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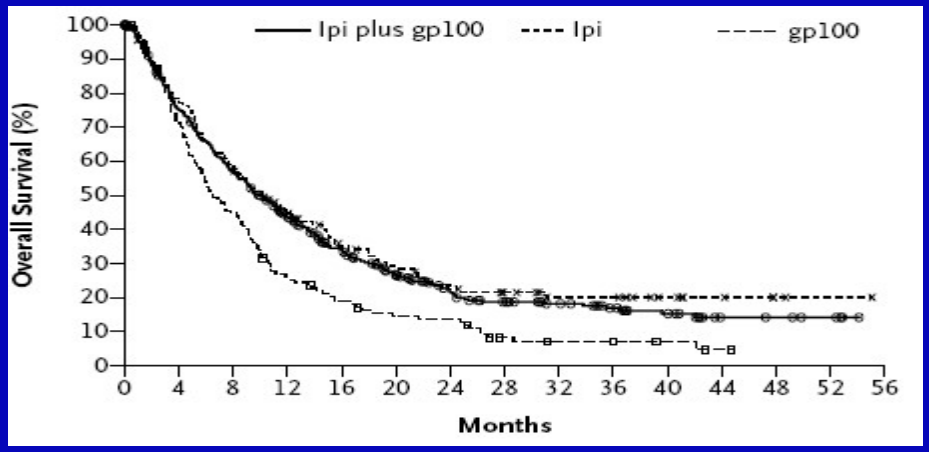
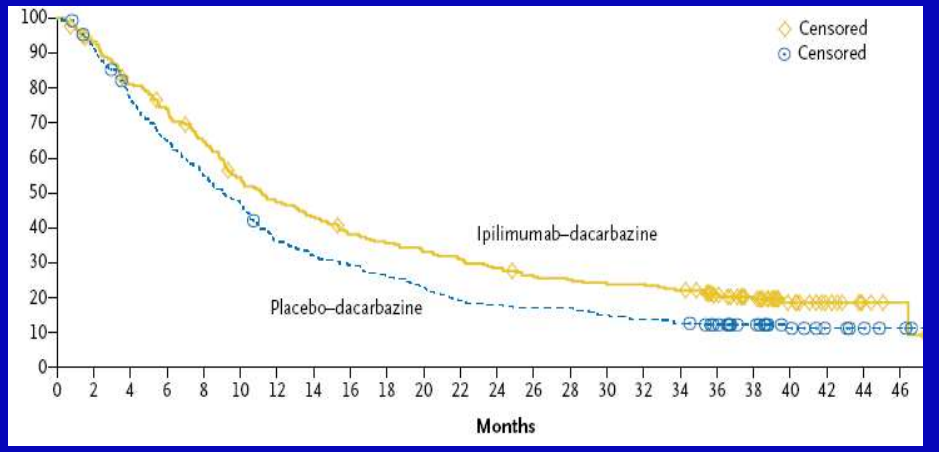
Clinical Results with Ipilimumab (2nd and 1st line)
Ipilimumab vs vaccine and Ipi + DTIC vs DTIC



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

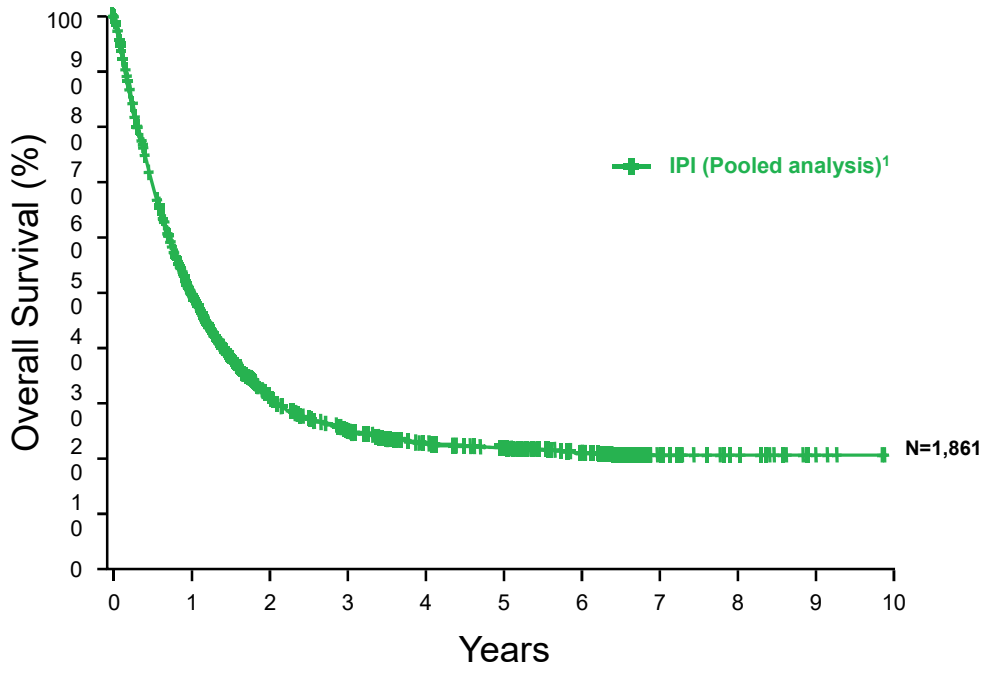
Hodi FS, et al. *N Engl J Med.* 2010;363:711-23.



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

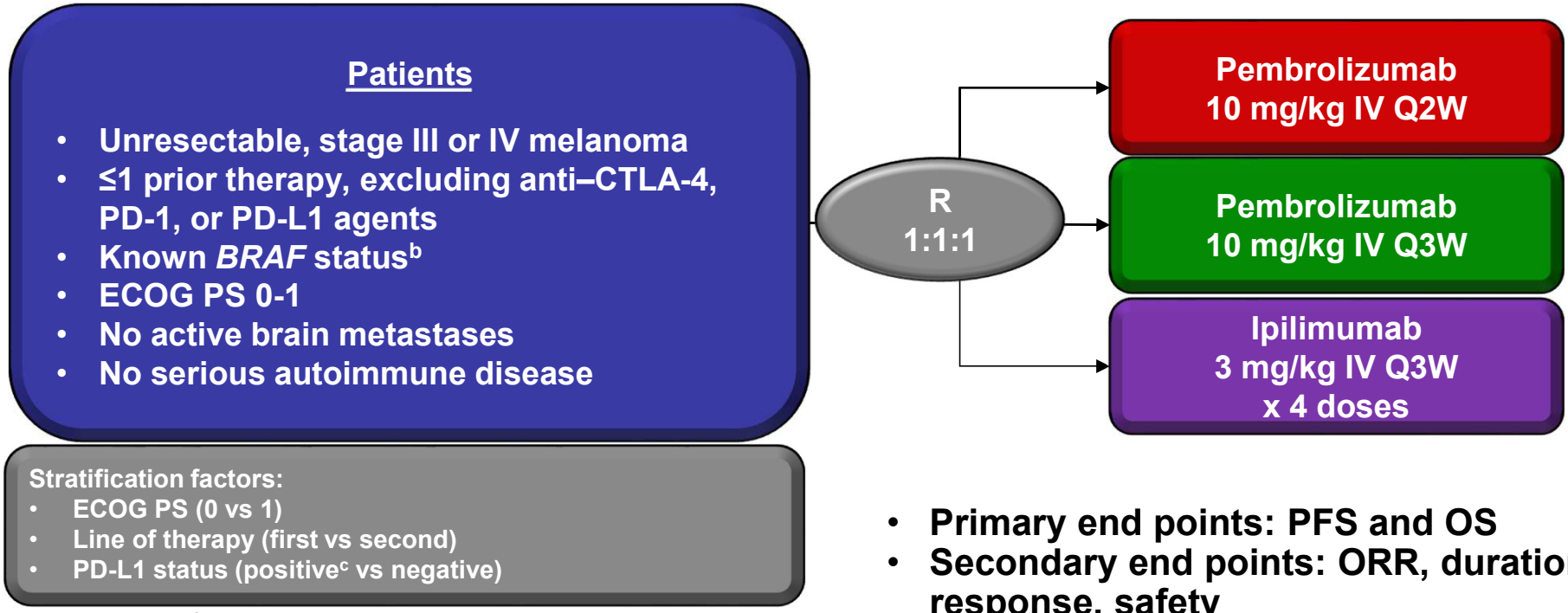
Robert C, et al. *N Engl J Med*. 2011;364:2517-26.

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.

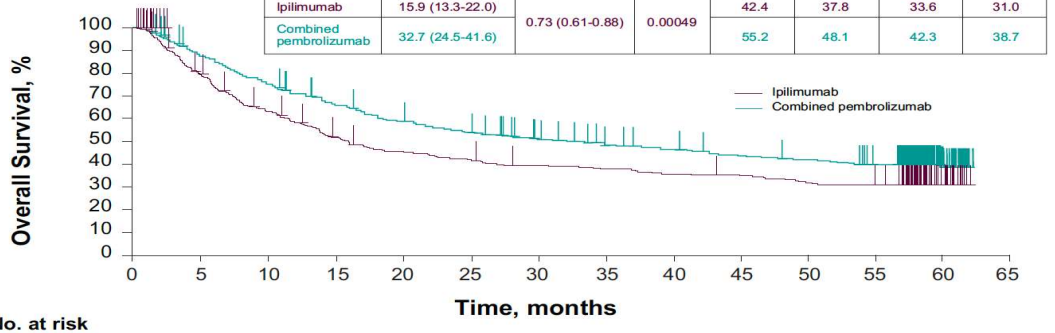
[b]Prior anti-BRAF targeted therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.

[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

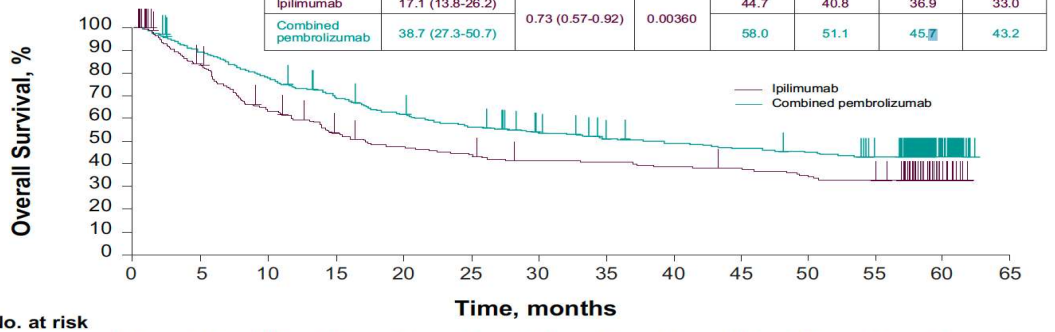
OS	Median[b] (95% CI), months	HR[c] (95% CI)[c]	*P* Value[d]	24-Month Rate,[b] %	36-Month Rate,[b] %	48-Month Rate,[b] %	60-Month Rate,[b] %
Ipilimumab	15.9 (13.3-22.0)	0.73 (0.61-0.88)	0.00049	42.4	37.8	33.6	31.0
Combined pembrolizumab	32.7 (24.5-41.6)			55.2	48.1	42.3	38.7



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

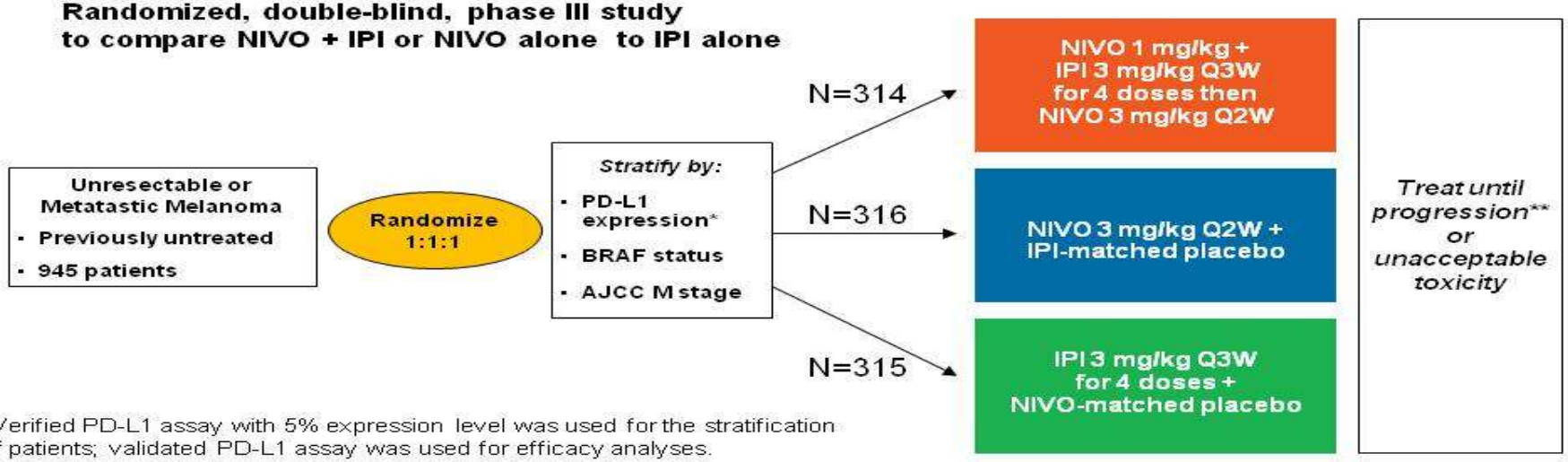


No. at risk														
Ipilimumab	181	140	105	86	76	70	64	63	60	58	52	49	8	0
Combined pembrolizumab	368	324	284	248	221	201	184	170	163	155	149	137	31	0

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



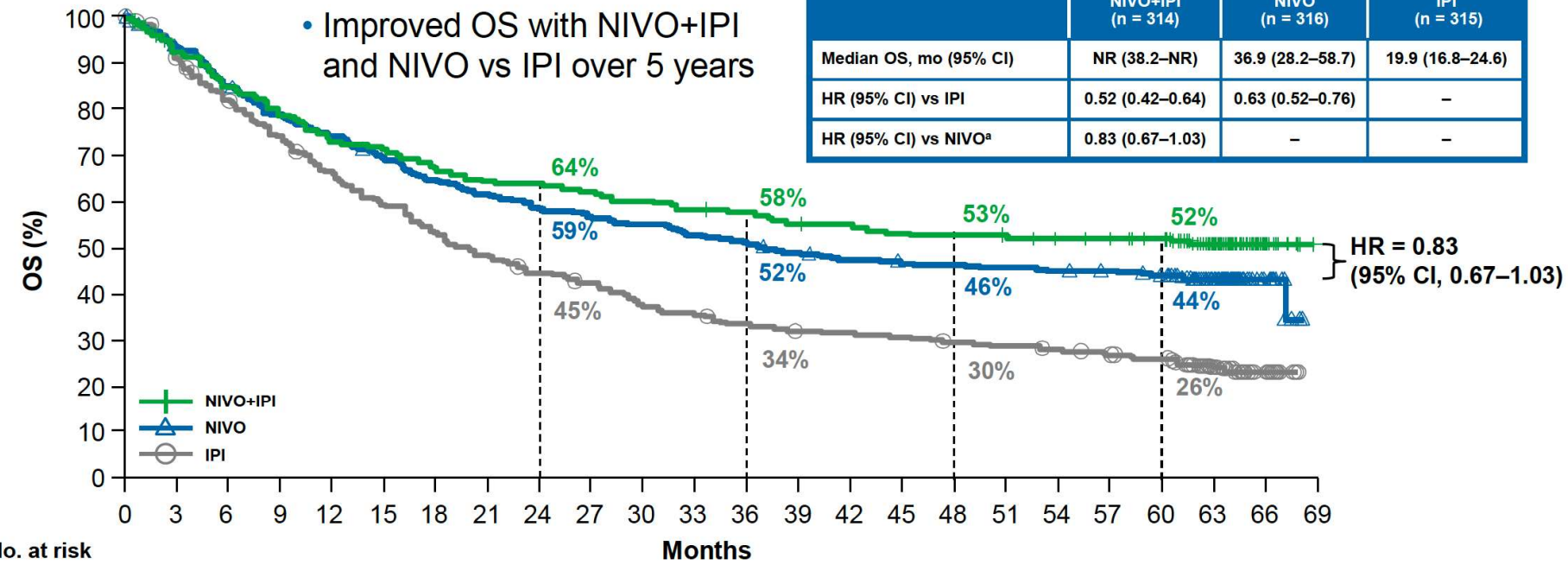
*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**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

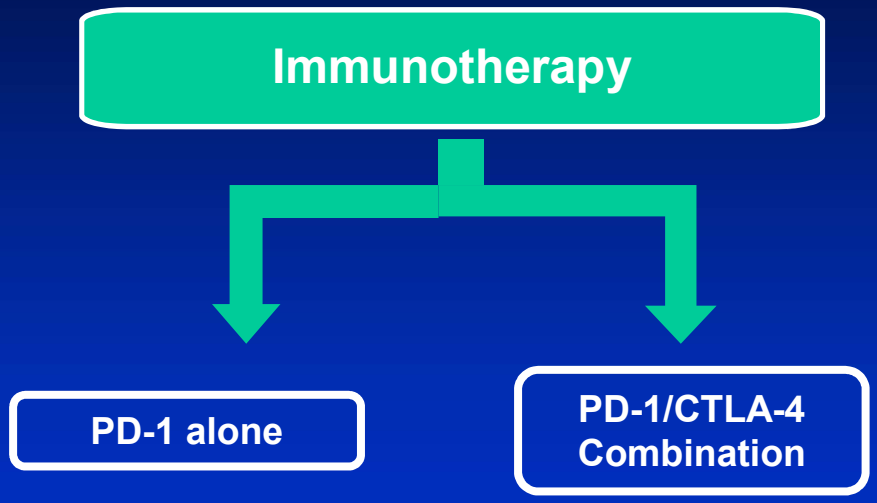
	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.67–1.03)	–	–



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?



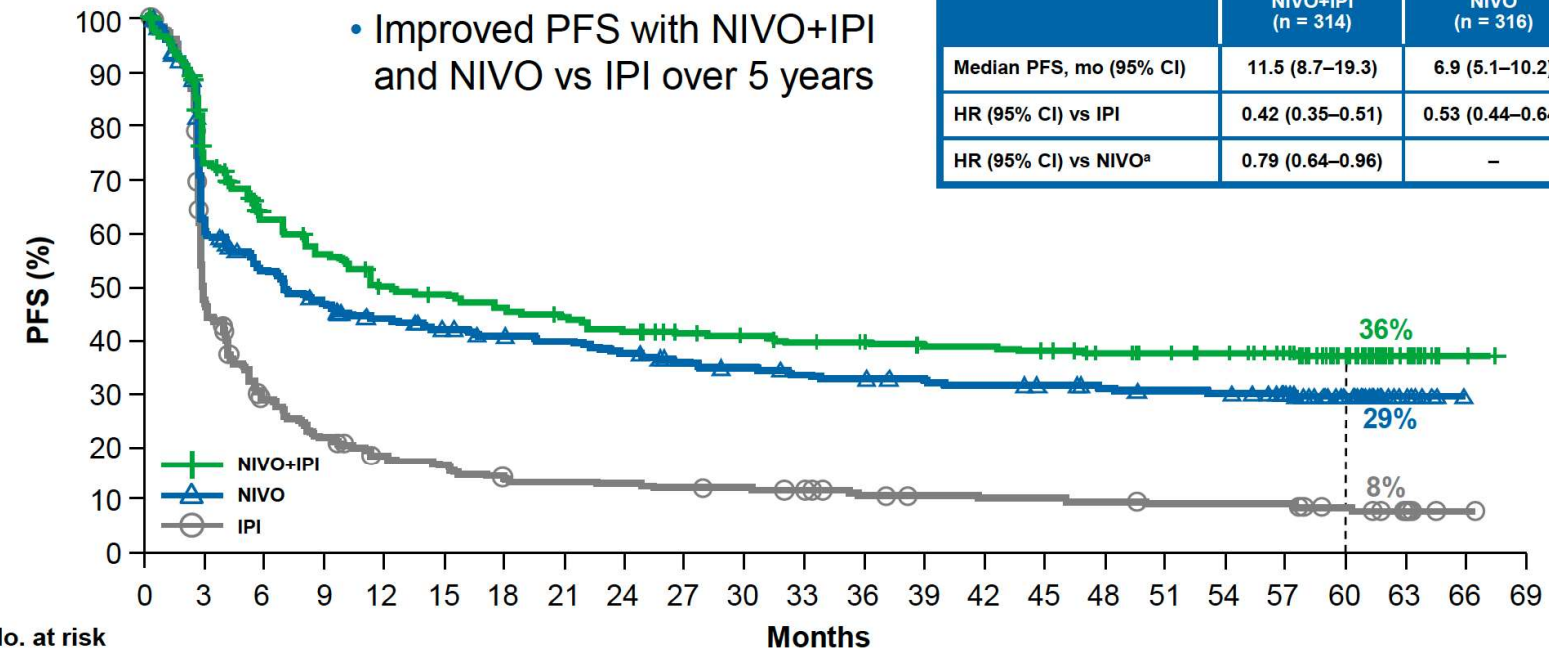
Decision Factors

- 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]

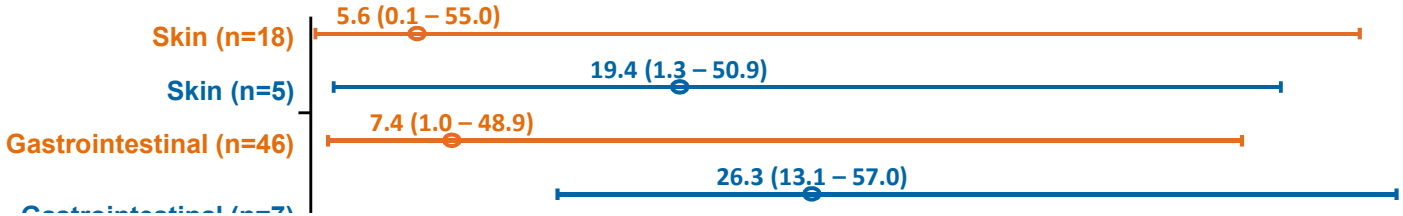
	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	58.5	86.3	20.8	86.2	27.7
Treatment-related AE leading to discontinuation	39.6	31.0	11.5	7.7	16.1	14.1
Treatment-related death,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

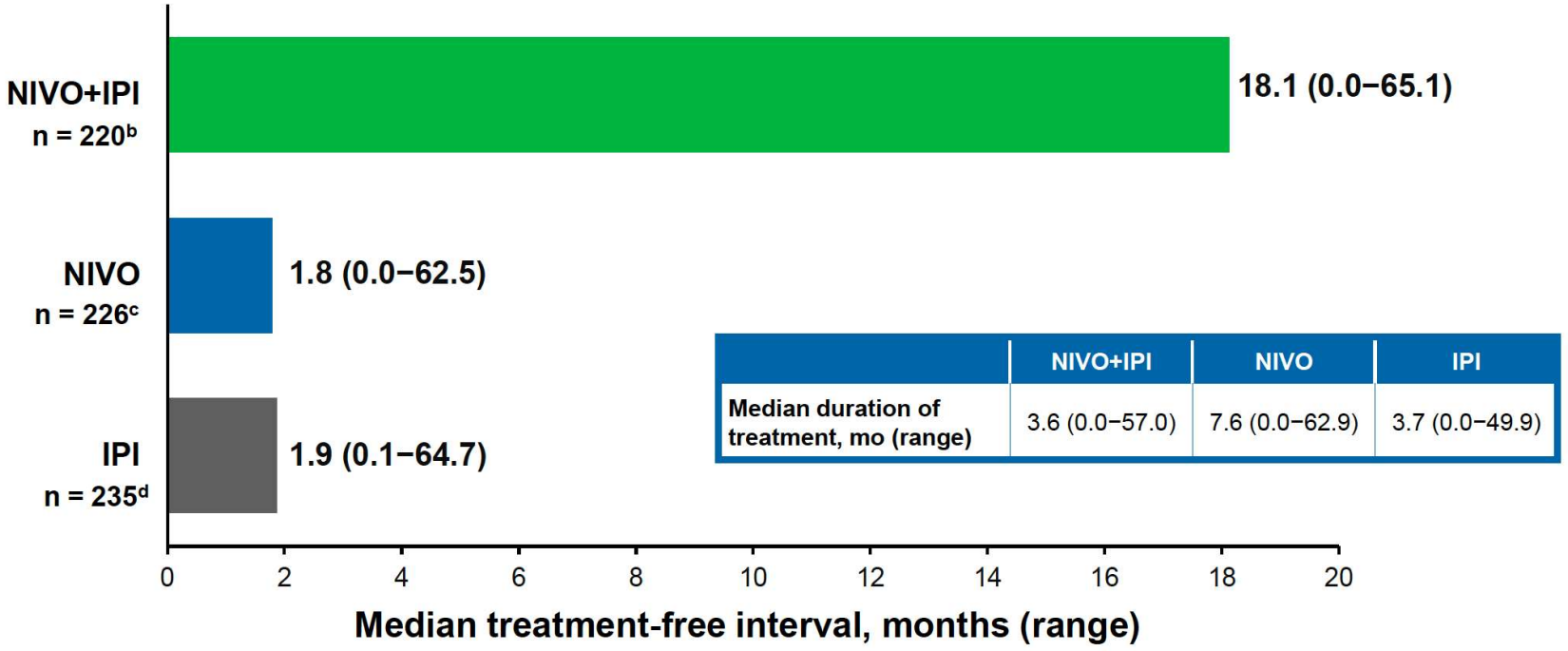
Longer Time to Resolution

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

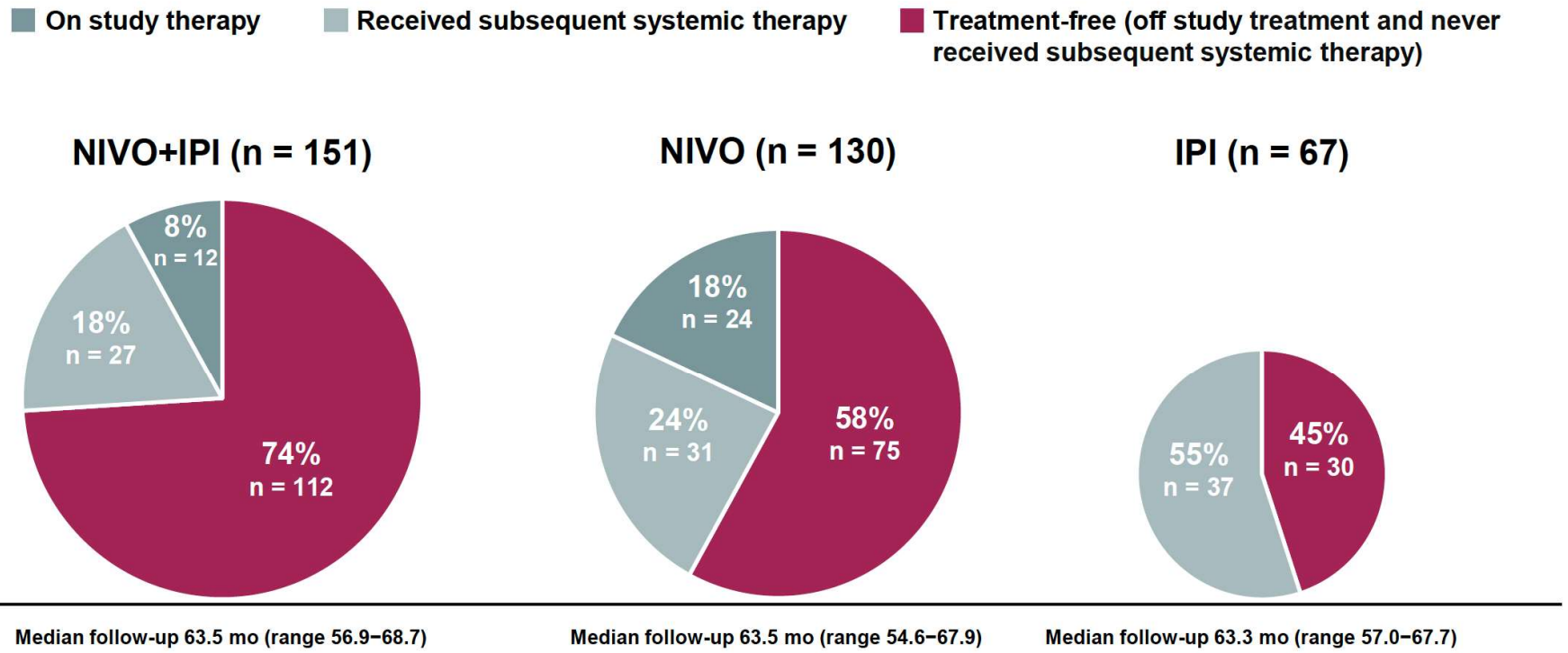


	NIVO+IPI	NIVO	IPI
Median duration of treatment, mo (range)	3.6 (0.0–57.0)	7.6 (0.0–62.9)	3.7 (0.0–49.9)

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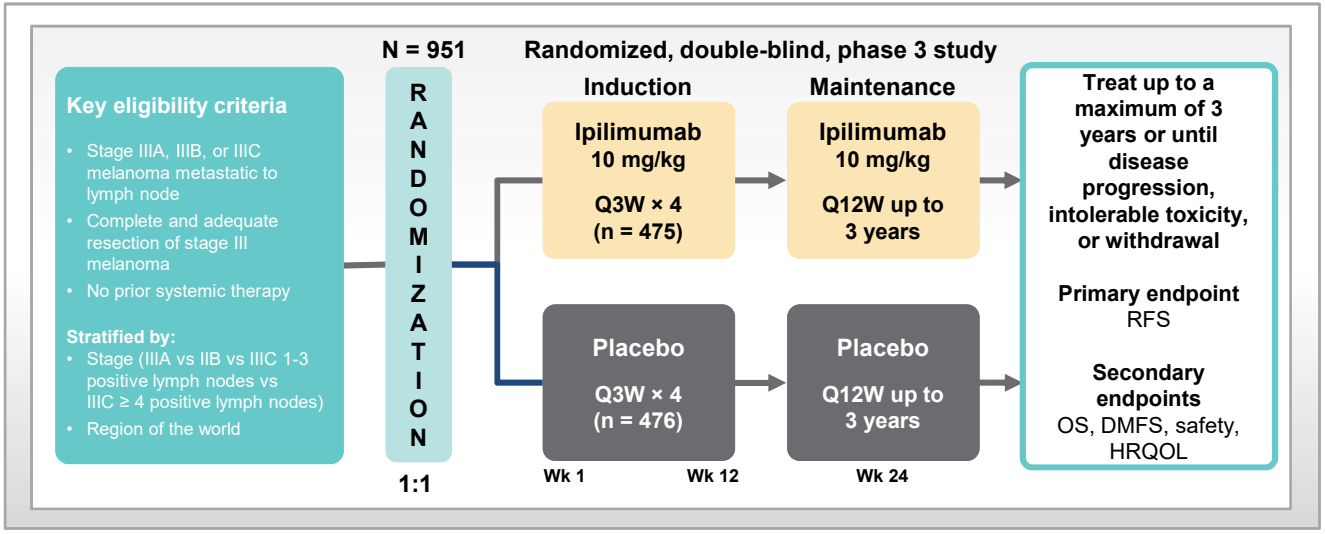
  - Anti-PD1+Anti-CTLA4 (ipilimumab + nivolumab)
- Adjuvant Therapy
  - Anti-PD1 (nivolumab, pembrolizumab)

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



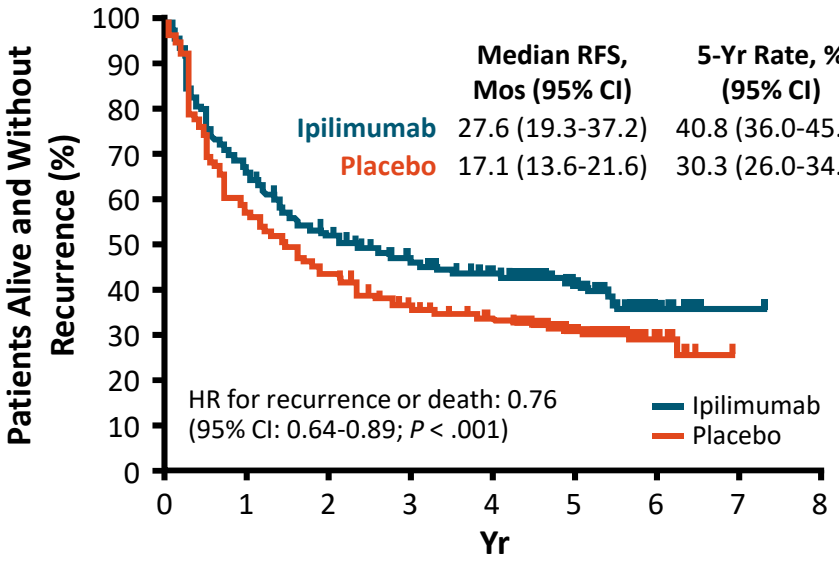
DMFS, distant metastasis-free survival; HRQOL, health-related quality of life; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; Q12W, every 12 weeks; RFS, relapse-free survival.

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.

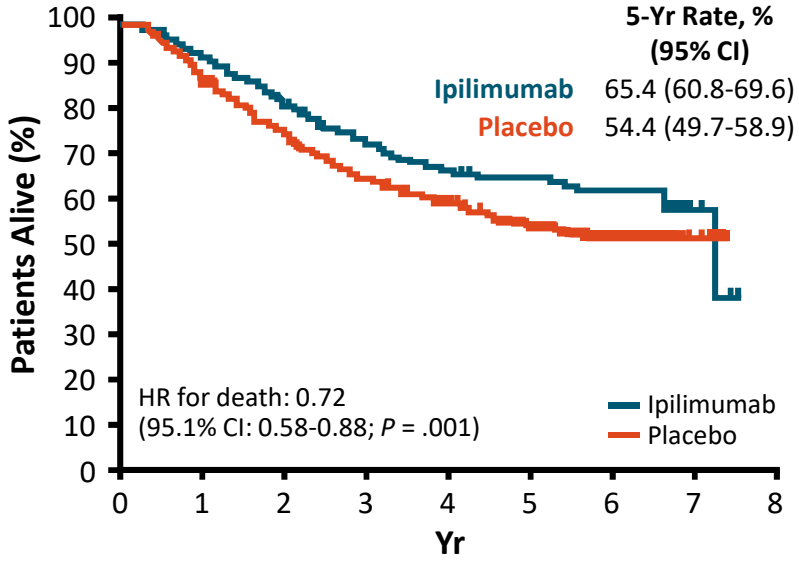
EORTC 18071: Phase III Trial of Ipilimumab 10 mg/kg vs Placebo in Stage III Melanoma

- 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.

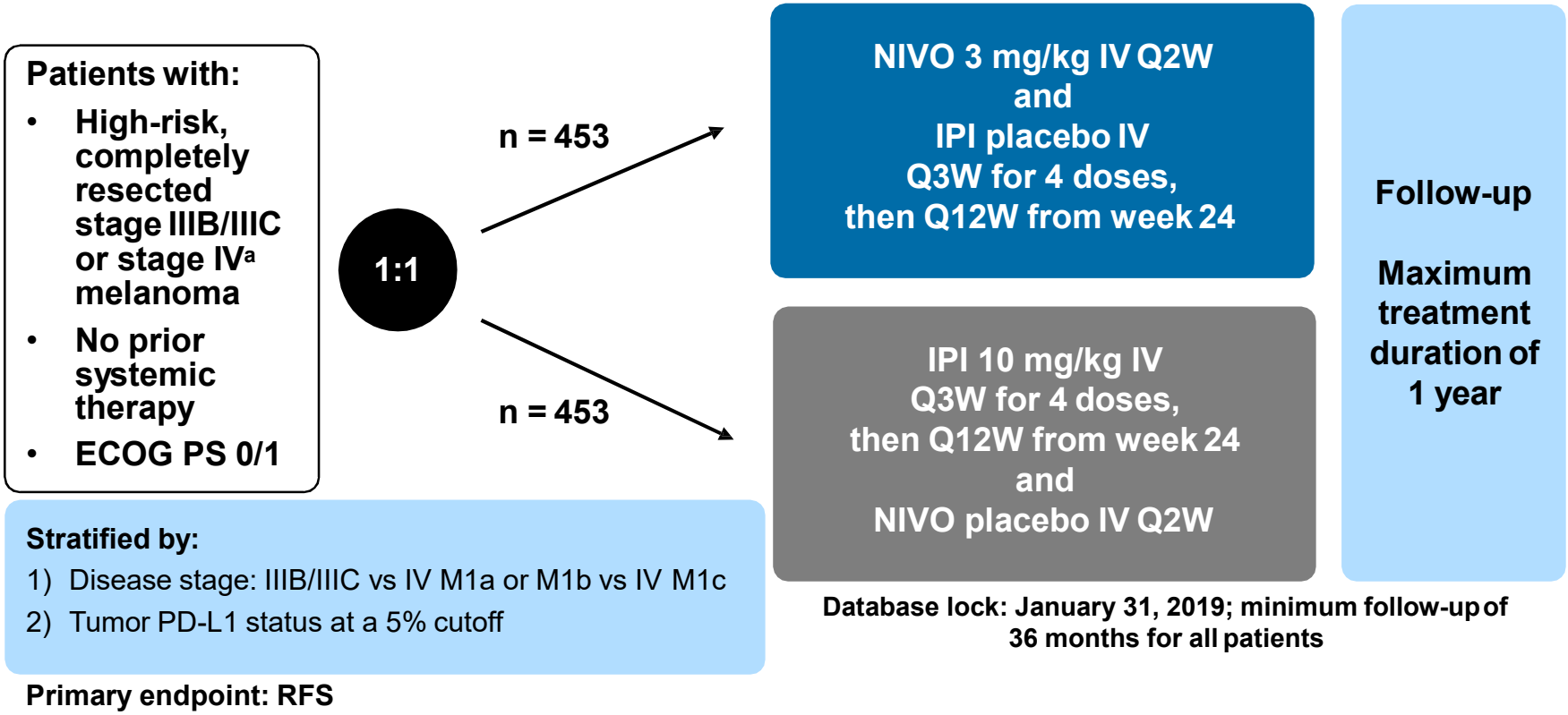
EORTC 18071: Safety

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.

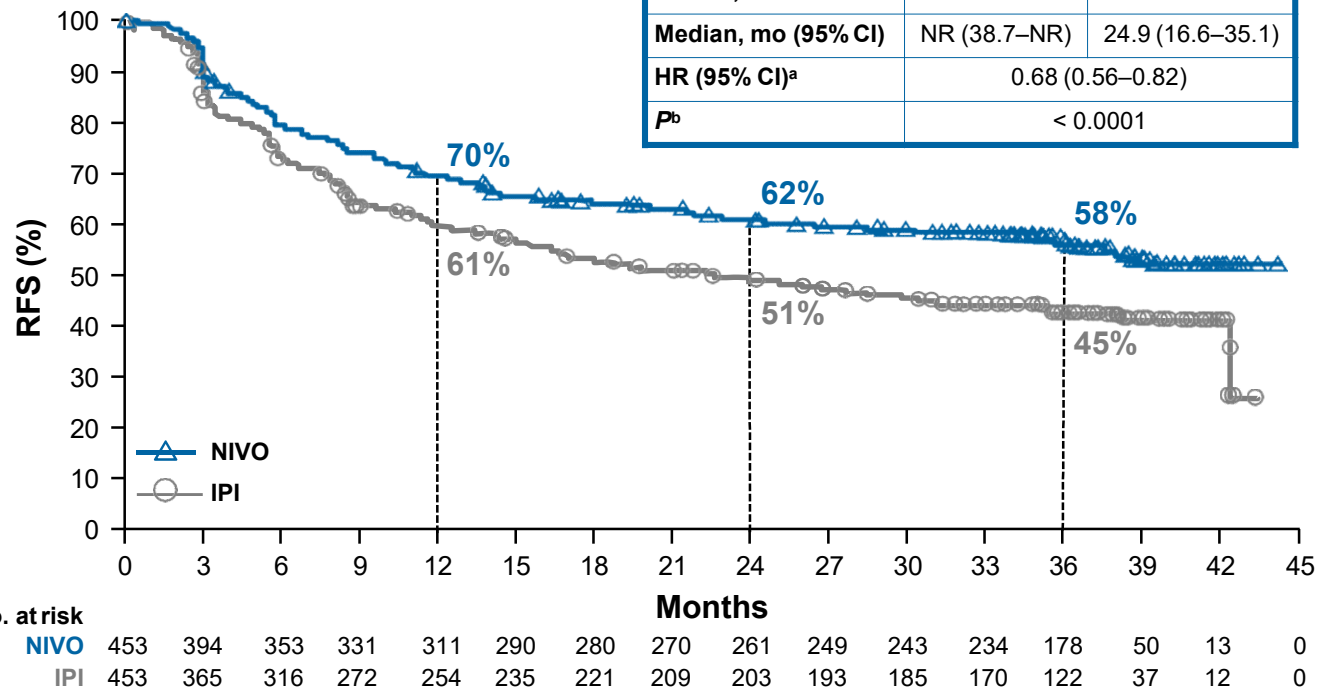
CheckMate 238: Study Design



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

Primary Endpoint: RFS in All Patients

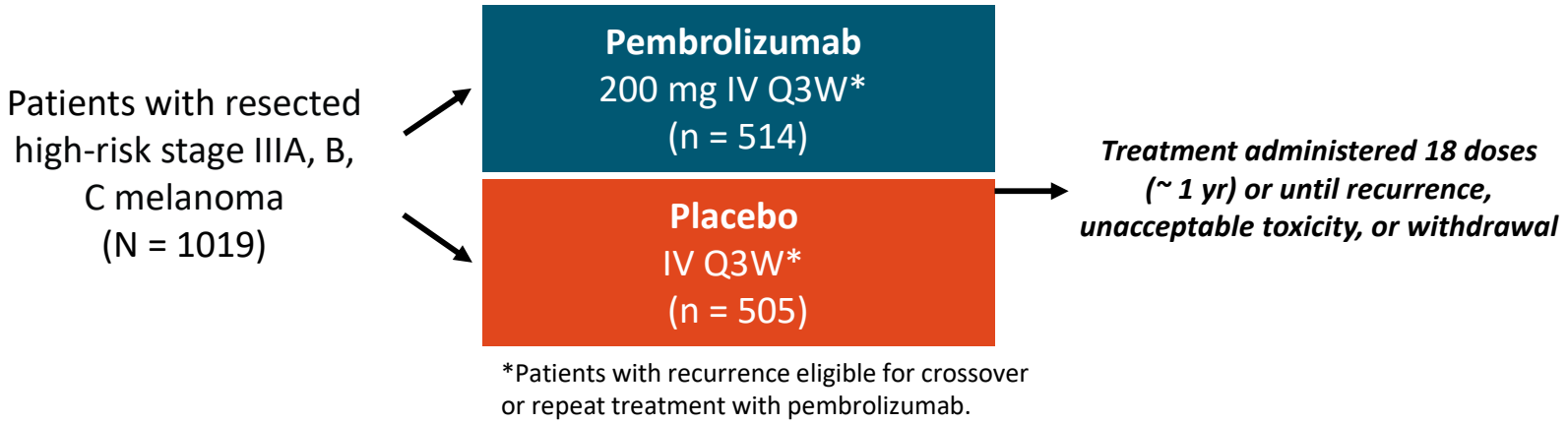
	NIVO (n = 453)	IPI (n = 453)
Events, n	188	239
Median, mo (95% CI)	NR (38.7–NR)	24.9 (16.6–35.1)
HR (95% CI)[a]	0.68 (0.56–0.82)	
P[b]	< 0.0001	



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

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

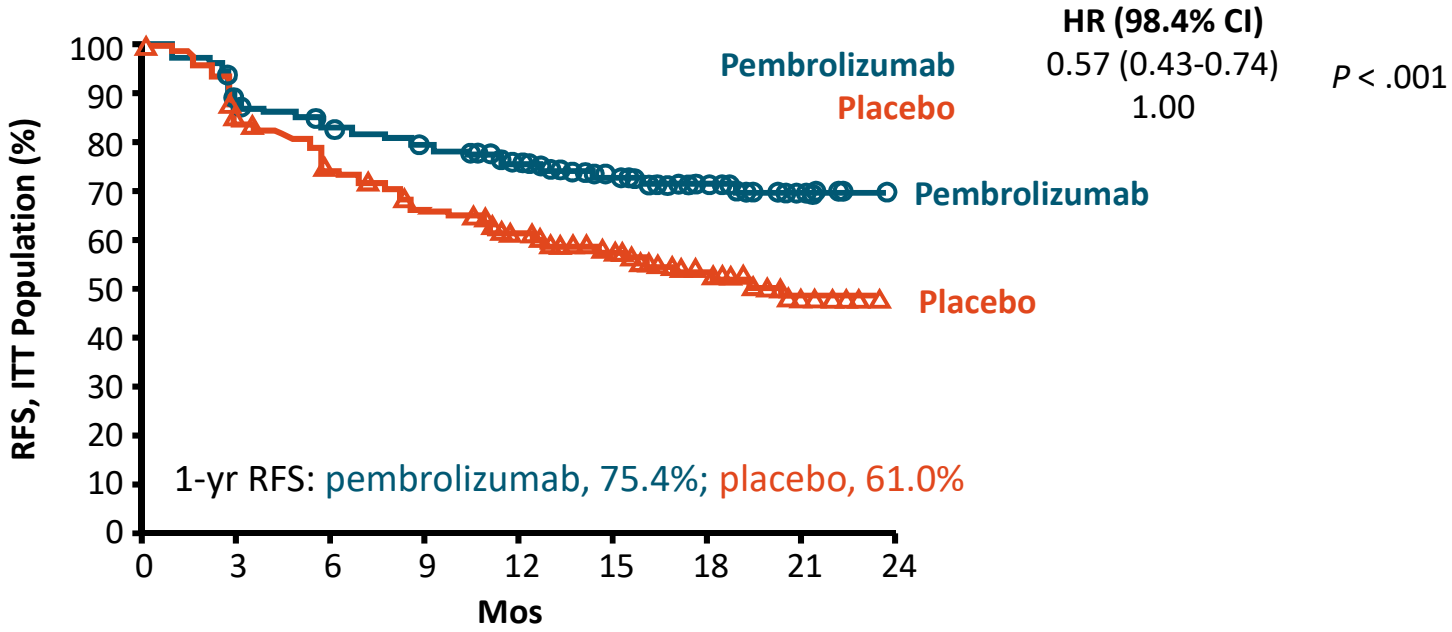
- Randomized, double-blind phase III study



- 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

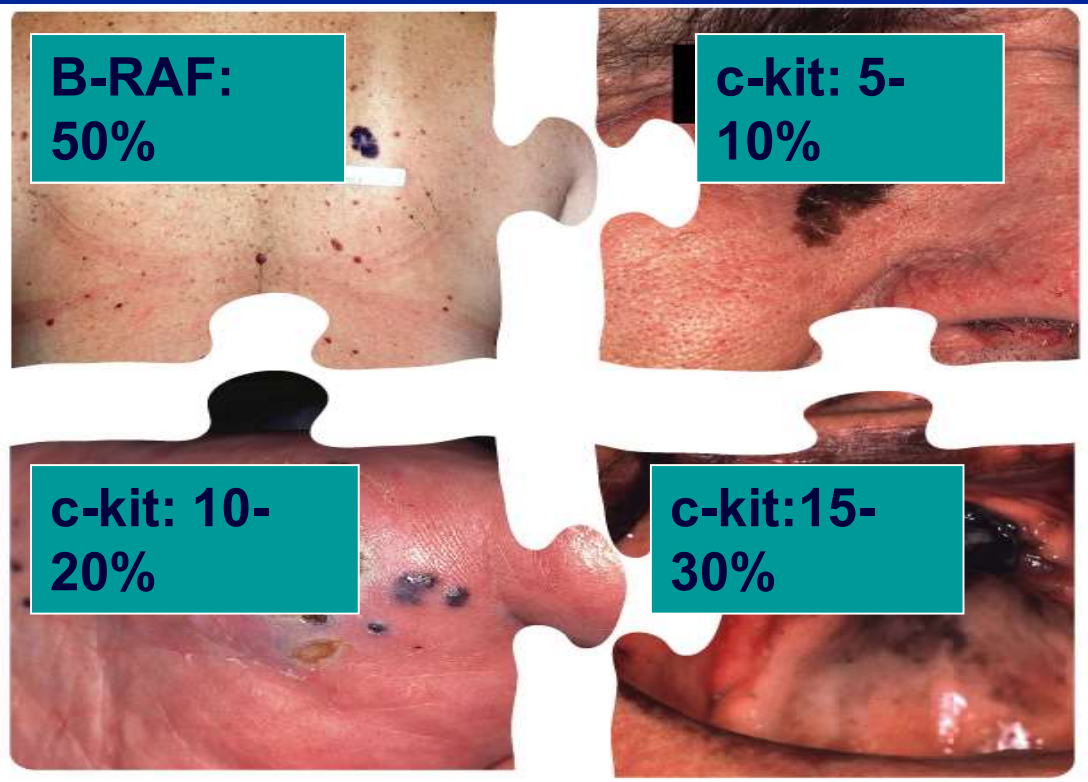
Eggermont. NEJM. 2018;378:1789.

Targeted Therapy

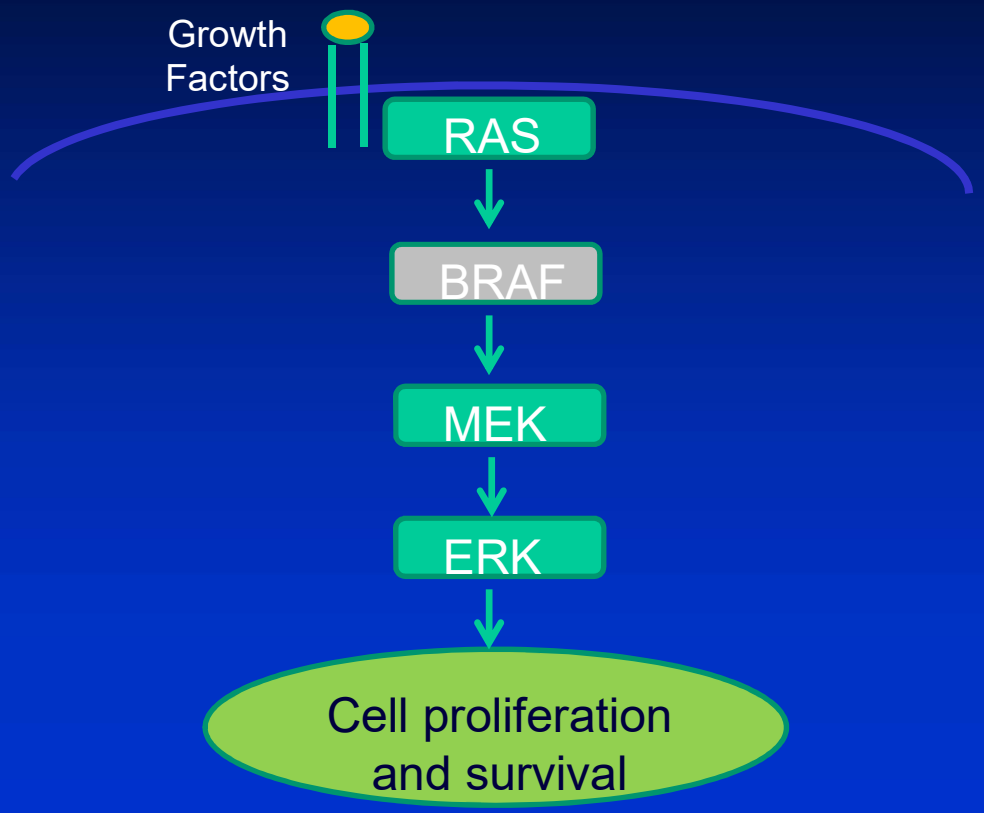
- Metastatic Disease
  - BRAF/MEK combination therapy
    - Dabrafenib/trametinib
    - Vemurafenib/cobimetinib
    - Encorafenib/binimetinib
- Adjuvant Therapy
  - BRAF/MEK combination
    - Dabrafenib/trametinib

Melanoma is not one disease

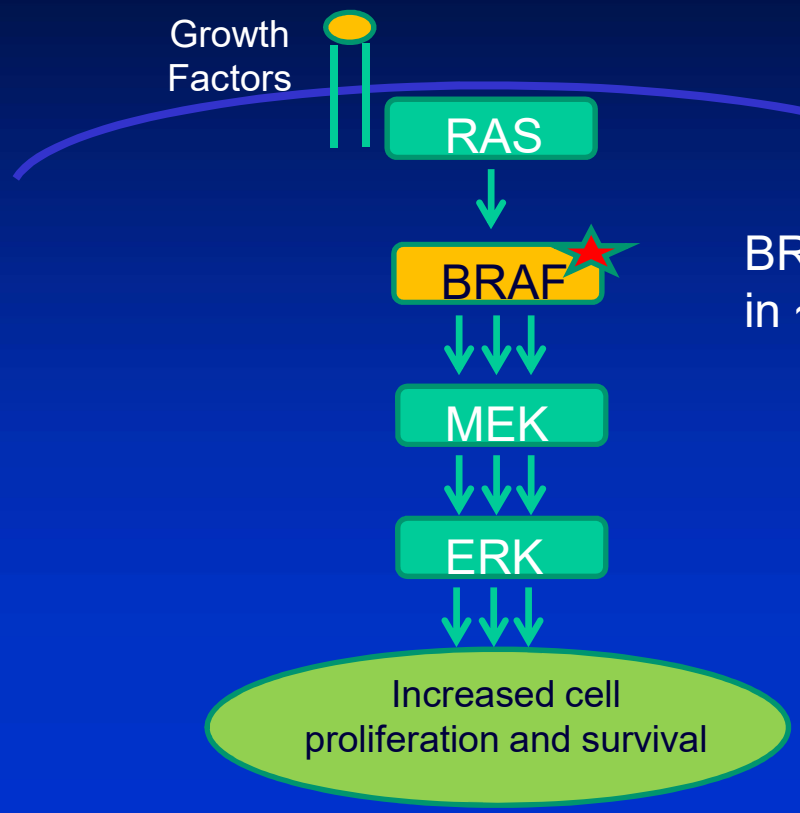
(Curtin et al, N Engl J Med 353: 2135-47, 2005)



MAPK Pathway

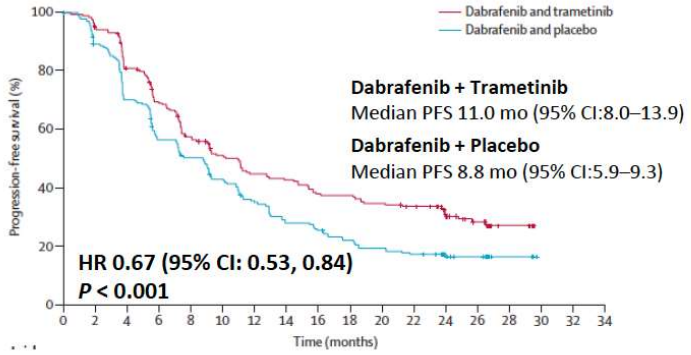


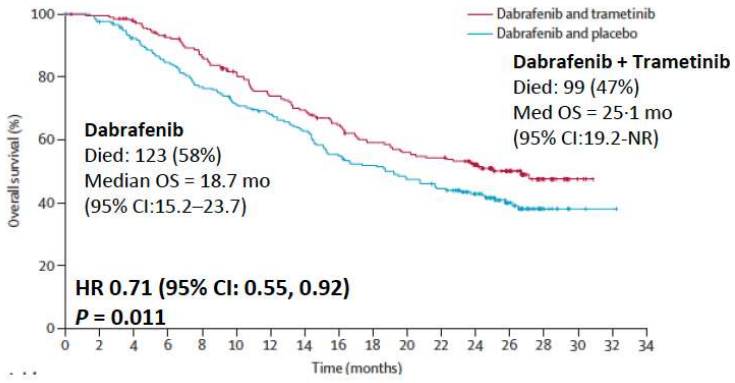
BRAF Mutation



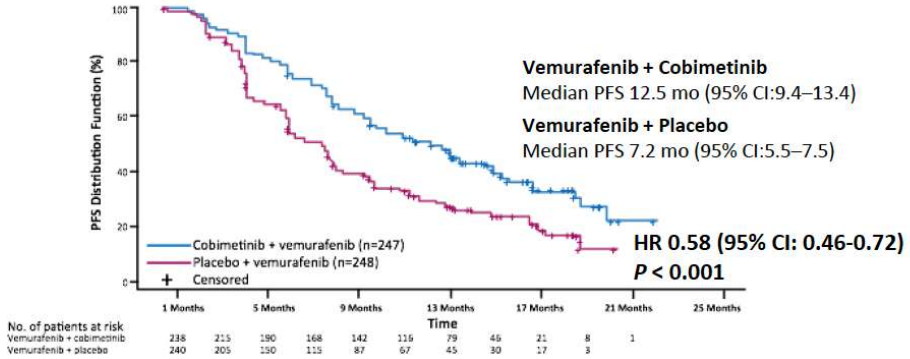
BRAF mutation is present in ~50% of melanomas

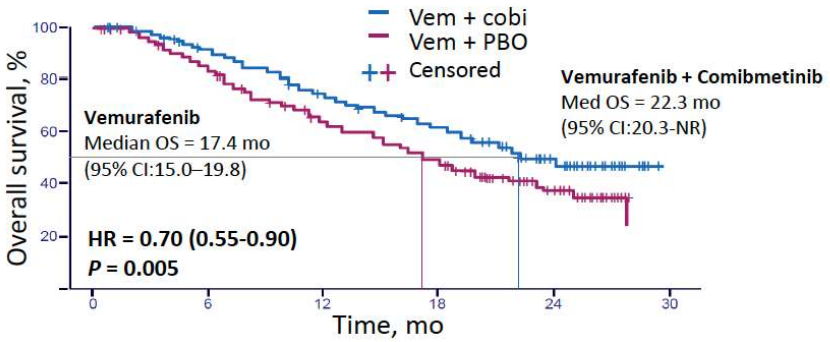
Combined BRAF/MEKi therapy is superior survival compared to single-agent BRAF inhibitors (BRAFi)





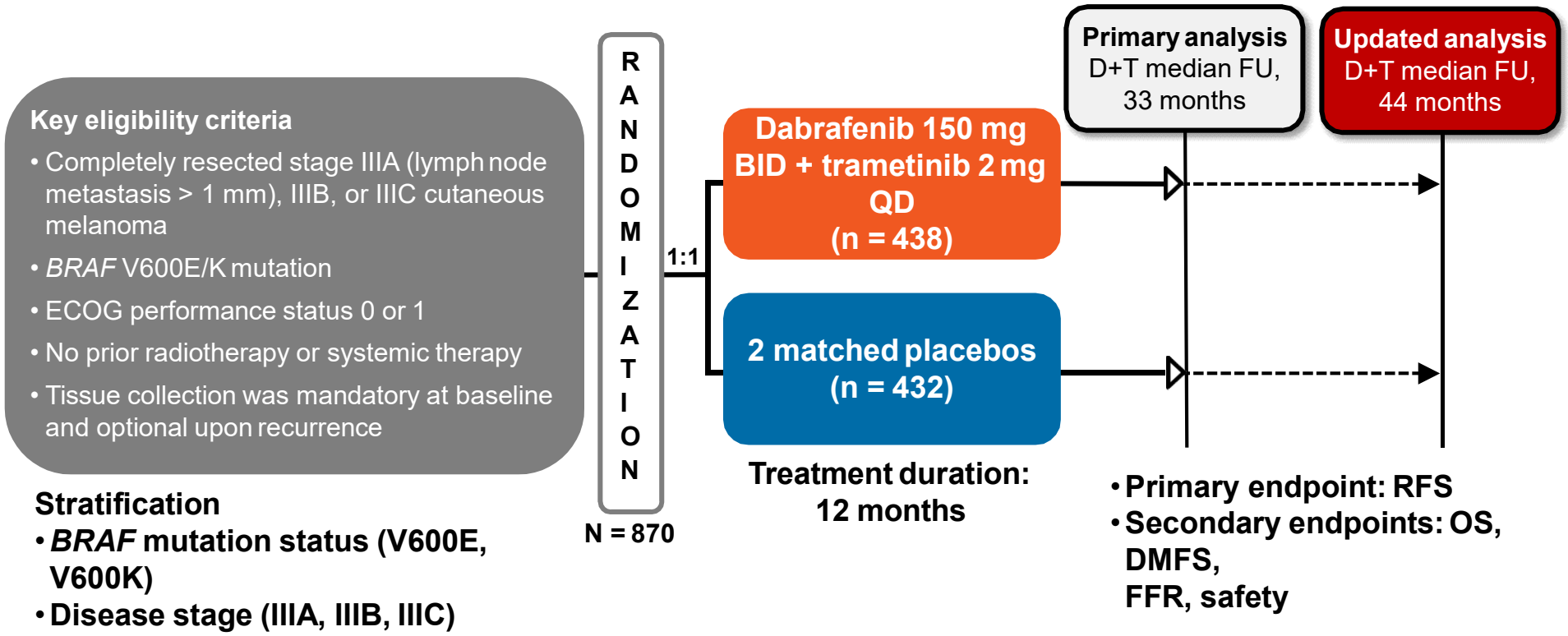
Long et al. NEJM 2014; Long et al. *Lancet* 2015.





Larkin et al. NEJM 2015

Adjuvant Therapy: Combi-AD: Study Design

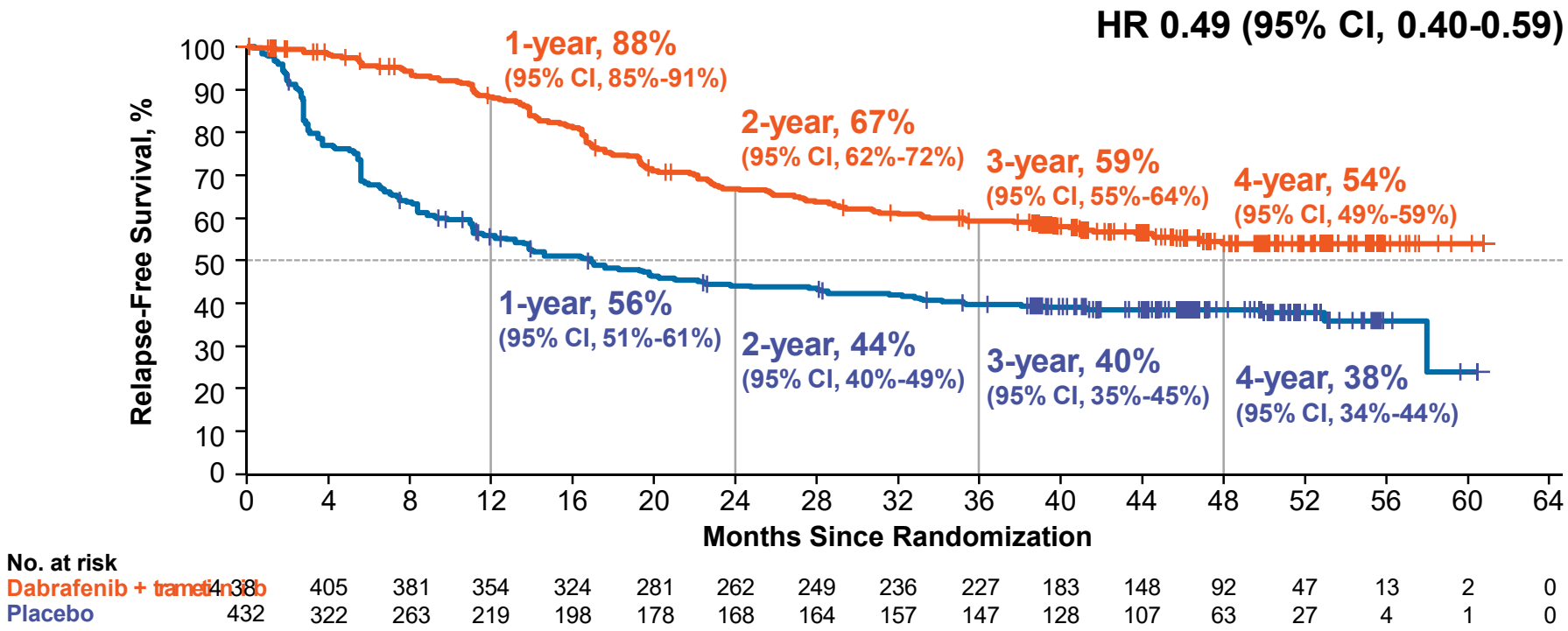


BID, twice daily; DMFS, distant metastasis–free survival; D+T, dabrafenib + trametinib; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; FU, follow-up; QD, once daily.

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



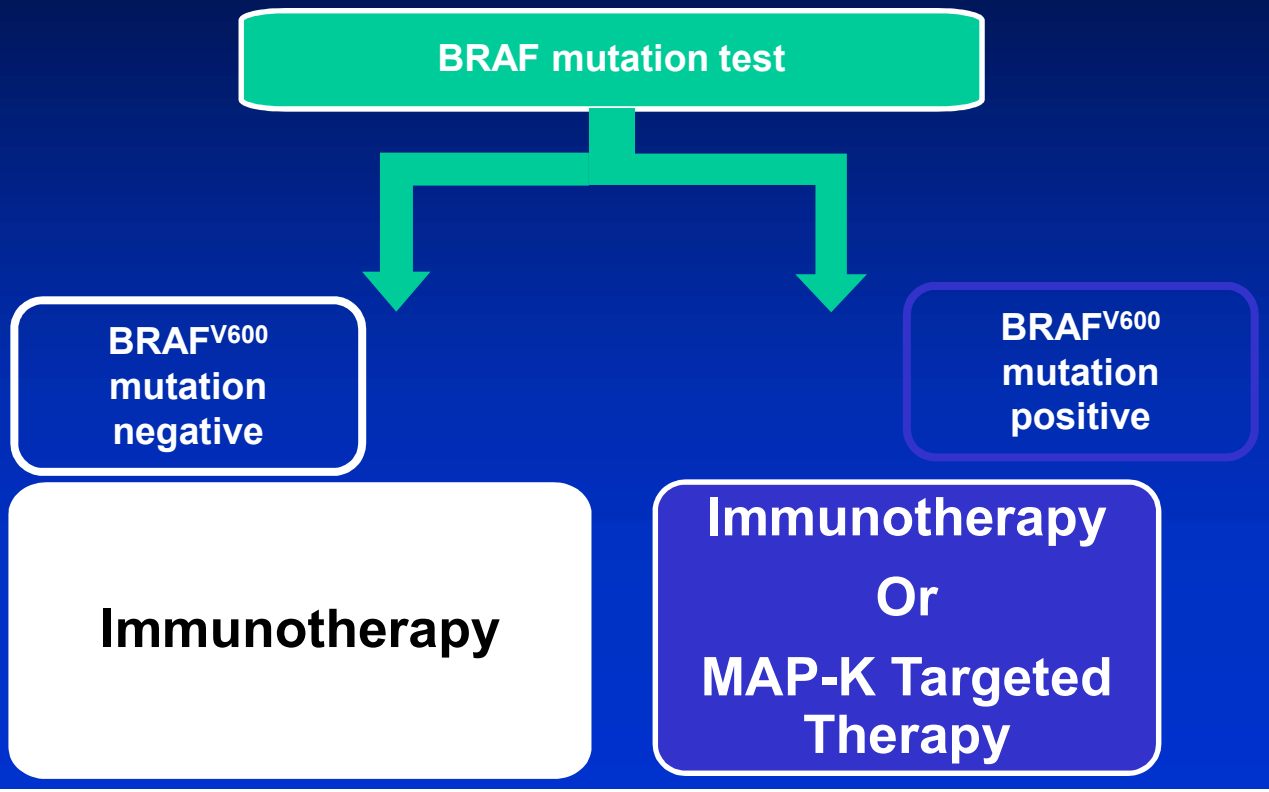
No. at risk																
Dabrafenib + trametinib	438	405	381	354	324	281	262	249	236	227	183	148	92	47	13	2	0
Placebo	432	322	263	219	198	178	168	164	157	147	128	107	63	27	4	1	0

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

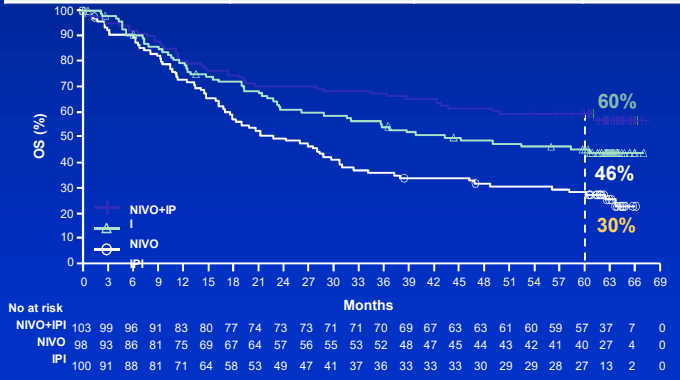


Immunotherapy OS in Patients With BRAF-Mutant and Wild-Type Tumors

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

BRAF-Mutant

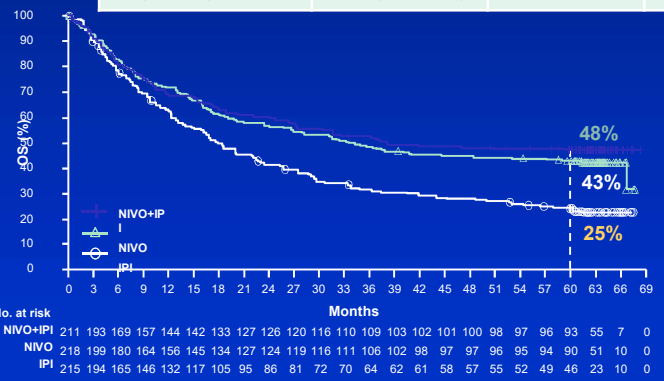
	NIVO+IPI (n=103)	NIVO (n=98)	IPI (n=100)
Median, mo (95% CI)	NR (50.7-NR)	45.5 (26.4-NR)	24.6 (17.9-31.0)
HR (95% CI) vs IPI	0.44 (0.30-0.64)	0.63 (0.44-0.90)	–
HR (95% CI) vs NIVO[a]	0.70 (0.46-1.05)	–	–



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

BRAF Wild-Type

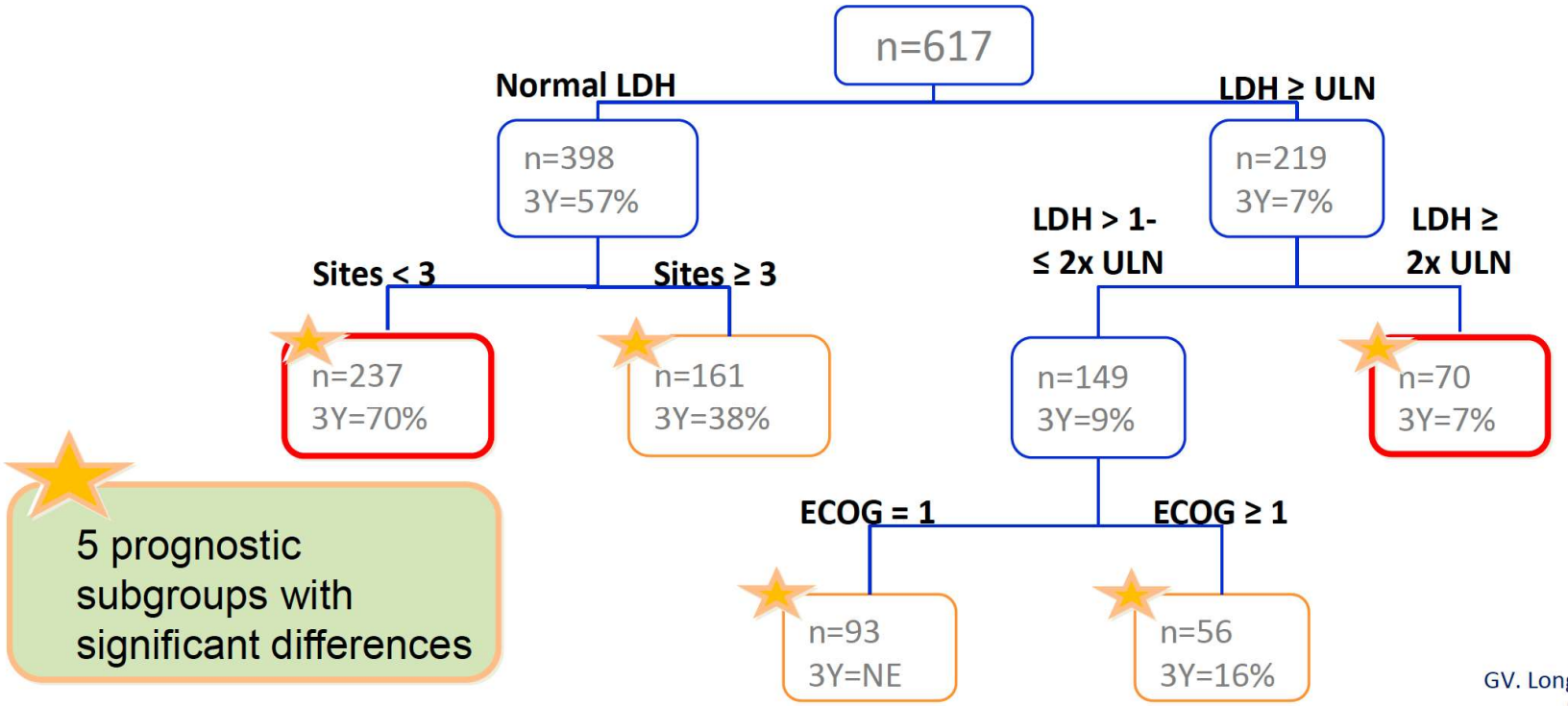
	NIVO+IPI (n=211)	NIVO (n=218)	IPI (n=215)
Median, mo (95% CI)	39.1 (27.5–NR)	34.4 (24.1-59.2)	18.5 (14.1-22.7)
HR (95% CI) vs IPI	0.57 (0.45-0.73)	0.64 (0.50-0.81)	–
HR (95% CI) vs NIVO[a]	0.89 (0.69-1.15)	–	–



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

[a]Descriptive analysis.

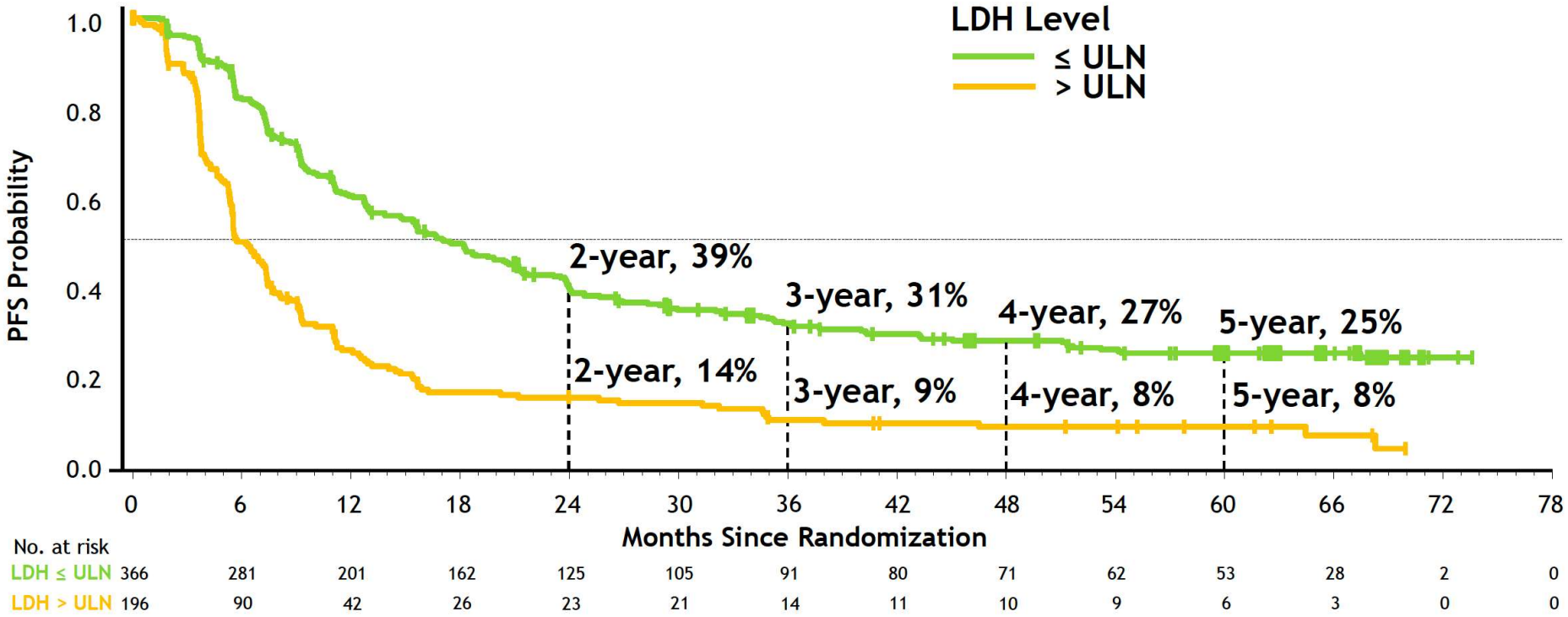
Baseline factors influencing outcome with targeted therapy



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

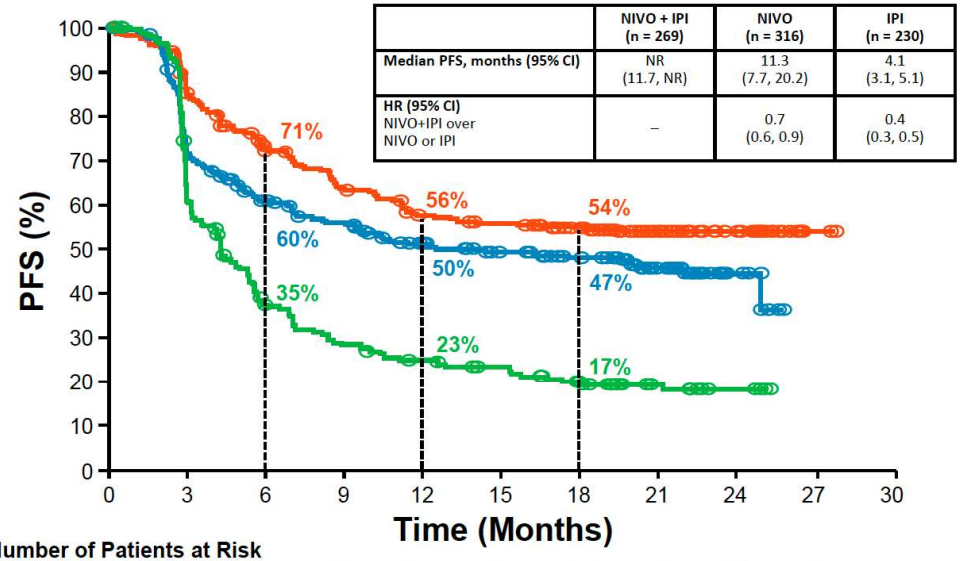
- Minimum follow-up of 18 months
- Patients were stratified according to baseline LDH values (LDH ≤ ULN, > ULN, or > 2x ULN)

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)

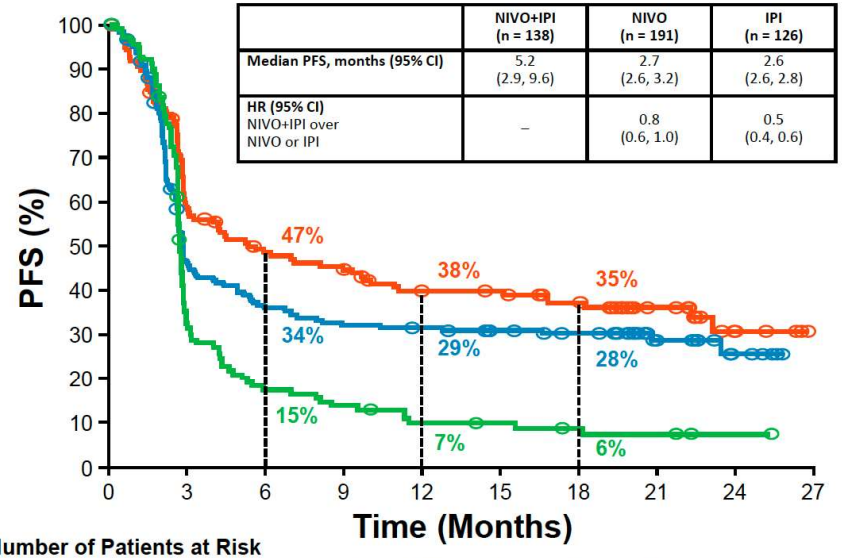


Number of Patients at Risk

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

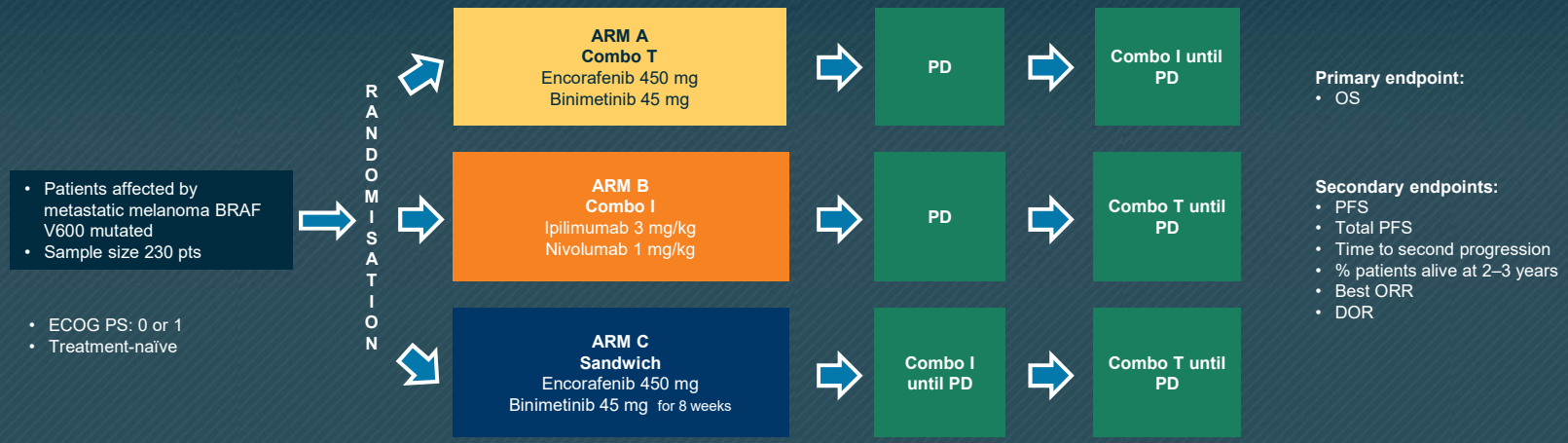
Secondary endpoints:
- PFS (RECIST version 1.1)
- Response rate (RECIST version 1.1)

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.

The Future

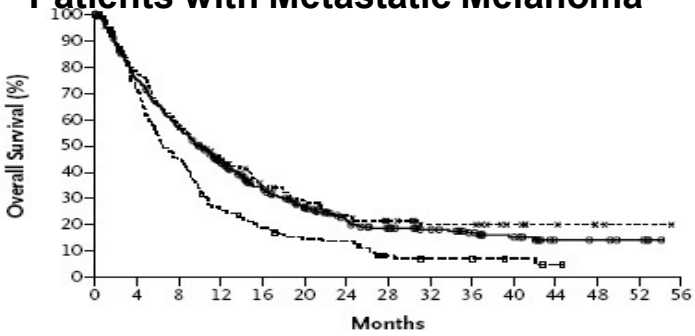
- Triple therapy for BRAF+ patients
- Reverse drug resistance

The Future

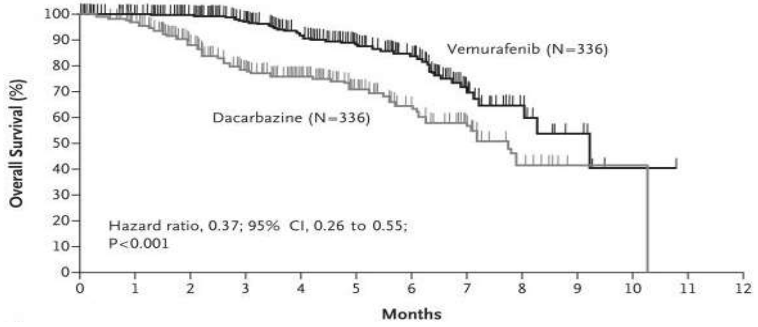
- Triple therapy for BRAF+ patients
- Reverse drug resistance

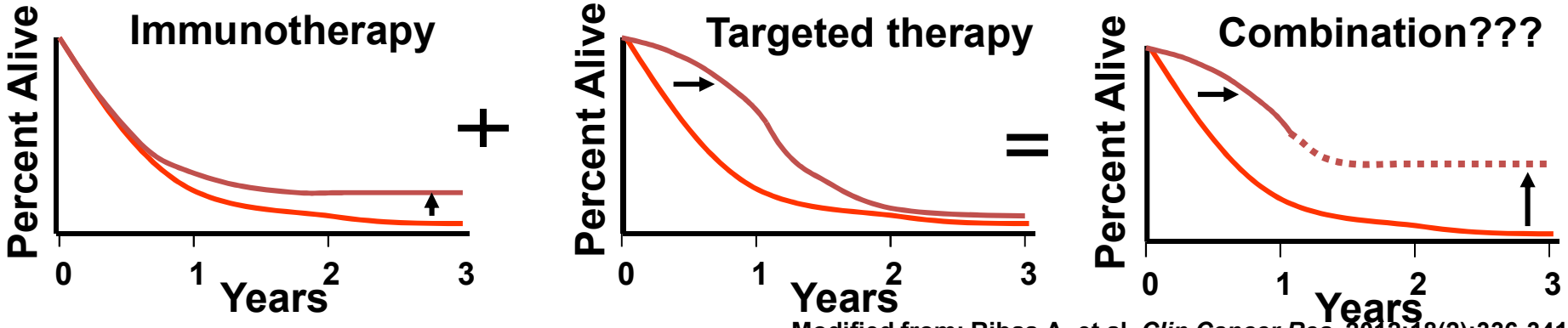
Combining Immunotherapy and Targeted Therapy for Melanoma?

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



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



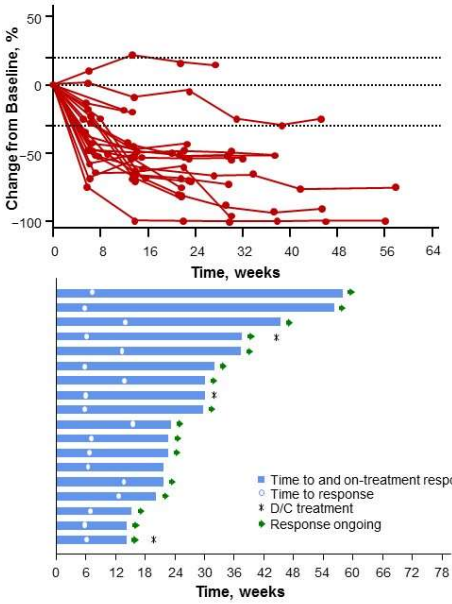


Modified from: Ribas A, et al. *Clin Cancer Res*. 2012;18(2):336-341.

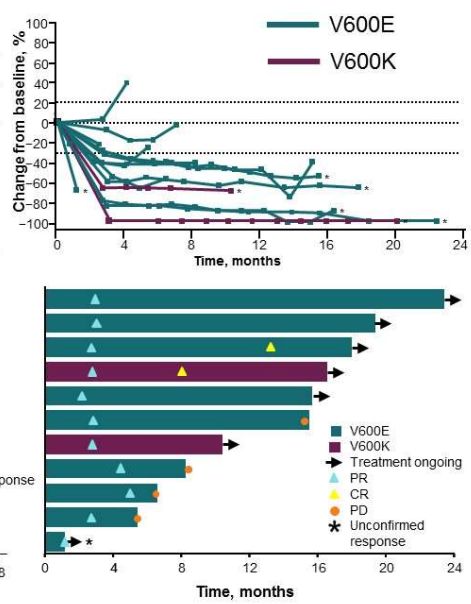
1. Hodi FS, et al. *N Engl J Med*. 2010;363(8):711-723. 2. Chapman PB, et al. *N Engl J Med*. 2011;364(26):2507-2516.

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

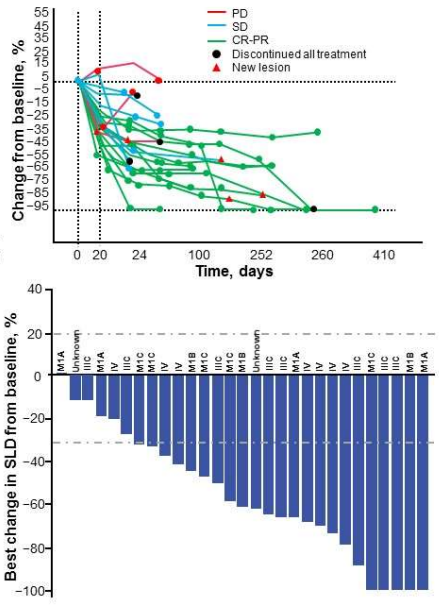
Dabrafenib + trametinib + durvalumab[1]



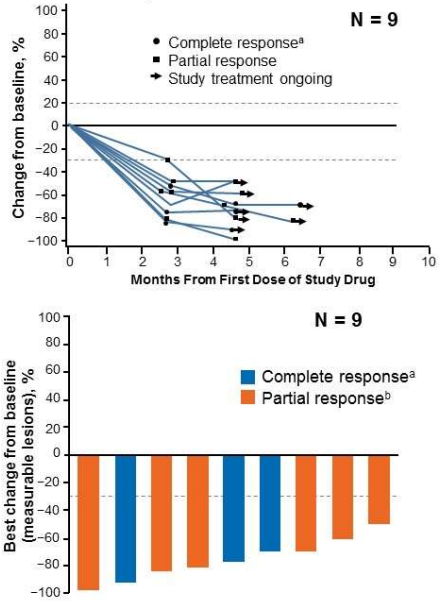
Dabrafenib + trametinib + pembrolizumab[2,3]



Vemurafenib + cobimetinib + atezolizumab[4]



Dabrafenib + trametinib + spartalizumab[5]

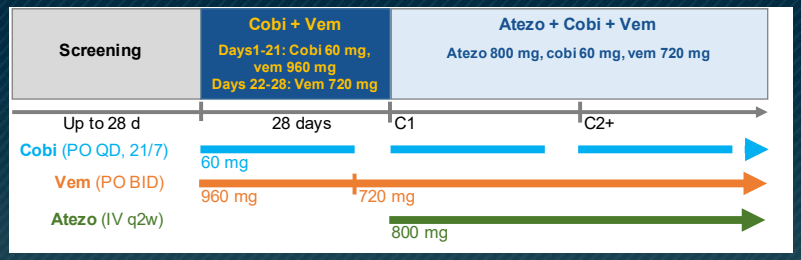


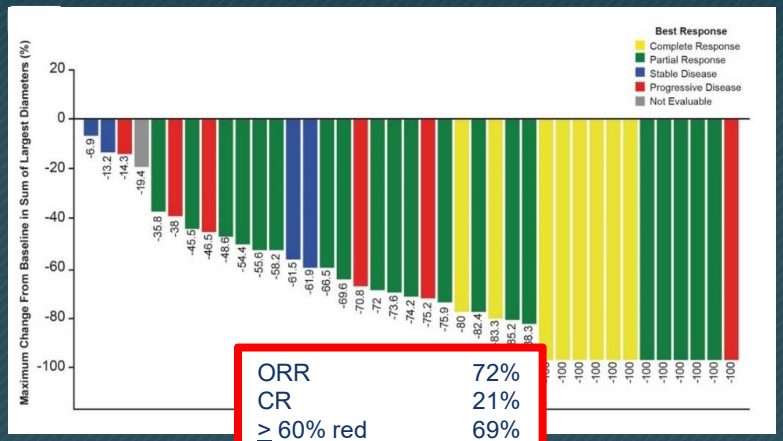
BID, twice daily; CR, complete response; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease. [a] Patients with CR and < 100% change in sum of diameters (SOD) have (a) 100% change for non-nodal target lesions and all nodal target lesions are < 10 mm and (b) CR for nontarget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

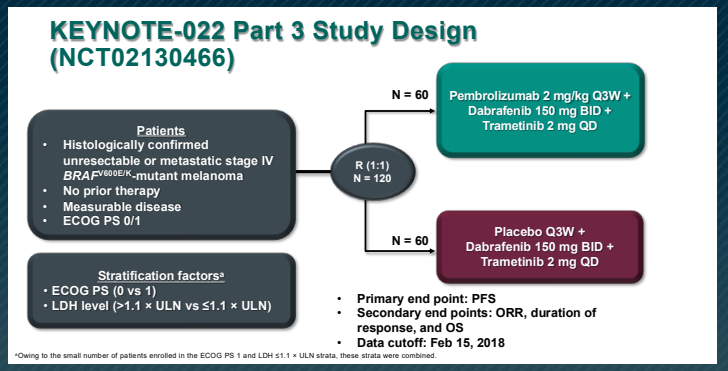
PRESENTED BY R DUMMER AT AACR 2018

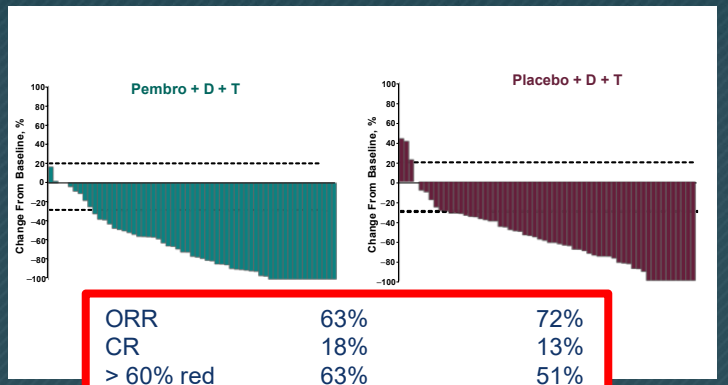
Courtesy of Dr Dummer





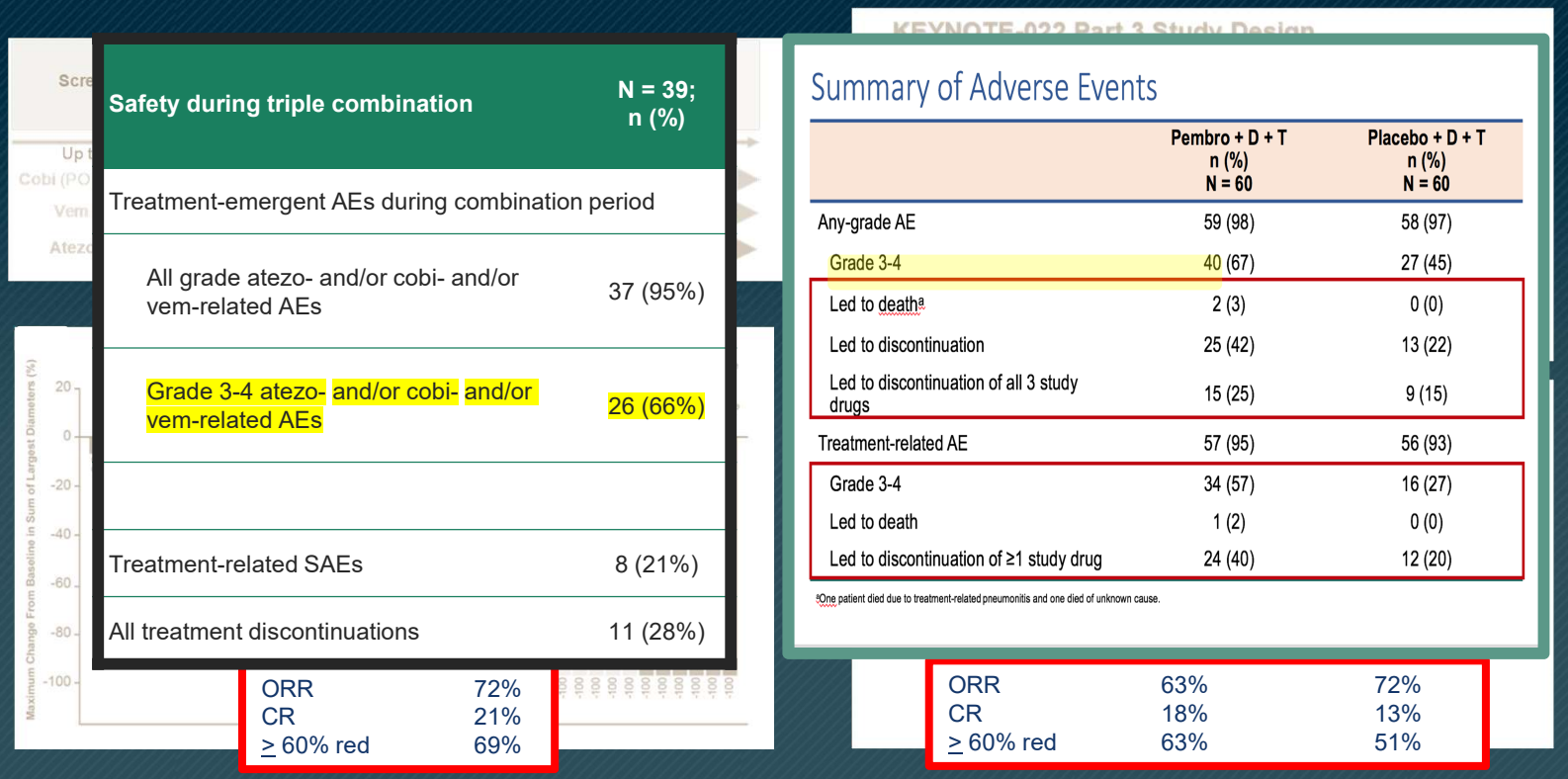
ORR	72%
CR	21%
≥ 60% red	69%





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

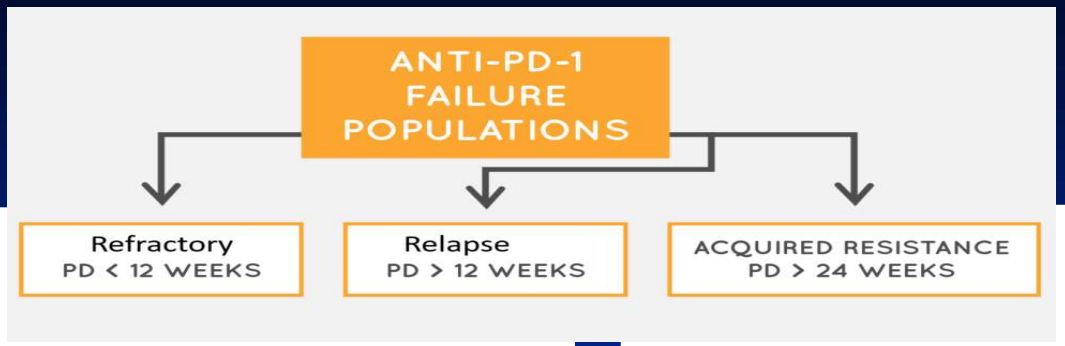


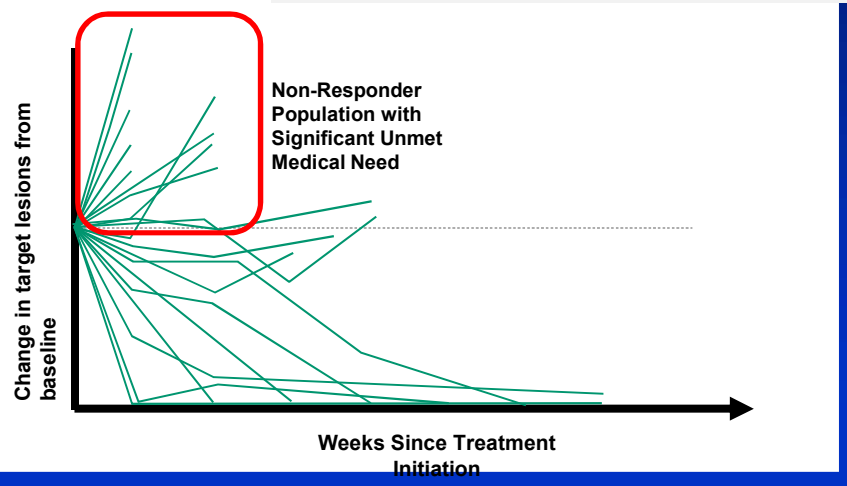
Ryan J. Sullivan.
1. Sullivan et al. *ASCO* 2017; in press
2. Ascierto et al. *ESMO* 2019; in press

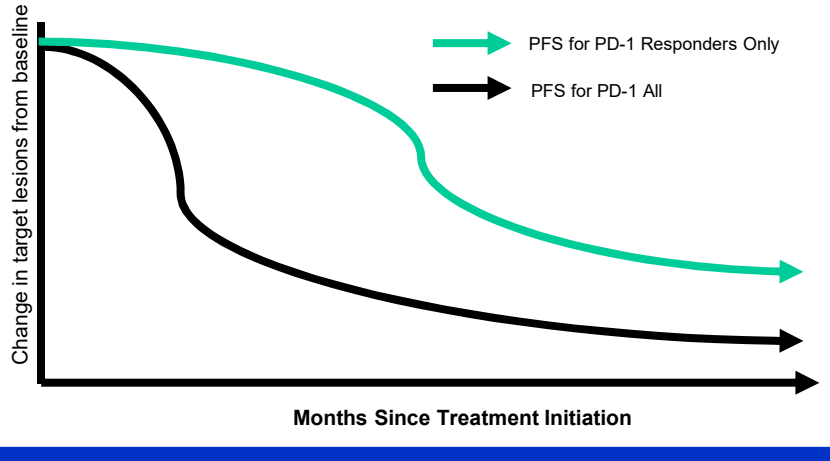
The Future

- Triple therapy for BRAF+ patients
- Reverse drug resistance

Anatomy of Anti-PD-1 Failures in Melanoma



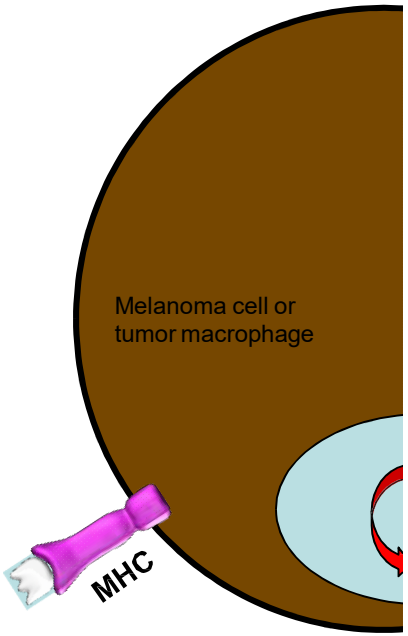


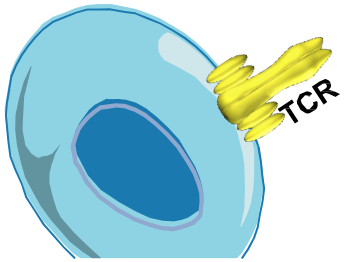


Figures adapted from Topalian et al.(April 2014), 32(10); 1020-1030

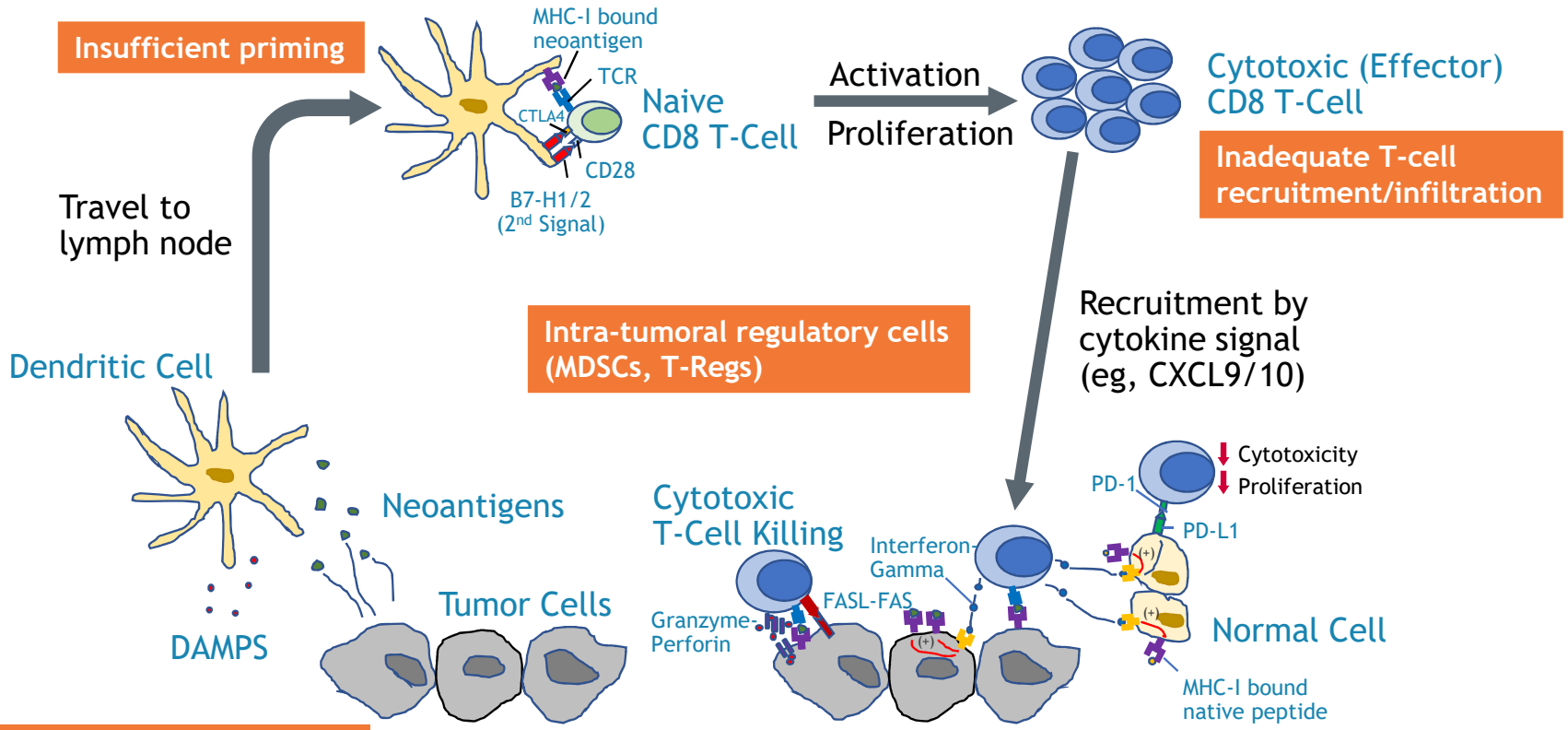
Primary resistance to PD-1 blockade therapy

- Primary resistance by low T cell infiltration and lack of PD-1:PD-L1 interactions in the tumor (Tumeh *et al*. Nature 2014)
- Low tumor immunogenicity (Rizvi *et al*. Science 2015)
- T cell exclusion from tumors (Spranger *et al*. Science 2015)
- Low IFN-g signaling (Ayers *et al*. J Clin Inv 2017)



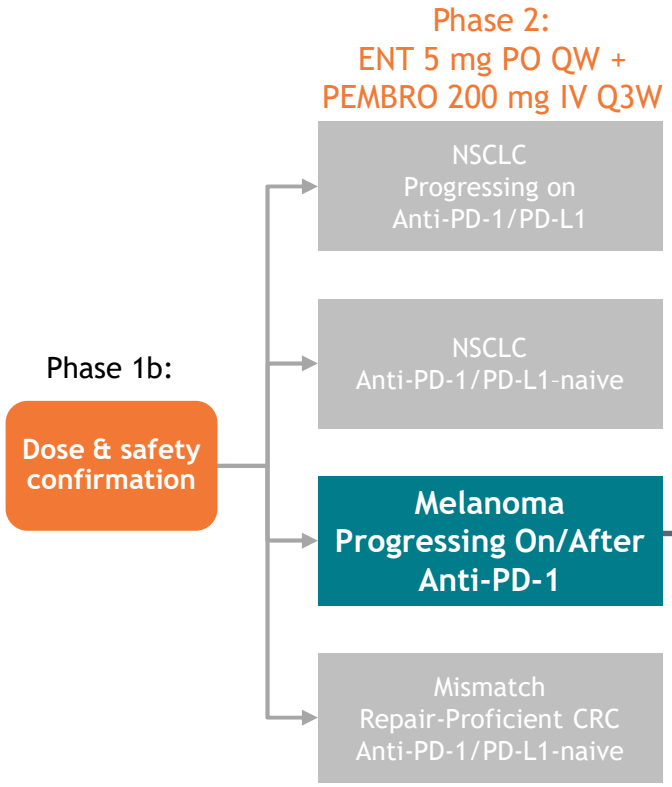


Secondary Resistance: Why Does Therapy Fail?



Liu D, Jenkins RW, Sullivan RJ. *Am J Clin Dermatol*. 2019;20(1):41-54.

ENCORE-601: Open-Label Study Evaluating ENT + PEMBRO in Patients With Recurrent or Metastatic Melanoma and Prior Progression On or After Anti-PD-1 Therapy



Inclusion Criteria:

- Recurrent or metastatic melanoma, measurable by RECIST 1.1
- Prior progression on or after anti-PD-(L)1 treatment
- Prior BRAF treatment if indicated
- ECOG Performance Status < 2
- Willingness to participate in baseline and on-treatment biopsy and blood samples

Primary Endpoint

- ORR (irRECIST)

Secondary Endpoints

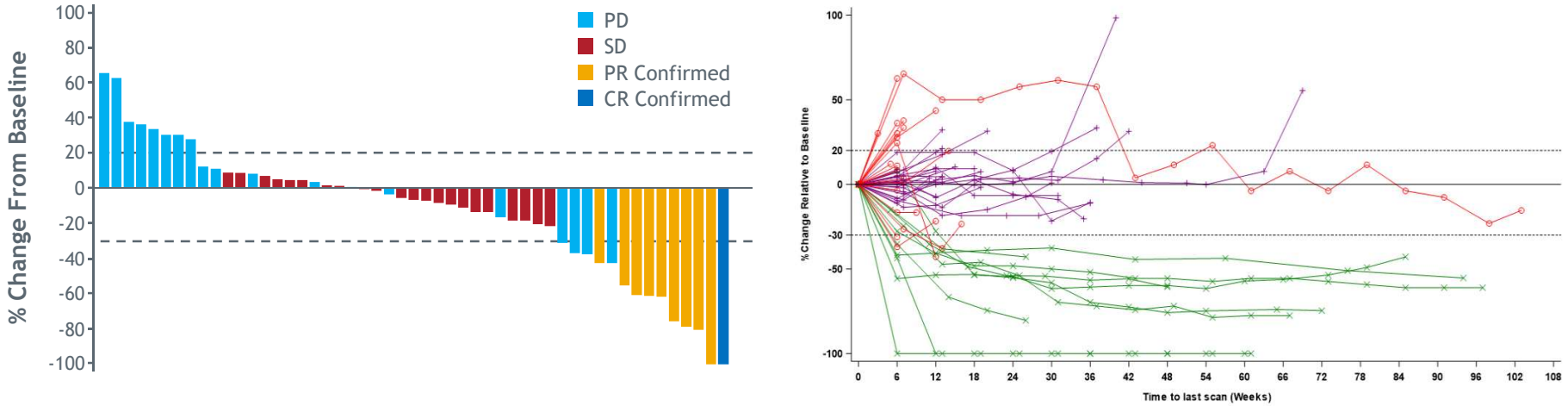
- CBR, PFS, OS, safety & tolerability

53 patients enrolled, last patient enrolled April 2018

Sullivan R, …….Agarwala, SS AACR 2019

CBR, clinical benefit rate; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; ENT, entinostat; irRECIST, immune-related Response Evaluation Criteria in Solid Tumors; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PEMBRO, pembrolizumab; PFS, progression-free survival; PO, orally; QW, once a week; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Change in Tumor Volume and Change in Tumor Volume Over Time per irRECIST in ENCORE-601

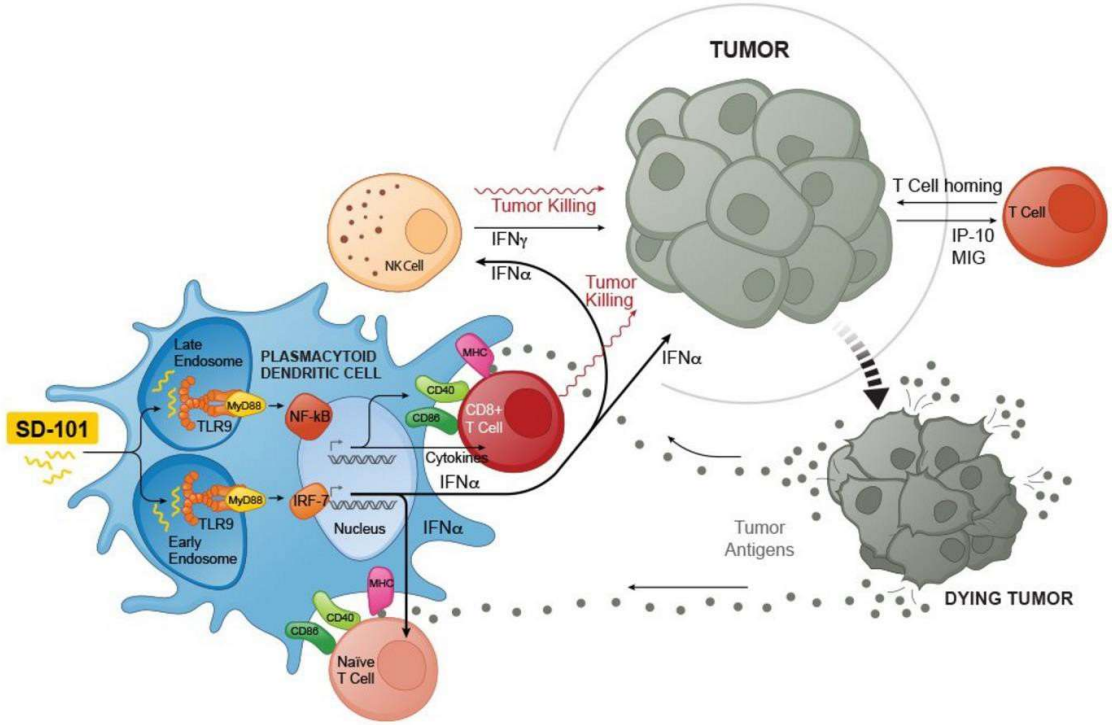


- 10 confirmed responses of 53 treated [19% ORR (95% CI: 9%-32%)]
  - 1 CR, 9 PRs
- Median duration of response: 13 months (range 3-20)
  - 4 responders ongoing
- An additional 9 patients have had SD for >6 months
  - 36% CBR (95% CI: 23%-50%)

Sullivan R, …….Agarwala, SS, AACR 2019

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; irRECIST, immune-related Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Intratumoral TLR9-agonist to reverse resistance to anti-PD-1



Graphic form Dynavax

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
- Reversing drug resistance is the area of major unmet need – clinical trials ongoing

Cancer Expert Now (CEN) Network

How Does it Work?

Text-based and live video mobile platforms connect international doctors with leading experts

Nm

Noetic Messenger:
A text-based platform

- Submit questions and patient cases by texting with top experts anytime, anywhere.
- Algorithm automatically identifies the best faculty to respond based on the disease type
- Like text messaging, but completely secure
- Average response time is 14 hours

NL

Noetic Live:
A live video- or teleconference

- Securely connects doctors with CEN experts using tele-video.
- Live, personalized discussion
- HIPAA compliant, proprietary system
- Scheduling system conveniently identifies available times and dates