New Developments in Melanoma: Early and Late Stage

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CMO, Cancer Expert Now

Overview

- Late Stage (Metastatic) Melanoma
- Early Stage Melanoma
  - Adjuvant Therapy
  - Neoadjuvant Therapy

Late Stage (Metastatic) Melanoma

- Combination immunotherapy has emerged as the standard of care first line therapy for most patients regardless of BRAF mutation status
- Is there a role of Triple therapy (combination BRAF/MEK plus anti-PD1)?
- Emerging options for refractory patients

Late Stage (Metastatic) Melanoma

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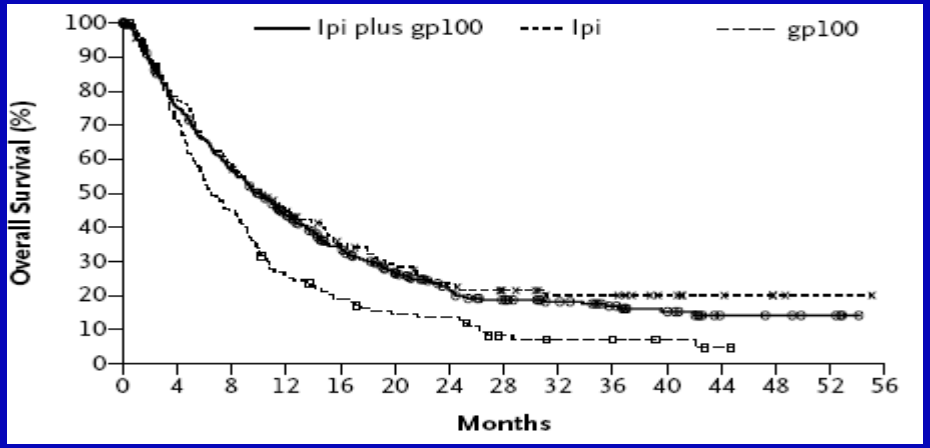
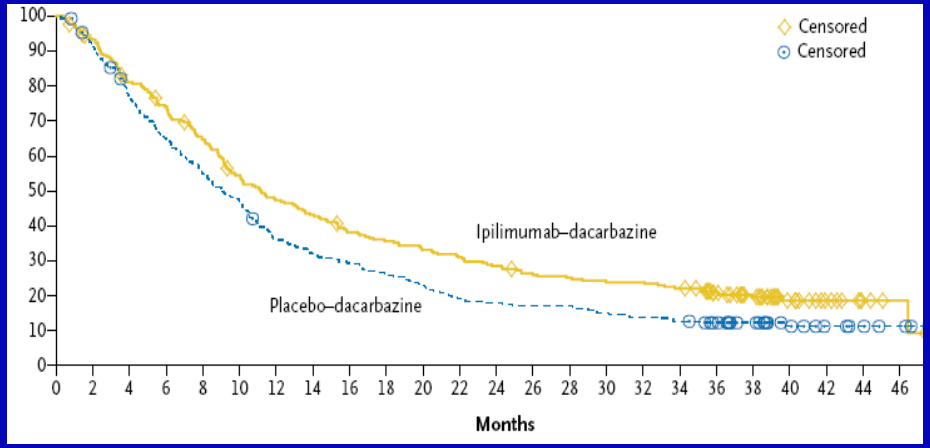
- Emerging options for refractory patients

Anti-CTLA4 Ipilimumab Changed the Landscape



HR: 0.66 and 0.68
Pre-treated pts
Ipi 3 mg/kg +/- gp100

Hodi FS, et al. *N Engl J Med.* 2010;363:711-23.



HR: 0.72
First line
Ipi 10 mg/kg + DTIC

Robert C, et al. *N Engl J Med*. 2011;364:2517-26.

Keynote-006 Front-line Pembrolizumab vs Ipilimumab

Patients

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

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

R
1:1:1

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

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

[a]Patients enrolled from 83 sites in 16 countries.

[b]Prior anti-BRAF targeted therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.

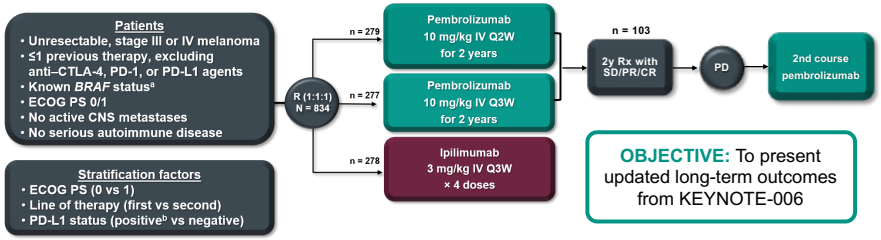
[c]Defined as membranous PD-L1 expression in ≥1% of tumor cells as assessed by IHC using the 22C3 antibody.

Long-Term Survival From Pembrolizumab Completion and Pembrolizumab Retreatment: Phase 3 KEYNOTE-006 in Advanced Melanoma

G. V. Long[1-4], J. Schachter[5], A. Arance[6], J.-J. Grob[7], L. Mortier[8], A. Daud[9], M. S. Carlino[1,2,10,11], A. Ribas[12], C. M. McNeil[2,13], M. Lotem[14], J. Larkin[15], P. Lorigan[16], B. Neyns[17], C. U. Blank[18], T. M. Petrella[19], O. Hamid[20], E. Jensen[21], C. Krepler[21], S. J. Diede[21], C. Robert[22]

ASCO 2020

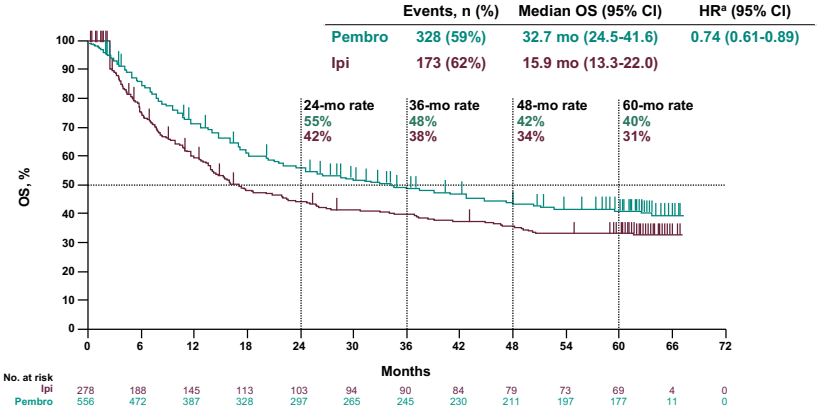
[1]Melanoma Institute Australia, Sydney, NSW, Australia; [2]University of Sydney, Sydney, NSW, Australia; [3]Royal North Shore Hospital, Sydney, NSW, Australia; [4]Mater Hospital, North Sydney, NSW, Australia; [5]Sheba Medical Center, Tel HaShomer Hospital, Tel Aviv, Israel, [6]Hospital Clinic de Barcelona, Barcelona, Spain; [7]Aix Marseille University, Hôpital de la Timone, Marseille, France; [8]Université Lille, Centre Hospitalier Regional Universitaire de Lille, Lille, France; [9]UCSF, San Francisco, CA, USA; [10]Blacktown Hospital, Blacktown, NSW, Australia; [11]Crown Princess Mary Cancer Centre, Westmead Hospital, Sydney, NSW, Australia; [12]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [13]Chris O'Brien Lifehouse, Camperdown, NSW, Australia; [14]Sharett Institute of Oncology, Hadassah Hebrew Medical Center, Jerusalem, Israel; [15]Royal Marsden Hospital, London, England; [16]University of Manchester and the Christie NHS Foundation Trust, Manchester, England; [17]Universitair Ziekenhuis Brussel, Brussels, Belgium; [18]Netherlands Cancer Institute, Amsterdam, Netherlands; [19]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [20]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [21]Merck & Co., Inc., Kenilworth, NJ, USA; [22]Gustave Roussy and Paris-Sud University, Villejuif, France



- Two pembrolizumab arms pooled as similar efficacy[2]
- Patients completing ≥94 weeks of pembrolizumab with SD/PR/CR were considered to have completed 2 years of treatment
- Patients could receive a 2nd course of 1 year of pembrolizumab if progressed after SD/PR/CR
- Data cut-off: July 31, 2019; median follow-up: 66.8 months (range, 65.0-70.4); time from last patient enrolled to data cutoff, 65.0 months

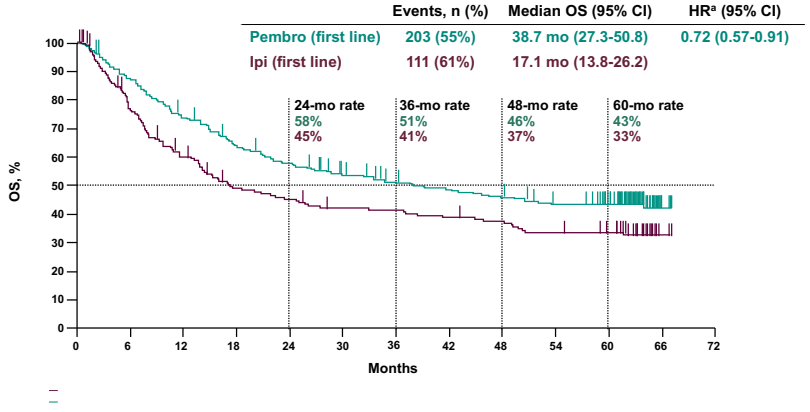
[a]Prior anti-BRAF therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.
[b]Defined as ≥1% staining in tumor and adjacent immune cells as assessed by IHC using 22C3 antibody.

Overall Survival: Total Population



Data cut-off: July 31, 2019. [a]Based on Cox regression model with treatment as a covariate stratified by line of therapy (1st vs 2nd), PD-L1 status (positive vs negative) and ECOG (0 vs 1); in instances where there were no patients in one of the treatment groups involved in a comparison for a particular stratum, that stratum was excluded from the treatment comparison.

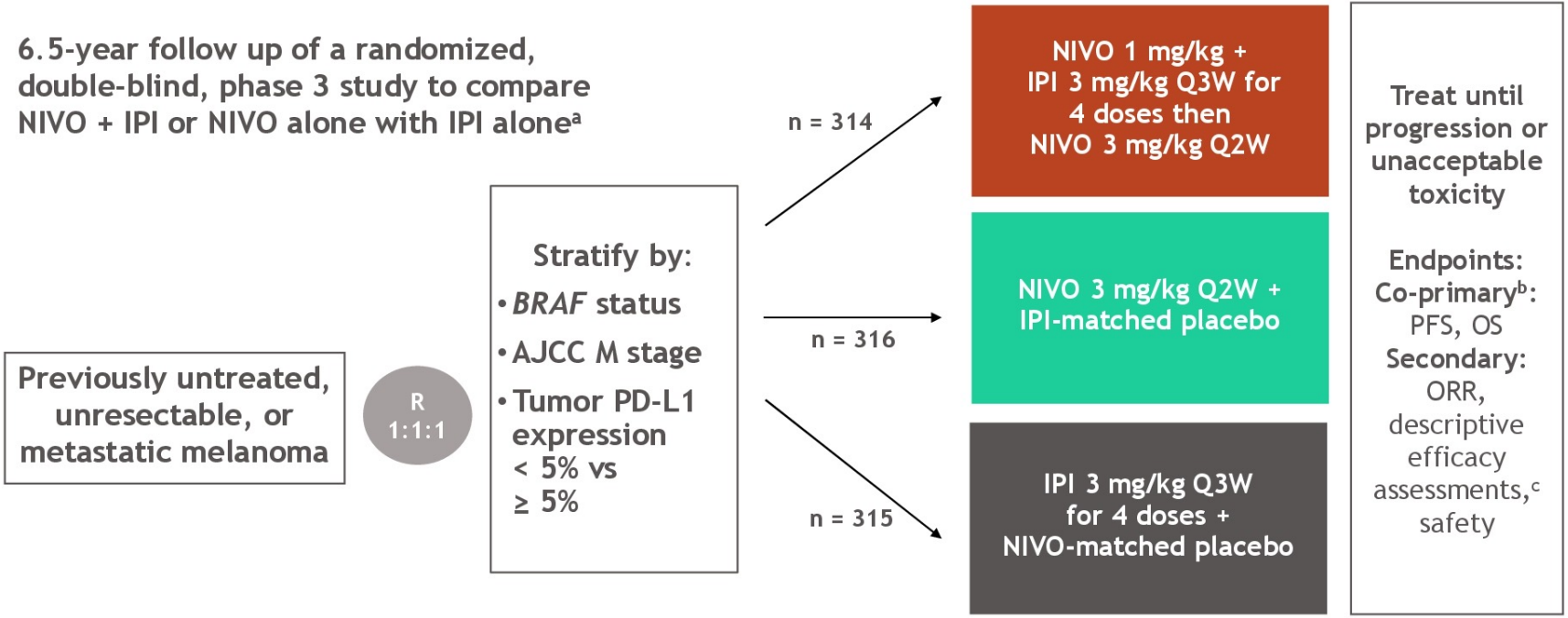
Overall Survival: First Line Patients



Data cut-off: July 31, 2019. [a]Based on Cox regression model with treatment as a covariate stratified by line of therapy (1st vs 2nd), PD-L1 status (positive vs negative) and ECOG (0 vs 1); in instances where there were no patients in one of the treatment groups involved in a comparison for a particular stratum, that stratum was excluded from the treatment comparison.

CheckMate 067: study design

6.5-year follow up of a randomized, double-blind, phase 3 study to compare NIVO + IPI or NIVO alone with IPI alone[a]

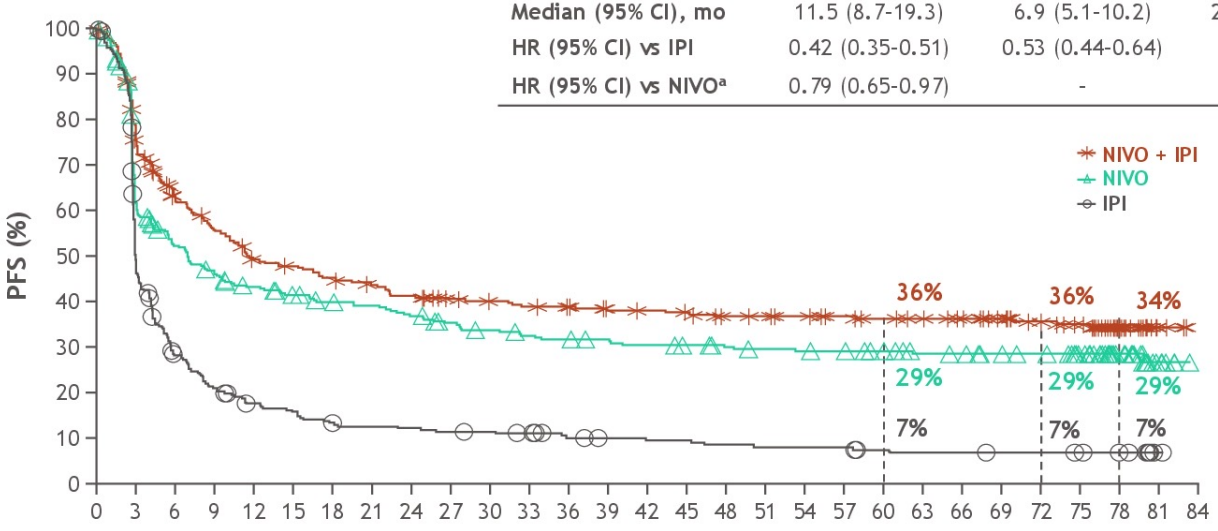


Database lock: October 19, 2020; minimum follow-up of 77 months for all patients

[a]The study was not powered for a comparison between NIVO+IPI and NIVO. [b]NIVO + IPI or NIVO vs IPI alone. [c]NIVO + IPI vs NIVO alone. AJCC, American Joint Committee on Cancer; M stage, metastasis stage; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks.

Progression-free survival

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	11.5 (8.7-19.3)	6.9 (5.1-10.2)	2.9 (2.8-3.2)
HR (95% CI) vs IPI	0.42 (0.35-0.51)	0.53 (0.44-0.64)	-
HR (95% CI) vs NIVO[a]	0.79 (0.65-0.97)	-	-



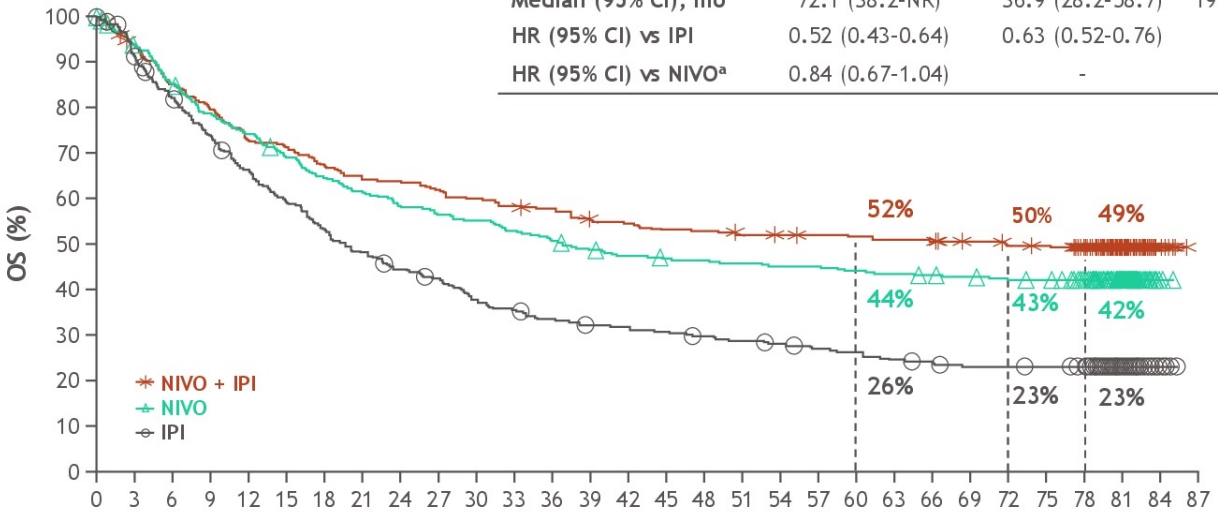
No. at risk

NIVO + IPI	314	218	174	155	136	131	124	117	110	104	101	98	96	92	90	88	83	82	80	77	74	72	69	64	58	52	29	3	0
NIVO	316	177	151	132	120	112	106	103	97	89	84	80	78	76	73	71	68	66	65	64	60	55	54	51	49	42	24	7	0
IPI	315	136	78	58	46	42	34	32	31	29	28	26	21	19	18	18	16	15	15	15	12	11	11	10	10	9	7	1	0

[a]Descriptive analysis.

Overall survival

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	72.1 (38.2-NR)	36.9 (28.2-58.7)	19.9 (16.8-24.6)
HR (95% CI) vs IPI	0.52 (0.43-0.64)	0.63 (0.52-0.76)	-
HR (95% CI) vs NIVO[a]	0.84 (0.67-1.04)	-	-

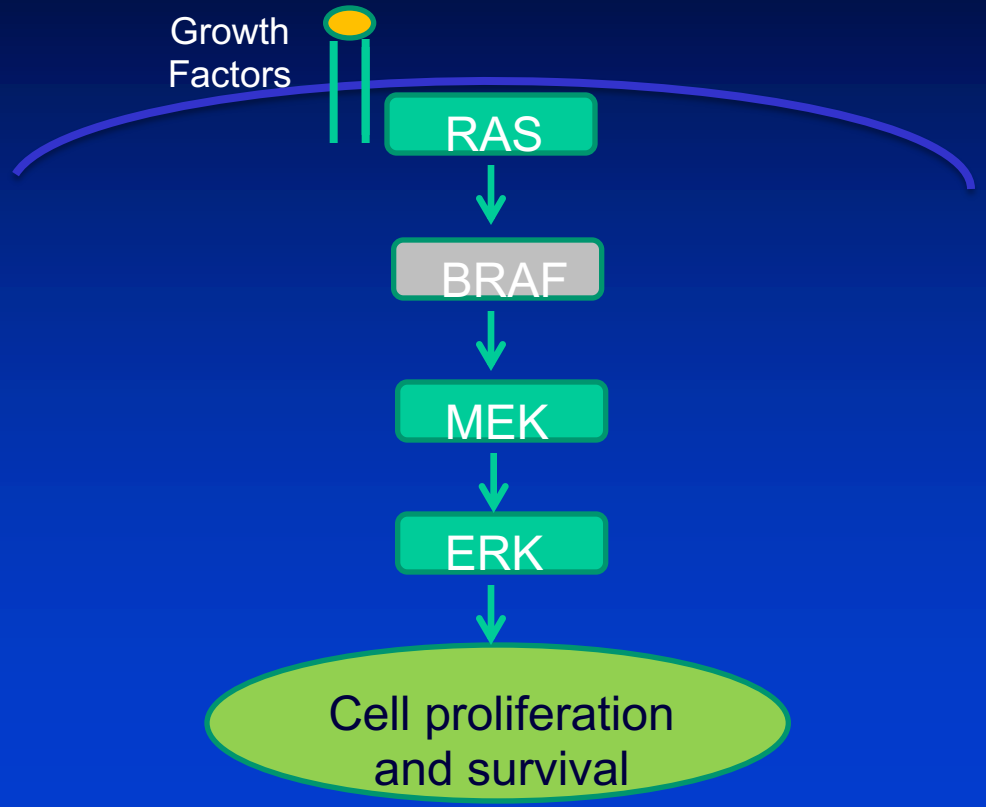


No. at risk

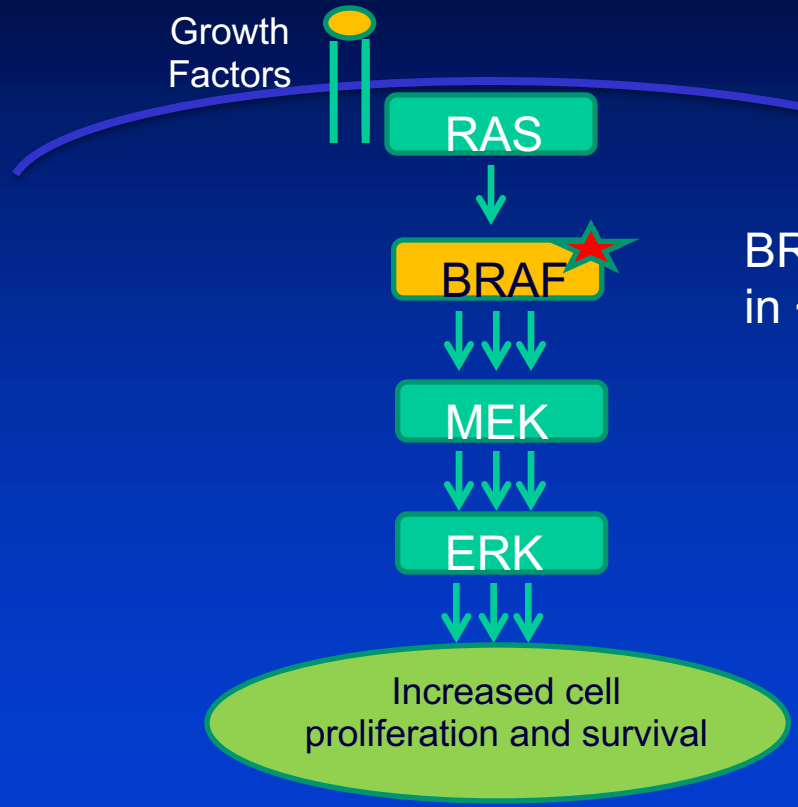
NIVO + IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	158	157	156	154	153	150	147	145	138	66	10	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	137	134	132	130	128	126	124	117	59	3	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	75	70	68	64	64	63	61	32	7	0

[a]Descriptive analysis.

Targeted Therapy: MAPK Pathway

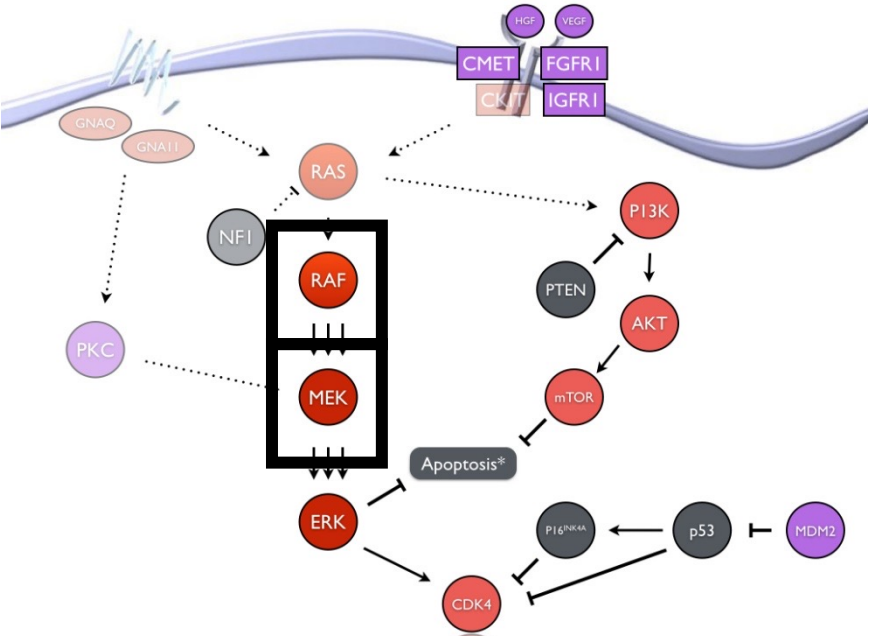


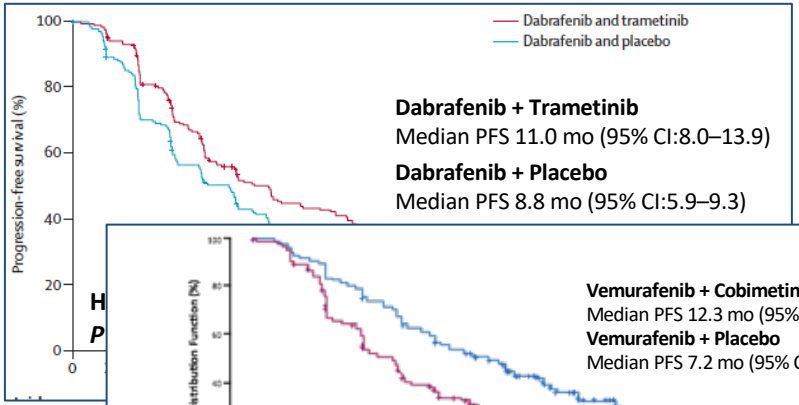
BRAF Mutation

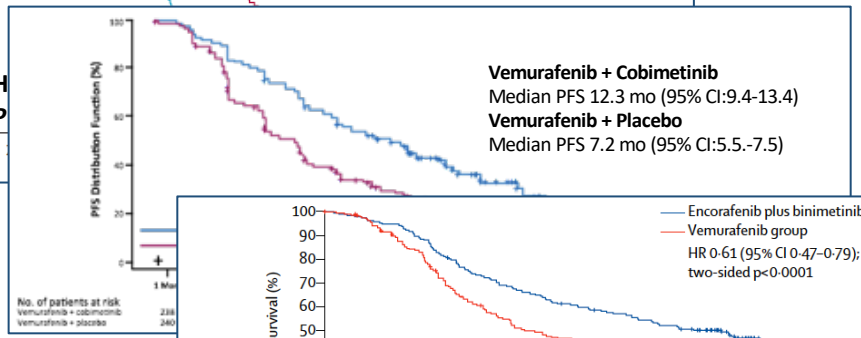


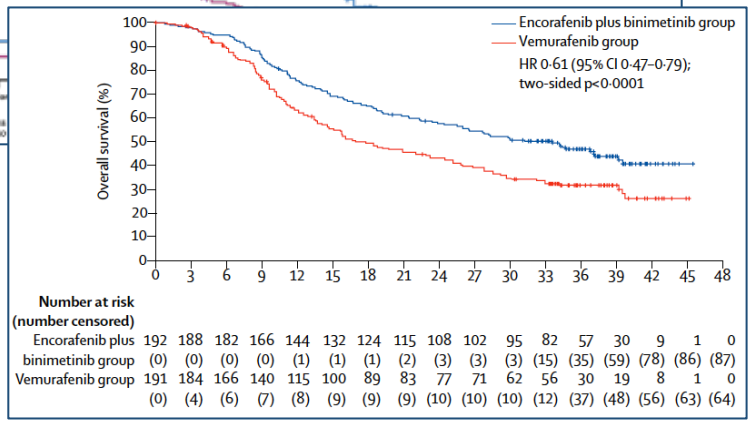
BRAF mutation is present in ~50% of melanomas

Dual BRAF and MEK Inhibition Is Associated With High Response Rates and Improved PFS and OS



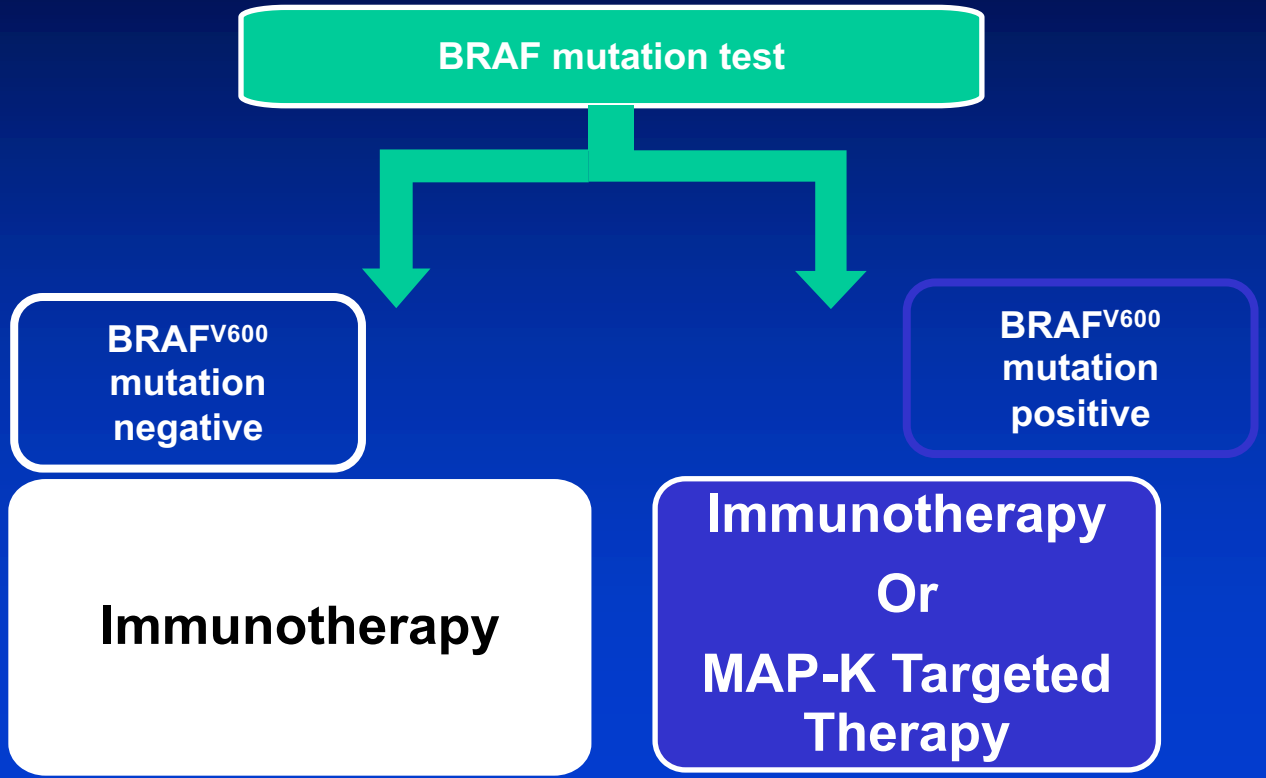






Long GV et al. *Lancet*. 2015.
Ascierto PA et al. *Lancet Oncol.* 2016.
Dummer R et al. *Lancet Oncol*. 2018.

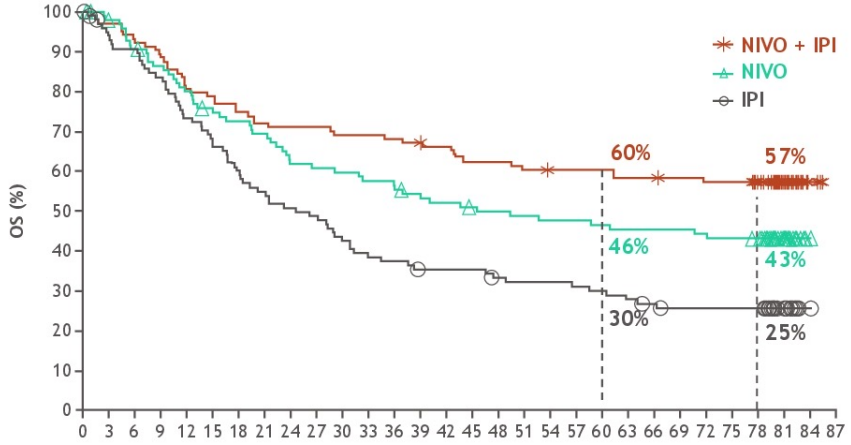
Melanoma Therapy Decision Point



OS by *BRAF* mutation status[a]

BRAF mutant

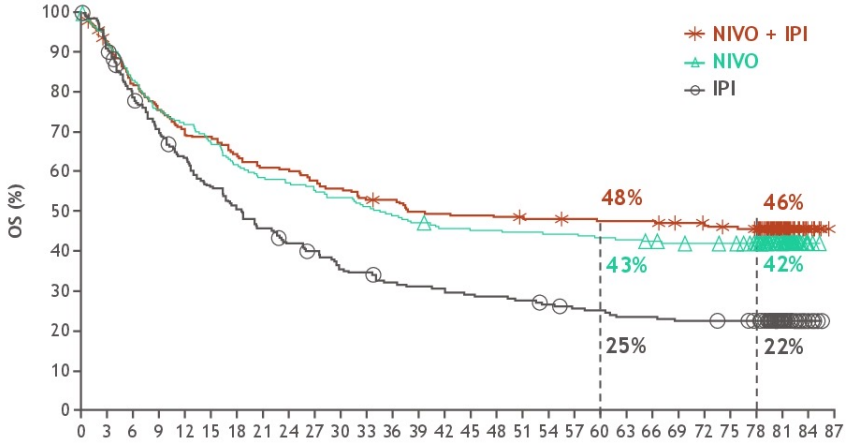
	NIVO + IPI (n = 103)	NIVO (n = 98)	IPI (n = 100)
Median (95% CI), mo	NR (50.7-NR)	45.5 (26.4-NR)	24.6 (17.9-31.0)
HR (95% CI) vs IPI	0.43 (0.30-0.60)	0.63 (0.44-0.90)	-
HR (95% CI) vs NIVO[b]	0.68 (0.46-1.0)	-	-



No. at risk																												
NIVO + IPI	103	99	96	91	83	80	77	74	73	73	71	71	70	69	67	63	63	61	60	60	60	58	58	57	56	56	51	29	3	0
NIVO	98	93	86	81	75	69	67	64	57	56	55	53	52	48	47	45	44	43	42	42	41	40	40	40	39	38	37	17	1	0
IPI	100	91	88	81	71	64	58	53	49	47	41	37	36	33	33	33	30	29	29	28	27	25	23	21	21	21	21	11	1	0

BRAF wild-type

	NIVO + IPI (n = 211)	NIVO (n = 218)	IPI (n = 215)
Median (95% CI), mo	39.1 (27.5-NR)	34.4 (24.1-59.2)	18.5 (14.1-22.7)
HR (95% CI) vs IPI	0.58 (0.45-0.74)	0.63 (0.50-0.80)	-
HR (95% CI) vs NIVO[b]	0.92 (0.71-1.18)	-	-



No. at risk																												
NIVO + IPI	211	193	169	157	144	142	133	127	126	120	116	110	109	103	102	101	100	98	98	97	96	96	95	93	91	89	87	37	7	0
NIVO	218	199	180	164	156	145	134	127	124	119	116	111	106	102	98	97	97	96	95	95	93	92	90	88	87	86	80	42	2	0
IPI	215	194	165	146	132	117	105	95	86	81	72	70	64	62	61	58	57	55	52	49	48	45	45	43	43	42	40	21	6	0

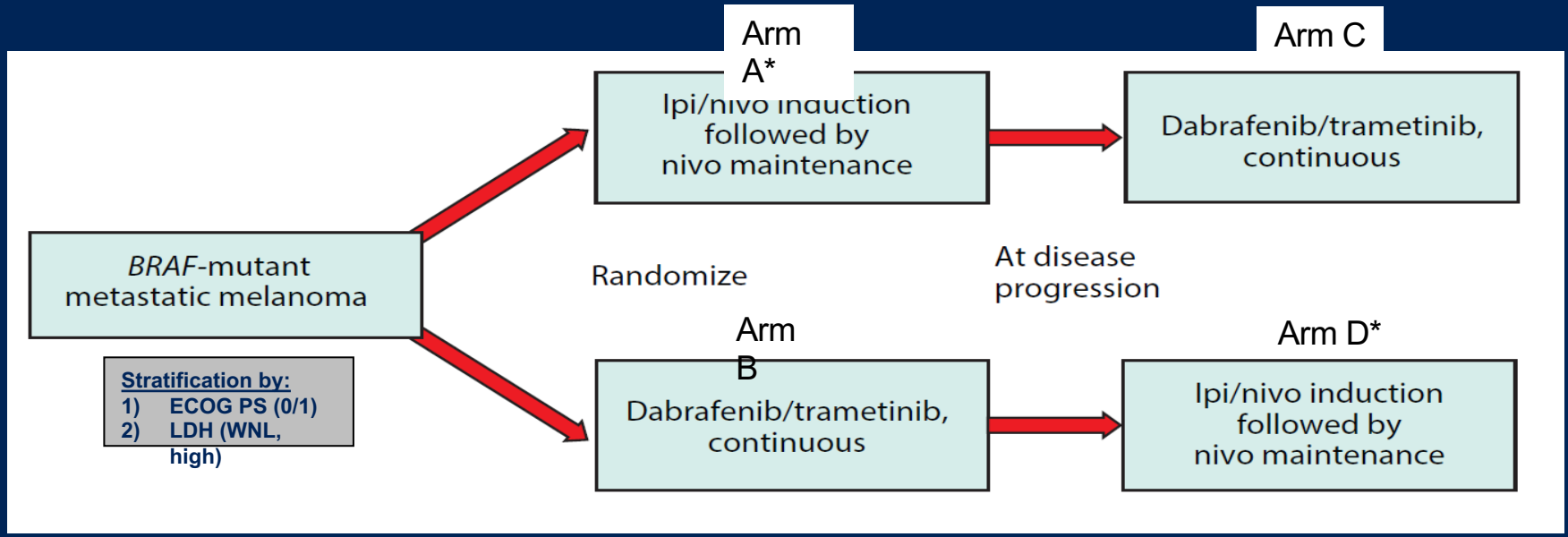
Key Ongoing Trials Evaluating Targeted Therapy Vs Combination Immunotherapy

	SECOMBIT	EORTC-1612-MG	DREAMseq
Population	Stage III (unresectable) or IV	stage III or IV (cutaneous or mucosal)	Stage III (unresectable) or IV
	BRAF V600-mutant	*BRAF V600E* or *V600K*-mutant	*BRAF V600*-mutant
N	251	270	300
Primary Endpoint	OS	PFS	OS
Primary Completion	April 2021	April 2022	October 2022
IO Regimen	NIVO 1 mg/kg IV + IPI 3 mg/kg IV Q3W x 4 → NIVO 3 mg/kg IV Q2W	NIVO 3 mg/kg Q3W + IPI 1 mg/kg Q3W x4 → NIVO 480 mg Q4W	NIVO 1 mg/kg + IPI 3 mg/kg **or** NIVO 3 mg/kg + IPI 1 mg/kg → NIVO 3 mg/kg maintenance
Targeted Regimen	Encorafenib 450 mg PO QD + Binimetinib 45 mg PO BID	Encorafenib 450 mg QD + Binimetinib 45 mg BID	Dabrafenib 150 mg PO BID + Trametinib 2 mg PO QD
Sequencing	Targeted → IO IO → Targeted Targeted → IO → Targeted	Targeted → IO IO only	Targeted → IO IO → Targeted

BID = twice daily; IO = immunotherapy; IPI = ipilimumab; IV = intravenous; NIVO = nivolumab; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PO = orally; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; QD = once daily.

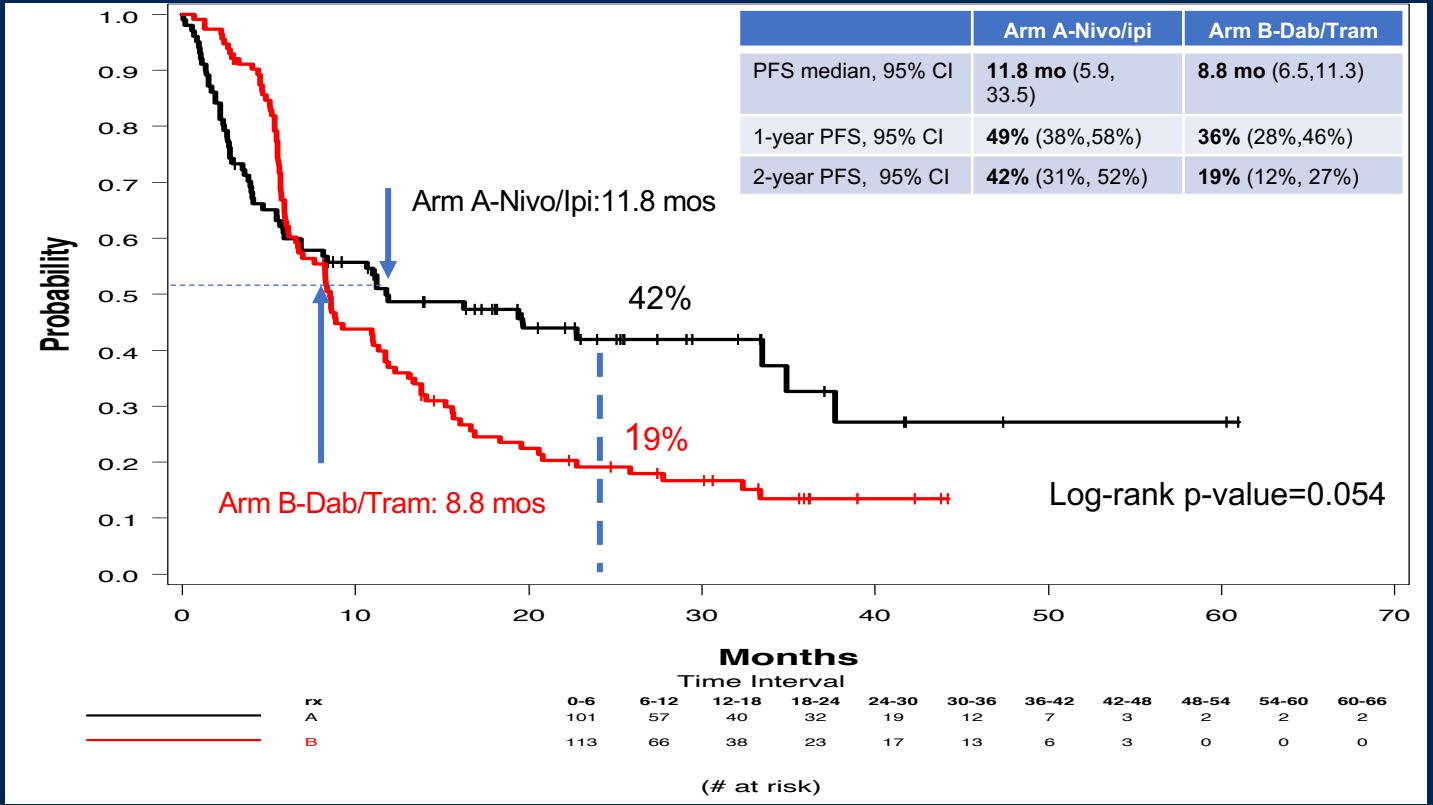
Clinical trial information: https://clinicaltrials.gov/ct2/show/NCT02631447; https://clinicaltrials.gov/ct2/show/NCT03235245; https://clinicaltrials.gov/ct2/show/NCT02224781

DREAMseq Trial Treatment Schema



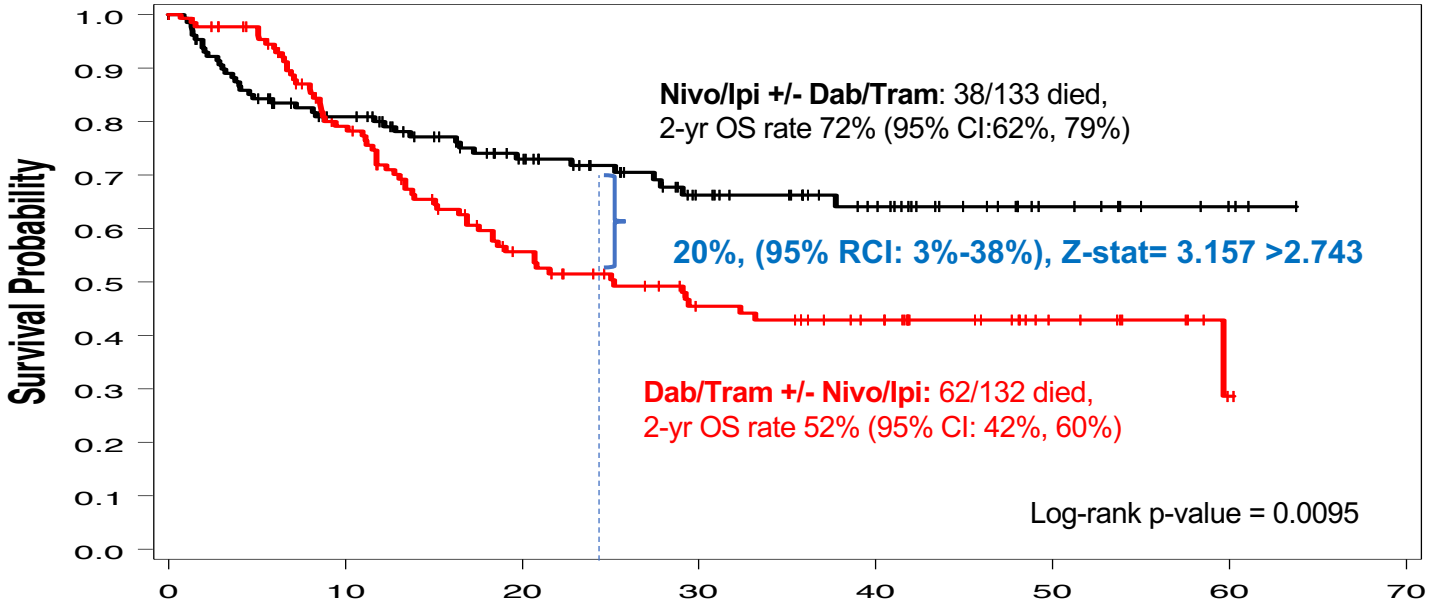
*Nivo/Ipi Induction = 12 wks; nivo maintenance = 72 wks

Progression Free Survival (PFS): Step1 (n=214)



	Arm A-Nivo/ipi	Arm B-Dab/Tram
PFS median, 95% CI	**11.8 mo** (5.9, 33.5)	**8.8 mo** (6.5,11.3)
1-year PFS, 95% CI	**49%** (38%,58%)	**36%** (28%,46%)
2-year PFS, 95% CI	**42%** (31%, 52%)	**19%** (12%, 27%)

Overall Survival (OS): Step 1 +/- Step 2



Time Interval

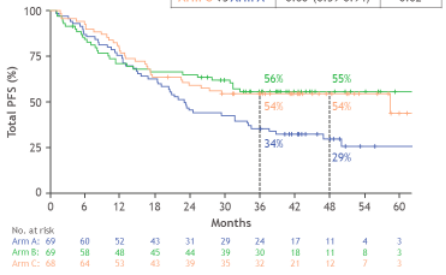
Treatment	0-6	6-12	12-18	18-24	24-30	30-36	36-42	42-48	48-54	54-60	60-66
IO+/-TT	133	99	87	71	55	42	33	23	15	6	3
TT+/-IO	132	115	78	60	47	35	30	18	15	6	1

(# at risk)

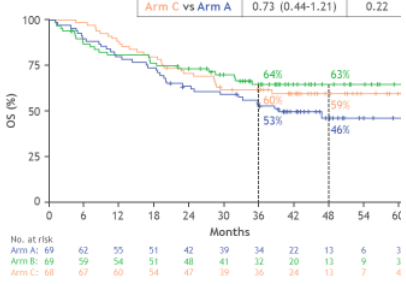
The Best Sequencing Is Combination Immunotherapy First

SECOMBIT: 4-year survival

Total PFS	HR (95% CI)[a]	*P* value
Arm B vs Arm A	0.58 (0.37-0.91)	0.01
Arm C vs Arm A	0.60 (0.39-0.94)	0.02



OS	HR (95% CI)[a]	*P* value
Arm B vs Arm A	0.66 (0.39-1.12)	0.13
Arm C vs Arm A	0.73 (0.44-1.21)	0.22

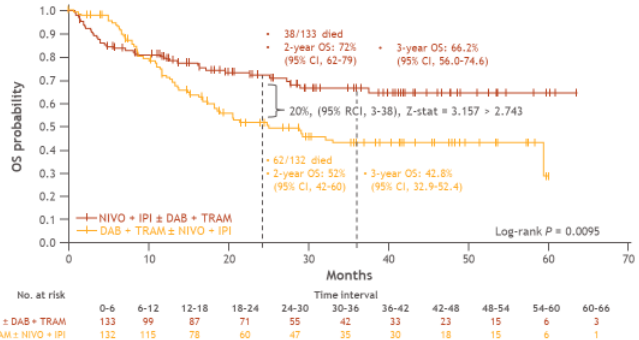


Adapted from Ascierto PA

This material may include information about investigational products and / or uses that are not approved for use in any country or in the country of your residence. Therefore, before prescribing any product, always refer to local materials such as the prescribing information and / or the Summary of Product Characteristics (SPC). Not all discussed therapies are approved for clinical use. Bristol Myers Squibb only recommends usage of approved products. Please check the product information of your country, approvals may vary. Refer to each country's local guidance for specific therapeutic strategies. Median follow-up was 43 months (estimated with the reverse Kaplan-Meier method). [a]Exploratory analysis. OS, overall survival; PFS, progression-free survival.

Ascierto PA et al. Presentation at the ESMO Congress; September 9-13, 2022; Paris, France. Abstract LBA41.

DREAMseq: overall survival (step 1 ± step 2)



No. at risk	Time interval									
	0-6	6-12	12-18	18-24	24-30	30-36	36-42	42-48	48-54	54-60	60-66
NIVO + IPI ± DAB + TRAM	133	99	87	71	55	42	33	23	15	6	3
DAB + TRAM ± NIVO + IPI	132	115	78	60	47	35	30	18	15	6	1

Adapted from Atkins MB.

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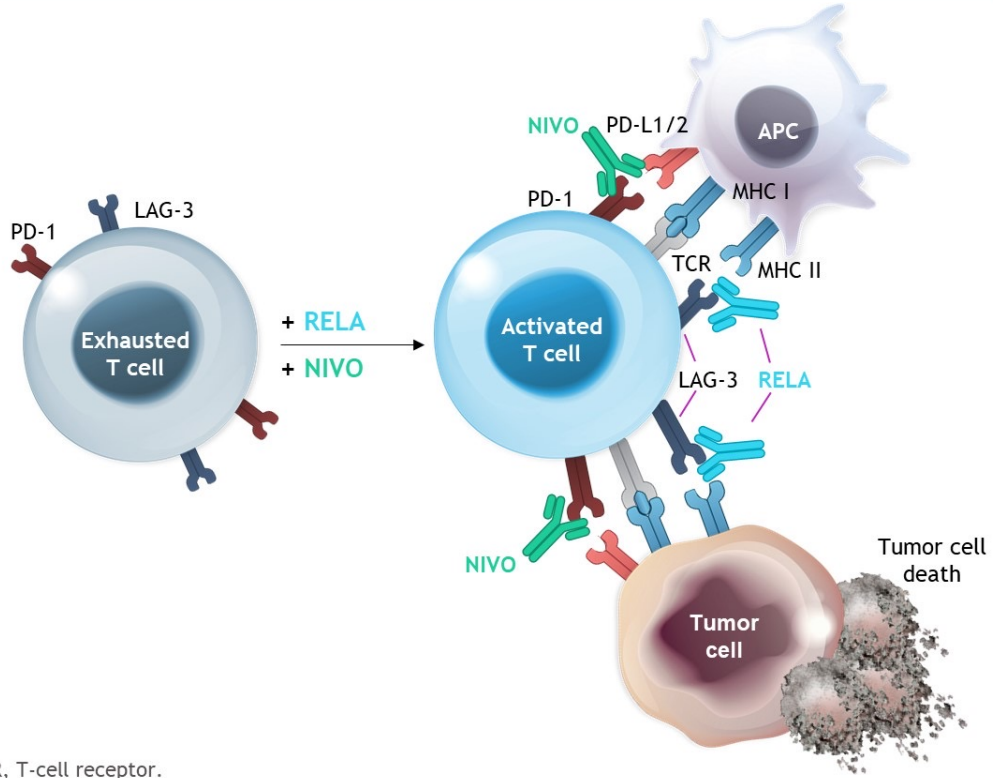
DAB, dabrafenib; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; TRAM, trametinib.

Atkins MB. Presentation at the American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022; Chicago, IL. Updates on abstract 356154.

An alternative to Ipi/Nivo?

Rationale for RELA + NIVO

- LAG-3 and PD-1 are distinct immune checkpoints, often co-expressed on tumor-infiltrating lymphocytes, and contribute to tumor-mediated T-cell exhaustion[1,2]
- In preclinical models, LAG-3 and PD-1 blockade demonstrated synergistic antitumor activity[1]
- RELA + NIVO demonstrated clinically meaningful antitumor activity including durable objective responses and was well tolerated in patients with melanoma that was relapsed/refractory to anti-PD-1 therapy[3,4]



APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor.

1. Woo S-R, et al. *Cancer Res* 2012;72:917-927; 2. Anderson AC, et al. *Immunity* 2016;44:989-1004; 3. Ascierto PA, et al. Oral presentation at ASCO Annual Meeting; June 2-6, 2017; Chicago, IL. Abstract 9520; 4. Ascierto PA, et al. Oral presentation at ESMO Congress; September 8-12, 2017; Madrid, Spain. Abstract LBA18.

Study design

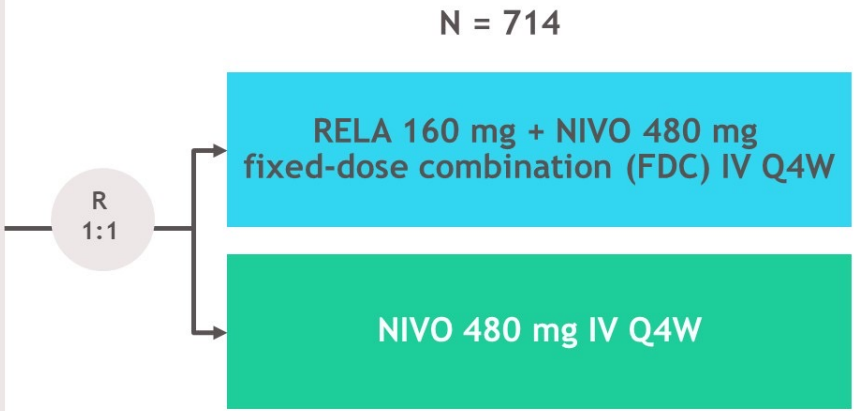
- **RELATIVITY-047** is a global, randomized, double-blind, phase 2/3 study

Key eligibility criteria

- Previously untreated unresectable or metastatic melanoma[a]
- ECOG PS 0–1

Stratification factors

- LAG-3[b]
- PD-L1[c]
- *BRAF*
- AJCC v8 M stage



Primary endpoint

- PFS by BICR[d]

Secondary endpoints

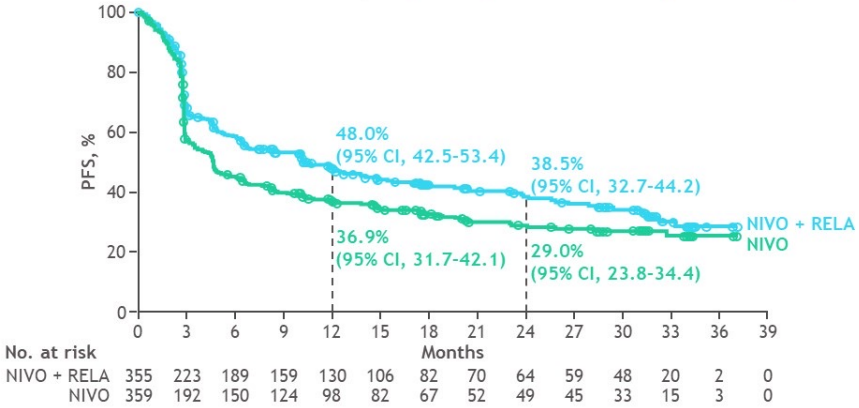
- OS
- ORR by BICR[d]

AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CTLA-4, cytotoxic T lymphocyte antigen-4; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; IV, intravenous; ORR, overall response rate; Q4W, every 4 weeks; R, randomization.
ClinicalTrials.gov: NCT03470922; Lipson E, et al. Poster presentation at ESMO Congress; October 19-23, 2018; Munich, Germany. Abstract 1302TiP.
[a]Prior adjuvant/neoadjuvant treatment permitted (anti-PD-1 or anti-CTLA-4 permitted if at least 6 months between the last dose and recurrence; interferon therapy permitted if the last dose was at least 6 weeks before randomization); [b]LAG-3 expression on immune cells was determined using an analytically validated IHC assay (LabCorp); [c]PD-L1 expression on tumor cells was determined using the validated Agilent/Dako PD-L1 IHC 28-8 pharmDx test; [d]First tumor assessment (RECIST v1.1) performed 12 weeks after randomization, every 8 weeks up to 52 weeks, and then every 12 weeks. Database lock date: March 9, 2021.

PFS, OS, and ORR in all randomized patients

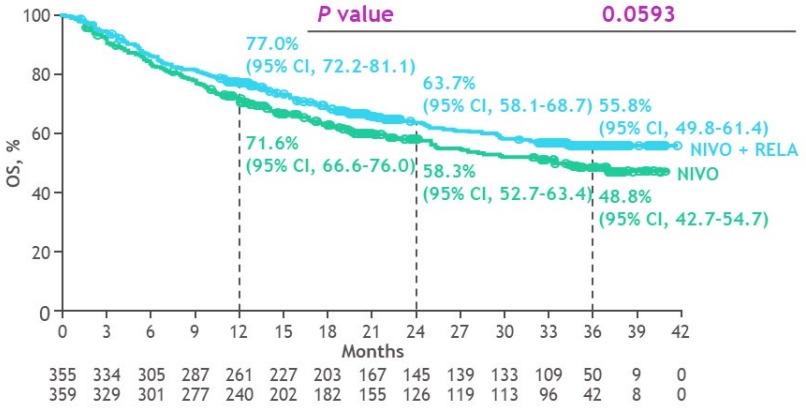
Updated PFS by BICR

	NIVO + RELA (n = 355)	NIVO (n = 359)
mPFS, mo (95% CI)	10.22 (6.51-14.75)	4.63 (3.48-6.44)
HR (95% CI)	0.78 (0.64-0.94)	



OS

	NIVO + RELA (n = 355)	NIVO (n = 359)
mOS, mo (95% CI)	NR (34.20-NR)	34.10 (25.23-NR)
HR (95% CI)	0.80 (0.64-1.01)	
P value	0.0593	



Confirmed ORR by BICR	NIVO + RELA (n = 355)	NIVO (n = 359)
ORR % (95% CI)	**43.1** (37.9-48.4)	**32.6** (27.8-37.7)

DBL date: October 28, 2021. Median follow-up: 19.3 mo

Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3, *BRAF* mutation status, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients; OS boundary for statistical significance was $P < 0.04302$ (2-sided) analyzed at 69% power; target HR, 0.75; ORR could not be formally tested and was descriptively analyzed. Minimum potential follow-up (time from last patient randomized to last patient last visit) was 8.7 mo.

Long GV, et al. Oral presentation at the American Society of Clinical Oncology (ASCO) 2022 March Plenary Series; March 15, 2022; Virtual. Abstract 360385.

Late Stage (Metastatic) Melanoma

- Combination immunotherapy has emerged as the standard of care first line therapy for most patients regardless of BRAF mutation status
- Is there a role of Triple therapy (combination BRAF/MEK plus anti-PD1)?
- Emerging options for refractory patients

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

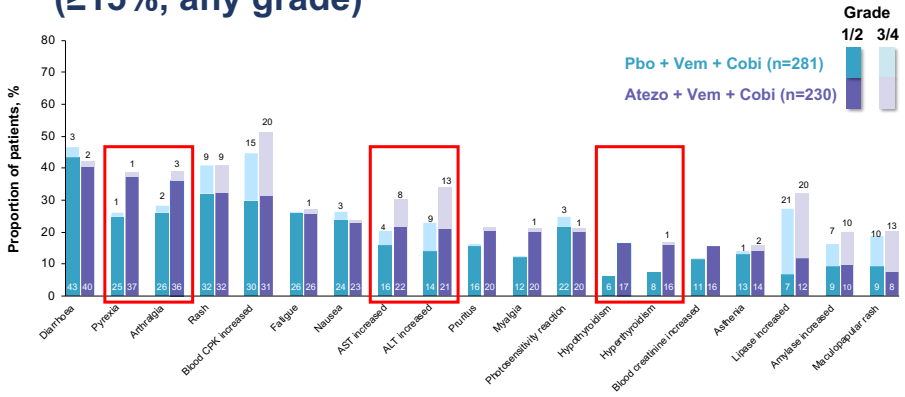
Grant A. McArthur, M.B., B.S., Ph.D.,[1] Daniil Stroyakovskiy, M.D.,[2] Helen Gogas, M.D., Ph.D.,[3] Caroline Robert, M.D., Ph.D.,[4] Karl Lewis, M.D.,[5] Svetlana Protsenko, M.D.,[6] Rodrigo Pereira, M.D.,[7] Thomas Eigentler, M.D.,[8] Piotr Rutkowski, M.D., Ph.D.,[9] Lev Demidov, M.D.,[10] Georgy Moiseevich 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]

AACR Annual Meeting 2020

[1]Melanoma and Skin Service and Cancer Therapeutics Program, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [2]Moscow City Oncology Hospital #62 of Moscow Healthcare Department, Moscow, Russia; [3]First Department of Medicine, Laiko General Hospital, National and Kapodistrian University of Athens, Greece; [4]Gustave Roussy and Université Paris-Saclay, Villejuif-Paris, France; [5]University of Colorado Comprehensive Cancer Center, Aurora, CO, USA; [6]Department of Chemotherapy and Innovative Technologies, N. N. Petrov National Medical Research Center of Oncology, St. Petersburg, Russia; [7]Hospital das Clínicas, Porto Alegre, Brazil; [8]University Hospital Tübingen, Tübingen, Germany; [9]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [10]N. N. Blokhin Russian Cancer Research Center, Ministry of Health, Moscow, Russia; [11]St. Petersburg Oncology Hospital, St. Petersburg, Russia; [12]Genentech, Inc., South San Francisco, CA, USA; [13]Roche Products Ltd., Welwyn Garden City, UK; [14]Haut-Tumour-Zentrum Hannover (HTZH), Klinik für Dermatologie, Allergologie und Venerologie, Medizinische Hochschule Hannover (MHH), Hannover, Germany; [15]Istituto Nazionale Tumori IRCCS Fondazione "G. Pascale," Naples, Italy.

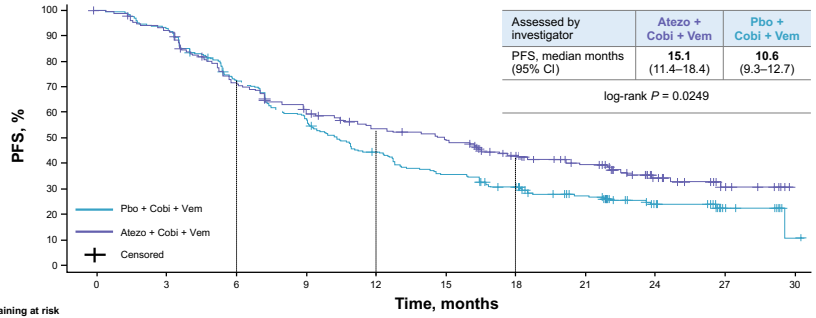
AACR Annual Meeting 2020

Common Treatment-Related AEs (≥15%, any grade)



AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase.
Listed AEs were reported at a frequency of ≥15%, along with corresponding frequencies for grade 3/4 events.

IMspire150: Primary Endpoint: Investigator-Assessed PFS



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)

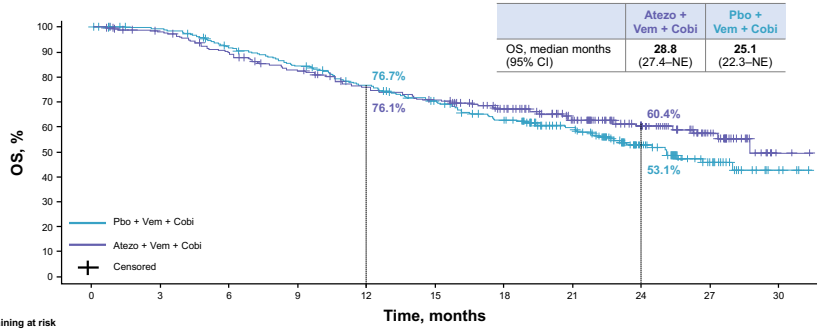
log-rank $P = 0.0249$

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.

IMspire150: 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	256	242	220	198	173	165	144	105	66	28	2

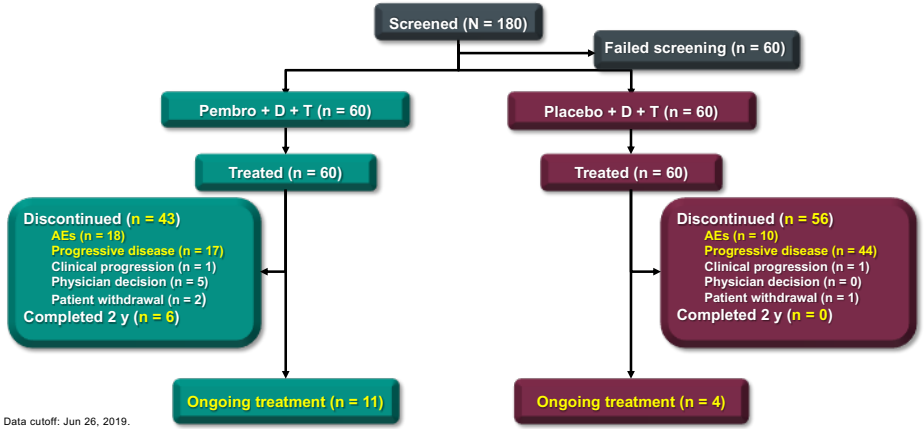
Updated Survival In Patients With *BRAF*-mutant Melanoma Administered Pembrolizumab, Dabrafenib And Trametinib

Pier Francesco Ferrucci[1a]; Paolo A. Ascierto[2a]; Michele Maio[3]; Michele Del Vecchio[4]; Victoria Atkinson[5]; Henrik Schmidt[6]; Jacob E. Schachter[7]; Paola Queirolo[8]; Georgina V. Long[9]; Rosalie Stephens[10]; Inge Marie Svane[11]; Michal Lotem[12]; Mahmoud Abu-Amna[13]; Eduard Gasal[14]; Razi Ghori[15]; Scott J. Diede[15]; Elizabeth Croydon[15]; Antoni Ribas[16]

[a]Both authors contributed equally

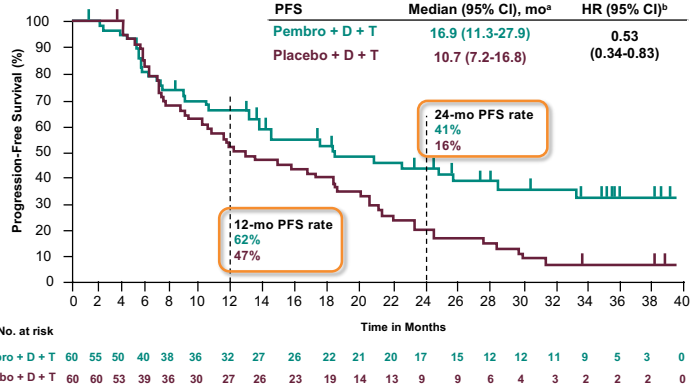
[1]Istituto Europeo di Oncologia IRCCS, Milan, Italy; [2]Istituto Nazionale Tumori IRCCS Fondazione "G. Pascale," Naples, Italy; [3]Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; [4]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [5]Gallipoli Medical Research Foundation, Greenslopes Private Hospital, Brisbane, QLD, Australia; [6]Aarhus University Hospital, Aarhus, Denmark; [7]Ella Lemelbaum Institute for Immuno-Oncology, The Chaim Sheba Medical Center at Tel HaShomer, Cancer Center (Oncology Institute), Ramat Gan, Israel; [8]IEO, European Institute of Oncology IRCCS, Milan, Italy; [9]Melanoma Institute Australia; the University of Sydney; Mater and Royal North Shore Hospitals, Sydney, NSW, Australia; [10]Auckland City Hospital, Auckland, New Zealand; [11]Herlev Hospital, University of Copenhagen, Herlev, Denmark; [12]Sharett Institute of Oncology, Hadassah Hebrew Medical Center, Jerusalem, Israel; [13]Rambam Health Care Campus, Haifa, Israel; [14]Novartis, East Hanover, NJ, USA; [15]Merck & Co., Inc., Kenilworth, NJ, USA; [16]UCLA and the Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA

Study Disposition



Data cutoff: Jun 26, 2019.

Progression-Free Survival



[a]Based on Kaplan-Meier estimate of PFS, per investigator assessment.
[b]Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (LDH >1.1 × ULN vs =1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.
Data cutoff: Jun 26, 2019.

Ascierto et al. Nature Med 2019

VIRTUAL ESMO congress 2020

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 Skłodowska-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

COMBI-i Study Design (Part 3)

N = 532

Key eligibility criteria
- *BRAF* V600 mutation–positive unresectable or metastatic melanoma
- Previously untreated
- No active brain metastases
- ECOG PS ≤ 2

RANDOMIZATION

- Spartalizumab 400 mg Q4W + dabrafenib 150 mg BID + trametinib 2 mg QD
- Placebo Q4W + dabrafenib 150 mg BID + trametinib 2 mg QD

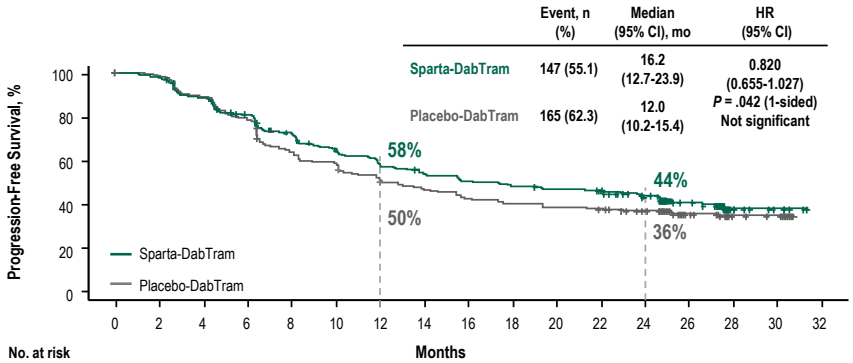
Randomization stratification
- ECOG PS
- LDH level

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

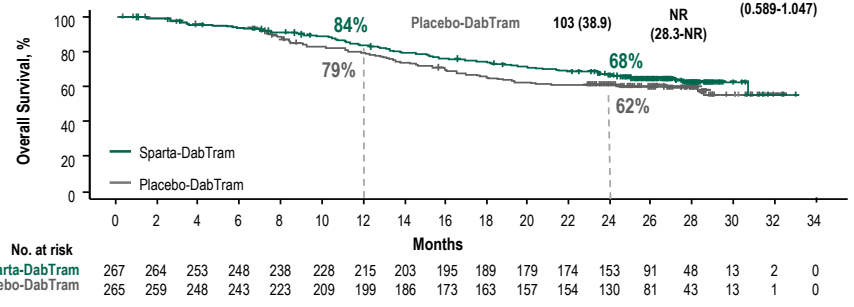


	Event, n (%)	Median (95% CI), mo	HR (95% CI)
Sparta-DabTram	147 (55.1)	16.2 (12.7-23.9)	0.820 (0.655-1.027)
Placebo-DabTram	165 (62.3)	12.0 (10.2-15.4)	*P* = .042 (1-sided) Not significant

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



	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

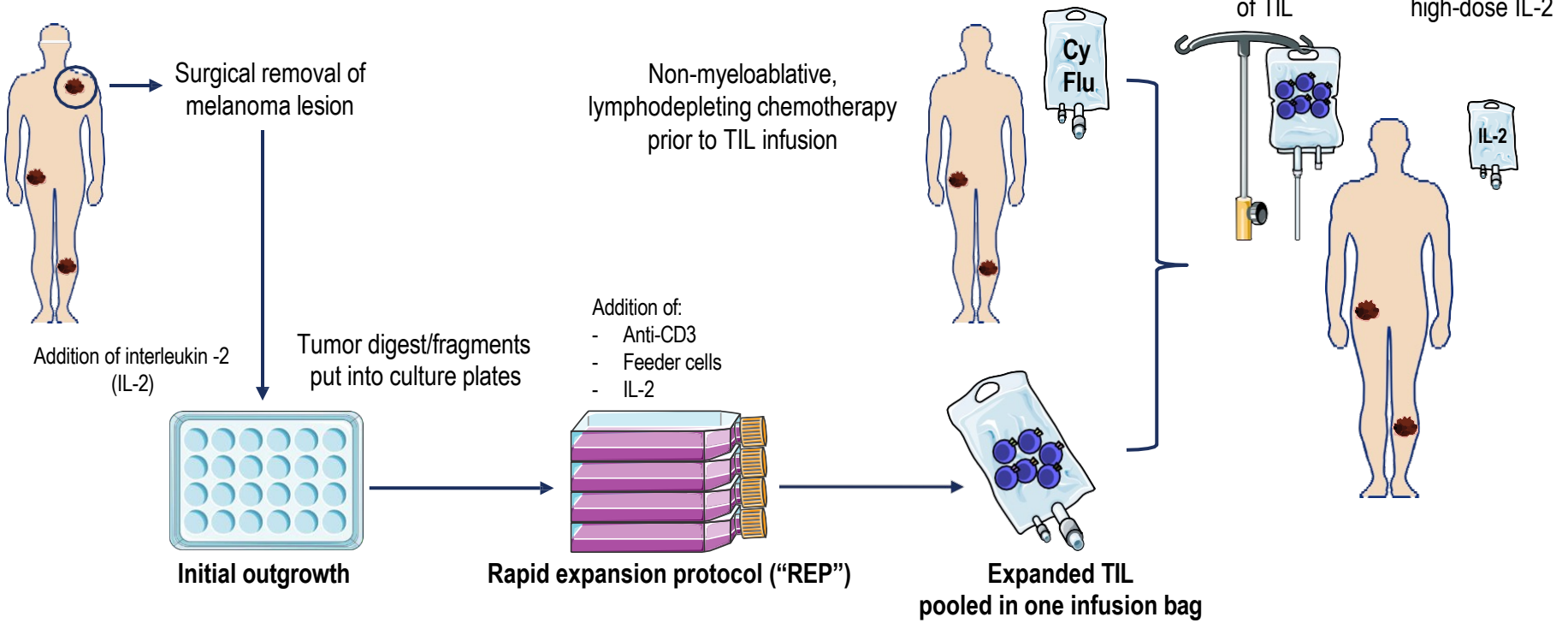
NR, not reached.

Late Stage (Metastatic) Melanoma

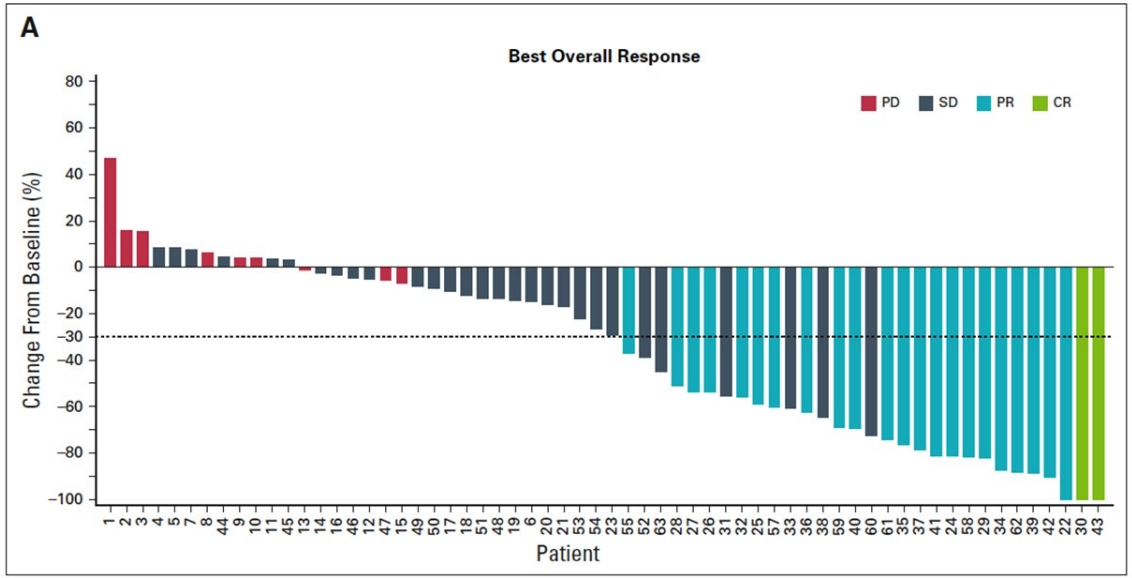
- Combination immunotherapy has emerged as the standard of care first line therapy for most patients regardless of BRAF mutation status
- Is there a role of Triple therapy (combination BRAF/MEK plus anti-PD1)?
- Emerging options for refractory patients

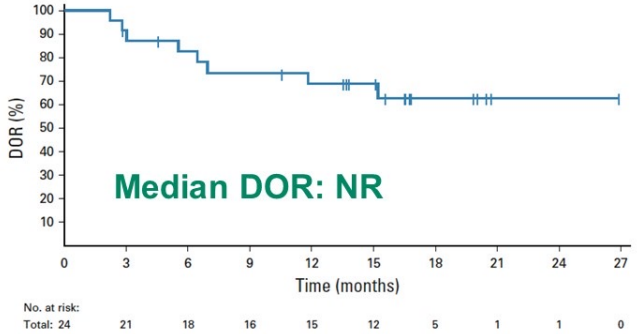
Tumor-infiltrating lymphocytes (TIL)

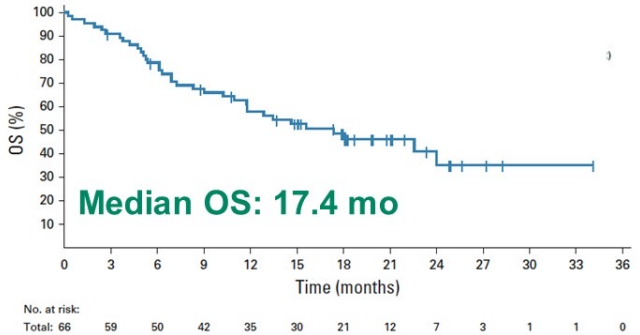
Preparation and treatment



Lifileucel for PD-1 Refractory Melanoma







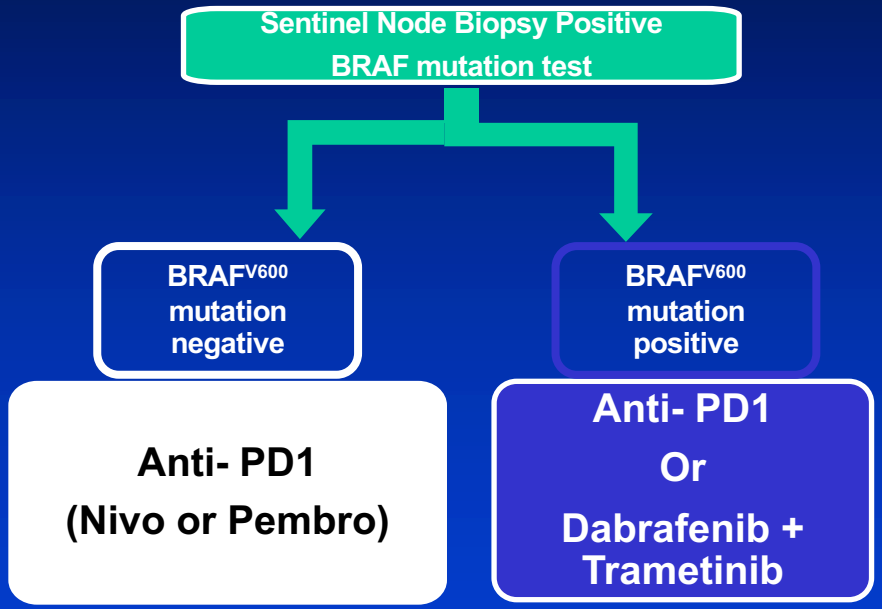
ORR: 36%
(95% CI, 25 to 49)

(Sarnaik et al. *J Clin Oncol* 2021)

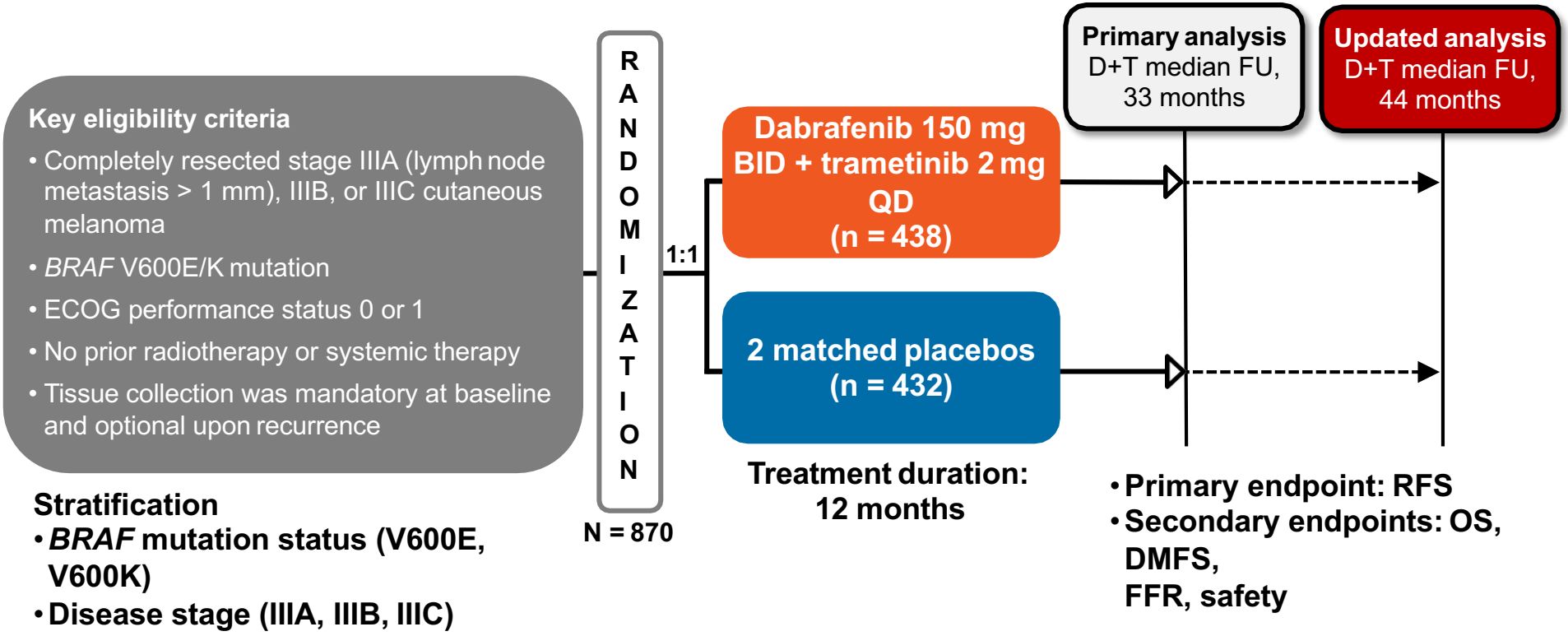
Overview

- Late Stage (Metastatic) Melanoma
- Early Stage Melanoma
  - Adjuvant Therapy
  - Neoadjuvant Therapy

Adjuvant Therapy Approach



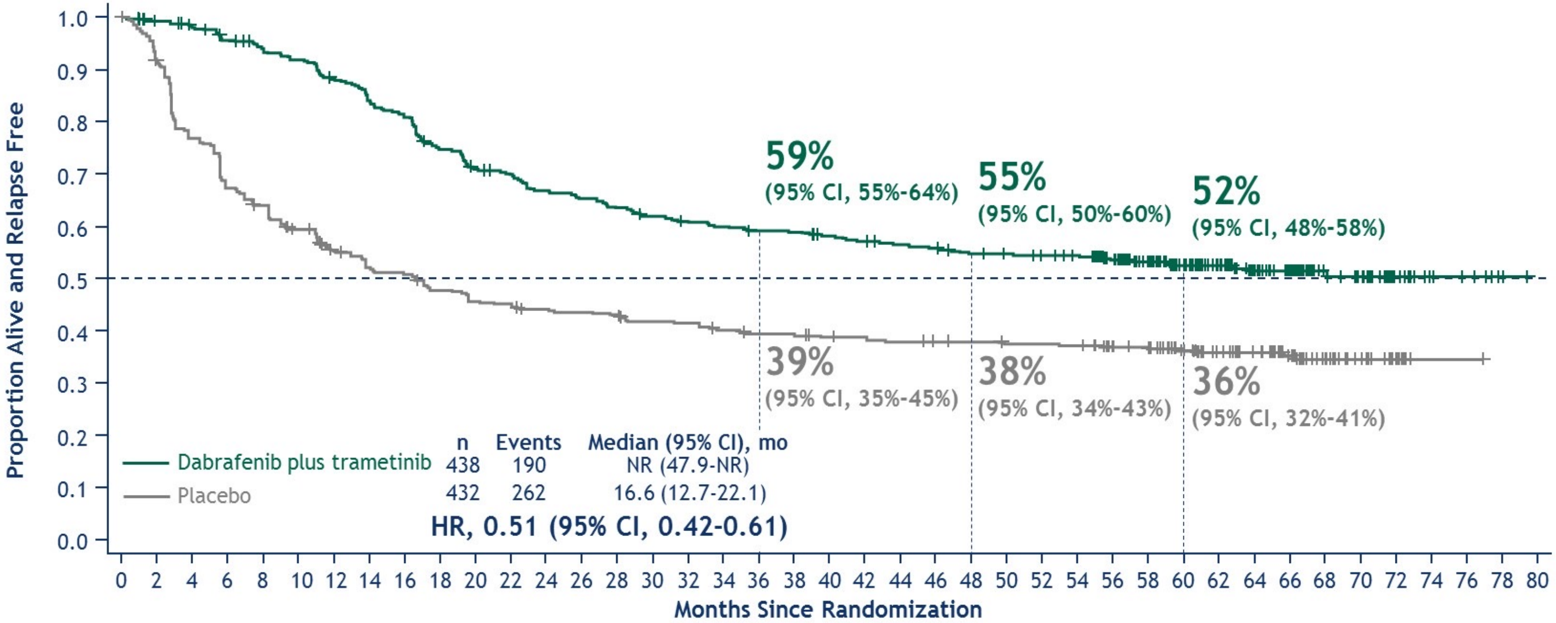
COMBI-AD: STUDY DESIGN—AND EXTENDED FOLLOW-UP ANALYSIS



BID, twice daily; DMFS, distant metastasis–free survival; D+T, dabrafenib + trametinib; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; FU, follow-up; QD, once daily.

Long GV, et al. *N Engl J Med*. 2017;377:1813-1823.

Relapse-Free Survival



No. at risk

Dabrafenib plus trametinib	438	413	405	391	381	372	354	335	324	298	281	275	262	256	249	242	236	233	229	228	221	217	213	210	204	202	199	195	176	156	133	109	92	80	45	38	17	8	6	2	0
Placebo	432	387	322	280	263	243	219	204	199	185	178	175	168	166	164	158	157	151	147	146	143	140	139	137	136	133	133	132	121	115	99	80	69	56	35	26	13	1	1	0	0

HR, hazard ratio; NR, not reached.

CheckMate 238: Study Design

Patients with:

- **High-risk, completely resected stage IIIB/IIIC or stage IV[a] melanoma**
- **No prior systemic therapy**
- **ECOG PS 0/1**

1:1

n = 453 → **NIVO 3 mg/kg IV Q2W and IPI placebo IV Q3W for 4 doses, then Q12W from week 24**

n = 453 → **IPI 10 mg/kg IV Q3W for 4 doses, then Q12W from week 24 and NIVO placebo IV Q2W**

Follow-up

Maximum treatment duration of 1 year

Stratified by:

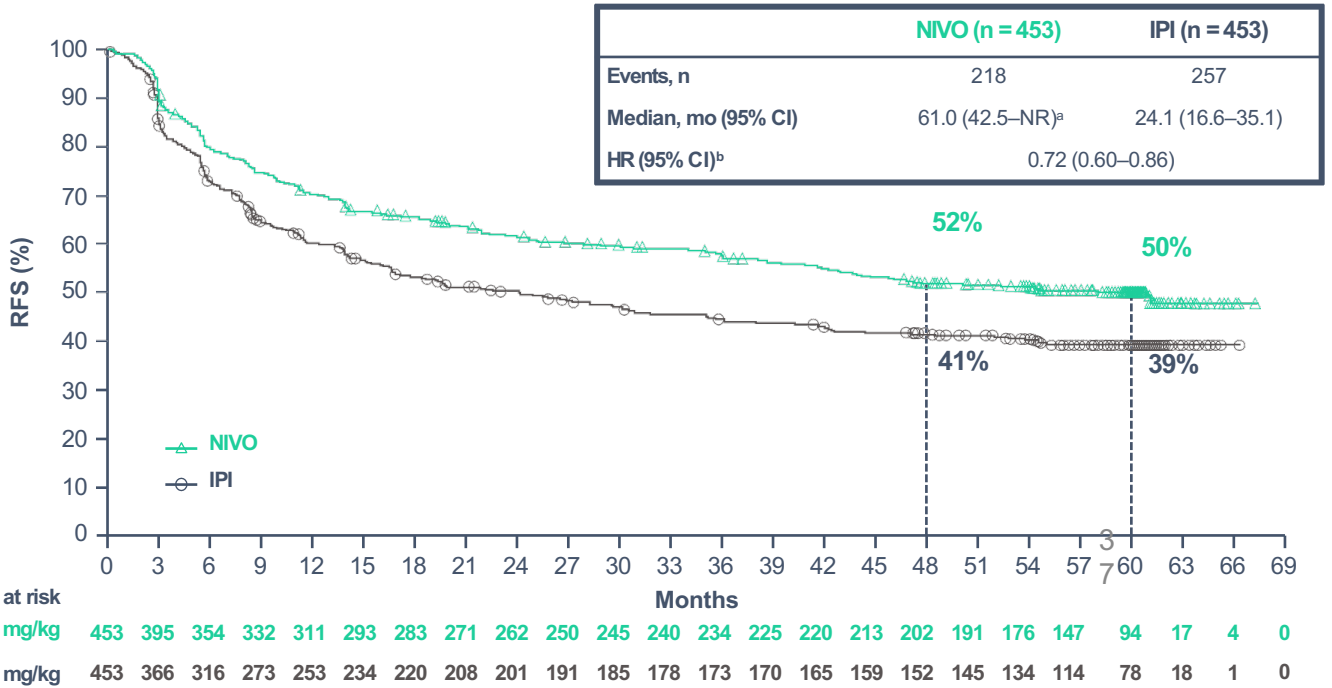
1) Disease stage: IIIB/IIIC vs IV M1a or M1b vs IV M1c
2) Tumor PD-L1 status at a 5% cutoff

Primary endpoint: RFS

Database lock: January 31, 2019; minimum follow-up of 36 months for all patients

NCT02388906.[a]Per American Joint Committee on Cancer (AJCC) Cancer Staging Manual, seventh edition.

Primary Endpoint
60 Month RFS in All Patients

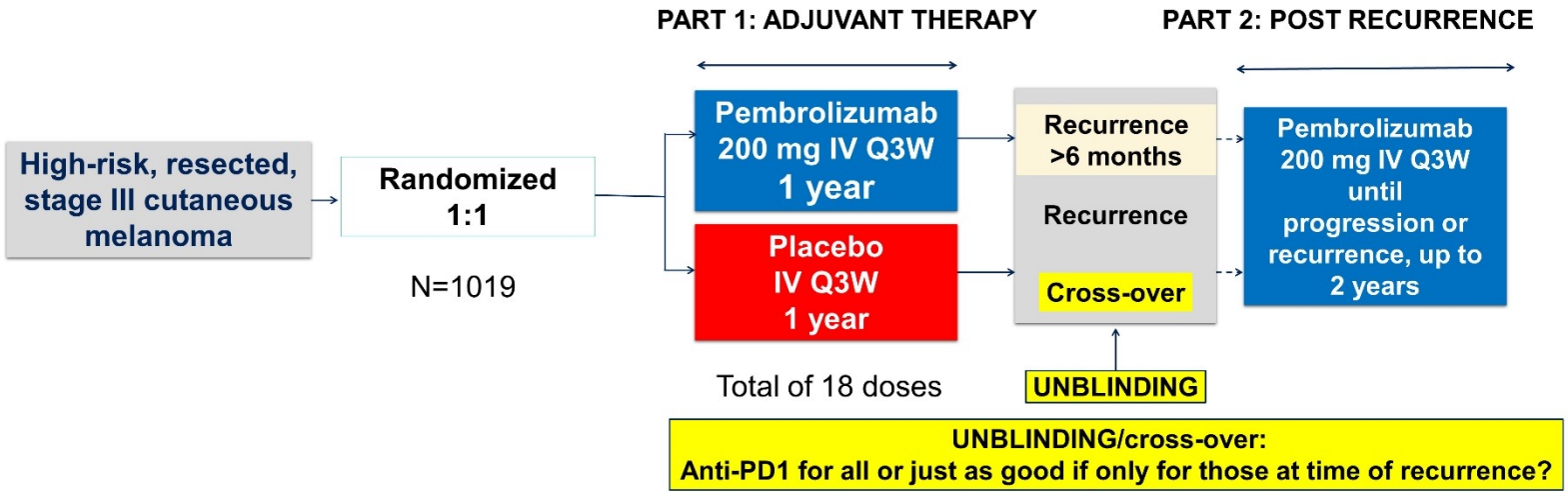


- New events since 4-year database lock: 6 (NIVO – 4 regional, 2 distant) and 4 (IPI – 1 each of local, distant, new primary, and death)

[a]Median not stable. [b]Stratified. Mo, month; NR, not reached.

Weber J et al. SMR 2021.

EORTC 1325/KEYNOTE-54 Study Design



Stratification factors:

✓**AJCC-7 Stage**: IIIA (>1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes

✓**Region**: North America, European countries, Australia/New Zealand, other countries

Primary Endpoints:

- **RFS (per investigator) in overall ITT population,** and **in patients with PD-L1-positive tumors**

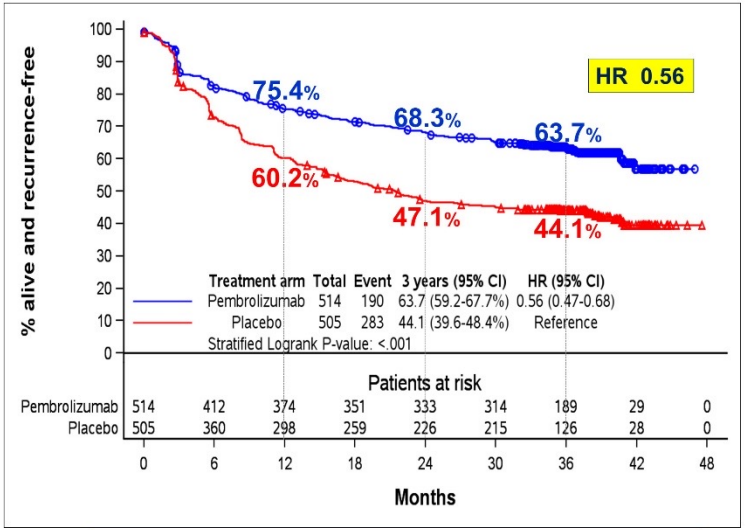
Secondary Endpoints:

- **DMFS and OS** in these 2 populations; **Safety, Health-related quality of life**

EORTC 1325/KEYNOTE-54: RFS ASCO (2020) and DMFS (ESMO 2020)

RFS updated analysis @ 3YR (ASCO 2020)[1]

- ***Cut-off date*** (30-Sep-2019); median follow-up: **3** years; **473 RFS events**

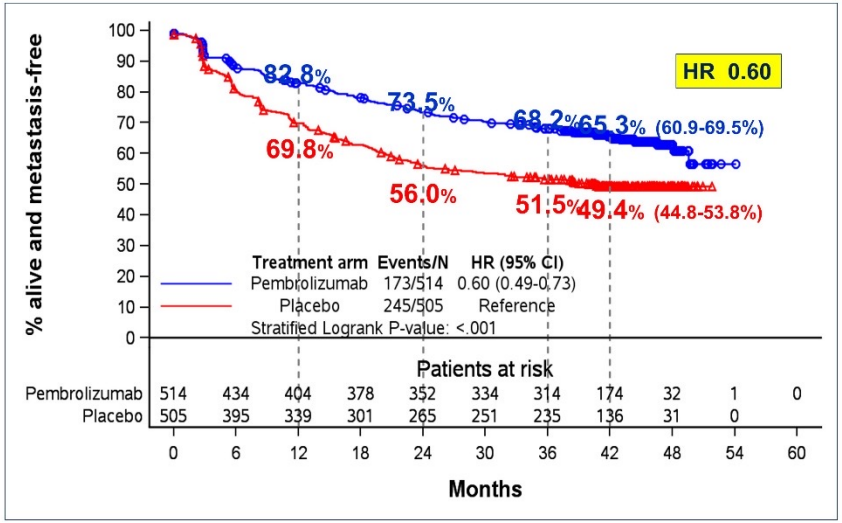


irAE: grade 1-5 (38%); grade 3-5 (7%)

[1]Eggermont AMM, et al. *J Clin Oncol* 2020;38:3925-36

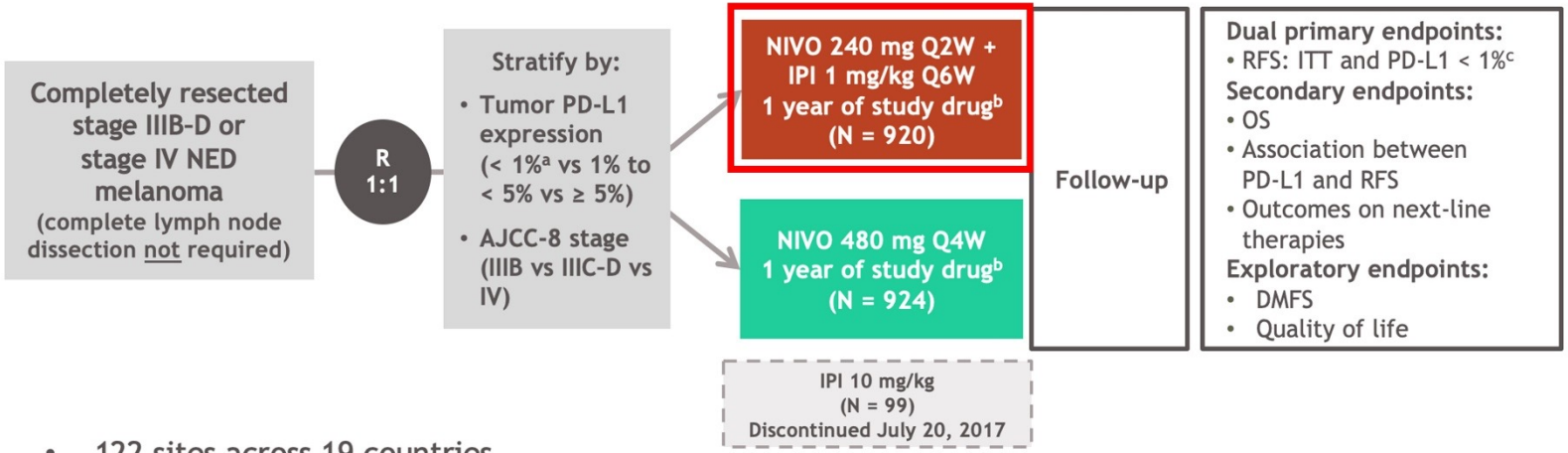
DMFS final analysis @ 3.5 YR (ESMO 2020)[2]

- ***Cut-off date*** (3-Apr-2020); median follow-up: **3.5** years; **418 DMFS events** (423 planned: ~87% power HR=0.725)



[2]Eggermont AMM, et al. *Lancet Oncol.* 2021;22:643-654

CheckMate 915 study design



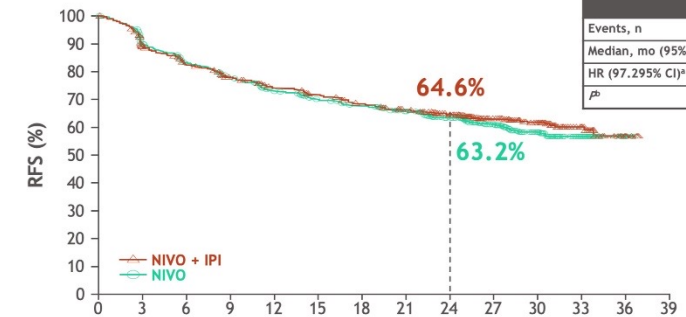
- 122 sites across 19 countries
- Database lock Sept 8, 2020
- Minimum follow-up of approximately 24 months (median 28 months)

Presented by GV Long, AACR 2021.

[a]Or indeterminate; [b]Until recurrence, unacceptable toxicity, or 1 year of treatment; [c]In November 2019, the data monitoring committee indicated that the dual primary endpoint of RFS in patients with tumor PD-L1 < 1% was not met; the study remained blinded until the ITT endpoint was evaluable. AJCC, American Joint Committee on Cancer; DMFS, distant metastasis-free survival; NED, no evidence of disease; PD-L1, programmed death-ligand 1.

Dual primary endpoint: RFS in ITT population

American Association for Cancer Research
FINDING CURES TOGETHER



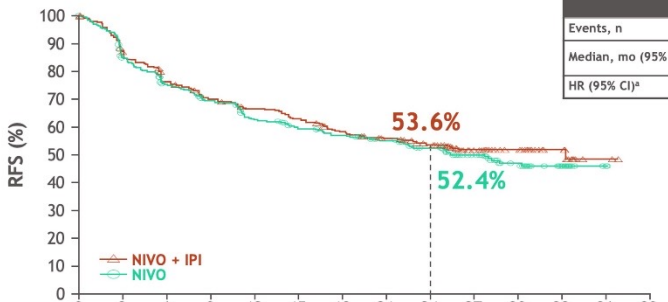
	NIVO + IPI (n = 920)	NIVO (n = 924)
Events, n	327	347
Median, mo (95% CI)	NR	NR
HR (97.295% CI)[a]	0.92 (0.77-1.09)	
P[b]	0.269	

No. at risk														
NIVO + IPI	920	783	720	669	630	605	572	547	505	371	193	74	9	0
NIVO	924	793	721	669	615	578	554	525	476	362	181	69	5	0

[a]Stratified; [b]Log-rank test. NR, not yet reached.

Dual primary endpoint: RFS in patients with tumor PD-L1 < 1%

American Association for Cancer Research
FINDING CURES TOGETHER



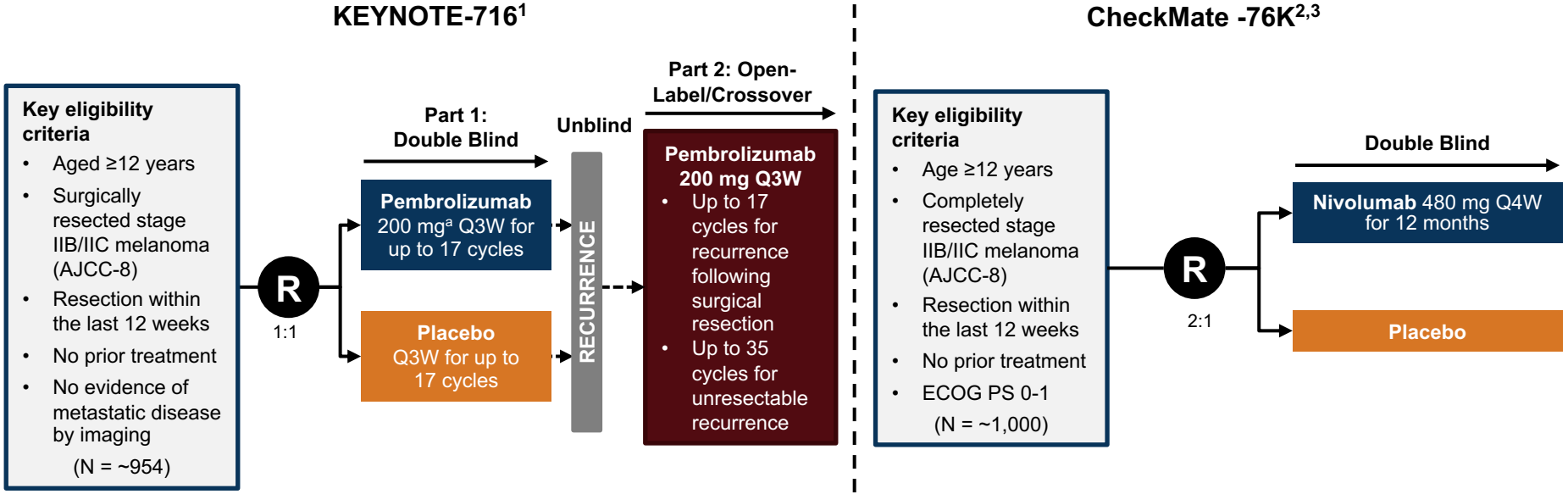
	NIVO + IPI (n = 349)	NIVO (n = 351)
Events, n	159	166
Median, mo (95% CI)	33.2 (22.2-NR)	25.3 (19.8-NR)
HR (95% CI)[a]	0.91 (0.73-1.14)	

No. at risk														
NIVO + IPI	349	293	254	232	218	206	187	176	162	112	49	21	2	0
NIVO	351	283	246	224	199	183	175	164	150	109	47	18	1	0

[a]Stratified. NR, not yet reached; PD-L1, programmed death-ligand 1.

Presented by GV Long, AACR 2021.

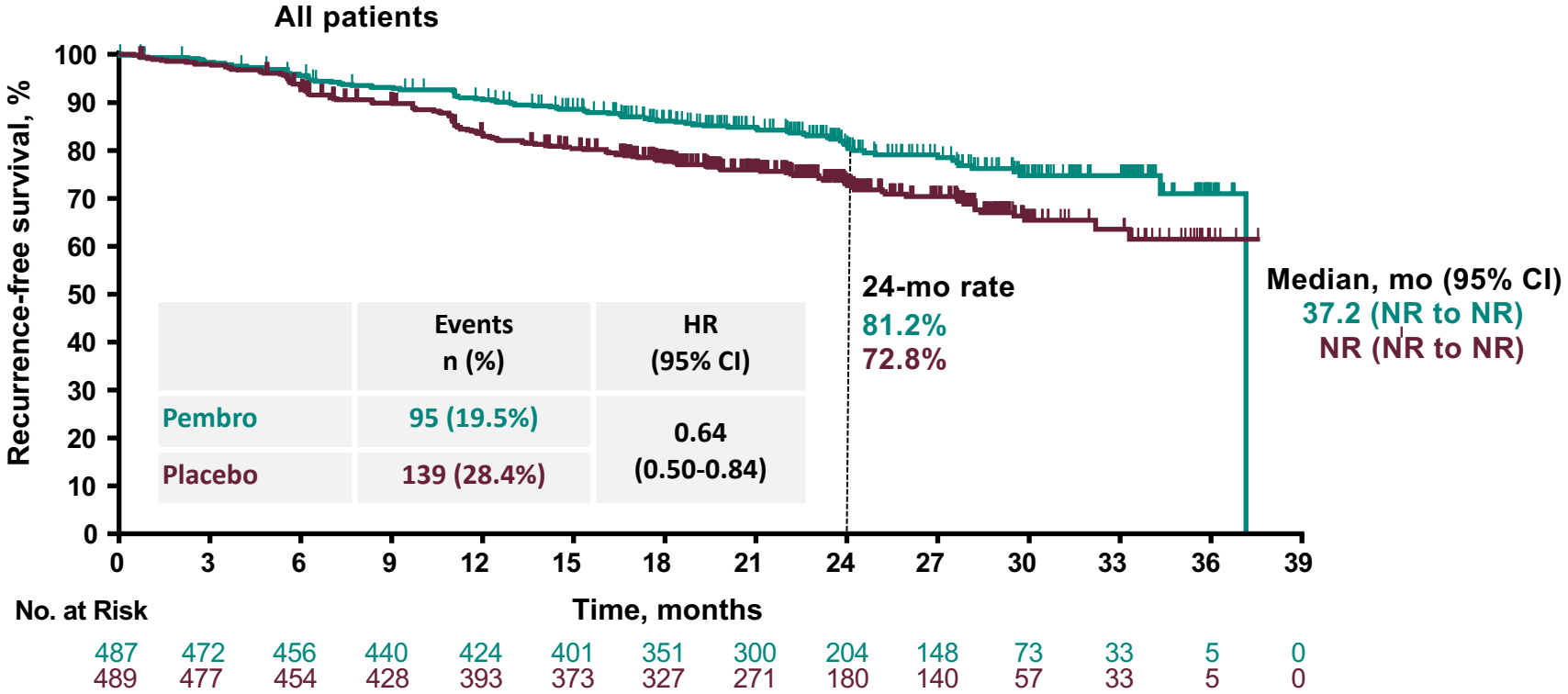
Ongoing Trials of Adjuvant Anti–PD-1 Antibodies for Stage IIB/C Melanoma



[a] Adult dosage; eligible patients aged 12 to <18 years receive 2 mg/kg Q3W.

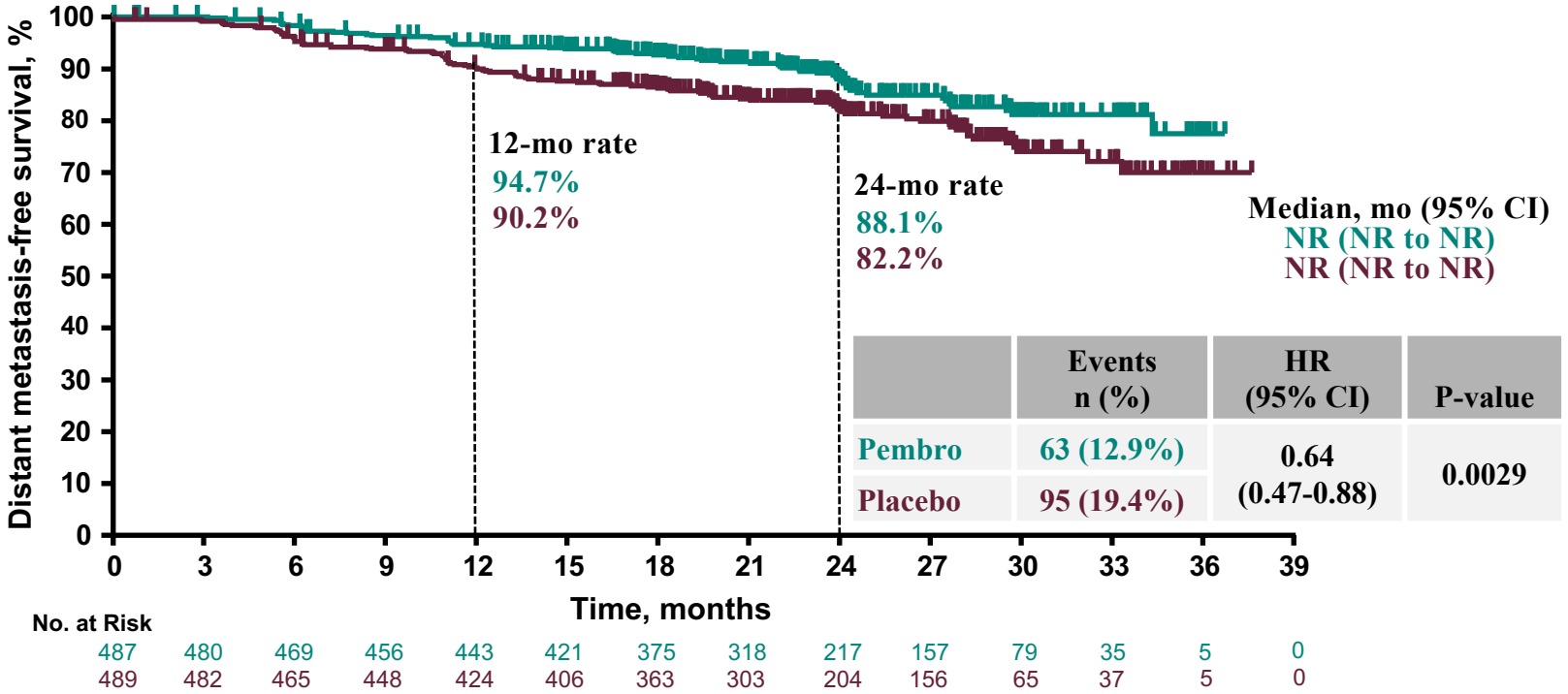
1. Carlino MS et al. 2019 American Society of Clinical Oncology Annual Meeting (ASCO 2019). Abstract TPS9596. 2. https://clinicaltrials.gov/ct2/show/NCT04099
3. https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-001230-34/AT.

Keynote 716: RFS With Longer Follow-up at IA3



HR for RFS with pembrolizumab versus placebo was 0.65 at IA1 and 0.61 at IA2; Median follow-up of 27.4 months (range, 14.0-39.4) at IA3; Data cut-off January 4, 2022.

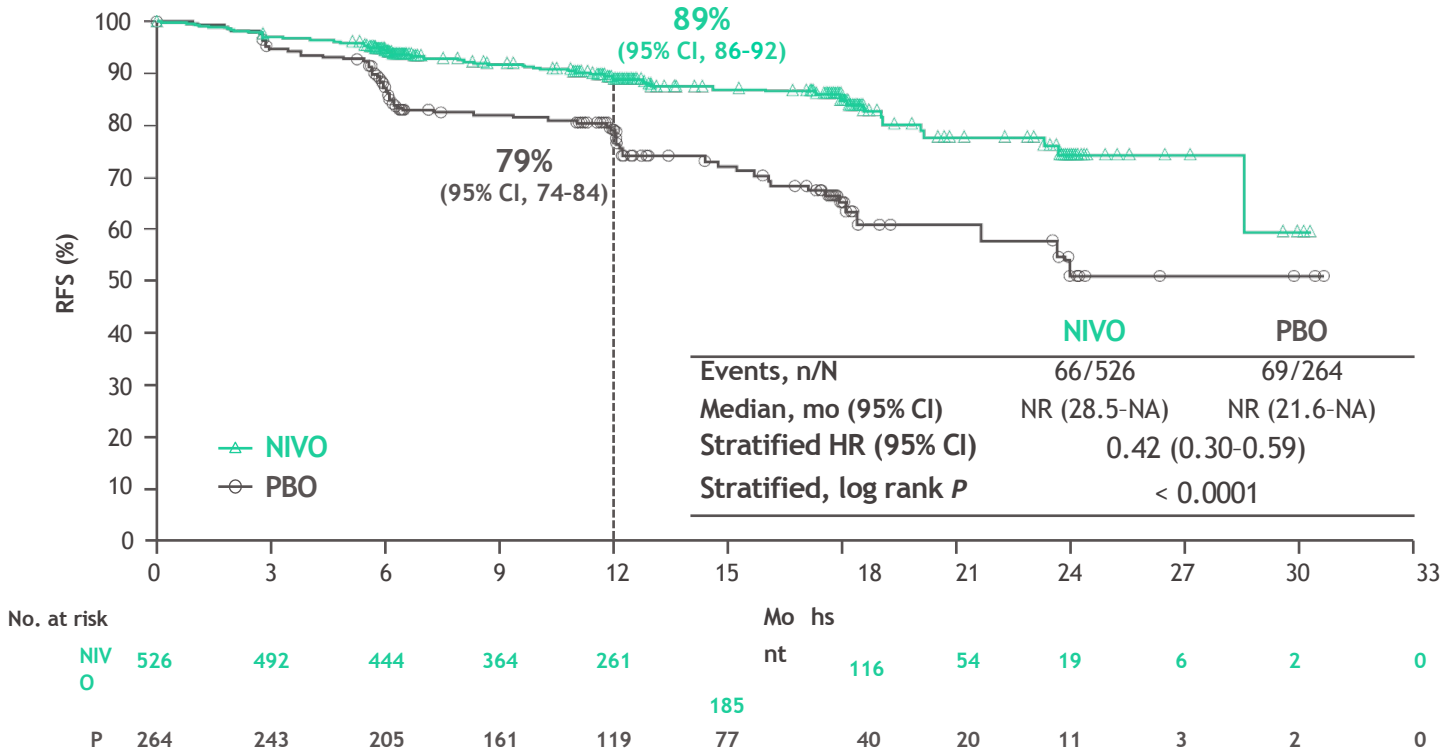
Keynote 716: DMFS: Secondary Endpoint



	Events n (%)	HR (95% CI)	P-value
Pembro	63 (12.9%)	0.64 (0.47-0.88)	0.0029
Placebo	95 (19.4%)		

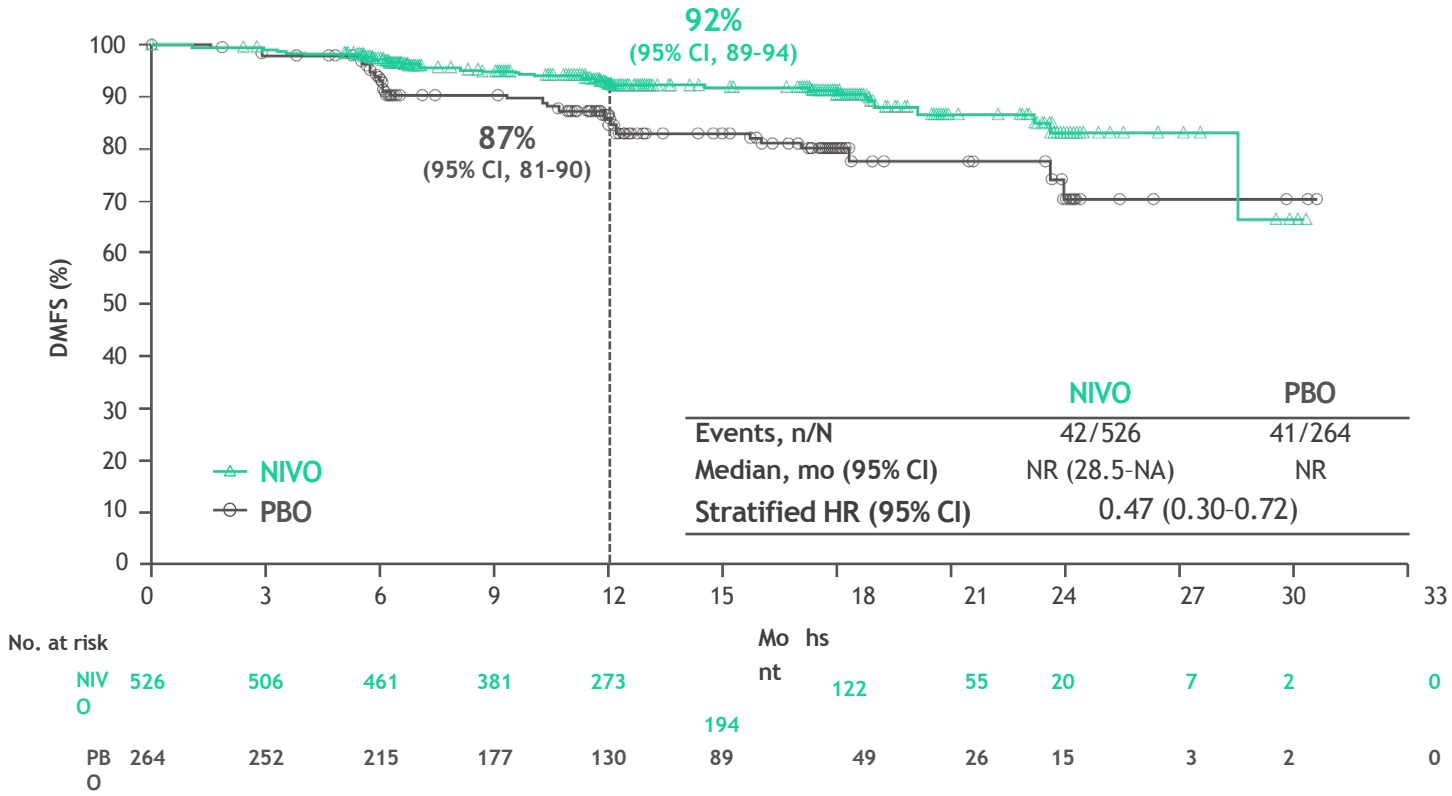
Median follow-up of 27.4 months (range, 14.0-39.4); Data cut-off January 4, 2022.

Checkmate 76K (Nivo vs. Placebo): Primary endpoint: RFS



NA, not available; NR, not reached.

Checkmate 76K (Nivo vs Placebo): Secondary endpoint: DMFS

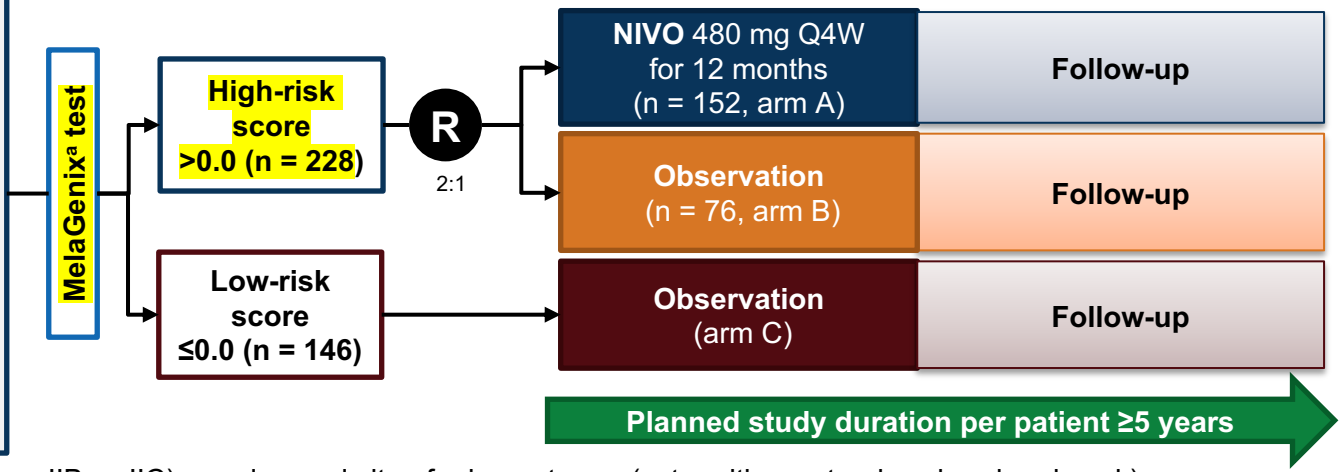


NivoMela: Adjuvant Treatment of High-Risk Stage II Melanoma[1]

- Adjuvant NIVO treatment in stage II high-risk melanoma: a randomized, controlled, phase 3 trial with biomarker-based risk stratification (investigator-initiated trial; sponsor: University Hospital Essen, Prof. Dr. Dirk Schadendorf; CA209-7DL)

Key eligibility criteria
- Aged ≥18 years
- Histologically confirmed, stage II (AJCC-8) cutaneous melanoma
- Negative SLNB
- Randomization ≤12 weeks after SLNB
- ECOG PS 0-1
- Adequate organ function
- Available tissue for MelaGenix test[2-4,a]

(N = ≈ 374)



- **Stratification:** tumor stage (IIA vs IIB vs IIC), gender, and site of primary tumor (extremities vs trunk vs head and neck)
- **Primary endpoint:** RFS (at 36 and 60 months)
- **Secondary endpoints:** DMFS, MSS, and OS (at 36 and 60 months); safety; and clinical utility of the MelaGenix GEP score

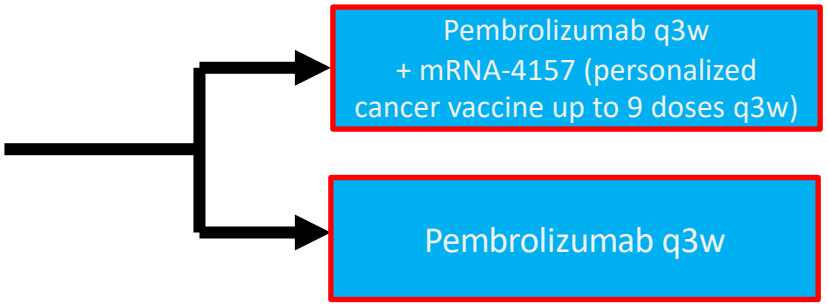
[a] MelaGenix is an 11-gene prognostic signature.[2-4]

1. https://clinicaltrials.gov/ct2/show/NCT04309409. 2. Brunner G et al. *J Cancer Res Clin Oncol*. 2013;139:249-258. 3. Brunner G et al. 2018 American Society of Clinical Oncology Annual Meeting (ASCO 2018). Abstract 9582. 4. Garbe C et al. ASCO 2019. Abstract 9518.

Phase 2 Randomized Study of Adjuvant Immunotherapy With Personalized Cancer Vaccine mRNA-4157 and Pembrolizumab Versus Pembrolizumab Alone

Key Elegibility Criteria:

- Resectable cutaneous melanoma metastatic to a lymph node and at high risk of recurrence
- Complete resection within 13 weeks prior to the first dose of pembrolizumab
- Disease free at study entry (after surgery)
- Has an FFPE tumor sample available
- PS 0 or 1



Pt may continue until disease recurrence, unacceptable toxicity, or they undergo up to 18 total cycles (approximately 1 year of treatment.

Overview

- Late Stage (Metastatic) Melanoma
- Early Stage Melanoma
  - Adjuvant Therapy
  - Neoadjuvant Therapy

Why neoadjuvant treatment?

- **Downstaging disease**

→ facilitate resection/less morbidity

- **Destruction of micrometastases**

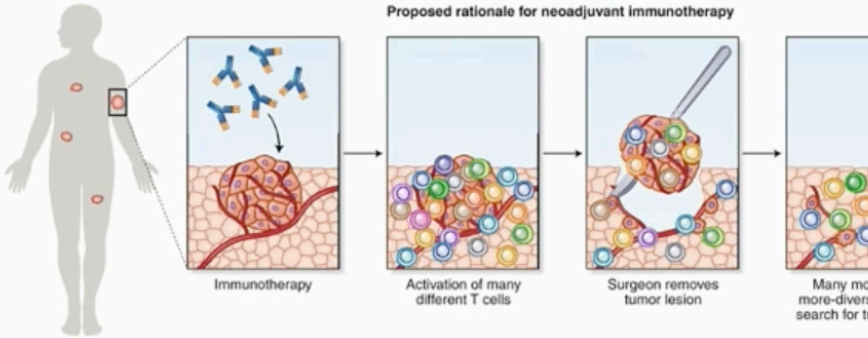
→ prevention of distant metastasis

- **More tumor antigens**

→ better and deeper immune response

- **Objectify the individual therapy response**

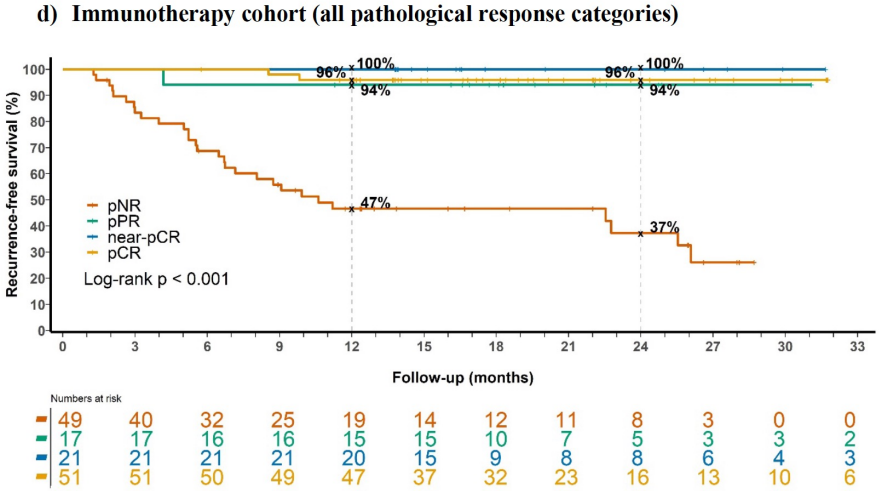
→ Personalised therapy



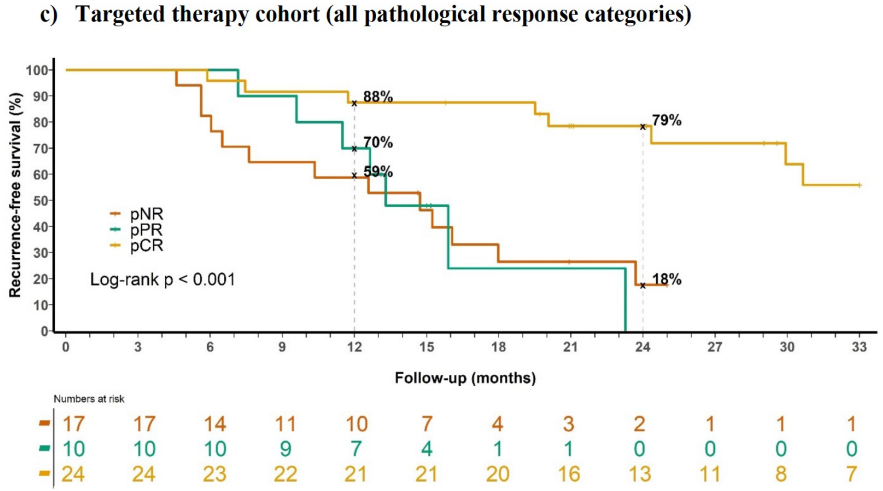
Versluis et al. Nature Medicine, 2020.

INMC pooled analysis: Pathologic response better surrogate marker for immunotherapy than for targeted therapy

Immunotherapy



Targeted Therapy



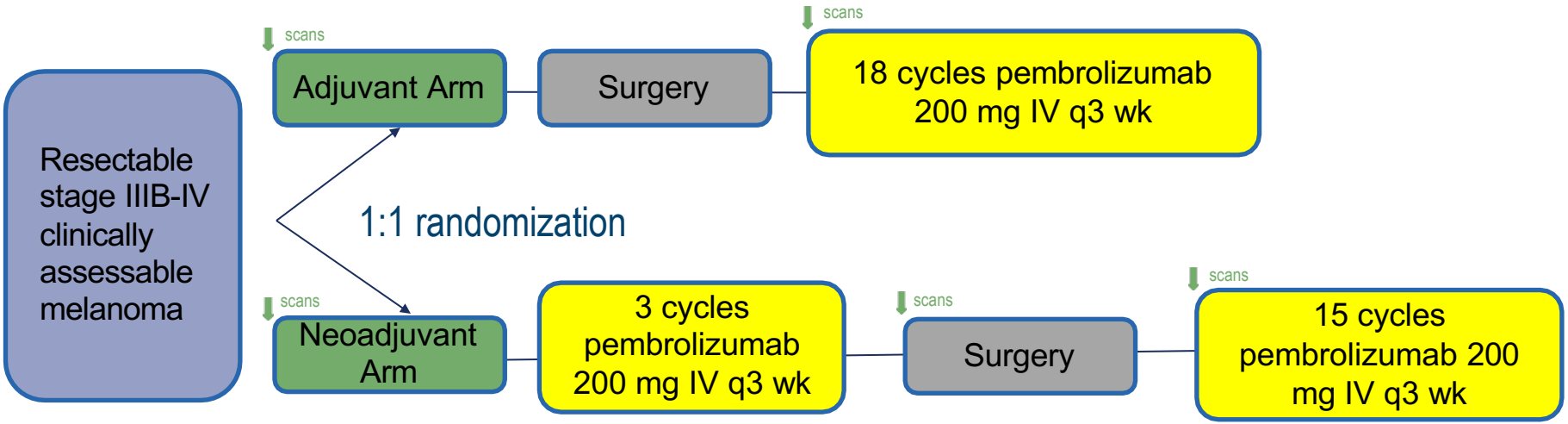
*No patient had a near-pCR

2021 ESMO congress

Menzies et al., Nat Med 2021

S1801 Study Schema

Primary endpoint: Event-free survival

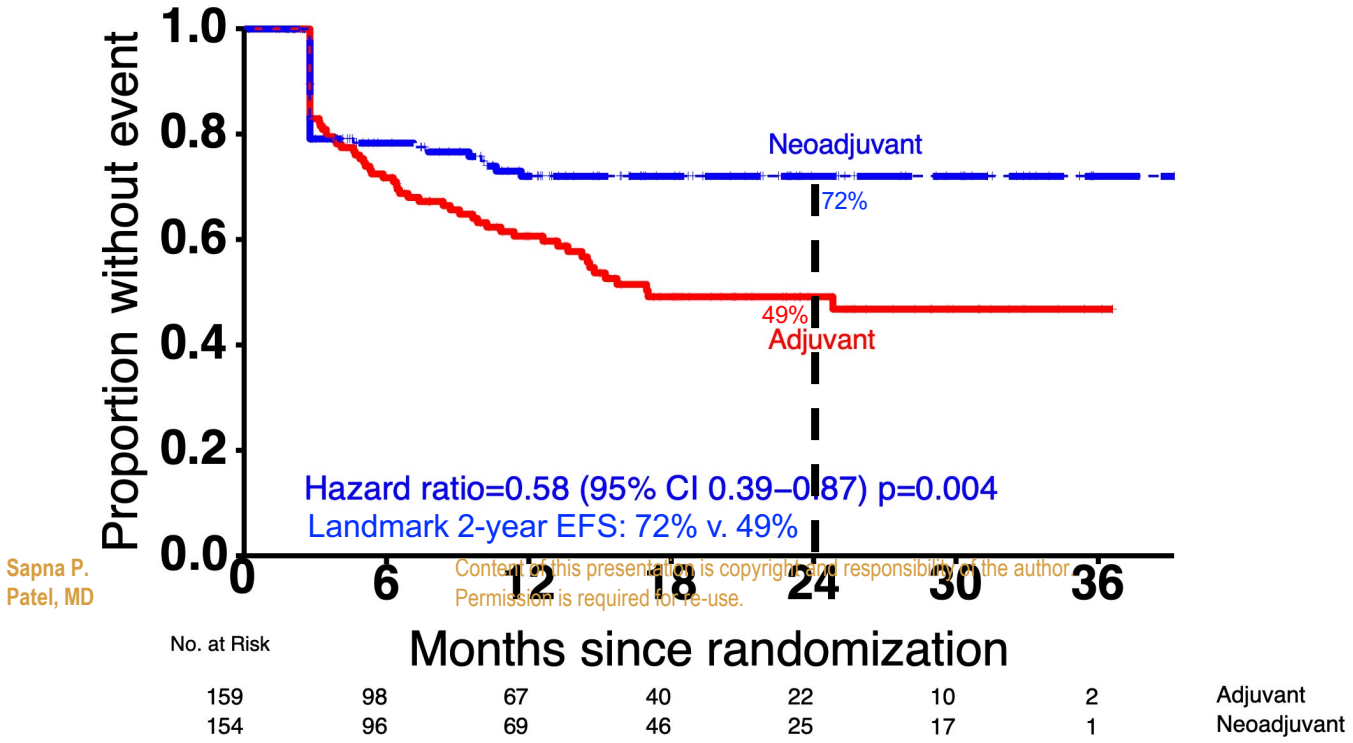


radiographic assessment (scans)

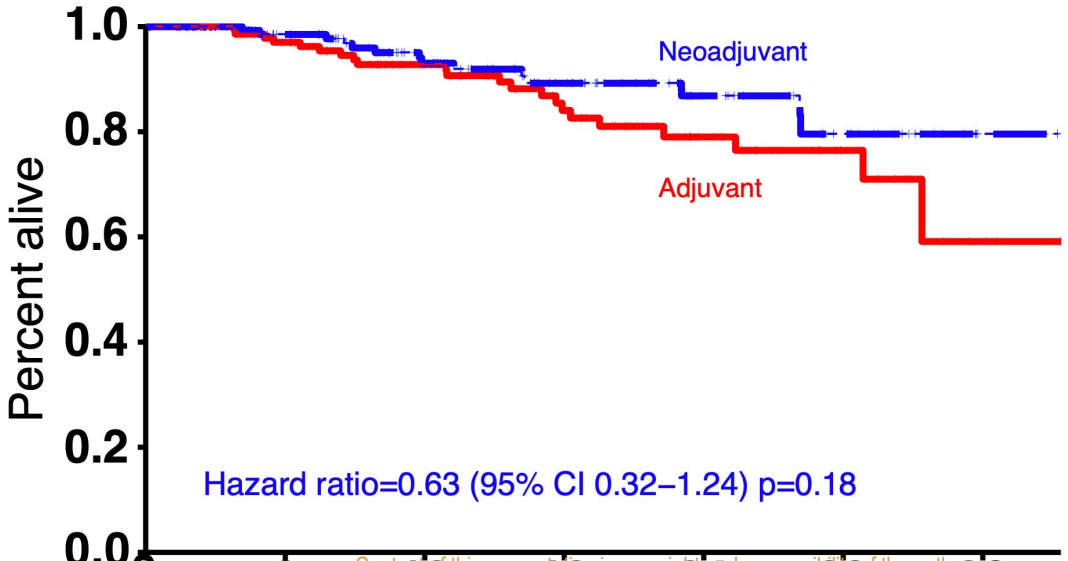
Additional criteria: strata included AJCC 8th ed. stage and LDH, adjuvant radiation allowed, concomitant radiation & pembrolizumab was not allowed, brain metastasis excluded, uveal melanoma excluded

Surgery type and extent was required to be pre-specified and carried out regardless of radiologic response to therapy

S1801 primary endpoint: Event-free survival



Overall survival



No. at Risk

159	124	93	60	33	15	3	Adjuvant
154	124	90	59	30	19	1	Neoadjuvant

Sapna P. Patel, MD

Summary & Conclusions

- For first-line therapy of metastatic melanoma, combination immunotherapy has emerged as the preferred first-line option regardless of BRAF mutation status
  - Ipi/Nivo in most patients
  - Rela/Nivo in selected patients
- Triple therapy for BRAF-MT patients is an approved option but the data are controversial
- Encouraging data for refractory patients with TIL-based therapies

Summary & Conclusions (2)

- For stage III patients after surgical resection adjuvant therapy options are
  - Single agent anti-PD1 (all patients)
  - BRAF/MEK combination (BRAF+ patients)
- New data for stage IIB and IIC melanoma suggest adjuvant immunotherapy is effective
- Neoadjuvant therapy for Stage III patients is an emerging option and additional data are awaited

Thank you!