Melanoma: What Is the Best Sequence of Therapy?

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Melanoma Treatment Options

- Immunotherapy
- Targeted Therapy

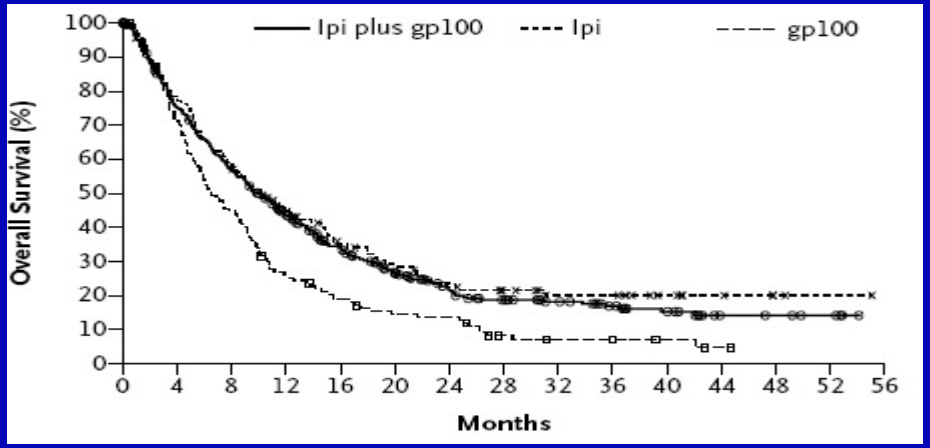
Immunotherapy for Melanoma

- Metastatic Disease
  - Anti-PD1 (nivolumab, pembrolizumab)
  - Anti-PD1+Anti-CTLA4 (ipilimumab + nivolumab)
- Adjuvant Therapy
  - Anti-PD1 (nivolumab, pembrolizumab)

Immunotherapy for Melanoma

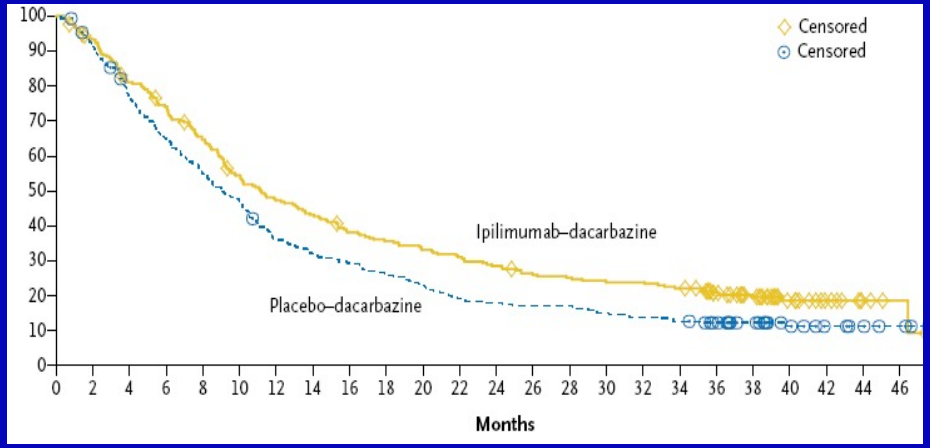
- Metastatic Disease
  - Anti-PD1 (nivolumab, pembrolizumab)
  - Anti-PD1+Anti-CTLA4 (ipilimumab + nivolumab)
- Adjuvant Therapy
  - Anti-PD1 (nivolumab, pembrolizumab)

Clinical Results with Ipilimumab (2nd and 1st line)
Ipilimumab vs vaccine and Ipi + DTIC vs DTIC



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

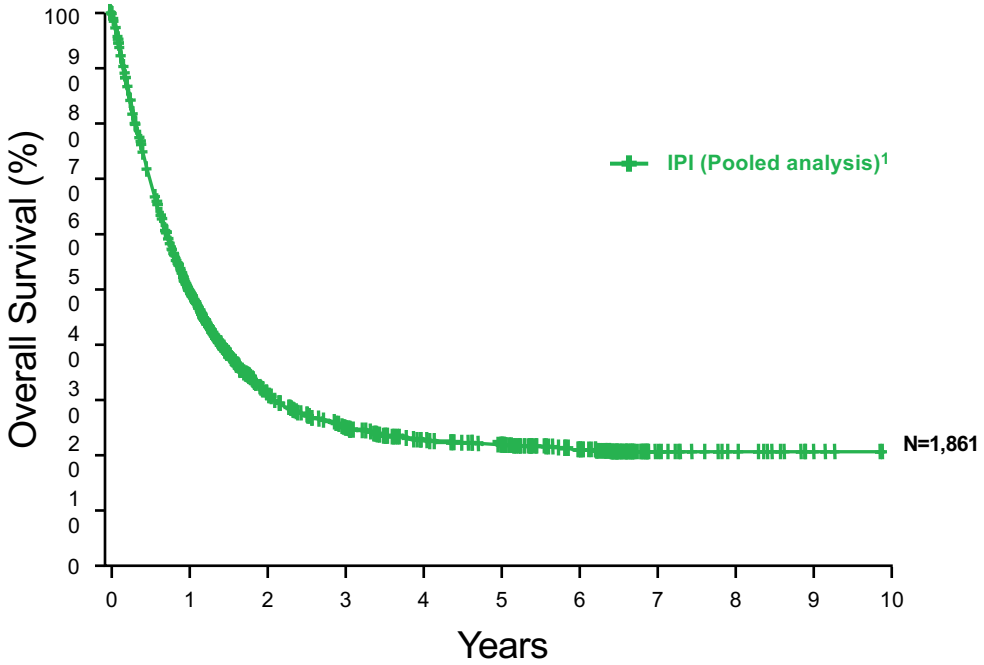
Hodi FS, et al. *N Engl J Med.* 2010;363:711-23.



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

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

Immune Checkpoint Inhibitors Provide Durable Long-term Survival for Patients with 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.

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.

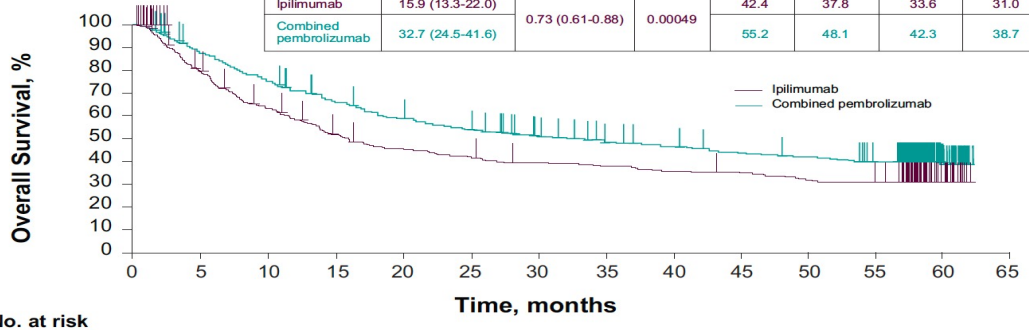
[b]Prior anti-BRAF targeted therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.

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

Keynote-006: 5-Year Survival (All Patients & Treatment Naïve)

A

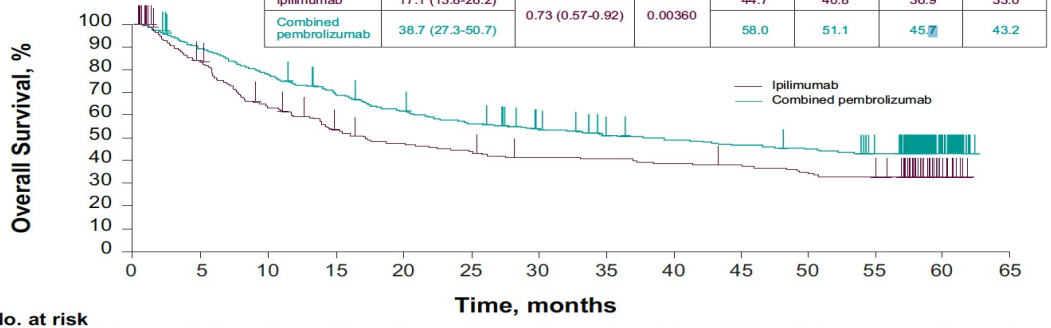
OS	Median[b] (95% CI), months	HR[c] (95% CI)[c]	*P* Value[d]	24-Month Rate,[b] %	36-Month Rate,[b] %	48-Month Rate,[b] %	60-Month Rate,[b] %
Ipilimumab	15.9 (13.3-22.0)	0.73 (0.61-0.88)	0.00049	42.4	37.8	33.6	31.0
Combined pembrolizumab	32.7 (24.5-41.6)			55.2	48.1	42.3	38.7



No. at risk														
Ipilimumab	277	202	158	127	111	102	94	90	85	83	75	72	19	0
Combined pembrolizumab	556	481	416	357	317	289	264	245	233	217	208	194	47	0

B

OS	Median[b] (95% CI), months	HR[c] (95% CI)[c]	*P* Value[d]	24-Month Rate,[b] %	36-Month Rate,[b] %	48-Month Rate,[b] %	60-Month Rate,[b] %
Ipilimumab	17.1 (13.8-26.2)	0.73 (0.57-0.92)	0.00360	44.7	40.8	36.9	33.0
Combined pembrolizumab	38.7 (27.3-50.7)			58.0	51.1	45.7	43.2

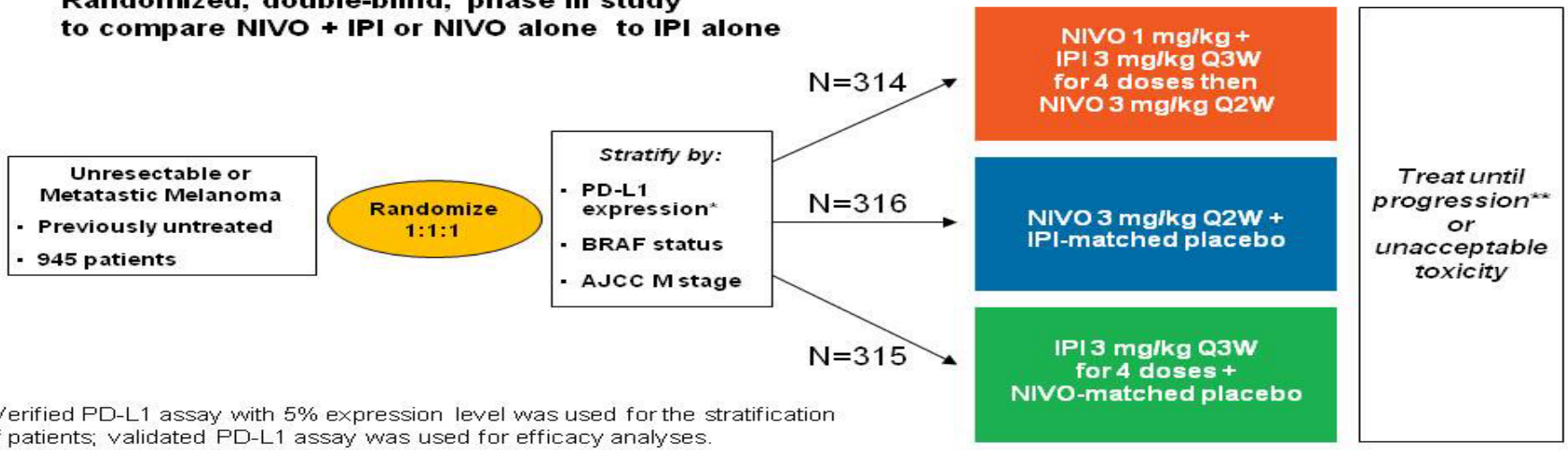


No. at risk														
Ipilimumab	181	140	105	86	76	70	64	63	60	58	52	49	8	0
Combined pembrolizumab	368	324	284	248	221	201	184	170	163	155	149	137	31	0

Robert et al: AACR 2019

CA209-067: Study Design

Randomized, double-blind, phase III study to compare NIVO + IPI or NIVO alone to IPI alone



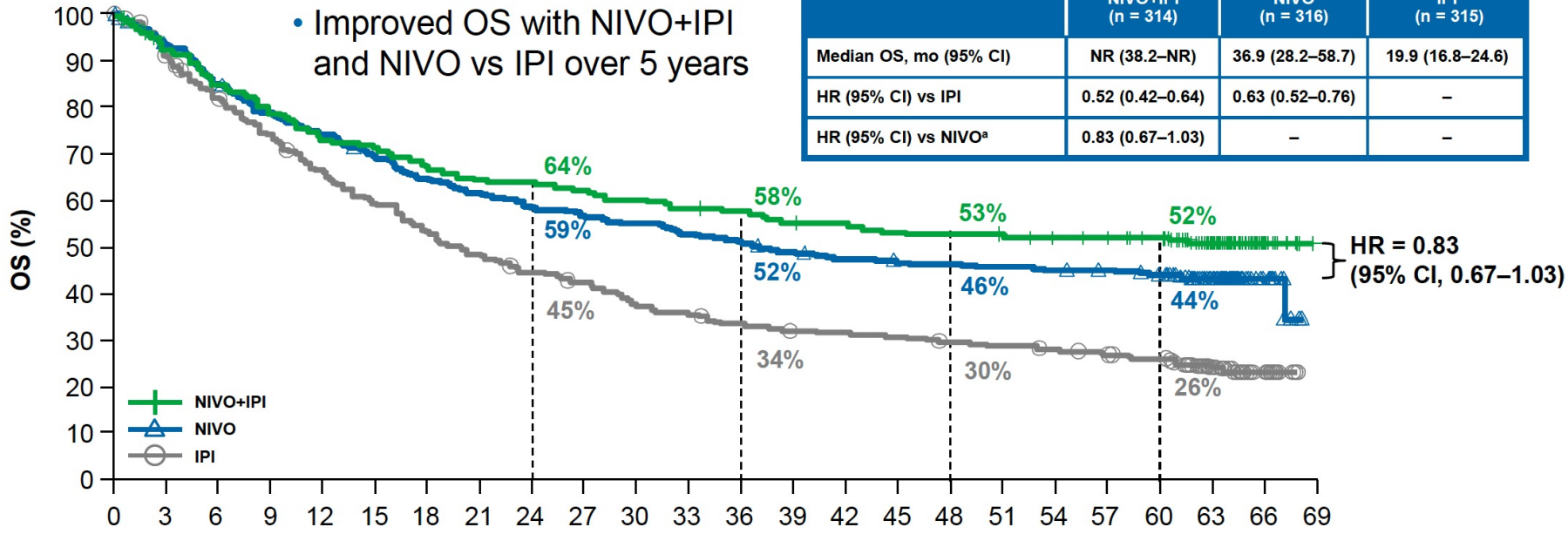
*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.

Overall Survival

- Improved OS with NIVO+IPI and NIVO vs IPI over 5 years

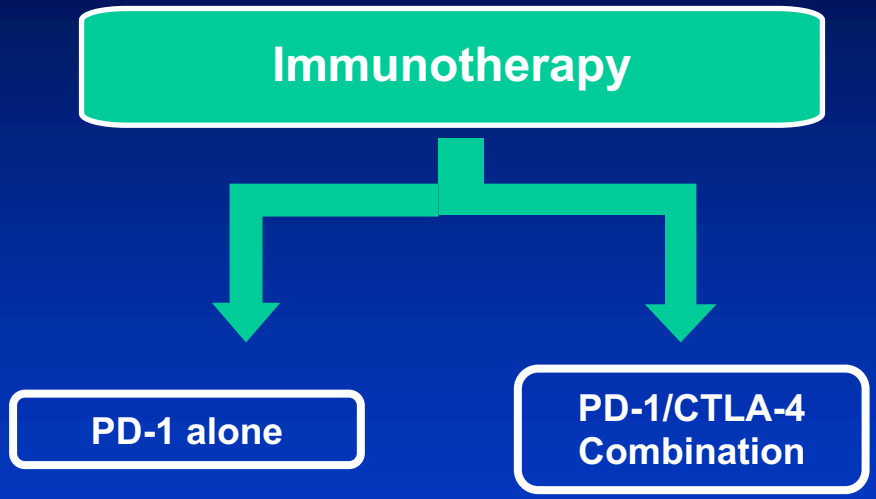
	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.67–1.03)	–	–



No. at risk

NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

Combination or monotherapy?



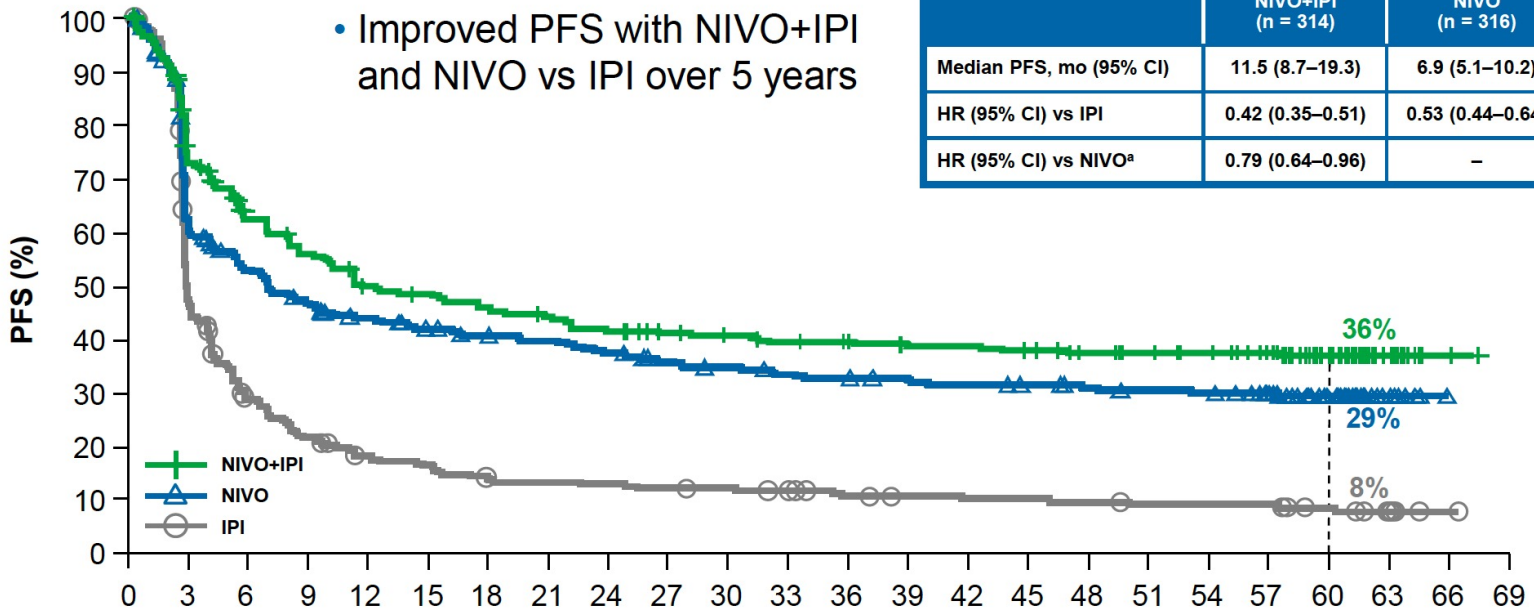
Decision Factors

- Efficacy
- Toxicity

Progression-Free Survival

- Improved PFS with NIVO+IPI and NIVO vs IPI over 5 years

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median PFS, mo (95% CI)	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 (0.64–0.96)	–	–



No. at risk

NIVO+IPI	314	218	174	155	136	131	124	117	110	104	101	97	95	91	90	88	82	79	76	69	45	19	2	0
NIVO	316	177	151	132	120	112	106	103	97	88	84	80	78	76	73	71	68	66	65	60	40	13	1	0
IPI	315	136	78	58	46	42	34	32	31	29	28	26	21	19	18	18	17	15	15	15	11	8	1	0

Decision Factors

- Efficacy
- Toxicity

Safety Summary

- With an additional 19 months of follow-up, safety was consistent with the initial report[1]

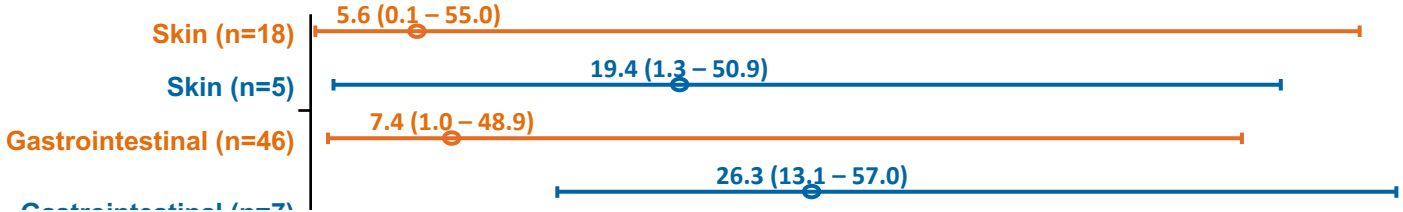
	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	58.5	86.3	20.8	86.2	27.7
Treatment-related AE leading to discontinuation	39.6	31.0	11.5	7.7	16.1	14.1
Treatment-related death, n (%)	2 (0.6)[a]		1 (0.3)[b]		1 (0.3)[b]	

- Most select AEs were managed and resolved within 3-4 weeks (85–100% across organ categories)
- ORR was 70.7% for pts who discontinued NIVO+IPI due to AEs, with median OS not reached

[a]Cardiomyopathy (NIVO+IPI, n=1); Liver necrosis (NIVO+IPI, n=1). Both deaths occurred >100 days after the last treatment.
[b]Neutropenia (NIVO, n=1); colon perforation (IPI, n=1).[1]

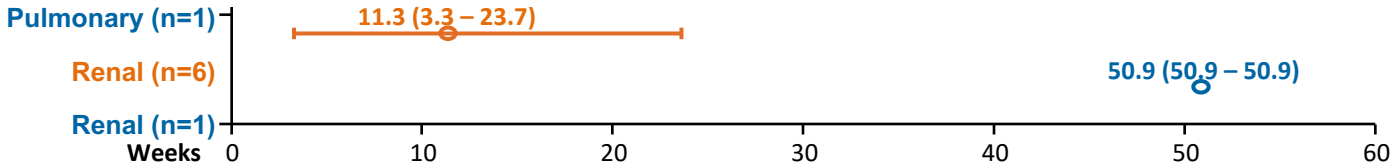
1. Larkin J, et al. *NEJM* 2015;373:23–34.

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



Toxicity Earlier

Longer Time to Resolution

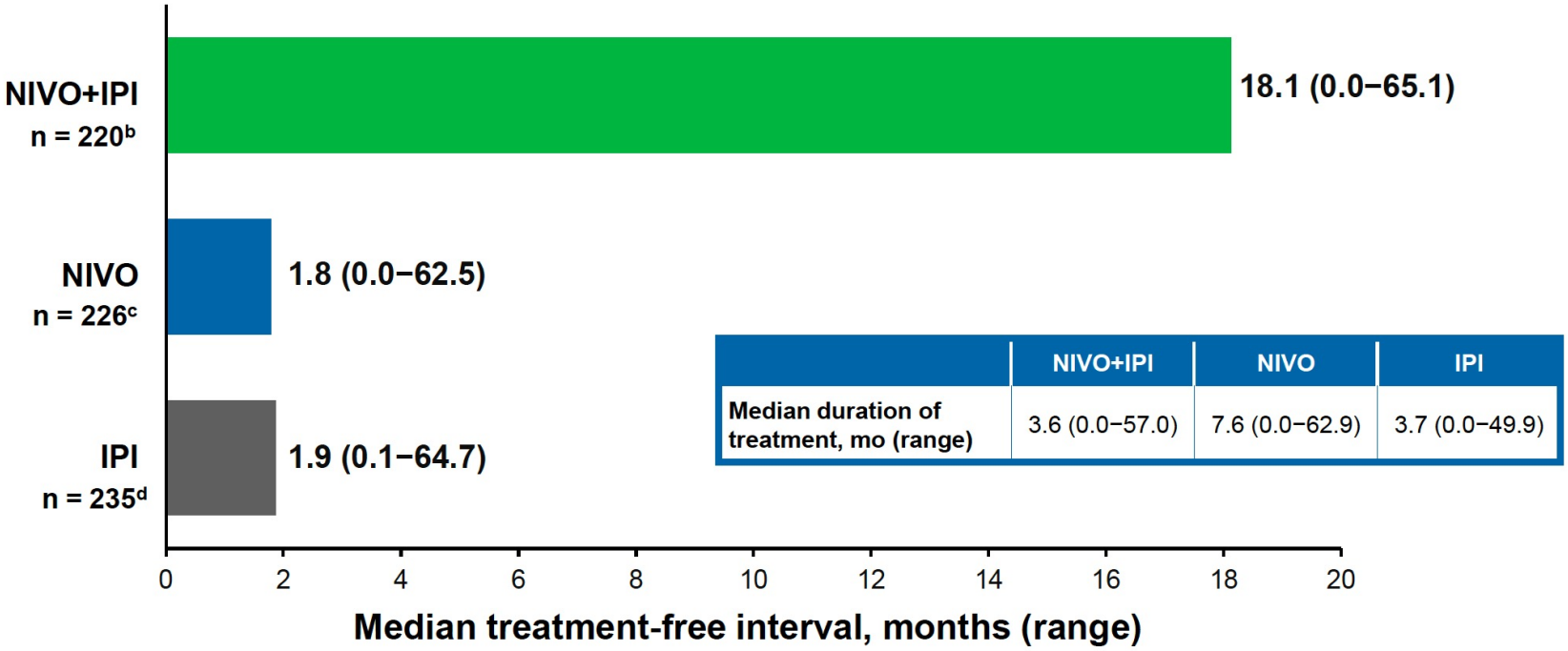


Circles represent medians; bars signify ranges

Larkin J et al ECC 2015

Longer Treatment-Free Interval With NIVO+IPI in Patients Who Discontinued Study Therapy[a]

Population analyzed: patients who (1) were alive or (2) who died following subsequent systemic therapy



	NIVO+IPI	NIVO	IPI
Median duration of treatment, mo (range)	3.6 (0.0–57.0)	7.6 (0.0–62.9)	3.7 (0.0–49.9)

[a]Post-hoc analysis;

Immunotherapy for Melanoma

- Metastatic Disease
  - Anti-PD1 (nivolumab, pembrolizumab)
  - Anti-PD1+Anti-CTLA4 (ipilimumab + nivolumab)
- Adjuvant Therapy
  - Anti-PD1 (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

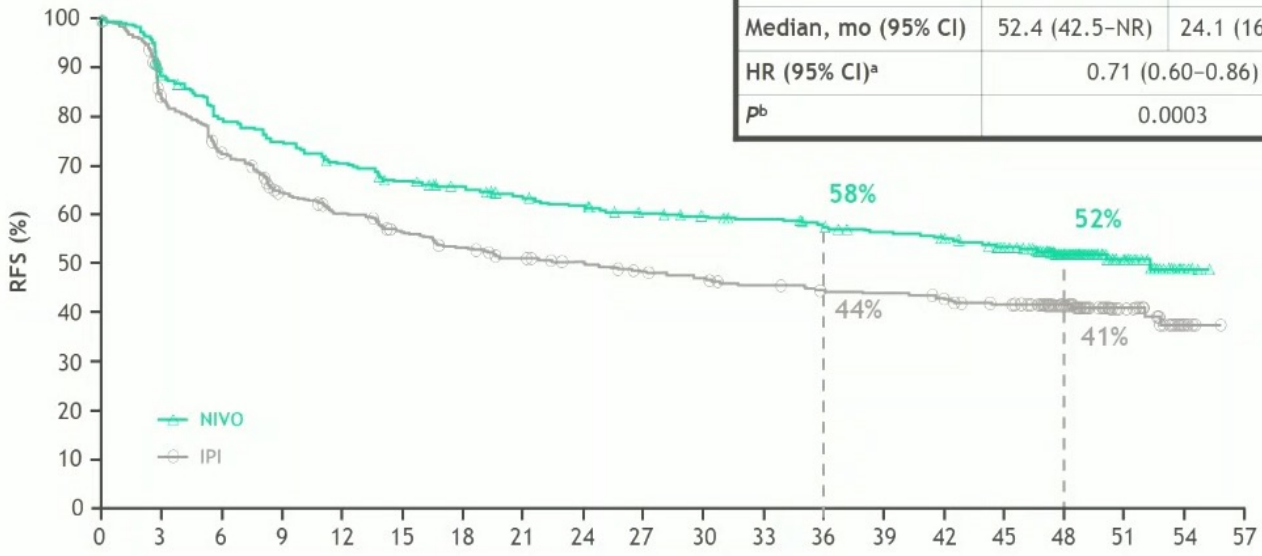
Primary endpoint: RFS

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	

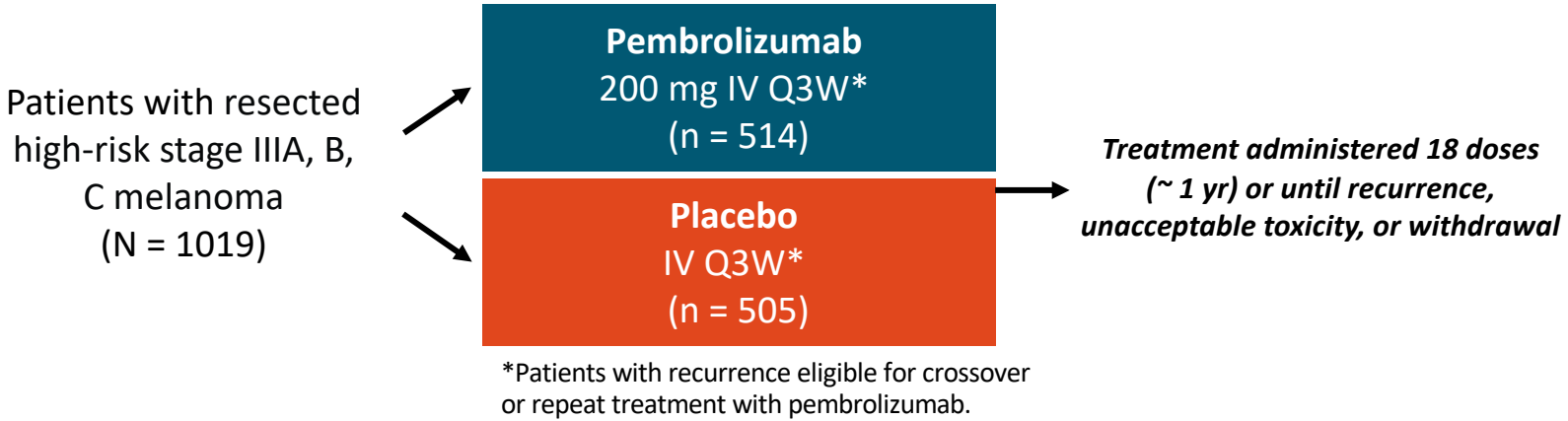


No. at risk																			
NIVO 3 mg/kg	453	395	354	332	311	293	283	271	262	250	245	240	233	224	218	206	147	37	11	0
IPI 10 mg/kg	453	366	316	273	253	234	220	208	201	191	185	177	171	168	163	154	113	32	10	0

[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

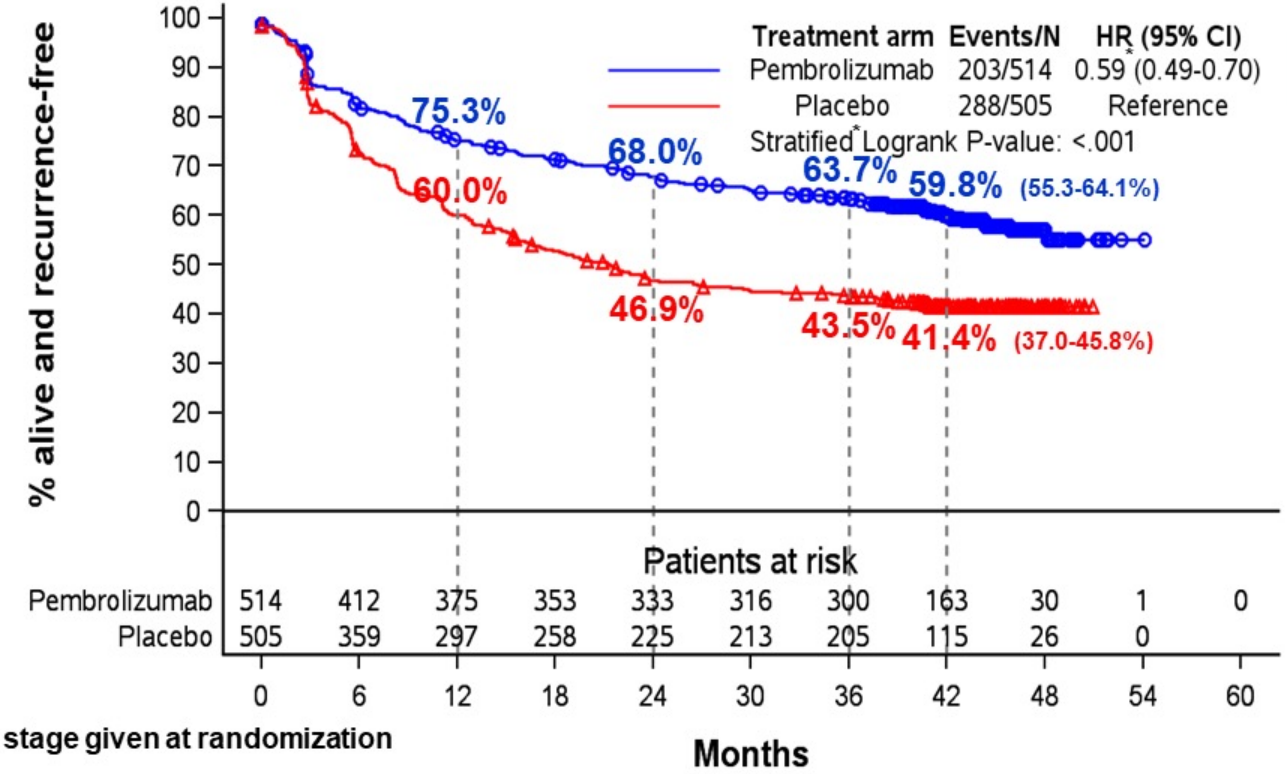


- Coprimary endpoints: RFS in ITT population, RFS in PD-L1+ subgroup
- Secondary endpoints: DMFS, OS, safety, QoL

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



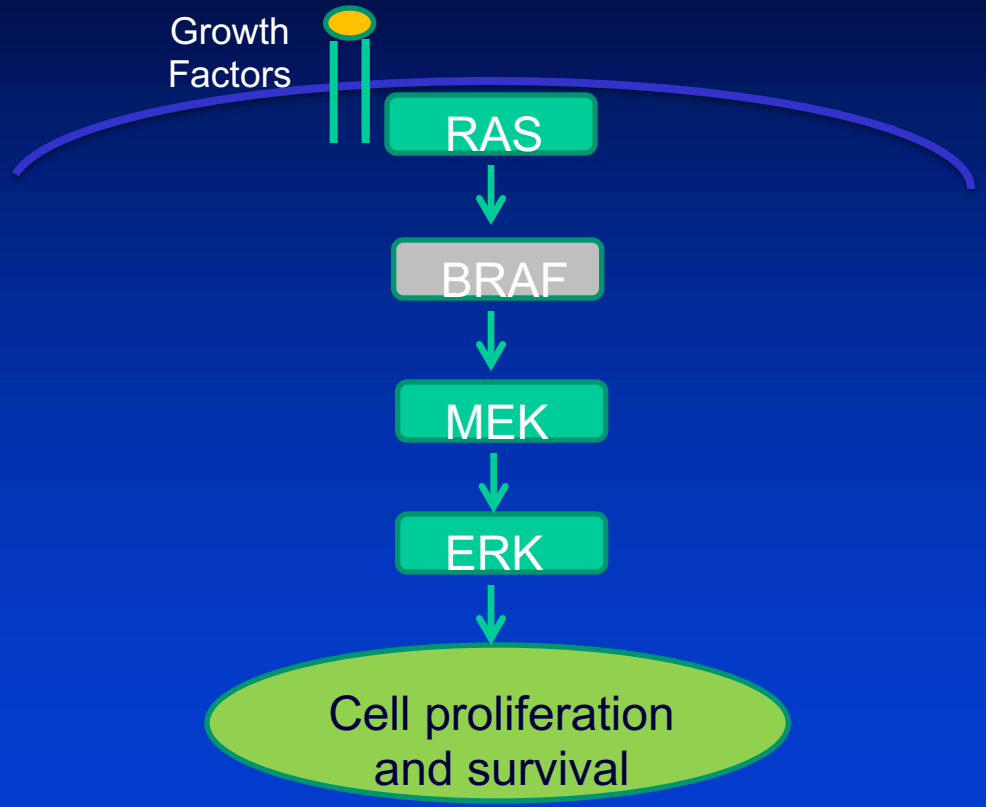
HR 0.59

*Stratified by stage given at randomization

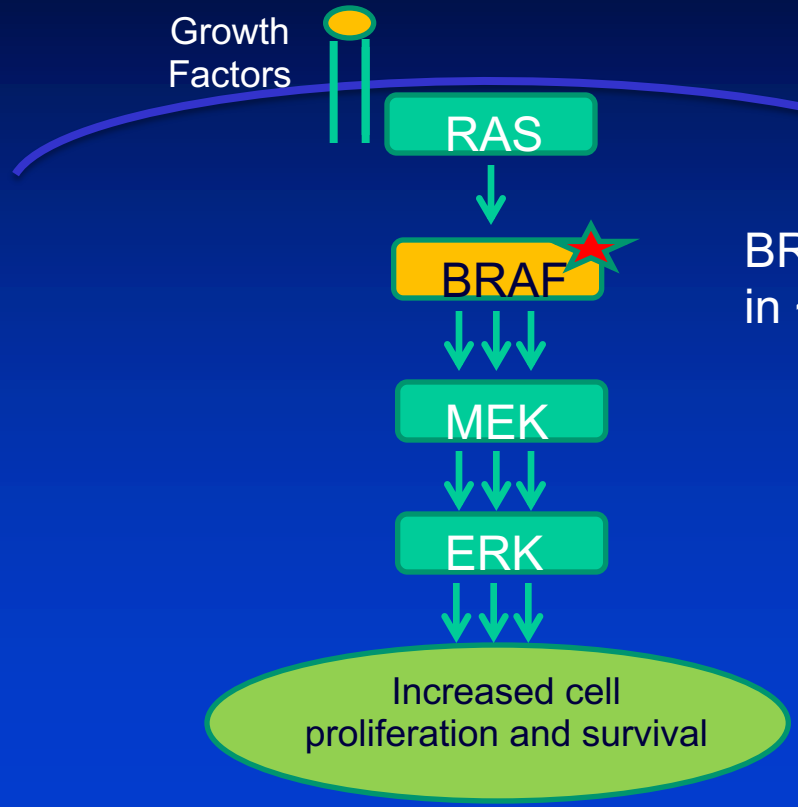
Targeted Therapy

- Metastatic Disease
  - BRAF/MEK combination therapy
    - Dabrafenib/trametinib
    - Vemurafenib/cobimetinib
    - Encorafenib/binimetinib
- Adjuvant Therapy
  - BRAF/MEK combination
    - Dabrafenib/trametinib

MAPK Pathway

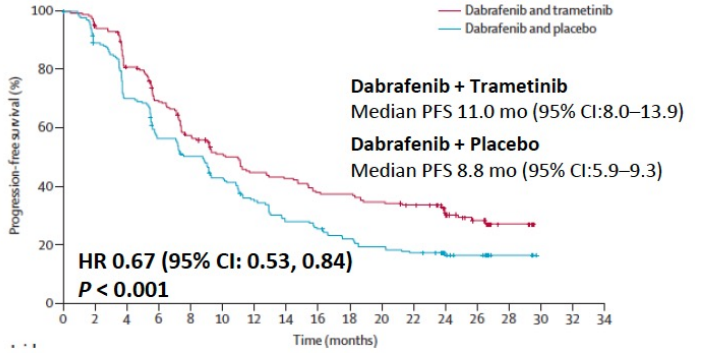


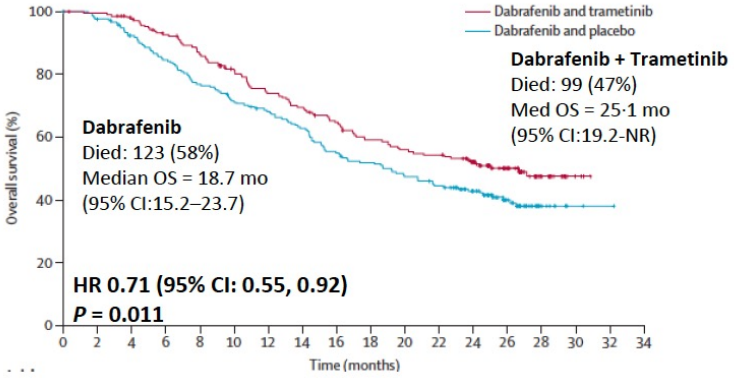
BRAF Mutation



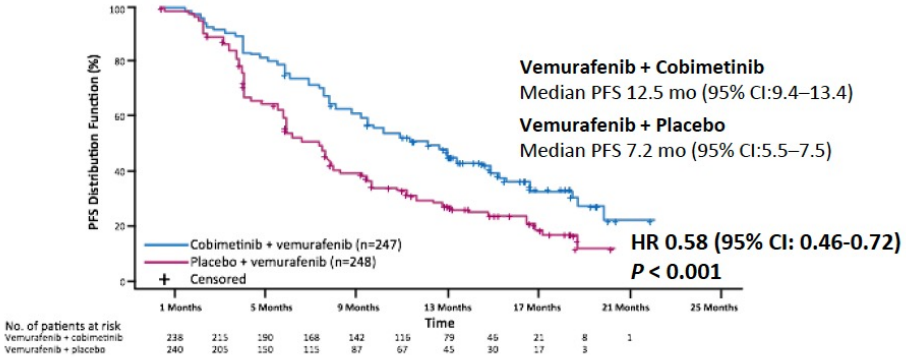
BRAF mutation is present in ~50% of melanomas

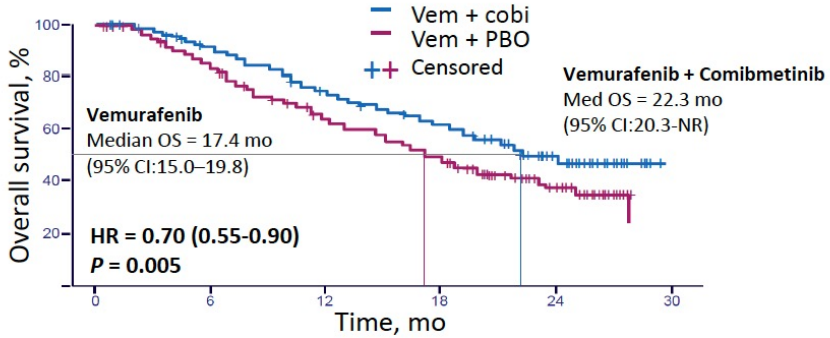
Combined BRAF/MEKi therapy is superior survival compared to single-agent BRAF inhibitors (BRAFi)





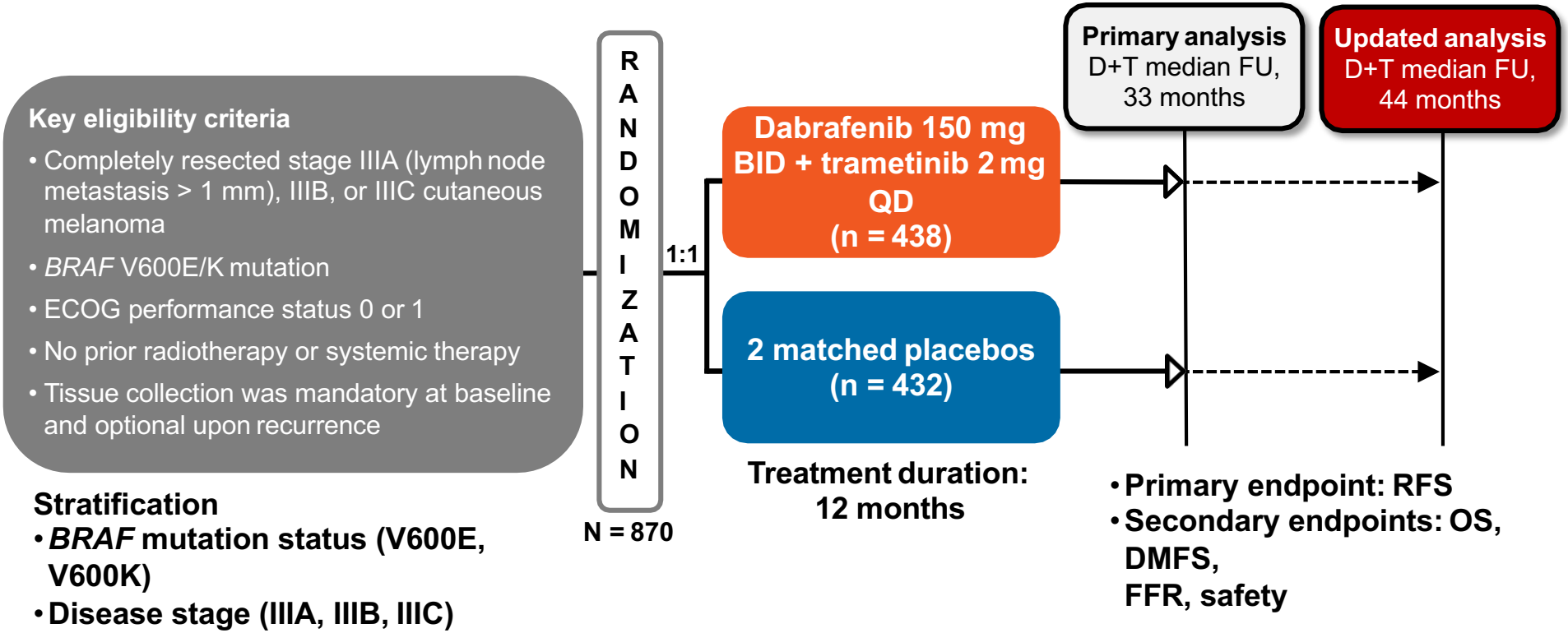
Long et al. NEJM 2014; Long et al. *Lancet* 2015.





Larkin et al. NEJM 2015

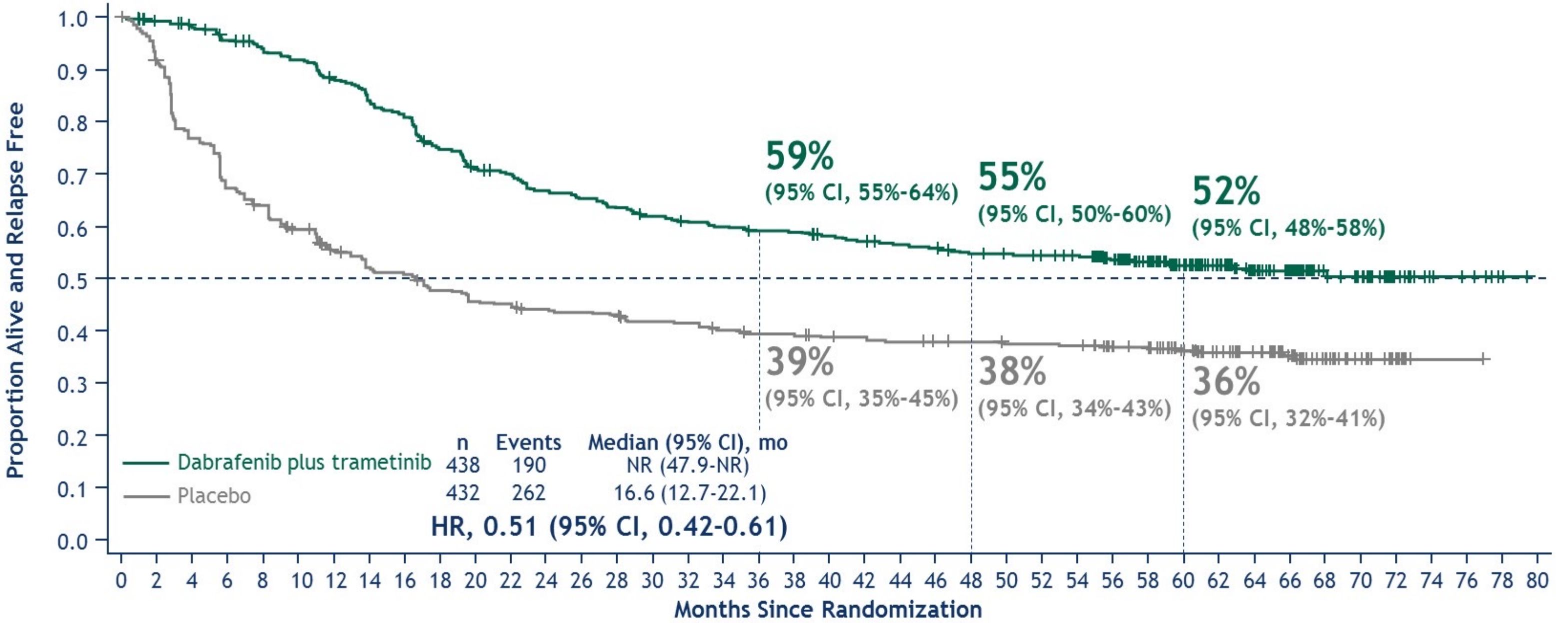
Adjuvant Therapy: Combi-AD: Study Design



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

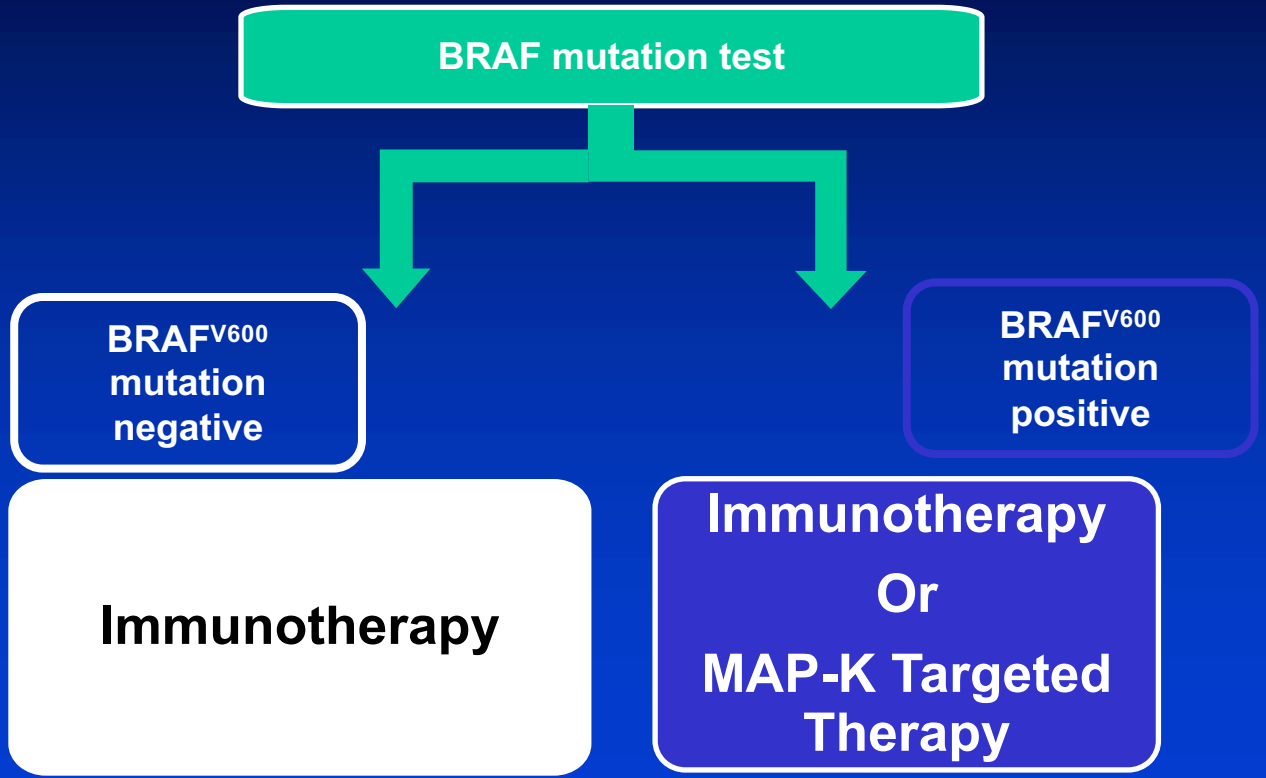
HR, hazard ratio; NR, not reached.

ASCO 2020

What is the Correct Sequence?

- Both immunotherapy and targeted therapy are good options
  - So we have a choice
- Choice applies only to BRAF-mutated patients (40% of US patients)
- Choice exists in both adjuvant therapy and metastatic disease

Melanoma Therapy Decision Point

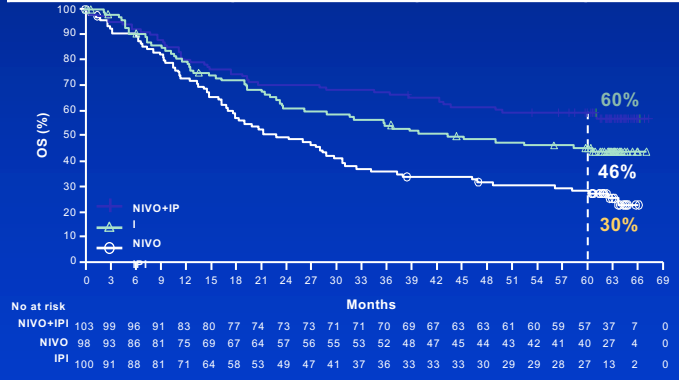


Immunotherapy Works Well in BRAF+ Disease

Improved OS and PFS with NIVO+IPI and NIVO versus IPI regardless of *BRAF* mutation status

BRAF-Mutant

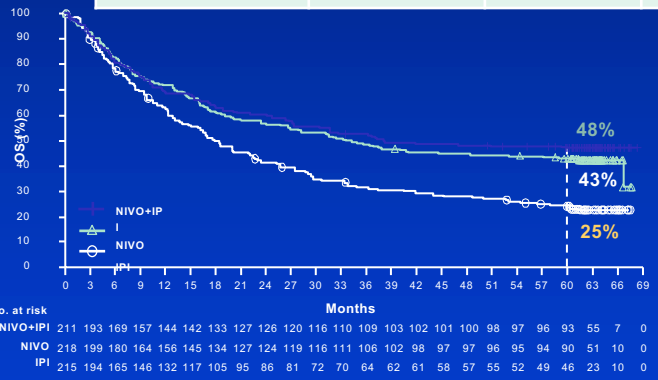
	NIVO+IPI (n=103)	NIVO (n=98)	IPI (n=100)
Median, mo (95% CI)	NR (50.7-NR)	45.5 (26.4-NR)	24.6 (17.9-31.0)
HR (95% CI) vs IPI	0.44 (0.30-0.64)	0.63 (0.44-0.90)	–
HR (95% CI) vs NIVO[a]	0.70 (0.46-1.05)	–	–



- 5-year PFS rates of 38% (NIVO+IPI), 22% (NIVO), and 11% (IPI)

BRAF Wild-Type

	NIVO+IPI (n=211)	NIVO (n=218)	IPI (n=215)
Median, mo (95% CI)	39.1 (27.5–NR)	34.4 (24.1-59.2)	18.5 (14.1-22.7)
HR (95% CI) vs IPI	0.57 (0.45-0.73)	0.64 (0.50-0.81)	–
HR (95% CI) vs NIVO[a]	0.89 (0.69-1.15)	–	–



- 5-year PFS rates of 35% (NIVO+IPI), 32% (NIVO), and 7% (IPI)

[a]Descriptive analysis.

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

- ECOG PS: 0 or 1
- Patients may have had prior systemic therapy in the adjuvant setting; however, this must not have included a CTLA-4 or PD-1 pathway blocking antibody or a BRAFi/MEKi

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

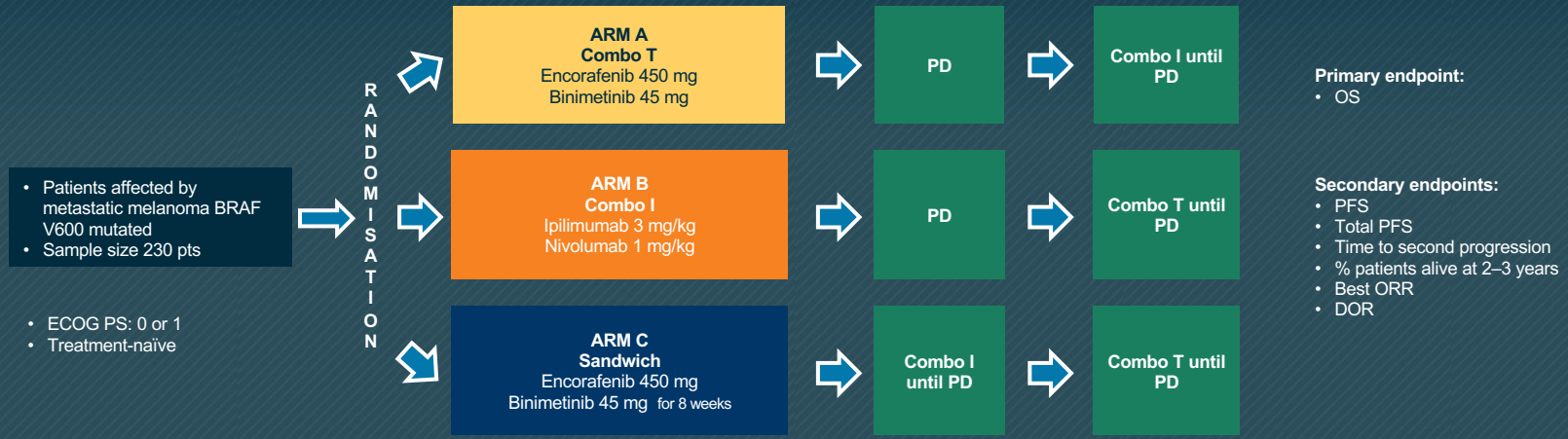
Secondary endpoints:
- PFS (RECIST version 1.1)
- Response rate (RECIST version 1.1)

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.

SECOMBIT: Phase 2 SEquential COMBo Immuno and Target Therapy Study in Treatment-naïve Patients With Metastatic BRAF V600 Mutant Melanoma

Prospective, randomised Phase 2 study to evaluate the best sequential approach with combo immunotherapy (ipilimumab + nivolumab) and combo target therapy (encorafenib + binimetinib) in patients with metastatic BRAF V600 mutant melanoma

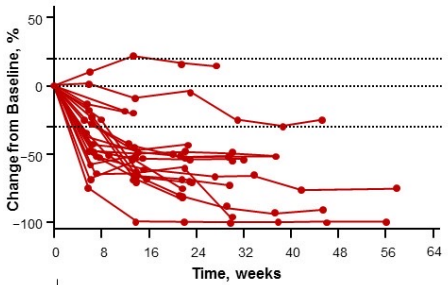


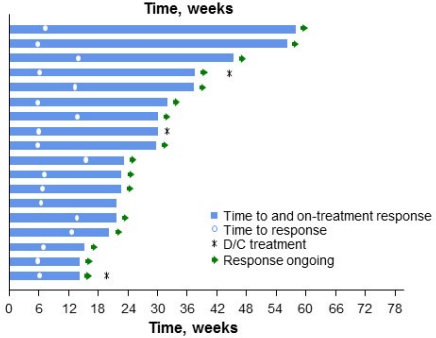
DOR, duration of response; ECOG-PS, Eastern Cooperative Oncology Group performance status; LGX = encorafenib (BRAFi); MEK162 = binimetinib (MEKi); ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PD, progressive disease.
Clinicaltrials.gov: NCT02631447.

Will sequence become irrelevant? Combining Targeted & Immunotherapy

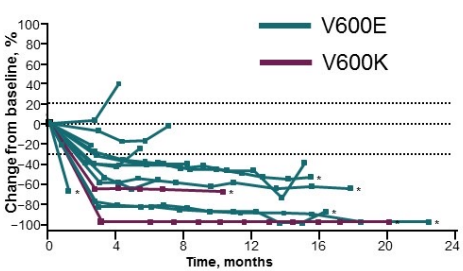
Clinical Trials Combining BRAFi + MEKi + anti–PD-1/L1

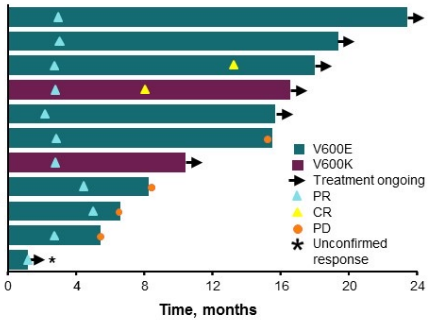
Dabrafenib + trametinib + durvalumab[1]



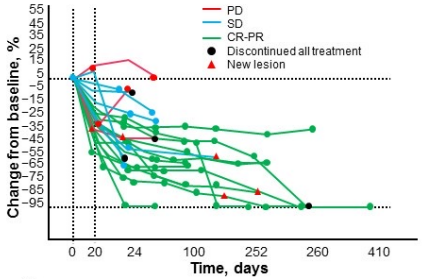


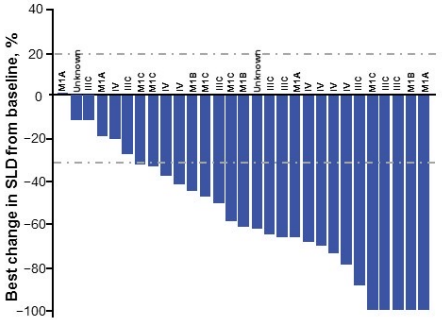
Dabrafenib + trametinib + pembrolizumab[2,3]



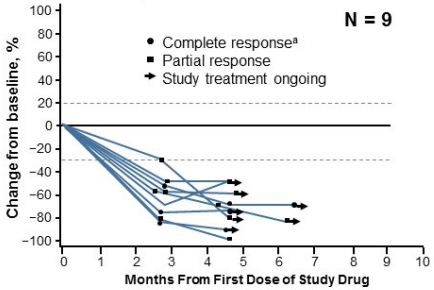


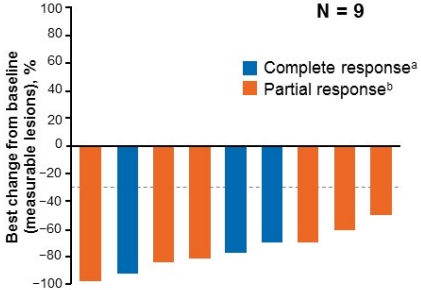
Vemurafenib + cobimetinib + atezolizumab[4]





Dabrafenib + trametinib + spartalizumab[5]





BID, twice daily; CR, complete response; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease. [a] Patients with CR and < 100% change in sum of diameters (SOD) have (a) 100% change for non-nodal target lesions and all nodal target lesions are < 10 mm and (b) CR for nontarget lesions. [b] Patients with PR and 100% change in SOD have (a) 100% change for all target lesions and (b) non-CR/non-PD response for nontarget lesions.

1. Ribas A, et al. *J Clin Oncol*. 2015; 33(suppl) [abstract 3003]; 2. Ribas A, et al. *J Clin Oncol*. 2016; 34(suppl) [abstract 3014]; 3. Ribas A, et al. *Ann Oncol*. 2017; 28(suppl 5) [abstract 1216O]; 4. Hwu P, et al. *Ann Oncol*. 2016; 27(suppl 6) [abstract 1109PD]; 5. Dummer, R, et al. *J Clin Oncol*. 2018;36(suppl 5S) [abstract 189].

PRESENTED BY R DUMMER AT AACR 2018

Courtesy of Dr Dummer

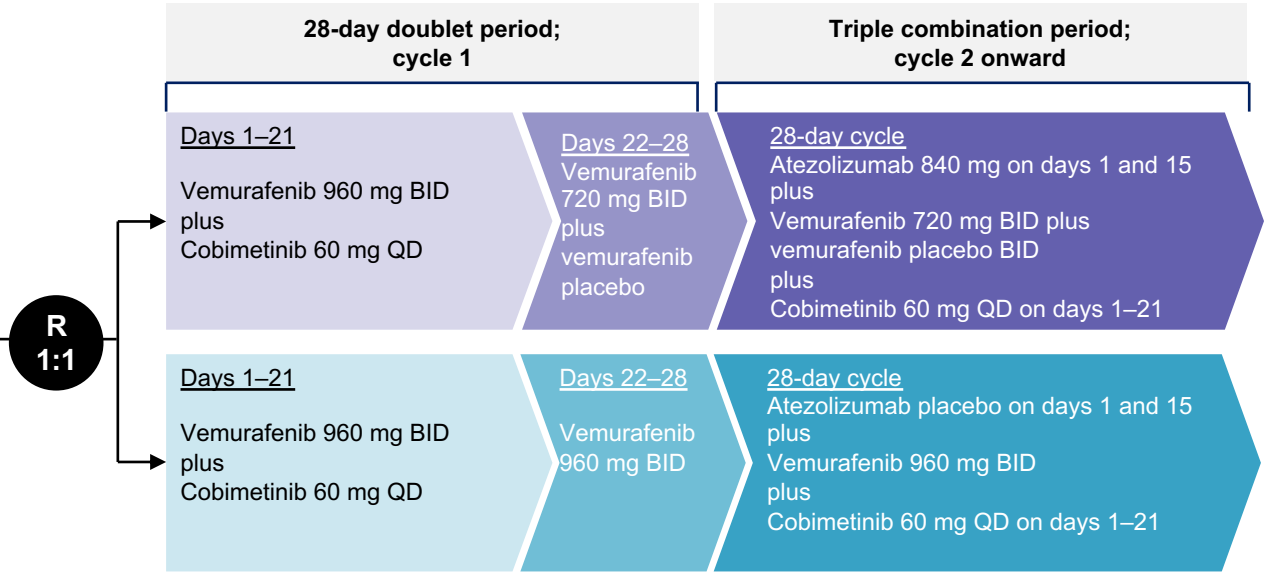
IMspire150 Study Design

- Previously untreated, advanced *BRAF*^{V600} mutation–positive melanoma
- ECOG PS 0 to 1
- Measurable disease by RECIST v1.1

Randomized 514 patients

Randomization stratified by:

- Geographic region and
- Centrally tested LDH level (≤ ULN versus > ULN)



Primary endpoint

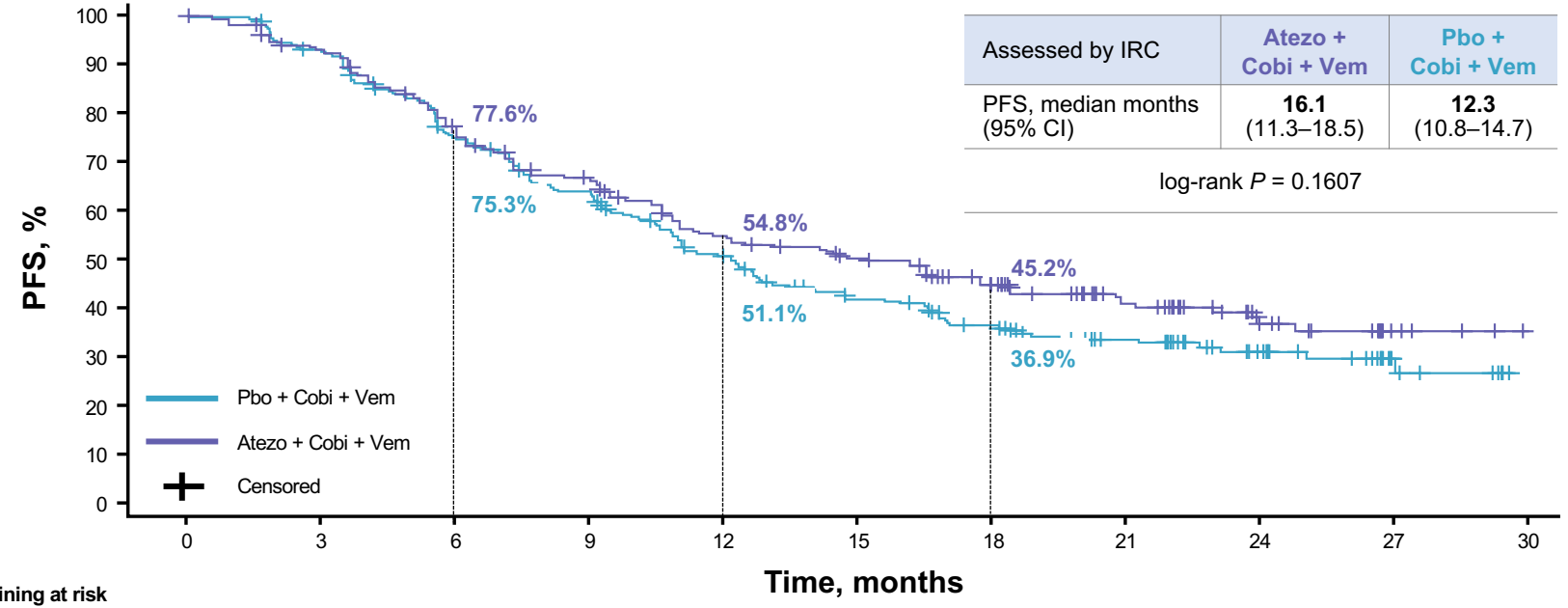
- Investigator-assessed PFS

Key secondary endpoints

- PFS assessed by an IRC
- Objective response (confirmed by observations at least 4 weeks apart)
- DOR
- OS

BID, twice daily; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; PS, performance status; QD, once daily; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal.

IMspire150: IRC-Assessed PFS



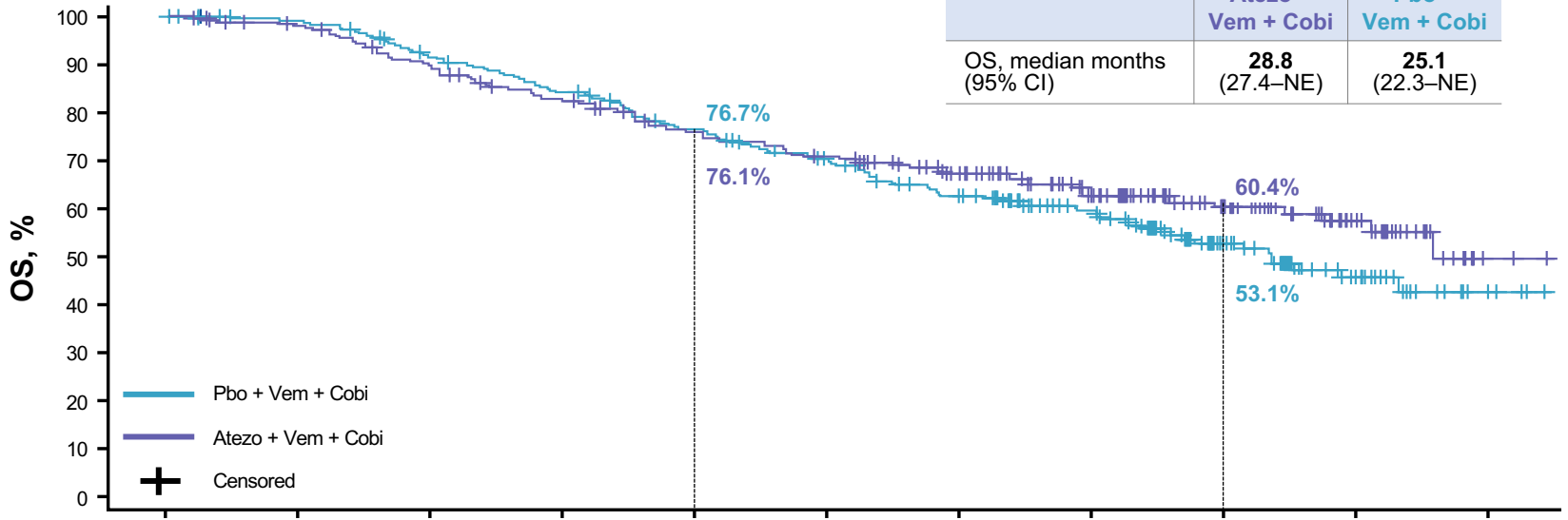
Assessed by IRC	Atezo + Cobi + Vem	Pbo + Cobi + Vem
PFS, median months (95% CI)	**16.1** (11.3–18.5)	**12.3** (10.8–14.7)
log-rank *P* = 0.1607		

Patients remaining at risk

Pbo + Cobi + Vem	258	228	180	150	113	88	71	52	28	10
Atezo + Cobi + Vem	256	226	184	152	120	107	85	58	27	6

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

Spartalizumab plus dabrafenib and trametinib (Sparta-DabTram) 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

Trial Analysis

- Histologically confirmed, unresectable or metastatic melanoma with BRAF V600 mutation
- N=532
- Previously untreated; no active BM; ECOG PS ≤2
- ≥2 cutaneous or subcutaneous or nodal lesions for tumor sample collection

R 1:1
Phase 3
Blinded

Spartalizumab 400 mg Q4W
+
Dabrafenib 150 mg PO BID (Days 1-28)
+
Trametinib 2 mg PO QD (Days 1-28)

Placebo
+
Dabrafenib 150 mg PO BID (Days 1-28)
+
Trametinib 2 mg PO QD (Days 1-28)

Primary Endpoint:
Part 3: Investigator-assessed PFS (RECIST 1.1)
Part 1: Incidence of DLTs
Part 2: Changes in PD-L1 levels & CD8+
Secondary Endpoints: OS, ORR, DOR, DCR, safety, PROs, PK

ASCO 2020 Efficacy Results in 36 Pts from Ph 1+2[1]

- ORR of 78% (28 pts) → CR rate of 44% (16 pts)
- mPFS of 23 months (95% CI: 12-NR)
- 24-month OS and PFS rates: 41% and 74%

Part 1 - Safety run-in: Dose determination for Phase 3 regimen of S + D and T
Part 2 - Biomarker cohort: To describe changes in the microenvironment and biomarkers
Part 3 - Randomized double blind: To compare the anti-tumor activity of S + D and T vs D and T

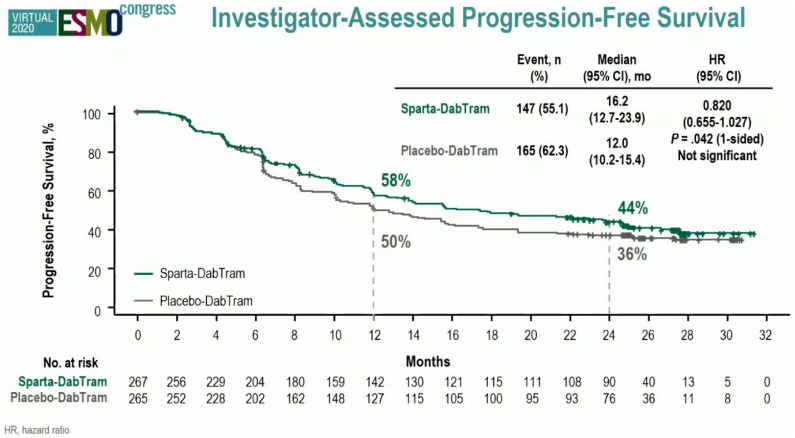
AUTHOR: Paul Nathan
SESSION: Proffered Paper
TYPE: Oral Session

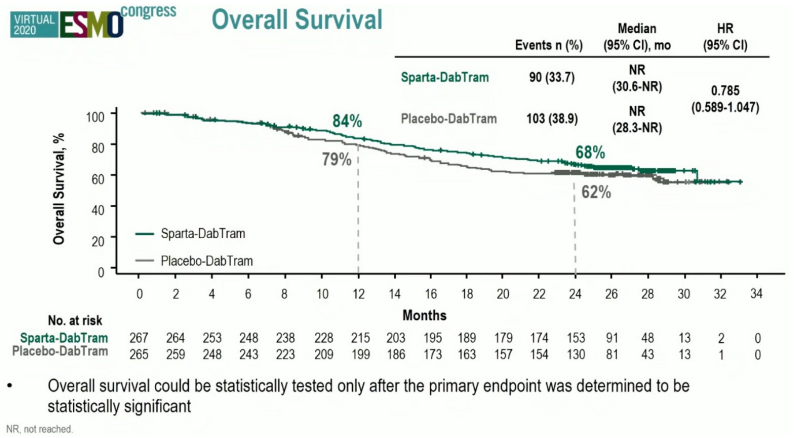
1. Long GV et al. American Society of Clinical Oncology Annual Meeting; May 29-31, 2020.

BID = twice daily; BM = brain metastases; CR = complete response; D = dabrafenib; DCR = disease control rate; DLT = dose limiting toxicity; DOR = duration of response; mPFS = median progression-free survival; NR = not reached; ORR= objective response rate; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; Ph = phase; PK = pharmacokinetics; PO = by mouth; PRO = patient-reported outcome; pts = patients; Q4W = every 4 weeks; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; S = spartalizumab; T = trametinib.

Clinical trial information: https://clinicaltrials.gov/ct2/show/NCT02967692

Spartalizumab plus dabrafenib and trametinib (Sparta-DabTram) 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

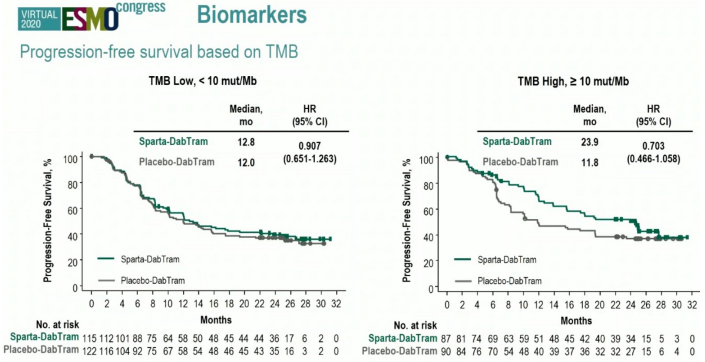




- Overall survival could be statistically tested only after the primary endpoint was determined to be statistically significant

	Sparta-DabTram n=267	PBO-DabTram n=265
ORR, % (95% CI)	68.5 (62.6-74.1)	64.2 (58.1-69.9)
CR, n (%)	53 (19.9)	47 (17.7)
DCR, %	84.3	86.4
mDOR, mo	NR	20.7

CR = complete response; Dab = dabrafenib; DCR = disease control rate; mDOR = median duration of response; mo = month(s); NR = not reached; ORR = objective response rate; PBO = placebo; Sparta = spartalizumab; TMB = tumor mutational burden; Tram = trametinib.



- Benefit with Sparta-DabTram vs PBO-DabTram was observed in patients with high TMB (≥10 Mut/Mb)

rmation: https://clinicaltrials.gov/ct2/show/NCT02967692

Summary & Conclusions

- Immunotherapy with checkpoint inhibitors is a standard of care for all suitable patients with melanoma
  - Single agent PD1 (adjuvant and metastatic)
  - Combination PD-1/CTLA-4 (metastatic only)
- For BRAF-MT patients the choice between targeted therapy and immunotherapy is still a clinical decision
- Combination of immunotherapy and targeted therapy is a newly approved option in the US for patients with metastatic melanoma
- The “best” sequence is not confirmed and is still a clinical decision based on clinician and patient preference