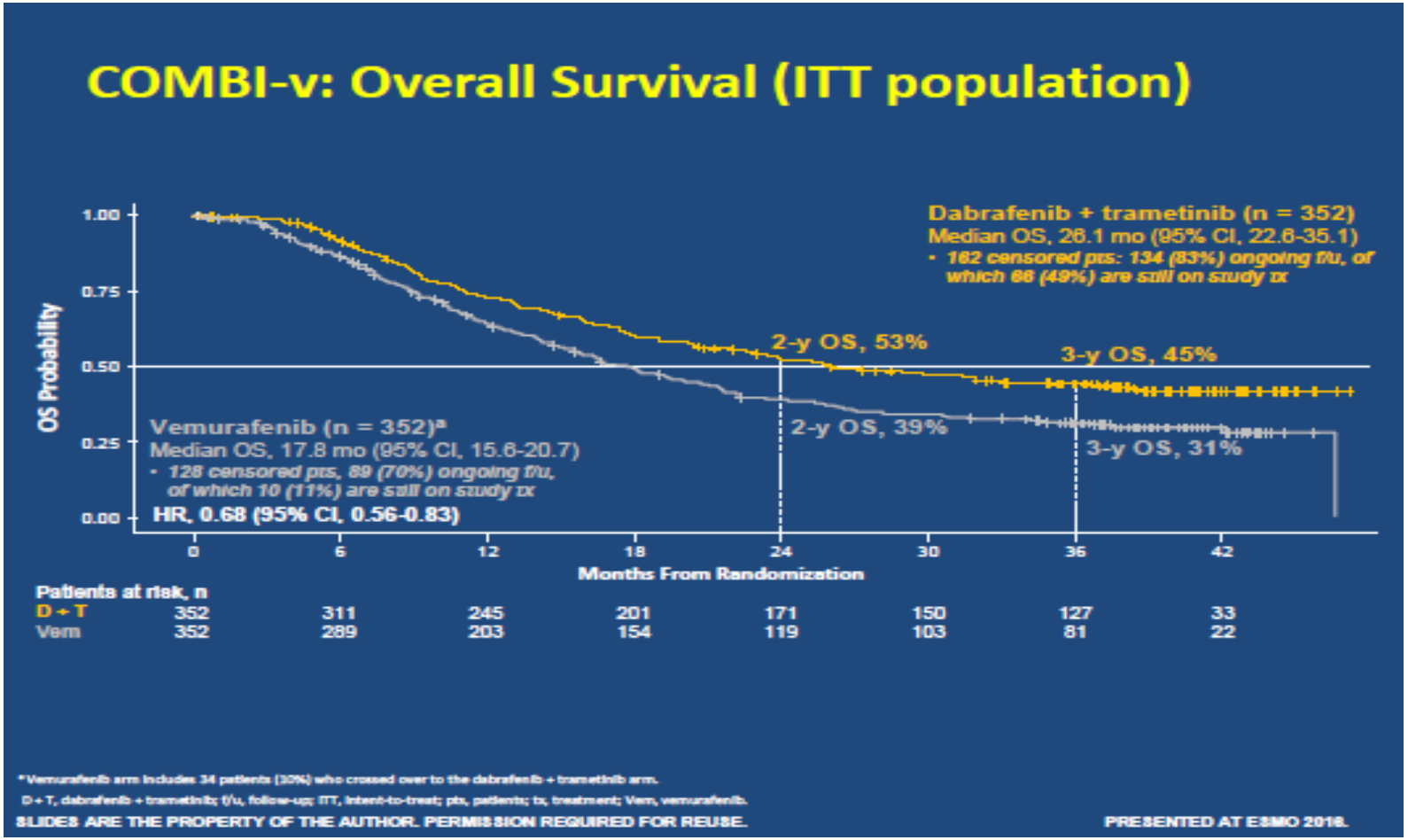
AEs Occurring in ≥20% of Patients



ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase.
*Multiple occurrences of a specific AE for a patient were counted once at the highest NCI CTCAE grade of the occurrence.

Data Cutoff: May 9, 2014

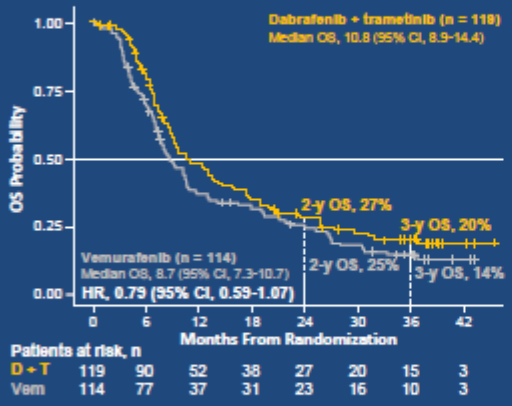
Updated data from COMBI-D and V



Robert et al ESMO 2016

COMBI-v: Elevated LDH (> ULN)

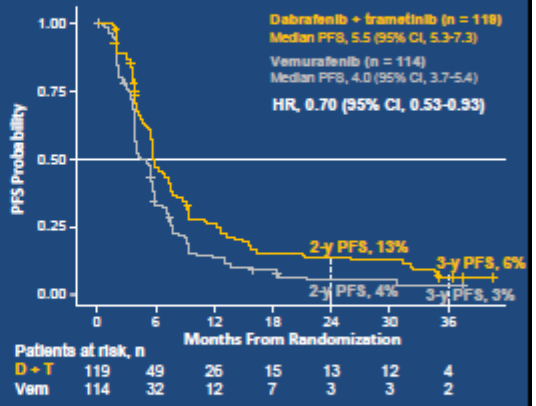
OS



Patients at risk, n

D + T	119	90	52	38	27	20	15	3
Vem	114	77	37	31	23	16	10	3

PFS

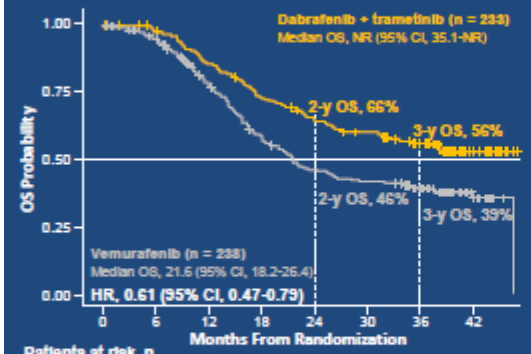


Patients at risk, n

D + T	119	49	26	15	13	12	4
Vem	114	32	12	7	3	3	2

COMBI-v: Normal LDH (≤ ULN)

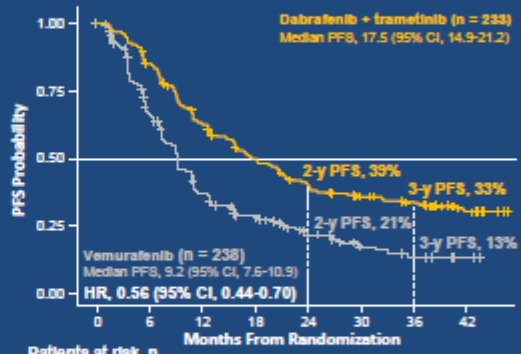
OS



Patients at risk, n

D + T	233	221	193	153	144	130	112	30
Vem	238	212	166	123	96	87	71	19

PFS

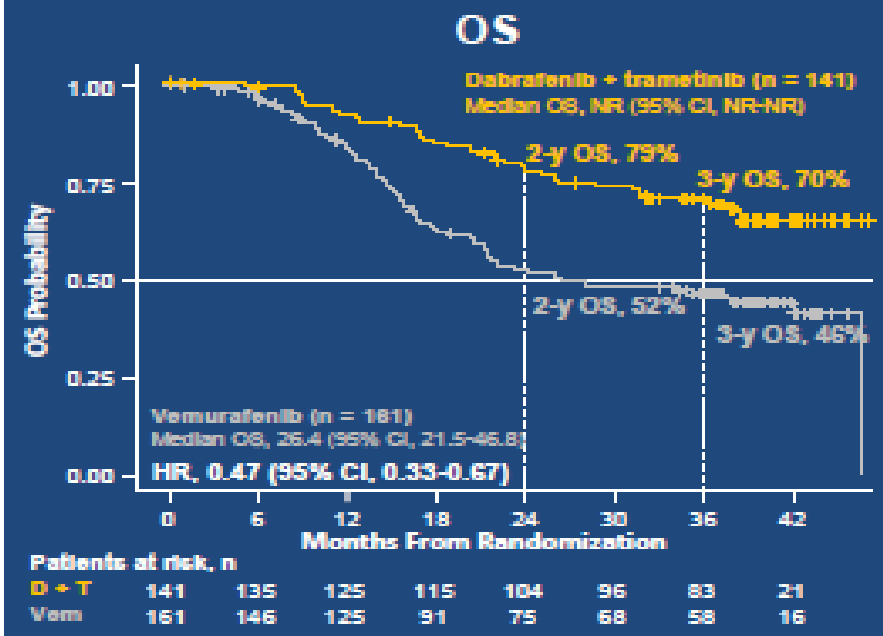


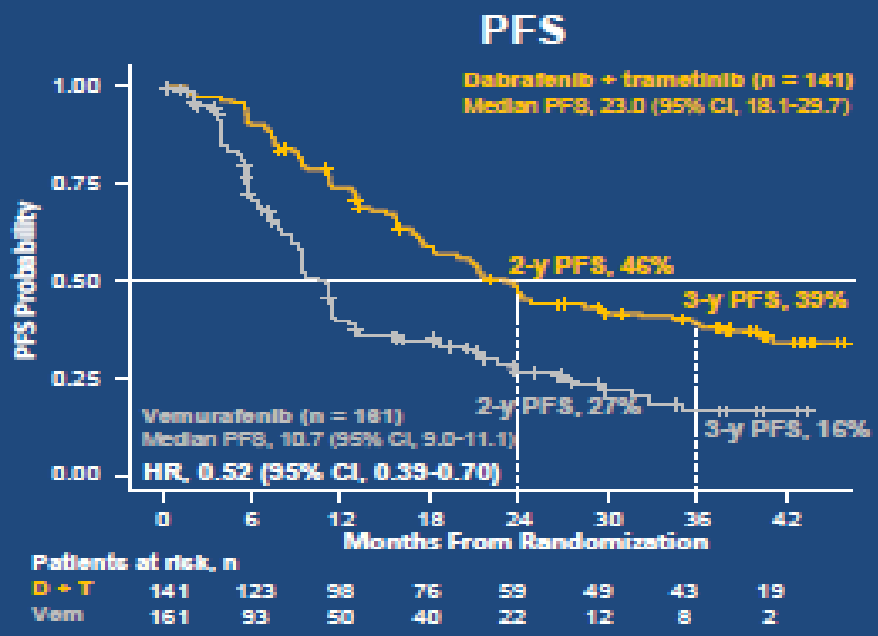
Patients at risk, n

D + T	233	187	136	105	80	68	59	25
Vem	238	130	70	48	24	13	9	2

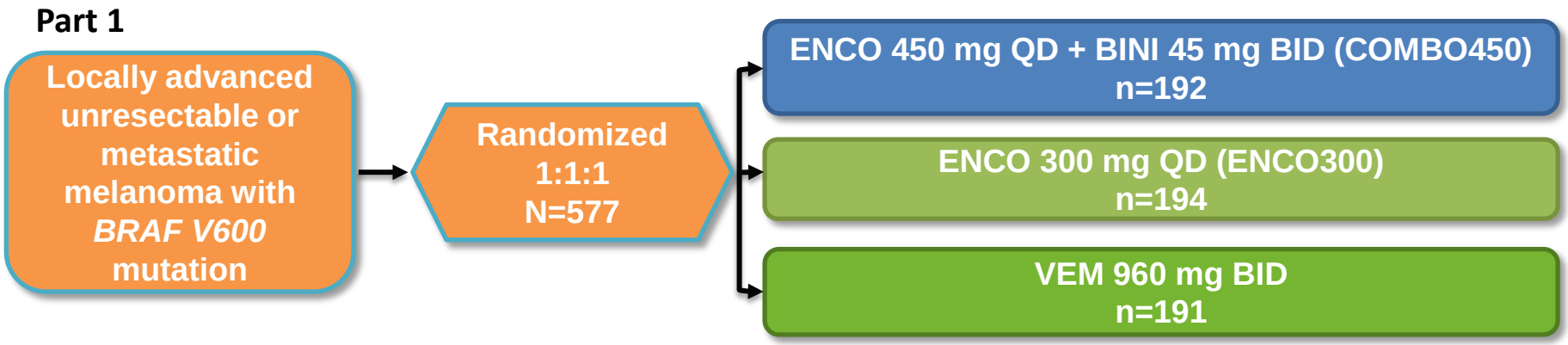
NR, not reached.

COMBI-v: Normal LDH and < 3 Organ Sites With Metastasis





Study Design and Objectives



- **Untreated or progressed on/after prior first-line immunotherapy**
- ***BRAF V600E* and/or *V600K***
- **ECOG PS 0–1**

Stratified by
- **AJCC stage**
- **ECOG status**
- ***BRAF* mutation status/prior first-line immunotherapy***

- **Primary endpoint: PFS† for COMBO450 vs VEM**
- **Key secondary endpoint (tested sequentially): PFS† for COMBO450 vs ENCO300**
- **Patient-reported outcomes: FACT-M, EORTC QLQ-C30**

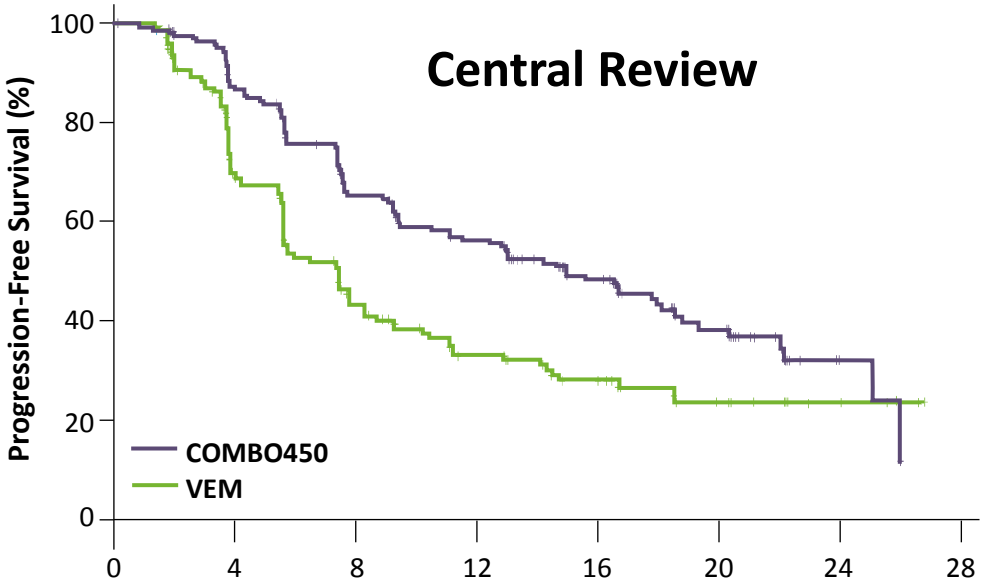
- Key secondary endpoint of overall survival for COMBO450 vs VEM not yet mature

Part 2 (ongoing): the primary objective is to further evaluate the contribution of BINI to combination therapy by comparing a lower dose of ENCO (300 mg QD) + BINI to single-agent ENCO (300 mg QD).

AJCC=American Joint Committee on Cancer; BID=twice daily; BINI=binimetinib; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; ECOG=Eastern Cooperative Oncology Group; ENCO=encorafenib; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-M=Functional Assessment of Cancer Therapy-Melanoma; PFS=progression-free survival; PS=performance status; QD=once daily; VEM=vemurafenib.
*Prior first-line immunotherapy replaced *BRAF* mutation status as a stratification factor after protocol amendment 2.
†PFS determined based on blinded independent radiology assessment.

Progression-Free Survival: COMBO450 vs VEM

Central Review



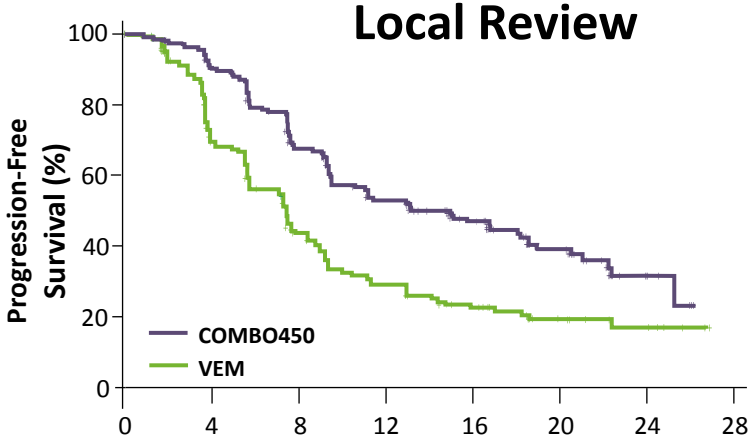
Patients at risk								
COMBO450	192	151	107	87	57	28	4	0
VEM	191	101	56	36	23	13	4	0

Median PFS in months (95% CI)

COMBO450	VEM
14.9 (11.0–18.5)	7.3 (5.6–8.2)

HR (95% CI), 0.54 (0.41–0.71)
P<0.001

Local Review



Patients at risk								
COMBO450	192	160	116	88	63	30	5	0
VEM	191	111	61	40	27	14	6	0

Median PFS in months (95% CI)

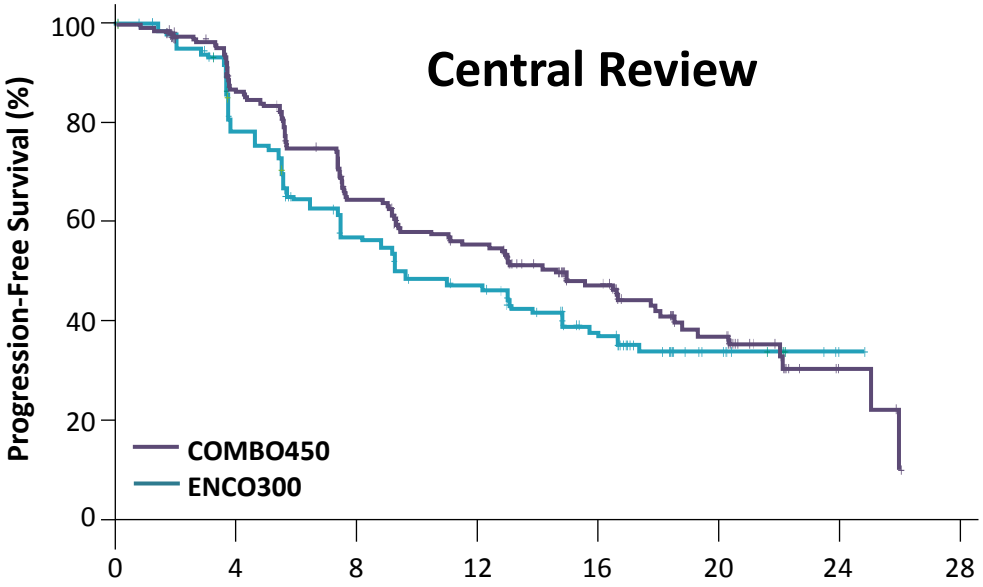
COMBO450	VEM
14.8 (10.4–18.4)	7.3 (5.7–8.5)

HR (95% CI), 0.49 (0.37–0.64)
P<0.001*

*Nominal *P* value.
BINI=binimetinib; CI=confidence interval; COMBO450=ENCO 450 mg QD + BINI 45 mg BID

Progression-Free Survival: COMBO450 vs ENCO300

Central Review



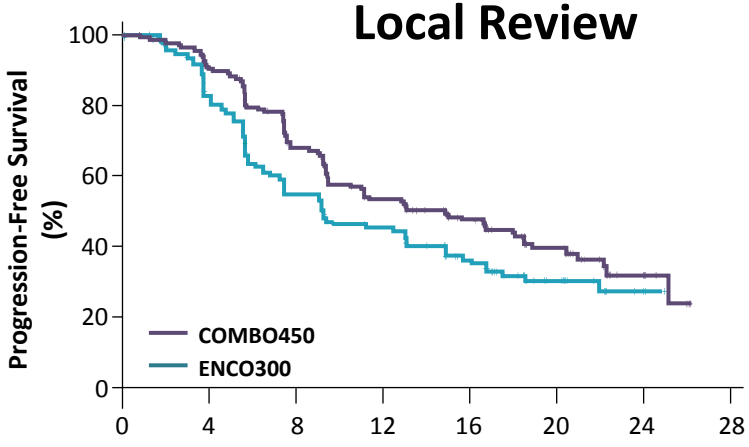
Patients at risk								
COMBO450	192	151	107	87	57	28	4	0
ENCO300	194	125	84	68	41	17	1	0

Median PFS in months (95% CI)

COMBO450	ENCO300
14.9 (11.0–18.5)	9.6 (7.5–14.8)

HR (95% CI), 0.75 (0.56–1.00)
P=0.051

Local Review



Patients at risk								
COMBO450	192	160	116	88	63	30	5	0
ENCO300	194	133	87	70	42	17	1	0

Median PFS in months (95% CI)

COMBO450	ENCO300
14.8 (10.4–18.4)	9.2 (7.4–12.9)

HR (95% CI), 0.68 (0.52–0.90)
P=0.006*

*Nominal *P* value.
BINI=binimetinib; CI=confidence interval; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; ENCO=encorafenib

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),* %	63 (56–70)	**75 (68–81)**	51 (43–58)	**58 (50–65)**	40 (33–48)	**49 (42–57)**
CR, %	8	16	5	9	6	7
PR, %	55	59	45	49	35	42
Median DOR (95% CI), mo	16.6 (12.7–20.4)	16.2 (11.1–20.4)	14.9 (11.0–NE)	14.8 (11.0–NE)	12.5 (6.9–16.9)	8.4 (5.8–11.0)
SD,† %	29	18	34	29	41	35
PD,‡ %	8	7	16	13	18	16
DCR (95% CI),§ %	92 (87–96)	93 (89–96)	84 (78–89)	87 (81–91)	82 (75–87)	84 (78–89)

BID=twice daily; BINI=binimetinib; CI=confidence interval; COMBO450=ENCO 450 mg QD + BINI 45 mg BID; CR=complete response; DCR=disease control rate; DOR=duration of response; ENCO=encorafenib; NE=not evaluable; ORR=overall response rate; PD=progressive disease; PR=partial response; QD=once daily; SD=stable disease; VEM=vemurafenib.

*ORR = CR + PR.

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

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

§DCR = CR + PR + SD.

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).

Phase III trials

	COMBI-D Dabrafenib &Trametinib vs. Dabrafenib	**COMBI-V** Dabrafenib &Trametinib vs. Vemurafenib	**Co-BRIM** Vemurafenib &Cobimetinib vs. Vemurafenib	**COLUMBUS** Encorafenib & Binimetinib vs. Encorafenib vs. Vemurafenib
Response Rate	69%	66%	70%	63%
Progression free survival	11.0m	12.0	12.3m	14.8m
Median Overall Survival	25.1	25.6	22.3m	NR*

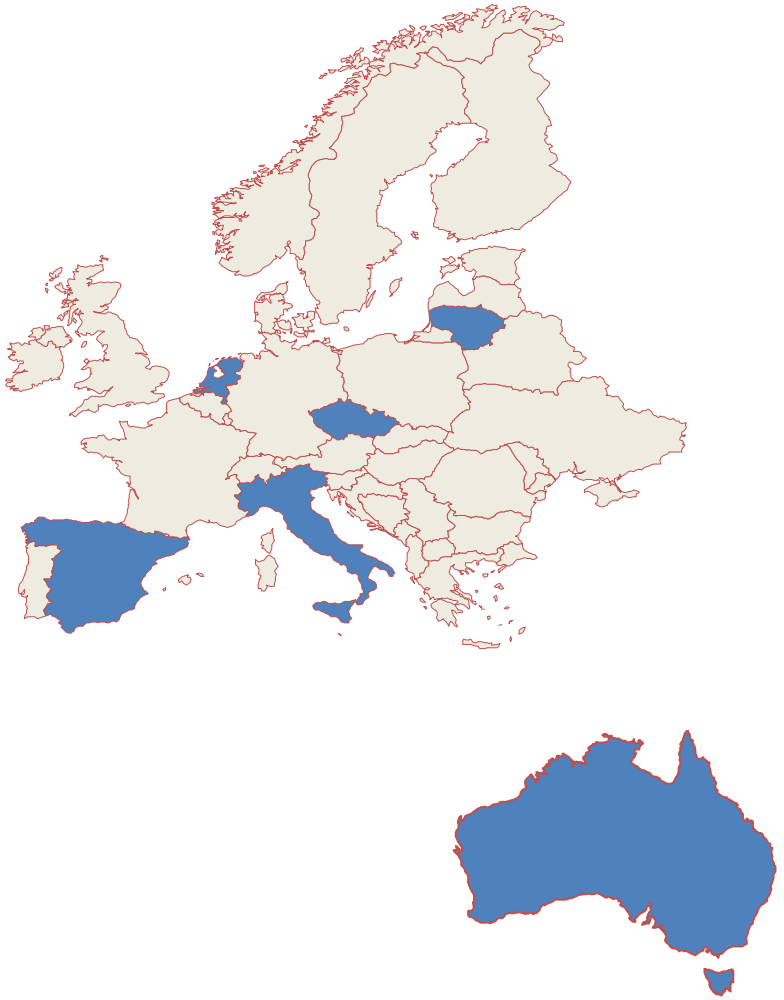
*COLOMBUS-reported SMR 2016-NO MEDIAN OS

Results only shown for combination arm of all trials

DESCRIBE-II: Dabrafenib + trametinib real-world study

Recruitment by country

Country, n (%)	N=271*
Australia	97 (35.8)
The Netherlands	58 (21.4)
Italy	57 (21.0)
Spain	28 (10.3)
Lithuania	24 (8.9)
Czech Republic	7 (2.6)



*Observed population.

Atkinson V, *et al*. Poster presented at ECC 2015, Abstract 3337.

DESCRIBE-II: Dabrafenib + trametinib real-world study

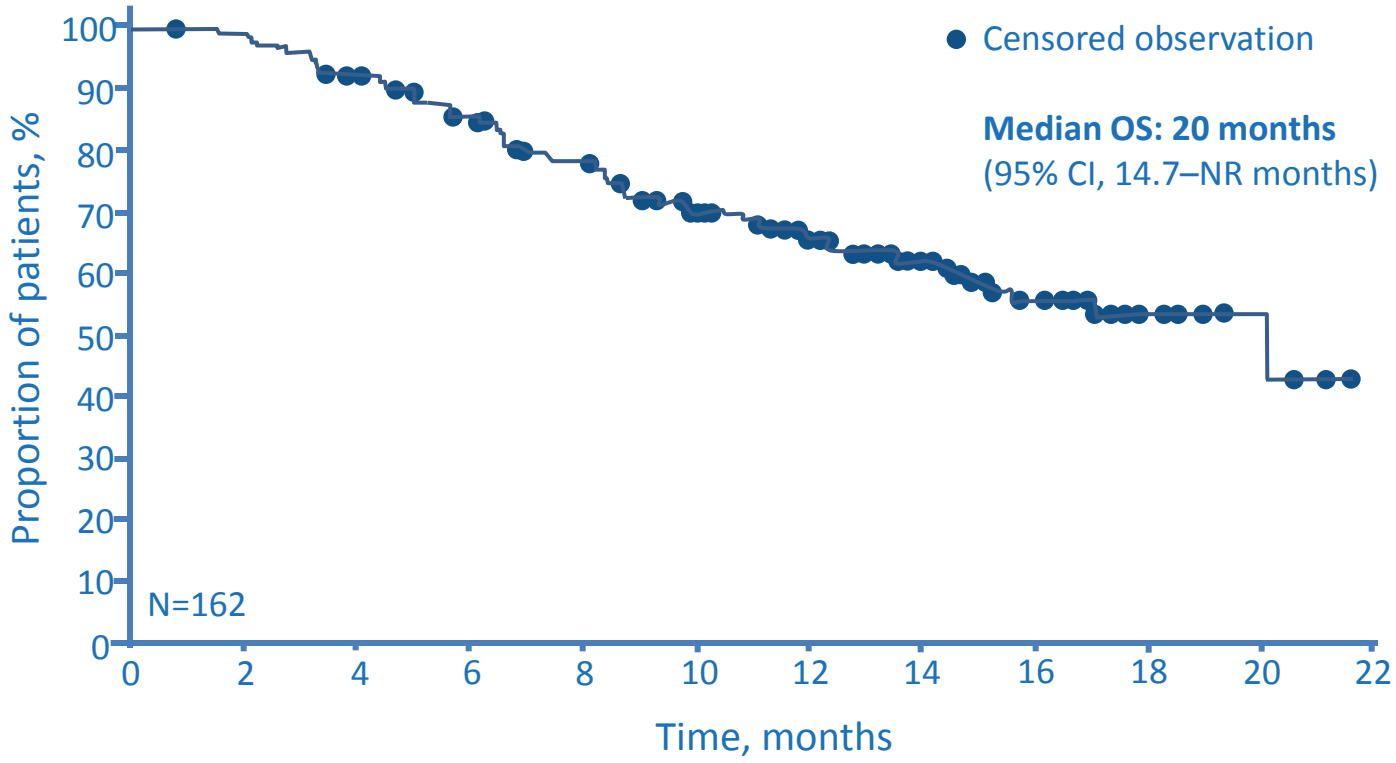
Patient and disease characteristics

Parameter	N=271*
Age, years	
Median	56
Range	22–87
Sex, n (%)	
Male	150 (55.4)
Female	121 (44.6)
Stage, n (%)	
IV	251 (92.6)
IIIc	20 (7.4)
Site of metastases, n (%)	
Visceral	169 (62.4)
Lymph nodes	136 (50.2)
Brain	99 (36.5)
Subcutaneous	88 (32.5)
Other	100 (36.9)
BRAF mutation status, n (%)#	N=219†
V600E	179 (81.7)
V600K	30 (13.7)
Other	10 (4.6)
ECOG PS, n (%)	N=167††
0	114 (68.3)
1	35 (21.0)
2	16 (9.6)
3	2 (1.2)

Atkinson V, *et al*. Poster presented at ECC 2015, Abstract 3337.

DESCRIBE-II: BRAF inhibitor-naïve population

OS



Number at risk	162	161	160	155	146	137	131	119	117	103	98	94	81	72	58	42	32	24	10	6	5	2	0

Atkinson V, *et al*. Poster presented at ECC 2015, Abstract 3337.

Key efficacy results	DESCRIBE CUP[1] (N=331)	Vemurafenib EAP[2] (N=2708)	DESCRIBE II CUP[3] BRAF-inhibitor naïve population (N=156)
ORR, %	45.9	34	69.9
Median PFS, months (95% CI)	5.2 (4.2–6.1)	5.6 (5.5–5.8)	7.5 (6.3–9.3)
Median OS, months (95% CI)	12.4 (10.2–15.0)	12.0 (11.9–13.3)	20 (14.7–NR)

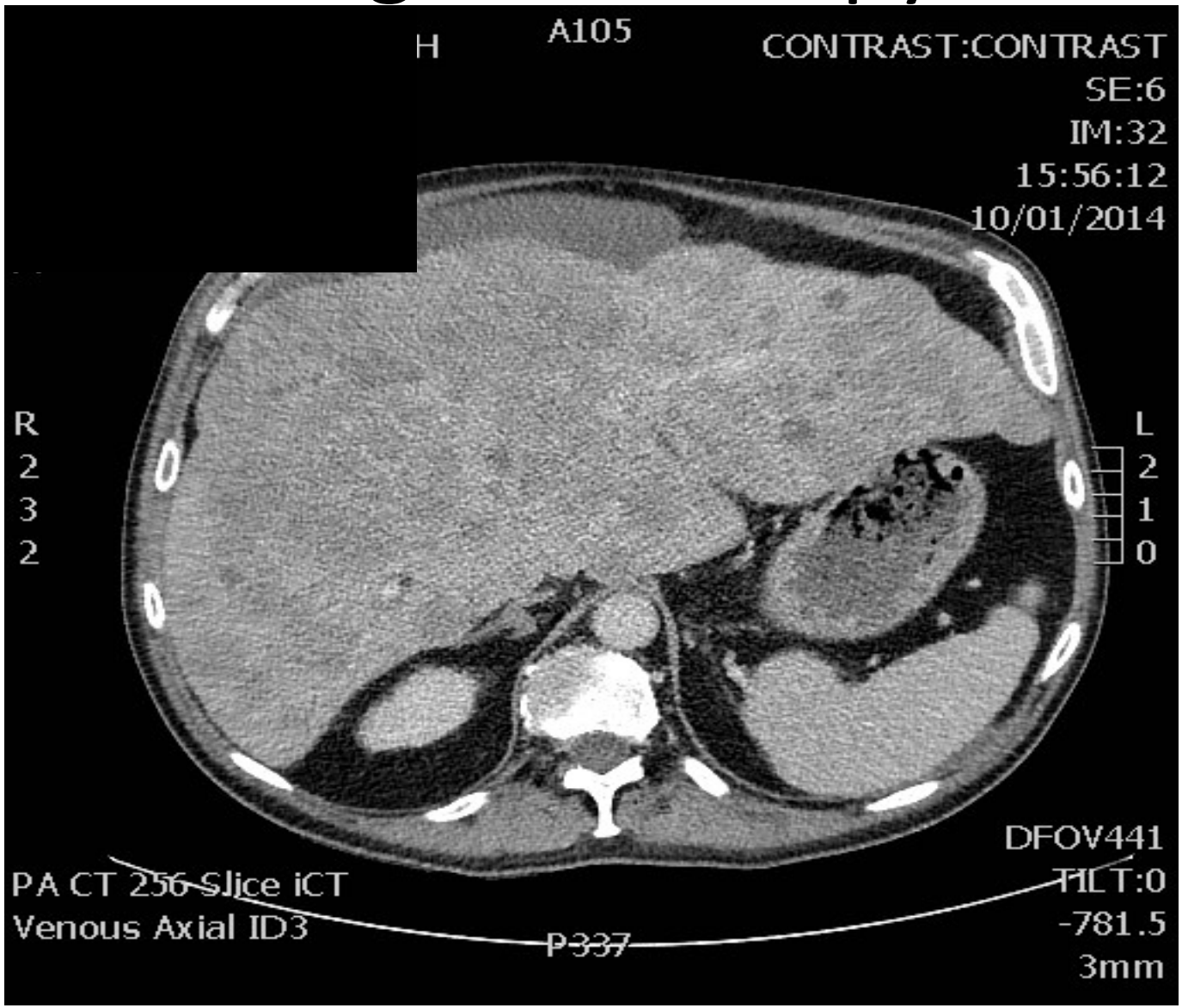
Phase III trials

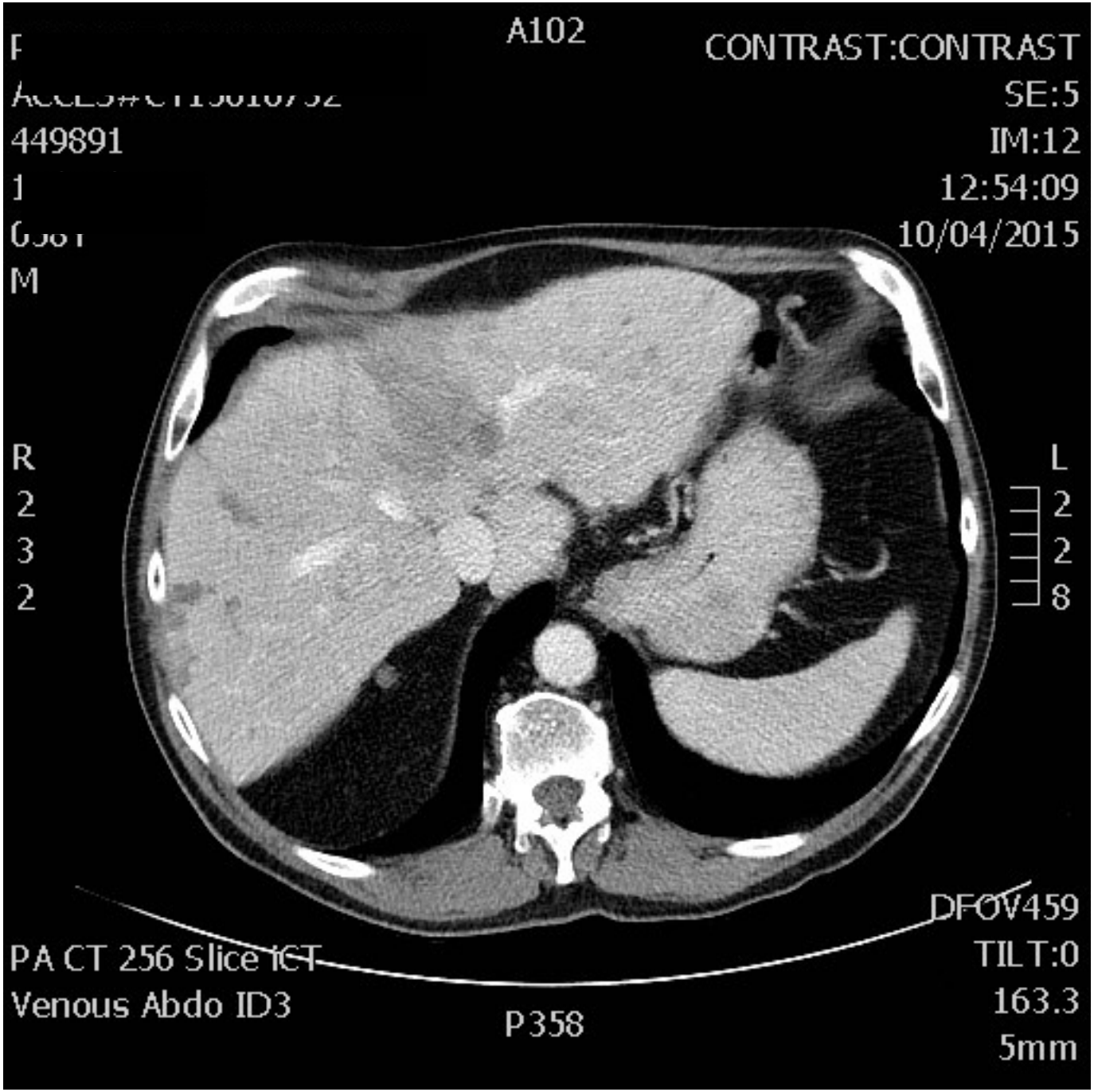
	COMBI-D Dabrafenib &Trametinib vs. Dabrafenib	**COMBI-V** Dabrafenib &Trametinib vs. Vemurafenib	**Co-BRIM** Vemurafenib &Cobimetinib vs. Vemurafenib	**COLUMBUS** Encorafenib & Binimetinib vs. Encorafenib vs. Vemurafenib
Response Rate	69%	66%	70%	63%
Progression free survival	11.0m	12.0	12.3m	14.8m
Median Overall Survival	25.1	25.6	22.3m	NR*

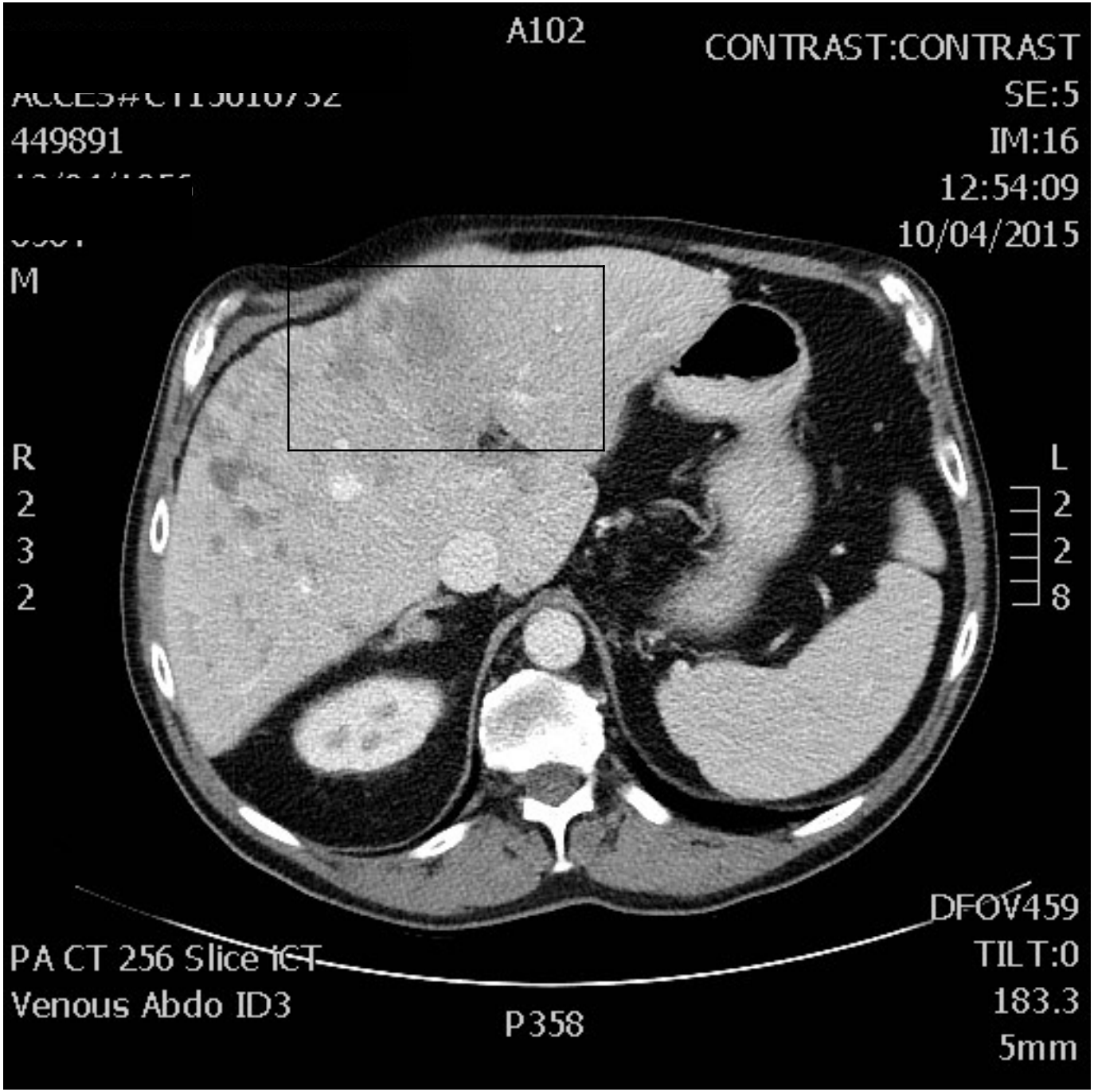
*COLOMBUS-reported SMR 2016-NO MEDIAN OS

Results only shown for combination arm of all trials

Targeted therapy

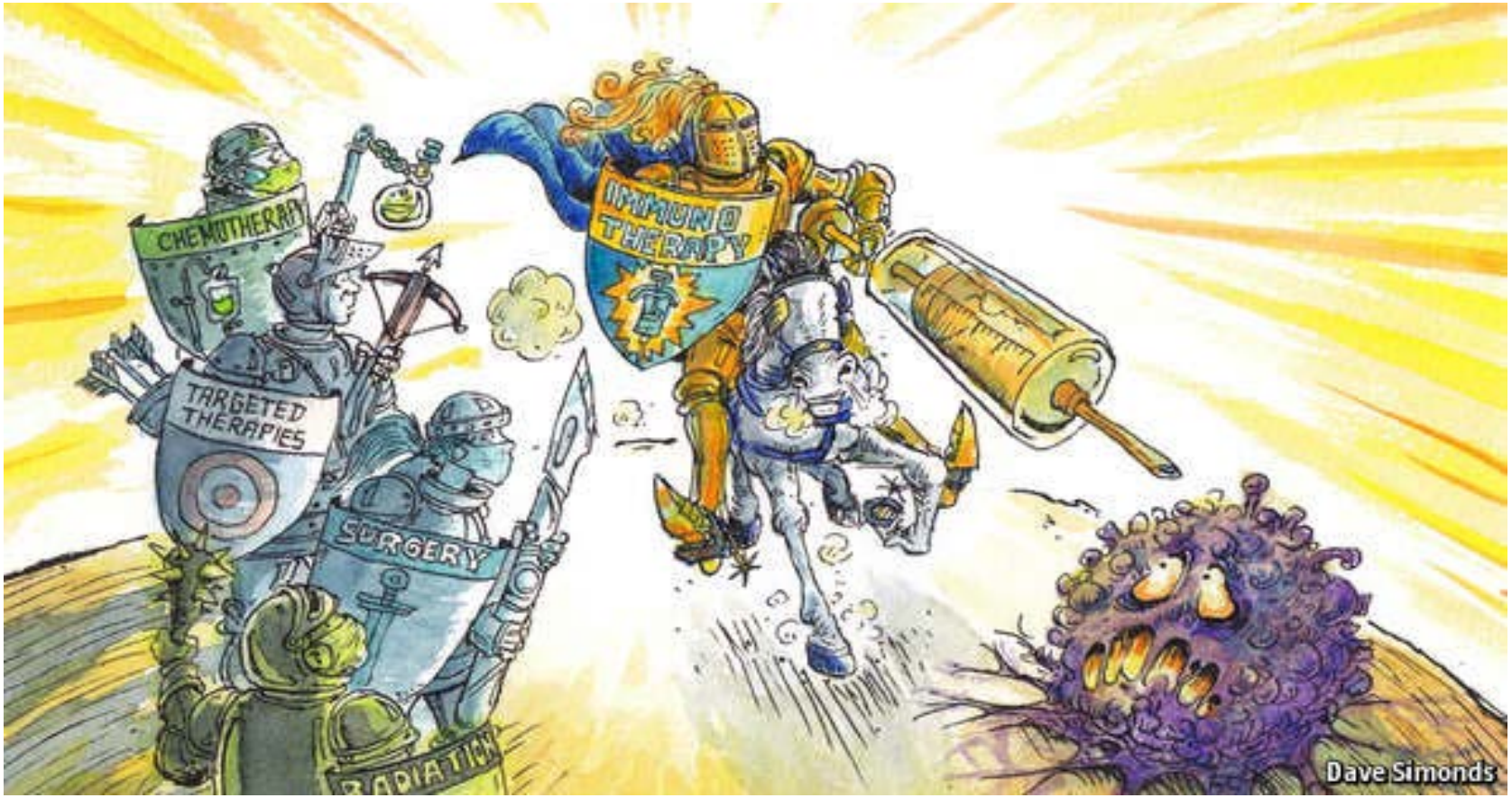



A102
CONTRAST:CONTRAST
SE:5
IM:12
12:54:09
10/04/2015
449891
M
R
L
2
3
2
2
8
DFOV459
TILT:0
163.3
5mm
PA CT 256 Slice ICT
Venous Abdo ID3
P358


A102
CONTRAST:CONTRAST
SE:5
449891
IM:16
12:54:09
10/04/2015
M
R
2
3
2
L
2
2
8
DFOV459
TILT:0
183.3
5mm
PA CT 256 Slice ICT
Venous Abdo ID3
P358

Targeted therapy

- Rapid onset of action- days
- Convenient (oral)
- High response rates
- Adverse events depend on choice of combination
- Can have durable response in certain sub-populations
- Likely not a cure

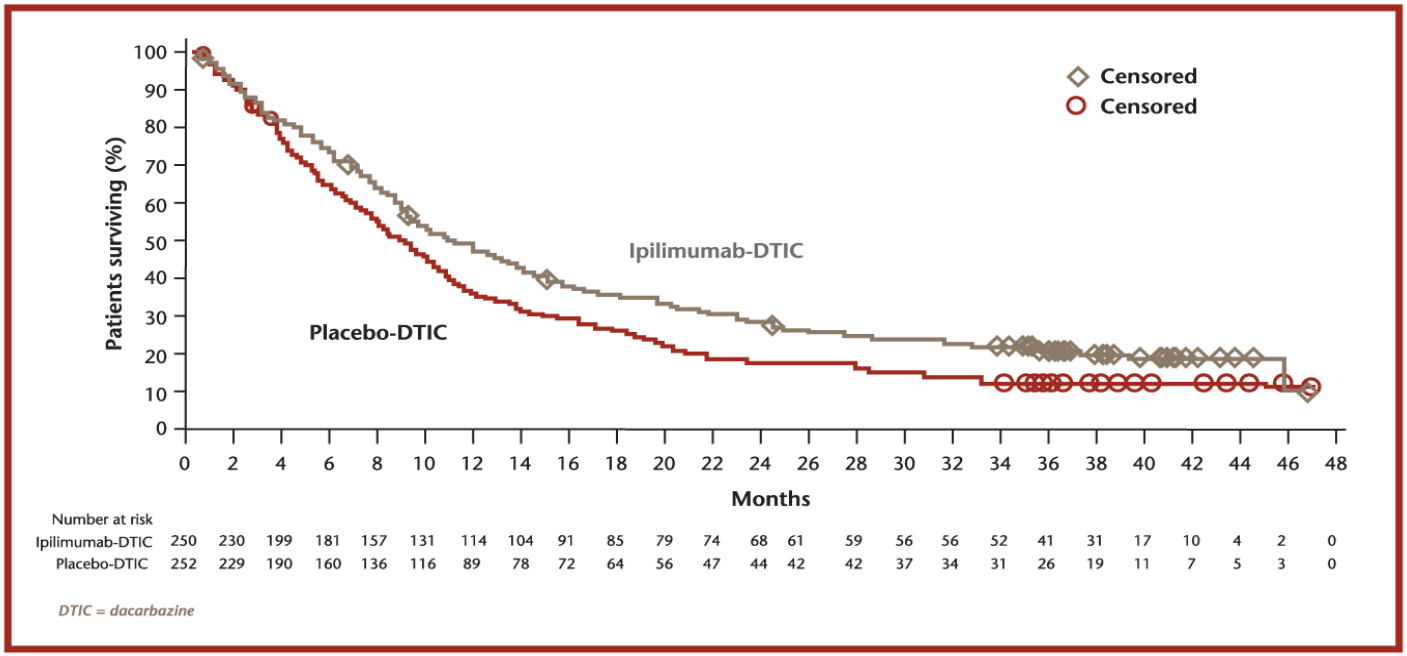


IMMUNOTHERAPY

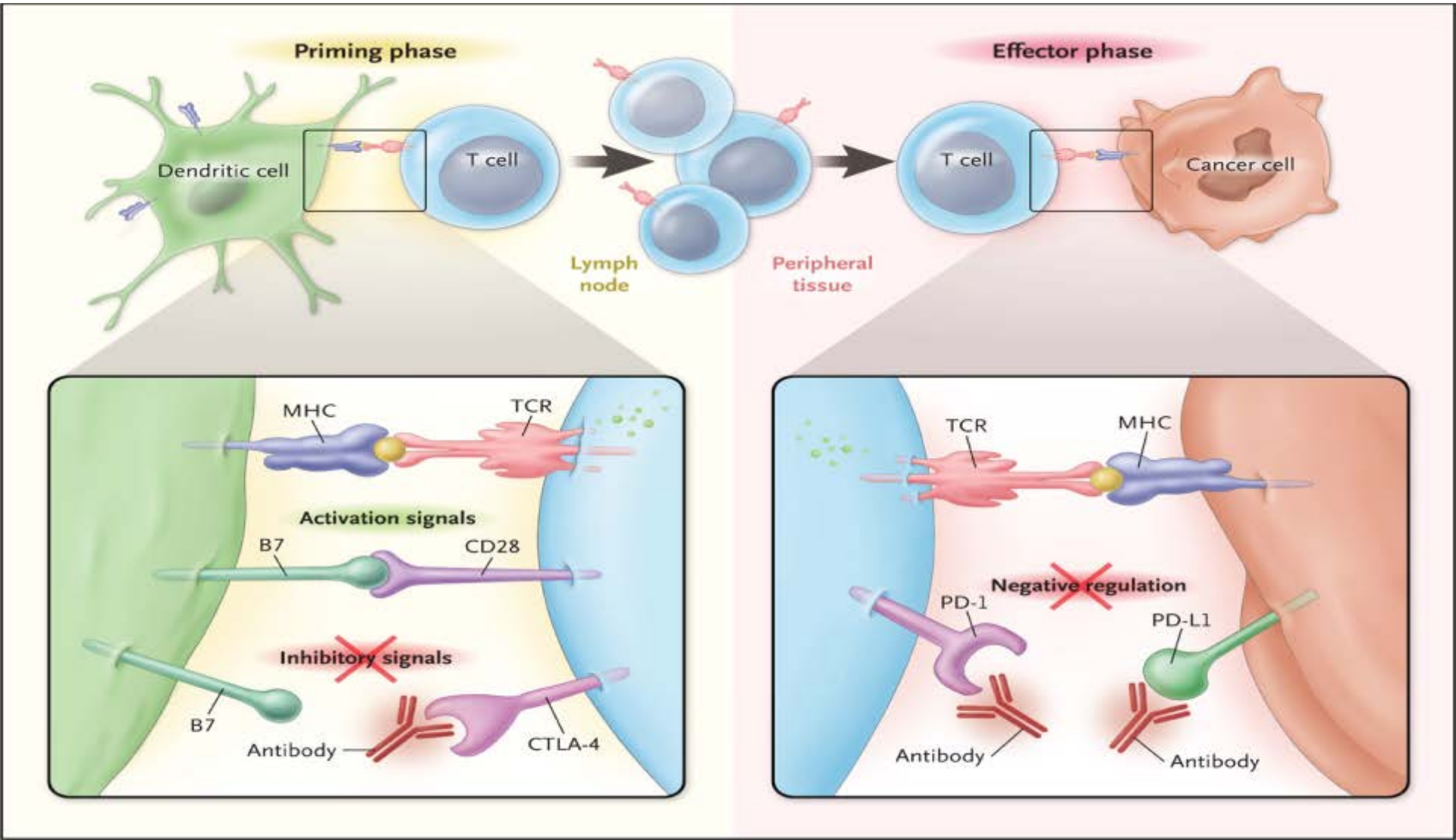
Immune system and melnaoma

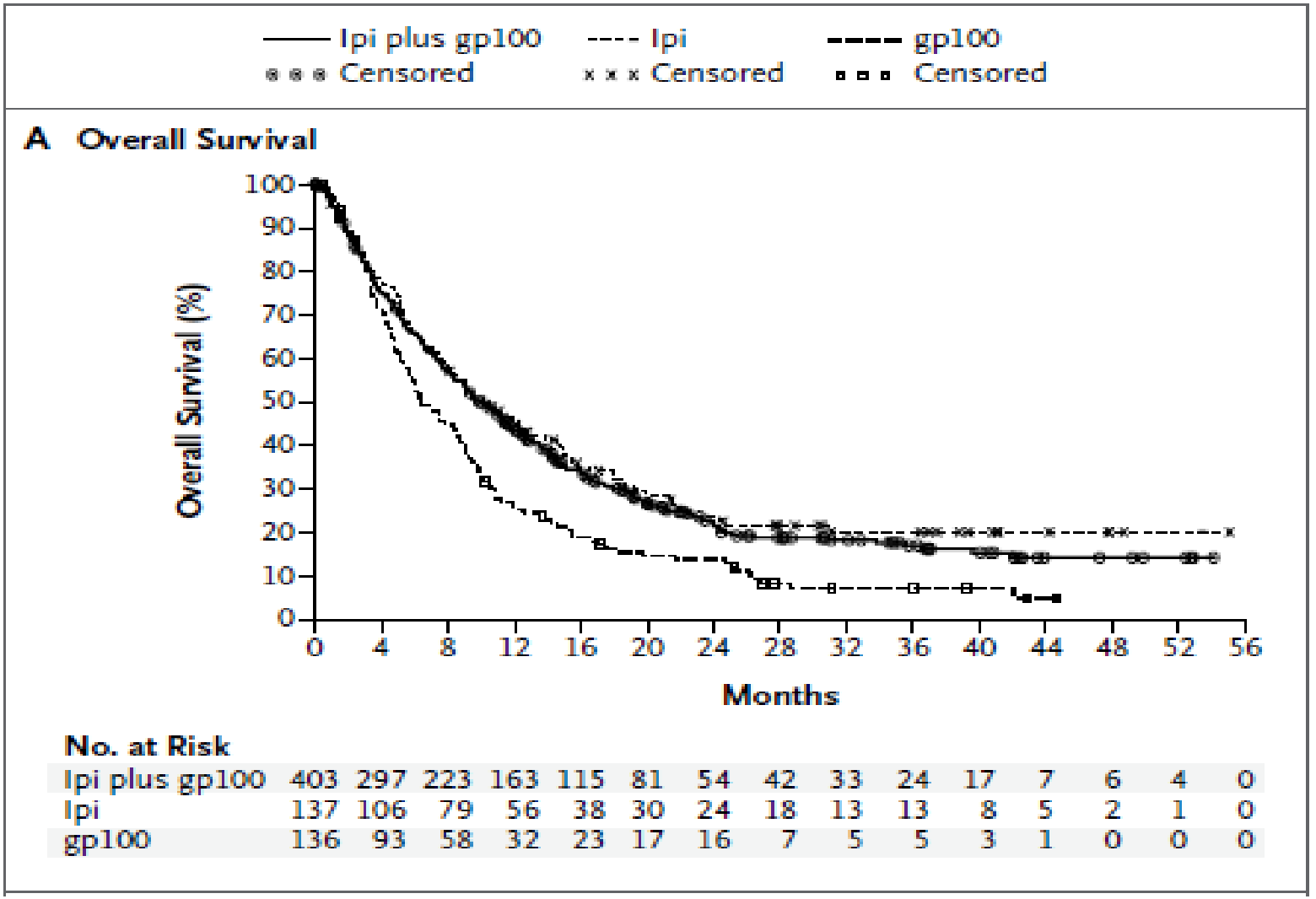
- 1st report of spontaneous remission in melanoma documented in 1860's
- For decades- there has been the "tail in the curve"

Figure 5. Overall survival for a phase III study of DTIC plus ipilimumab versus DTIC plus placebo in previously untreated metastatic melanoma patients[52]



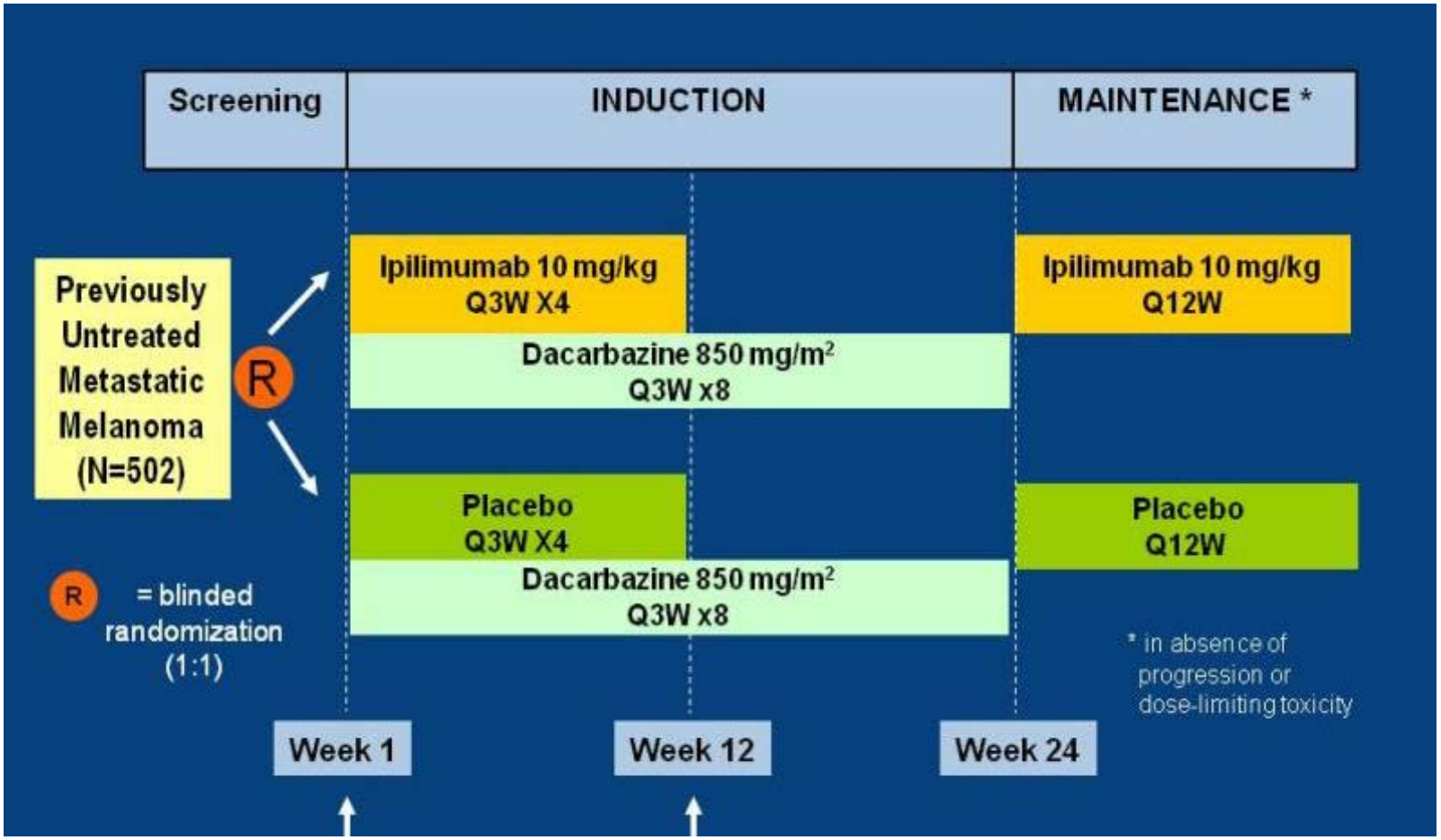
Immunotherapy





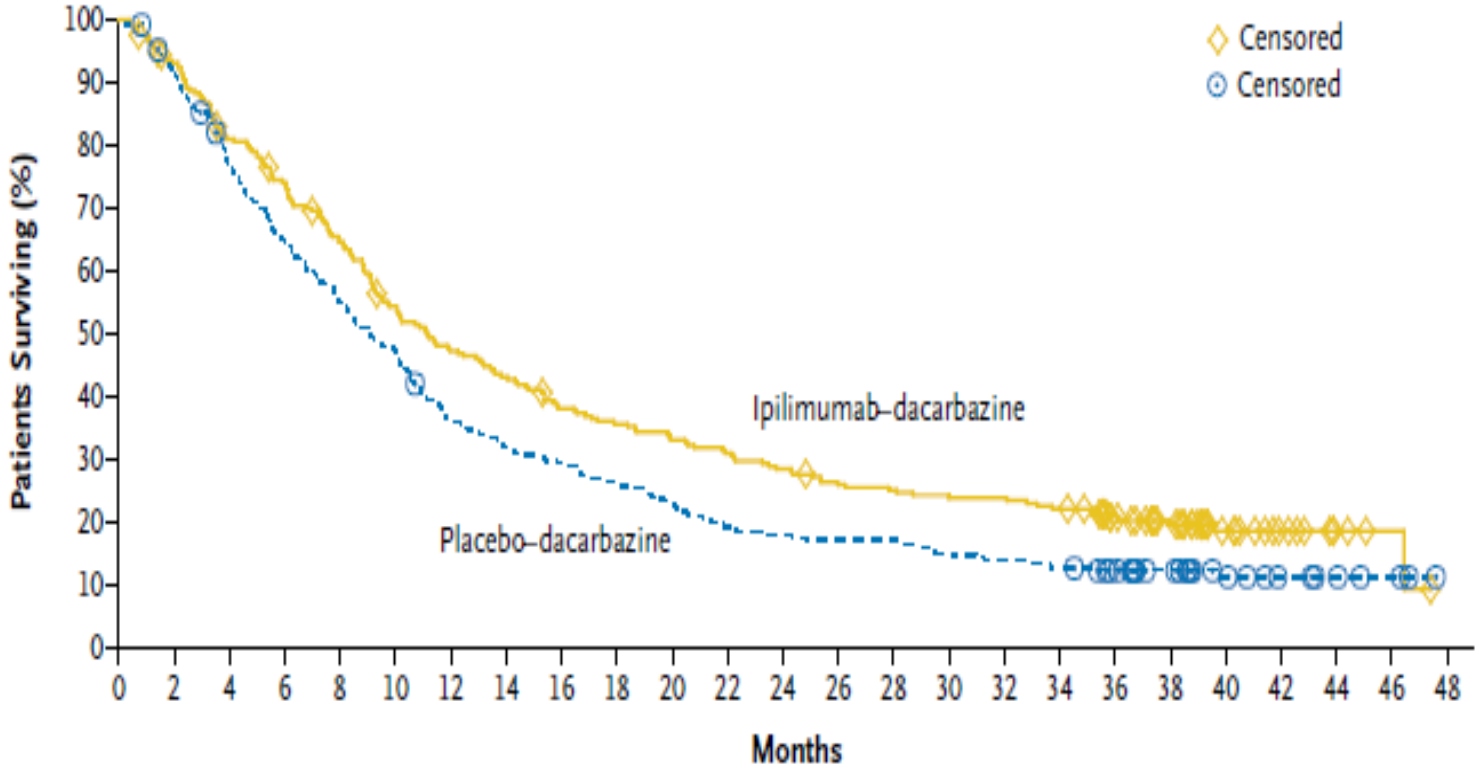
Hodi NEJM 2010

Ipilimumab and Dacarbazine



Roberts June 2011NEJM

A



No. at Risk

Ipilimumab–dacarbazine	250	230	199	181	157	131	114	104	91	85	79	74	68	61	59	56	56	52	41	31	17	10	4	2	0
Placebo–dacarbazine	252	229	190	160	136	116	89	78	72	64	56	47	44	42	42	37	34	31	26	19	11	7	5	3	0

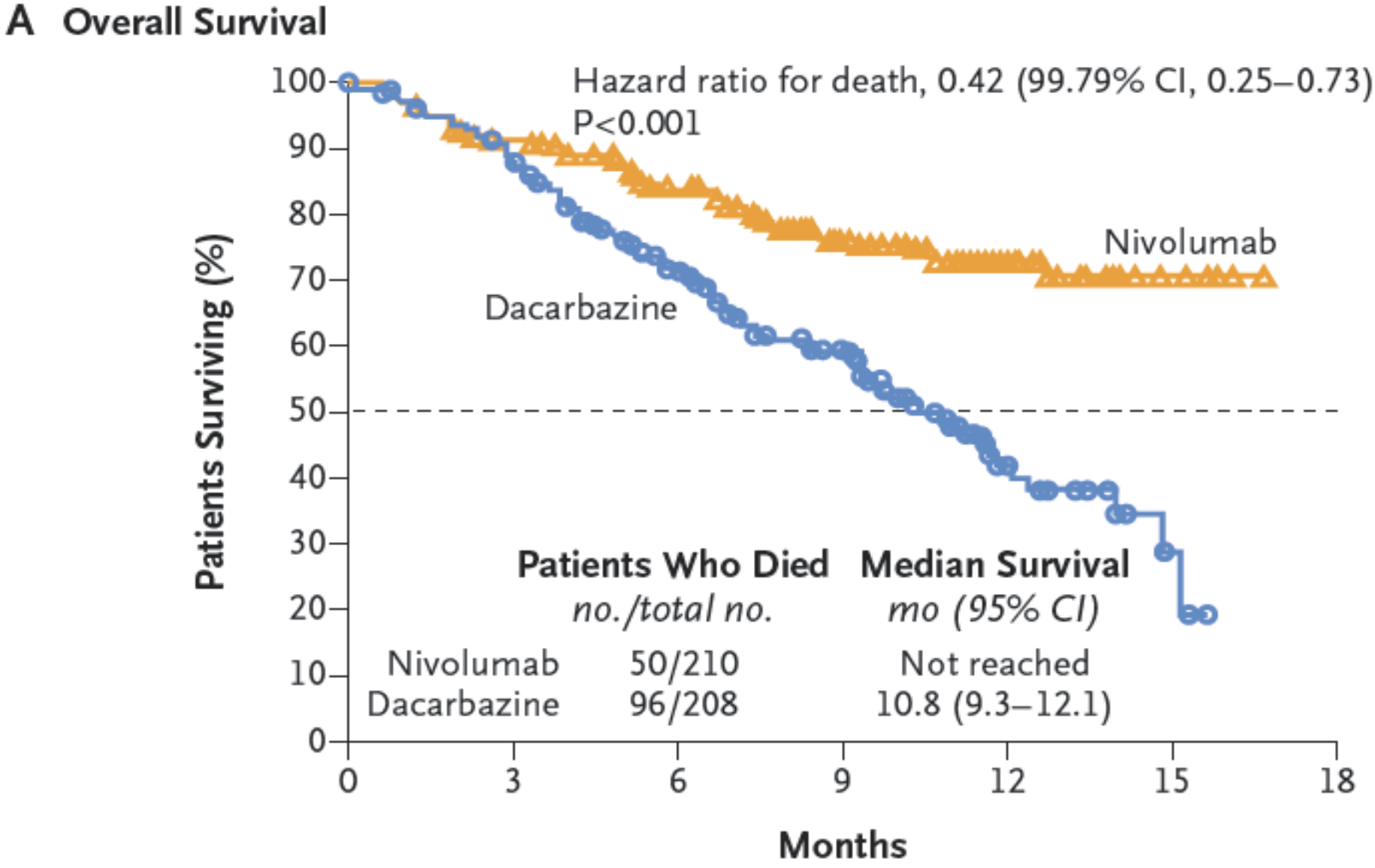
Median OS and Landmark OS Rates to 5 Years

Treatment Group	Median OS, months [95% CI]	Overall survival rate, % [95% CI]				
		1-year	2-year	3-year	4-year	5-year
Ipilimumab + DTIC (n=250)	11.2 [9.5-13.8]	47.6 [41.2-53.7]	28.9 [23.3-34.7]	**21.3 [16.3-26.6]**	**19.1 [14.4-24.3]**	**18.2 [13.6-23.4]**
Placebo + DTIC (n=252)	9.1 [7.8-10.5]	36.4 [30.4-42.4]	17.8 [13.3-22.8]	**12.1 [8.4-16.5]**	**9.7 [6.4-13.7]**	**8.8 [5.7-12.8]**

ORIGINAL ARTICLE

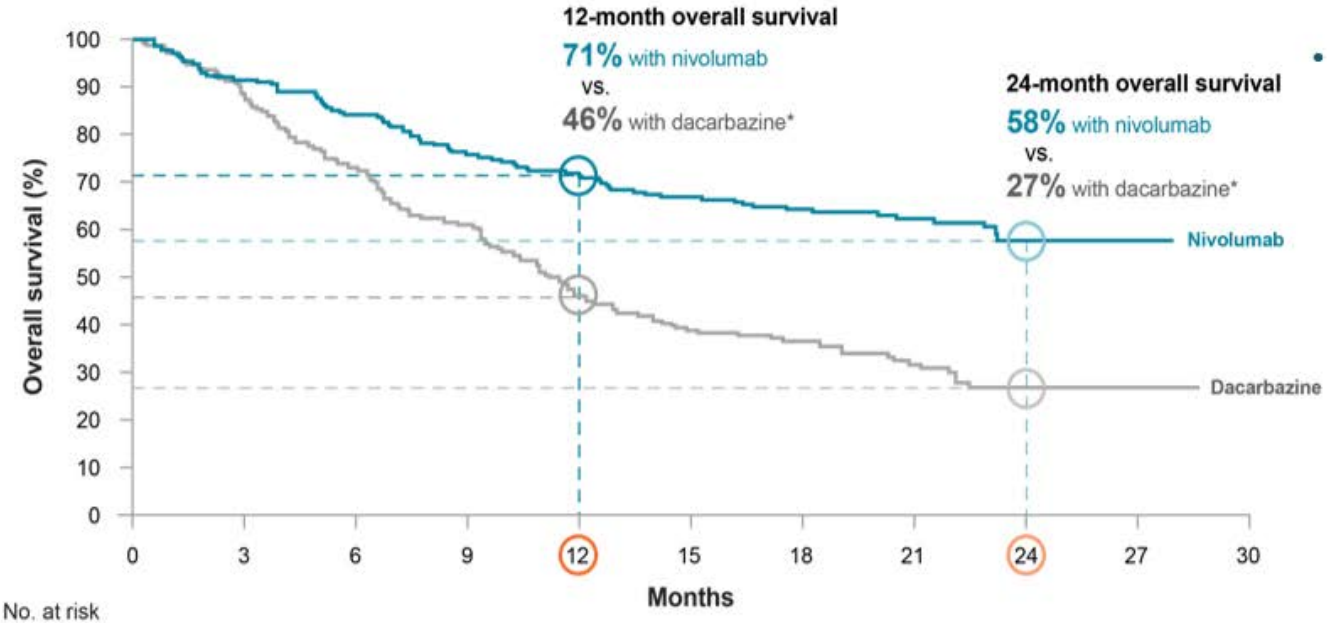
Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation

Caroline Robert, M.D., Ph.D., Georgina V. Long, M.D., Ph.D., Benjamin Brady, M.D., Caroline Dutriaux, M.D., Michele Maio, M.D., Laurent Mortier, M.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Catriona McNeil, M.D., Ph.D., Ewa Kalinka-Warzocha, M.D., Ph.D., Kerry J. Savage, M.D., Micaela M. Hernberg, M.D., Ph.D., Celeste Lebbé, M.D., Ph.D., Julie Charles, M.D., Ph.D., Catalin Mihalcioiu, M.D., Vanna Chiarion-Sileni, M.D., Cornelia Mauch, M.D., Ph.D., Francesco Cognetti, M.D., Ana Arance, M.D., Ph.D., Henrik Schmidt, M.D., D.M.Sc., Dirk Schadendorf, M.D., Helen Gogas, M.D., Lotta Lundgren-Eriksson, M.D., Christine Horak, Ph.D., Brian Sharkey, Ph.D., Ian M. Waxman, M.D., Victoria Atkinson, M.D., and Paolo A. Ascierto, M.D.


A Overall Survival
Hazard ratio for death, 0.42 (99.79% CI, 0.25–0.73)
P<0.001
Nivolumab
Dacarbazine
Patients Surviving (%)
100
90
80
70
60
50
40
30
20
10
0
Patients Who Died
no./total no.
Median Survival
mo (95% CI)
Nivolumab 50/210 Not reached
Dacarbazine 96/208 10.8 (9.3–12.1)
0 3 6 9 12 15 18
Months
No. at Risk
Nivolumab 210 185 150 105 45 8 0
Dacarbazine 208 177 123 82 22 3 0

CheckMate 066: Overall survival in treatment-naïve, *BRAF* wild-type, advanced melanoma (primary endpoint; updated analysis)[1,2]

Overall survival in *BRAF* WT advanced melanoma: Kaplan-Meier estimate[1]



- **Nivolumab reduced the risk of death by 57% vs. dacarbazine**
  – median overall survival not reached (95% CI 23.1–NR) vs. 11.2 months (95% CI 9.6–13.0; HR=0.43; 95% CI 0.33–0.57; p<0.001)[1]

*p-value for 12-month and 24-month overall survival not reported.

Adapted from Atkinson V *et al.* (SMR 2015).[1] Phase III study of nivolumab monotherapy (3 mg/kg; q2w) vs. dacarbazine (1000 mg/kg; q3w) in 418 treatment-naïve *BRAF* wild-type advanced (unresectable stage III or metastatic stage IV) melanoma patients. Median follow-up for overall survival was 18.5 months for nivolumab vs. 10.9 months for dacarbazine.[1,2]

CI=confidence interval; HR=hazard ratio; NIVO=nivolumab; NR=not reached; WT=wild-type.

References: 1. Atkinson V *et al.* Two-year survival and safety update in patients with treatment-naïve advanced melanoma receiving nivolumab or dacarbazine in CheckMate 066. Presented at the 12th International Congress of the Society for Melanoma Research; 18–21 November 2015; San Francisco, CA, USA (abstract).
2. Robert C *et al. N Engl J Med* 2015;372:320–30.

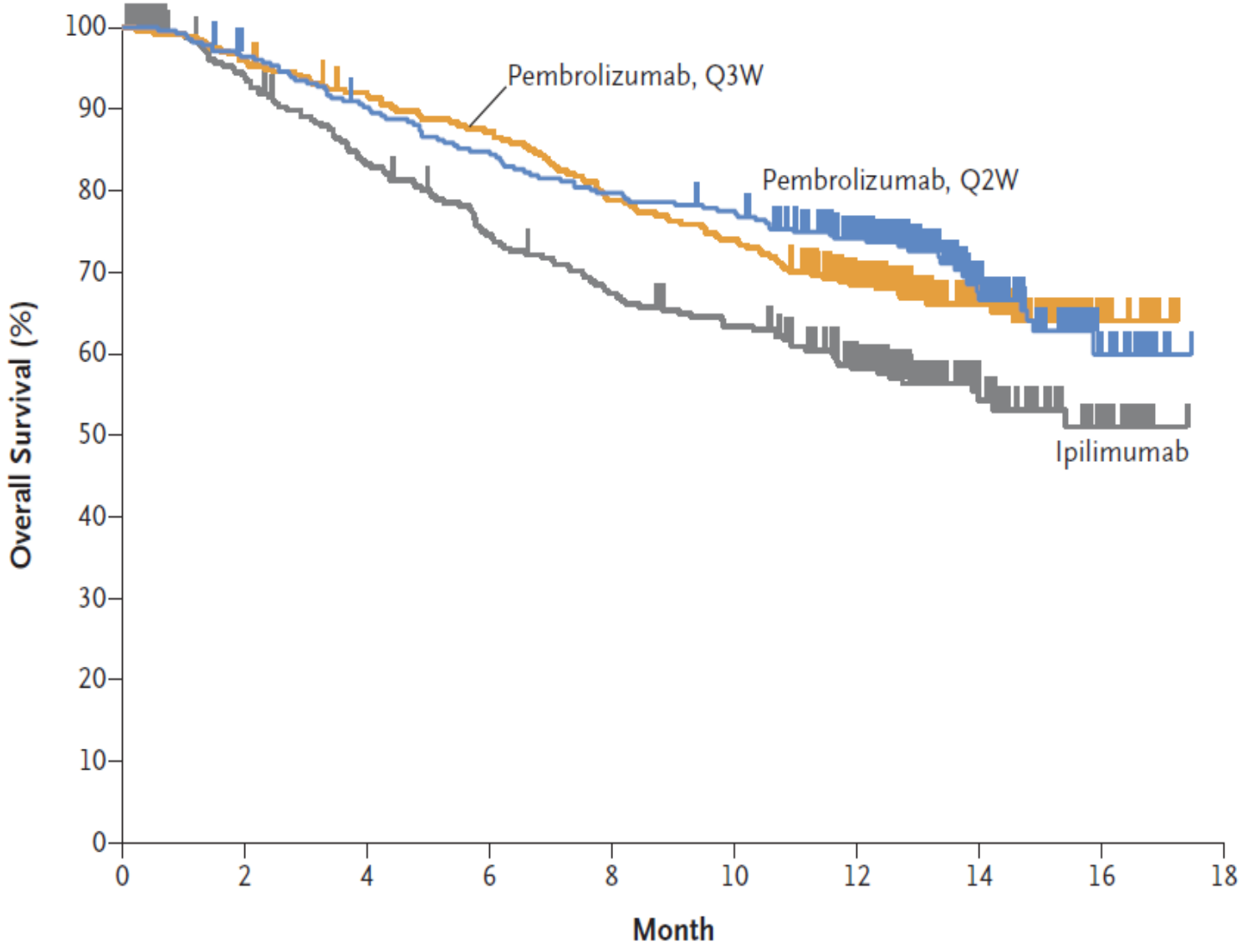
ORIGINAL ARTICLE

Pembrolizumab versus Ipilimumab in Advanced Melanoma

Caroline Robert, M.D., Ph.D., Jacob Schachter, M.D., Georgina V. Long, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean Jacques Grob, M.D., Ph.D., Laurent Mortier, M.D., Ph.D., Adil Daud, M.D., Matteo S. Carlino, M.B., B.S., Catriona McNeil, M.D., Ph.D., Michal Lotem, M.D., James Larkin, M.D., Ph.D., Paul Lorigan, M.D., Bart Neyns, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Omid Hamid, M.D., Christine Mateus, M.D., Ronnie Shapira-Frommer, M.D., Michele Kosh, R.N., B.S.N., Honghong Zhou, Ph.D., Nageatte Ibrahim, M.D., Scot Ebbinghaus, M.D., and Antoni Ribas, M.D., Ph.D., for the KEYNOTE-006 investigators*

ABSTRACT

B Overall Survival



No. at Risk

Pembrolizumab, Q2W	279	266	248	233	219	212	177	67	19	0
Pembrolizumab, Q3W	277	266	251	238	215	202	158	71	18	0
Ipilimumab	278	242	212	188	169	157	117	51	17	0

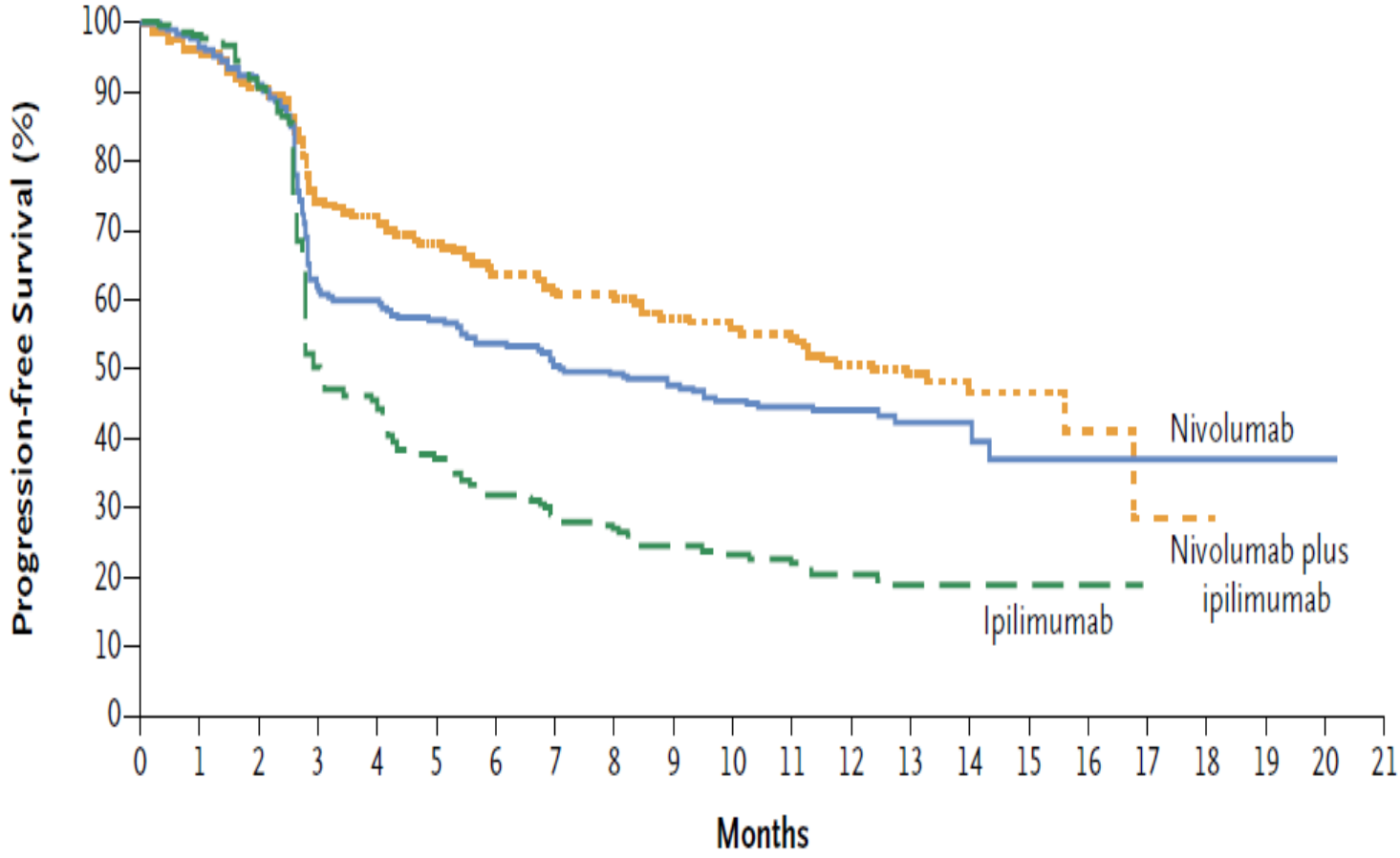
ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao, D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill, J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Marquez-Rodas, G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahan, M.A. Postow, K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak, F.S. Hodi, and J.D. Wolchok

ABSTRACT

A Intention-to-Treat Population



No. at Risk

Nivolumab	316	292	271	177	170	160	147	136	132	124	106	86	50	38	14	9	6	2	1	1	1	0
Nivolumab plus ipilimumab	314	293	275	219	208	191	173	164	163	151	137	116	65	54	18	11	7	2	1	0	0	0
Ipilimumab	315	285	265	137	118	95	77	68	63	54	47	42	24	17	7	4	3	0	0	0	0	0

AACR American Association for Cancer Research
ANNUAL MEETING 2017 WASHINGTON, DC

Abstract Number CT075

Overall Survival Results From a Phase III Trial of Nivolumab Combined With Ipilimumab in Treatment-naïve Patients With Advanced Melanoma (CheckMate 067)

James Larkin,[1] Vanna Chiarion-Sileni,[2] Rene Gonzalez,[3] Piotr Rutkowski,[4] Jean-Jacques Grob,[5] C. Lance Cowey,[6] Christopher D. Lao,[7] Dirk Schadendorf,[8] Pier Francesco Ferrucci,[9] Michael Smylie,[10] Reinhard Dummer,[11] Andrew Hill,[12] John Haanen,[13] Michele Maio,[14] Grant McArthur,[15] Dana Walker,[16] Linda Rollin,[16] Christine Horak,[16] F. Stephen Hodi,[17,*] Jedd D. Wolchok[18,*]

[1]Royal Marsden Hospital, London, UK; [2]Oncology Institute of Veneto IRCCS, Padua, Italy; [3]University of Colorado Cancer Center, Denver, CO, USA; [4]Maria Sklodowska-Curie Memorial Cancer Center & Institute of Oncology, Warsaw, Poland; [5]Hospital de la Timone, Marseille, France; [6]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [7]University of Michigan, Ann Arbor, MI, USA; [8]Department of Dermatology, University of Essen, Essen, Germany; [9]European Institute of Oncology, Milan, Italy; [10]Cross Cancer Institute, Alberta, Canada; [11]Universitäts Spital, Zurich, Switzerland; [12]Tasman Oncology Research, QLD, Australia; [13]Netherlands Cancer Institute, Amsterdam, The Netherlands; [14]University Hospital of Siena, Siena, Italy; [15]Peter MacCallum Cancer Centre, Victoria, Australia; [16]Bristol-Myers Squibb, Princeton, NJ, USA; [17]Dana-Farber Cancer Institute, Boston, MA, USA; [18]Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; *Contributed equally to this study.

Updated Response To Treatment

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
ORR, % (95% CI)*	**58.9** (53.3–64.4)	**44.6** (39.1–50.3)	**19.0** (14.9–23.8)
Best overall response — %			
Complete response	17.2	14.9	4.4
Partial response	41.7	29.7	14.6
Stable disease	11.5	9.8	21.3
Progressive disease	23.6	38.6	51.1
Unknown	6.1	7.0	8.6
Median duration of response, months (95% CI)	**NR** (NR–NR)	**31.1** (31.1–NR)	**18.2** (8.3–NR)

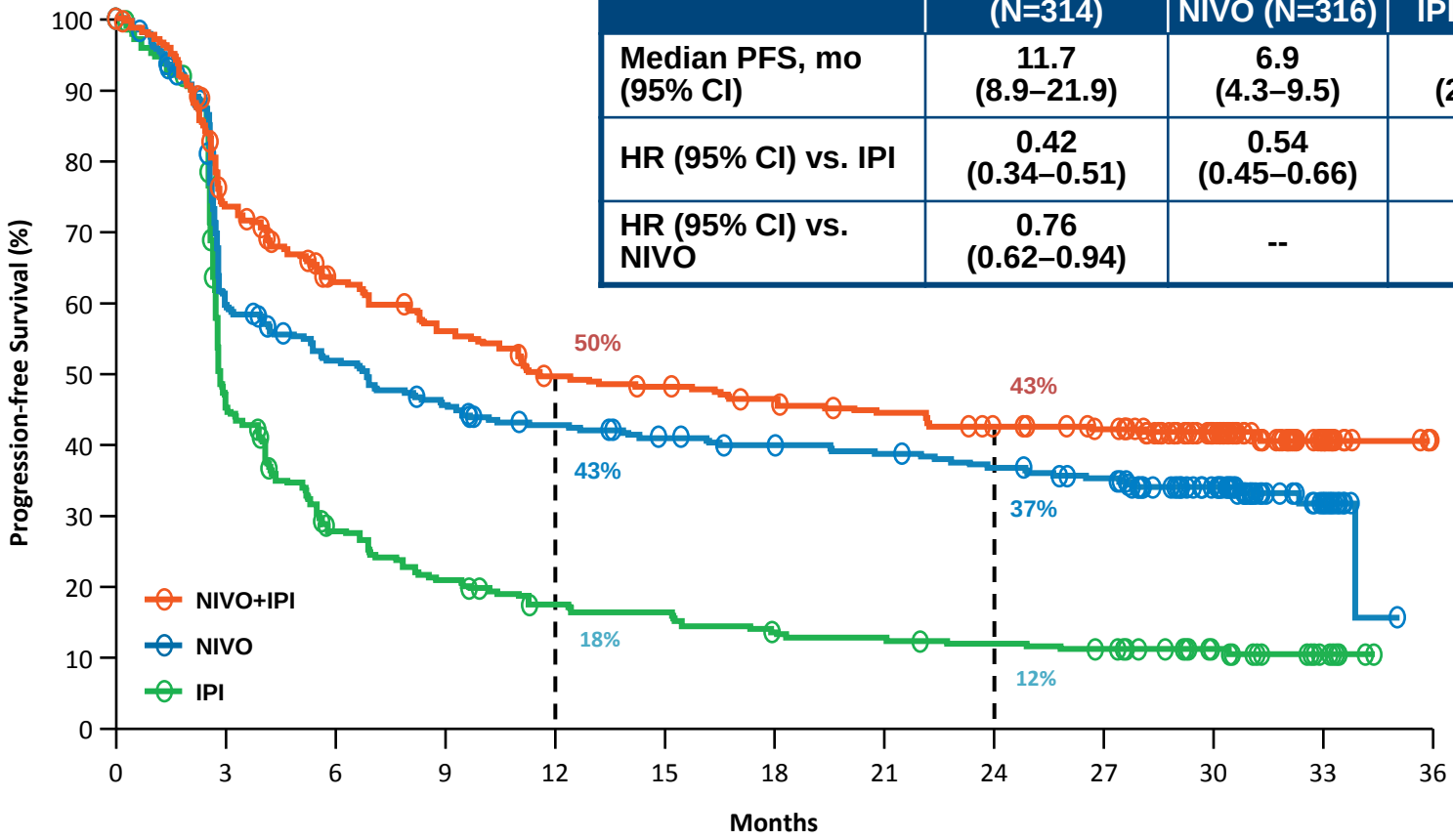
*By RECIST v1.1; NR = not reached

- At the 18-month DBL, the CR rate for NIVO+IPI, NIVO and IPI was 12.1%, 9.8% and 2.2%, respectively

Database lock: Sept 13, 2016, minimum f/u of 28 months

Updated Progression-Free Survival

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, mo (95% CI)	11.7 (8.9–21.9)	6.9 (4.3–9.5)	2.9 (2.8–3.2)
HR (95% CI) vs. IPI	0.42 (0.34–0.51)	0.54 (0.45–0.66)	--
HR (95% CI) vs. NIVO	0.76 (0.62–0.94)	--	--



Patients at risk:

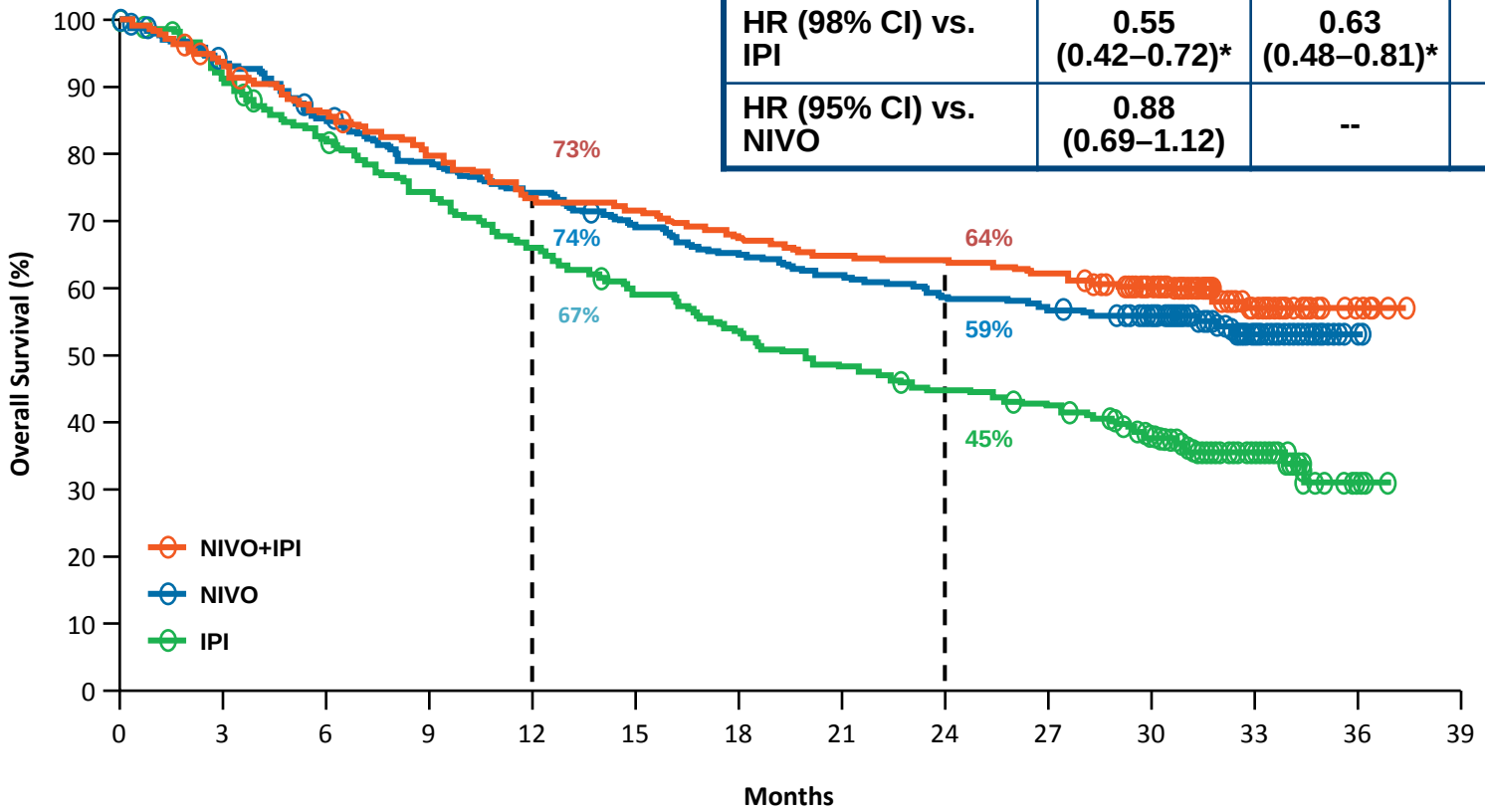
NIVO+ IPI	314	218	176	156	137	132	125	118	110	104	71	16	0
NIVO	316	178	151	132	120	112	107	103	97	88	62	16	0
IPI	315	136	77	58	46	43	35	33	30	27	16	5	0

Database lock: Sept 13, 2016, minimum f/u of 28 months

Overall Survival

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median OS, mo (95% CI)	NR	NR (29.1–NR)	20.0 (17.1–24.6)
HR (98% CI) vs. IPI	0.55 (0.42–0.72)*	0.63 (0.48–0.81)*	--
HR (95% CI) vs. NIVO	0.88 (0.69–1.12)	--	--

*P<0.0001



Patients at risk:

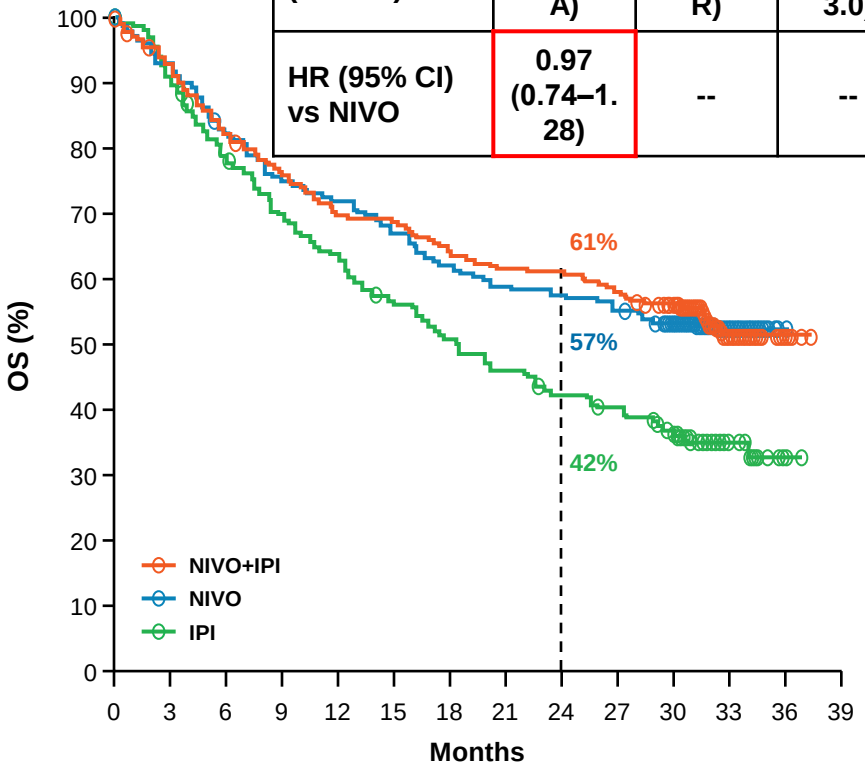
NIVO+IPI	314	292	265	247	226	221	209	200	198	192	170	49	7	0
NIVO	316	292	265	244	230	213	201	191	181	175	157	55	3	0
IPI	315	285	254	228	205	182	164	149	136	129	104	34	4	0

Database lock: Sept 13, 2016, minimum f/u of 28 months

OS in Patients with *BRAF* Wild-type and Mutant Tumors

BRAF Wild-type

	NIVO+IPI	NIVO	IPI
Median, mo (95% CI)	NR (27.6–NA)	NR (25.8–NR)	18.5 (14.8–23.0)
HR (95% CI) vs NIVO	0.97 (0.74–1.28)	--	--

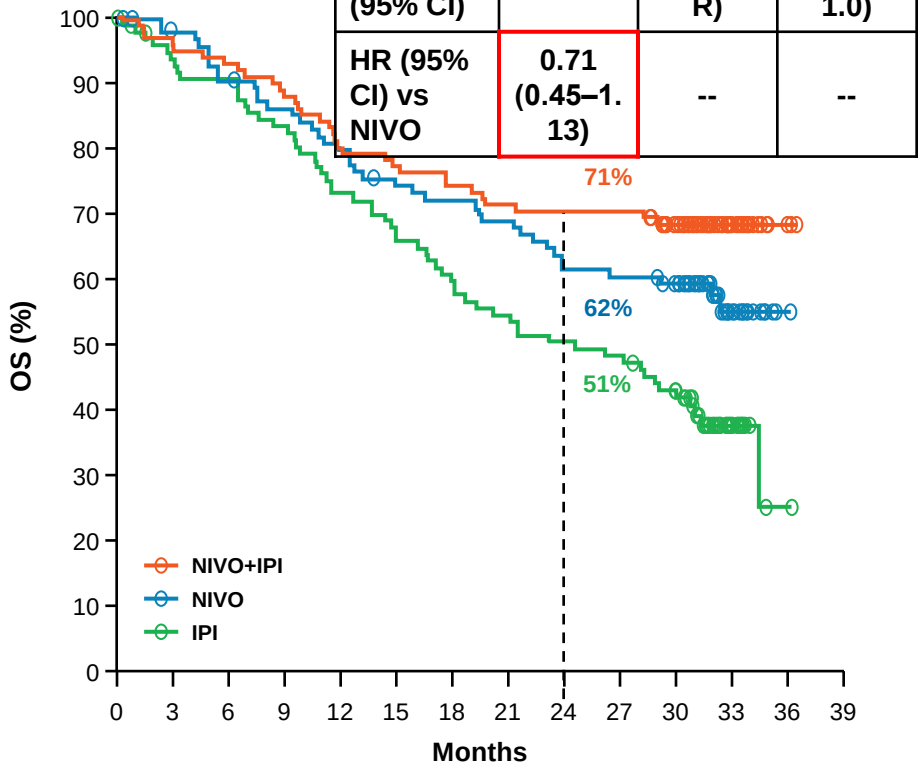


Patients at risk:

NIVO+IPI	212	194	170	157	144	142	133	127	126	120	108	31	5	0
NIVO	218	199	179	163	155	144	134	127	124	119	105	38	2	0
IPI	215	194	166	147	134	118	106	96	87	82	67	21	3	0

BRAF Mutant

	NIVO+IPI	NIVO	IPI
Median, mo (95% CI)	NR	NR (26.4–NR)	24.6 (17.9–31.0)
HR (95% CI) vs NIVO	0.71 (0.45–1.13)	--	--



Patients at risk:

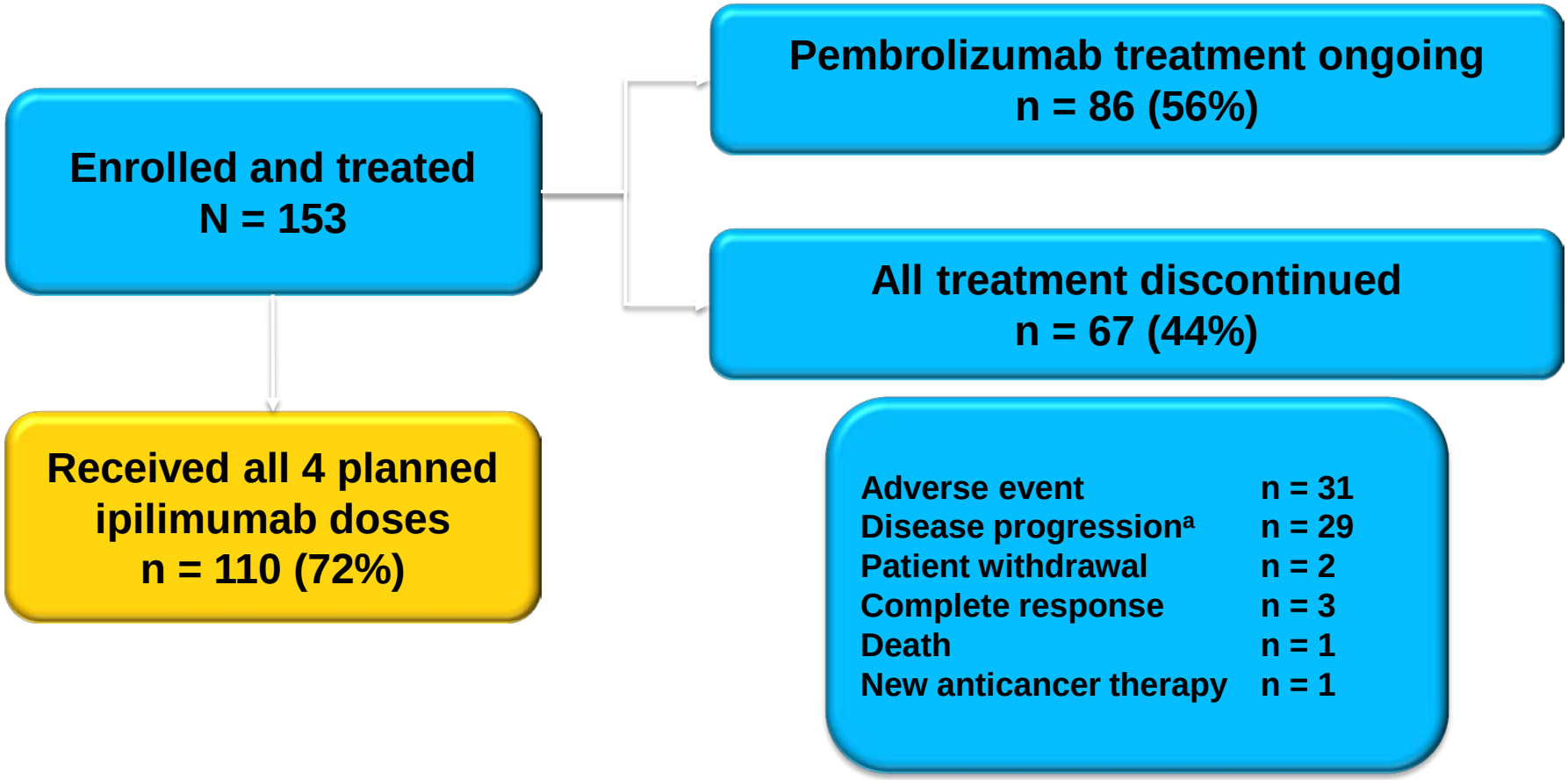
NIVO+IPI	102	98	95	90	82	79	76	73	72	72	62	18	2	0
NIVO	98	93	86	81	75	69	67	64	57	56	52	17	1	0
IPI	100	91	88	81	71	64	58	53	49	47	37	13	1	0

Pembrolizumab Plus Ipilimumab For Advanced Melanoma: Results of the KEYNOTE-029 Expansion Cohort

- Georgina V. Long, Victoria Atkinson, Jonathan S. Cebon, Michael B. Jameson, Bernie M. Fitzharris, Catriona M. McNeil, Andrew G. Hill, Antoni Ribas, Michael B. Atkins, John A. Thompson, Wen-Jen Hwu, F. Stephen Hodi, Alexander M. Menzies, Alexander D. Guminski, Richard Kefford, Xinxin Shu, Scot Ebbinghaus, Nageatte Ibrahim, Matteo S. Carlino

Presenter: GV Long

Treatment Disposition: Part 1B



Pembrolizumab in combination with ipilimumab is not TGA registered for the treatment of advanced melanoma

Presenter: GV Long

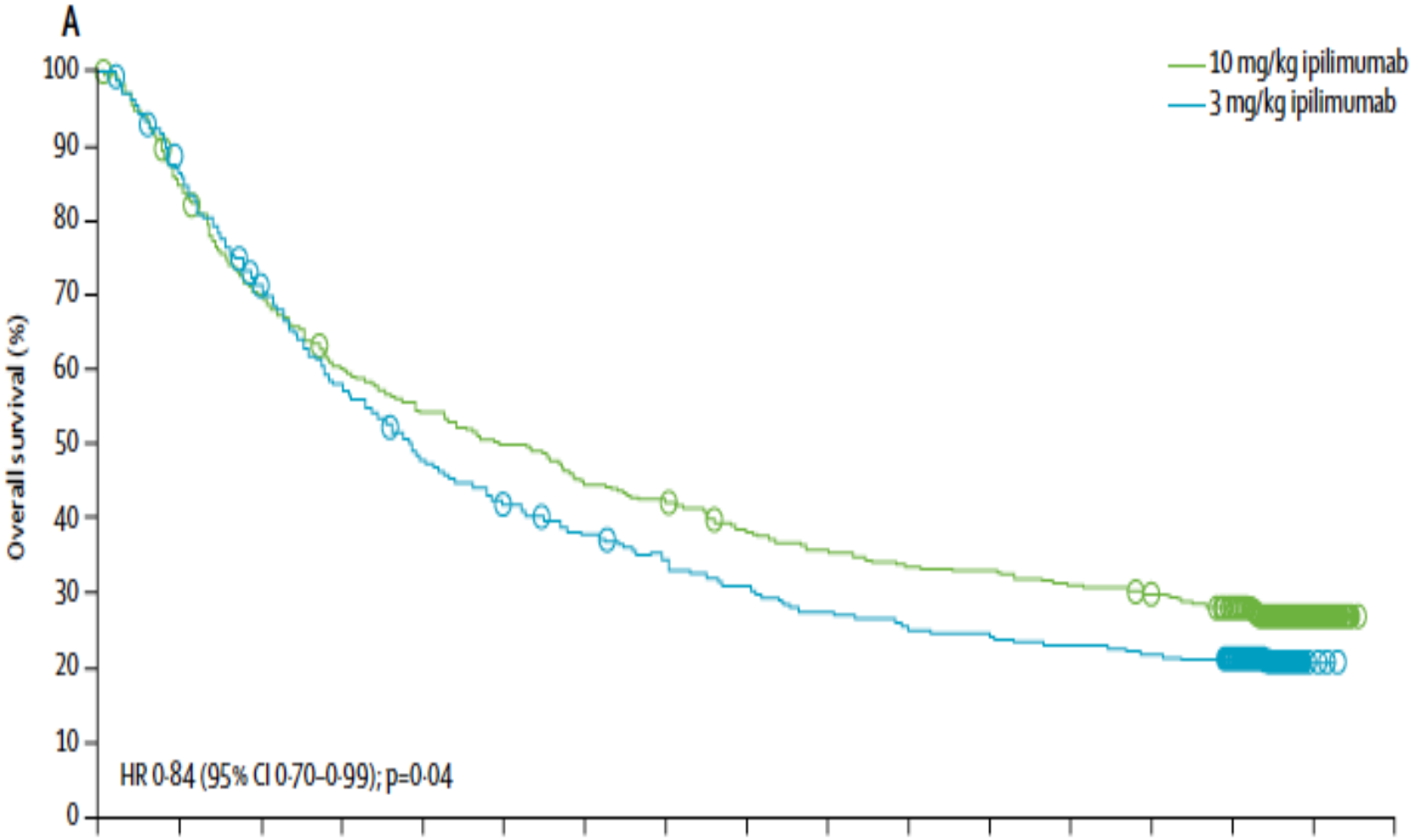
Response (RECIST v1.1, Independent Central Review)

	N = 153
ORR, % (95% CI)	57% (49%-65%)
DCR, % (95%CI)	78% (71%-85%)
Best overall response, n (%)	
Complete response	15 (10%)
Partial response	72 (47%)
Stable disease	33 (22%)
Progressive disease	30 (20%)
No assessment[a]	3 (2%)

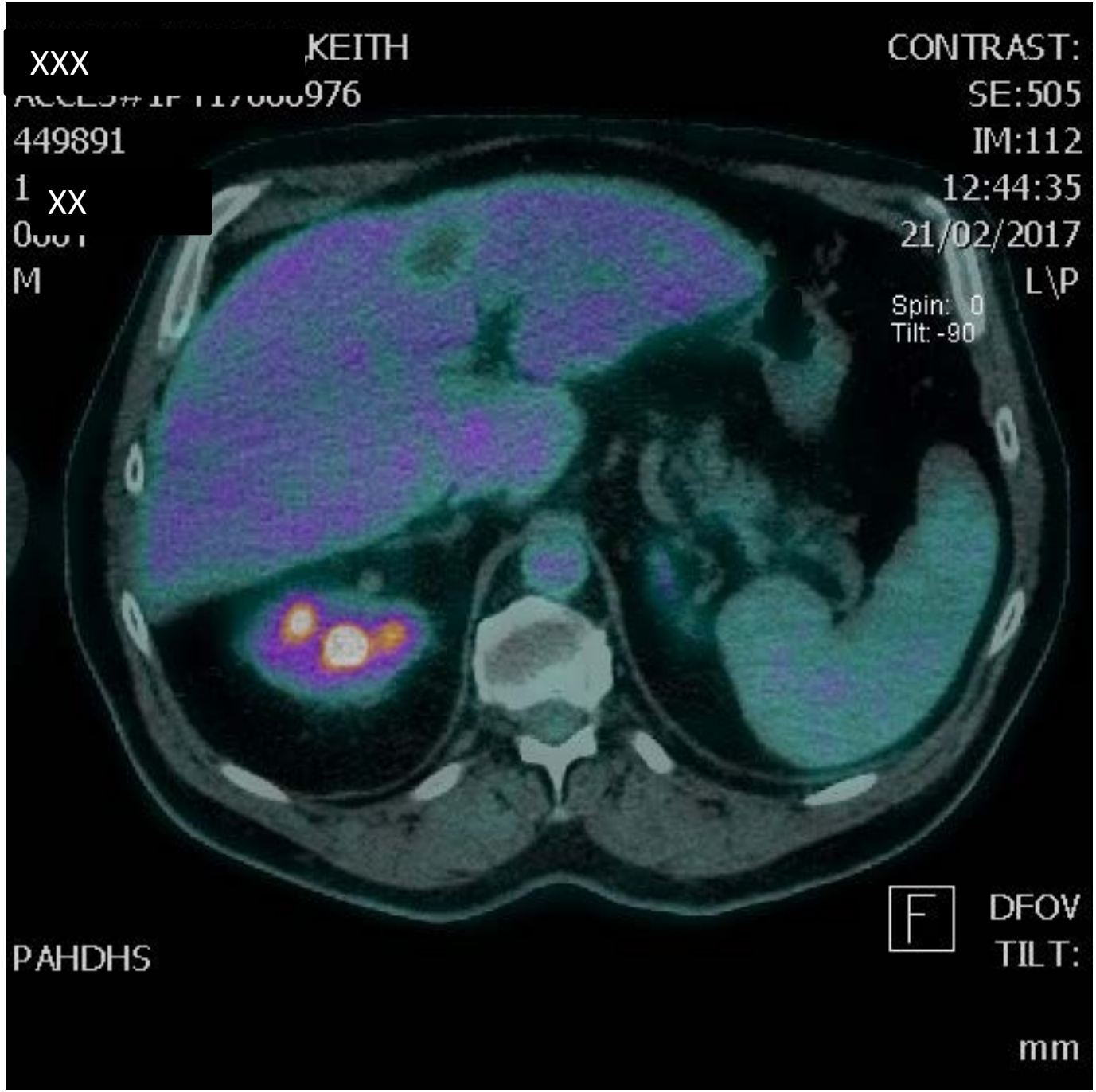
- 85/87 (98%) responders maintained response at time of data cut-off
- Response duration: 6+ to 43+ weeks

Pembrolizumab in combination with ipilimumab is not TGA registered for the treatment of advanced melanoma

[a]No postbaseline scan performed.
All responses are confirmed.
Data cutoff date: Mar 17, 2016.



Ascierto et al Lancet Oncology 2017


XXX
KEITH
976
449891
1
XX
M
CONTRAST:
SE:505
IM:112
12:44:35
21/02/2017
L\P
Spin: 0
Tilt: -90
F
DFOV
TILT:
PAHDHS
mm

Immunotherapy

- Slower onset to action-weeks to months
- Works regardless of mutational status
- Monotherapy is well tolerated
- Combination therapy is more effective but at the cost of adverse events
- Unique spectrum of adverse events-some irreversible
- ? Is there a proportion who are cured?

Pending completed immunotherapy Phase III trials in metastatic disease

- Pembrolizumab and Epocadostat
- Pembrolizumab and T-VEC
- Ipilimumab 1mg/kg and Nivolumab 3mg/kg vs Nivolumab 1mg/kg and Ipilimumab 3mg/kg
- Dabrafenib and Trametinib vs Ipilimumab/Nivolumab and crossover on progression

Pending Adjuvant therapy trials

- Dabrafenib/Trametinib vs Placebo in resected Stage III BRAF mt melanoma
- Vemurafenib vs Placebo in Resected Stage IIC and III BRAF mt melanoma
- Pembrolizumab vs Placebo in Resected Stage III melanoma
- Nivolumab vs Ipilimumab in Resected Stage III-IV melanoma.

The verdict

Targeted therapy	Immune therapy
Only effective in 40% melanoma	Effective regardless of mutation status
Effective any line of therapy	?better 1st line
Convenient/well tolerated	Single agent is well tolerated
Enduring response for some	Enduring response ?cure for some

The winner is..

- Patients
- We have increasingly effective choices, where previously there were none
- Survival is improved, as is response rate and knowledge of how to manage adverse events

THANK YOU-QUESTIONS