Immunotherapy For Melanoma

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Immunotherapy for Melanoma

- Metastatic Disease
- Adjuvant Therapy
- Immuno or targeted therapy for BRAF+ patients?
- What's new and promising
  - Neoadjuvant therapy
  - New agents

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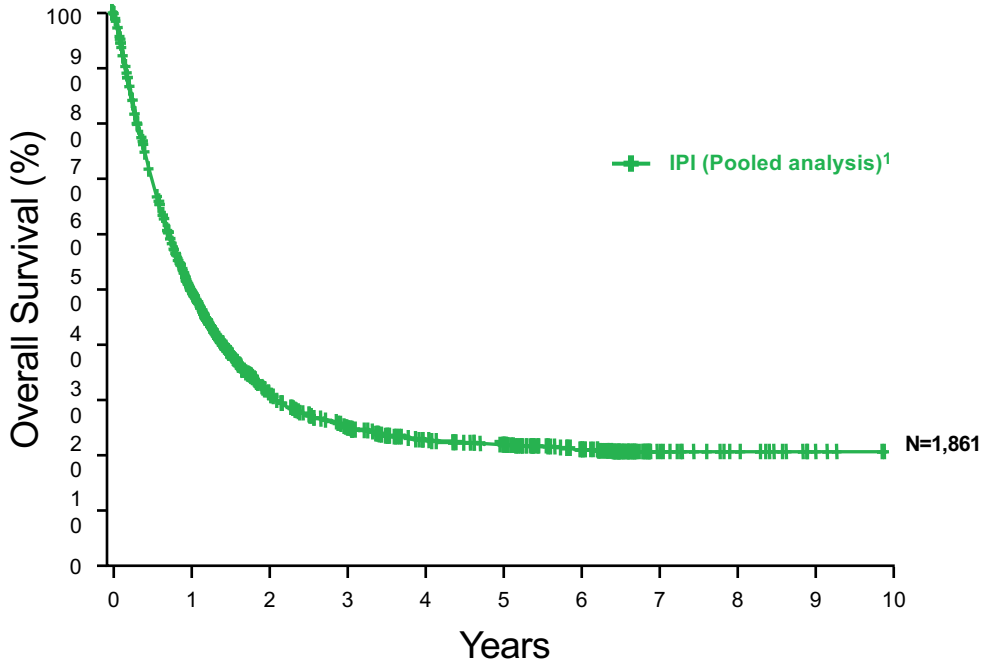
Immunotherapy for Melanoma
Metastatic Disease

- Anti-PD1 alone
  (nivolumab, pembrolizumab)
- Anti-PD1+Anti-CTLA4 combination
  (ipilimumab + nivolumab)

Long-term Data with Single-agent Ipilimumab in Advanced Melanoma



1. Schadendorf et al. *J Clin Oncol* 2015;33:1889-1894; 2. Current analysis; 3. Poster presentation by Dr. Victoria Atkinson at SMR 2015 International Congress.

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

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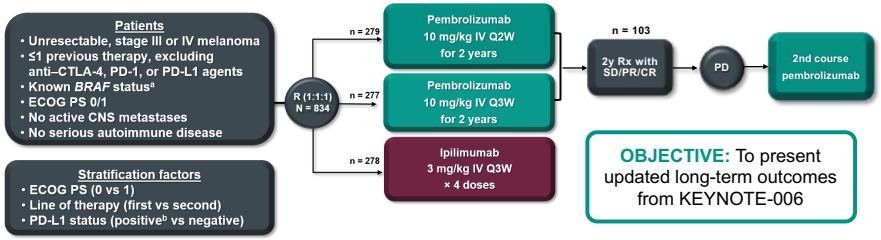
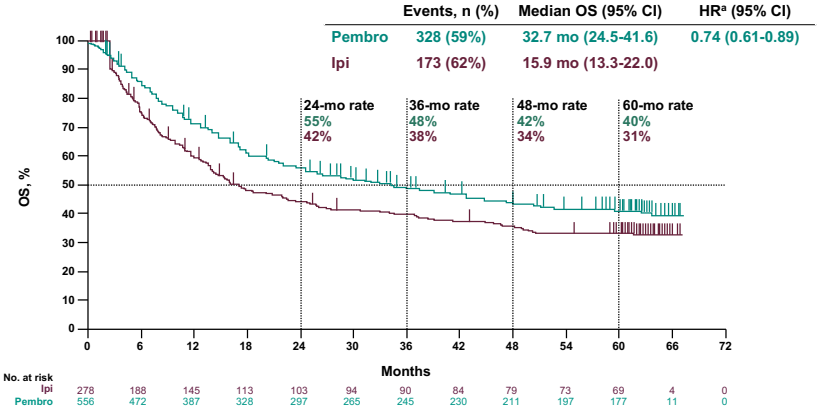


- Two pembrolizumab arms pooled as similar efficacy[2]
- Patients completing ≥94 weeks of pembrolizumab with SD/PR/CR were considered to have completed 2 years of treatment
- Patients could receive a 2nd course of 1 year of pembrolizumab if progressed after SD/PR/CR
- Data cut-off: July 31, 2019; median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

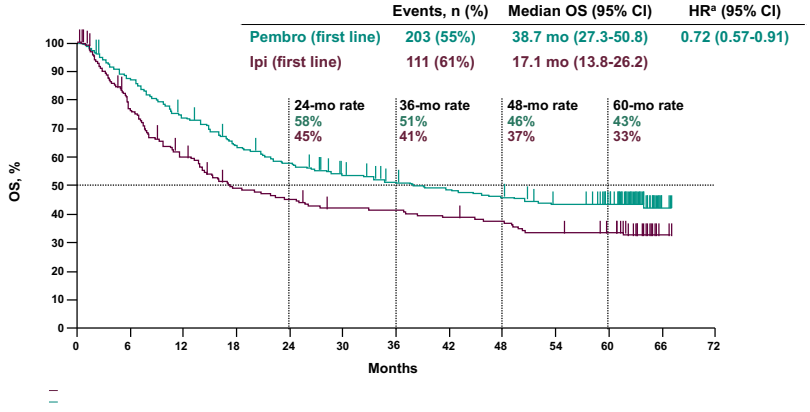
[a]Prior anti-BRAF therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.
[b]Defined as ≥1% staining in tumor and adjacent immune cells as assessed by IHC using 22C3 antibody.

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



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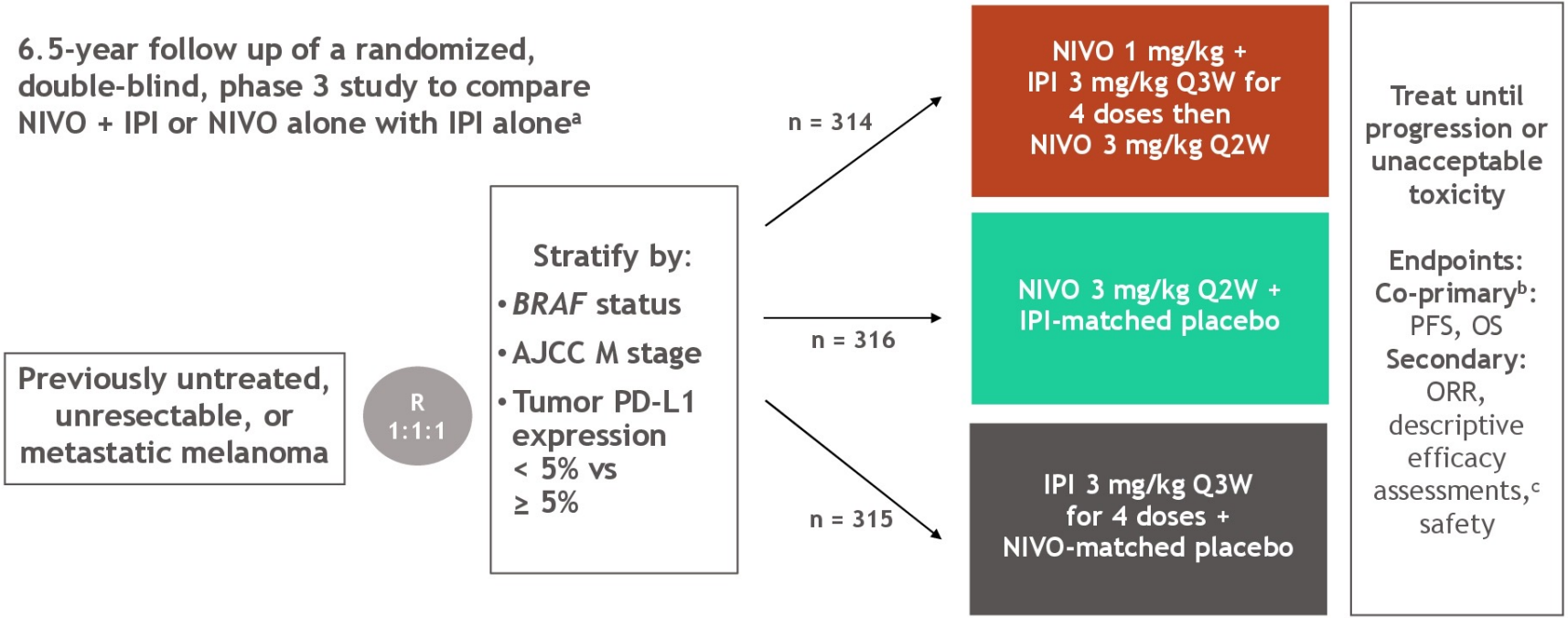
CheckMate 067: study design

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



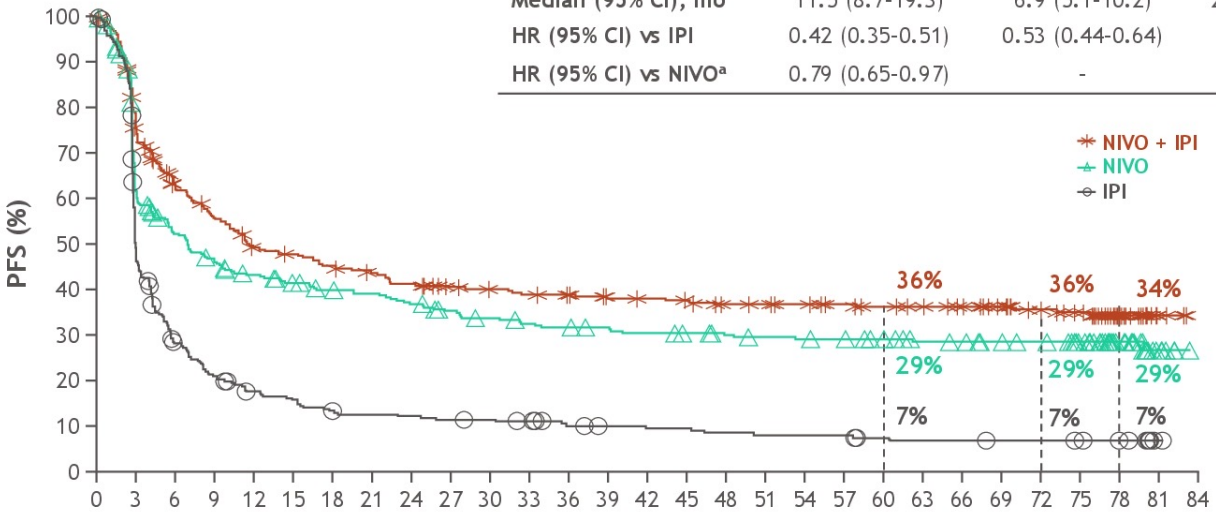
Database lock: October 19, 2020; minimum follow-up of 77 months for all patients

[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.

Wolchok et al. Melanoma. CheckMate 067. 6.5-year outcomes in advanced melanoma. ASCO2021. oral

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)	-	-

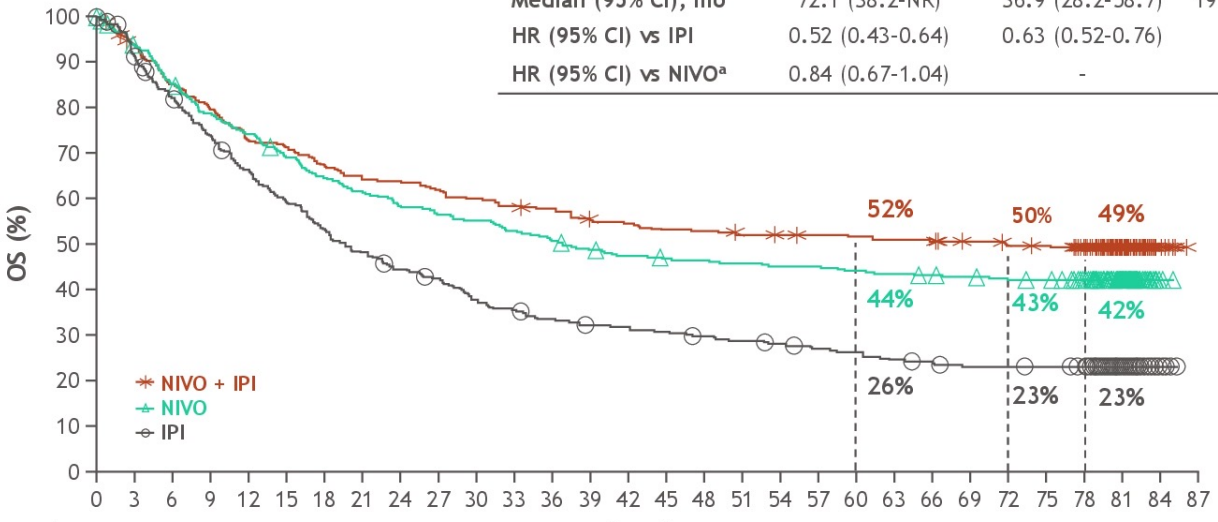


[a]Descriptive analysis.

Wolchok et al. Melanoma. CheckMate 067. 6.5-year outcomes in advanced melanoma. ASCO2021. oral

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)	-	-



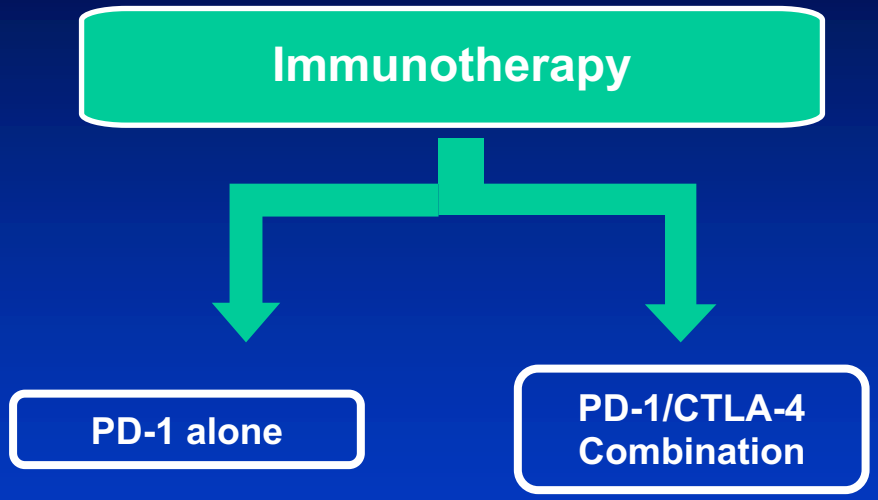
No. at risk

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

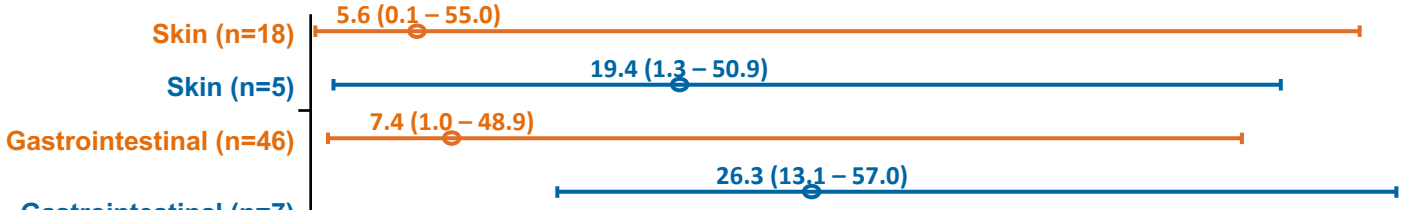
[a]Descriptive analysis.

Wolchok et al. Melanoma. CheckMate 067. 6.5-year outcomes in advanced melanoma. ASCO2021. oral

Combination Immuno or Monotherapy?

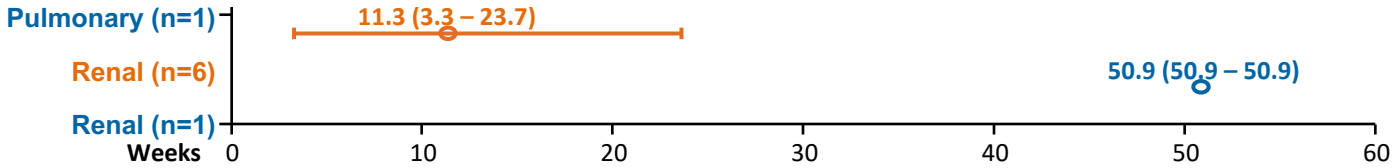


Checkmate 067: Safety
Onset Grade 3–4 Treatment-Related Select AEs



Toxicity Earlier

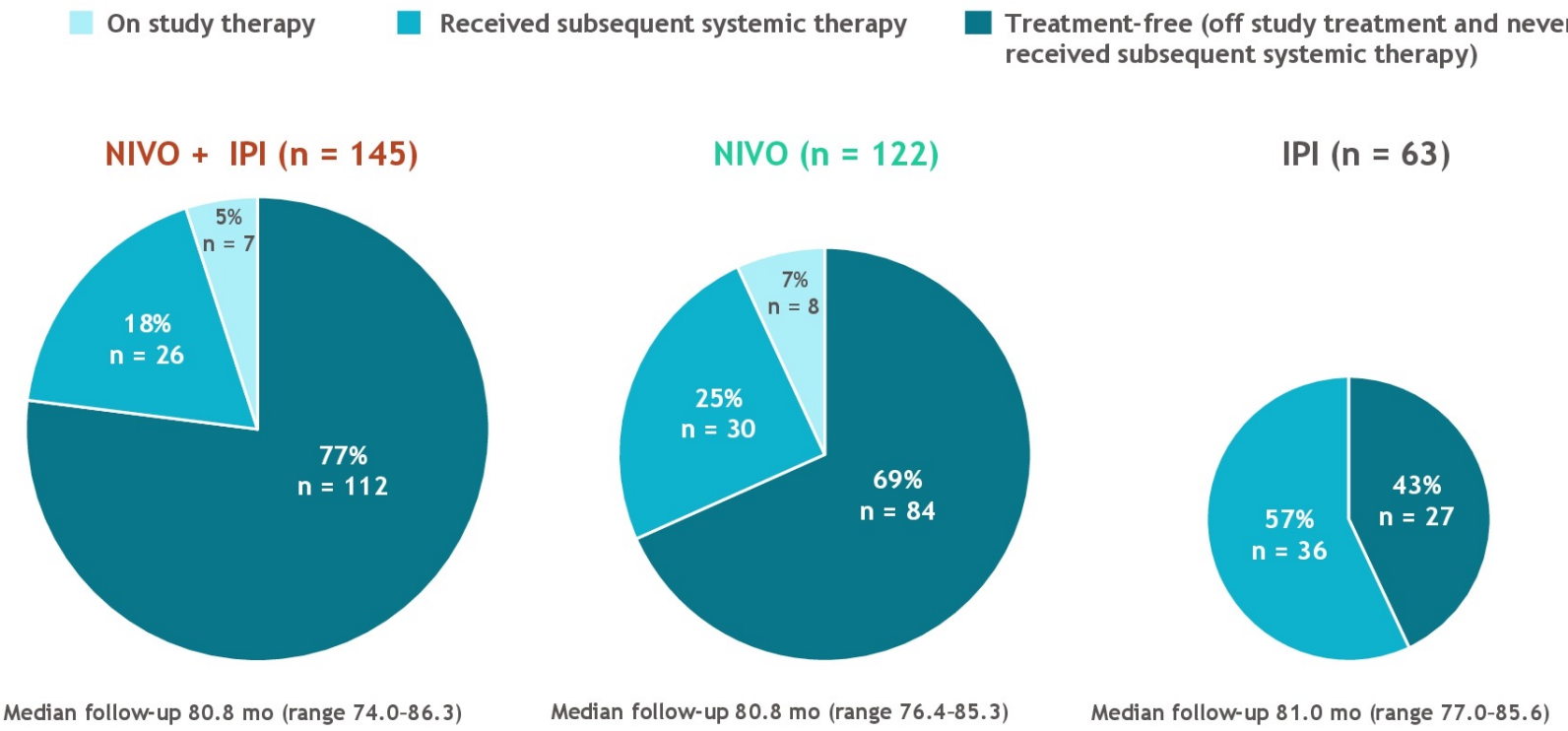
Longer Time to Resolution



Circles represent medians; bars signify ranges

Larkin J et al ECC 2015

Patients alive and treatment-free at 6.5 years



Wolchok et al. Melanoma. CheckMate 067. 6.5-year outcomes in advanced melanoma. ASCO2021. oral

Combination immunotherapy ipilimumab + nivolumab has become the preferred treatment option (if you select immunotherapy)

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Immunotherapy for Melanoma
Adjuvant Therapy

– Anti-PD1 alone
(nivolumab, pembrolizumab)

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

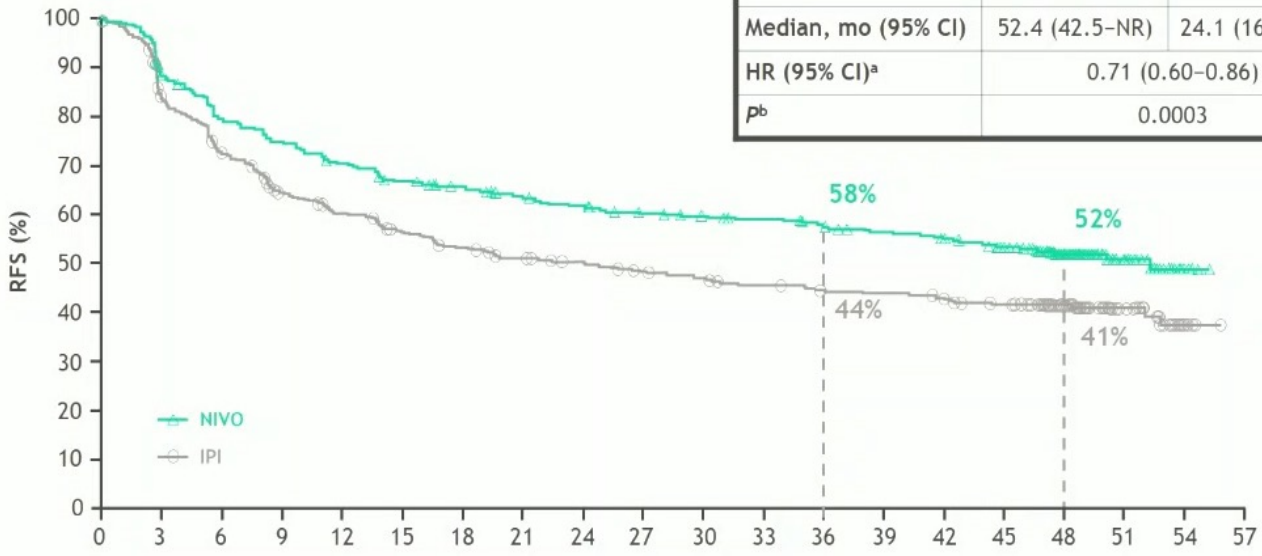
Primary endpoint: RFS

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: 48-month RFS in all patients

	NIVO (n = 453)	IPI (n = 453)
Events, n	212	253
Median, mo (95% CI)	52.4 (42.5–NR)	24.1 (16.6–35.1)
HR (95% CI)[a]	0.71 (0.60–0.86)	
P[b]	0.0003	

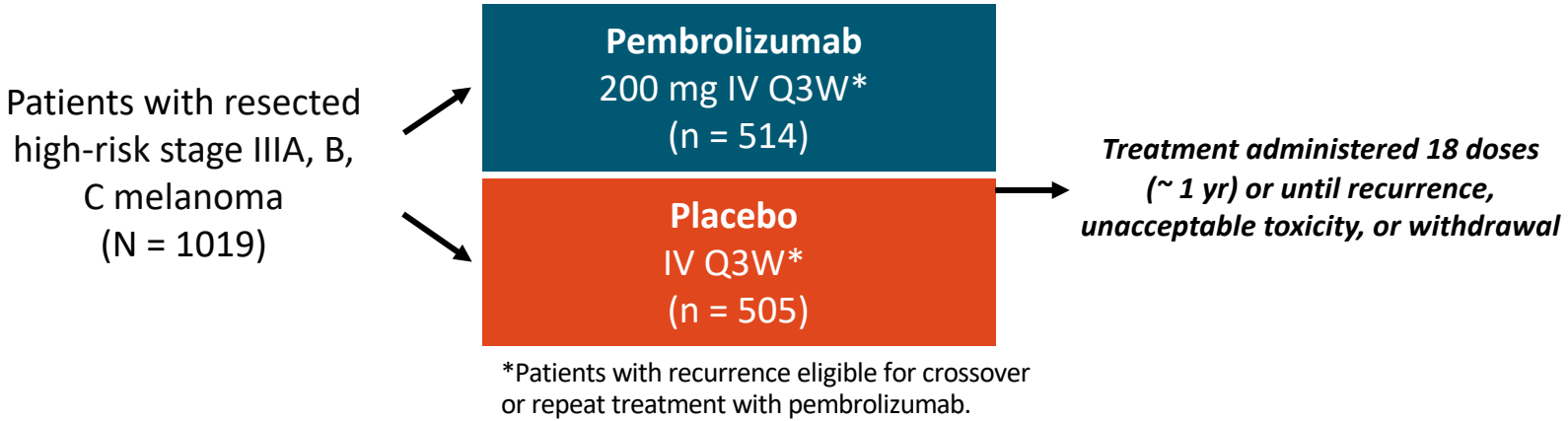


No. at risk																			
NIVO 3 mg/kg	453	395	354	332	311	293	283	271	262	250	245	240	233	224	218	206	147	37	11	0
IPI 10 mg/kg	453	366	316	273	253	234	220	208	201	191	185	177	171	168	163	154	113	32	10	0

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

KEYNOTE-054: Adjuvant Pembrolizumab vs Placebo for Stage III Melanoma (Part 1)

- Randomized, double-blind phase III study

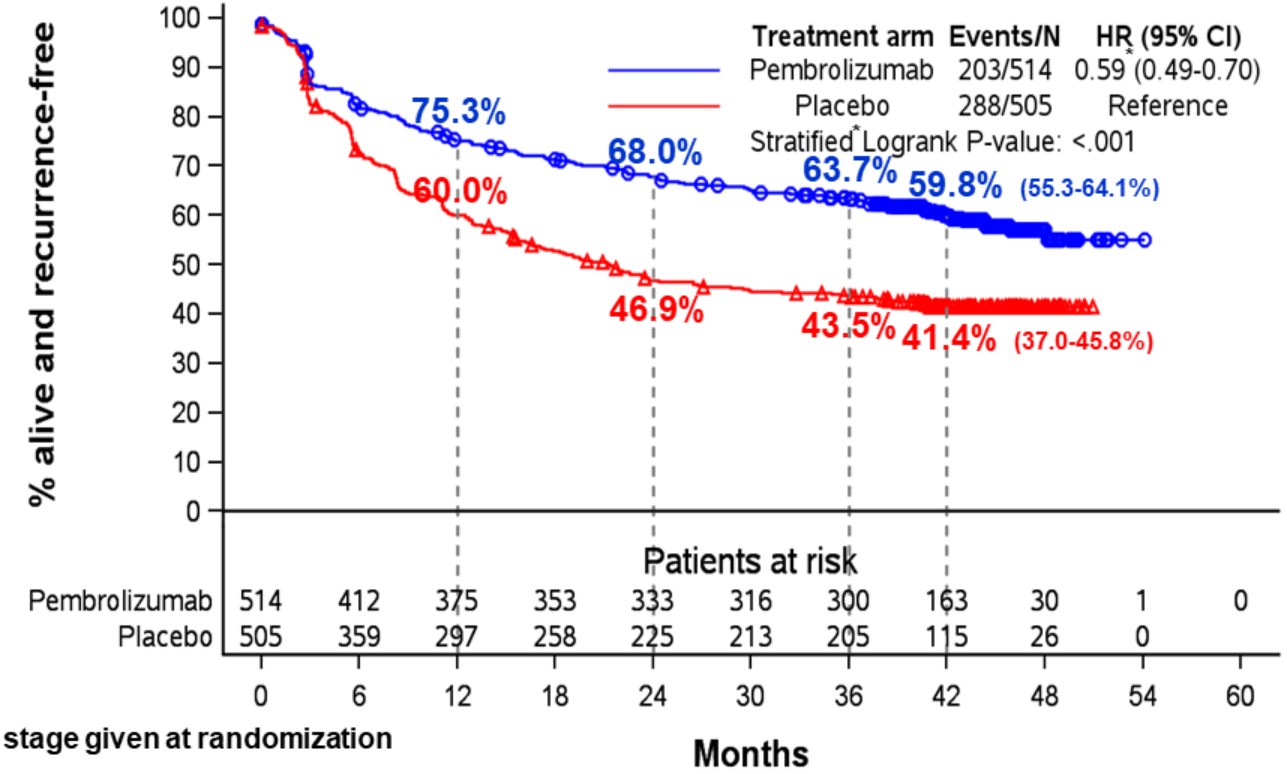


- Coprimary endpoints: RFS in ITT population, RFS in PD-L1+ subgroup
- Secondary endpoints: DMFS, OS, safety, QoL

Eggermont. NEJM. 2018;378:1789.

Updated RFS analysis (ESMO 2020)

- **Cut-off date** (3-Apr-2020); median duration of follow-up: **3.5** years; **491** RFS events



HR 0.59

*Stratified by stage given at randomization

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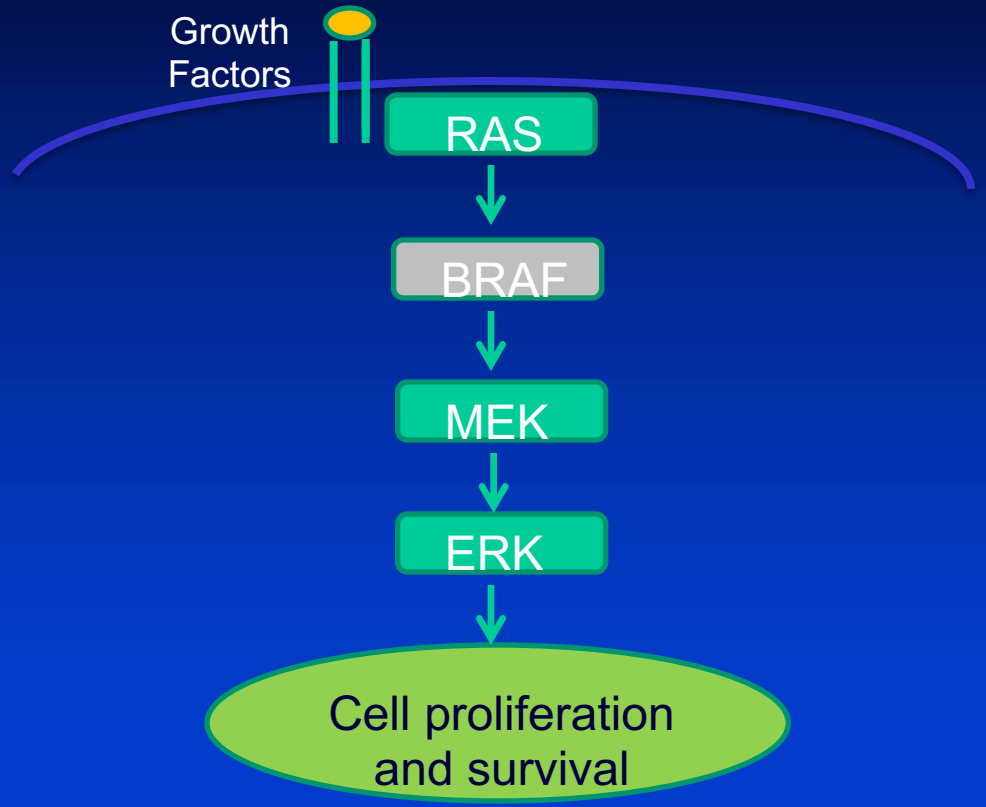
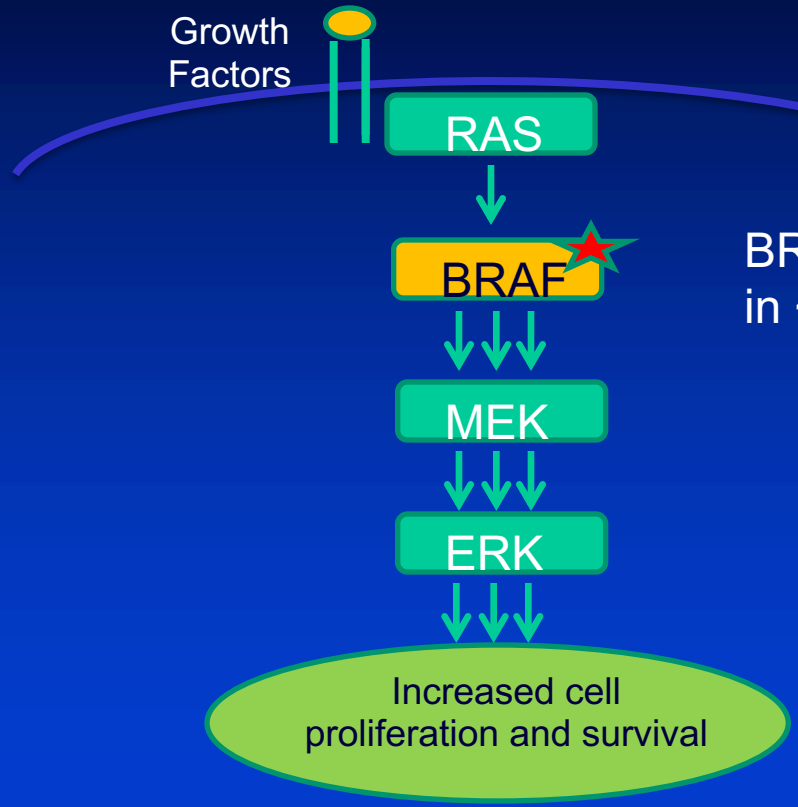
What is the First-line Treatment for BRAF+ Patients? Immunotherapy or Targeted Therapy?

- What is the data with targeted therapy alone?
- What is the correct sequence?
- Should you combine both targeted and immunotherapy?

MAPK Pathway

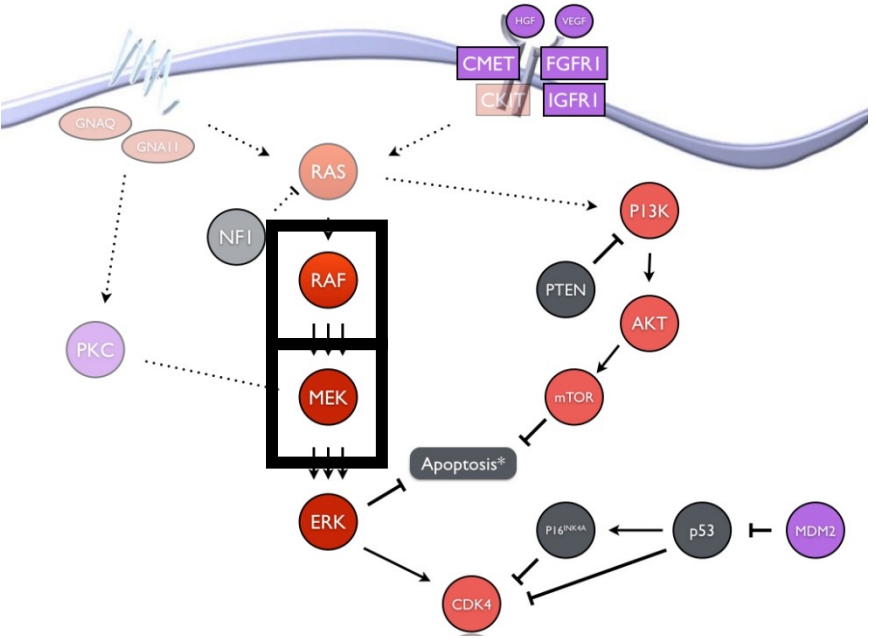


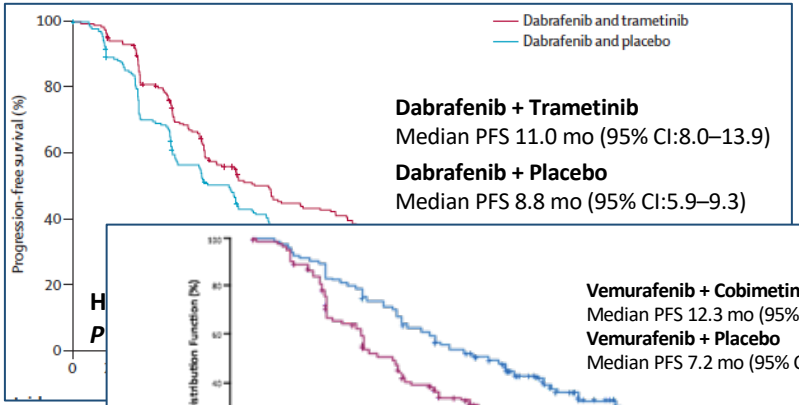
BRAF Mutation

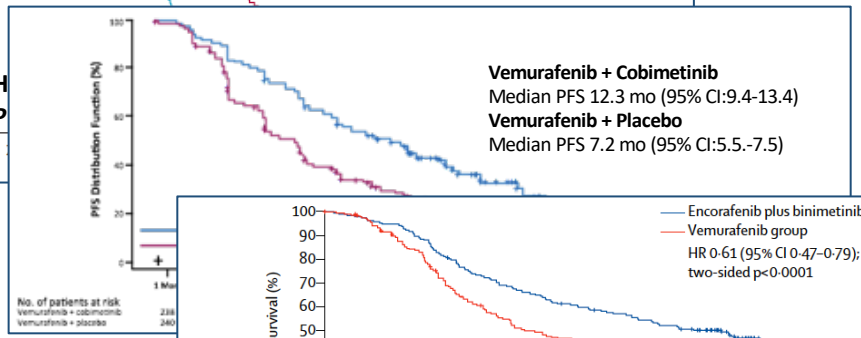


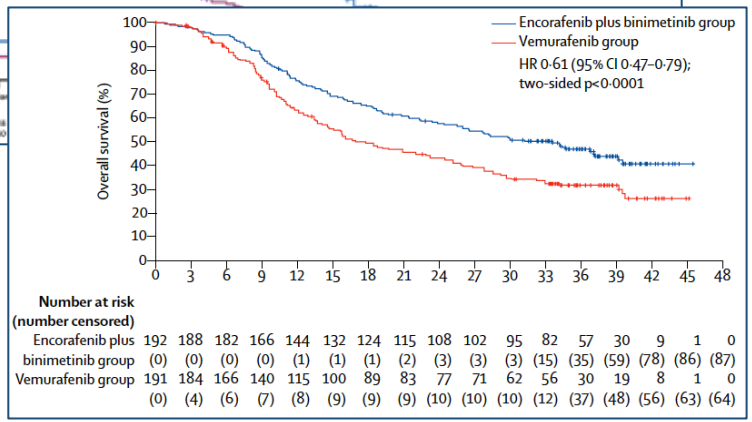
BRAF mutation is present in ~50% of melanomas

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



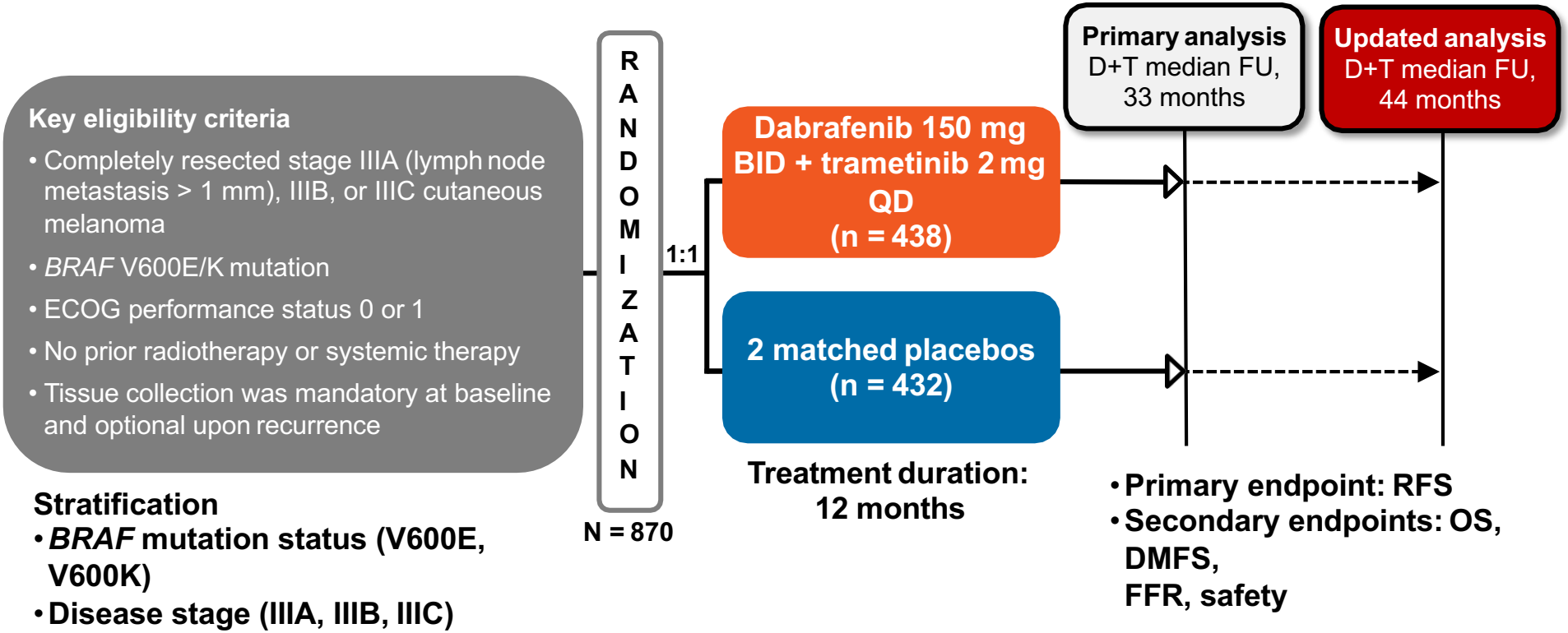






Long GV et al. *Lancet*. 2015.
Ascierto PA et al. *Lancet Oncol.* 2016.
Dummer R et al. *Lancet Oncol*. 2018.

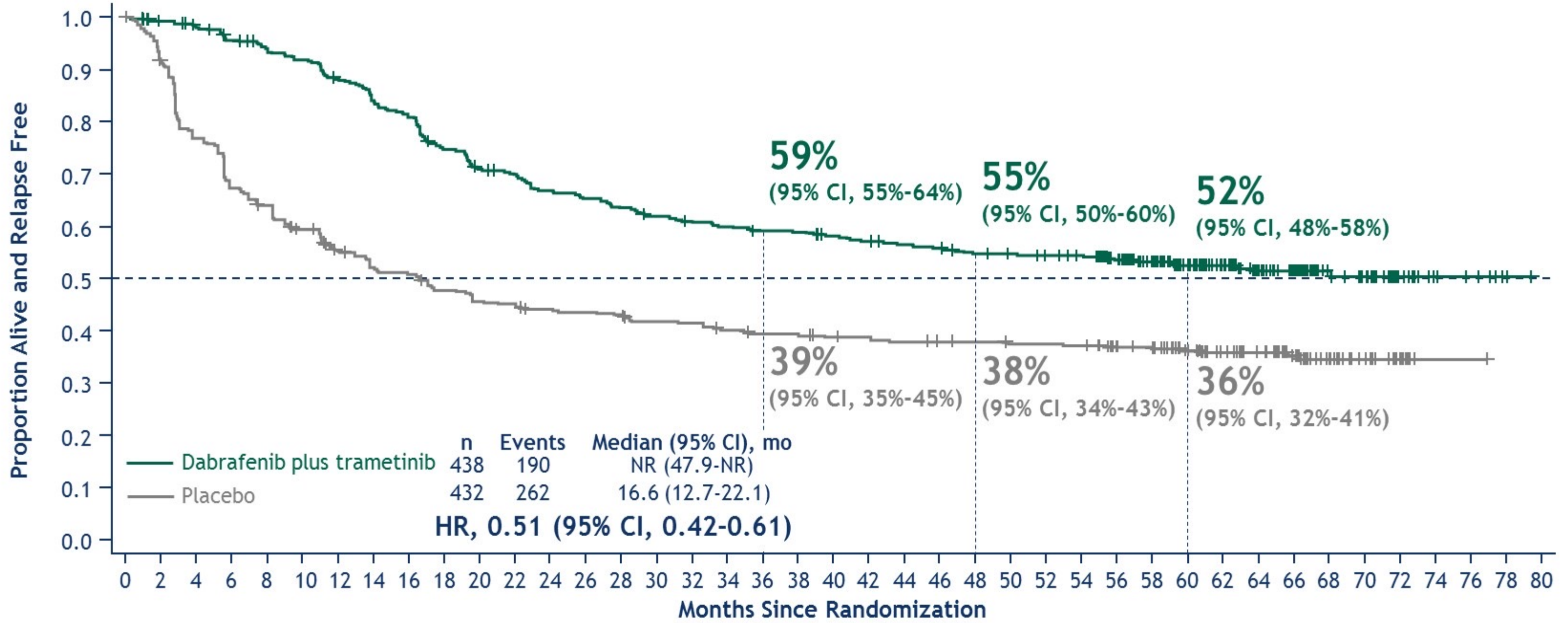
Adjuvant Therapy: Combi-AD: Study Design



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

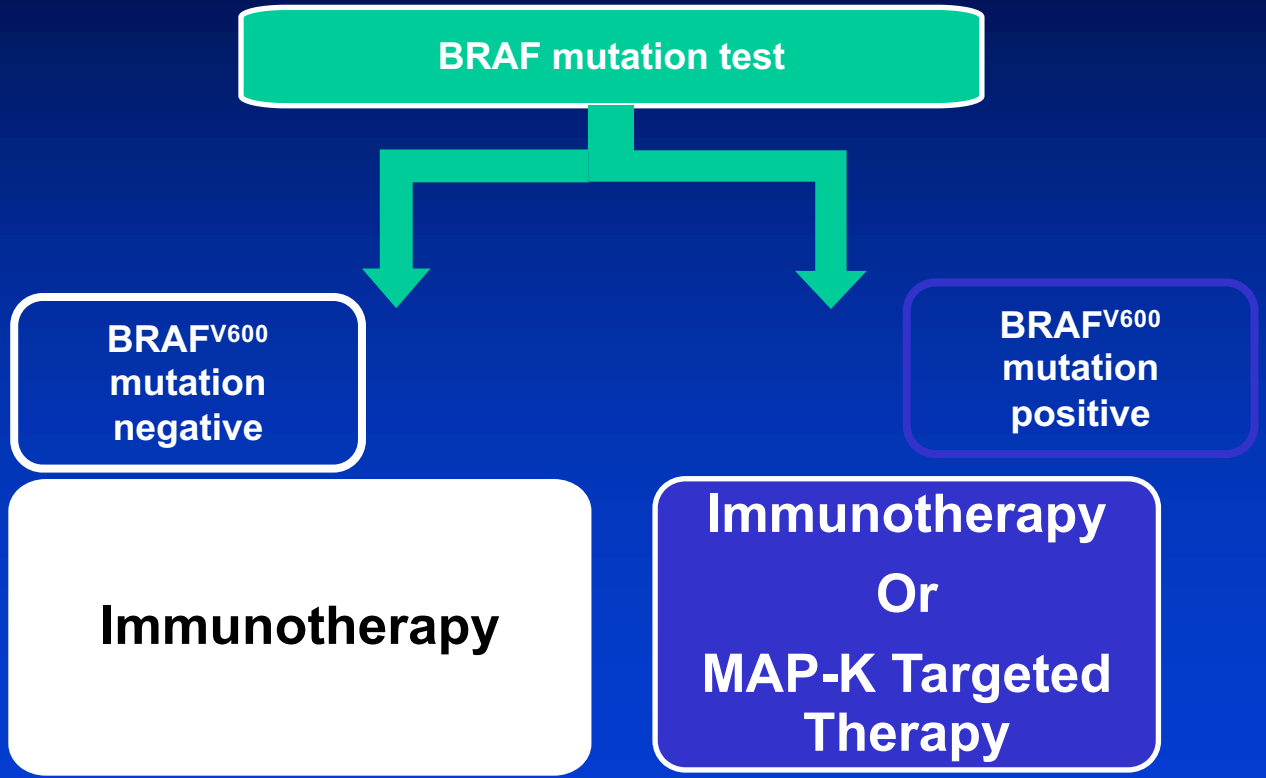
HR, hazard ratio; NR, not reached.

ASCO 2020

What is the First-line Treatment for BRAF+ Patients? Immunotherapy or Targeted Therapy?

- What is the data with targeted therapy alone?
- What is the correct sequence?
- Should you combine both targeted and immunotherapy?

Melanoma Therapy Decision Point



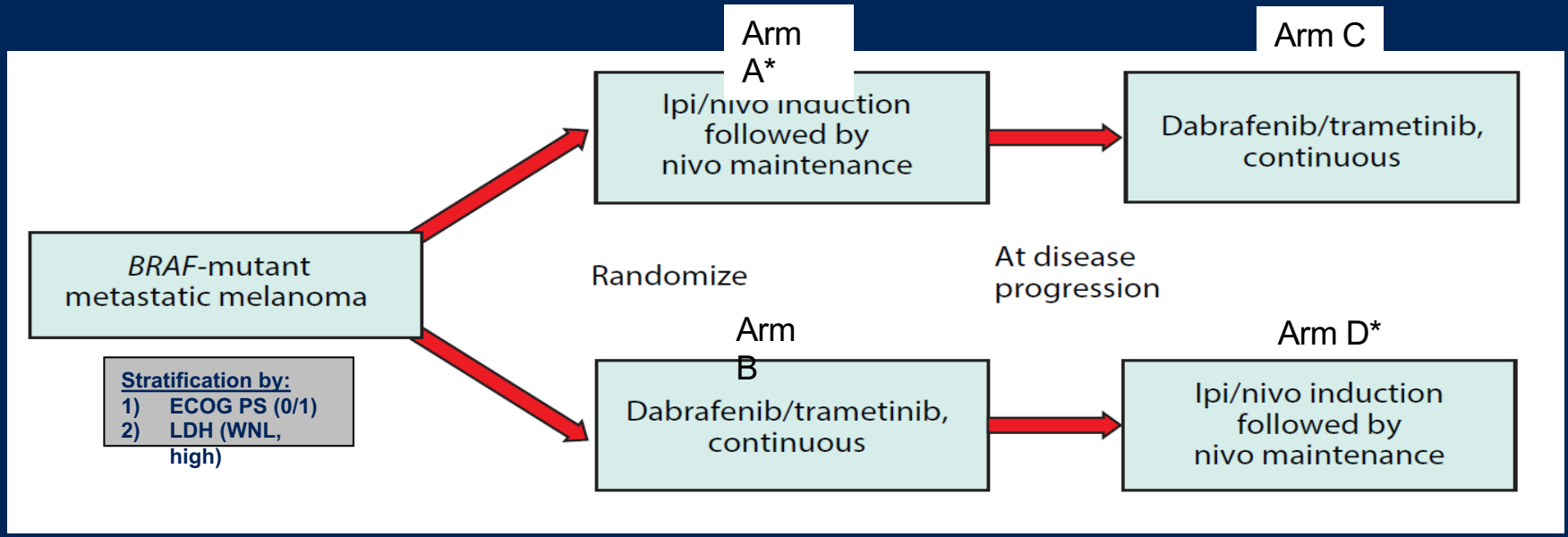
Key Ongoing Trials Evaluating Targeted Therapy Vs Combination Immunotherapy

	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.

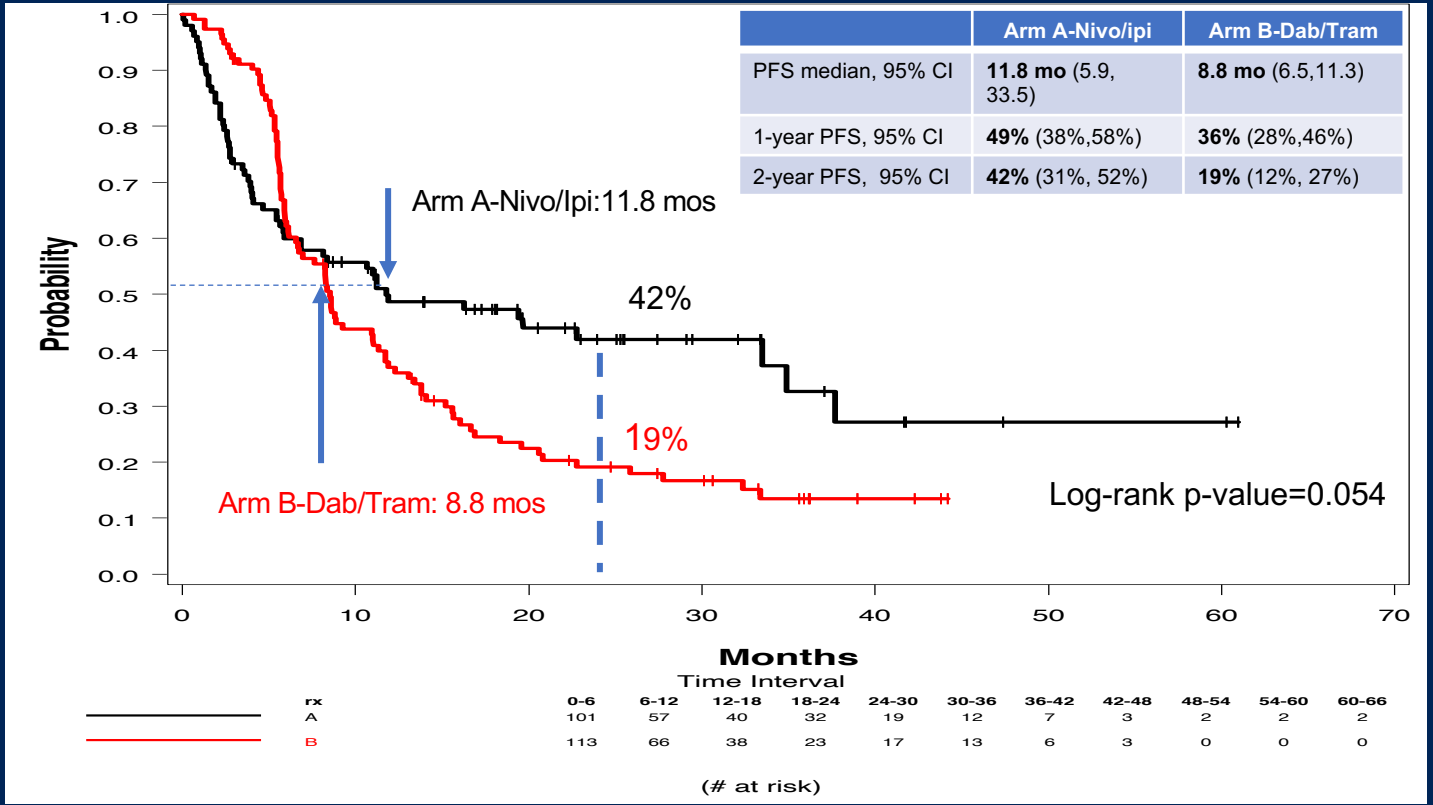
Clinical trial information: https://clinicaltrials.gov/ct2/show/NCT02631447; https://clinicaltrials.gov/ct2/show/NCT03235245; https://clinicaltrials.gov/ct2/show/NCT02224781

DREAMseq Trial Treatment Schema



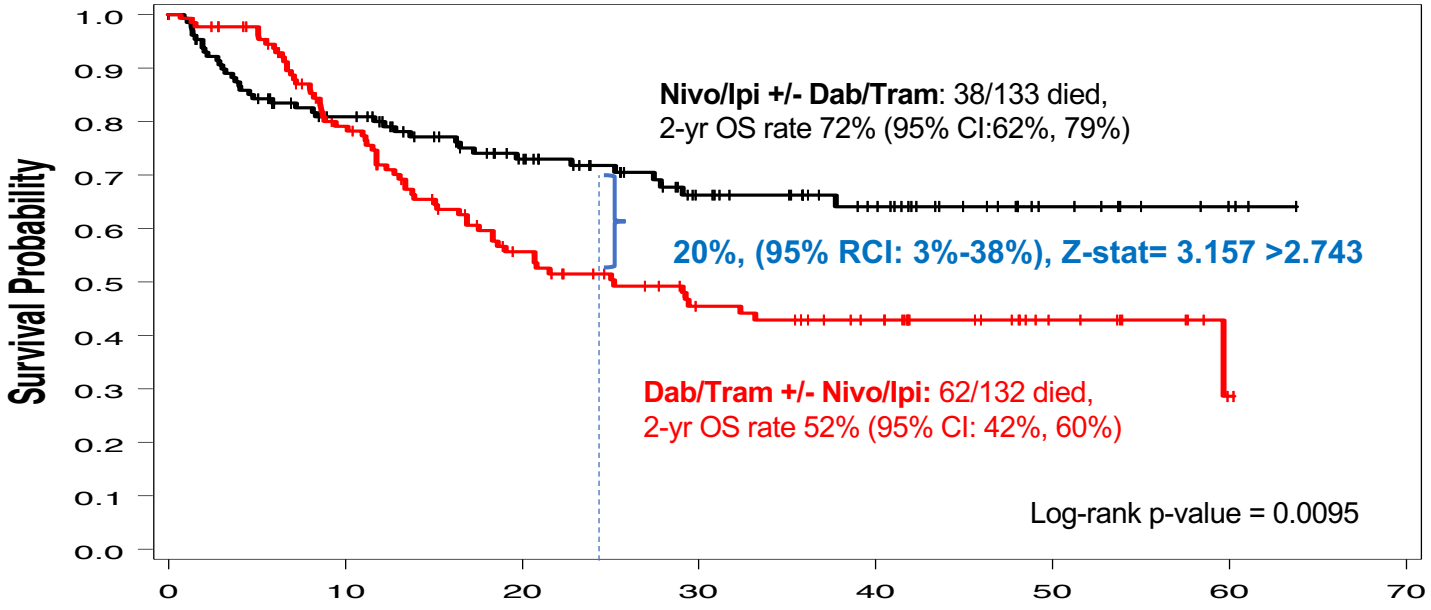
*Nivo/Ipi Induction = 12 wks; nivo maintenance = 72 wks

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)

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Is This a Marriage Made in Heaven?

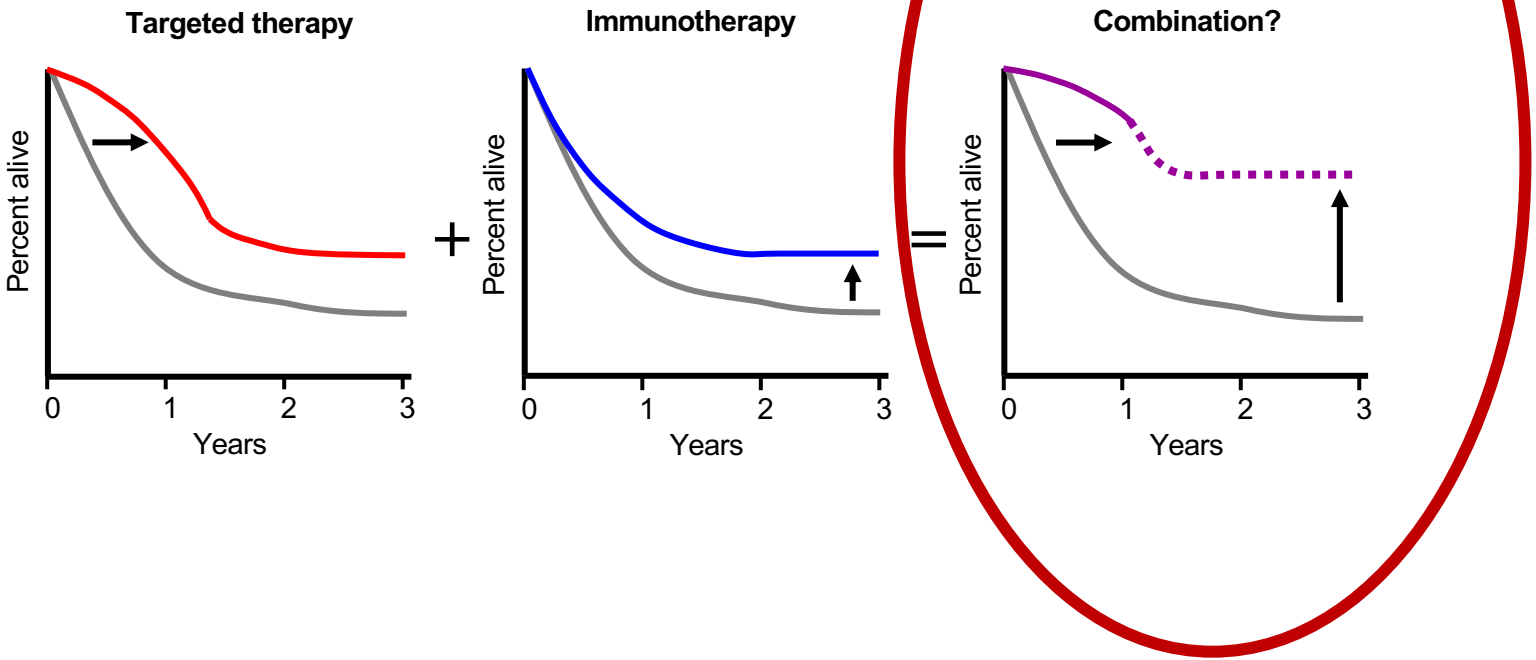

Figure modified from Ribas A et al. *Clin Cancer Res.* 2012, and Hamid O et al. SMR 2015.

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

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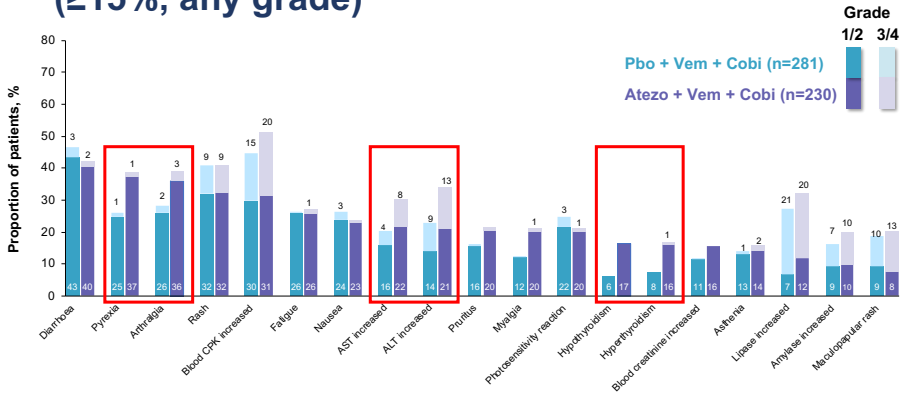
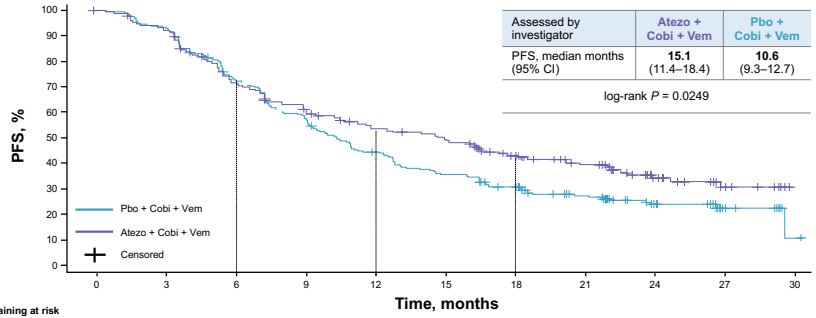
AACR Annual Meeting 2020

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)

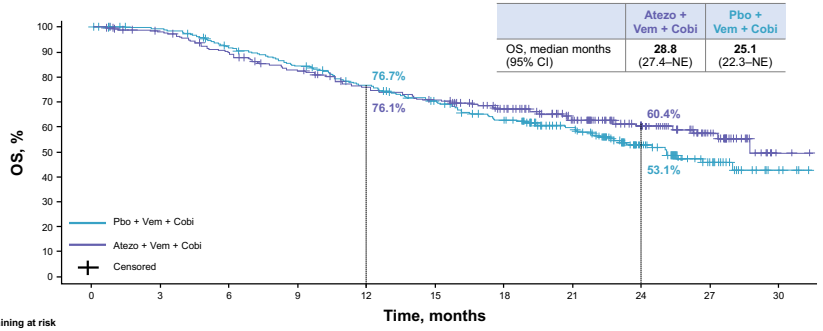
log-rank $P = 0.0249$

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

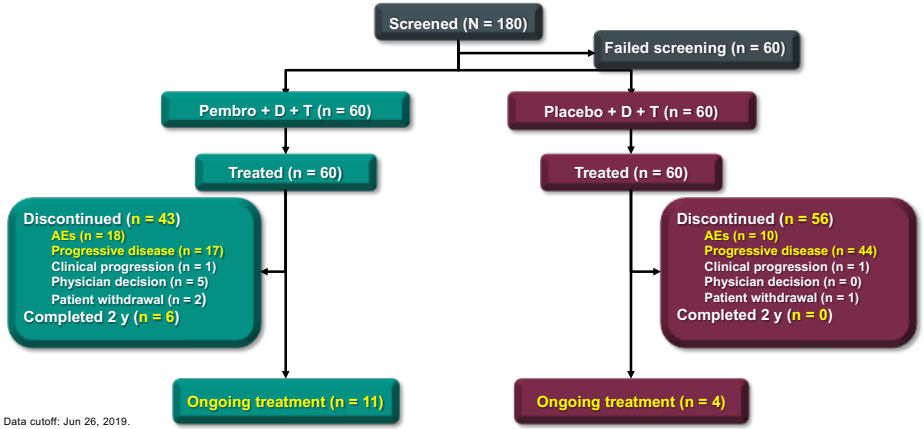
Pier Francesco Ferrucci[1a]; Paolo A. Ascierto[2a]; Michele Maio[3]; Michele Del Vecchio[4]; Victoria Atkinson[5]; Henrik Schmidt[6]; Jacob E. Schachter[7]; Paola Queirolo[8]; Georgina V. Long[9]; Rosalie Stephens[10]; Inge Marie Svane[11]; Michal Lotem[12]; Mahmoud Abu-Amna[13]; Eduard Gasal[14]; Razi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

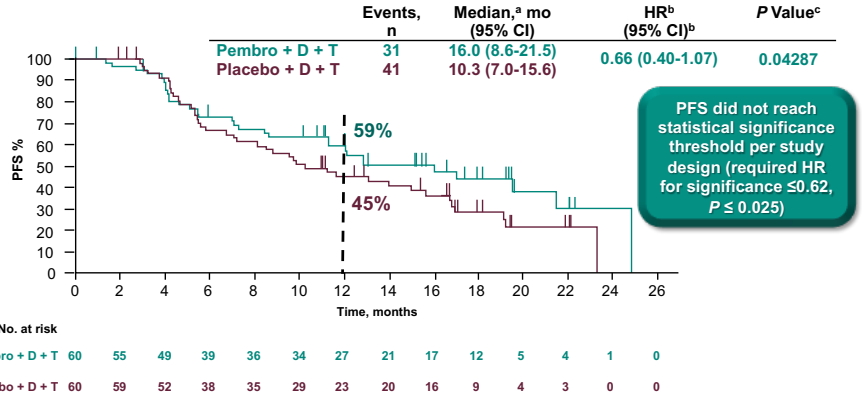
SMR 2019.

Study Disposition



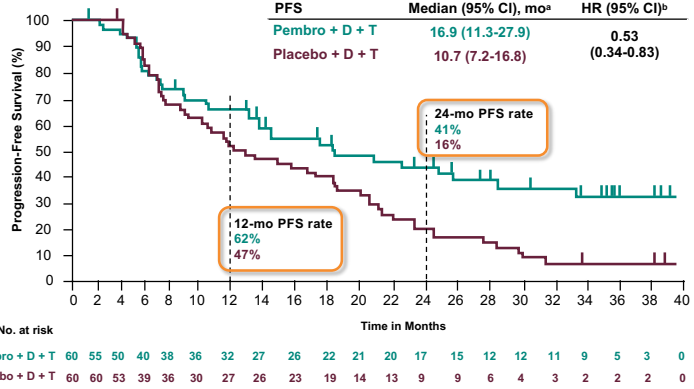
Data cutoff: Jun 26, 2019.

Progression-Free Survival



Ascierto et al. Nature Med 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.

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

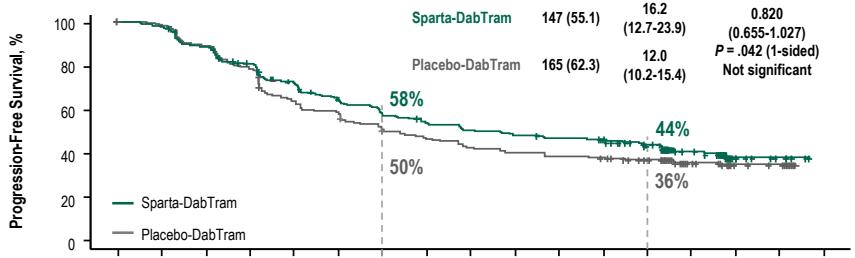
Primary endpoint: Investigator-assessed PFS using RECIST 1.1

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

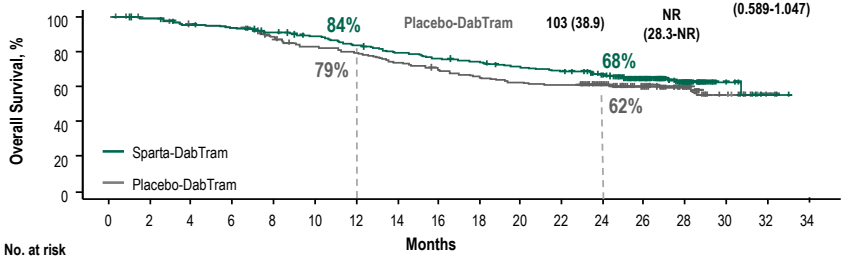


No. at risk																
Sparta-DabTram	267	256	229	204	180	159	142	130	121	115	111	108	90	40	13	5	0
Placebo-DabTram	265	252	228	202	162	148	127	115	105	100	95	93	76	36	11	8	0

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.

Immunotherapy for Melanoma

- Metastatic Disease
- Adjuvant Therapy
- Immuno or targeted therapy for BRAF+ patients?
- What's new and promising
  - Neoadjuvant therapy
  - New agents

Potential Advantages of Neoadjuvant Therapy

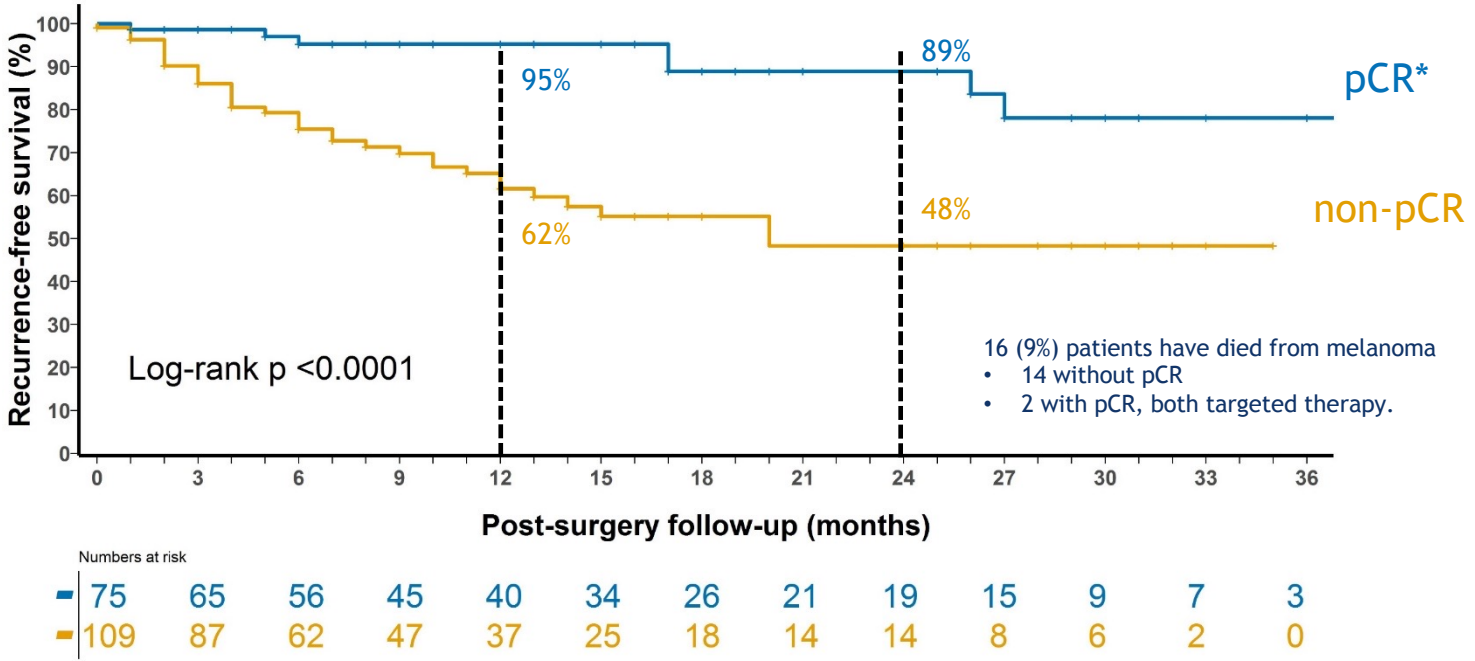
- Tumor shrinkage → decreased surgical morbidity
- Destruction of micrometastases → prevent distant disease spread
- Objective measure of patient's response to therapy → personalization of adjuvant therapy
- Opportunity to collect high-quality serial biospecimens to facilitate understanding of drug response and resistance
- Potential pathway for new drug evaluation/registration

Recent Neoadjuvant Trials

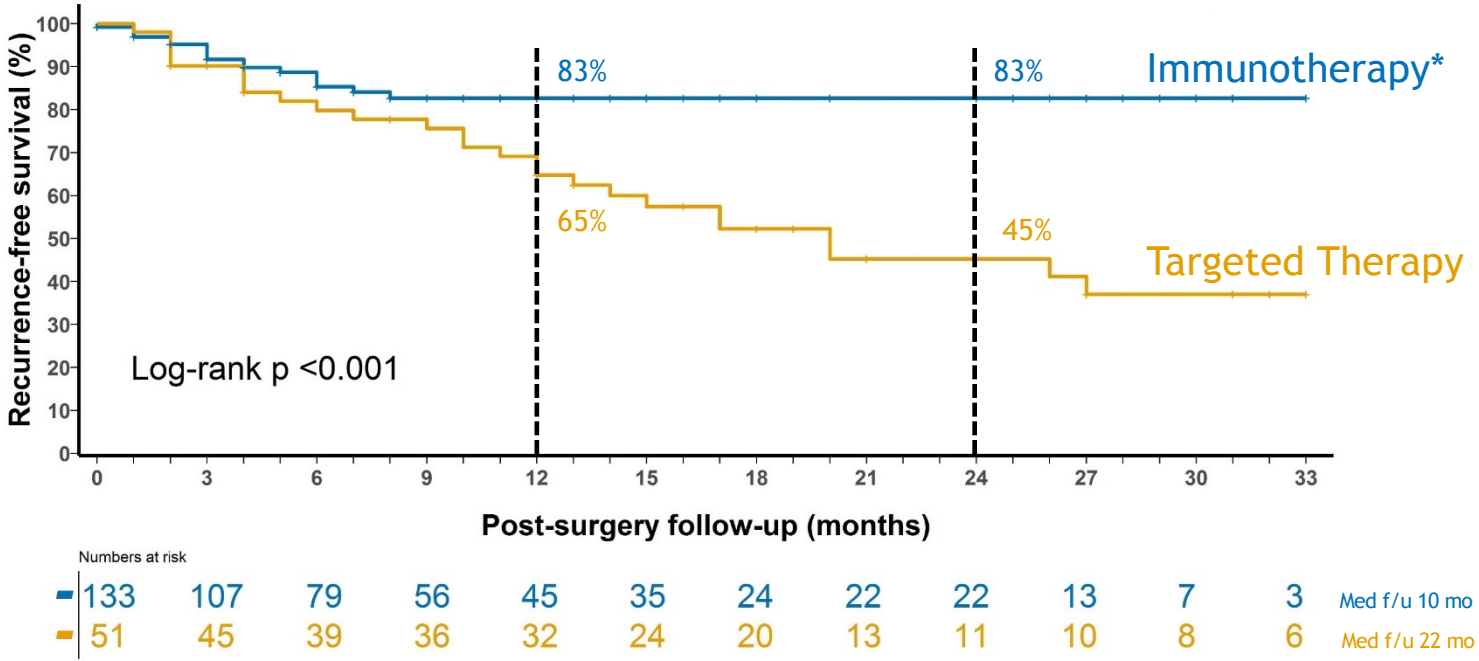
Reference	Drug	Duration	N	pCR rate	Neo/Adj Total
Long Lancet Oncol 2019[1]	Dab/Tram	12 weeks	35	49%	52 weeks
Amaria Lancet Oncol 2018[2]	Dab/Tram	8 weeks	21	58%	52 weeks
Amaria Nat Med 2018[3]	Ipi/Nivo Nivo	12 weeks	11 12	45% 25%	38 weeks
Huang Nat Med 2018[4]	Pembro	3 weeks	27	19%	52 weeks
Rozeman Lancet Oncol 2019[5]	Ipi/Nivo	6 weeks	86 (Arm B = 29)	57% (Arm B)	6 weeks

1. Long GV et al. *Lancet Oncol.* 2019;20(7):961-971; 2. Amaria RN et al. *Lancet Oncol.* 2018;19(2):181-193; 3. Amaria RN et al. *Nat Med.* 2018;24(11):1649-1654; 4. Huang AC et al. *Nat Med.* 2019;25(3):454-461; 5. Rozeman EA et al. *Lancet Oncol.* 2019;20(7):948-960.

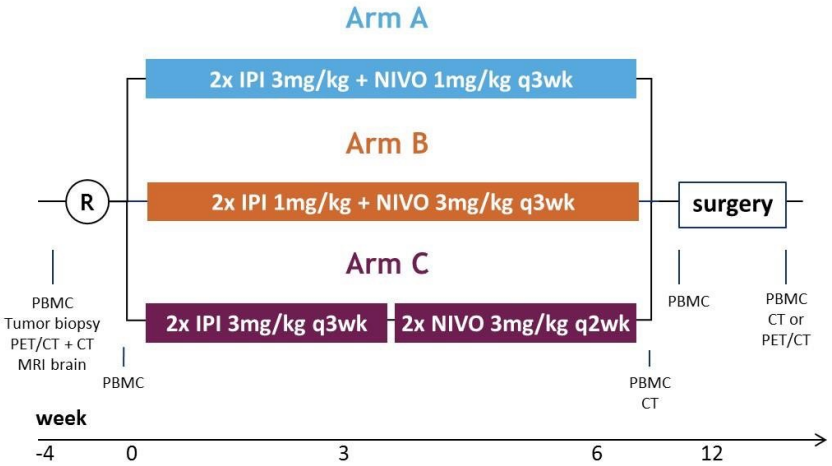
Pooled analysis: RFS by pathological response
N=184, Overall pCR=41%



Pooled analysis: RFS by drug class



The OpACIN-neo study identified neoadjuvant IPI 1 mg/kg + NIVO 3 mg/kg as the optimal treatment scheme



	Grade 3-4 toxicity	Pathologic Response
Arm A	40%	80%
Arm B	20%	77%
Arm C	50%	65%

Rozeman et al., Lancet Oncology, 2019

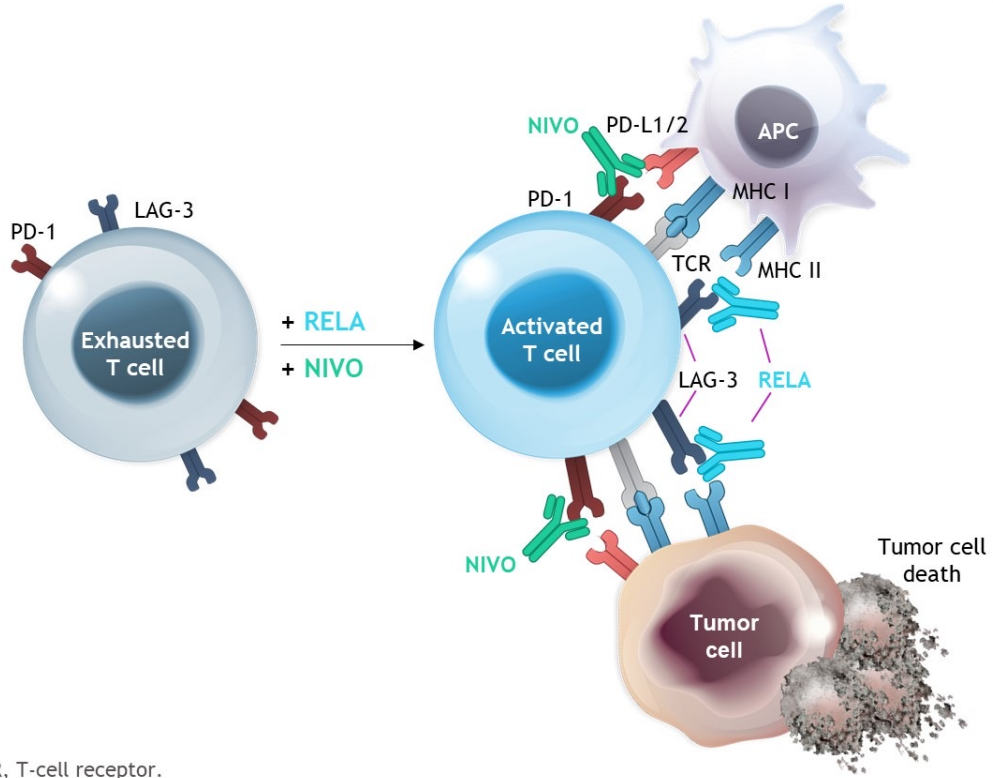
Dosing in Arm A, B, and C based on data from Blank, et al. Nat Med 2018, Long, et al. Lancet Oncol 2017, Meerveld-Eggink et al. Ann Oncol 2017

Immunotherapy for Melanoma

- Metastatic Disease
- Adjuvant Therapy
- Immuno or targeted therapy for BRAF+ patients?
- What's new and promising
  - Neoadjuvant therapy
  - New agents

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

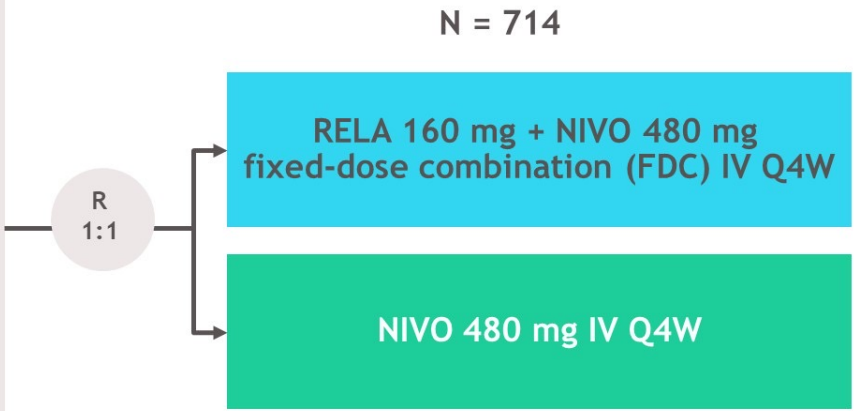
- **RELATIVITY-047** is a global, randomized, double-blind, phase 2/3 study

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

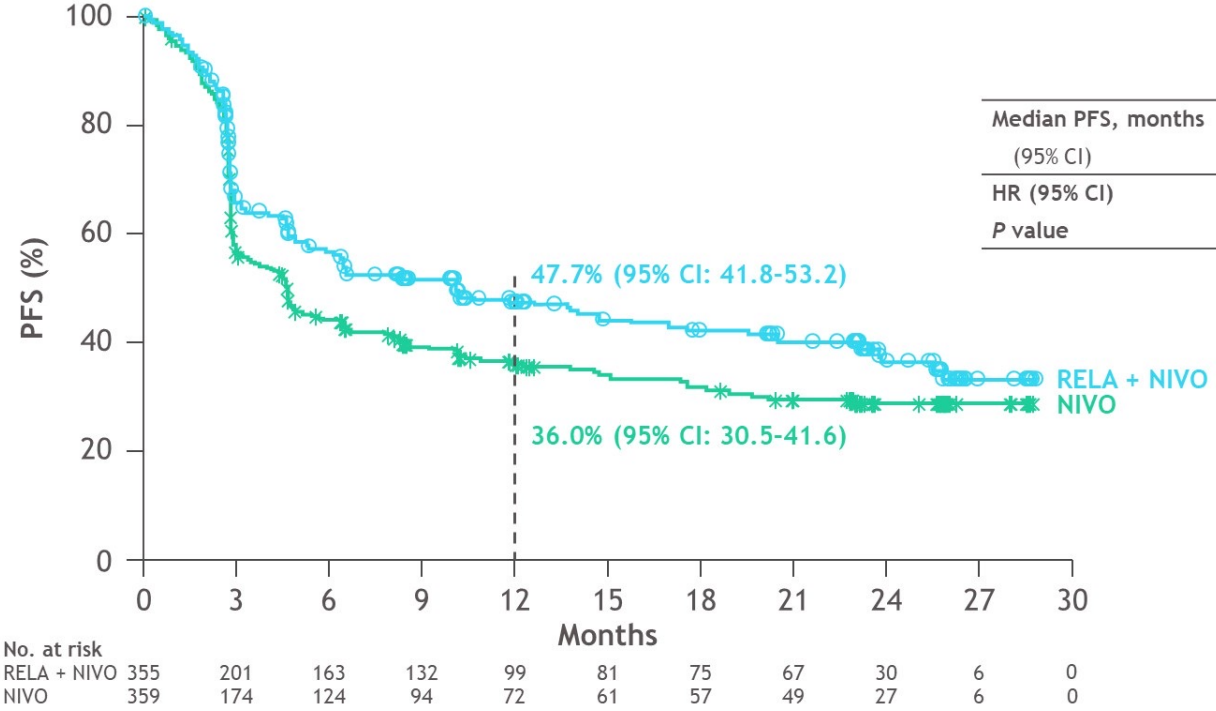
- PFS by BICR[d]

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.

RELATIVITY 047 demonstrated superior PFS benefit by BICR for RELA + NIVO FDC vs NIVO

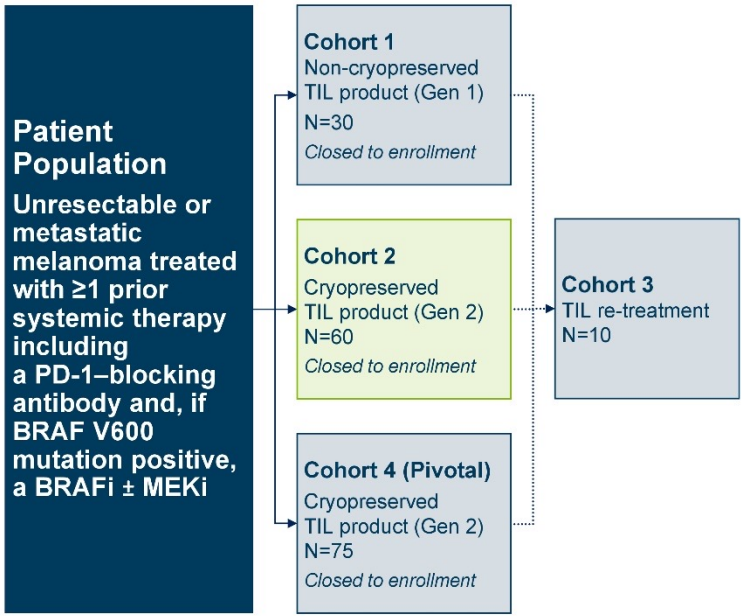


	RELA + NIVO (n = 355)	NIVO (n = 359)
Median PFS, months	10.12	4.63
(95% CI)	(6.37-15.74)	(3.38-5.62)
HR (95% CI)	0.75 (0.62-0.92)	
P value	0.0055	

CI, confidence interval; HR, hazard ratio.
All randomized patients. Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3 (≥ 1% vs < 1%), *BRAF* (mutation positive vs mutation wild-type), AJCC M stage (M0/M1any[0] vs M1any[1]). PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

C-144-01 Study Design

Phase 2, multicenter study to assess the efficacy and safety of autologous TIL (lifileucel) for treatment of patients with metastatic melanoma (NCT02360579)



Cohort 2 Endpoints

- Primary: Efficacy per investigator-assessed ORR using RECIST 1.1 response criteria
- Secondary: Safety and additional parameters of efficacy

Key Eligibility Criteria

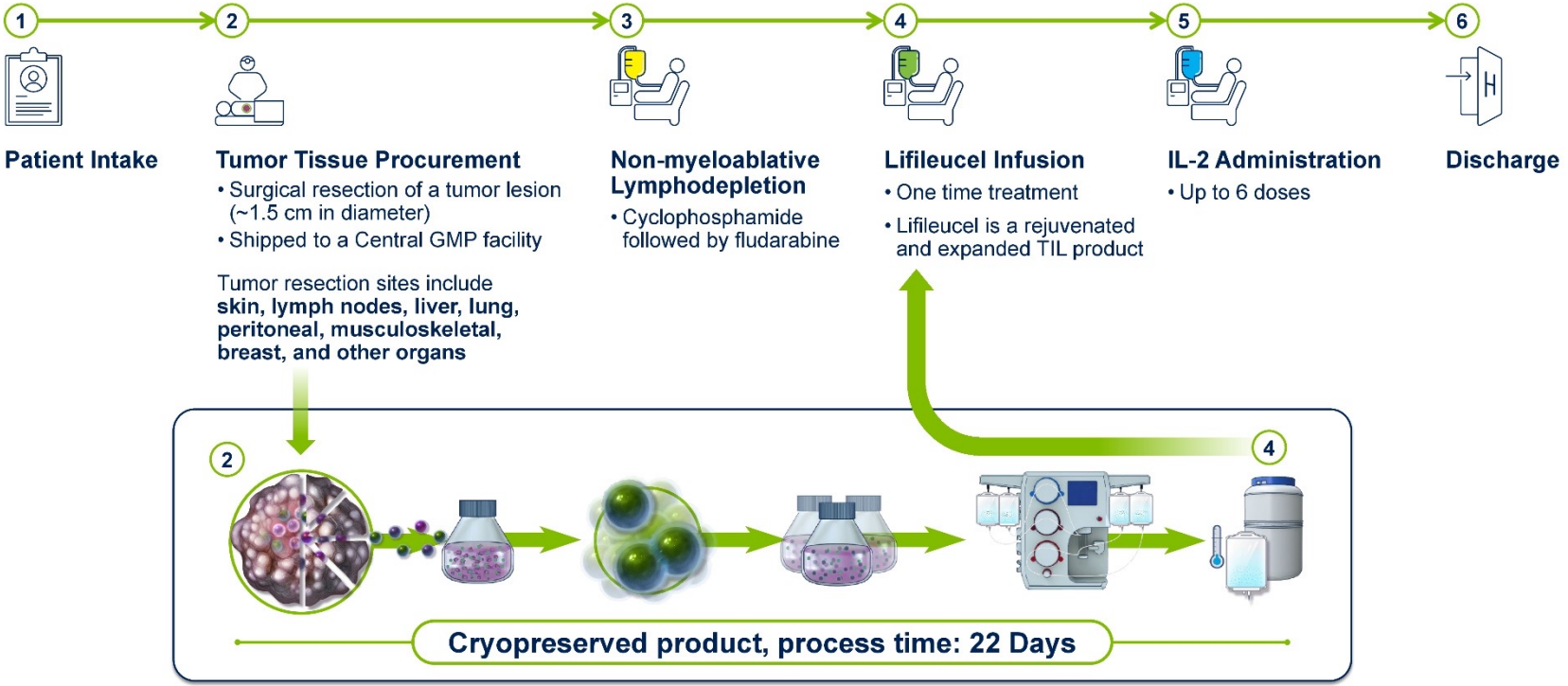
- Radiographic confirmation of progression
- One tumor lesion resectable for TIL generation (~1.5 cm in diameter) and ≥1 target tumor lesion for RECIST 1.1 response assessment
- Age ≥18 years at the time of consent
- ECOG performance status of 0–1

Methods

- Patients were enrolled from April 2017 to January 2019 at 26 sites across the US and EU
- Concomitant anticancer therapy was not permitted
- Imaging-evaluable disease was required
- All responses required confirmation
- Data cutoff: 22 April 2021

BRAFi, BRAF inhibitor; ECOG, Eastern Cooperative Oncology Group; MEKi, MEK inhibitor; ORR, objective response rate; PD-1, programmed cell death protein 1; RECIST, Response Evaluation Criteria in Solid Tumors; TIL, tumor infiltrating lymphocytes.

Patient Journey and TIL Manufacturing



Objective Response Rate

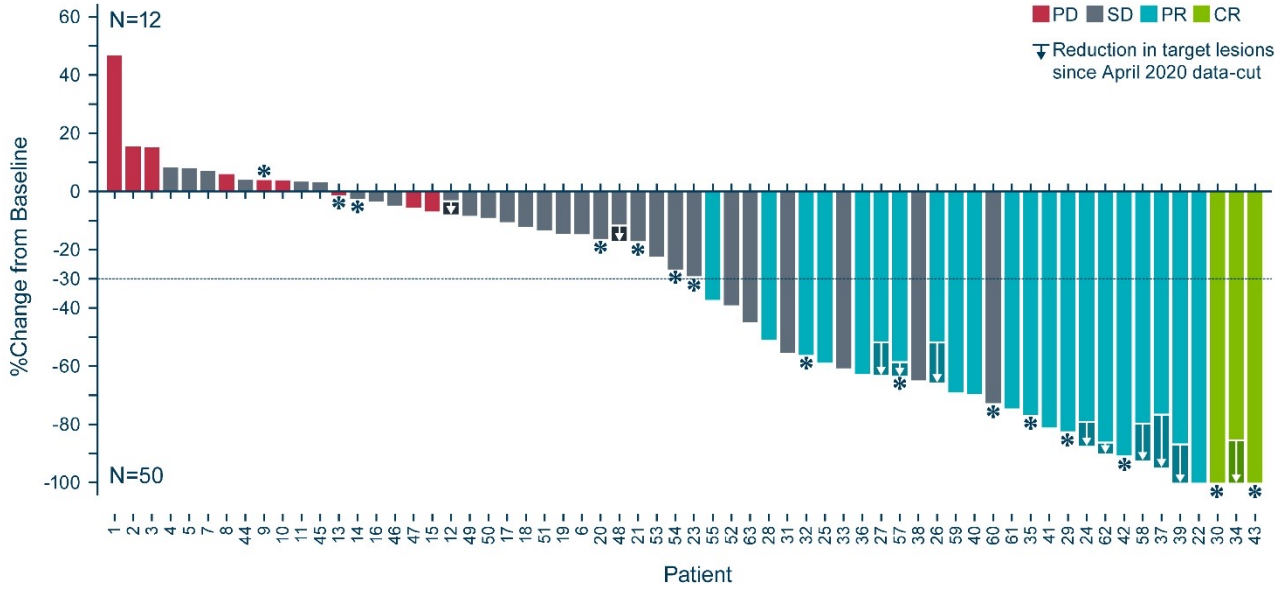
Response, n (%)	N=66
Objective Response Rate	**24 (36.4)**
Complete response	3 (4.5)
Partial response	21 (31.8)
Stable disease	29 (43.9)
Progressive disease	9 (13.6)
Non-evaluable*	4 (6.1)
Disease control rate	53 (80.3)
Median Duration of Response	**Not Reached**
Min, max (months)	2.2, 38.5+

- Mean number of TIL cells infused: 27.3×10^9

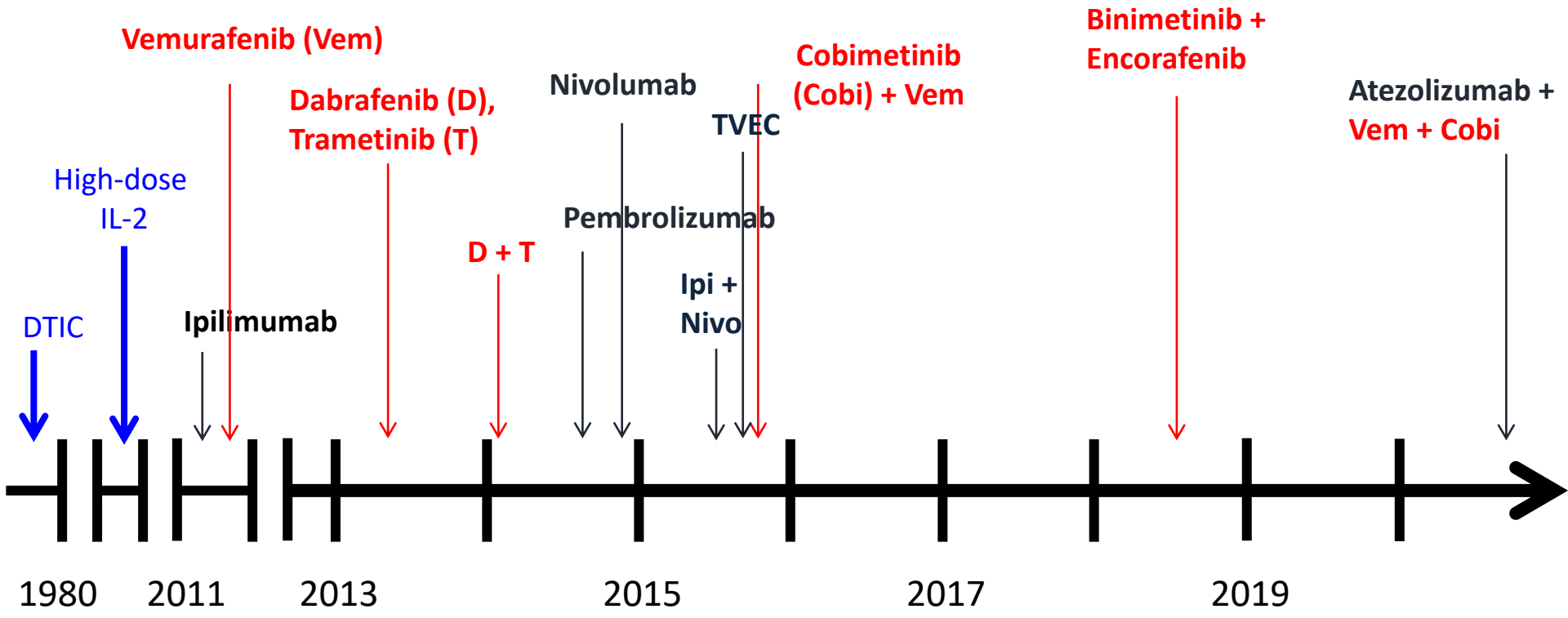
- After a median study follow-up of 33.1 months, **median DOR was not reached** (range 2.2, 38.5+ months)

Best Overall Response

- 81% (50/62) of patients had a reduction in tumor burden
- 11 patients (17.7%) had further SOD reduction since April 2020 datacut



Advanced Melanoma Treatment Landscape 2021



Summary & Conclusions (1)

- Immunotherapy is an option for all patients
  - Single agent PD1 (nivo or pembro)
  - Combination PD-1/CTLA-4 (ipi/nivo)
- Toxicity of combination immunotherapy is higher but benefits are durable with a longer treatment-free interval
- Targeted therapy (BRAF/MEK combination) is an option for BRAF-MT patients

Summary & Conclusions (2)

- Randomized trial data show that first-line combination immunotherapy is superior to targeted therapy
- Triple therapy for BRAF-MT patients is an approved option but the data are somewhat controversial
- Neoadjuvant therapy is an important area of research and a potential paradigm change
- Future directions are looking at other front-line combinations and options for resistant disease