Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

Cutaneous Melanoma Webinar

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Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES Open Access

An update on the Society for Immunotherapy of Cancer consensus statement on tumor immunotherapy for the treatment of cutaneous melanoma: version 2.0

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Webinar Agenda

6:00–6:05 p.m. EDT	Welcome and Introductions
6:05–6:40 p.m. EDT	Review of SITC Cancer Immunotherapy Guideline – Cutaneous Melanoma 2.0
6:40–6:55 p.m. EDT	Question and Answer Session
6:55–7:00 p.m. EDT	Closing Remarks

To Submit a Question

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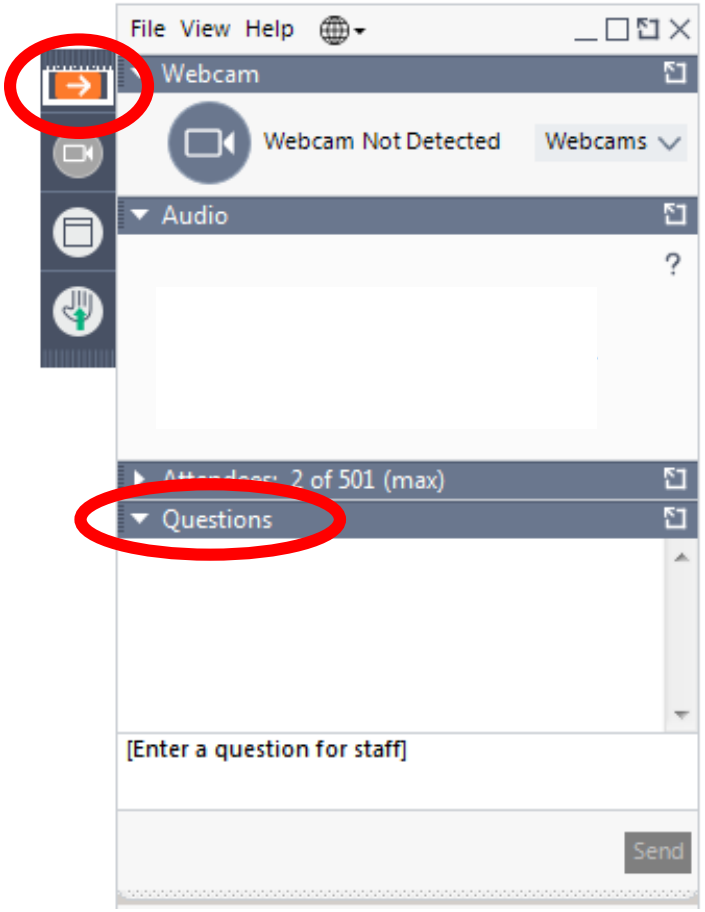

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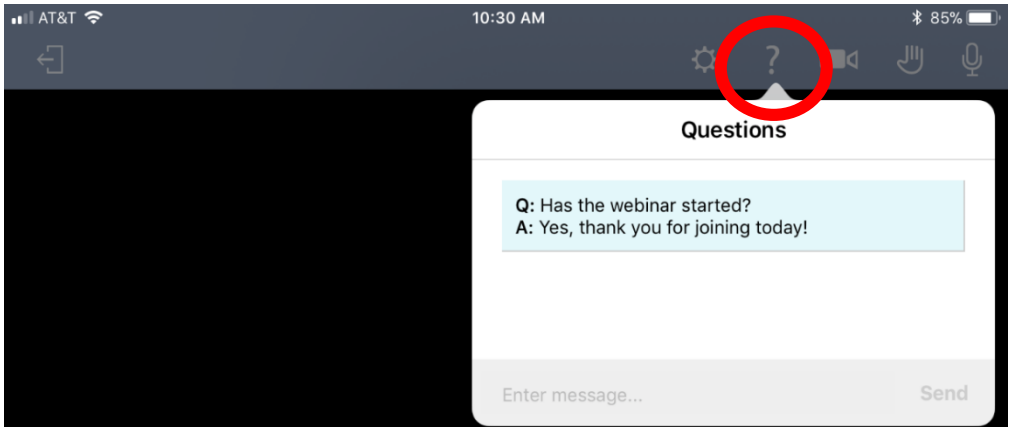

Advances in Immunotherapy for Melanoma

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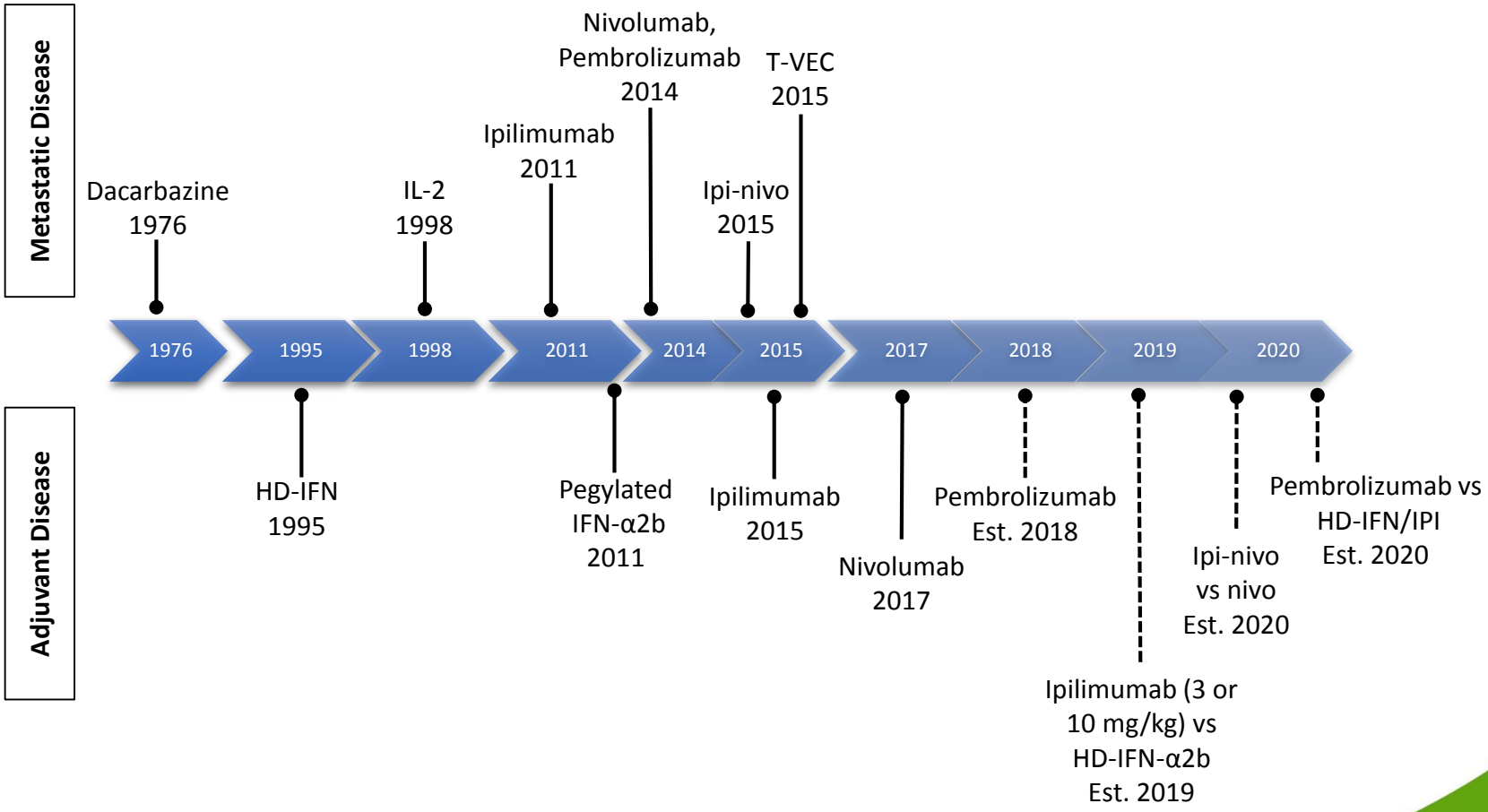

FDA, US Food and Drug Administration
1 . Kirkwood JM, et al. *J Clin Oncol*, 1996;14(1)1996:7-17; 2. Herndon TM, et al. *Oncologist.* 2012;17(10):1323–1328. 4. US FDA. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm469944.htm. Accessed September 8, 2016; 5. ESMO 2017 6. Merck Press Release

Changes in AJCC Staging for Melanoma

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Change	Summary of Change
Determinants of Primary Tumor (T) Status	1. Tumor thickness measured to the nearest 0.1 mm 2. Definitions of T1a and T1b have been revised a. T1a melanomas include those <0.8 mm without ulceration b. T1b melanomas include those 0.8-1 mm with or without ulceration and those <0.8 mm with ulceration 3. Mitotic rate is no longer a T1 category criterion but should be documented for all invasive primary melanomas
Determinants of Regional Lymph Node (N) Status	1. The presence or absence of non-nodal regional metastases (i.e., microsatellites, satellites or in-transit metastases) is categorized in the N-category criterion based upon the number (if any) of tumor-involved regional lymph nodes
AJCC Prognostic Stage III Groups	1. Stage III groupings have been redefined and increased from three to four subgroups, with the addition of a stage IIID subgroup 2. Stage III disease is associated with heterogeneous outcomes; five-year melanoma-specific survival rates range from 93 percent for stage IIIA disease to 32 percent for stage IIID disease
Definition of Distant Metastasis (M)	1. A new M1d designation for metastases involving the CNS has been created. 2. M1c no longer includes CNS metastasis. 3. Although an elevated lactate dehydrogenase (LDH) is no longer an M1c criterion, LDH remains an important predictor of survival in stage IV and is now recorded for any M1 anatomic site of disease.

AJCC Staging for Melanoma – 8th Edition

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T CLASSIFICATION	THICKNESS (mm)	ULCERATION STATUS
T1	≤1.0	a: Breslow < 0.8 mm w/o ulceration b: Breslow 0.8-1.0 mm w/o ulceration or ≤ 1.0 mm w/ ulceration.
T2	1.1-2.0	a: w/o ulceration b: w/ ulceration
T3	2.1-4.0	a: w/o ulceration b: w/ ulceration
T4	>4.0	a: w/o ulceration b: w/ ulceration

N CLASSIFICATION	# NODES	CLINICAL DETECTABILITY/MSI STATUS
N1	0-1 node	a: clinically occult[1], no MSI[2] b: clinically detected[1], no MSI[2] c: 0 nodes, MSI present[2]
N2	1-3 nodes	a: 2-3 nodes clinically occult[1], no MSI[2] b: 2-3 nodes clinically detected[1], no MSI[2] c: 1 node clinical or occult[1], MSI present[2]
N3	>1 nodes	a: >3 nodes, all clinically occult[1], no MSI[2] b: >3 nodes, ≥1 clinically detected[1] or matted, no MSI[2] c: >1 nodes clinical or occult[1], MSI present[2]

ANATOMIC STAGE/PROGNOSTIC GROUPS							
Clinical Staging[3]				Pathologic Staging[4]			
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b	..	..		T1b	..	..
	T2a	..	..	IB	T2a	..	..
Stage IIA	T2b	N0	M0	IIA	T2b	M0	M0
	T3a	..	..		T2a	..	..
Stage IIB	T3b	..	..	IIB	T3b	..	..
	T4a	..	..		T4a	..	..
Stage IIC	T4b	..	..	IIC	T4b	..	..
Stage III	Any T	≥N1	M0	IIIA	T1-2a	N1a	M0
	..	..	..		T1-2a	N2a	..
	..	..	..	IIIB	T0	N1b-c	M0
	..	..	..		T1-2a	N1b-c	..
	..	..	..		T1-2a	N2b	..
	..	..	..		T2b-3a	N1a-2b	..
	..	..	..	IIIC	T0	N2b-c	M0
	..	..	..		T0	N3b-c	..
	..	..	..		T1a-3a	N2c-3c	..
	..	..	..		T3b-4a	Any N	..
	..	..	..		T4b	N1a-2c	..
	..	..	..	IIID	T4b	N3a-c	M0
Stage IV	Any N	Any N	M1	IV	Any T	Any N	M1

Recommendations for Stage II Patients

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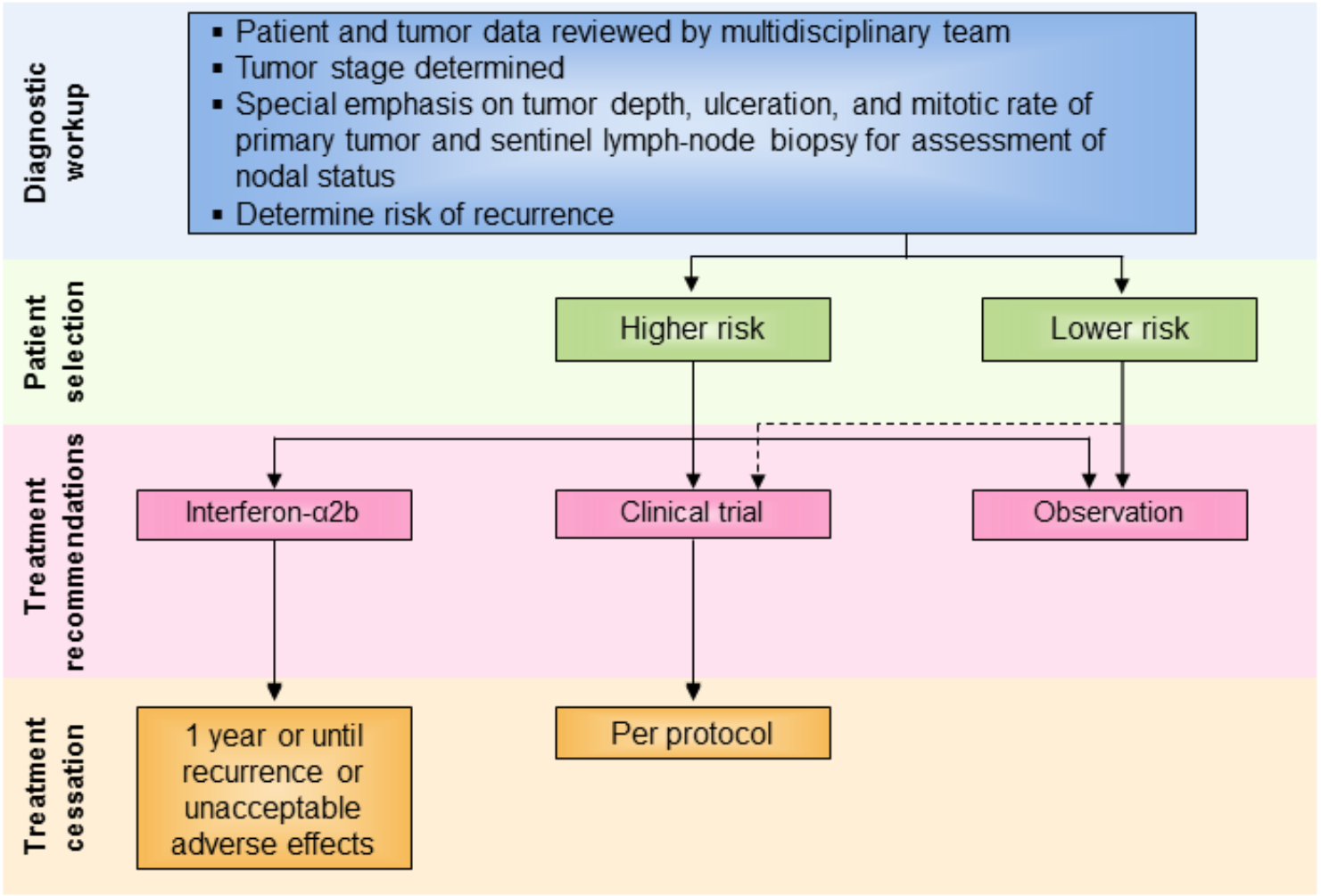
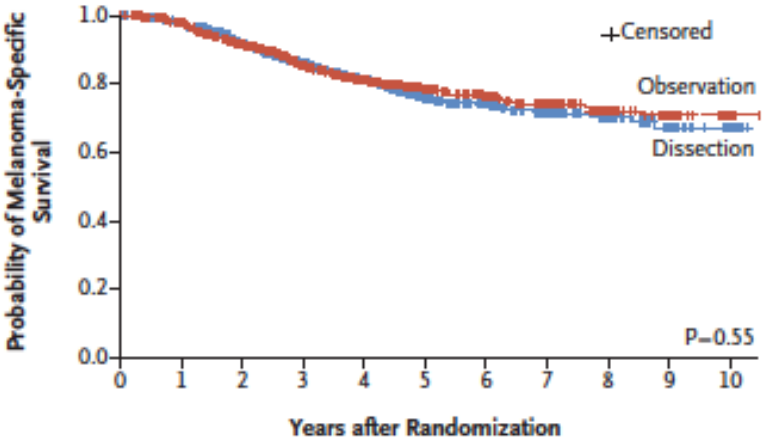
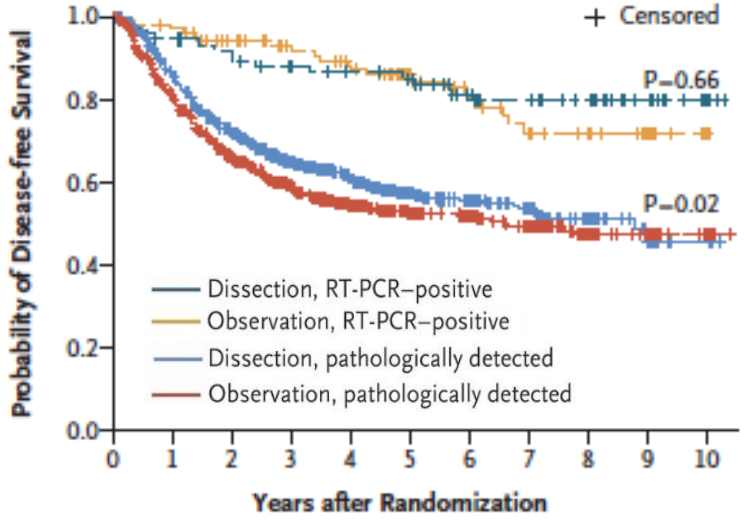


Emerging Data Concerning Surgery





- Multicenter Selective Lymphadenectomy Trial-II (MSLT-II)
  - 1934 patients enrolled
  - Similar Melanoma-specific survival between CLND/noCLND cohorts
  - Improved disease-free survival with CLN dissection

Faries et al. NEJM 2017

Adjuvant Ipilimumab in Stage III Melanoma

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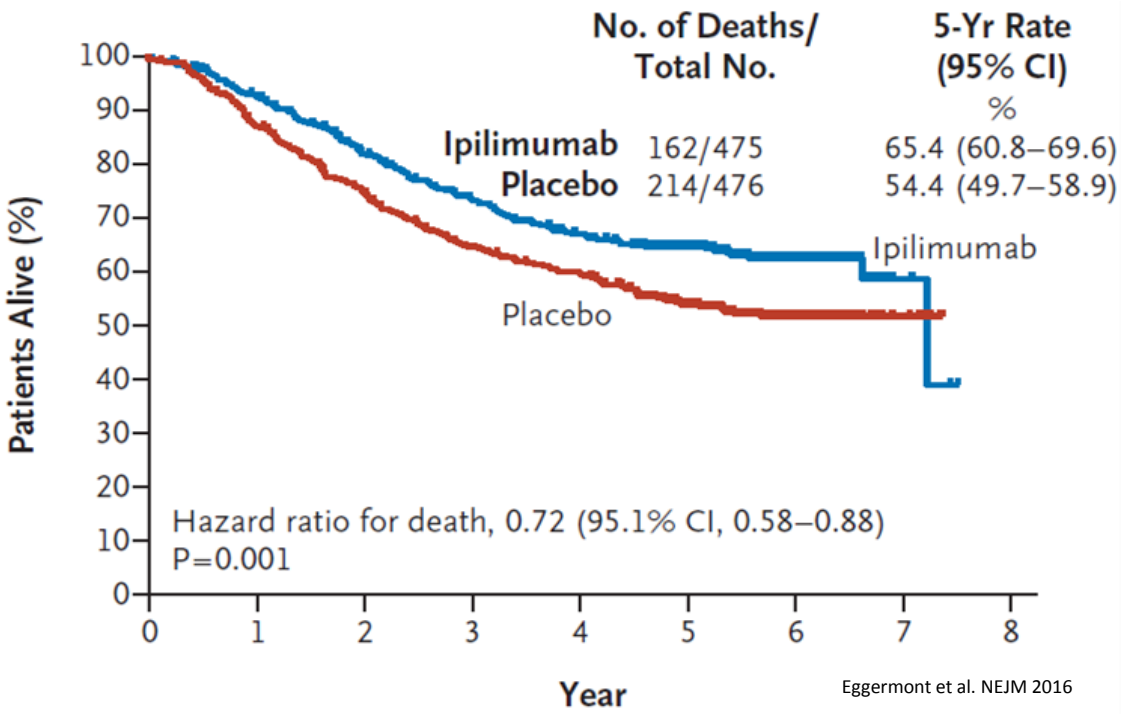
- EORTC 18071 phase III trial
  - Anti-CTLA-4 mAb ipilimumab (10 mg/kg)
  - Placebo



Eggermont et al. NEJM 2016

Adjuvant Nivolumab vs Ipilimumab in Stage III Melanoma

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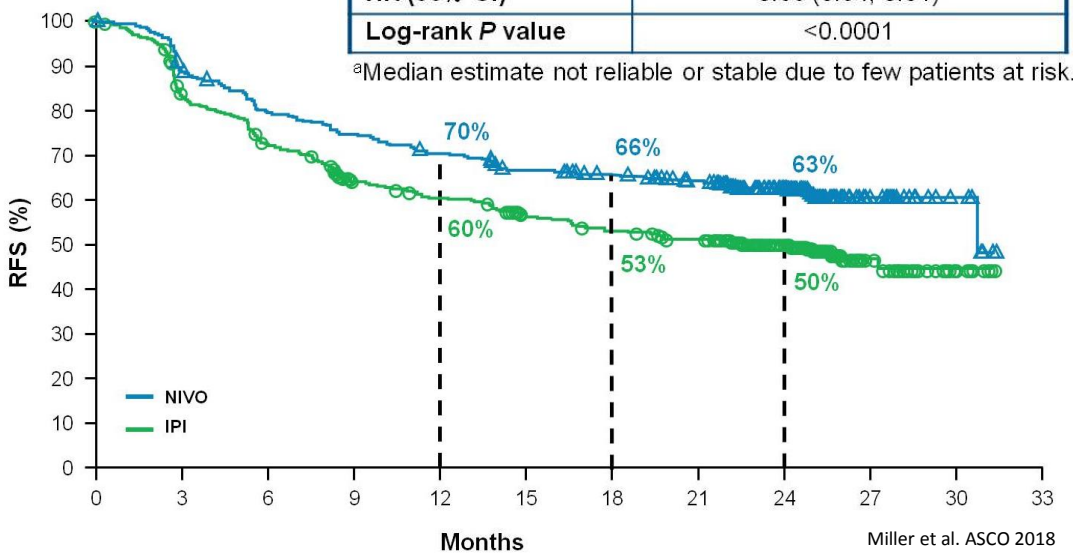
- CheckMate 238 Phase III trial
  - Anti-PD-1 mAb nivolumab (3mg/kg Q2W for up to 1 year
  - Anti-CTLA-4 mAb ipilimumab (10mg/kg Q3W for four doses, then every 3 months for up to 1 year

	NIVO	IPI
Events/patients	171/453	221/453
Median (95% CI)	30.8 (30.8, NR)[a]	24.1 (16.6, NR)
HR (95% CI)	0.66 (0.54, 0.81)	
Log-rank *P* value	<0.0001	

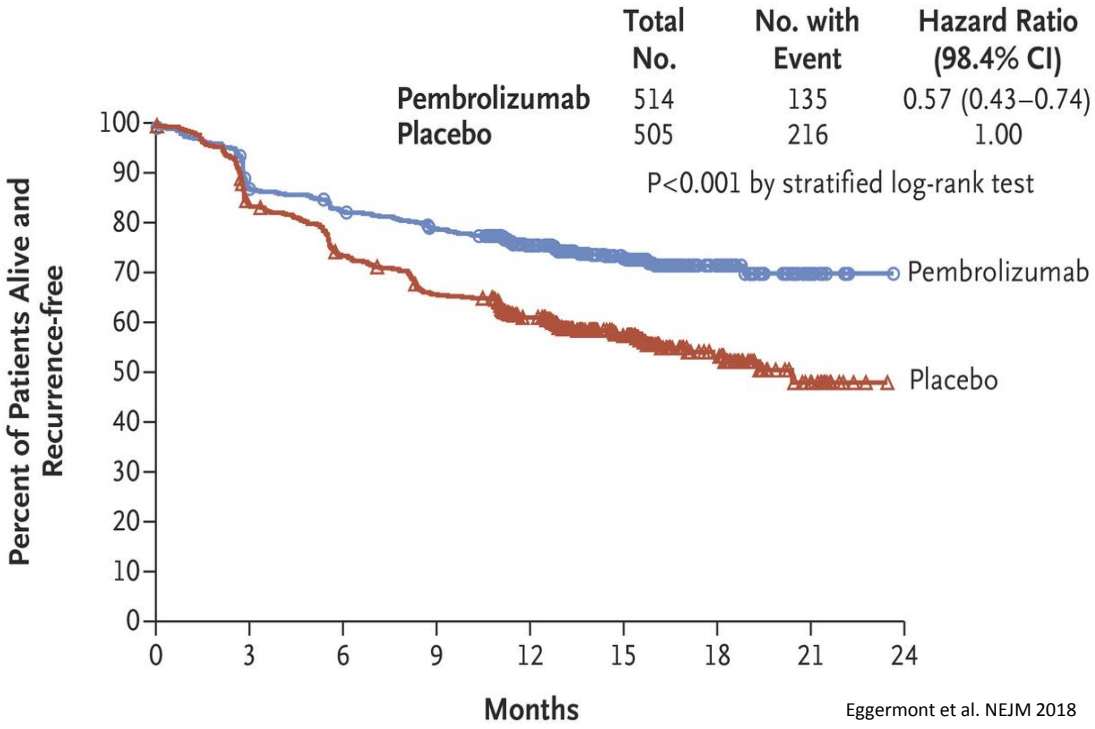
[a]Median estimate not reliable or stable due to few patients at risk.



Miller et al. ASCO 2018

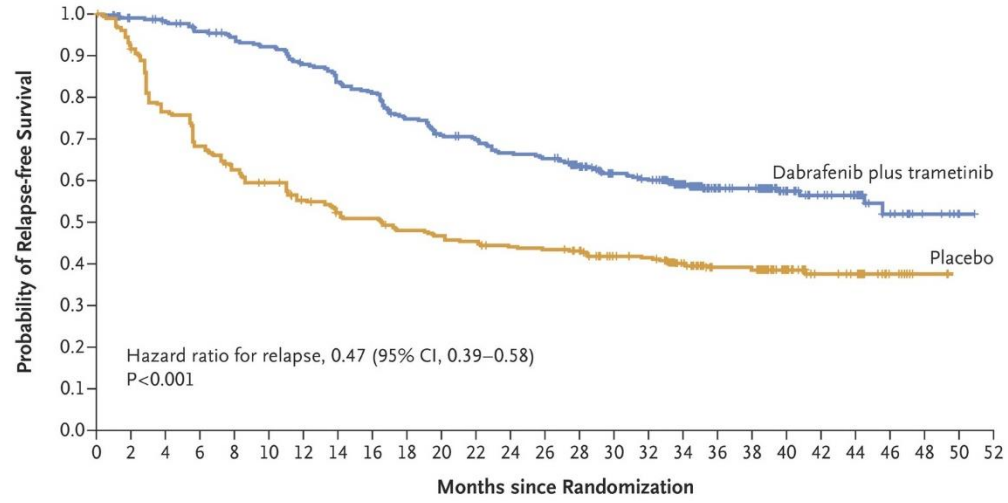
Adjuvant Pembrolizumab in Stage III Melanoma

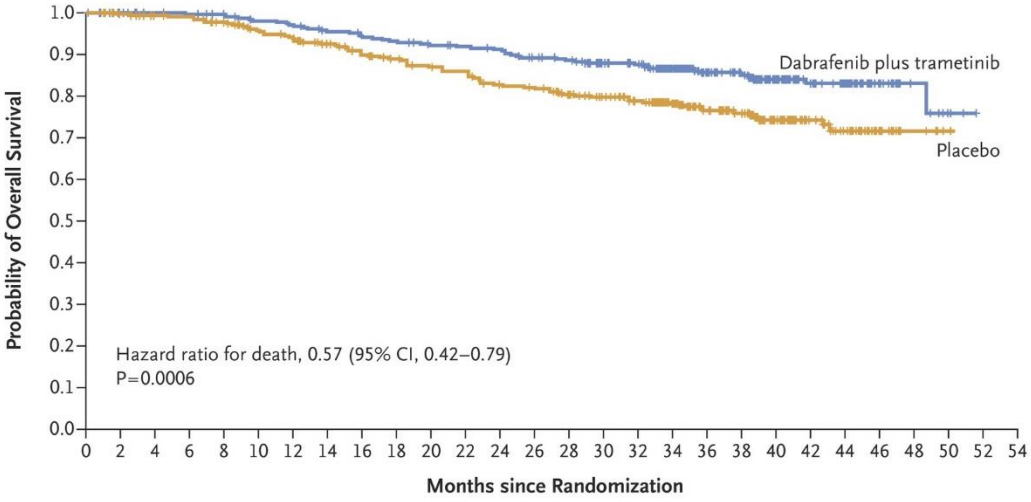
- EORTC 1325/KEYNOTE-054 phase III trial
  - Anti-PD-1 mAb pembrolizumab (Q3W for up to 1 year)
  - Placebo



Eggermont et al. NEJM 2018

Adjuvant Dabrafenib + Trametinib in Stage III *BRAF*-mutated Melanoma





- COMBI-AD phase III trial
  - BRAF V600K or V600E patients
  - BRAF inhibitor dabrafenib (150mg twice daily) + MEK inhibitor trametinib (2mg once daily) for one year
  - Placebo

Long et al. NEJM 2017

Adjuvant Recommendations for Stage IIIA Patients

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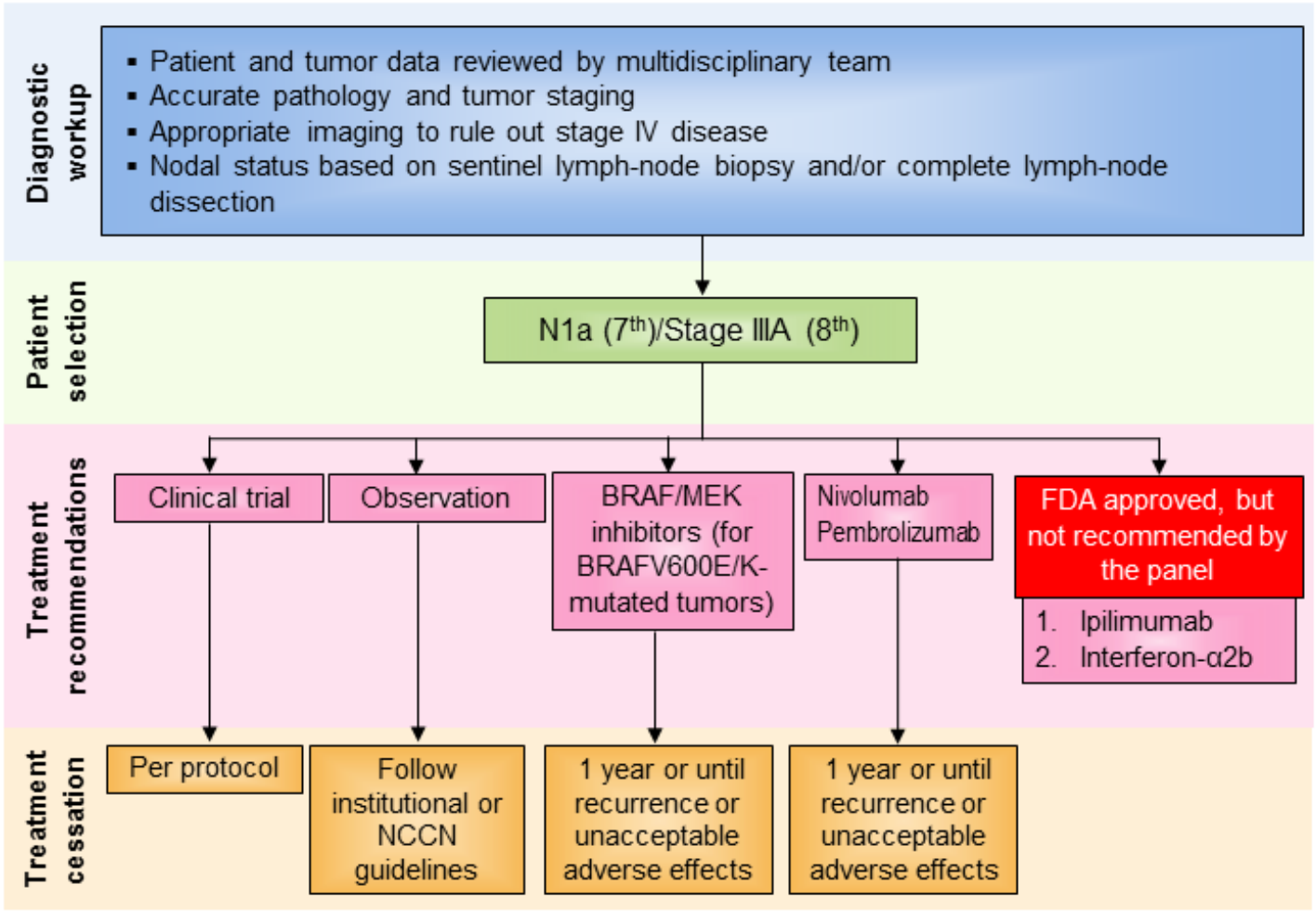

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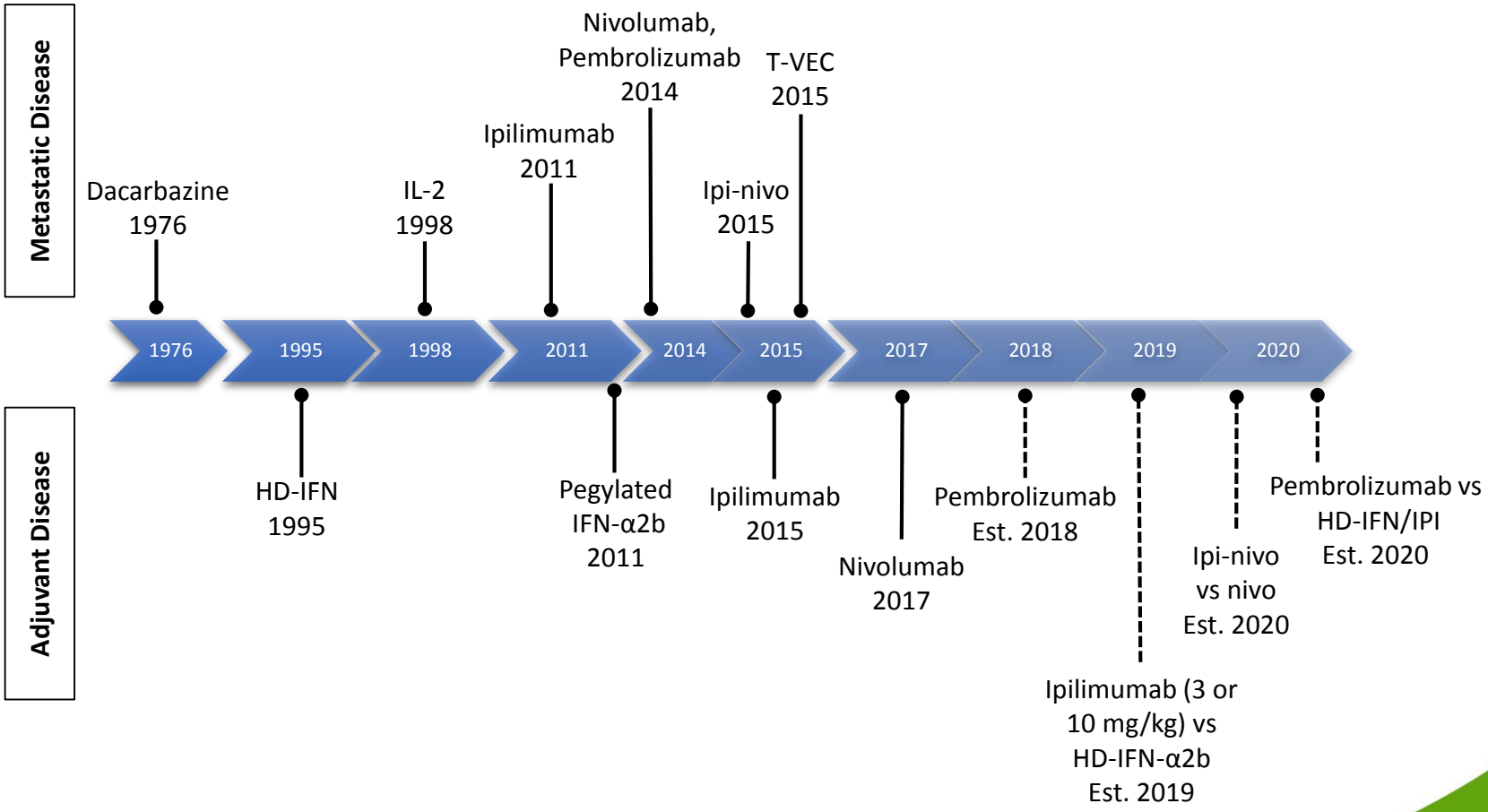

FDA, US Food and Drug Administration
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Adjuvant Recommendations for Stage III N1b, N2-N3 Patients

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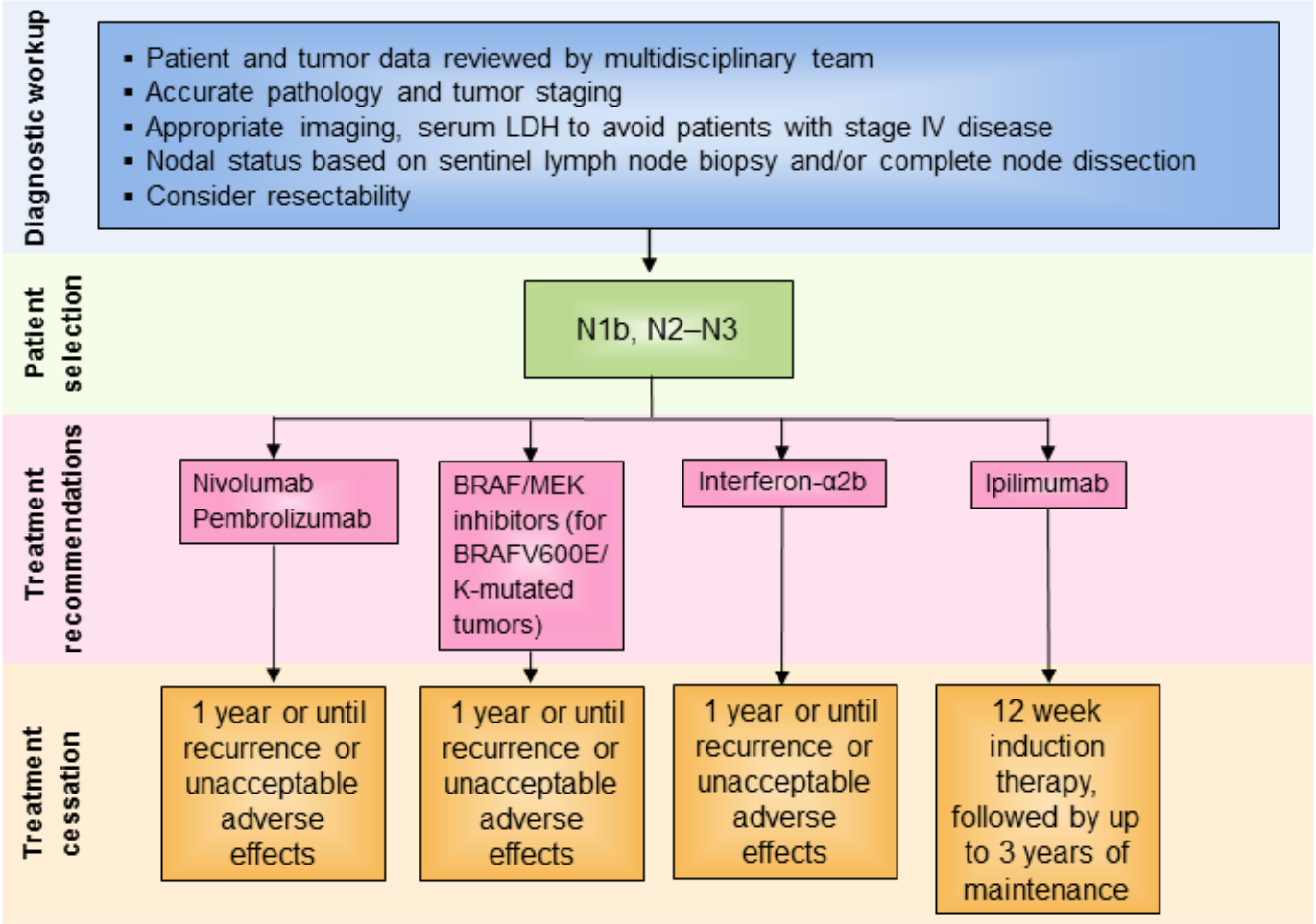

First-line Pembrolizumab vs Ipilimumab in Stage IV Melanoma

Phase III KEYNOTE-006 Trial

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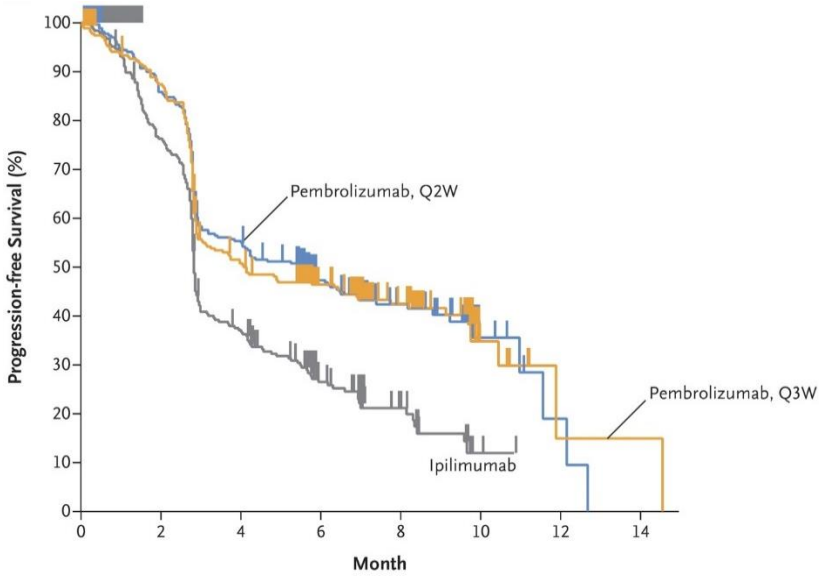

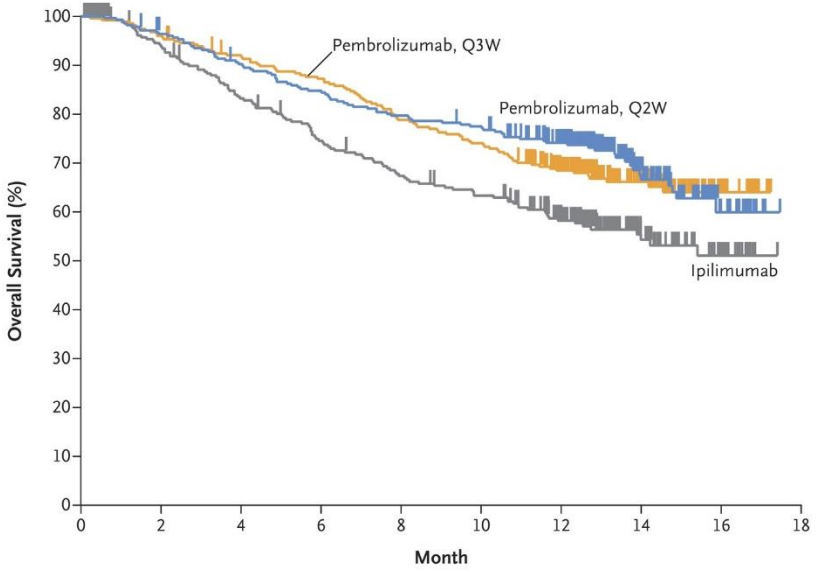

Robert et al. NEJM 2015

First-line Nivolumab & Ipilimumab in Stage IV Melanoma

Phase III CheckMate 067 Trial

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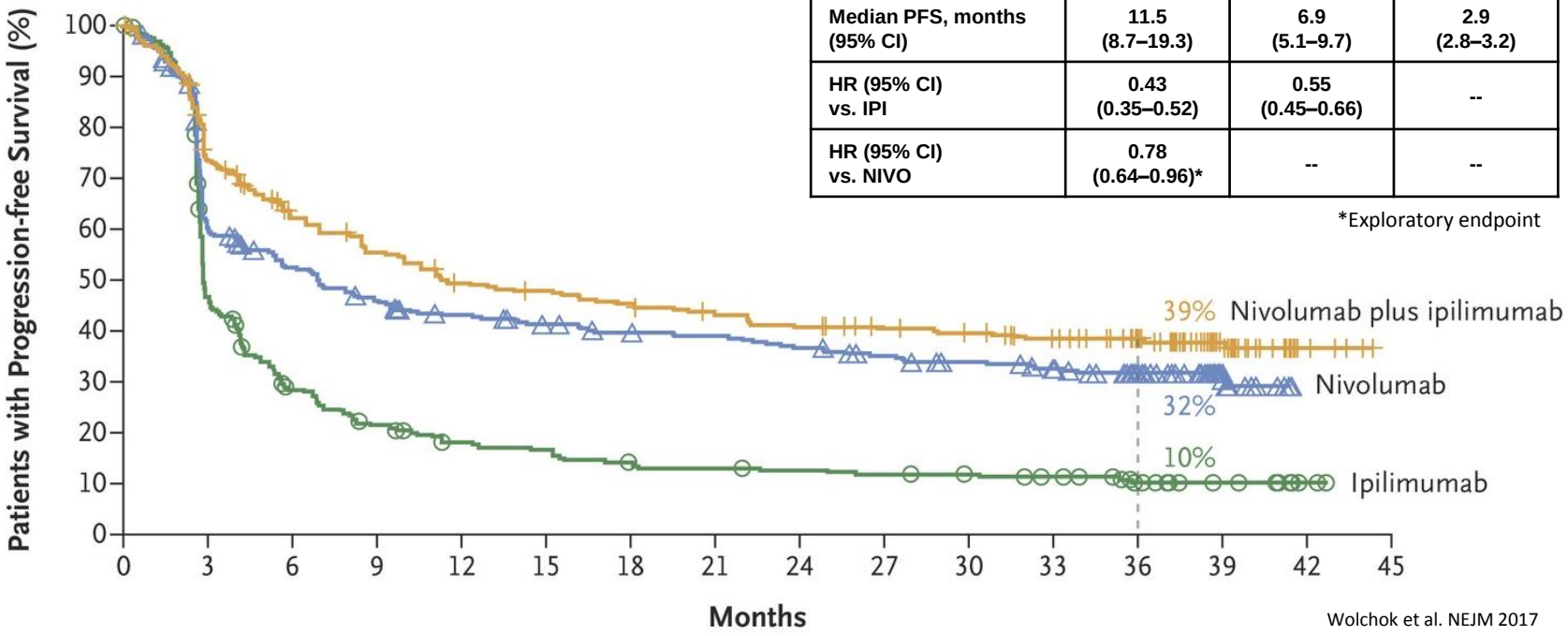
	NIVO+IPI (n=314)	NIVO (n=316)	IPI (n=315)
Median PFS, months (95% CI)	11.5 (8.7–19.3)	6.9 (5.1–9.7)	2.9 (2.8–3.2)
HR (95% CI) vs. IPI	0.43 (0.35–0.52)	0.55 (0.45–0.66)	--
HR (95% CI) vs. NIVO	0.78 (0.64–0.96)*	--	--

*Exploratory endpoint



Wolchok et al. NEJM 2017

First-line Nivolumab & Ipilimumab in Stage IV Melanoma

Phase III CheckMate 067 Trial

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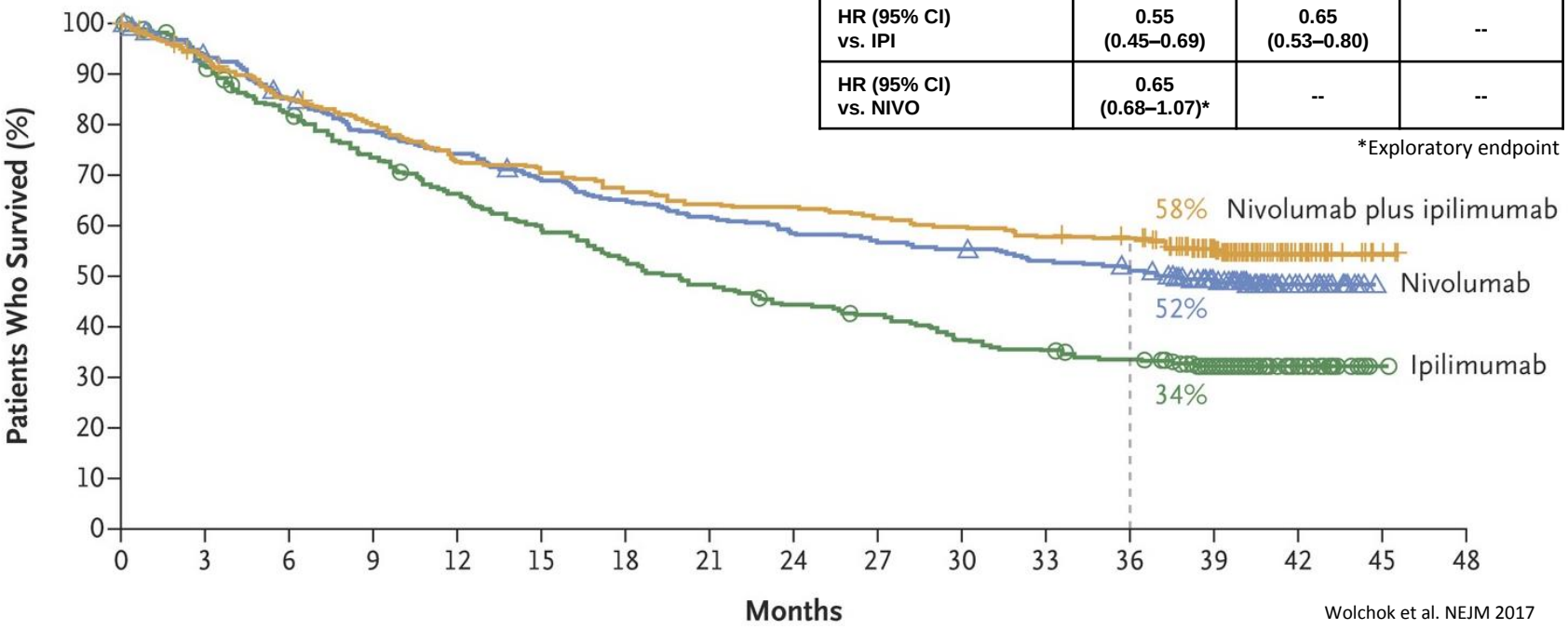
	NIVO+IPI (n=314)	NIVO (n=316)	IPI (n=315)
Median OS, months (95% CI)	NR (38.2–NR)	37.6 (29.1-NR)	19.9 (16.9–24.6)
HR (95% CI) vs. IPI	0.55 (0.45–0.69)	0.65 (0.53–0.80)	--
HR (95% CI) vs. NIVO	0.65 (0.68–1.07)*	--	--

*Exploratory endpoint



Wolchok et al. NEJM 2017

First-line Dabrafenib + Trametinib in Stage IV *BRAF*-mutated Melanoma

Phase III COMBI-d/COMBI-v Trials

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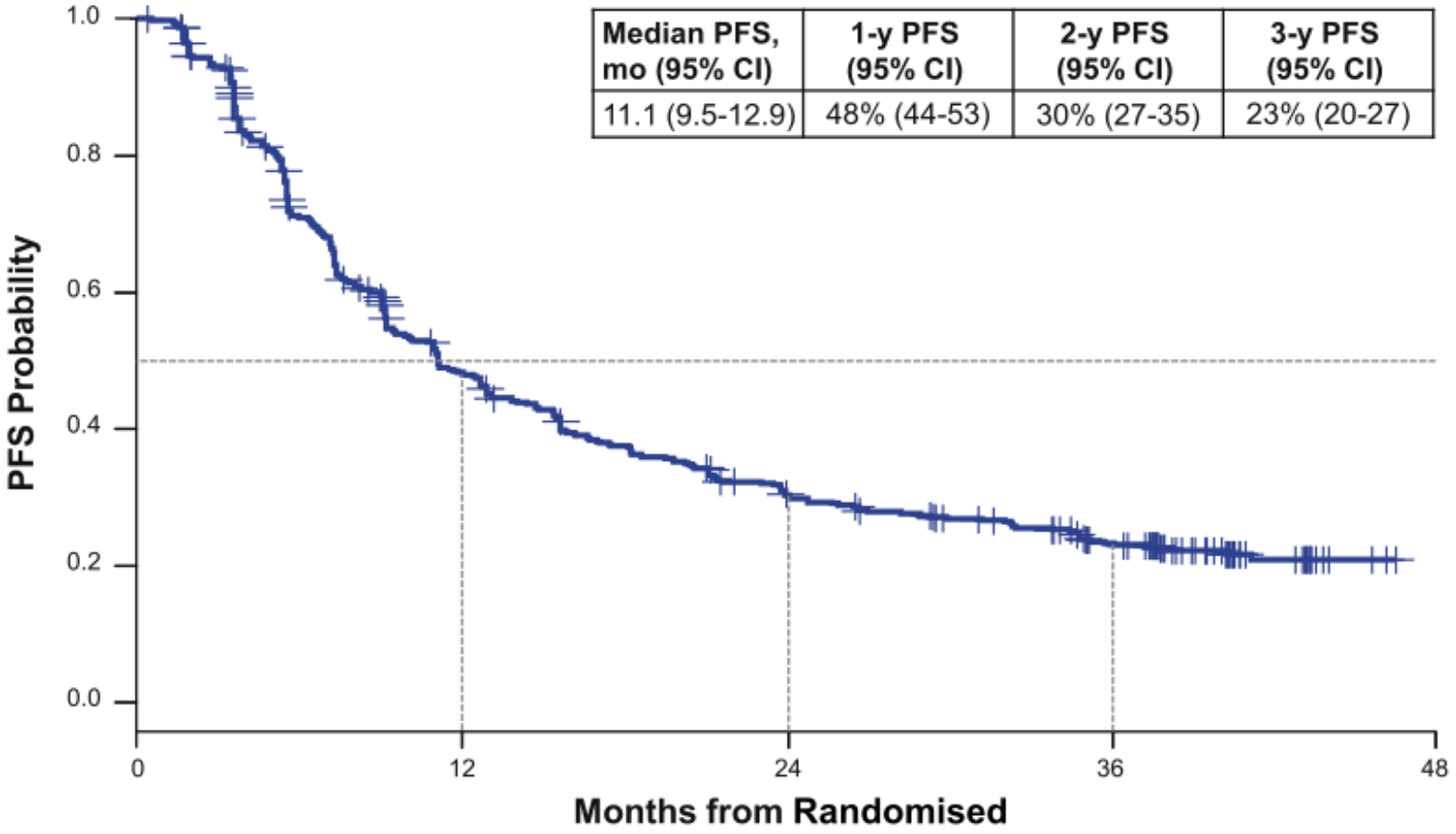
Median PFS, mo (95% CI)	1-y PFS (95% CI)	2-y PFS (95% CI)	3-y PFS (95% CI)
11.1 (9.5-12.9)	48% (44-53)	30% (27-35)	23% (20-27)



Schadendorf et al. Eur. J Canc. 2017

First-line Dabrafenib + Trametinib in Stage IV *BRAF*-mutated Melanoma

Phase III COMBI-d/COMBI-v Trials

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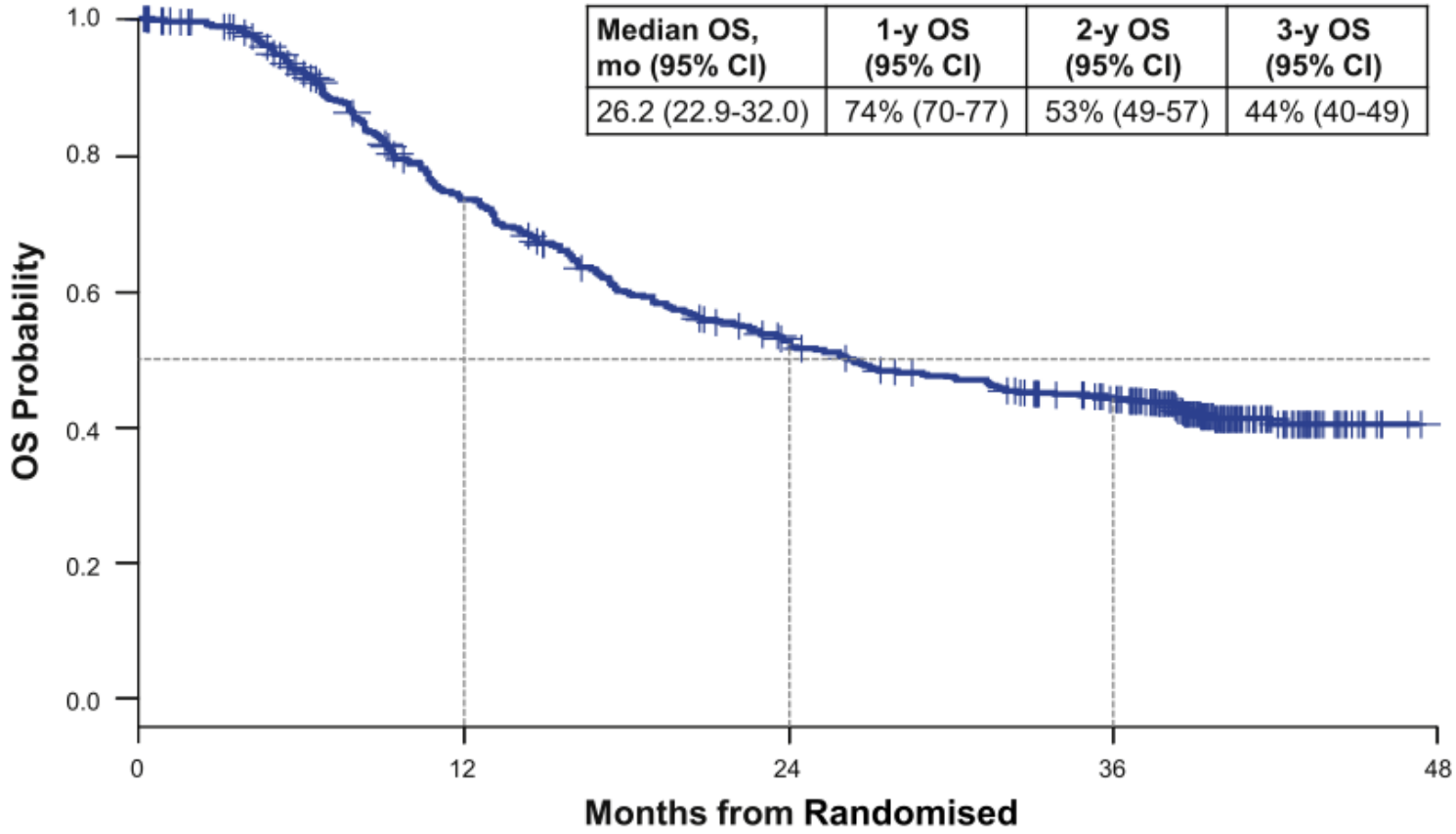
Median OS, mo (95% CI)	1-y OS (95% CI)	2-y OS (95% CI)	3-y OS (95% CI)
26.2 (22.9-32.0)	74% (70-77)	53% (49-57)	44% (40-49)



Schadendorf et al. Eur. J Canc. 2017

First-line Nivolumab & Ipilimumab in *BRAF*+/- Stage IV Melanoma

Phase III CheckMate 067 Trial

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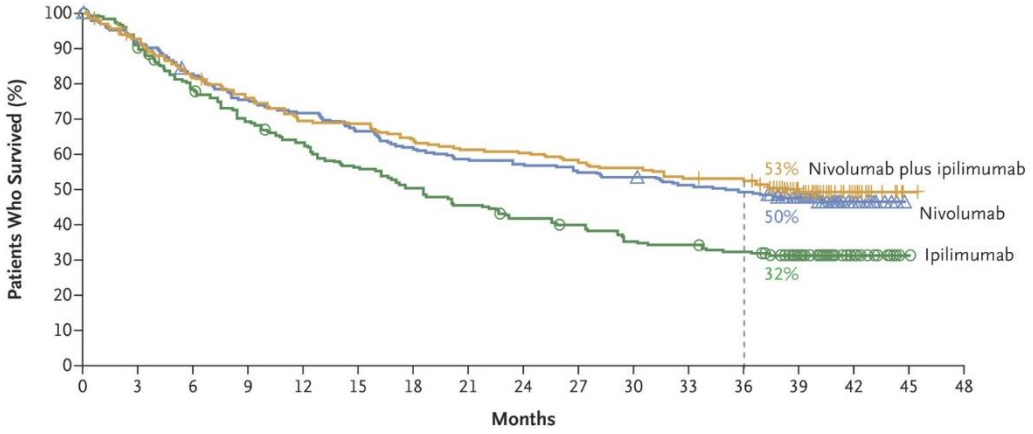
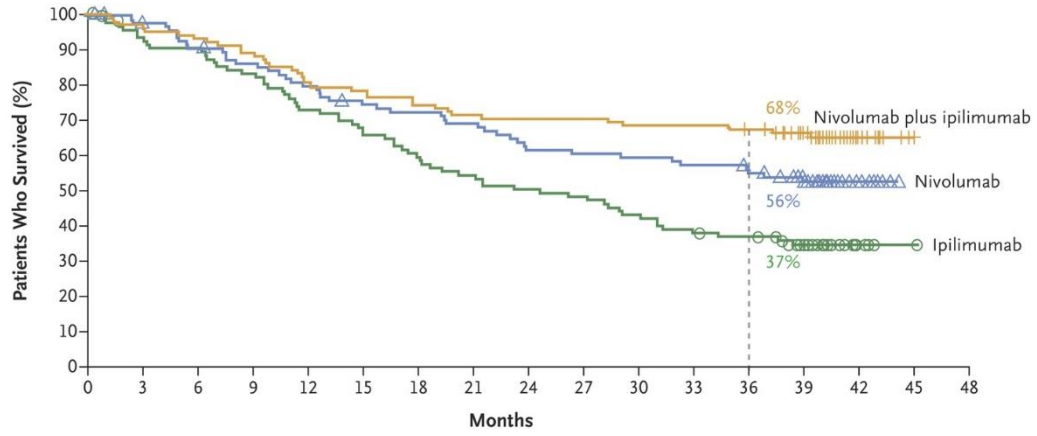


BRAF Wild-type

	NIVO+IPI	NIVO	IPI
Median, mo (95% CI)	39.1 (27.6 –NR)	35.8 (25.8–NR)	18.5 (14.1–22.7)
HR vs NIVO	0.94	--	--



BRAF Mutant

	NIVO+IPI	NIVO	IPI
Median, mo (95% CI)	NR	NR	24.6 (17.1–31.0)
HR (95% CI) vs NIVO	0.69 (0.44–1.07)	--	--

Wolchok et al. NEJM 2017

Talimogene laherparepvec (T-VEC) in Stage IV Melanoma

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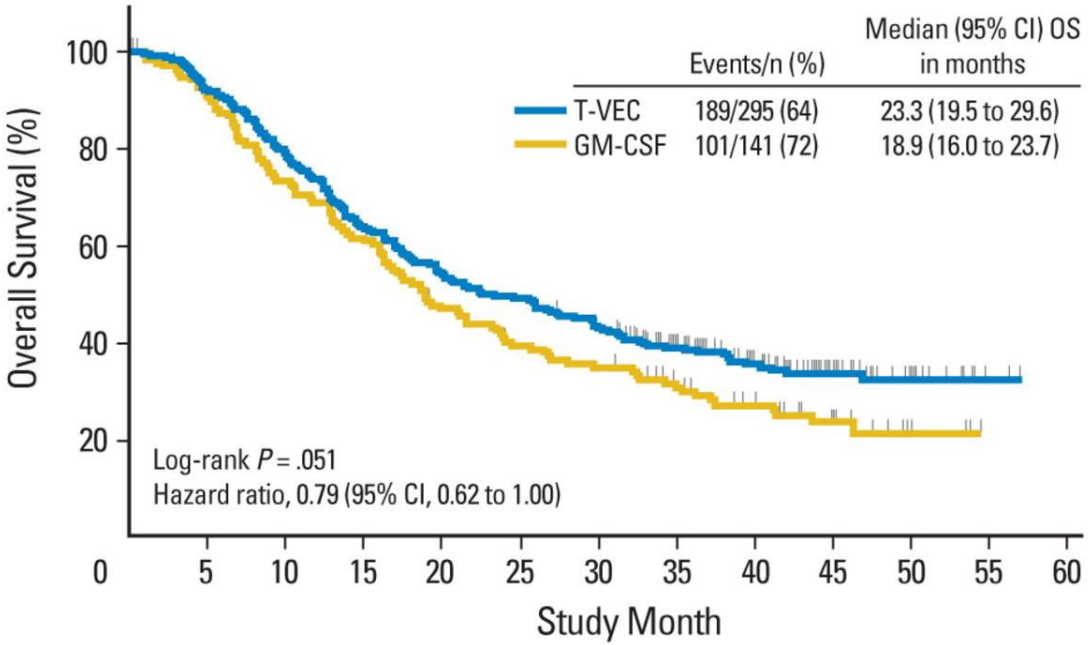
- Phase III OPTiM Trial
  - Oncolytic, genetically-engineered herpes virus
  - **Intralesional** T-VEC 10^6 pfu/mL, 10^8 pfu/mL 3 weeks after initial dose, then Q2W
  - Subcutaneous GM-CSF



Andtbacka, Kaufman et al. JCO 2015

Recommendations for Stage III Unresectable N1b, N2-N3 Melanoma

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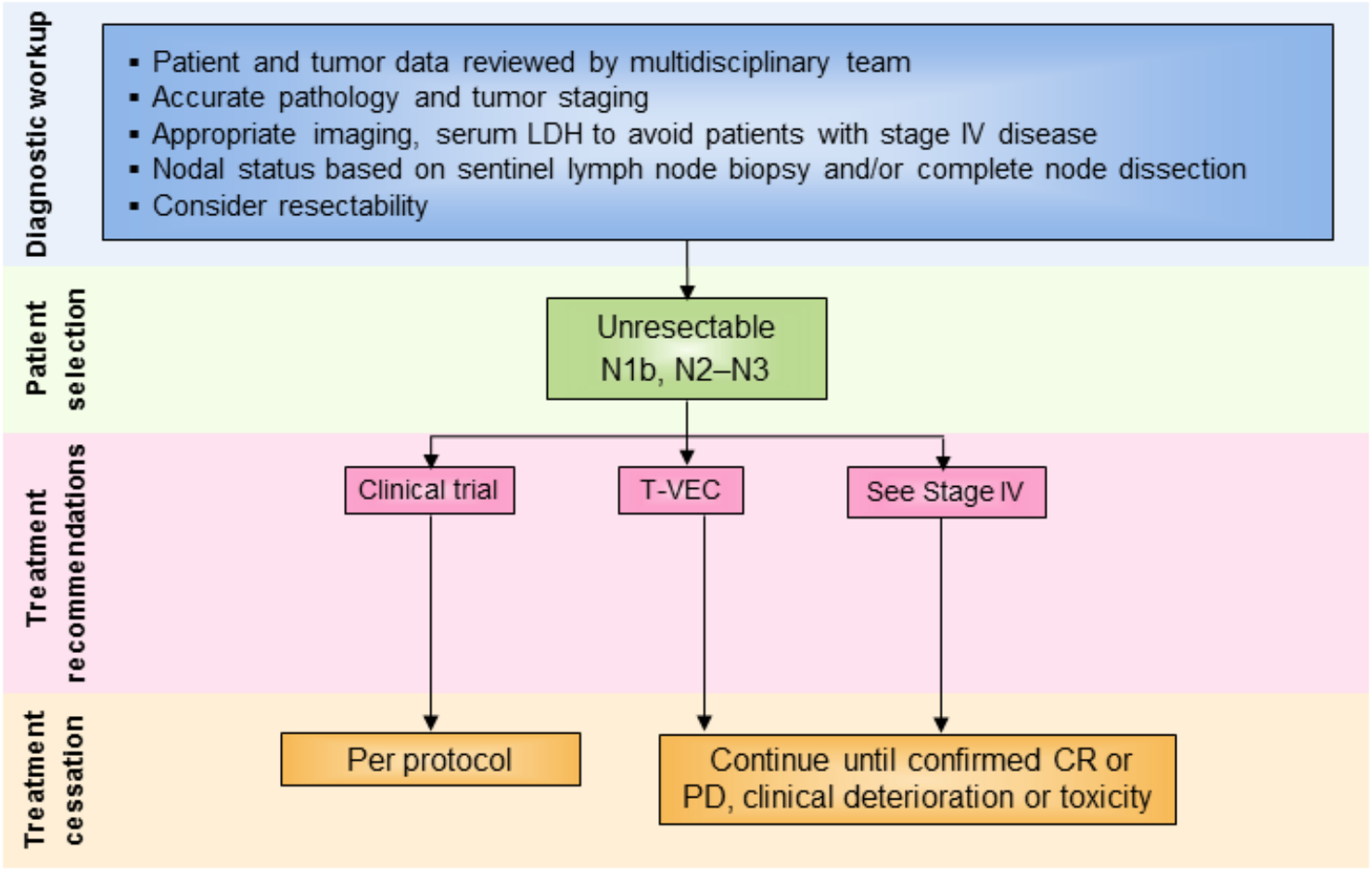

First-line Recommendations for Stage IV Patients

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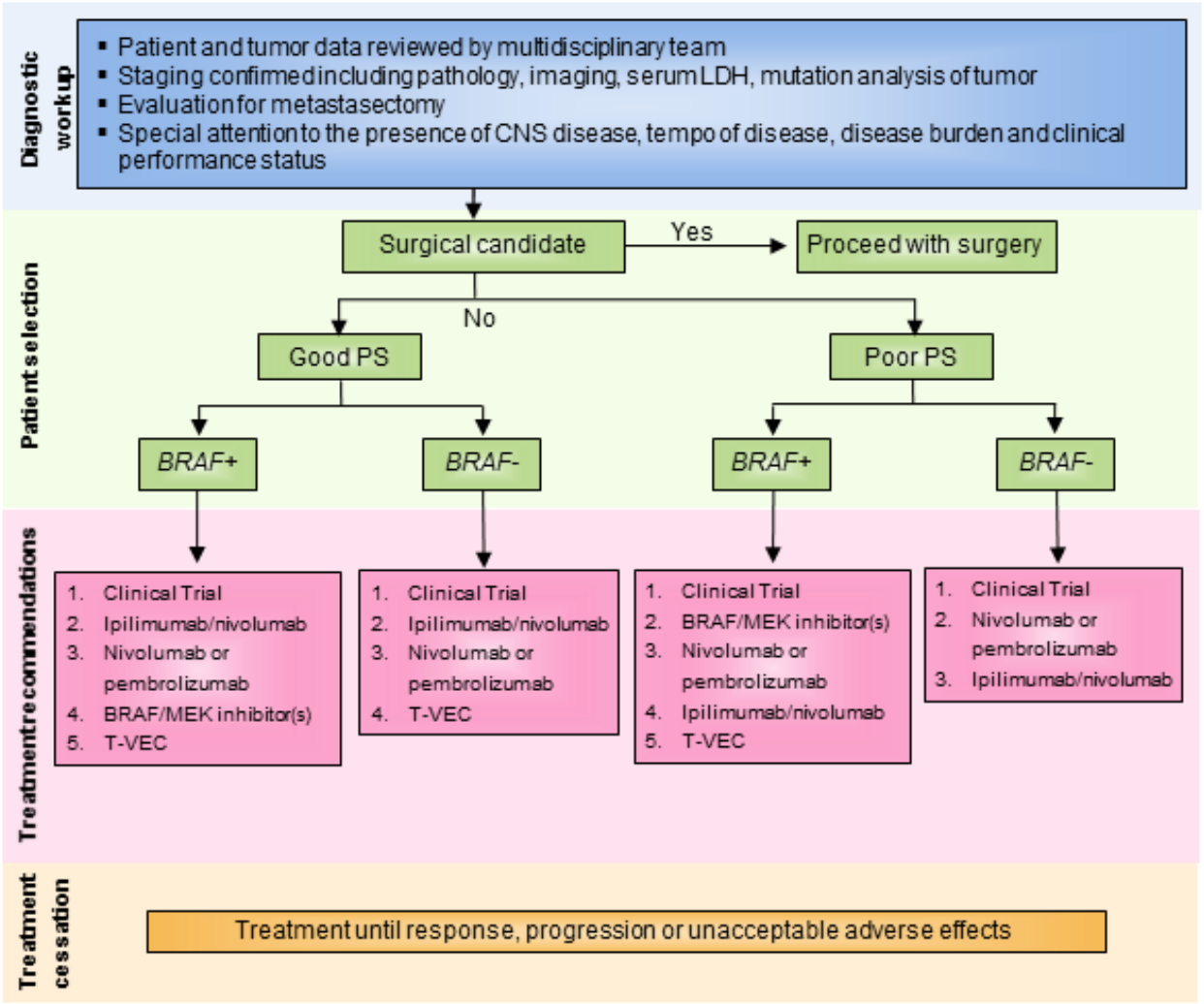

Second-line Recommendations for Stage IV Patients

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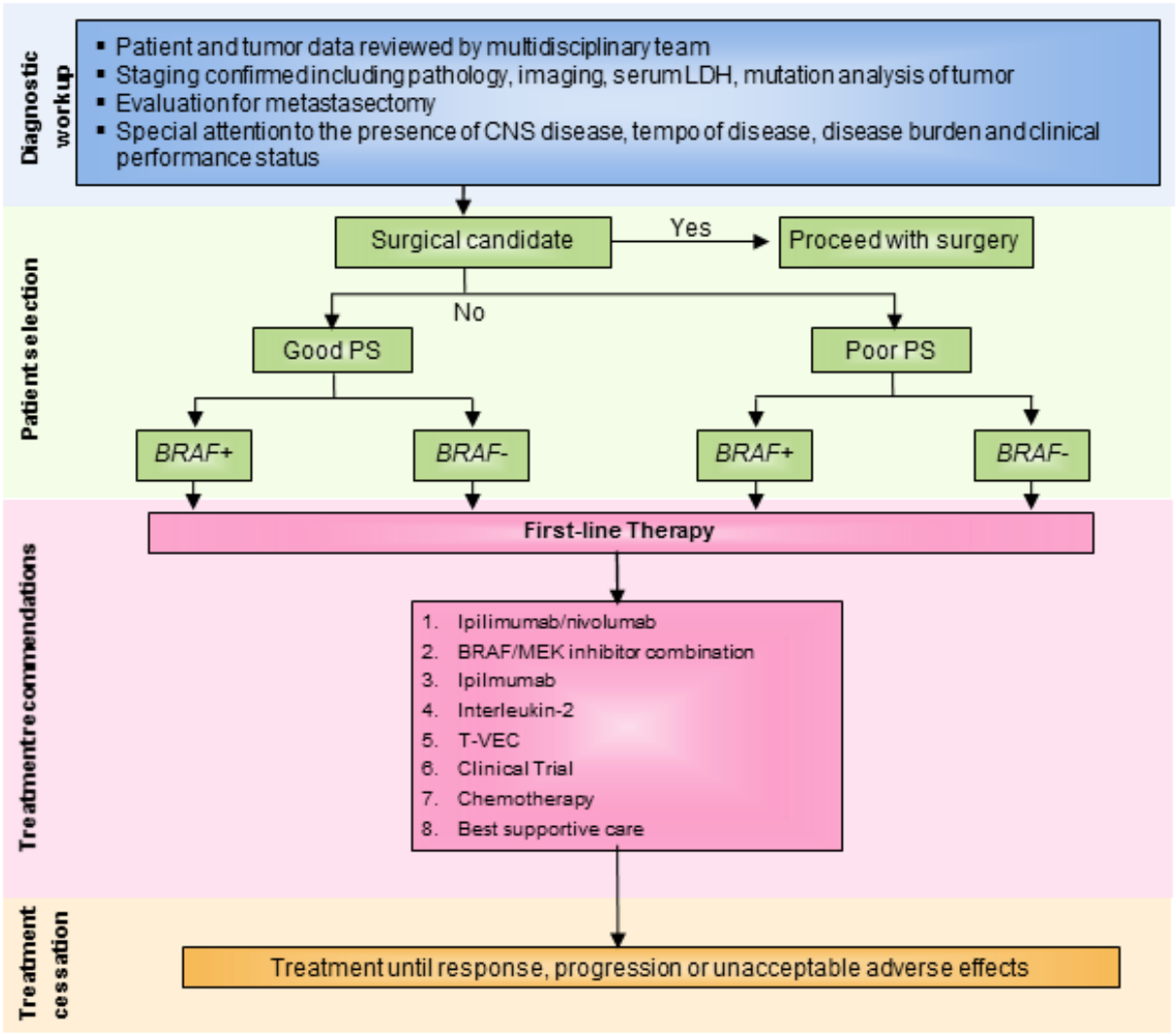

Nivolumab + Ipilimumab for Patients with Asymptomatic Brain Metastases

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	Global	Intracranial	Extracranial
Best overall response, n (%)			
Complete response	4 (5)	16 (21)	5 (7)
Partial response	36 (48)	25 (33)	32 (43)
Stable disease	4 (5)	4 (5)	2 (3)
Progressive disease[a]	18 (24)	18 (24)	16 (21)
Not evaluable[b]	13 (17)	12 (16)	20 (27)
Objective response rate, % (95% CI)	53 (41-65)	55 (43-66)	49 (38-61)
Clinical benefit rate, % (95% CI)[c]	59 (47-70)	60 (48-71)	52 (40-64)

Tawbi et al. ASCO 2017

Tumor PD-L1 Status in Melanoma

Phase III CheckMate 066 Trial

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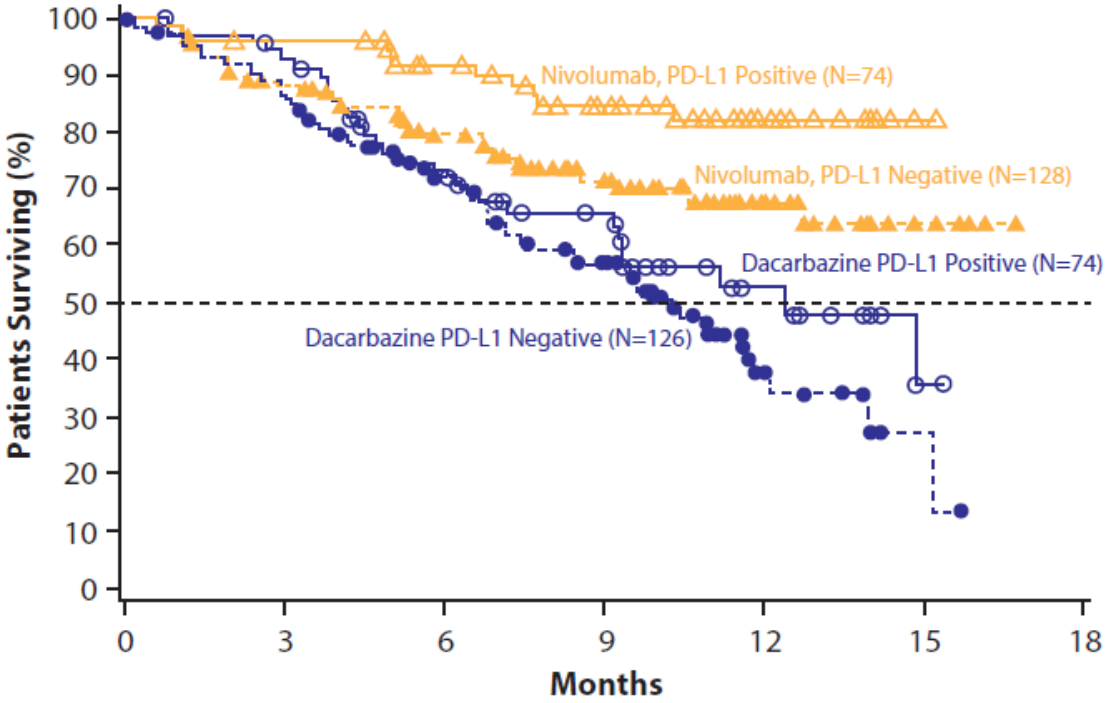

	Patients Who Died *n/N*	Median Survival *mo (95% CI)*
Nivolumab PD-L1 Positive	11/74	N.R.
Nivolumab PD-L1 Negative	37/128	N.R.
Dacarbazine PD-L1 Positive	29/74	12.4 (9.2–N.R.)
Dacarbazine PD-L1 Negative	64/126	10.2 (7.6–11.8)

Robert et al. NEJM 2015

Tumor PD-L1 Status in Melanoma

Phase III CheckMate 067 Trial

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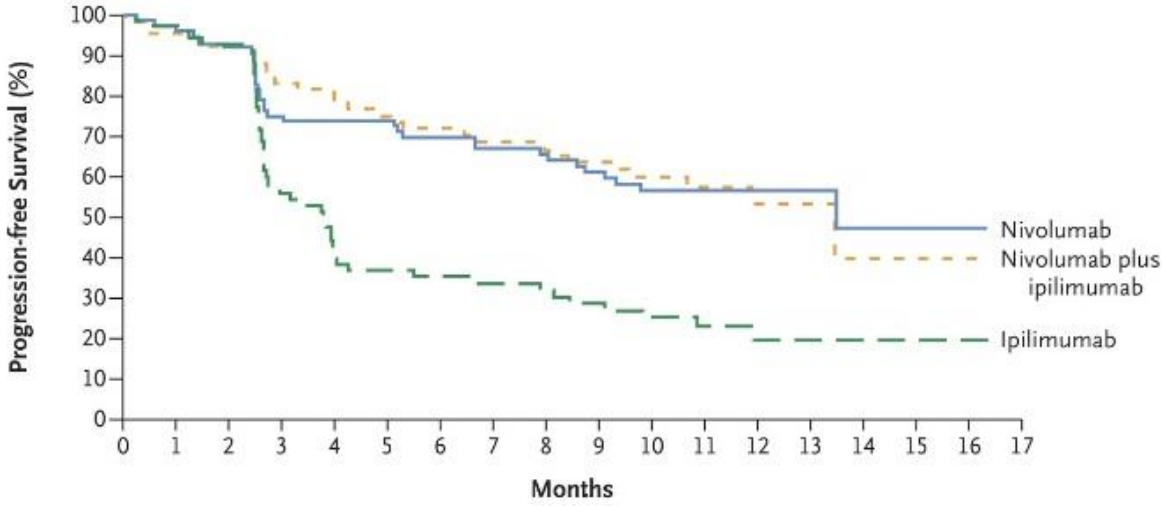
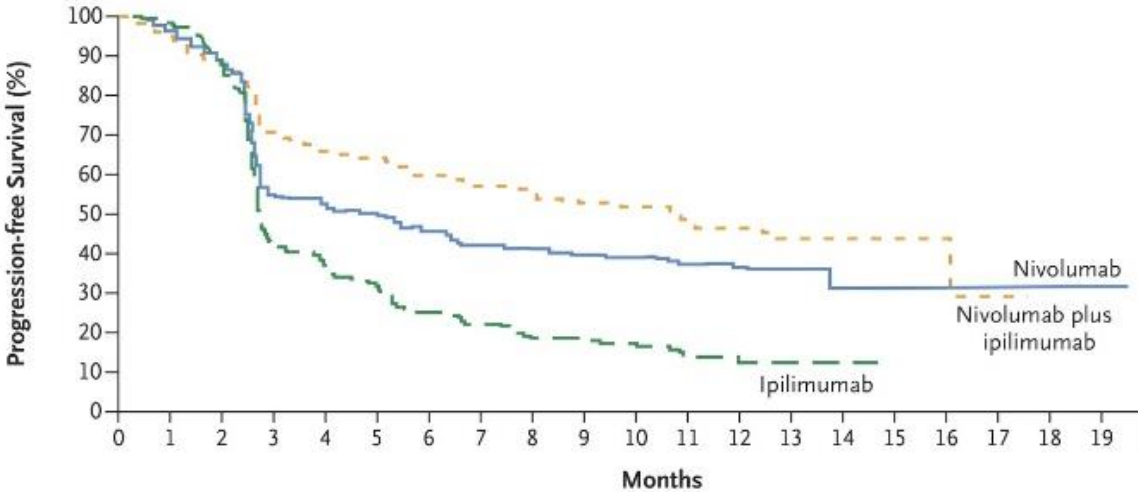


Tumor PD-L1 Positive



Tumor PD-L1 Negative

Larkin et al. NEJM 2015

Recommendations Concerning Biomarkers in Melanoma

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- The panel recognized importance of identifying predictive biomarkers
- At present, no validated biomarkers exist that reliably predict response
- Of considerable interest
  - PD-L1 expression
  - Mutation burden
  - Lymphocyte infiltration
  - Interferon-γ
  - Cytokine gene signatures
- The panel does not recommend PD-L1 status be used outside of clinical trials at this time

Immune-related Adverse Events (irAEs)

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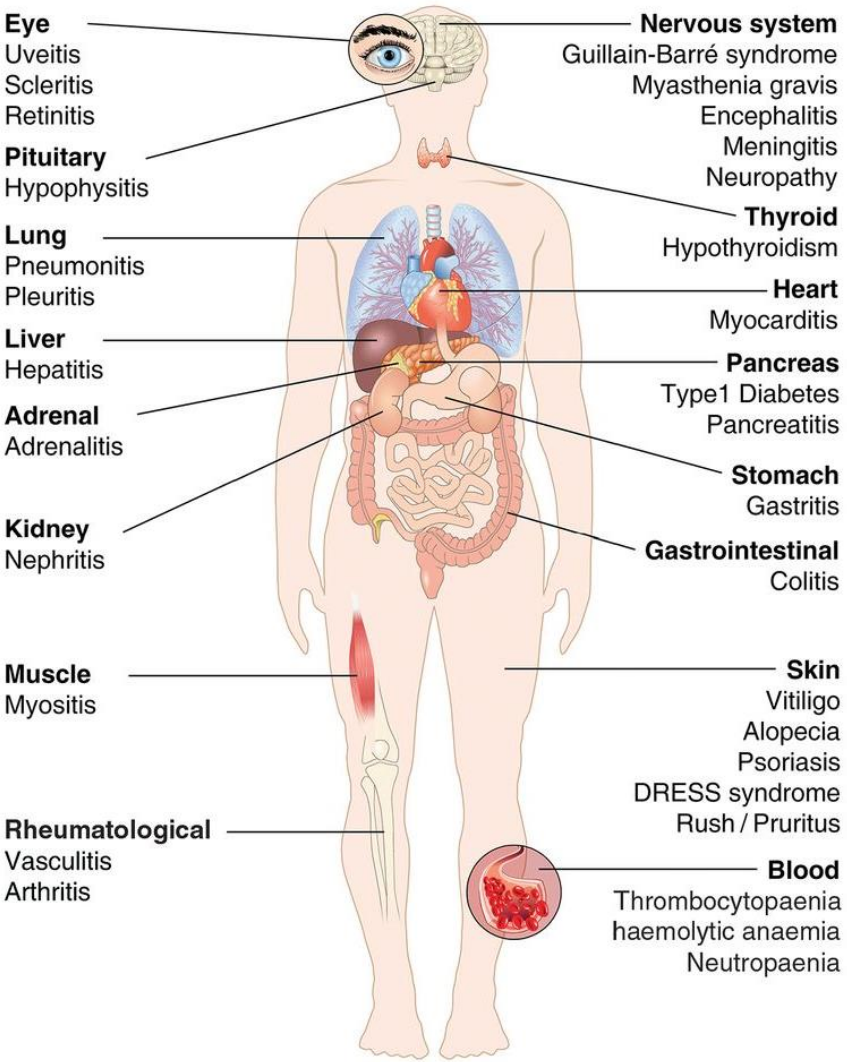

Varricchi et al. ESMO Open 2017

Immune-related Adverse Events in Melanoma

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Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine amino-transferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate amino-transferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

Larkin et al. NEJM 2015

Recommendations Concerning irAEs in Melanoma

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- Clinicians should be alert and monitor for irAEs during therapy and several months post-treatment

- The panel agreed that baseline and routine labs should include
  - Complete blood count
  - Liver enzymes
  - Metabolic panel
  - Serum LDH
  - Thyroid function studies (free T4, TSH)

- Assess additional hormone levels in patients with suspected treatment-related hypophysitis
  - Free T4, TSH, ACTH, morning cortisol, cosyntropin stimulation test, LH, FSH, testosterone, prolactin
  - Early endocrinology referral

- Most panelists recommended testing prior to each infusion for most drugs, and less frequent surveillance during follow-up

SITC Toxicity Management Guidelines

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Cancer Immunotherapy
GUIDELINES

Puzanov et al. Journal for ImmunoTherapy of Cancer (2017) 5:95
DOI 10.1186/s40425-017-0300-z

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES Open Access

Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group

I. Puzanov[1†], A. Diab[2†], K. Abdallah[3], C. O. Bingham III[4], C. Brogdon[5], R. Dadu[2], L. Hamad[1], S. Kim[2], M. E. Lacouture[6], N. R. LeBoeuf[7], D. Lenihan[8], C. Onofrei[9], V. Shannon[2], R. Sharma[1], A. W. Silk[12], D. Skondra[10], M. E. Suarez-Almazor[2], Y. Wang[2], K. Wiley[11], H. L. Kaufman[12†], M. S. Ernstoff[1*†] and on behalf of the Society for Immunotherapy of Cancer Toxicity Management Working Group

Immunotherapies in Development for Melanoma

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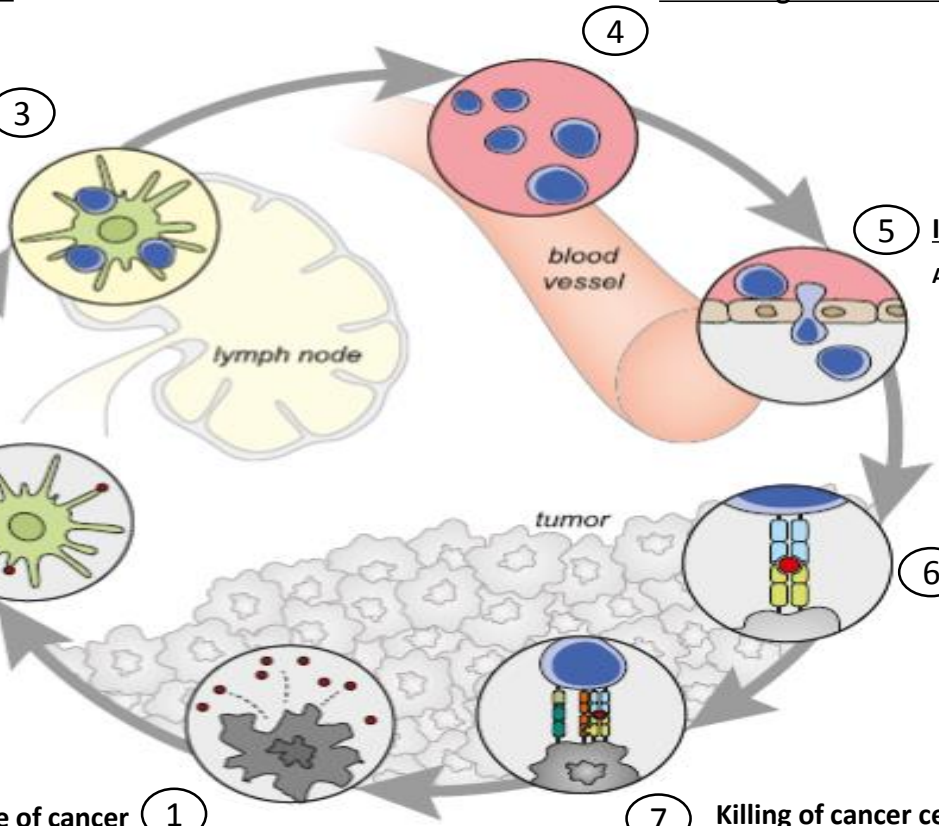
Priming and activation

Anti-CTLA4
Anti-CD137 (agonist)
Anti-OX40 (agonist)
Anti-CD27 (agonist)
IL-2
IL-12

Trafficking of T cells to tumors



Infiltration of T cells into tumors

Anti-VEGF

Cancer antigen presentation

Vaccines
Anti-CD40 (agonist)
TLR agonists
HDAC inhibitors

Recognition of cancer cells by T cells

CAR Ts

Release of cancer cell antigens

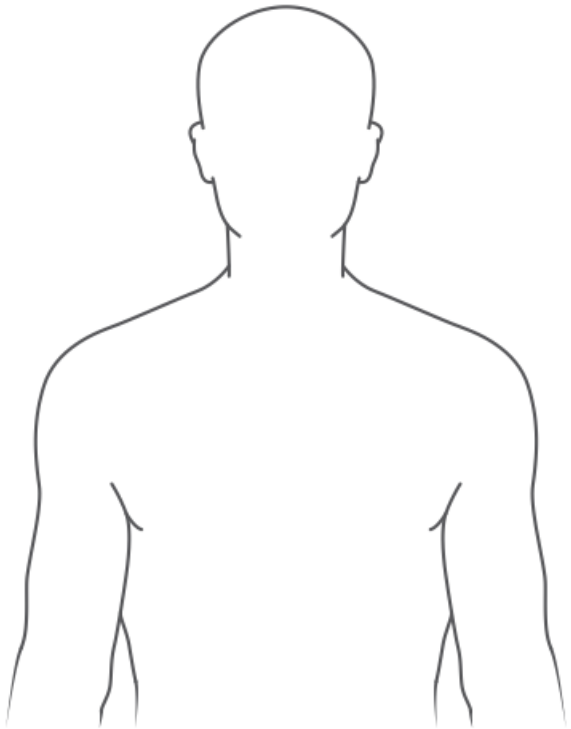
Chemotherapy
Radiation therapy
Targeted therapy

Killing of cancer cells

Anti-PD-L1
Anti-PD-1
IDO inhibitors
Other Checkpoints

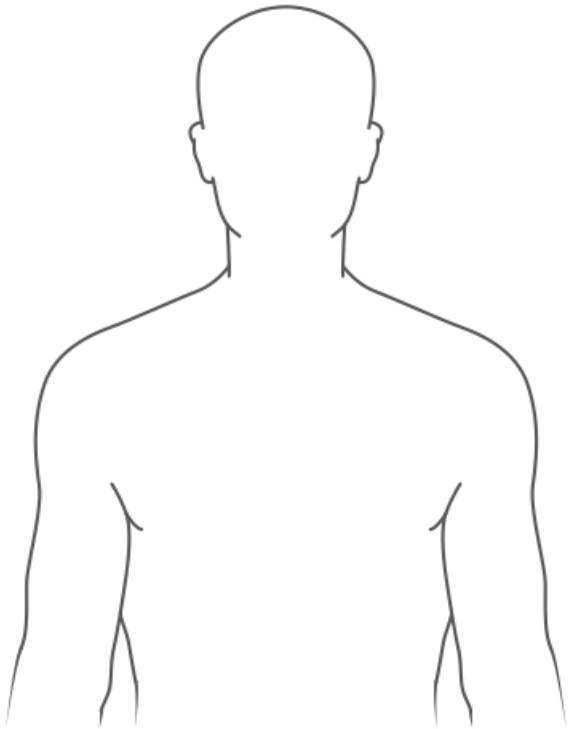
Chen et al. Immunity 2013
Courtesy of Dr. Michael Atkins

Case Study



New patient with metastatic,
BRAF V600-mutant melanoma

Case Study



New patient with metastatic,
BRAF V600-mutant melanoma

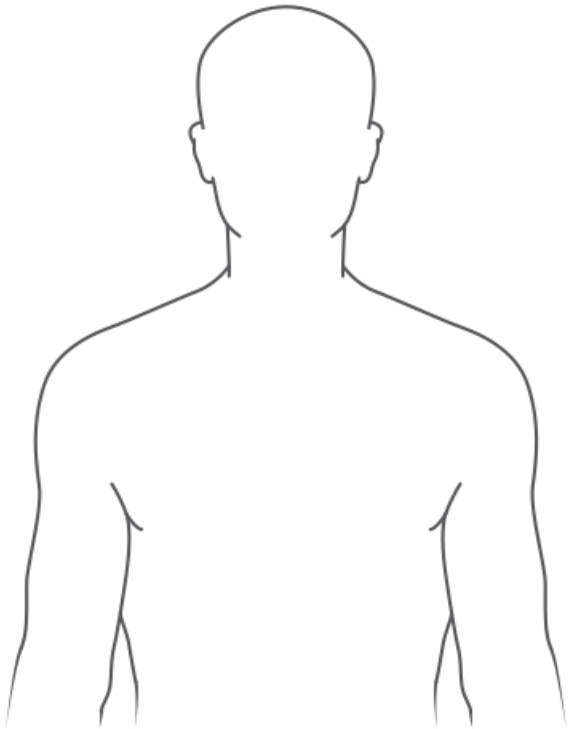
Clinical Factors

Combined immune checkpoint therapy

High LDH (>2x ULN)

Brain Mets (not steroid dependent)

Case Study



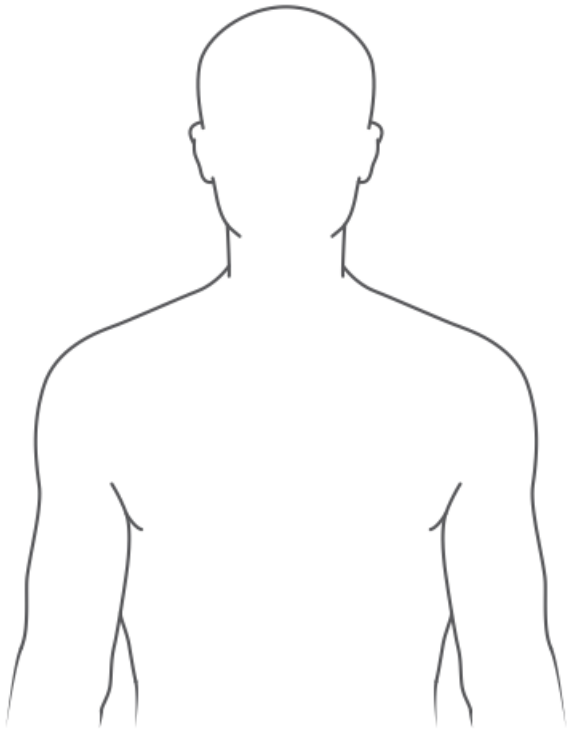
New patient with metastatic, BRAF V600-mutant melanoma

Clinical Factors

Combined immune checkpoint therapy
High LDH (>2x ULN)
Brain Mets (not steroid dependent)

BRAF-targeted therapy
Brain Mets (steroid dependent)
Rapidly fatal disease without emergent intervention

Case Study



New patient with metastatic, BRAF V600-mutant melanoma

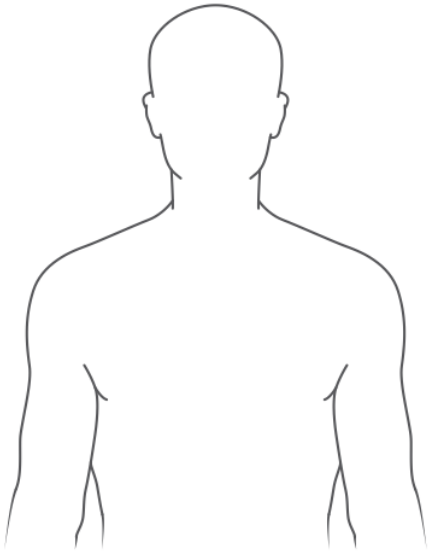
Clinical Factors

Combined immune checkpoint therapy
High LDH (>2x ULN)
Brain Mets (not steroid dependent)

The Case for Upfront Therapy for Everyone Else!

BRAF-targeted therapy
Brain Mets (steroid dependent)
Rapidly fatal disease without emergent intervention

This is not an either/or choice….



New patient with metastatic, BRAF V600-mutant melanoma

Combined immune checkpoint therapy

BRAF-targeted therapy

This is not an either/or choice….

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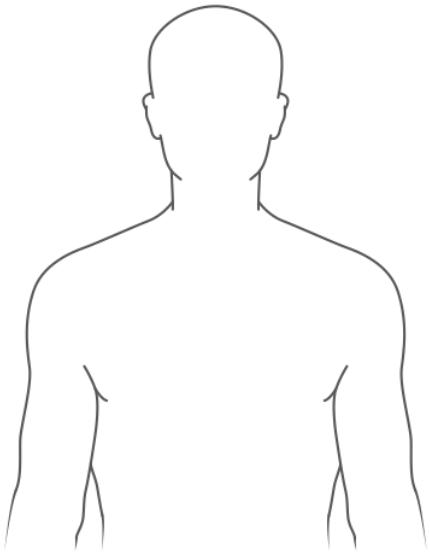
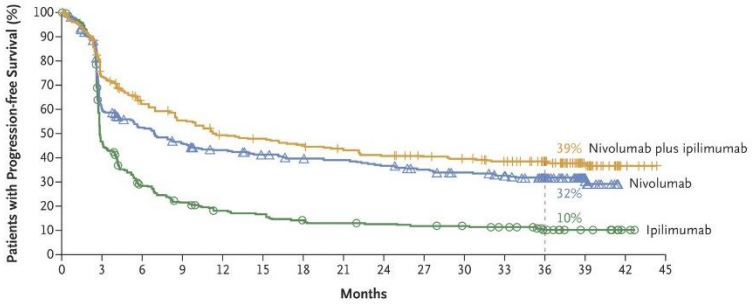


New patient with metastatic, BRAF V600-mutant melanoma

Combined immune checkpoint therapy

BRAF-targeted therapy



This is not an either/or choice….

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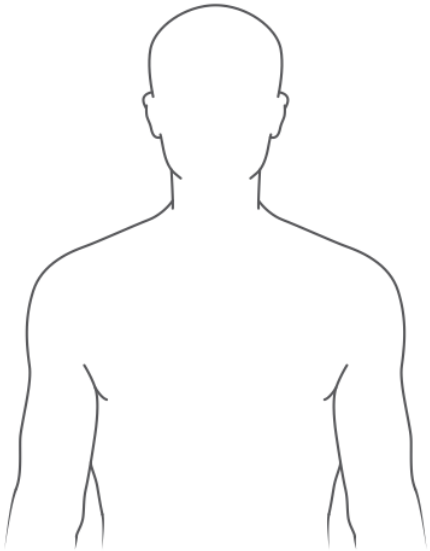
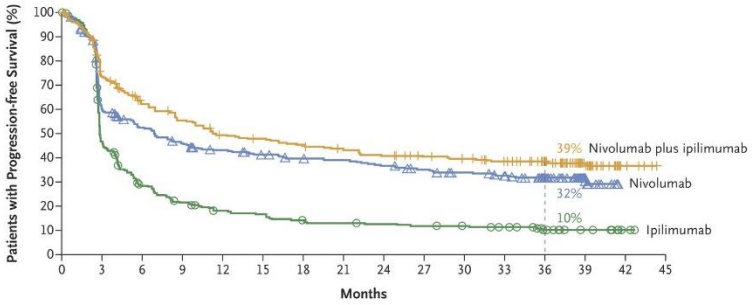
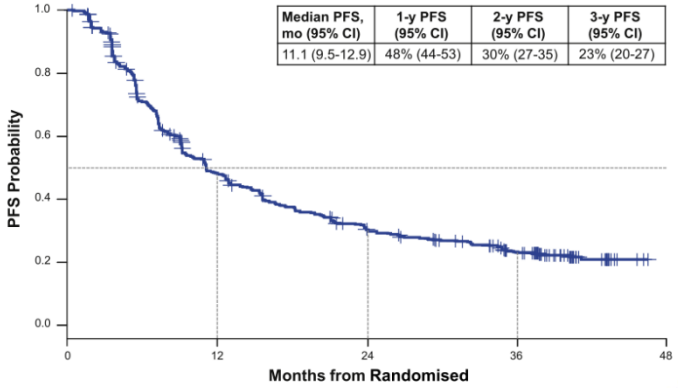


New patient with metastatic, BRAF V600-mutant melanoma

Combined immune checkpoint therapy



BRAF-targeted therapy



This is not an either/or choice….

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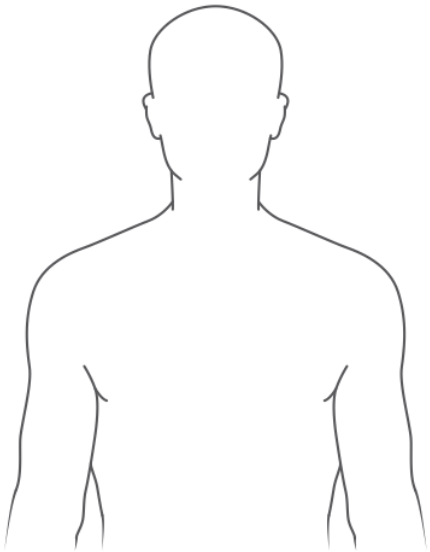
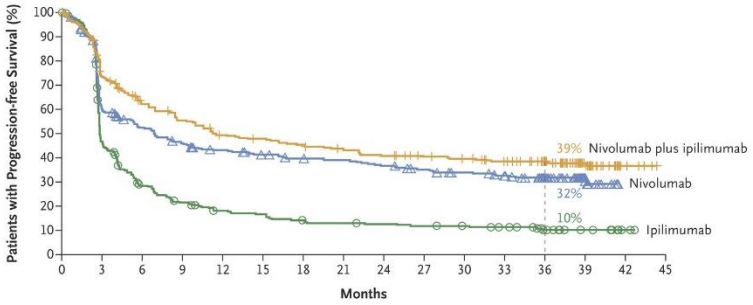
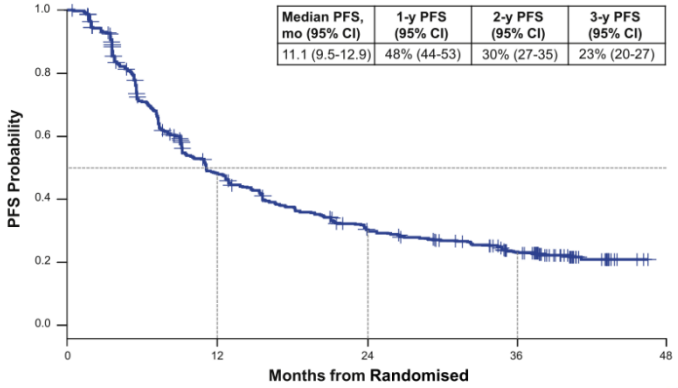


New patient with metastatic, BRAF V600-mutant melanoma

Combined immune checkpoint therapy

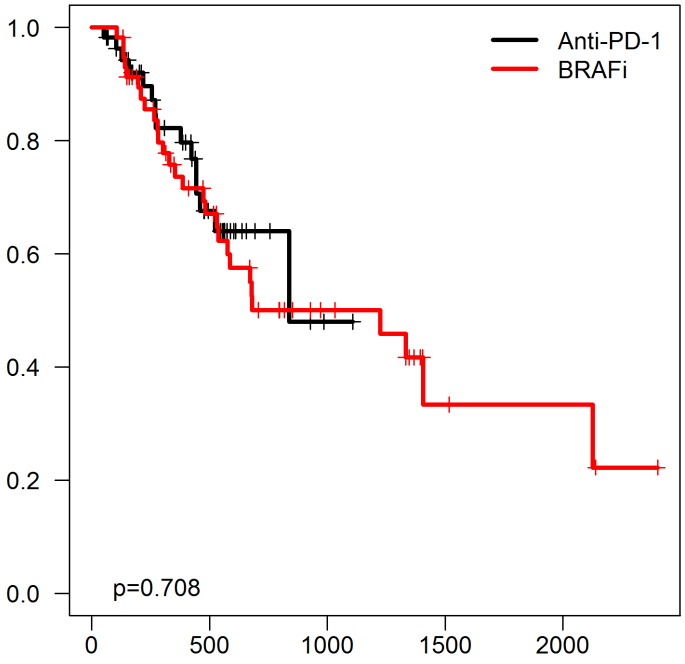
BRAF-targeted therapy



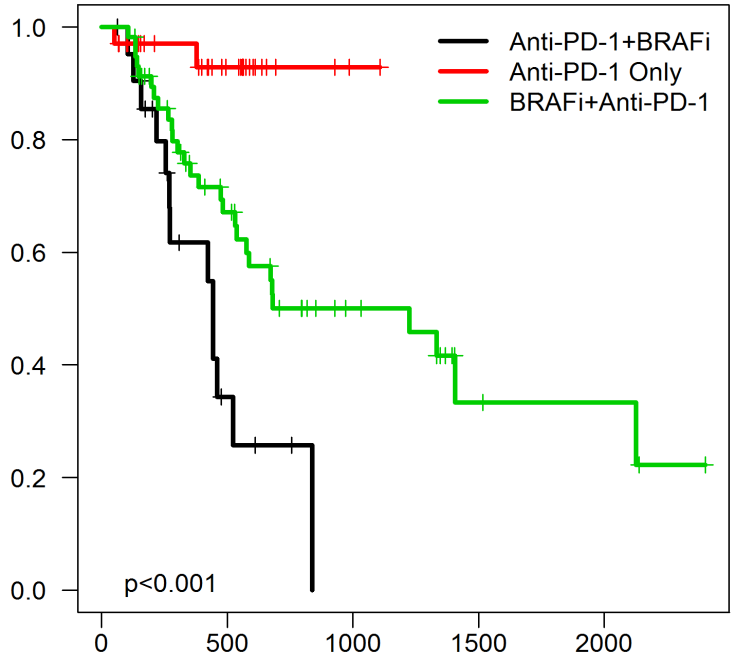


Median PFS, mo (95% CI)	1-y PFS (95% CI)	2-y PFS (95% CI)	3-y PFS (95% CI)
11.1 (9.5-12.9)	48% (44-53)	30% (27-35)	23% (20-27)

Contemplating the options….



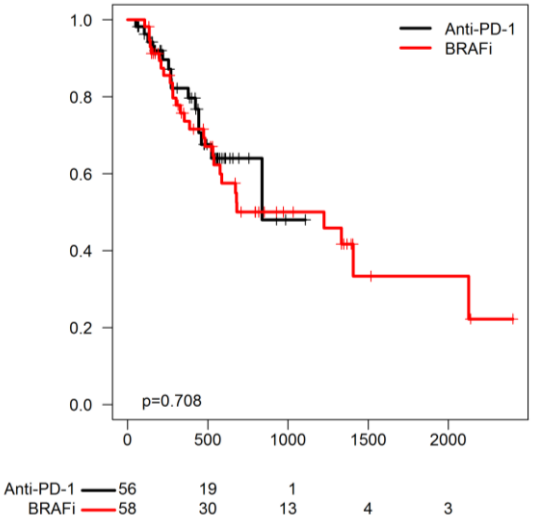
Anti-PD-1	56	19	1		
BRAFi	58	30	13	4	3

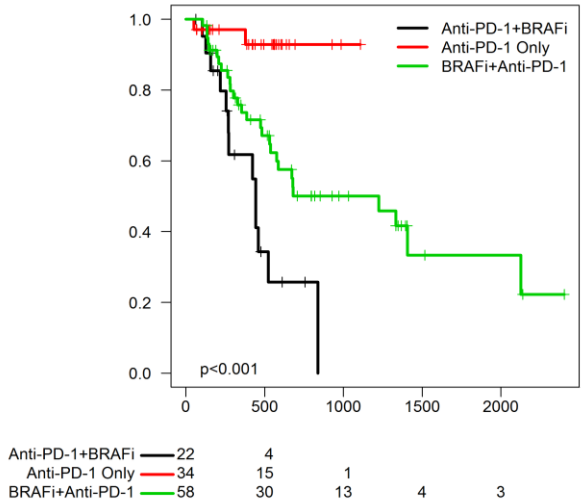


Anti-PD-1+BRAFi	22	4			
Anti-PD-1 Only	34	15	1		
BRAFi+Anti-PD-1	58	30	13	4	3

Johnson et al. J Immunother. 2017

Contemplating the options….

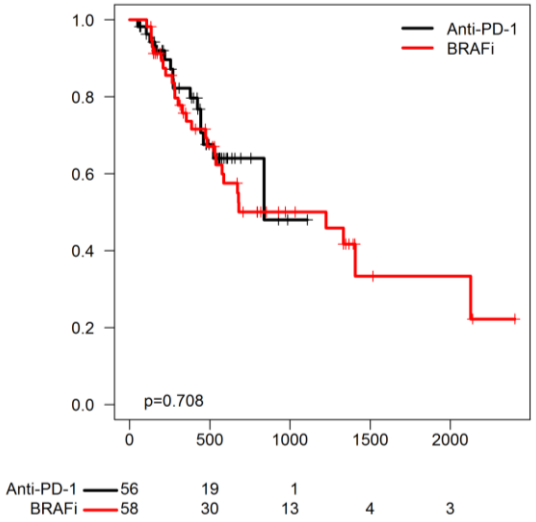


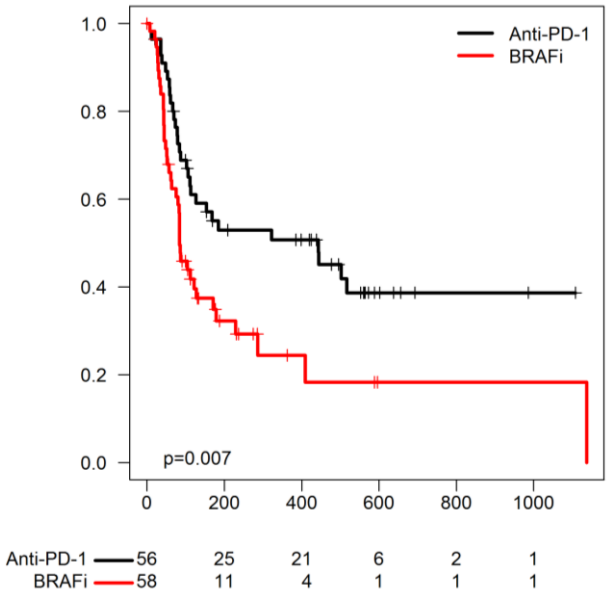


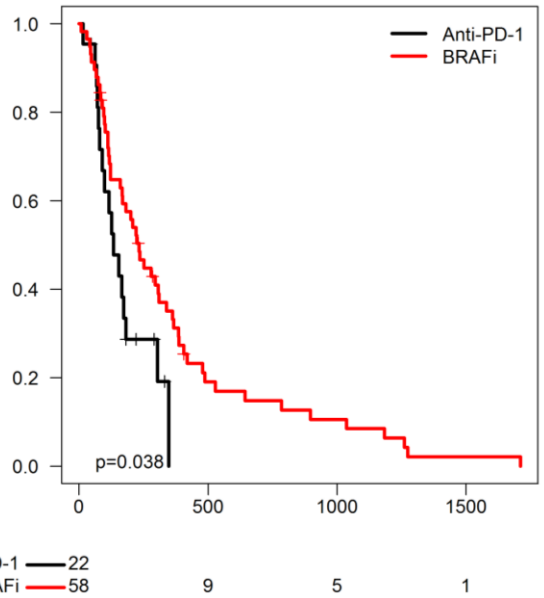
Variable	Anti-PD-1 first (n=56)	BRAFi first (n=58)	p-value
	Number (%)	Number (%)	
Brain Metastases			
Yes	5 (9)	14 (24)	0.05
Lactate Dehydrogenase			
Normal	40 (74)	27 (54)	0.05
Anti-PD-1 agent			
Nivo or pembro	34 (61)	53 (92)	<0.001
Atezolizumab	3 (5)	3 (5)	
Ipi + Nivo	19 (34)	2 (3)	
BRAF inhibitor			
BRAFi monotherapy	13 (23)	26 (45)	*
BRAFi + MEKi	9 (16)	32 (55)	
None	34 (61)	0	
Prior therapy			
Prior ipilimumab	12 (21)	16 (28)	0.86
Prior IL-2	12 (21)	12 (21)	
Prior chemotherapy	3 (5)	4 (7)	

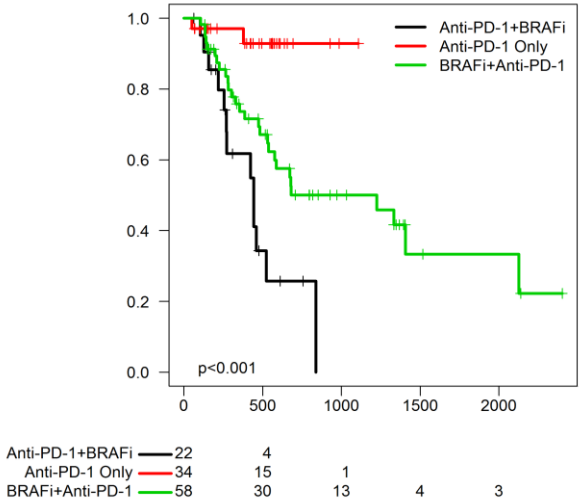
Johnson et al. J Immunother. 2017

Contemplating the options….









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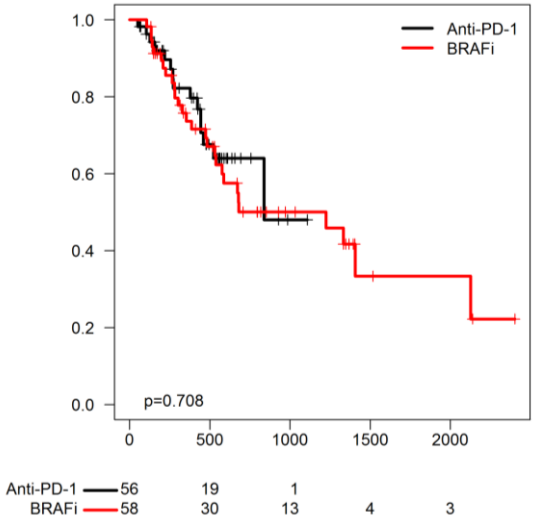

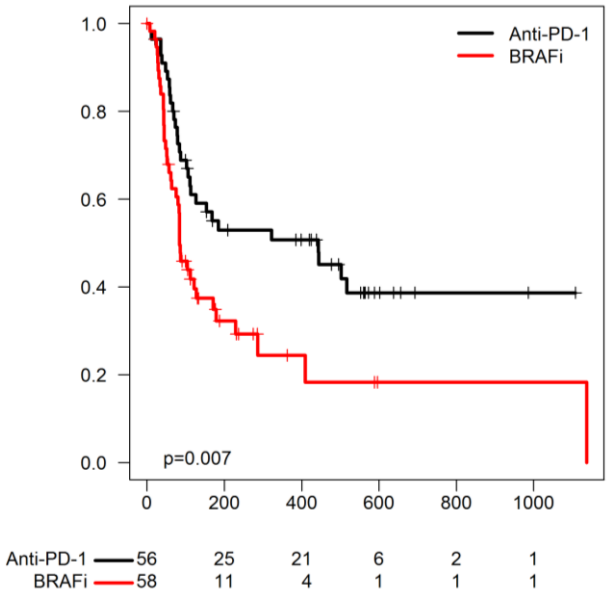

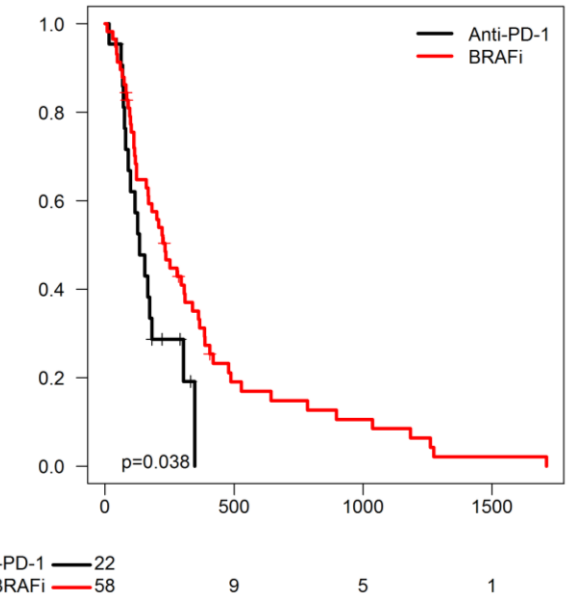

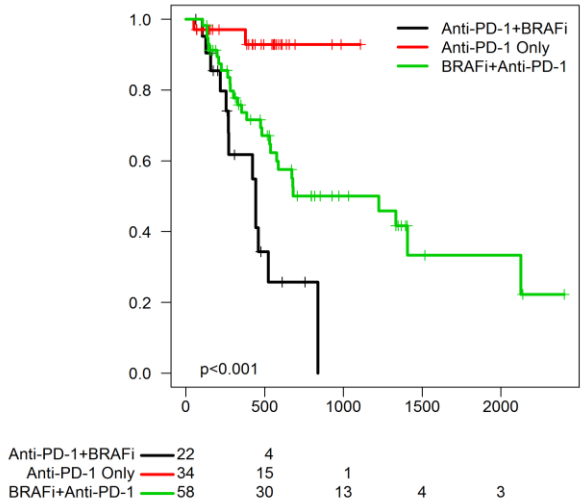

BRAF targeted therapy after progression on anti-PD-1/PD-L1 therapy is not particularly effective

Johnson et al. J Immunother. 2017

Retrospective data suggests that outcomes are worse when BRAF-targeted therapy follows anti-PD-1 therapy…

…and best outcomes are in patients who have terrific response to anti-PD-1 therapy

A prospective trial is needed to fully answer these questions

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