Immunotherapy & Targeted Therapy for Melanoma

Sanjiv S. Agarwala, MD

Immunotherapy for Melanoma

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

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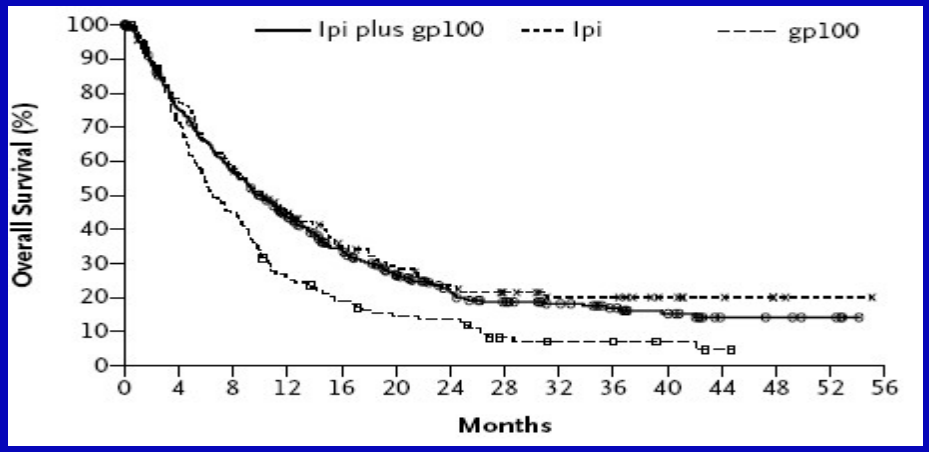
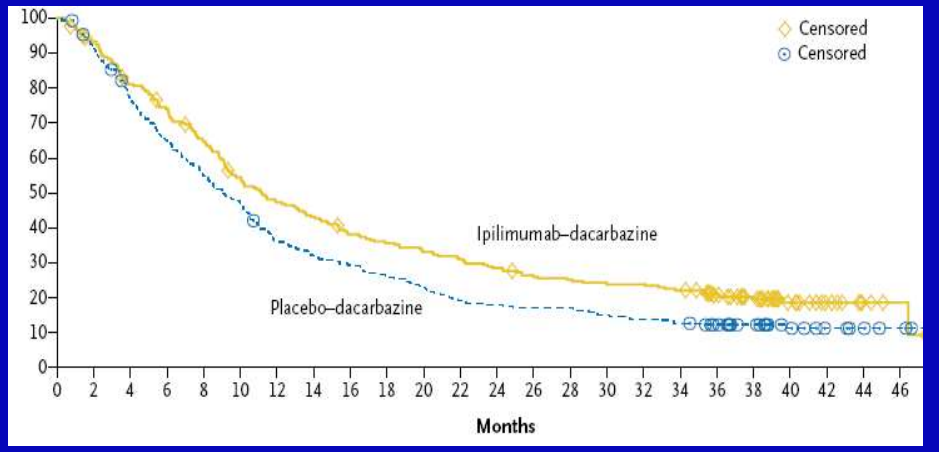
Clinical Results with Ipilimumab (2nd and 1st line)
Ipilimumab vs vaccine and Ipi + DTIC vs DTIC



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

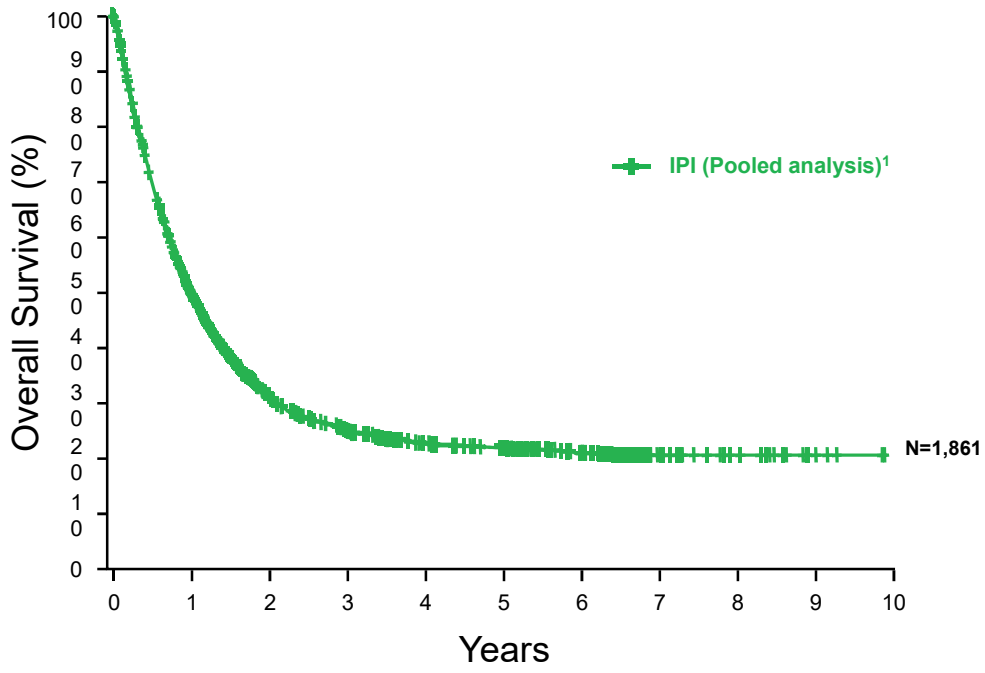
Hodi FS, et al. *N Engl J Med.* 2010;363:711-23.



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

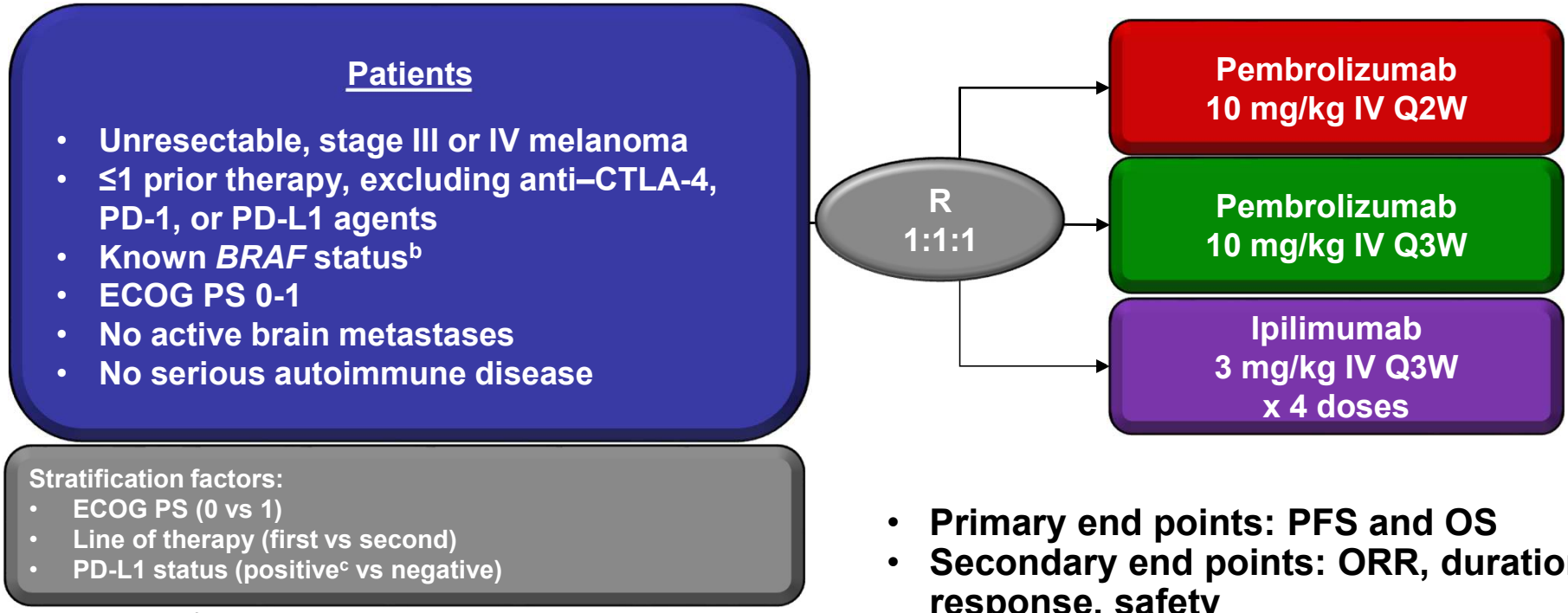
Robert C, et al. *N Engl J Med*. 2011;364:2517-26.

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



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

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

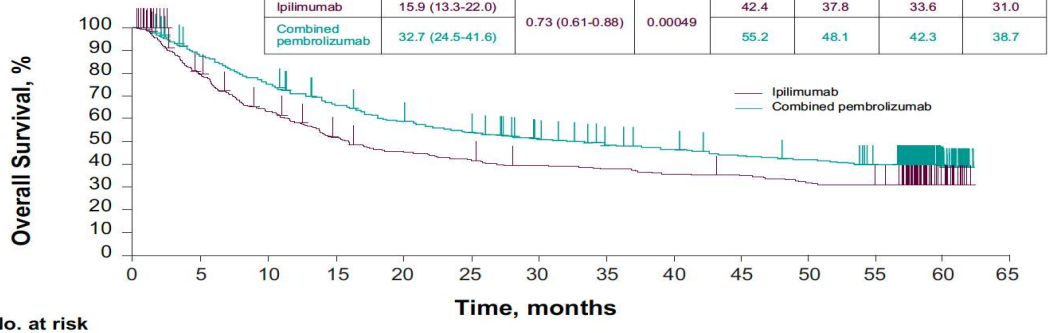
[b]Prior anti-BRAF targeted therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.

[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

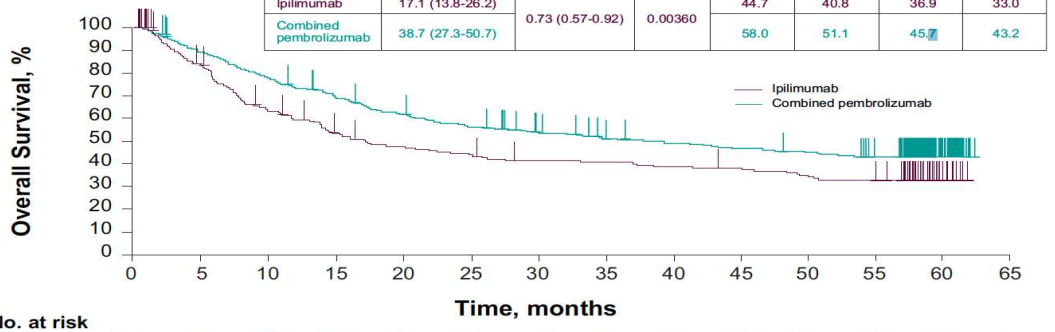
OS	Median[b] (95% CI), months	HR[c] (95% CI)[c]	*P* Value[d]	24-Month Rate,[b] %	36-Month Rate,[b] %	48-Month Rate,[b] %	60-Month Rate,[b] %
Ipilimumab	15.9 (13.3-22.0)	0.73 (0.61-0.88)	0.00049	42.4	37.8	33.6	31.0
Combined pembrolizumab	32.7 (24.5-41.6)			55.2	48.1	42.3	38.7



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

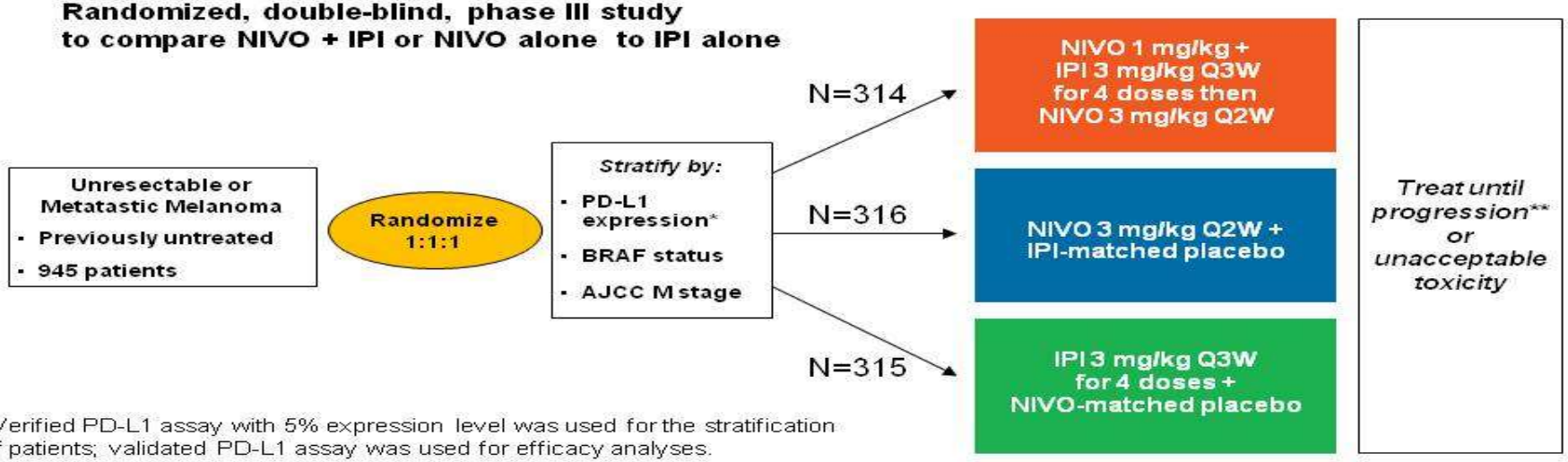


No. at risk														
Ipilimumab	181	140	105	86	76	70	64	63	60	58	52	49	8	0
Combined pembrolizumab	368	324	284	248	221	201	184	170	163	155	149	137	31	0

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



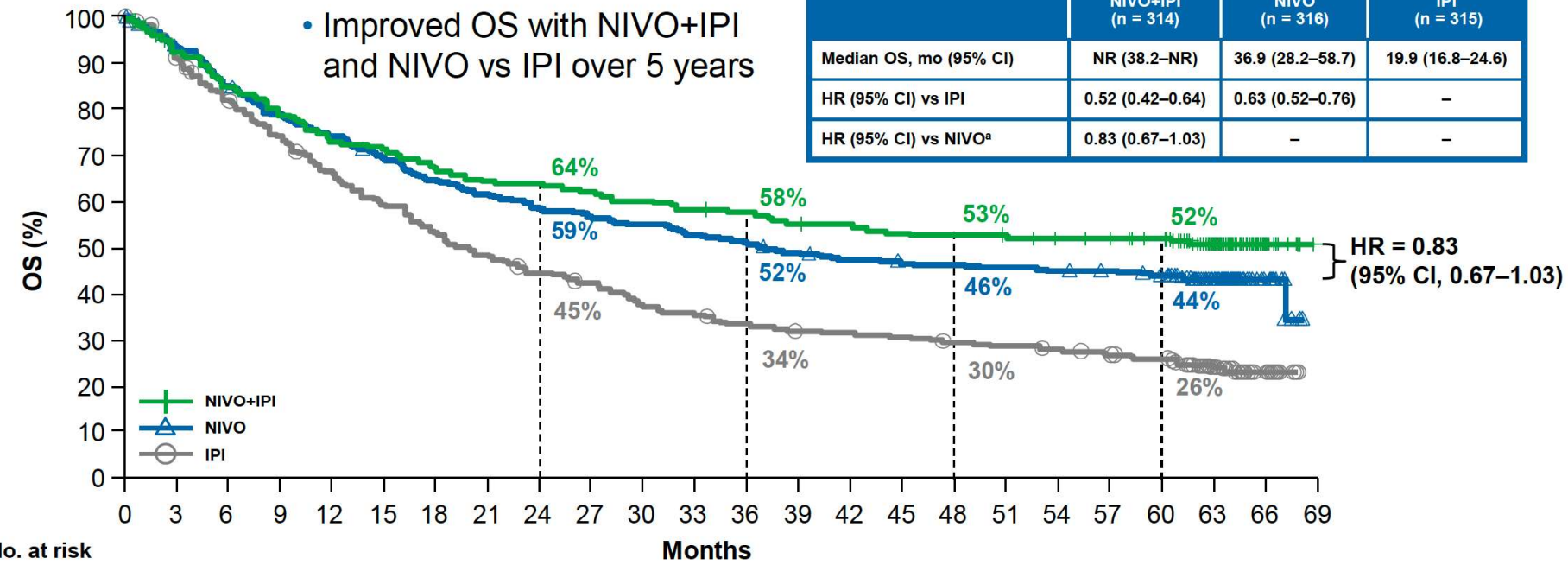
*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**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

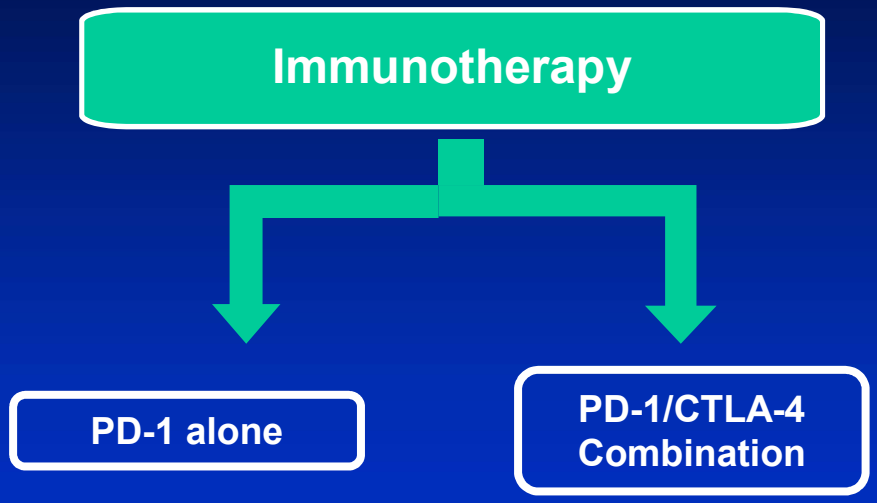
	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.67–1.03)	–	–



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?



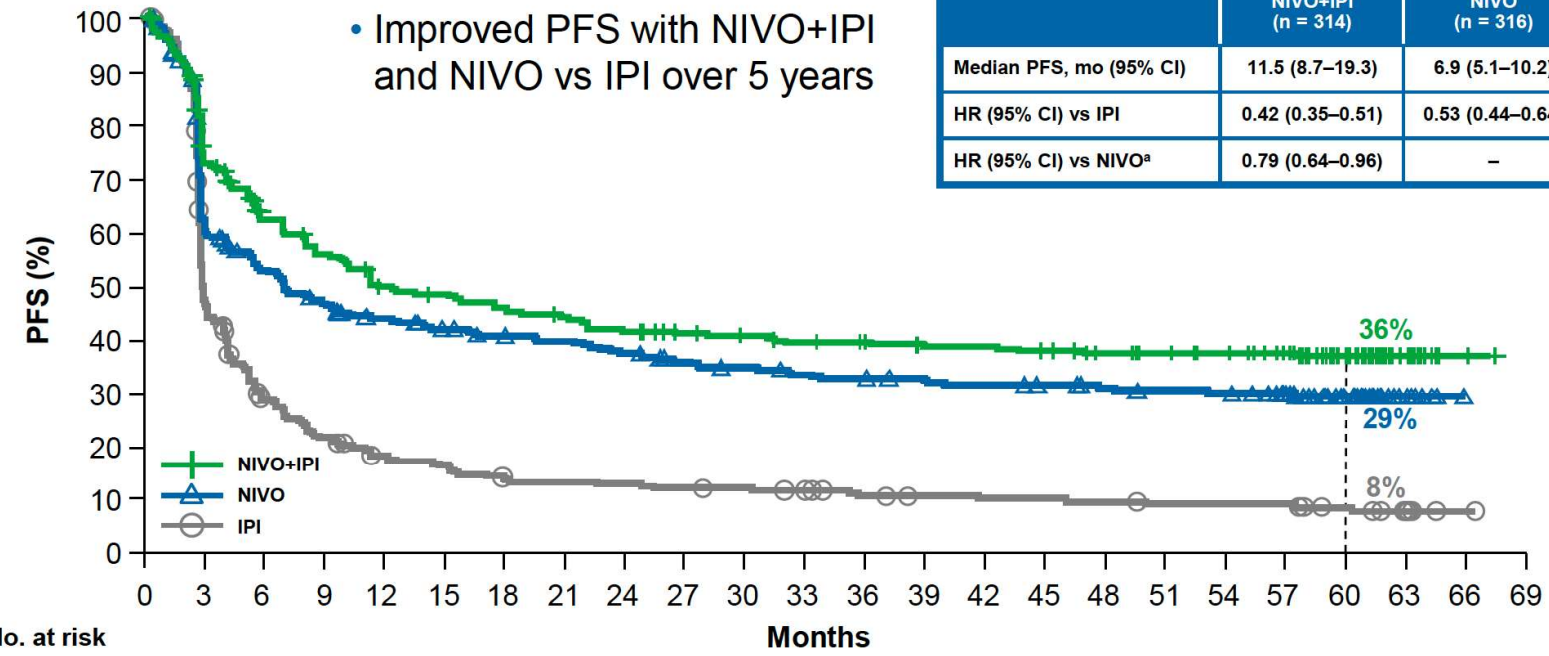
Decision Factors

- 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]

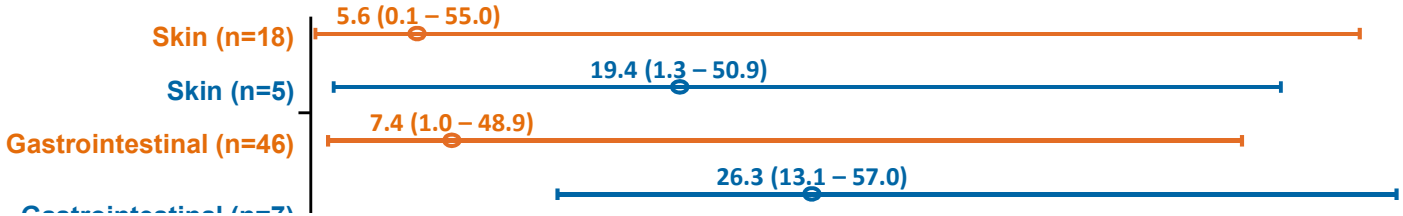
	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	58.5	86.3	20.8	86.2	27.7
Treatment-related AE leading to discontinuation	39.6	31.0	11.5	7.7	16.1	14.1
Treatment-related death,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

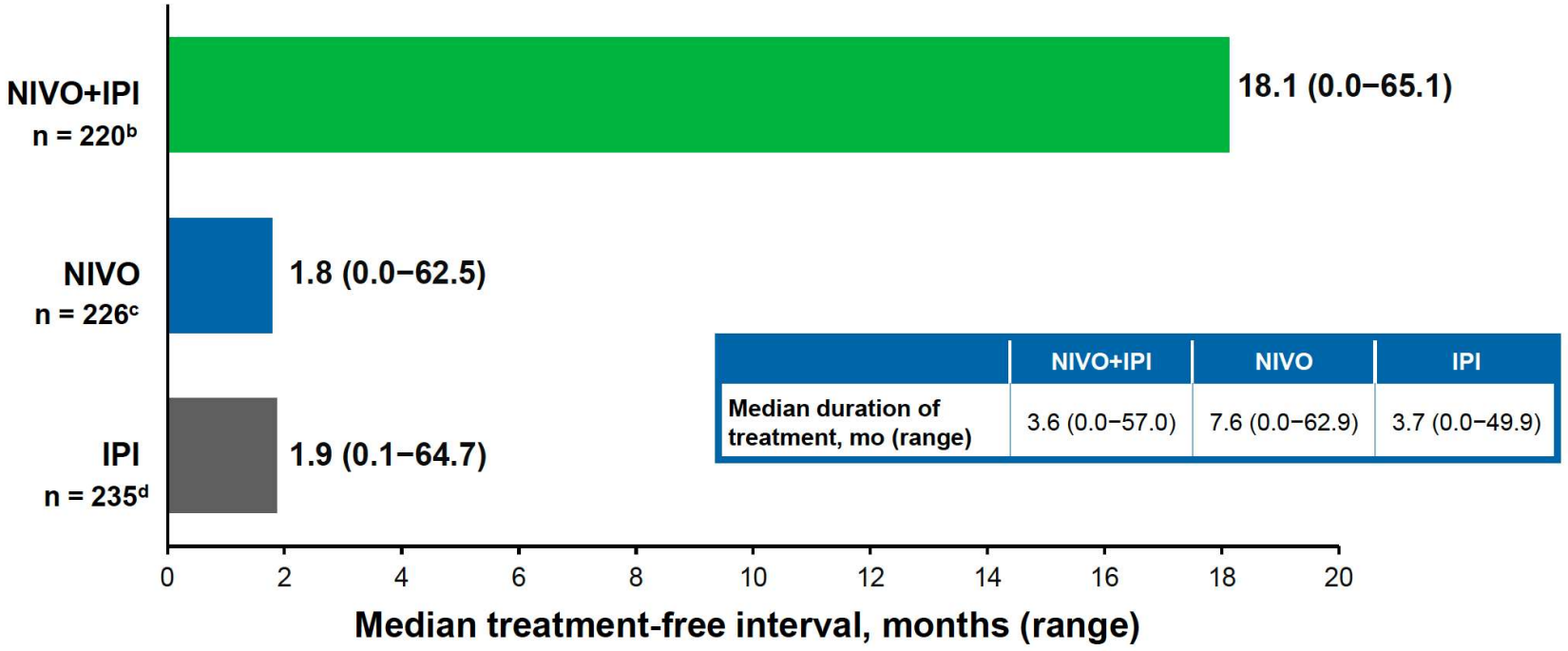
Longer Time to Resolution

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

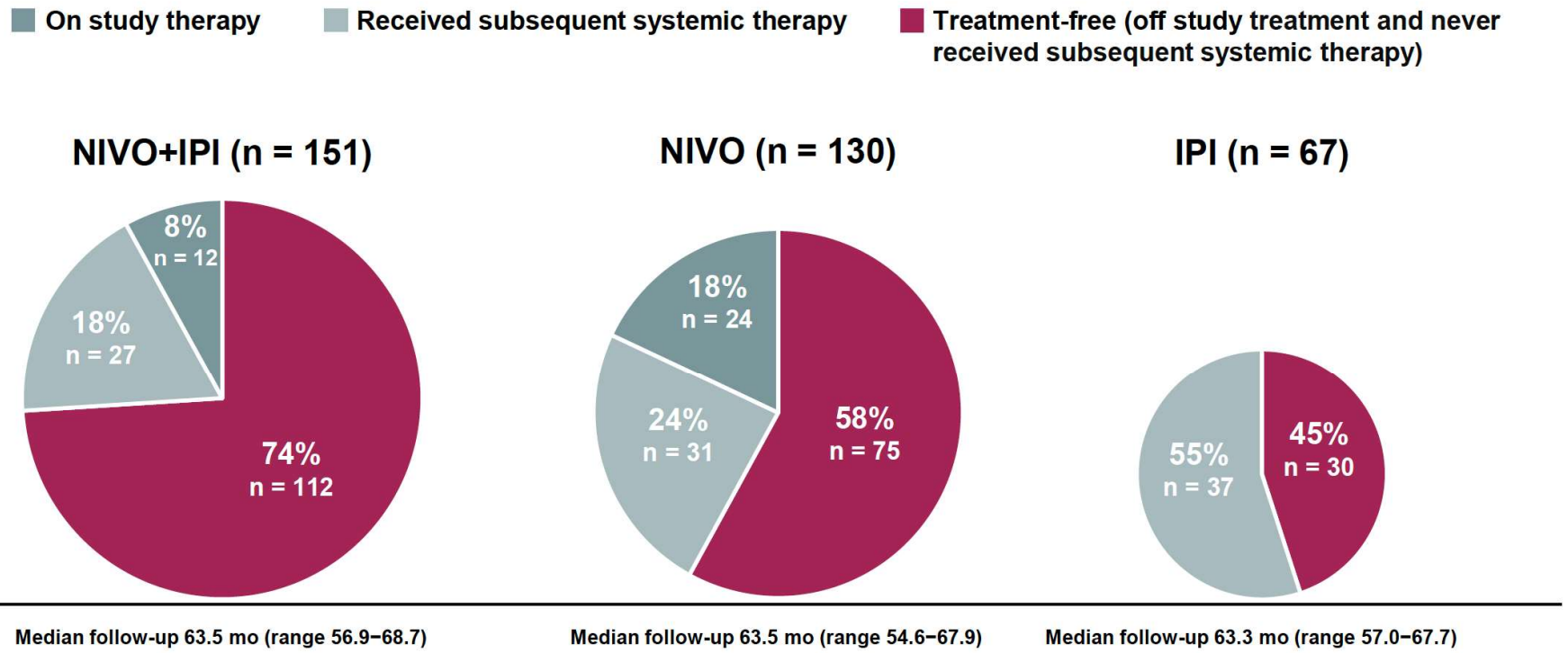


	NIVO+IPI	NIVO	IPI
Median duration of treatment, mo (range)	3.6 (0.0–57.0)	7.6 (0.0–62.9)	3.7 (0.0–49.9)

[a]Post-hoc analysis;

Higher Proportion of Patients Alive and Treatment-Free at 5 Years With NIVO+IPI[a]

Population analyzed: patients who were alive and followed on study



Median follow-up 63.5 mo (range 56.9–68.7)

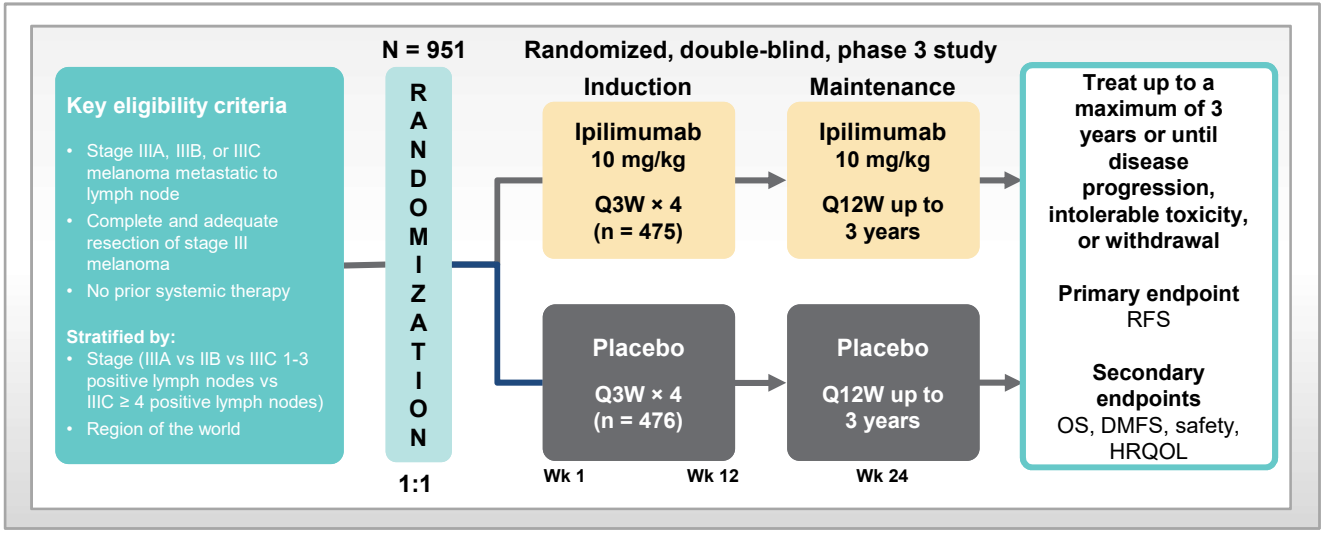
Median follow-up 63.5 mo (range 54.6–67.9)

Median follow-up 63.3 mo (range 57.0–67.7)

Immunotherapy for Melanoma

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

EORTC 18071 Ipilimumab vs Placebo Phase 3 Study Design[1,2]



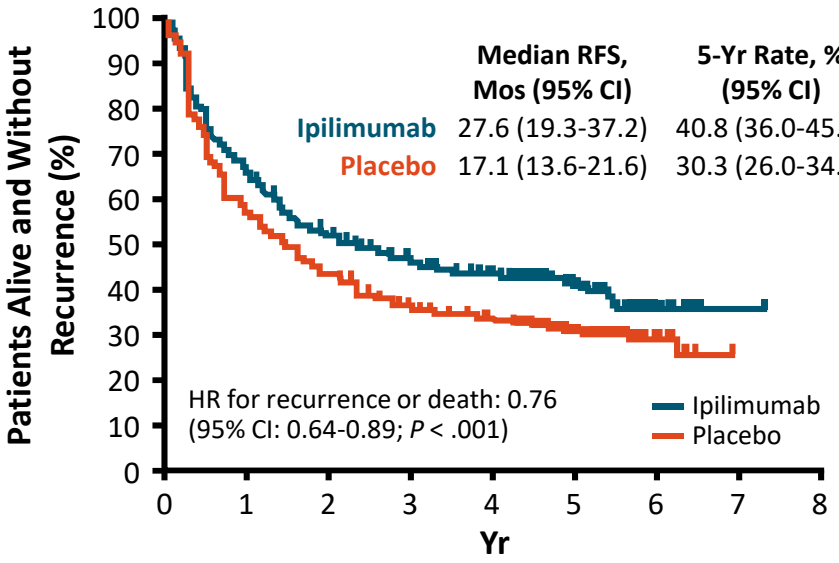
DMFS, distant metastasis-free survival; HRQOL, health-related quality of life; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; Q12W, every 12 weeks; RFS, relapse-free survival.

1. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2015;16(5):522-530.
2. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Ipilimumab (IPI) vs placebo (PBO) after complete resection of stage III melanoma: final overall survival results from the EORTC 18071 randomized, double-blind, phase 3 trial. Presented at: European Society for Medical Oncology 2016 Congress ; October 8, 2016; Copenhagen, Denmark.

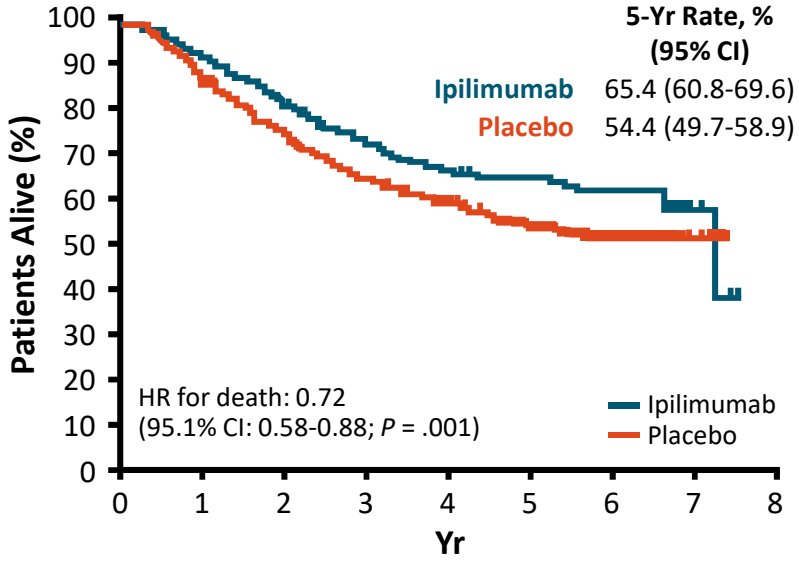
EORTC 18071: Phase III Trial of Ipilimumab 10 mg/kg vs Placebo in Stage III Melanoma

- Randomized, double-blind phase III trial of **ipilimumab** 10 mg/kg vs **placebo** as adjuvant therapy for stage III melanoma after surgical resection (N = 951)

RFS



OS



Eggermont. NEJM. 2016;375:1845.

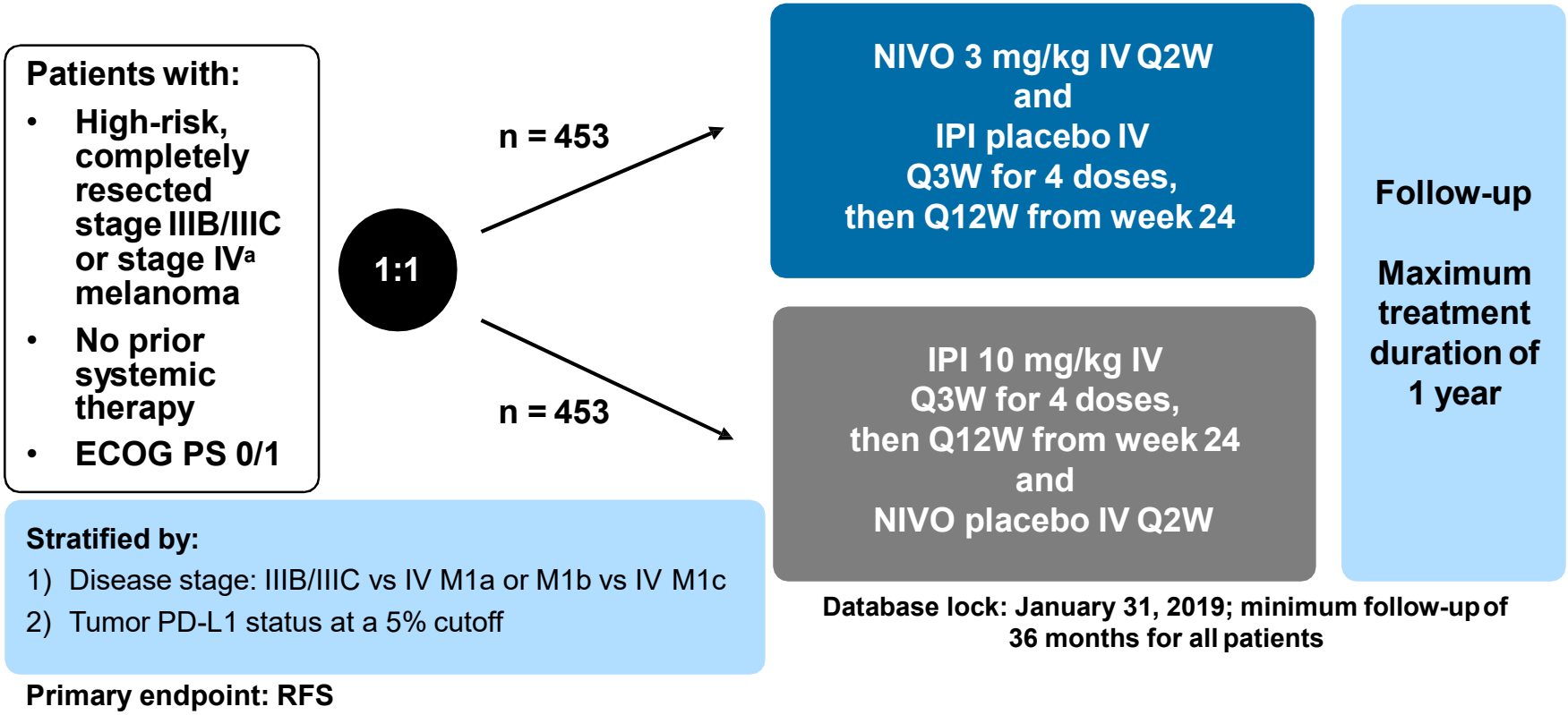
EORTC 18071: Safety

AEs, %	Ipilimumab (n = 471)	
	Any Grade	Grade 3/4
Any AE	98.7	54.1
Treatment-related AE	94.1	45.4
Treatment-related AE leading to d/c	48.0	32.9
Any immune-related AE	90.4	41.6

- Deaths due to treatment-related AEs
  - 5 patients (1.1%) in ipilimumab arm (3 colitis, 1 myocarditis, 1 multiorgan failure with Guillain-Barre syndrome)

Eggermont. NEJM. 2016;375:1845. Eggermont. ESMO 2016. Abstr LBA2_PR.

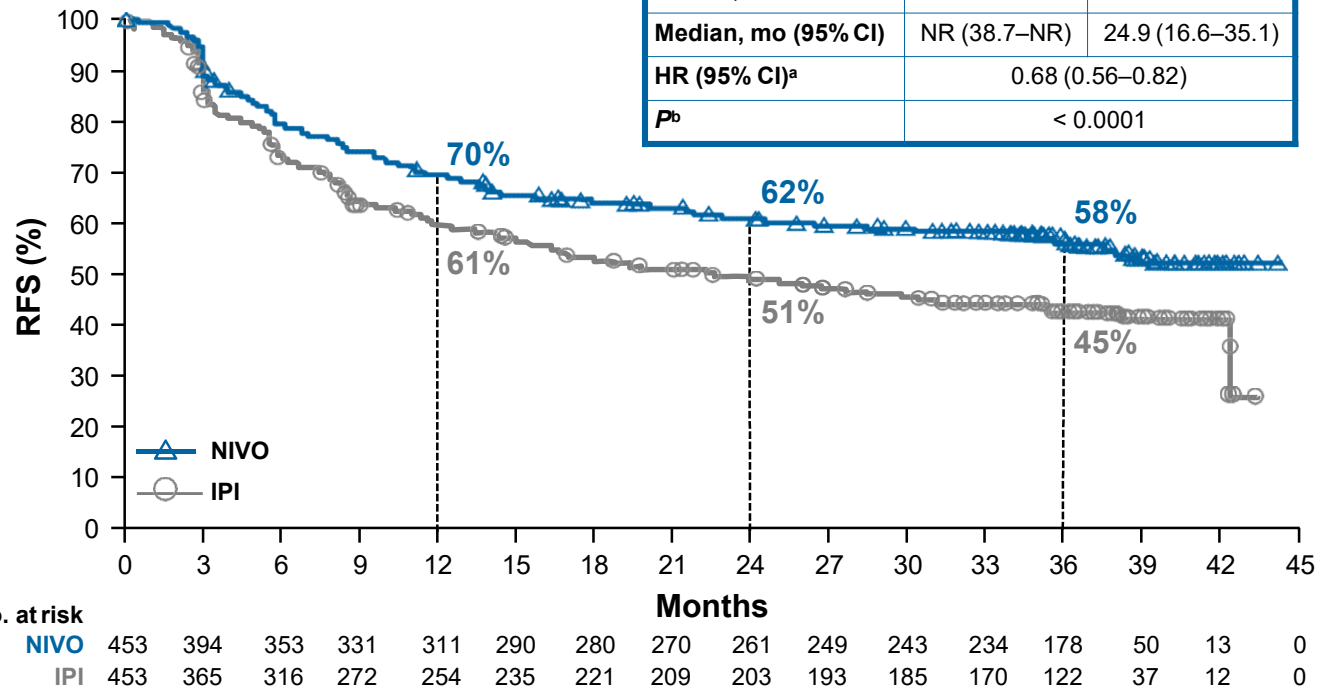
CheckMate 238: Study Design



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

Primary Endpoint: RFS in All Patients

	NIVO (n = 453)	IPI (n = 453)
Events, n	188	239
Median, mo (95% CI)	NR (38.7–NR)	24.9 (16.6–35.1)
HR (95% CI)[a]	0.68 (0.56–0.82)	
P[b]	< 0.0001	

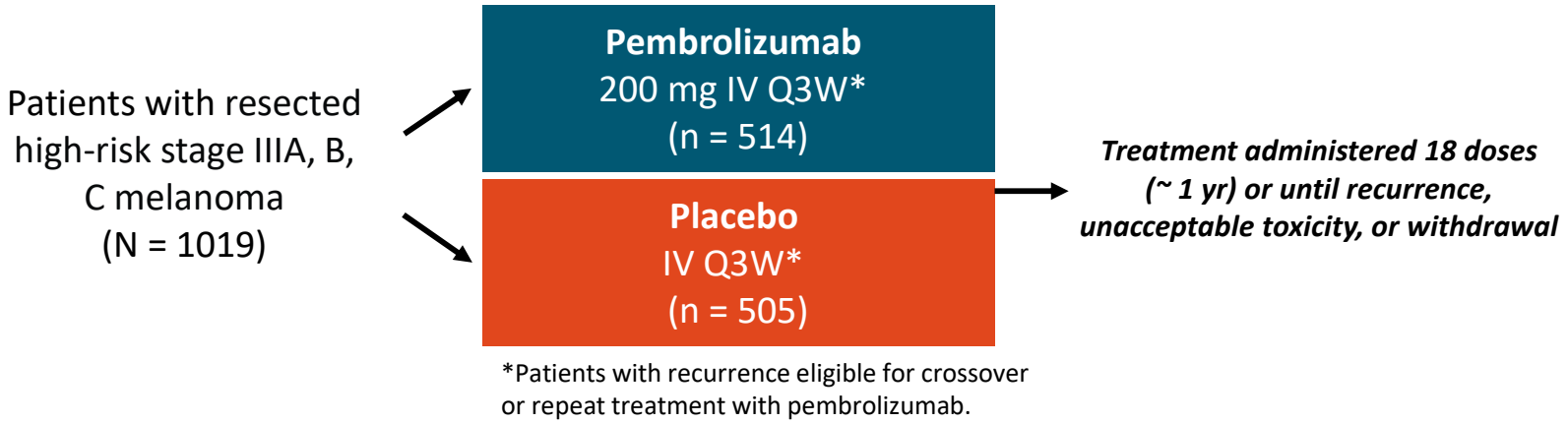


No. at risk															
NIVO	453	394	353	331	311	290	280	270	261	249	243	234	178	50	13	0
IPI	453	365	316	272	254	235	221	209	203	193	185	170	122	37	12	0

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

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

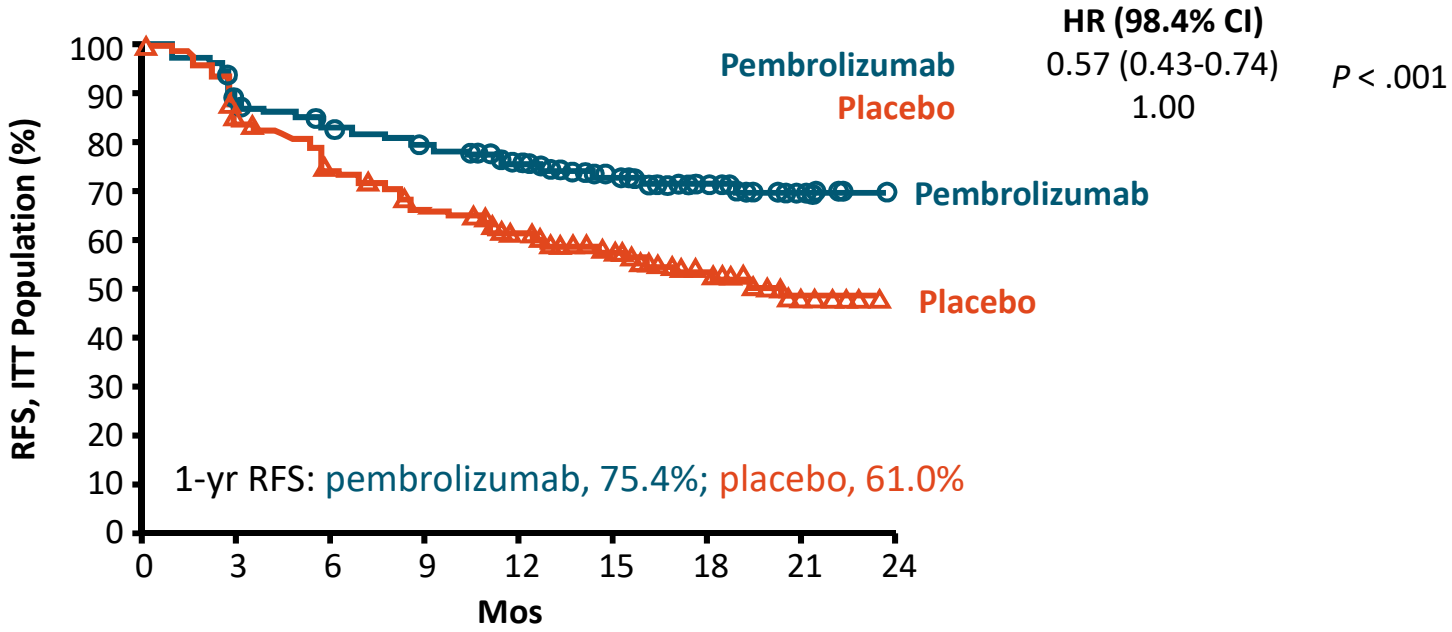
- Randomized, double-blind phase III study



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

Eggermont. NEJM. 2018;378:1789.

KEYNOTE-054: Relapse-Free Survival



- Median follow-up: 15.1 mos

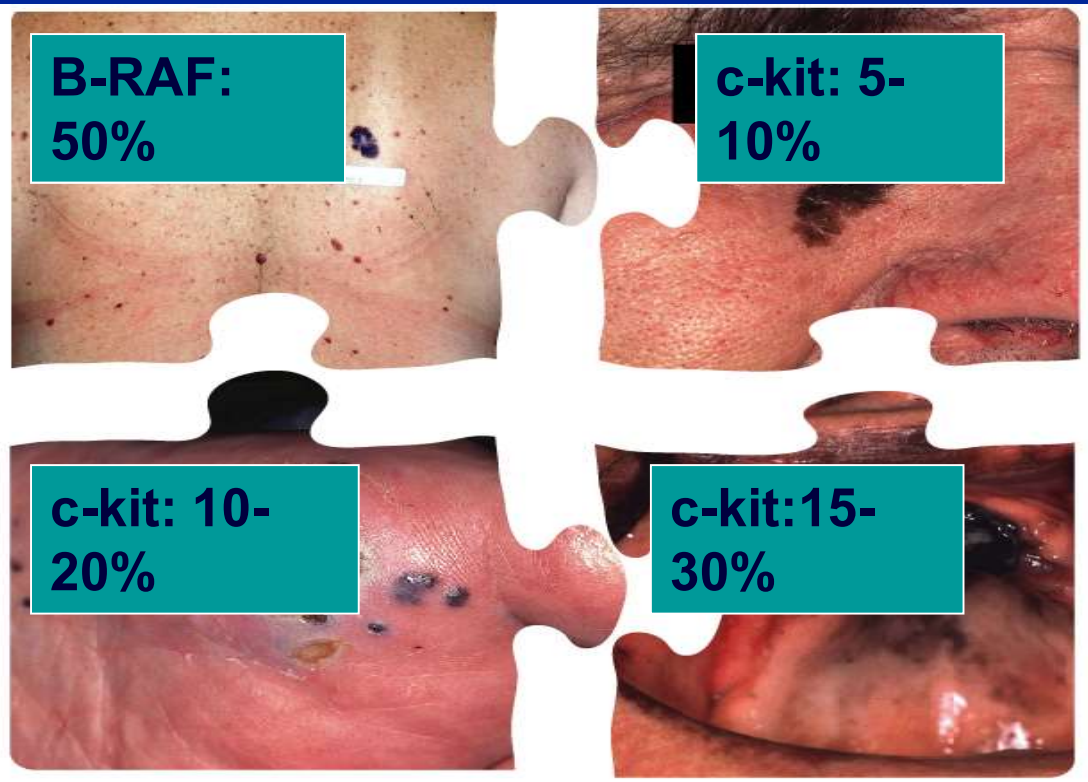
Eggermont. NEJM. 2018;378:1789.

Targeted Therapy

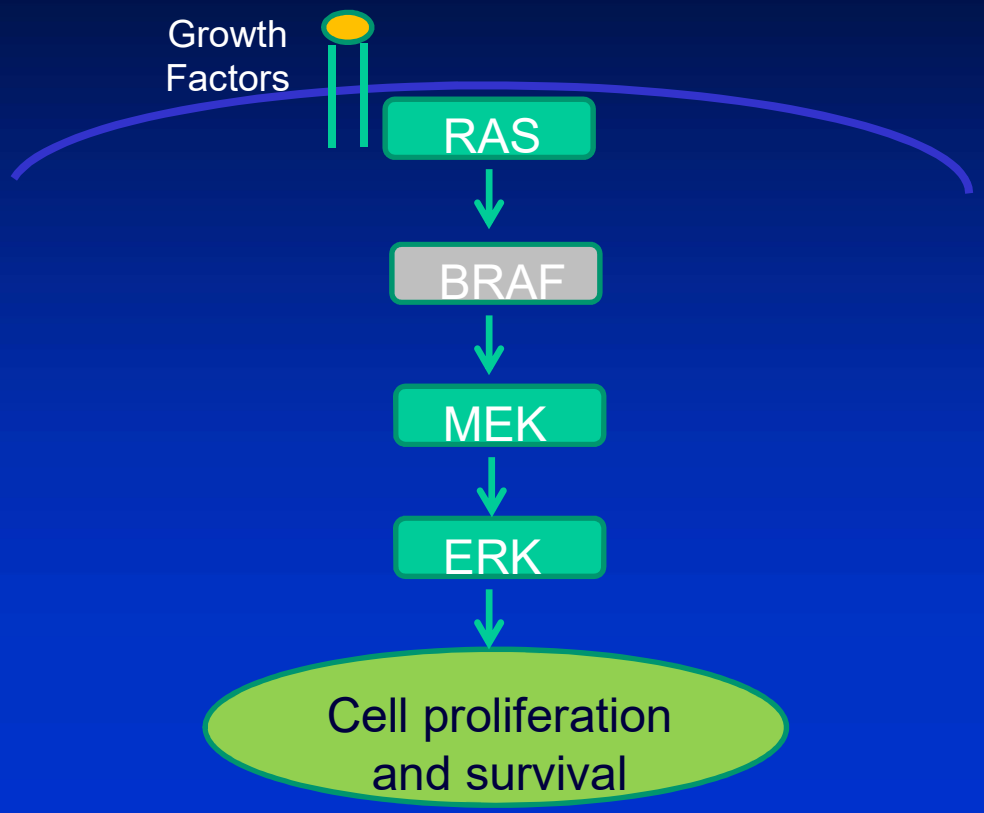
- Metastatic Disease
  - BRAF/MEK combination therapy
    - Dabrafenib/trametinib
    - Vemurafenib/cobimetinib
    - Encorafenib/binimetinib
- Adjuvant Therapy
  - BRAF/MEK combination
    - Dabrafenib/trametinib

Melanoma is not one disease

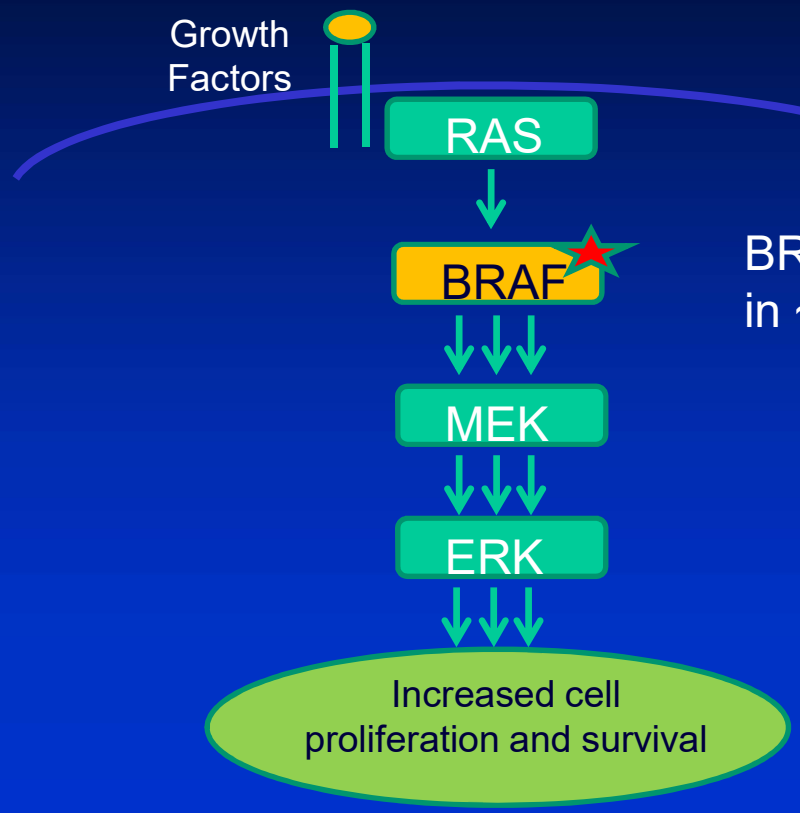
(Curtin et al, N Engl J Med 353: 2135-47, 2005)



MAPK Pathway

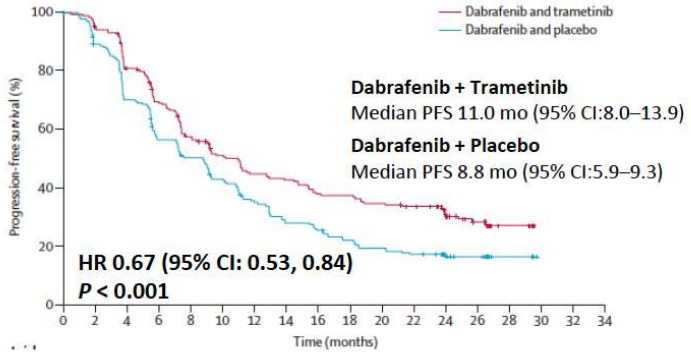


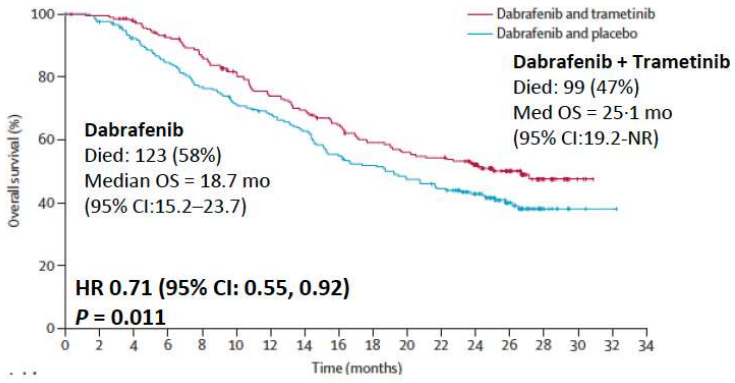
BRAF Mutation



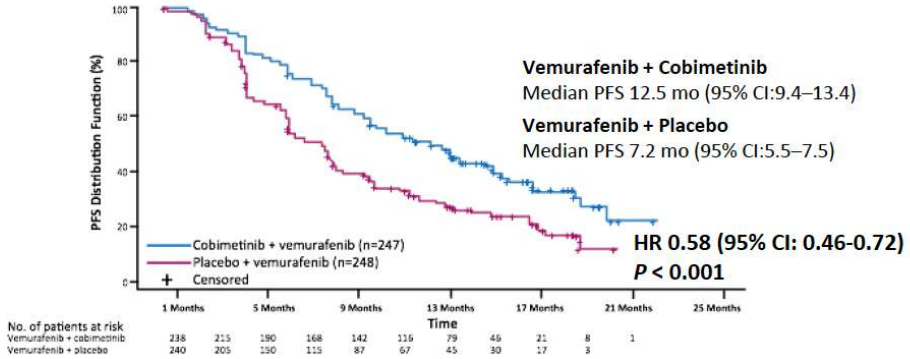
BRAF mutation is present in ~50% of melanomas

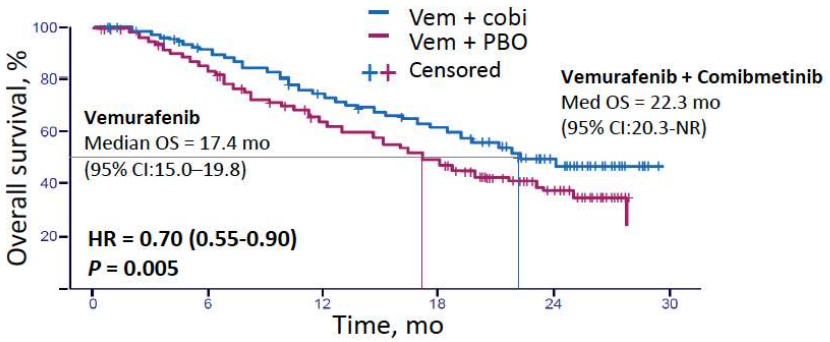
Combined BRAF/MEKi therapy is superior survival compared to single-agent BRAF inhibitors (BRAFi)





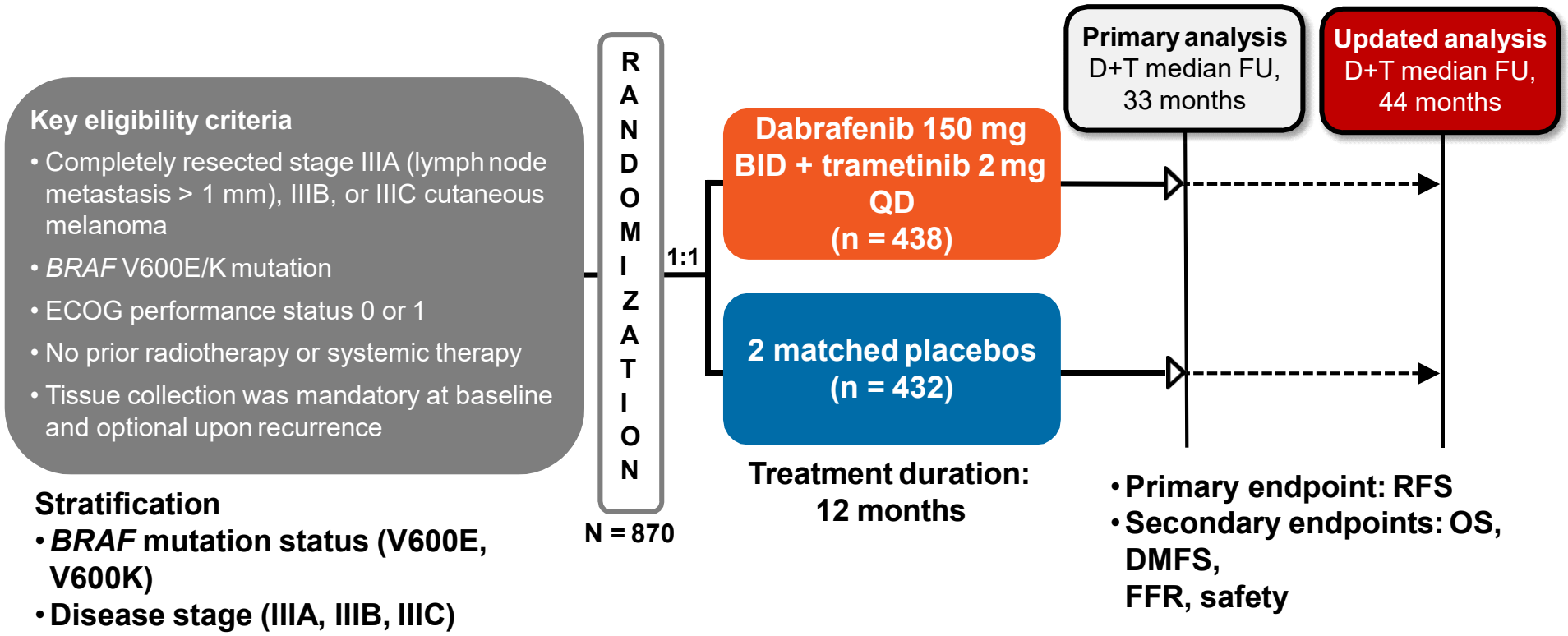
Long et al. NEJM 2014; Long et al. *Lancet* 2015.





Larkin et al. NEJM 2015

Adjuvant Therapy: Combi-AD: Study Design

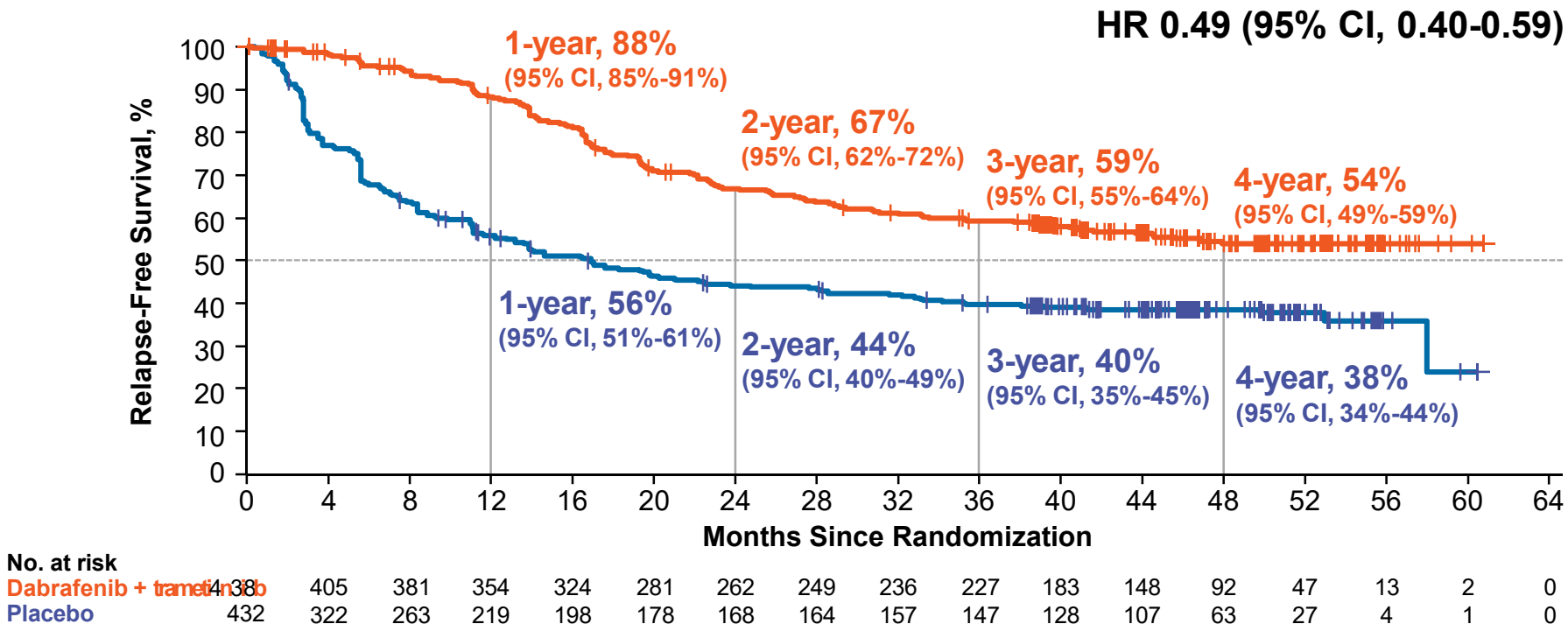


BID, twice daily; DMFS, distant metastasis–free survival; D+T, dabrafenib + trametinib; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; FU, follow-up; QD, once daily.

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

PRESENTED BY GV LONG AT ESMO 2018

COMBI-A/D: RELAPSE-FREE SURVIVAL



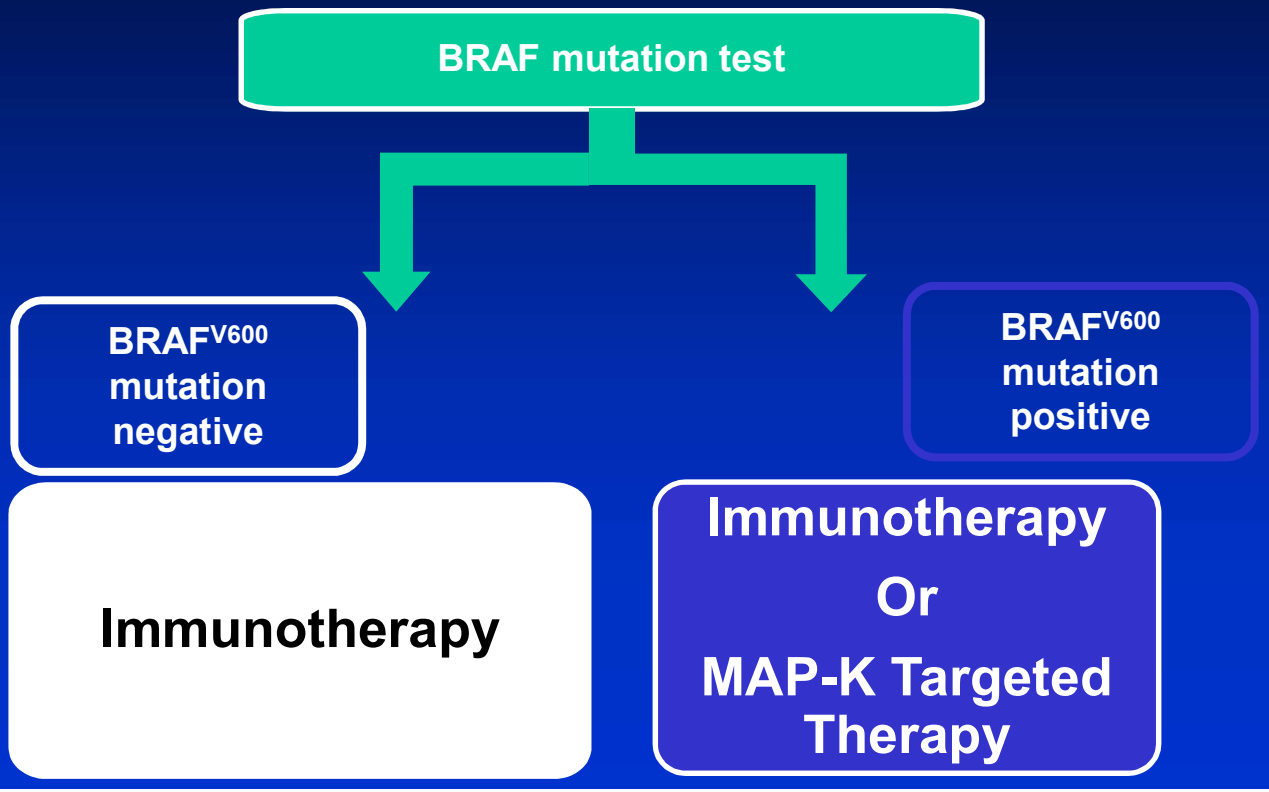
No. at risk																
Dabrafenib + trametinib	438	405	381	354	324	281	262	249	236	227	183	148	92	47	13	2	0
Placebo	432	322	263	219	198	178	168	164	157	147	128	107	63	27	4	1	0

PRESENTED BY GV LONG AT ESMO 2018

Choosing Between Immunotherapy & Targeted Therapy

- Applies only to BRAF-mutated patients (50% of US patients)
- Choice exists in both adjuvant therapy and metastatic disease

Melanoma Therapy Decision Point

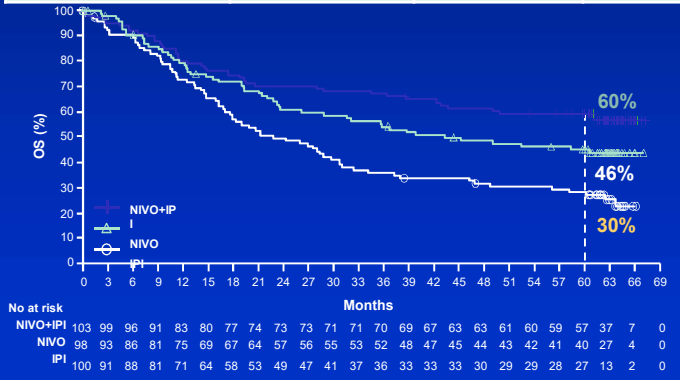


Immunotherapy OS in Patients With BRAF-Mutant and Wild-Type Tumors

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

BRAF-Mutant

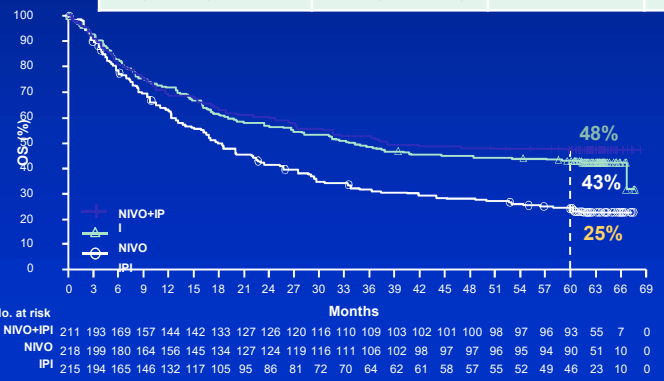
	NIVO+IPI (n=103)	NIVO (n=98)	IPI (n=100)
Median, mo (95% CI)	NR (50.7-NR)	45.5 (26.4-NR)	24.6 (17.9-31.0)
HR (95% CI) vs IPI	0.44 (0.30-0.64)	0.63 (0.44-0.90)	–
HR (95% CI) vs NIVO[a]	0.70 (0.46-1.05)	–	–



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

BRAF Wild-Type

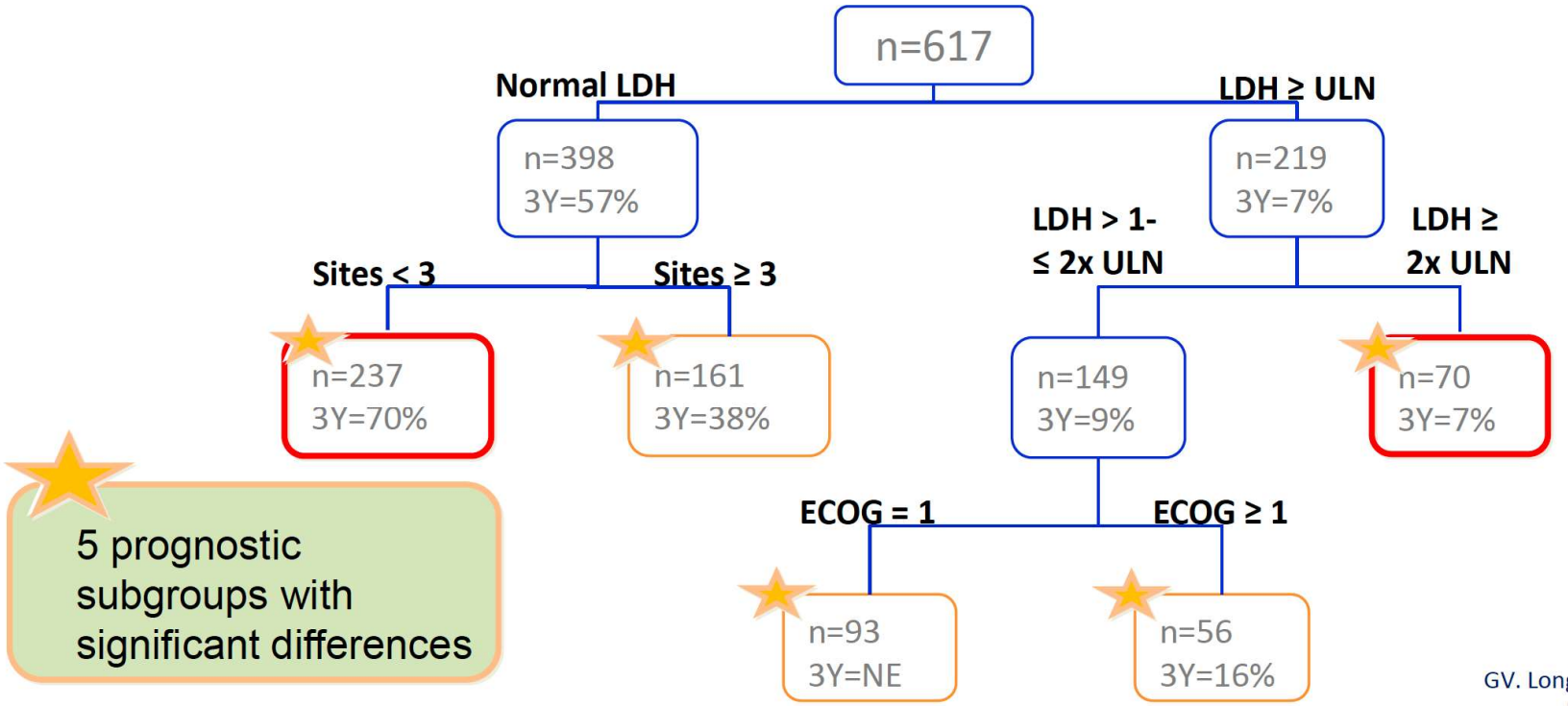
	NIVO+IPI (n=211)	NIVO (n=218)	IPI (n=215)
Median, mo (95% CI)	39.1 (27.5–NR)	34.4 (24.1-59.2)	18.5 (14.1-22.7)
HR (95% CI) vs IPI	0.57 (0.45-0.73)	0.64 (0.50-0.81)	–
HR (95% CI) vs NIVO[a]	0.89 (0.69-1.15)	–	–



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

[a]Descriptive analysis.

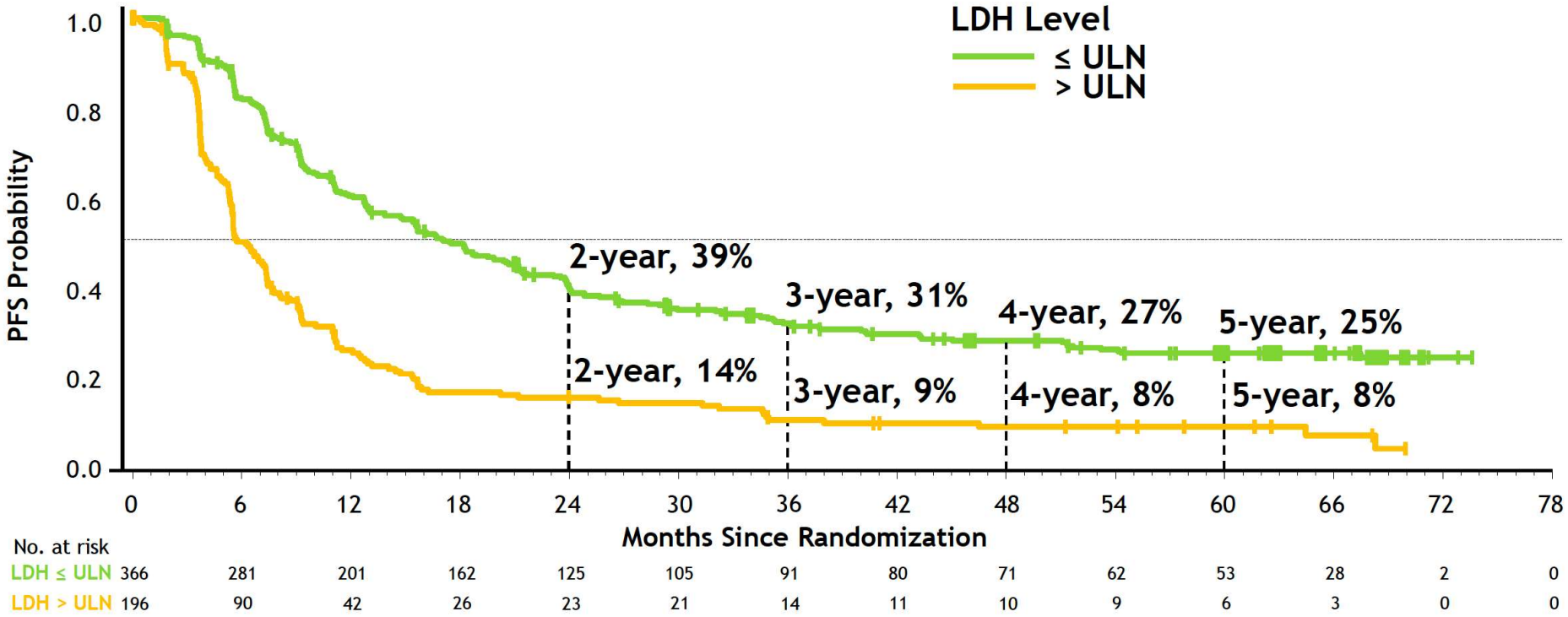
Baseline factors influencing outcome with targeted therapy



5 prognostic subgroups with significant differences

Adapted from:
GV. Long, SMR 2015, JCO 2016
K. Flaherty, ASCO 2016

Dabrafenib plus Trametinib: PFS by baseline LDH level



Robert et al. NEJM 2019

Efficacy of Nivolumab plus Ipilimumab patients with advanced melanoma and elevated LDH: a pooled analysis.

	Pooled population of treatment-näive patients with advanced melanoma (N = 1270)		
	NIVO+IPI	NIVO	IPI
Studies	CheckMate 067 CheckMate 069	CheckMate 066 CheckMate 067	CheckMate 067 CheckMate 069
Total number of patients	407	507	356

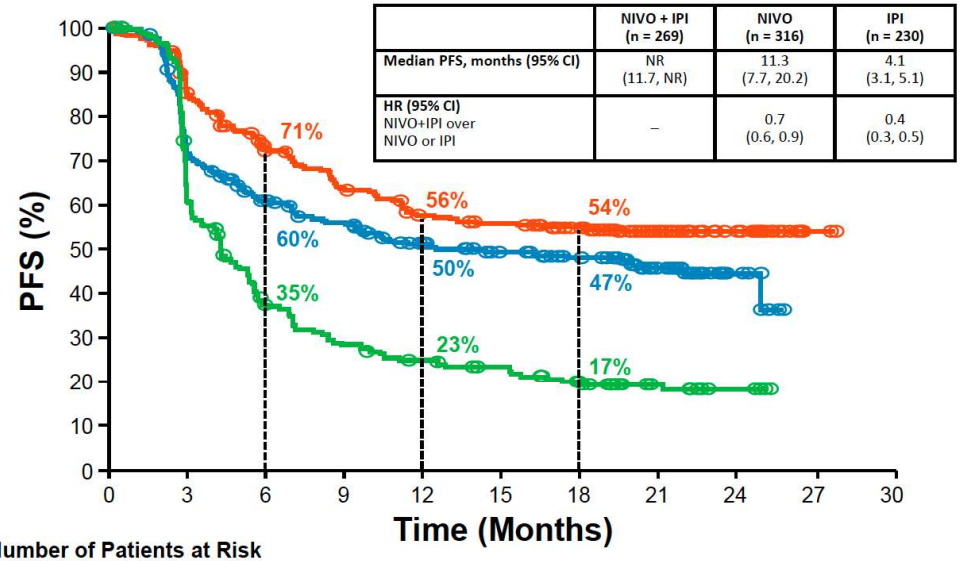
- Minimum follow-up of 18 months
- Patients were stratified according to baseline LDH values (LDH ≤ ULN, > ULN, or > 2x ULN)

Larkin et al. SMR 2016

Progression-free survival

LDH ≤ ULN

	NIVO + IPI (n = 269)	NIVO (n = 316)	IPI (n = 230)
Median PFS, months (95% CI)	NR (11.7, NR)	11.3 (7.7, 20.2)	4.1 (3.1, 5.1)
HR (95% CI) NIVO+IPI over NIVO or IPI	–	0.7 (0.6, 0.9)	0.4 (0.3, 0.5)

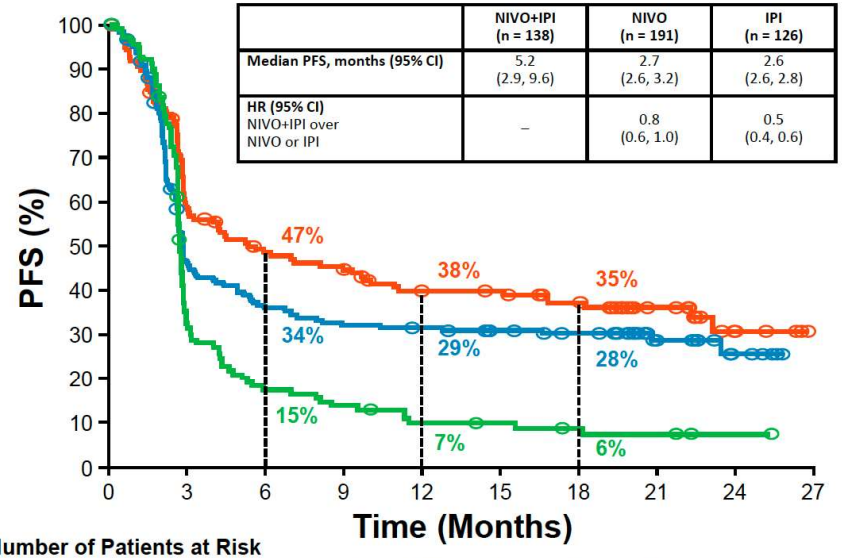


Number of Patients at Risk

NIVO+IPI	269	213	172	149	131	125	106	67	28	2	0
NIVO	316	213	173	155	133	118	105	51	10	0	0
IPI	230	126	71	53	43	37	24	15	5	0	0

LDH > ULN

	NIVO+IPI (n = 138)	NIVO (n = 191)	IPI (n = 126)
Median PFS, months (95% CI)	5.2 (2.9, 9.6)	2.7 (2.6, 3.2)	2.6 (2.6, 2.8)
HR (95% CI) NIVO+IPI over NIVO or IPI	–	0.8 (0.6, 1.0)	0.5 (0.4, 0.6)



Number of Patients at Risk

NIVO+IPI	138	74	59	53	44	43	36	18	4	0	
NIVO	191	74	58	51	49	42	37	15	5	0	
IPI	126	32	16	12	7	6	4	3	1	0	

NIVO+IPI NIVO IPI

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

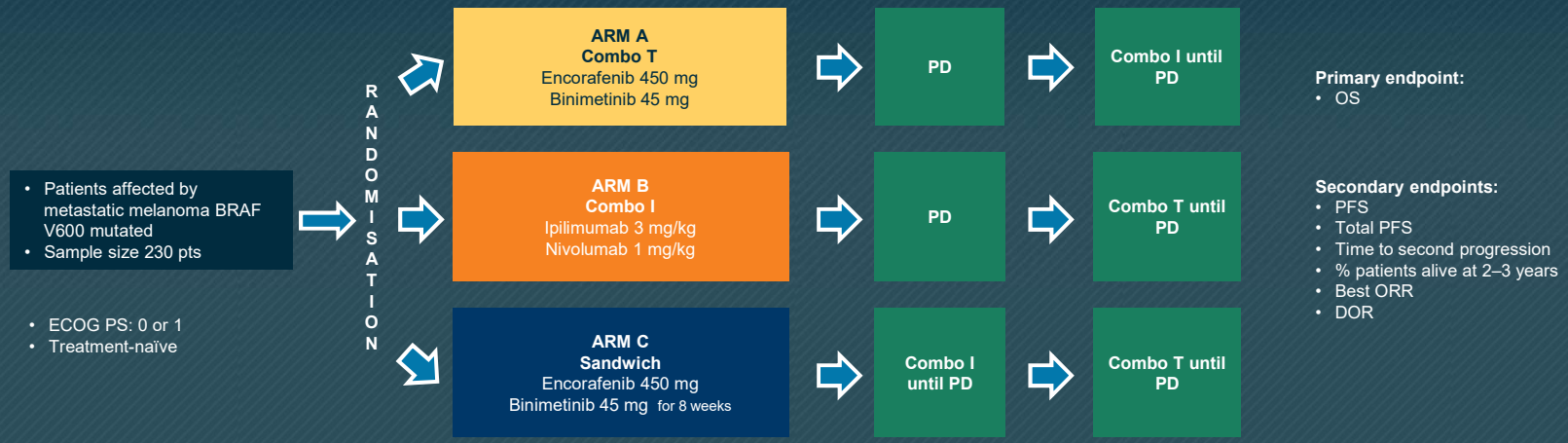
Secondary endpoints:
- PFS (RECIST version 1.1)
- Response rate (RECIST version 1.1)

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

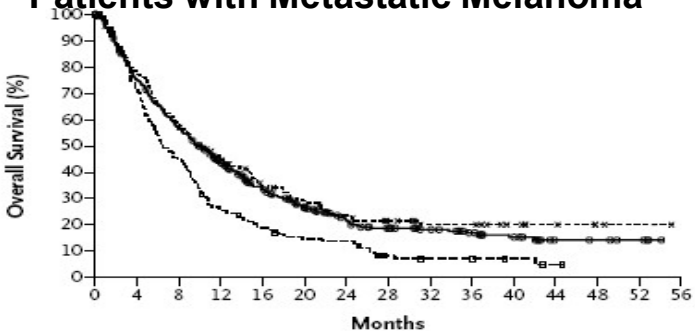


DOR, duration of response; ECOG-PS, Eastern Cooperative Oncology Group performance status; LGX = encorafenib (BRAFi); MEK162 = binimetinib (MEKi); ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PD, progressive disease.
Clinicaltrials.gov: NCT02631447.

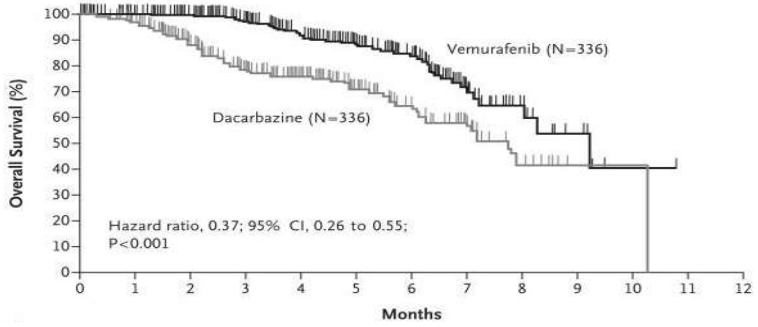
Will the Decision be “Moot” in the Future?

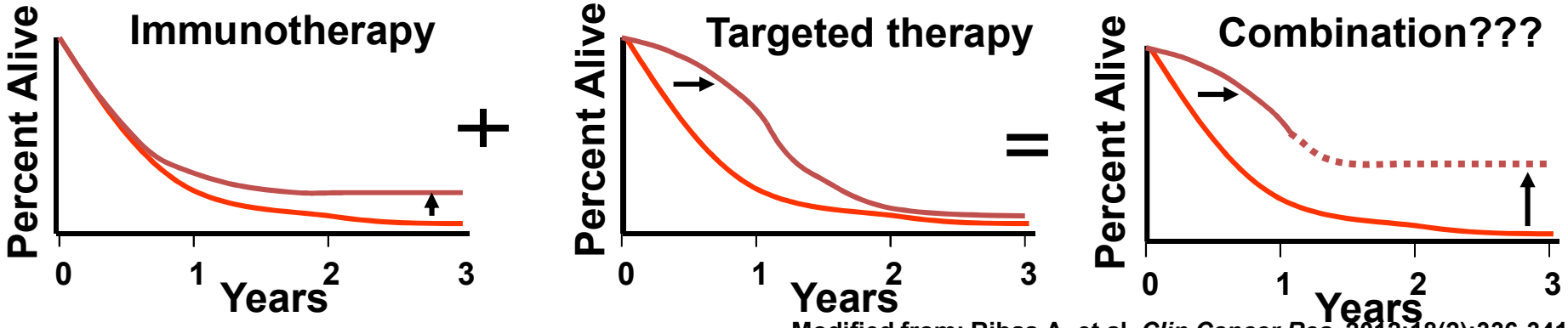
Combining Immunotherapy and Targeted Therapy for Melanoma?

Improved Survival With Ipilimumab in Patients with Metastatic Melanoma[1]



Improved Survival With Vemurafenib in Melanoma With BRAF V600E Mutation[2]



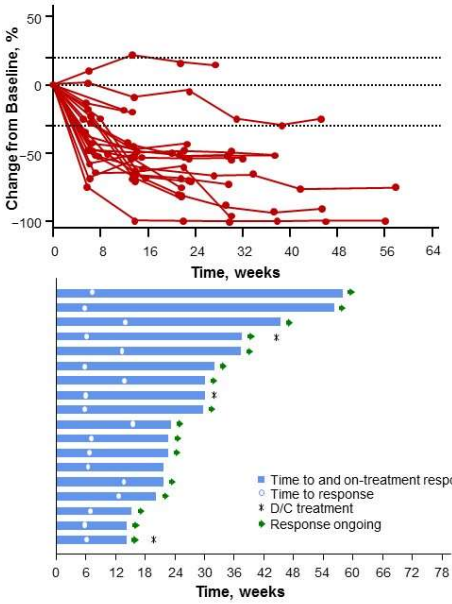


Modified from: Ribas A, et al. *Clin Cancer Res*. 2012;18(2):336-341.

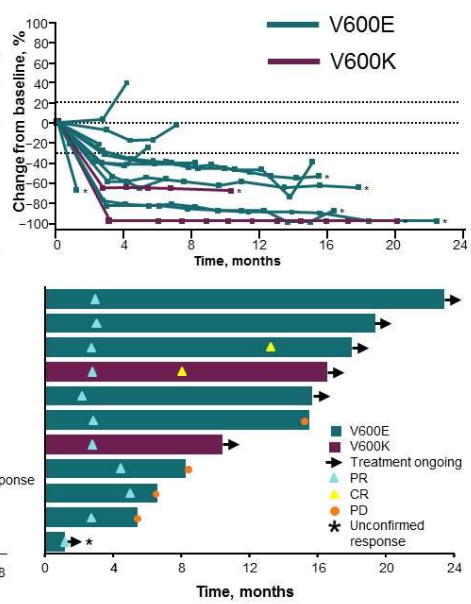
1. Hodi FS, et al. *N Engl J Med*. 2010;363(8):711-723. 2. Chapman PB, et al. *N Engl J Med*. 2011;364(26):2507-2516.

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

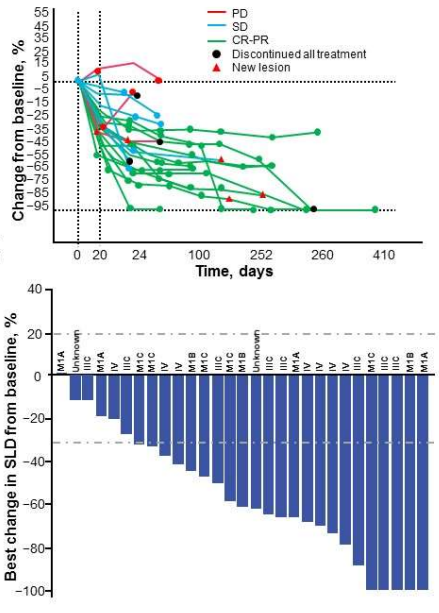
Dabrafenib + trametinib + durvalumab[1]



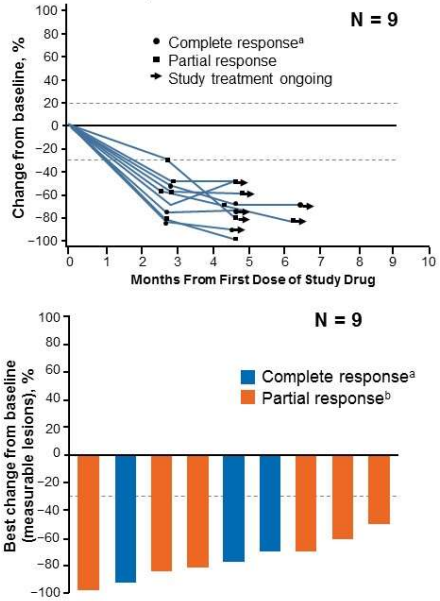
Dabrafenib + trametinib + pembrolizumab[2,3]



Vemurafenib + cobimetinib + atezolizumab[4]



Dabrafenib + trametinib + spartalizumab[5]

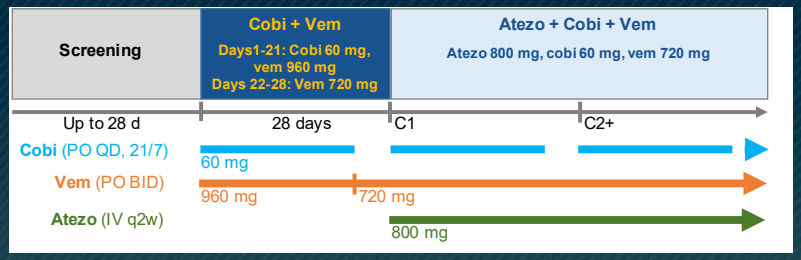


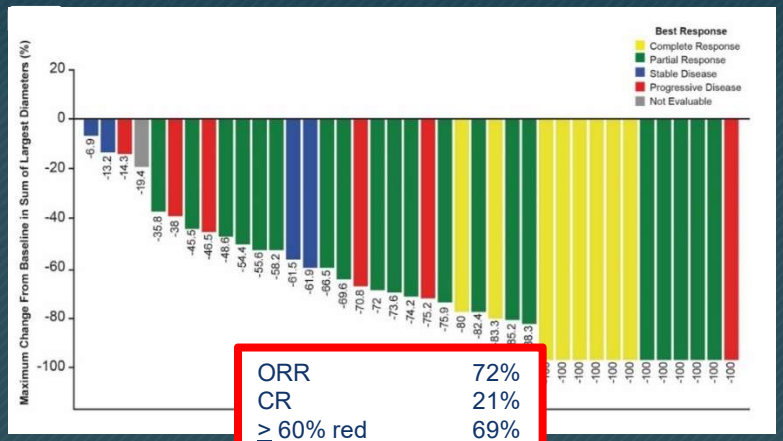
BID, twice daily; CR, complete response; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease. [a] Patients with CR and < 100% change in sum of diameters (SOD) have (a) 100% change for non-nodal target lesions and all nodal target lesions are < 10 mm and (b) CR for nontarget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

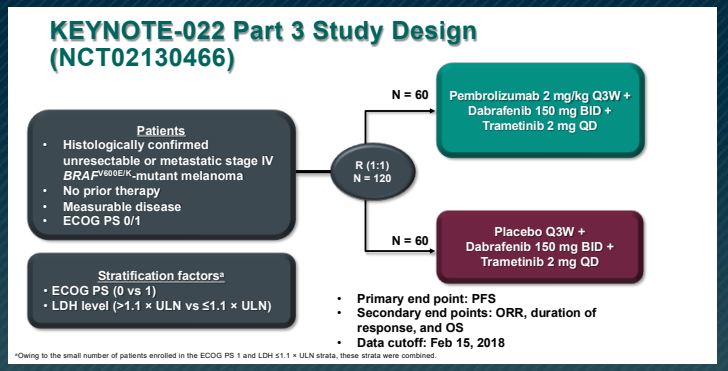
PRESENTED BY R DUMMER AT AACR 2018

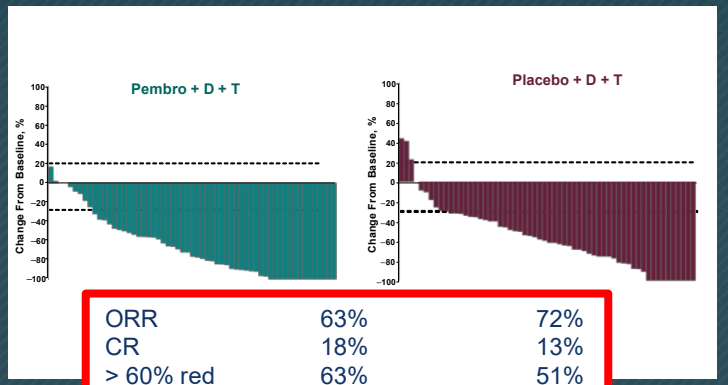
Courtesy of Dr Dummer





ORR	72%
CR	21%
≥ 60% red	69%





ORR	63%	72%
CR	18%	13%
≥ 60% red	63%	51%

Ryan J. Sullivan.
1. Sullivan et al. *ASCO* 2017; in press
2. Ascierto et al. *ESMO* 2019; in press

Safety during triple combination	N = 39; n (%)
Treatment-emergent AEs during combination period	
All grade atezo- and/or cobi- and/or vem-related AEs	37 (95%)
Grade 3-4 atezo- and/or cobi- and/or vem-related AEs	26 (66%)
Treatment-related SAEs	8 (21%)
All treatment discontinuations	11 (28%)

ORR	72%	
CR	21%	
≥ 60% red	69%	

Summary of Adverse Events

	Pembro + D + T n (%) N = 60	Placebo + D + T n (%) N = 60
Any-grade AE	59 (98)	58 (97)
Grade 3-4	40 (67)	27 (45)
Led to death[a]	2 (3)	0 (0)
Led to discontinuation	25 (42)	13 (22)
Led to discontinuation of all 3 study drugs	15 (25)	9 (15)
Treatment-related AE	57 (95)	56 (93)
Grade 3-4	34 (57)	16 (27)
Led to death	1 (2)	0 (0)
Led to discontinuation of ≥1 study drug	24 (40)	12 (20)

[a]One patient died due to treatment-related pneumonitis and one died of unknown cause.

ORR	63%	72%
CR	18%	13%
≥ 60% red	63%	51%

Ryan J. Sullivan.
1. Sullivan et al. *ASCO* 2017; in press
2. Ascierto et al. *ESMO* 2019; in press

Summary

- 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 CPB is still a clinical decision
- Combination of immunotherapy and targeted therapy is an active area of investigation

Pick the incorrect Answer

1. Immunotherapy is an option for all patients with advanced melanoma
2. The percentage of BRAF mutated US patients is 80%
3. Combination immunotherapy appears superior to monotherapy but with higher toxicity
4. In the adjuvant therapy of melanoma, the choice between immunotherapy and targeted therapy is based on clinical judgment and not on trial data