Metastatic melanoma:
how to individualize therapeutic approach in 2020 ?

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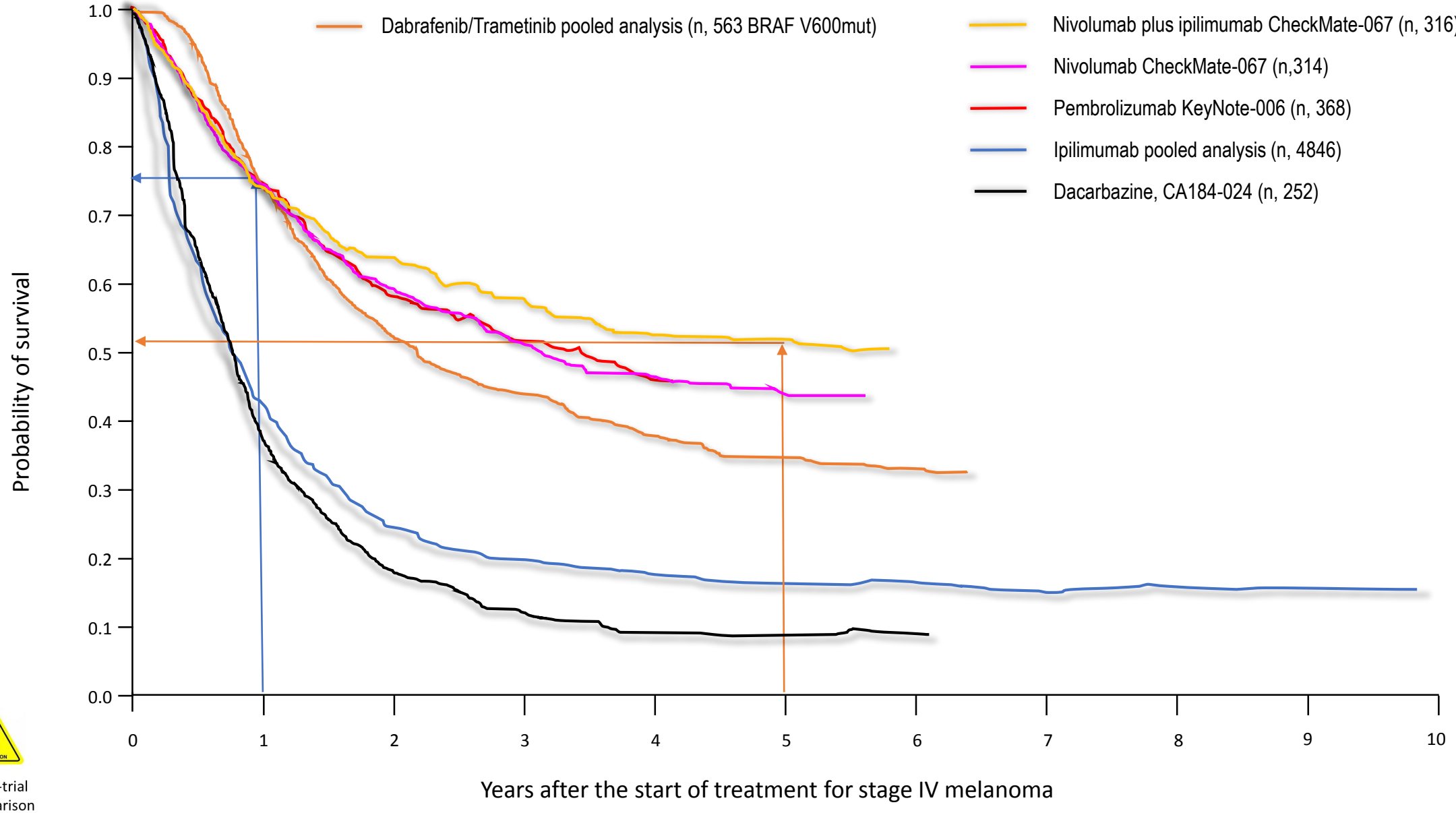
DISCLOSURES

- Personal financial compensation from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, AstraZeneca for public speaking, consultancy and participation in advisory board meetings
- My institution (UZ Brussel) received research funding related to research projects conducted by my team from Pfizer, Novartis, Roche, Merck-Serono

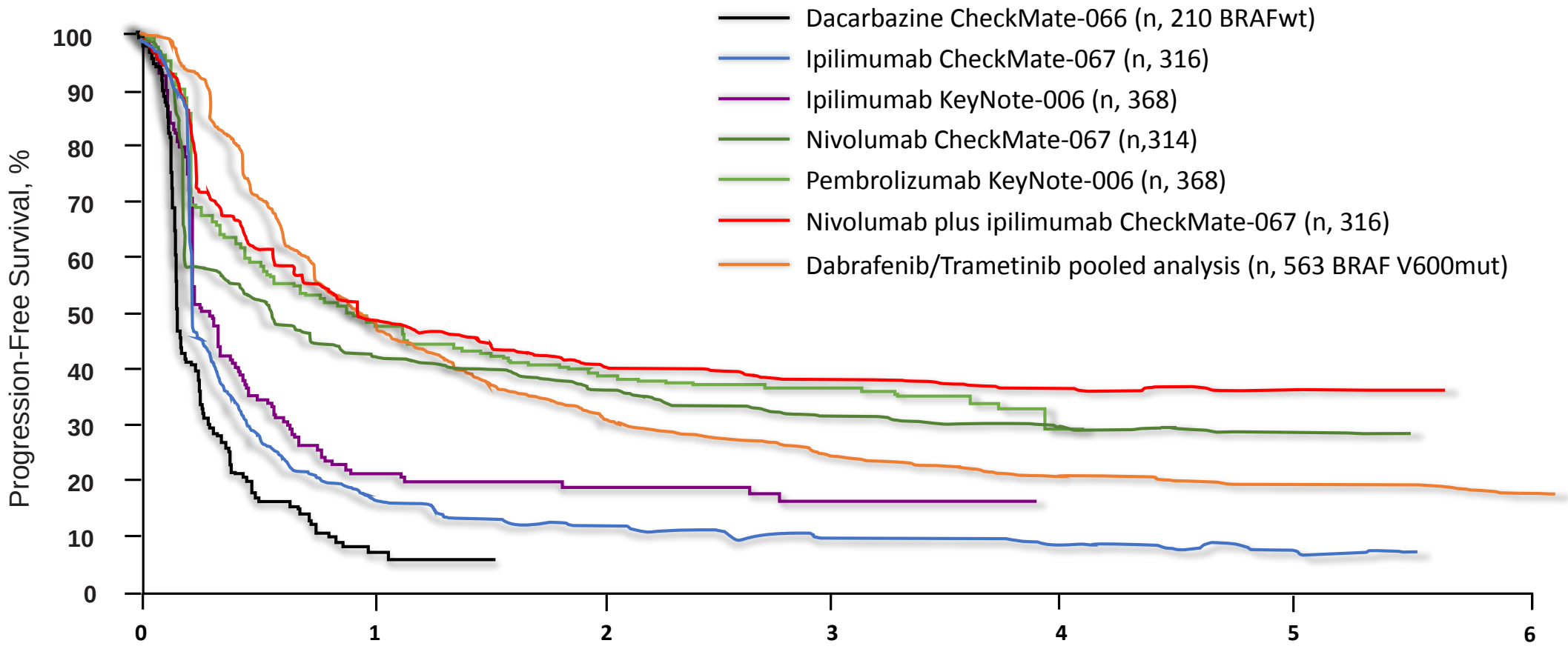
Overall Survival of Advanced Melanoma Patients According to First Line Therapy



Cross-trial comparison

Adapted from A. Rogiers et al. Journal of Oncology, 2019

Progression-Free Survival of Advanced Melanoma Patients on First Line Therapy

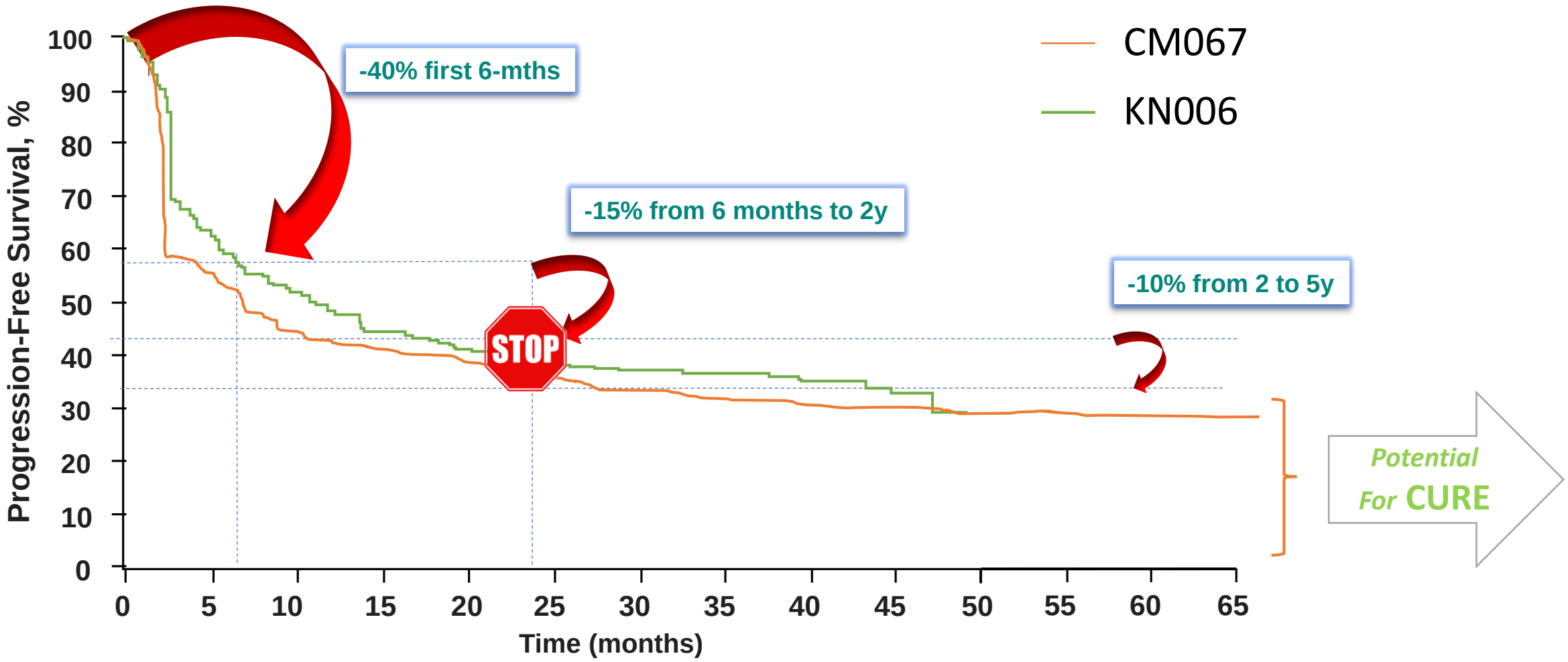


CAUTION

Cross-trial comparison

Adapted from A. Rogiers et al. Journal of Oncology, 2019

Overlay of Progression-Free Survival Estimates of First-Line Treatment with Pembrolizumab (KeyNote-006) or Nivolumab (CeckMate-067)



Adapted from Larkin J. et al. NEJM 2019

Adapted from Robert et al. Lancet Oncology 2019

Review

September 24, 2020

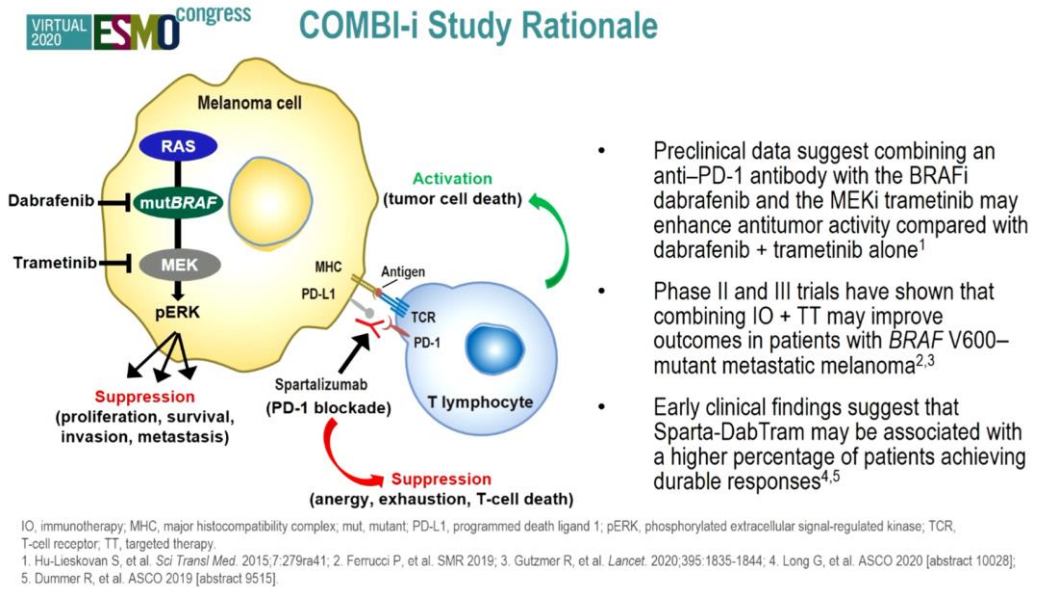
Rationale for Immune Checkpoint Inhibitors Plus Targeted Therapy in Metastatic Melanoma

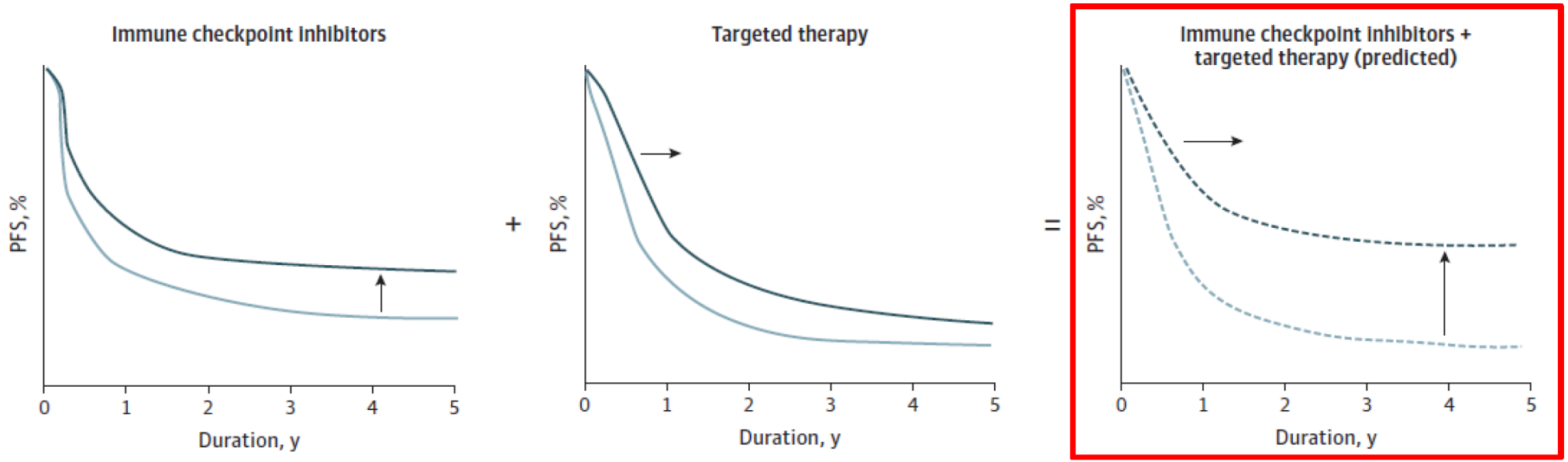
A Review

Reinhard Dummer, MD[1]; Paolo A. Ascierto, MD[2]; Paul Nathan, MD, PhD[3]; et al

» Author Affiliations

JAMA Oncol. Published online September 24, 2020. doi:10.1001/jamaoncol.2020.4401





Evaluation of Atezolizumab, Cobimetinib, and Vemurafenib in Previously Untreated Patients With *BRAF*^{V600} Mutation–Positive Advanced Melanoma: Primary Results From the Phase 3 IMspire150 Trial

Grant A. McArthur, M.B., B.S., Ph.D.,[1] Daniil Stroyakovskiy, M.D.,[2] Helen Gogas, M.D., Ph.D.,[3] Caroline Robert, M.D., Ph.D.,[4] Karl Lewis, M.D.,[5] Svetlana Protsenko, M.D.,[6] Rodrigo Pereira, M.D.,[7] Thomas Eigentler, M.D.,[8] Piotr Rutkowski, M.D., Ph.D.,[9] Lev Demidov, M.D.,[10] Georgy Moiseevich Manikhas, M.D.,[11] Yibing Yan,[12] Kuan-Chieh Huang, Ph.D.,[12] Anne Uyei, M.D.,[12] Virginia McNally, Ph.D.,[13] Ralf Gutzmer, M.D.,[14] Paolo Ascierto, M.D.[15]

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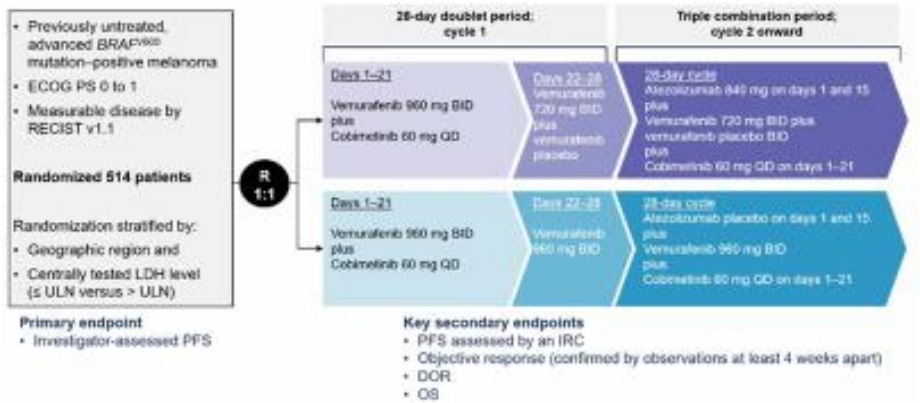

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Spartalizumab plus dabrafenib and trametinib in patients with previously untreated *BRAF* V600–mutant unresectable or metastatic melanoma: results from the randomized part 3 of the Phase III COMBI-i trial

Paul D. Nathan,[1] Reinhard Dummer,[2] Georgina V. Long,[3] Paolo A. Ascierto,[4] Hussein A. Tawbi,[5] Caroline Robert,[6] Piotr Rutkowski,[7] Oleg Leonov,[8] Caroline Dutriaux,[9] Mario Mandalà,[10] Paul Lorigan,[11] Pier Francesco Ferrucci,[12] Keith T. Flaherty,[13] Jan C. Brase,[14] Steven Green,[15] Tomas Haas,[15] Aisha Masood,[16] Eduard Gasal,[16] Antoni Ribas,[17] Dirk Schadendorf[18]

[1]Department of Medical Oncology, Mount Vernon Cancer Centre, Northwood, UK; [2]Department of Dermatology, University Hospital Zürich Skin Cancer Center, Zürich, Switzerland; [3]Department of Medical Oncology, Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia; [4]Department of Melanoma, Cancer Immunotherapy and Development Therapeutics, Istituto Nazionale Tumori IRCCS "G. Pascale," Napoli, Italy; [5]Department of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]Dermatology Service and Melanoma Research Unit, Gustave Roussy and Paris-Sud-Paris-Saclay University, Villejuif, France; [7]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [8]Department of Medical Oncology, Clinical Oncological Dispensary, Omsk, Russian Federation; [9]Service de Dermatologie, Centre Hospitalier Universitaire de Bordeaux, Hôpital Saint-André, Bordeaux, France; [10]Department of Oncology and Haematology, Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy; [11]Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK; [12]Cancer Biotherapy Unit, Department of Experimental Oncology, European Institute of Oncology, IRCCS, Milan, Italy; [13]Department of Medicine and Cancer Center, Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [14]Precision Medicine, Novartis Pharma AG, Basel, Switzerland; [15]Clinical Development and Analytics, Novartis Pharma AG, Basel, Switzerland; [16]Oncology Clinical Development, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [17]Department of Medicine, Division of Hematology-Oncology, University of California, Los Angeles, Los Angeles, CA, USA; [18]Department of Dermatology, Comprehensive Cancer Center (Westdeutsches Tumorzentrum), University Hospital Essen, Essen, and German Cancer Consortium, Heidelberg, Germany

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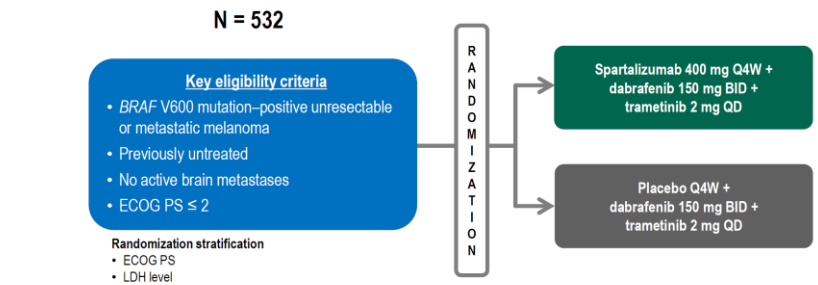
COMBI-i Study Design (Part 3)

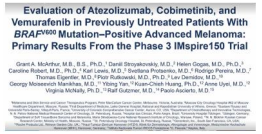


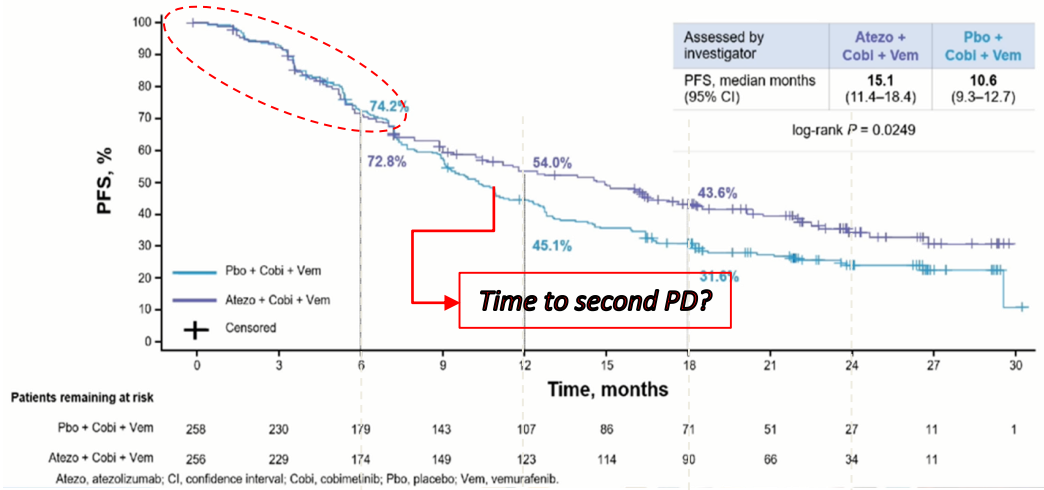
Primary endpoint: Investigator-assessed PFS using RECIST 1.1

Secondary endpoints: OS, ORR, DOR, DCR, safety, PRO, PK

BID, twice daily; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q4W, every 4 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

Investigator-Assessed Progression-Free Survival


Evaluation of Atezolizumab, Cobimetinib, and Vemurafenib in Previously Untreated Patients With *BRAF*^{V600} Mutation–Positive Advanced Melanoma: Primary Results From the Phase 3 IMspire150 Trial

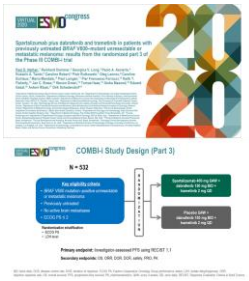


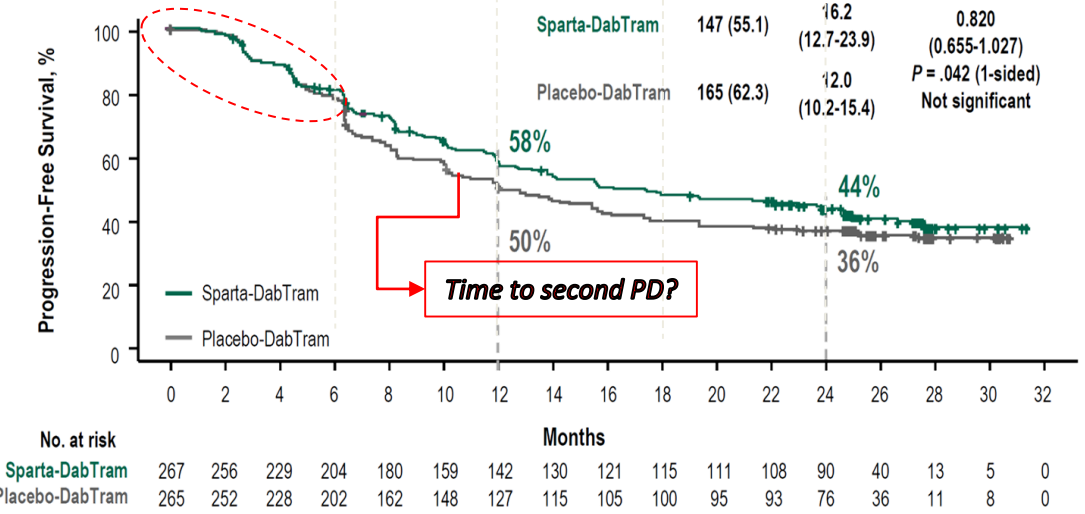
Assessed by investigator	Atezo + Cobi + Vem	Pbo + Cobi + Vem
PFS, median months (95% CI)	15.1 (11.4–18.4)	10.6 (9.3–12.7)

log-rank $P = 0.0249$

Patients remaining at risk											
Pbo + Cobi + Vem	258	230	179	143	107	86	71	51	27	11	1
Atezo + Cobi + Vem	256	229	174	149	123	114	90	66	34	11	

Atezo, atezolizumab; CI, confidence interval; Cobi, cobimetinib; Pbo, placebo; Vem, vemurafenib.



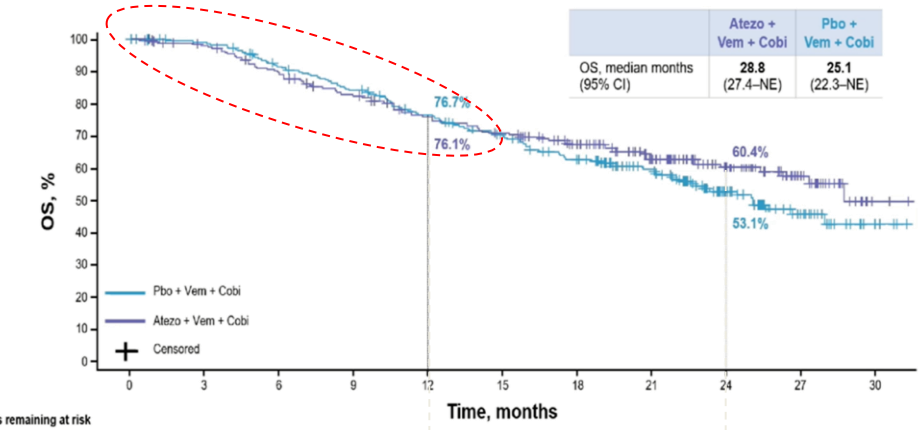


	Event, n (%)	Median (95% CI), mo	HR (95% CI)
Sparta-DabTram	147 (55.1)	16.2 (12.7-23.9)	0.820 (0.655-1.027)
Placebo-DabTram	165 (62.3)	12.0 (10.2-15.4)	$P = .042$ (1-sided) Not significant

No. at risk																	
Sparta-DabTram	267	256	229	204	180	159	142	130	121	115	111	108	90	40	13	5	0
Placebo-DabTram	265	252	228	202	162	148	127	115	105	100	95	93	76	36	11	8	0

HR, hazard ratio.

Overall Survival



	Atezo + Vem + Cobi	Pbo + Vem + Cobi
OS, median months (95% CI)	28.8 (27.4–NE)	25.1 (22.3–NE)

Patients remaining at risk											
Pbo + Vem + Cobi	258	249	225	206	175	161	139	105	57	26	5
Atezo + Vem + Cobi	242	220	198	173	165	144	105	68	28	2	

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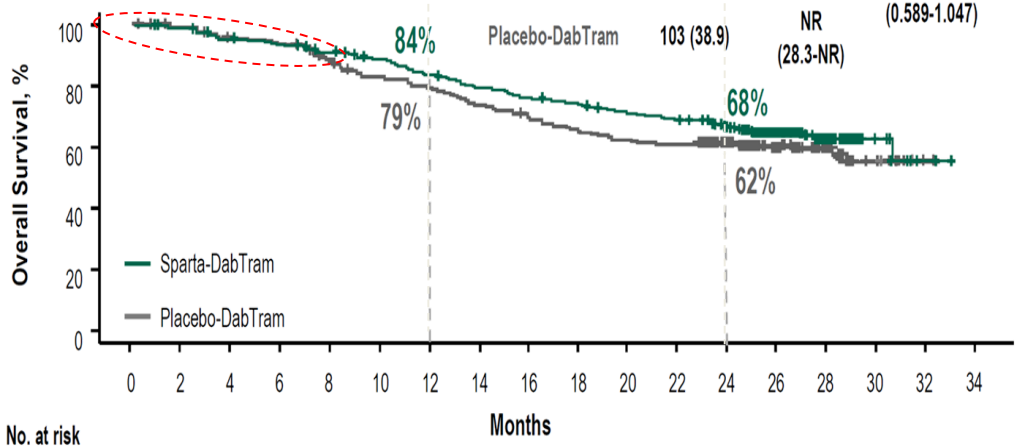
Overall Survival



	Events n (%)	Median (95% CI), mo	HR (95% CI)
Sparta-DabTram	90 (33.7)	NR (30.6-NR)	0.785 (0.589-1.047)
Placebo-DabTram	103 (38.9)	NR (28.3-NR)	

No. at risk																	
Sparta-DabTram	267	264	253	248	238	228	215	203	195	189	179	174	153	91	48	13	2	0
Placebo-DabTram	265	259	248	243	223	209	199	186	173	163	157	154	130	81	43	13	1	0

- Overall survival could be statistically tested only after the primary endpoint was determined to be statistically significant

Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced *BRAF*^{V600} mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial

Rolf Gutzmer, David Stroyakovskiy, Helen Gogas, Caroline Robert, Karl Lewis, Svetlana Protsenko, Rodrigo P Pereira, Thomas Eigentler, Piotr Rutkowski, Lev Demidov, Georgy Manikhas, Yibing Yan, Evan-Cheh Hoang, Anne Uyl, Virginia McNally, Grant A McArthur*, Paolo A Ascierto*

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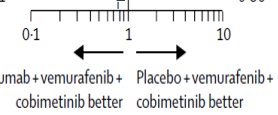
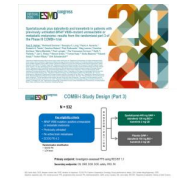
	Atezolizumab + vemurafenib + cobimetinib (n=256)		Placebo + vemurafenib + cobimetinib (n=258)		Hazard ratio	95% Wald CI
	n	Events	n	Events		
Randomised treatment group	256	148	258	179	0·77	(0·62–0·96)
Age group, years						
<65	195	114	199	134	0·82	(0·64–1·06)
≥65	61	34	59	45	0·63	(0·40–0·99)
Race						
White	243	138	246	170	0·76	(0·60–0·95)
Non-white	13	10	12	9	1·07	(0·43–2·65)
Sex						
Male	150	81	149	101	0·75	(0·56–1·01)
Female	106	67	109	78	0·81	(0·58–1·13)
Geographical region (IWRS)						
North America	13	7	14	10	0·85	(0·32–2·27)
Europe	203	124	203	142	0·79	(0·62–1·00)
Australia, New Zealand, or other	40	17	41	27	0·69	(0·37–1·27)
Serum lactate dehydrogenase at baseline (IWRS)						
≤upper limit	172	88	173	106	0·76	(0·57–1·01)
>upper limit	84	60	85	73	0·81	(0·58–1·14)
Eastern Cooperative Oncology group performance status						
0	195	103	198	136	0·68	(0·53–0·88)
1	61	45	56	42	1·08	(0·71–1·65)
Melanoma staging						
IIIC	14	4	16	11	0·37	(0·12–1·17)
IV	242	144	240	168	0·80	(0·64–1·00)
Previous adjuvant therapy						
Yes	41	20	30	22	0·57	(0·31–1·04)
No	215	128	228	157	0·81	(0·64–1·03)
PD-L1 expression						
IC 1/2/3	160	89	158	108	0·80	(0·60–1·06)
IC 0	85	53	86	62	0·76	(0·53–1·10)
Organ involvement						
<3	205	109	197	131	0·74	(0·58–0·96)
≥3	51	39	57	48	0·94	(0·61–1·44)
Sum of longer diameter						
<44 mm	109	55	99	65	0·70	(0·49–1·01)
≥44 mm	147	93	155	114	0·83	(0·63–1·10)
Histological subtype (initial diagnosis)						
Superficial spreading	85	54	83	58	0·86	(0·59–1·24)
Nodular	84	49	80	56	0·72	(0·49–1·06)
Other	86	44	93	65	0·72	(0·49–1·07)
Distant metastasis, stage (study entry)						
M0	13	4	16	11	0·42	(0·13–1·33)
M1A	41	18	35	20	0·72	(0·38–1·37)
M1B	56	29	42	27	0·80	(0·47–1·36)
M1C	145	97	163	121	0·86	(0·66–1·13)





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Progression-Free Survival By Subgroups

		HR (95% CI)	Sparta-DabTram, n/n (%)	Placebo-DabTram, n/n (%)
Age	< 65 years (n = 384)	0.92 (0.71-1.20)	105/189 (55.6)	119/195 (61.0)
	≥ 65 years (n = 148)	0.61 (0.40-0.95)	42/78 (53.8)	46/70 (65.7)
Sex	Male (n = 307)	0.82 (0.61-1.10)	84/148 (56.8)	101/159 (63.5)
	Female (n = 225)	0.80 (0.56-1.14)	63/119 (52.9)	64/106 (60.4)
LDH levels	< 1 × ULN (n = 323)	0.88 (0.65-1.21)	75/162 (46.3)	84/161 (52.2)
	≥ 1 to < 2 × ULN (n = 138)	0.78 (0.52-1.17)	47/70 (67.1)	49/68 (72.1)
	≥ 2 × ULN (n = 71)	0.72 (0.42-1.25)	25/35 (71.4)	32/36 (88.9)
ECOG PS	0 (n = 391)	0.84 (0.64-1.10)	102/195 (52.3)	115/196 (58.7)
	1 (n = 133)	0.73 (0.48-1.11)	42/67 (62.7)	48/66 (72.7)
No. of sites of metastasis	< 3 (n = 288)	1.06 (0.77-1.46)	78/145 (53.8)	74/143 (51.7)
	≥ 3 (n = 243)	0.63 (0.46-0.87)	69/121 (57.0)	91/122 (74.6)
Disease stage (AJCC 7)	IIIC (n = 31)	2.47 (0.68-8.93)	7/16 (43.8)	6/15 (40.0)
	IV M1 (n = 501)	0.78 (0.62-0.98)	140/251 (55.8)	159/250 (63.6)
Sum of lesion diameters at baseline	< 66 mm (n = 331)	1.07 (0.79-1.46)	79/163 (48.5)	84/168 (50.0)
	≥ 66 mm (n = 195)	0.52 (0.37-0.73)	67/100 (67.0)	81/95 (85.3)
PD-L1 status	Negative, < 1% (n = 213)	0.84 (0.60-1.18)	64/98 (65.3)	79/115 (68.7)
	Positive, ≥ 1% (n = 264)	0.76 (0.54-1.07)	65/138 (47.1)	72/126 (57.1)
TMB	Low, < 10 mut/Mb (n = 237)	0.91 (0.65-1.26)	69/115 (60.0)	77/122 (63.1)
	High, ≥ 10 mut/Mb (n = 177)	0.70 (0.47-1.06)	45/87 (51.7)	54/90 (60.0)

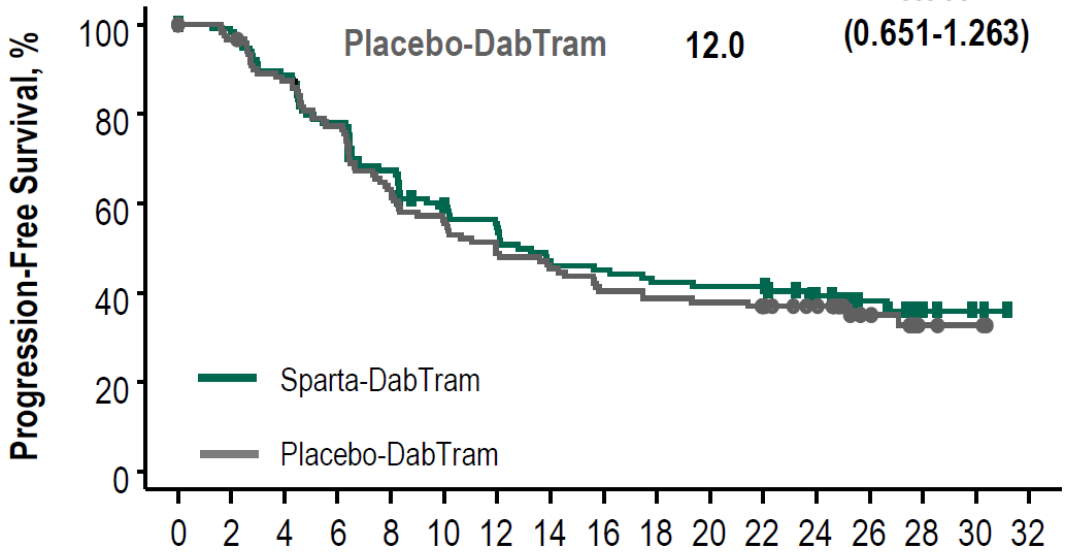
Mb, megabase; mut, mutation; TMB, tumor mutational burden.

Biomarkers

Progression-free survival based on TMB

TMB Low, < 10 mut/Mb

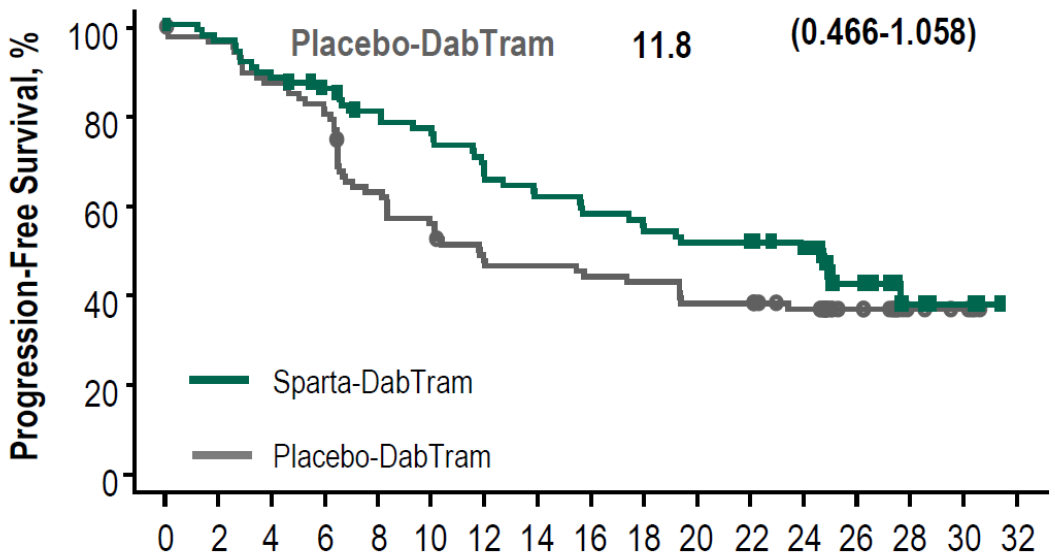
	Median, mo	HR (95% CI)
Sparta-DabTram	12.8	0.907 (0.651-1.263)
Placebo-DabTram	12.0	



No. at risk																	
Sparta-DabTram	115	112	101	88	75	64	58	50	48	45	44	44	36	17	6	2	0
Placebo-DabTram	122	116	104	92	75	67	58	54	48	46	45	43	35	16	3	2	0

TMB High, ≥ 10 mut/Mb

	Median, mo	HR (95% CI)
Sparta-DabTram	23.9	0.703 (0.466-1.058)
Placebo-DabTram	11.8	



No. at risk																	
Sparta-DabTram	87	81	74	69	63	59	51	48	45	42	40	39	34	15	5	3	0
Placebo-DabTram	90	84	76	70	54	48	40	39	37	36	32	32	27	15	6	4	0

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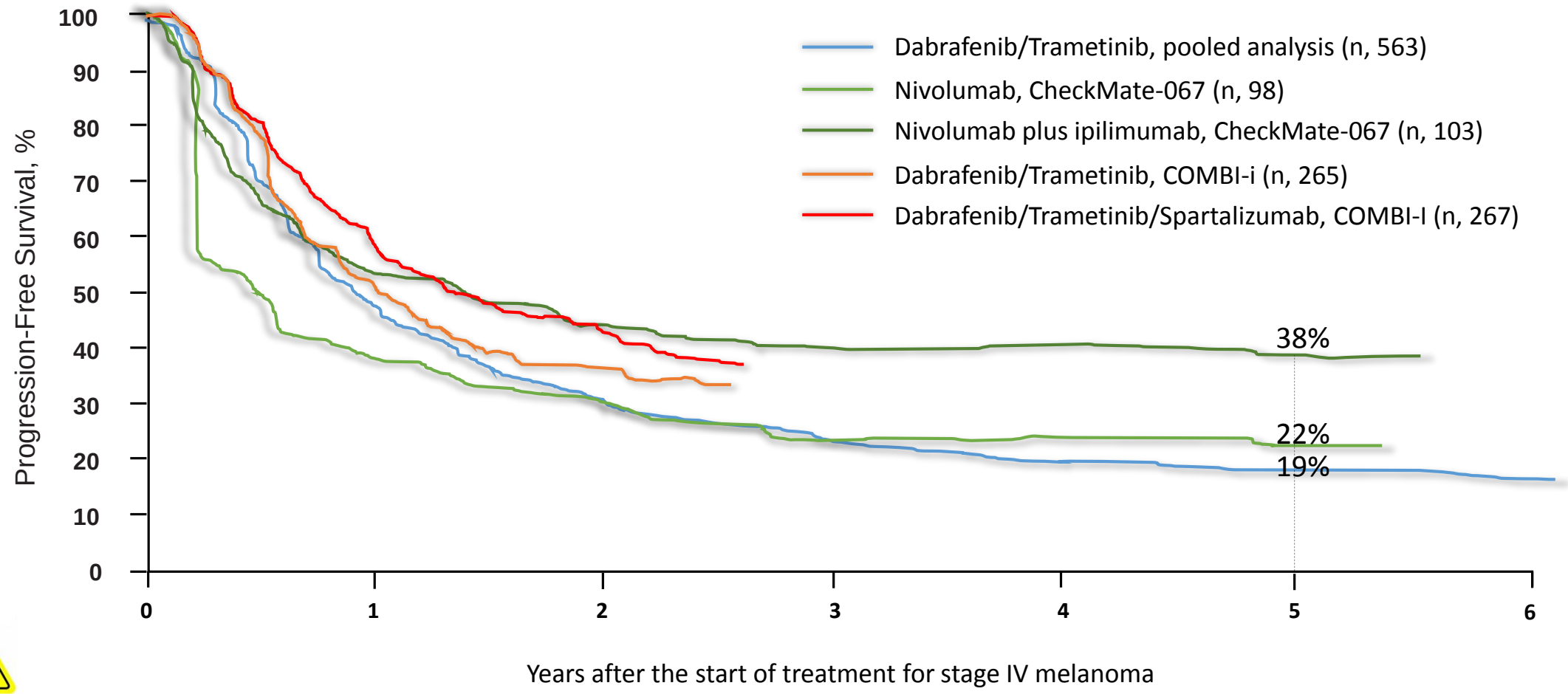
Triplet Combos safety profile

	KEYNOTE-022 (n = 60)		IMspire 150 (n = 230)		Combi-I (n = 267)	
Patients reporting event	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Any Adverse Event, n, (%)	60 (100)	42 (70)	NR	NR	265 (99.3)	188 (70.4)
Treatment-related AE, n, (%)	**57 (95)**	**35 (58.3)**	**228 (99)**	**182 (79)**	**263 (98.5)**	**146 (54.7)**
Deaths	**2 (3)**		7 (3.0)		NR	
Treatment-related deaths, n, (%)	**1 (2)**		**2 (0.8)**		**NR**	
Treatment-related AE leading to discontinuation ≥ 1 study drug, n, (%)	28 (46.7)		NR		85 (31.8)	
Treatment-related AE leading to discontinuation of all 3 study drugs, n, (%)	**18 (30)**		**29 (13)**		**33 (12.4)**	

NR = not reported

Ferrucci et al. SMR 2019
Gutzmer et al. The Lancet 2020
Nathan et al. ESMO 2020

Progression-Free Survival of Advanced BRAF V600-Mutant Melanoma Patients on First Line Therapy



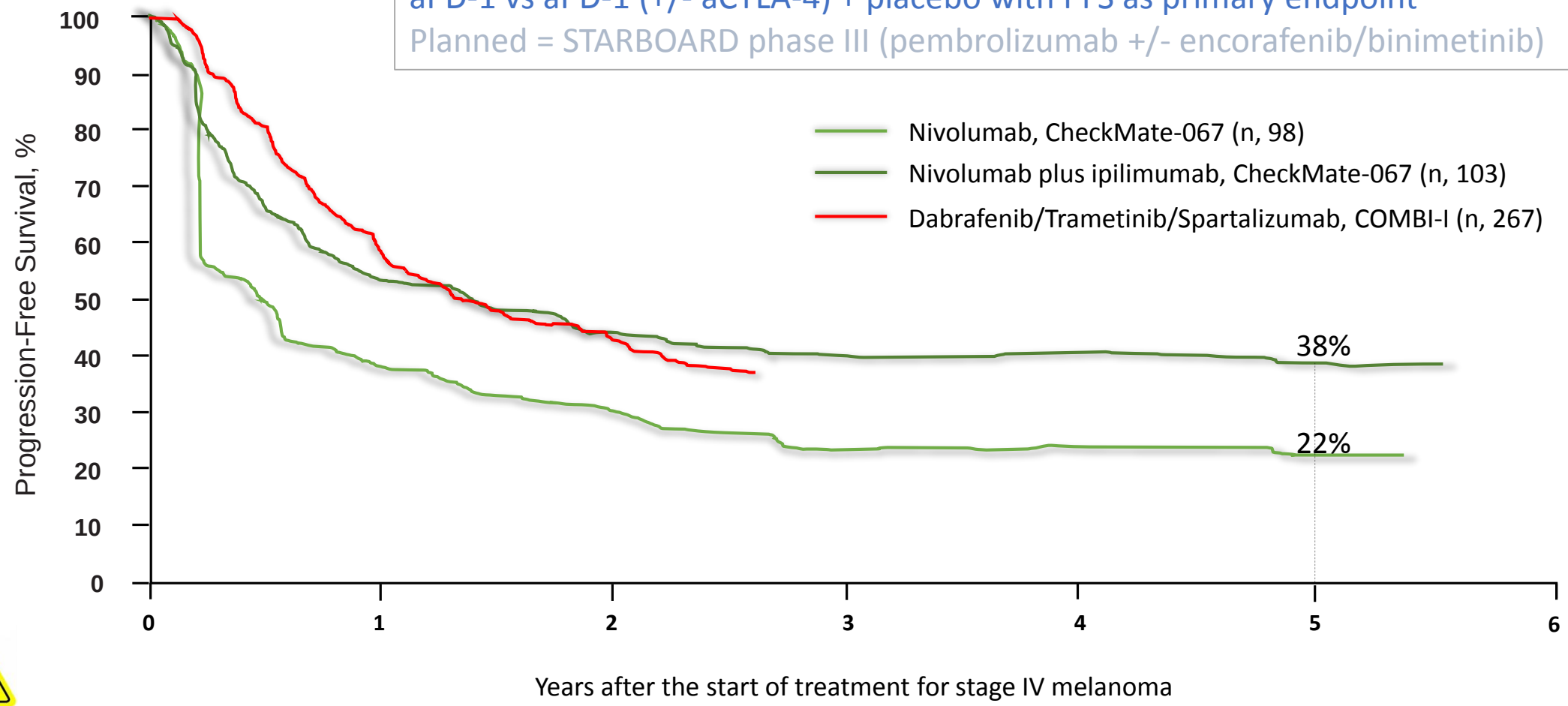
Cross-trial comparison

Adapted from A. Rogiers et al. Journal of Oncology, 2019

Progression-Free Survival of Advanced BRAF V600-Mutant Melanoma Patients on First Line Therapy

Hypothetical outcome of a phase III clinical trial comparing PFS of BRAF/MEKi + aPD-1 vs aPD-1 (+/- aCTLA-4) + placebo with PFS as primary endpoint

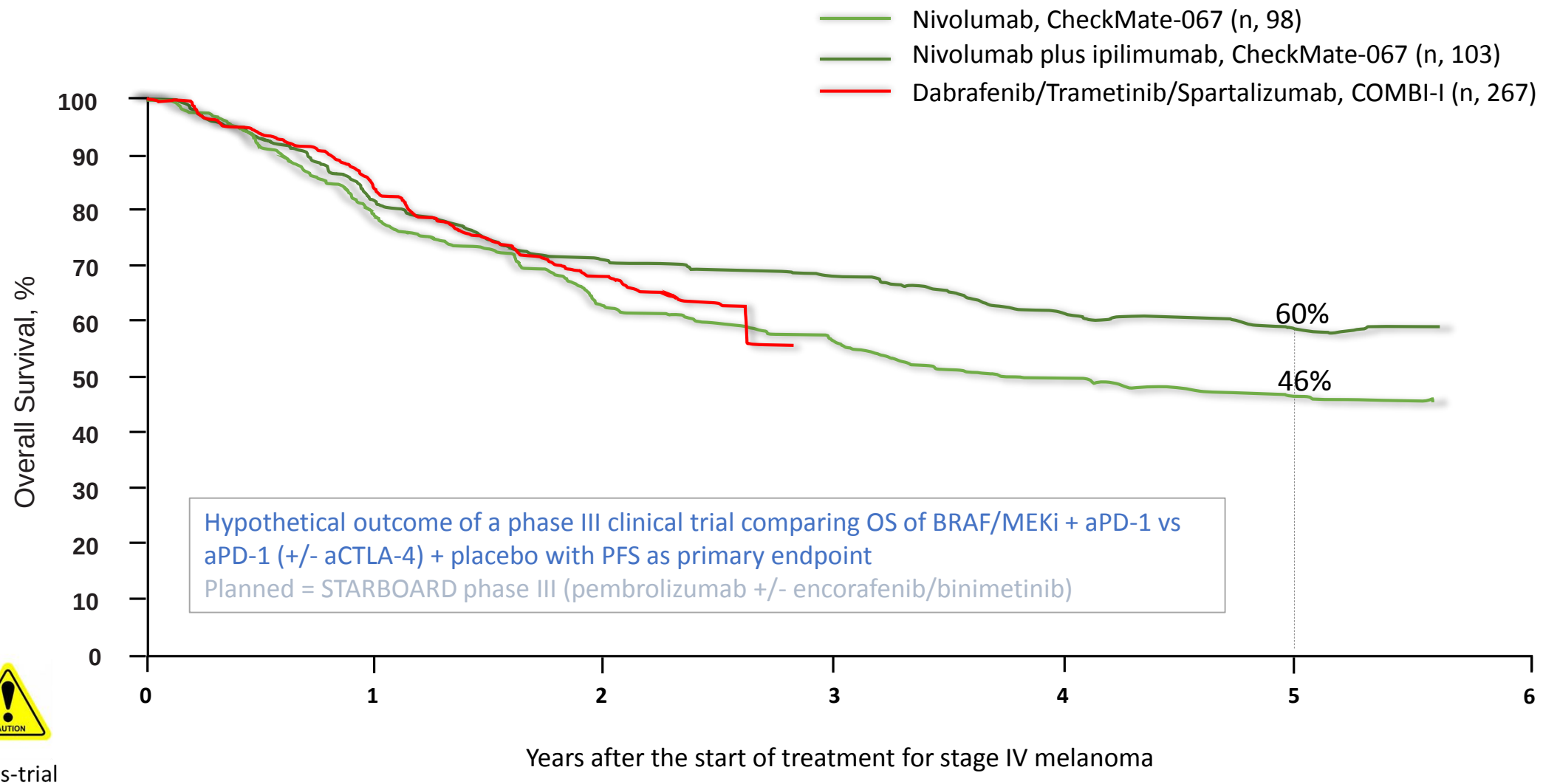
Planned = STARBOARD phase III (pembrolizumab +/- encorafenib/binimetinib)



Cross-trial comparison

Adapted from A. Rogiers et al. Journal of Oncology, 2019

Overall Survival of Advanced BRAF V600-Mutant Melanoma Patients by First Line Therapy



Cross-trial comparison

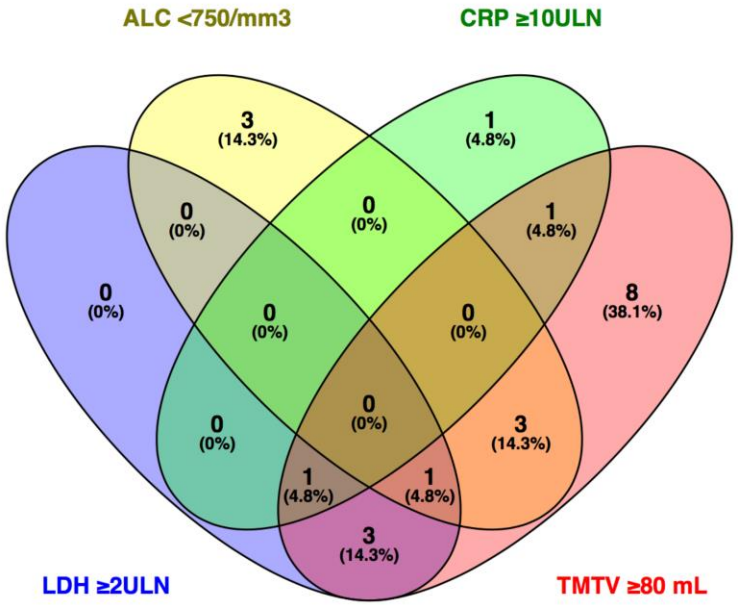
Adapted from A. Rogiers et al. Journal of Oncology, 2019

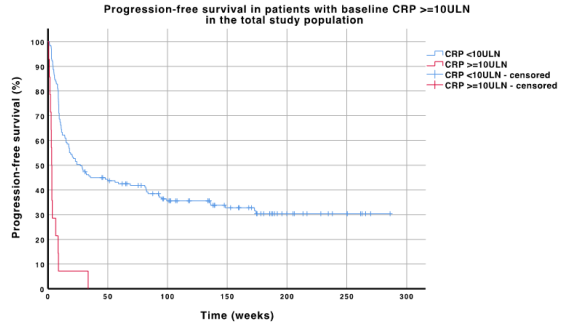
cancers

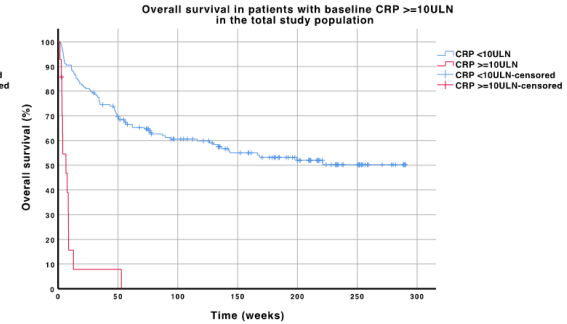
MDPI

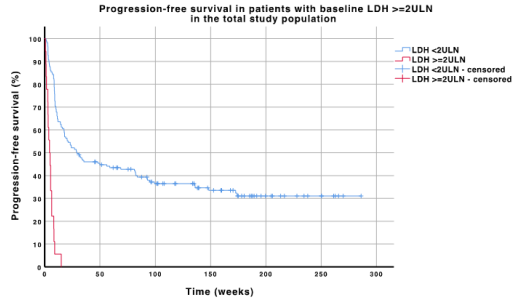
Article

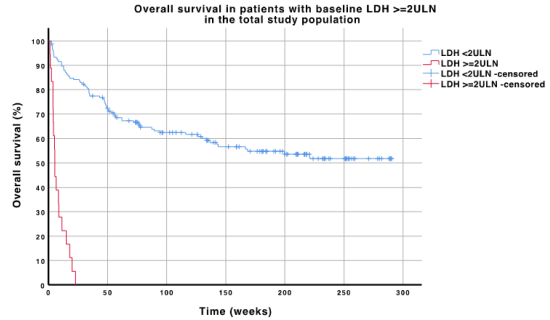
A COMPREHENSIVE ANALYSIS OF BASELINE CLINICAL CHARACTERISTICS AND BIOMARKERS ASSOCIATED WITH OUTCOME IN ADVANCED MELANOMA PATIENTS TREATED WITH PEMBROLIZUMAB

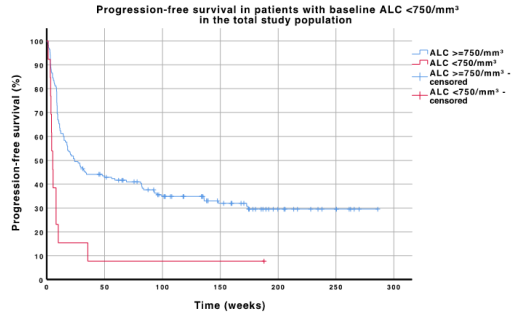


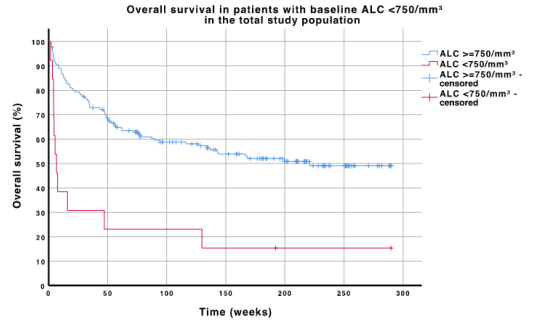






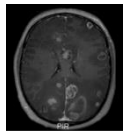
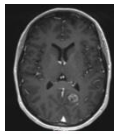
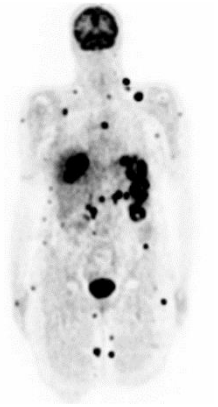
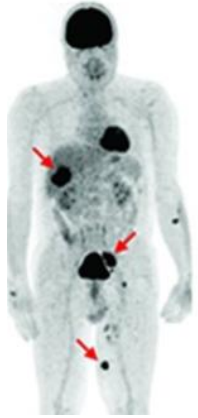
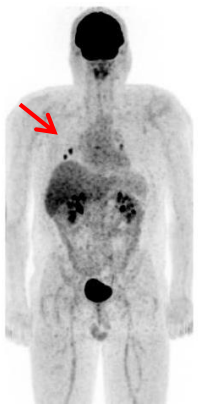
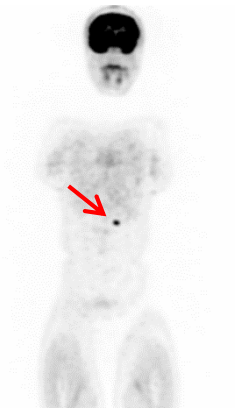






Awada G. et al. Manuscript in preparation

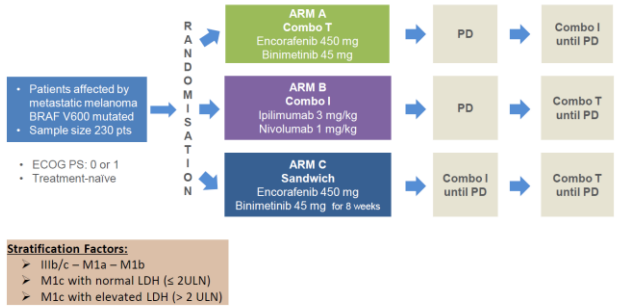
Prognostic Clinical Subgroups in Patients with Unresectable BRAF V600-mutant Melanoma

Imaging of the CNS			No CNS metastases	
Whole-body imaging				
AJCC Stage M-stage	**IV-M1c**	**IV-M1c**	**IV-M1b/c**	**IIIC/IV-M1a/b**
Symptoms/PS	Severe PS ≥2	Minor to moderate PS 0-1	None or minor PS 0-1	None or minor PS 0-1
Clinical progression	Rapid	Medium/Slow	Medium/Slow	Slow
Tumor burden	High	Medium	Medium/Low	Low
Brain metastases	Symptomatic	Asymptomatic or resectable	Absent	Absent
CRP/LDH	>10xULN/>2xULN	<10xULN/<2xULN	<10xULN/<2xULN	Normal
Natural prognosis	<6 mths	6-12 mths	12-18 mths	18-24 mths
First-line treatment	BRAF/MEKi (BRAFwt= UN)	Ipi/Nivo	aPD-1 (+/_ aCTLA-4)	aPD-1 (+/_ aCTLA-4)

Sequencing of BRAF/MEK-targeted and PD-1+/-CTLA-4 Inhibition in BRAF V600-mutant melanoma

VIRTUAL 2020 ESMO congress

SEQUENTIAL COMBO IMMUNO AND TARGET THERAPY (SECOMBIT): STUDY DESIGN



Primary endpoint:
- OS

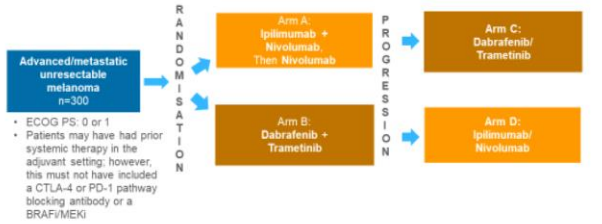
Secondary endpoints:
- PFS
- Total PFS
- Time to second progression
- % patients alive at 2–3 years
- Best ORR
- DOR

DOR, duration of response; ECOG-PS, Eastern Cooperative Oncology Group performance status; LGX = encorafenib (BRAFi); MEK162 = binimetinib (MEKi); ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PD, progressive disease.

Clinicaltrials.gov: NCT02631447.

NCT02224781: Phase 3 Study of Dabrafenib + Trametinib Followed by Ipilimumab + Nivolumab vs Ipilimumab + Nivolumab Followed by Dabrafenib + Trametinib

Randomised Phase 3 trial of dabrafenib + trametinib followed by ipilimumab + nivolumab at progression vs ipilimumab + nivolumab followed by dabrafenib + trametinib at progression in patients with advanced BRAF V600 mutant melanoma



Primary endpoint:
- OS rate, defined as the proportion of patients alive after 2 years of follow-up time

Secondary endpoints:
- PFS (RECIST version 1.1)
- Response rate (RECIST version 1.1)

Objective:
Does the initial treatment with the dabrafenib-trametinib combination (and subsequent ipilimumab-nivolumab) or ipilimumab-nivolumab combination (and subsequent dabrafenib-trametinib combination) improve the 2-year OS significantly in patients with unresectable stage III or stage IV BRAFV600 mutant melanoma?

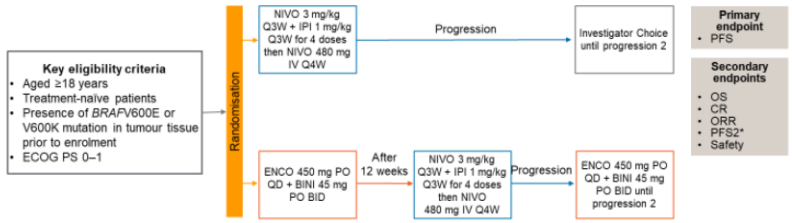
ECOG-PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Clinicaltrials.gov: NCT02224781.

EORTC EBIN: study design

Objective: to assess whether PFS can be improved with a sequential approach, using a 12-week induction of encorafenib + binimetinib, followed by combination nivolumab + ipilimumab, compared with nivolumab + ipilimumab alone, in patients with *BRAF*V600 mutation-positive unresectable or metastatic melanoma

Multicentre, two-arm, open-label, randomised comparative Phase 2 study

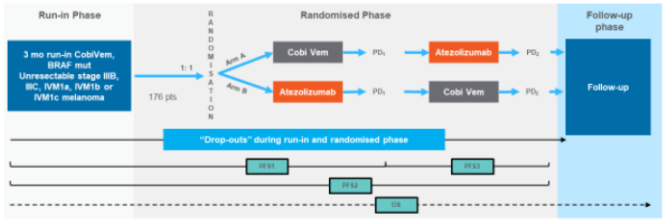


*PFS2 is defined as the time from randomisation to second objective disease progression, or death from any cause, whichever first

BID, twice daily; BINI, binimetinib; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ENCO, encorafenib; IPI, ipilimumab; IV, intravenous; NIVO, nivolumab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; Q4W, every 4 weeks; QD, once daily. ClinicalTrials.gov. NCT03235245. Available from: https://clinicaltrials.gov/(Accessed 15 October 2018)

ImmunoCobiVem: Phase 2 Sequencing Study of Cobimetinib + Vemurafenib Followed by Atezolizumab (Anti–PD-L1) in Patients With BRAF V600 Mutant Melanoma

Phase 2, open-label, randomised, controlled trial evaluating the efficacy and safety of a sequencing schedule of cobimetinib + vemurafenib followed by immunotherapy with an anti–PD-L1 antibody in patients with unresectable or metastatic BRAF V600 mutant melanoma



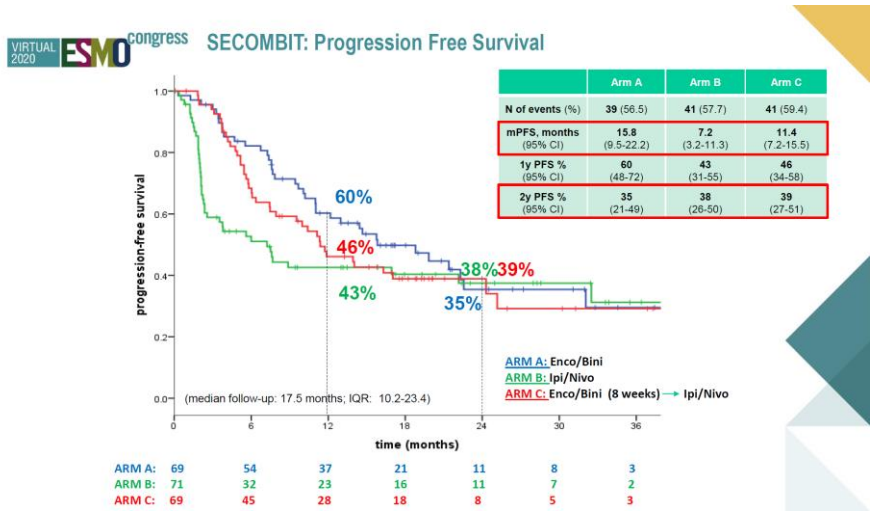
Primary endpoint:
- Time to PFS2

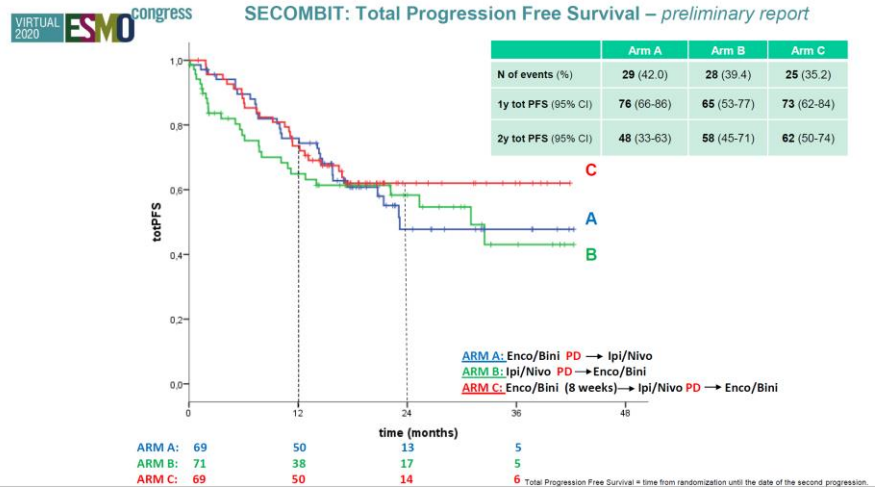
Secondary endpoints:
- Safety, toxicity
- 12-, 48-month OS rate
- 12-, 24- disease control rate
- PFS1, PFS3

OS, overall survival; PD, progressive disease; PD-L1, programmed death ligand 1; PFS, progression-free survival.

Clinicaltrials.gov: NCT02902029.

SECOMBIT





SEQUENTIAL COMBO IMMUNO AND TARGET THERAPY (SECOMBIT): BORR

	Arm A (n. 69)	Arm B (n. 71)	Arm C (n. 69)
BORR. %*(95% CI)	**82.6** (73.7-91.6)	**45.1** (33.5-53.6)	**78.3** (68.5-88.0)
DCR. % (95% CI)	**89.8** (82.7-97.0)	**55.0** (43.3-66.5)	**92.8** (86.6-98.9)
Best overall response N (%)			
Complete response	**15** (21.7)	**11** (15.5)	**20** (29.0)
Partial response	**42** (60.9)	**21** (29.6)	**34** (49.3)
Stable disease	**5** (7.2)	**7** (9.9)	**10** (14.5)
Progressive disease	**3** (4.3)	**27** (38.0)	**3** (4.3)

SEQUENTIAL COMBO IMMUNO AND TARGET THERAPY (SECOMBIT): SAFETY OVERVIEW

	ARM A (n = 69)		ARM B (n = 71)		ARM C (n = 69)	
Patients reporting event	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Any Adverse Event n, (%)	63 (91)	34 (49)	68 (96)	52 (73)	58 (84)	35 (51)
Treatment-related AE, n, (%)	**53 (77)**	**19 (28)**	**59 (83)**	**38 (54)**	**56 (81)**	**22 (32)**
Treatment-related AE leading to discontinuation, n, (%)	7 (10)		8 (11)		3 (4)	

- No new safety signals were observed as compared with the data from clinical trials with IPI+NIVO and ENCO+BINI
- No Treatment-related deaths

Real World Sequencing Outcomes with Immunotherapy and Targeted Therapy in BRAF+ Metastatic Melanoma (The NOBLE Study Series)

1108P

Author(s): A Betof Warner, MD, PhD[1]; A Tarhini, MD, PhD[2]; ML Johnson, PhD[3]; B Kang, PhD[4]; A Nakasato, MD[4]; M Vance, DO[4]; YL Ling, PhD[4]; J Tang, MSc[5]; J Patel, PhD[4]

Affiliations: [1] Memorial Sloan Kettering Cancer Center, New York, NY; [2] H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; [3] Department of Pharmaceutical Health Outcomes and Policy, University of Houston, Houston, Texas; [4] Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936, USA; [5] Asclepius Analytics Ltd., New York, NY

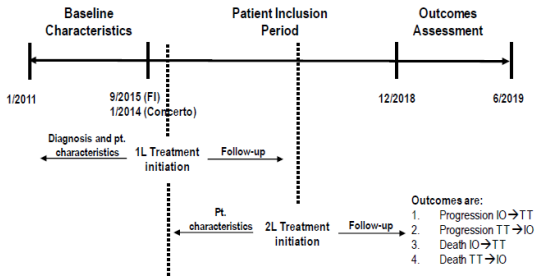
Introduction

- Initial treatment decision-making for BRAF V600-mutated Metastatic Melanoma (MM) patients remains complex.
- Targeted Therapy (TT) with BRAF-MEK inhibition is associated with high overall response rate (ORR) but is thought to be of limited duration, while immune checkpoint inhibitors (IO) are associated with lower ORR but can be more durable.
- In absence of head-to-head clinical trial data, it is unclear which treatment sequence (1L IO to 2L TT vs 1L TT to 2L IO) provides maximum benefit to patients. This study compares outcomes in the real-world across the two treatment sequences.

Methods

- We included BRAF+ MM patients who received both 1L and 2L therapies (either IO or TT) from Jan 1, 2014 up to Dec 31, 2018.
- Using the NOBLE study registry, we obtained data from both academic and community sites in the US from two oncology-specific EHR-derived databases: Flatiron Health and Concerto
- We analyzed patient characteristics descriptively and used Kaplan-Meier curves with a Cox regression model to compare progression free survival (PFS) and overall survival (OS) across the two treatment sequences (1L IO to 2L TT vs 1L TT to 2L IO),
- Patients were censored at the initiation of 3L or last follow-up on 2L.
- Time-dependent covariate analysis was used to capture the time on 1L therapy in addition to time on 2L therapy.
- To adjust for differences in patient characteristics across the two sequences, we used inverse probability of treatment weighting (IPTW) based on propensity scores.
- Propensity scores were obtained using patient demographic and clinical characteristics: age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, modified Charlson comorbidity index (CCI) score, lactate dehydrogenase (LDH), brain metastasis, bone metastases, lung metastases, liver metastasis, other metastases, and number of metastases.

Figure 1. Study Design

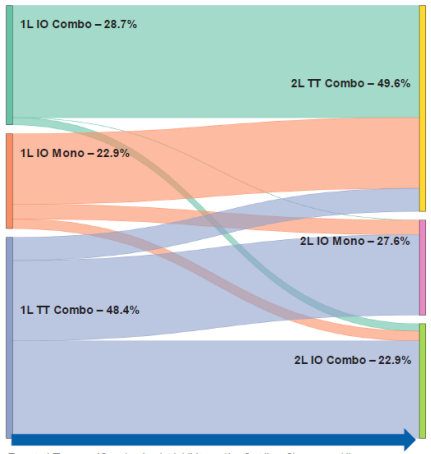


1L – first line; 2L – second line; FI – Flatiron; TT – Targeted Therapy; IO – checkpoint inhibitors;

Results

- 296 patients included of whom 150 received IO in 1L and TT in 2L, and 146 received TT in 1L and IO in 2L.
- Approximately half of the patients received TT as both 1L or 2L therapy (Figure 2).
- The most common IO therapy was IO Combo (ipilimumab + nivolumab) in both 1L and 2L.
- Patients who received TT in 1L and IO in 2L were more likely to have ECOG status of 1 at initiation of 1L therapy (Table 1).
- Comparable PFS and OS rates were observed regardless of treatment sequence used.
- Regardless of treatment sequence, patients progressed relatively rapidly through both 1L and 2L therapies (combined PFS of 13.2 months for TT-IO and 12 for IO-TT after IPTW adjustment). (Figure 3)
- The 2-year OS was 76% for TT-IO compared to 77% for IO-TT.

Figure 2. Patient flow from 1L to 2L



TT – Targeted Therapy; IO – checkpoint inhibitors; 1L – first line; 2L – second line

Distribution of 1L and 2L therapy, among patients with 2L therapy use N = 341 (45 patients did not switch)

1L Therapy			2L Therapy: IO Combo (23.0%)		IO Mono (27.6%)		TT Combo (49.6%)		% based on row totals
			78		94		169		
IO Combo	(28.7%)	0	0.0%	6	6.1%	92	93.9%	
IO Mono	(22.9%)	12	15.4%	8	10.3%	58	74.4%	
TT Combo	(48.4%)	66	40.0%	80	48.5%	19	11.5%	

Table 1. Baseline Demographic and Clinical Characteristics of the cohort

	IO to TT N = 150		TT to IO N = 146		p-value
	N	%	N	%	
Age (mean, SD) in years	58.9	13.5	59.2	15.7	0.895
Sex					
Male	89	59.3%	88	60.3%	0.869
Race					
White	135	95.1%	128	92.1%	0.561
Non-White	7	4.9%	11	7.9%	
ECOG Status					
0: Fully active	71	65.7%	43	50.0%	0.005
1: Restricted in strenuous activities	26	24.1%	38	44.2%	
2: Ambulatory capable of self-care	5	4.6%	5	5.8%	
3+: Capable of limited self-care	6	5.6%	0	0.0%	
CCI, (mean, SD)	0.3	0.8	0.3	0.6	0.990
Metastatic sites					
Number of sites (mean, SD)	2.4	1.6	2.8	1.8	0.042
Brain metastases	50	33.3%	52	35.6%	0.679
Bone metastases	49	32.7%	48	32.9%	0.969
Lung metastases	87	58.0%	80	54.8%	0.578
Liver metastases	40	26.7%	36	24.7%	0.692
Biomarker Testing					
PD-L1 positive	3	9.1%	2	9.1%	1.000
KIT positive	1	1.7%	2	4.3%	0.418
NRAS positive	0	0.0%	0	0.0%	1.000
LDH Test					
Low LDH	22	25.6%	20	25.0%	0.060
Normal LDH	50	58.1%	35	43.8%	
Elevated LDH	14	16.3%	25	31.1%	
ALT Test					
Low ALT	67	54.5%	47	42.7%	0.008
Normal ALT	42	34.1%	58	52.7%	
Elevated ALT	14	11.4%	5	4.5%	
AST Test					
Low AST	26	21.1%	20	18.3%	0.103
Normal AST	93	75.6%	78	71.6%	
Elevated AST	4	3.3%	11	10.1%	

TT – Targeted Therapy; IO – checkpoint inhibitors; 1L – first line; 2L – second line; CCI – Charlson Comorbidity index; Mets – metastases; SD – Standard Deviation

Figure 3. Progression Free Survival (n=292)

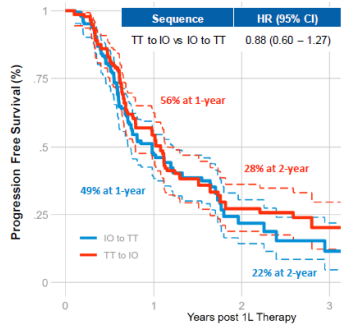
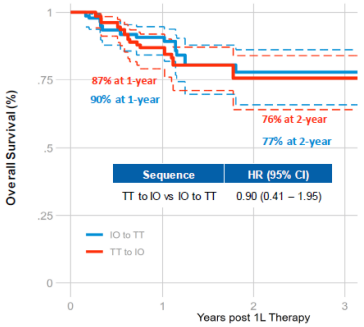


Figure 4. Overall Survival (n=292)



TT – Targeted Therapy; IO – checkpoint inhibitors; 1L – first line; patients censored at initiation of third line therapy; 4 patients had missing data and so were excluded from survival analysis

Discussion

- Irrespective of treatment sequence, current mainstay IO and TT treatments for BRAF+ metastatic melanoma patients provides similar outcomes in the real-world
- Since clinical trials are designed to demonstrate efficacy of the treatments. they typically exclude patients with high tumor burden, brain metastasis, and elevated LDH, however, data for the NOBLE study series was obtained from more than 150 sites in the US and is representative of the community practice and real -world outcomes.
- The accuracy and completeness of data collected in this study are limited by the quality of data in the patient's medical chart.

Conclusion

- In BRAF+ MM patients, real-world registry data showed similar risk of progression and mortality irrespective of initial choice of treatment.
- Most cases of progression occurred within the first-year of therapy. Based on the high incidence of disease progression, continued research to find new therapies is warranted.
- In absence of head-to-head clinical trial data, this real-world study provides insight into two treatment sequences outcomes.

References -

1. Ascierto PA, Caraco C, Gershenwald JE, et al. The Great Debate at "Melanoma Bridge", Napoli, December 2nd, 2017. J Transl Med. 2018;16(1):101.

2. Ghate S, Ionescu-Ittu R, Burne R, et al. Patterns of treatment and BRAF testing with immune checkpoint inhibitors and targeted therapy in patients with metastatic melanoma presumed to be BRAF positive. Melanoma Res. 2019;29(3):301-310.

3. Robert C, Grob JJ, Stroyakovskiy D, et al. Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma. N Engl J Med. 2019;381(7):626-636.

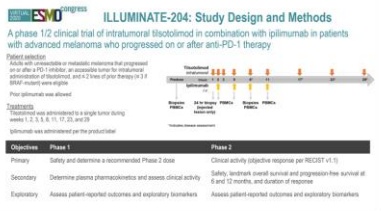
Disclosures

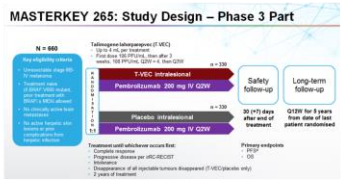
B Kang, A Nakasato, M Vance, YL Ling, J Patel are employees of Novartis. J Tang received consulting fee from Novartis.

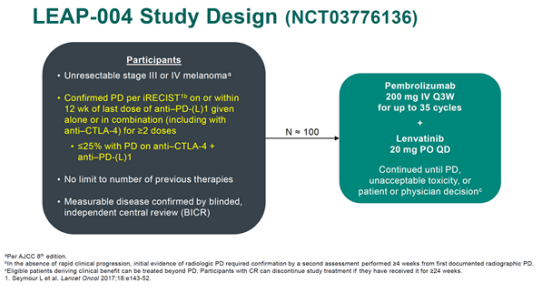
Poster presented at ESMO Congress 2020, Madrid, Spain, 18-22 September 2020.

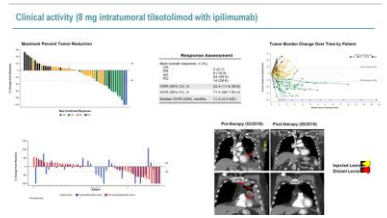
This study was sponsored by Novartis Pharmaceuticals.

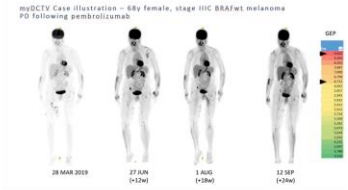
What's next in metastatic melanoma











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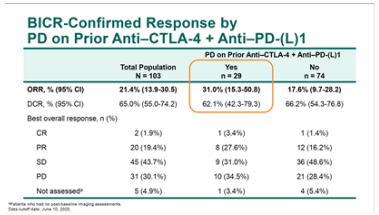
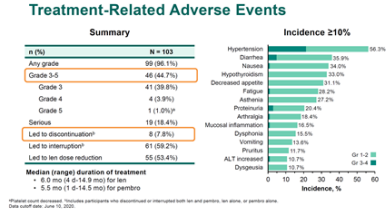
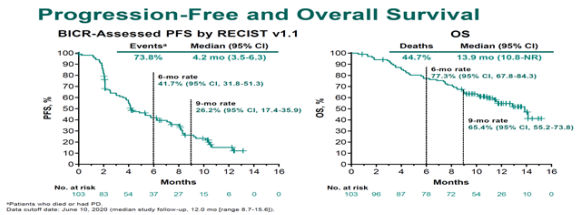
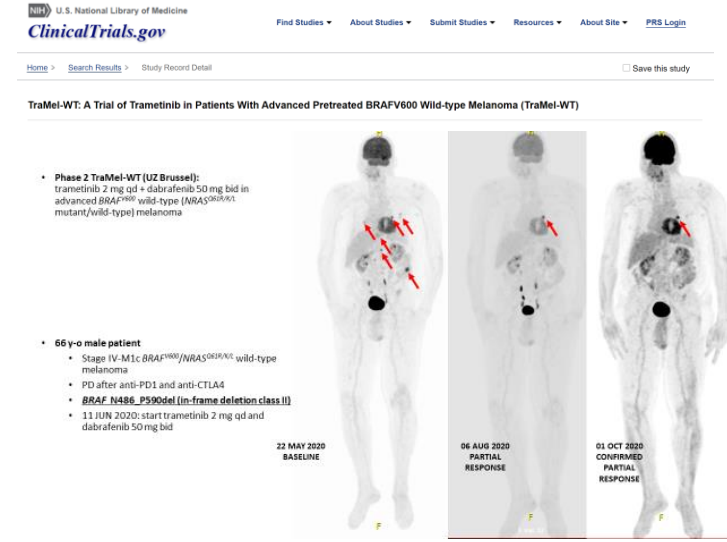


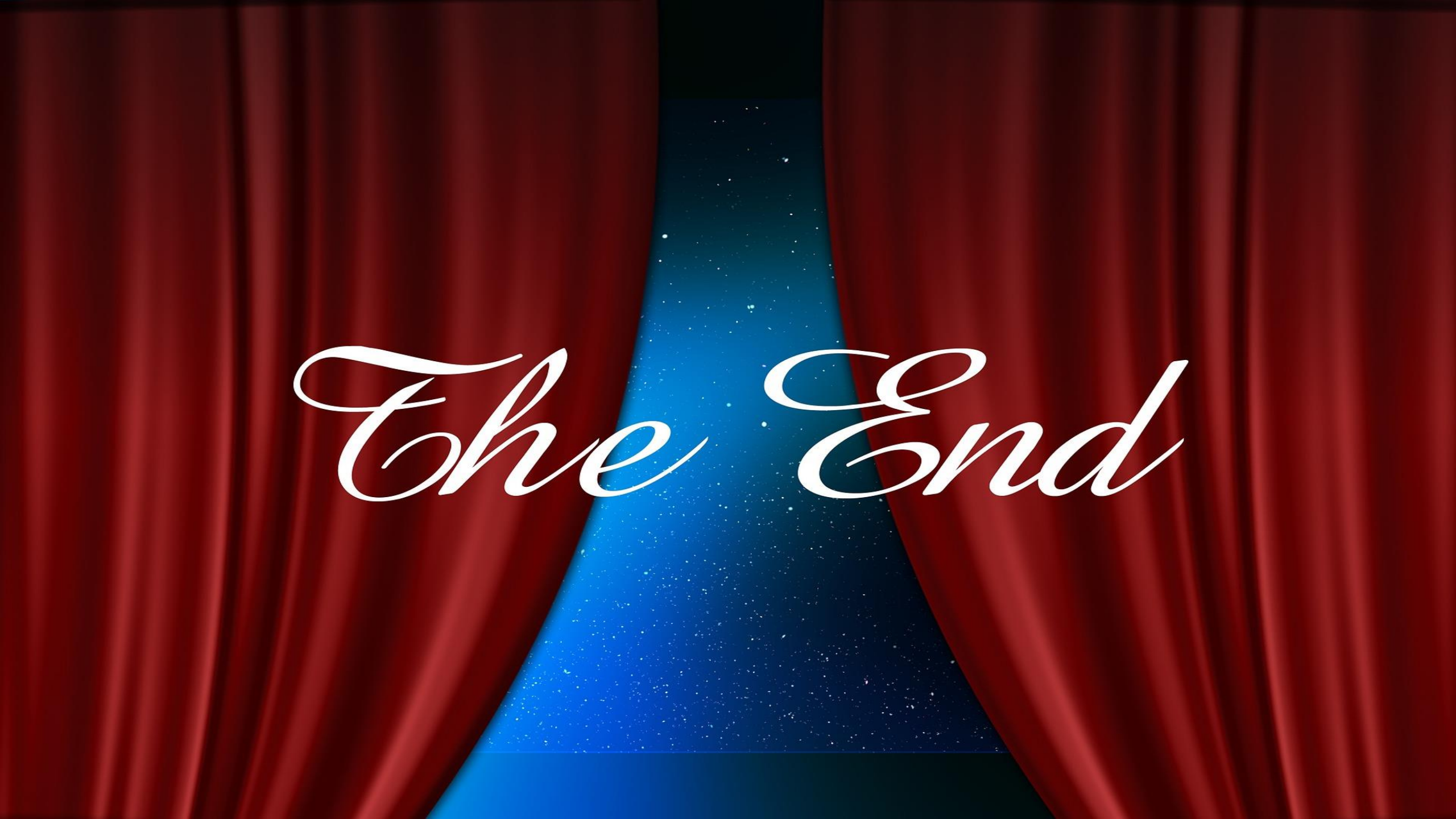






Conclusions

- In treatment naive BRAF V600-mutant patients , first-line “triplet therapy” with BRAF/MEK-inhibitors plus an anti-PD-1/-L1 mAb did not demonstrate a sufficiently large and clinical meaningful benefit when compared to BRAF/MEK-inhibitors as a monotherapy to be considered a new standard of care (Imspire150 and COMBI-i)
  - Numerical PFS/OS (up to 2y of FU) are best results ever reported for BRAF V600mut melanoma
- BRAF/MEK-inhibitors remain a valid first-line treatment option for BRAF V600-mutant melanoma patients, especially in those patients with baseline clinical characteristics that predict a lower chance for the activity of PD-1 ($^{+}/_{-}$ CTLA-4) blocking mAb
- Optimal sequencing of therapy, including an elective treatment switch prior to progression, remains a subject of ongoing clinical research
  - Early data (SECOMBIT) and real-world data (NOBLE) suggest that for most patients either sequence may result in comparable outcome for most patients
- Exposure to dabrafenib/trametinib or anti-PD-1 therapy in the adjuvant setting will influence treatment choices in the metastatic setting


The End