Melanoma Updates

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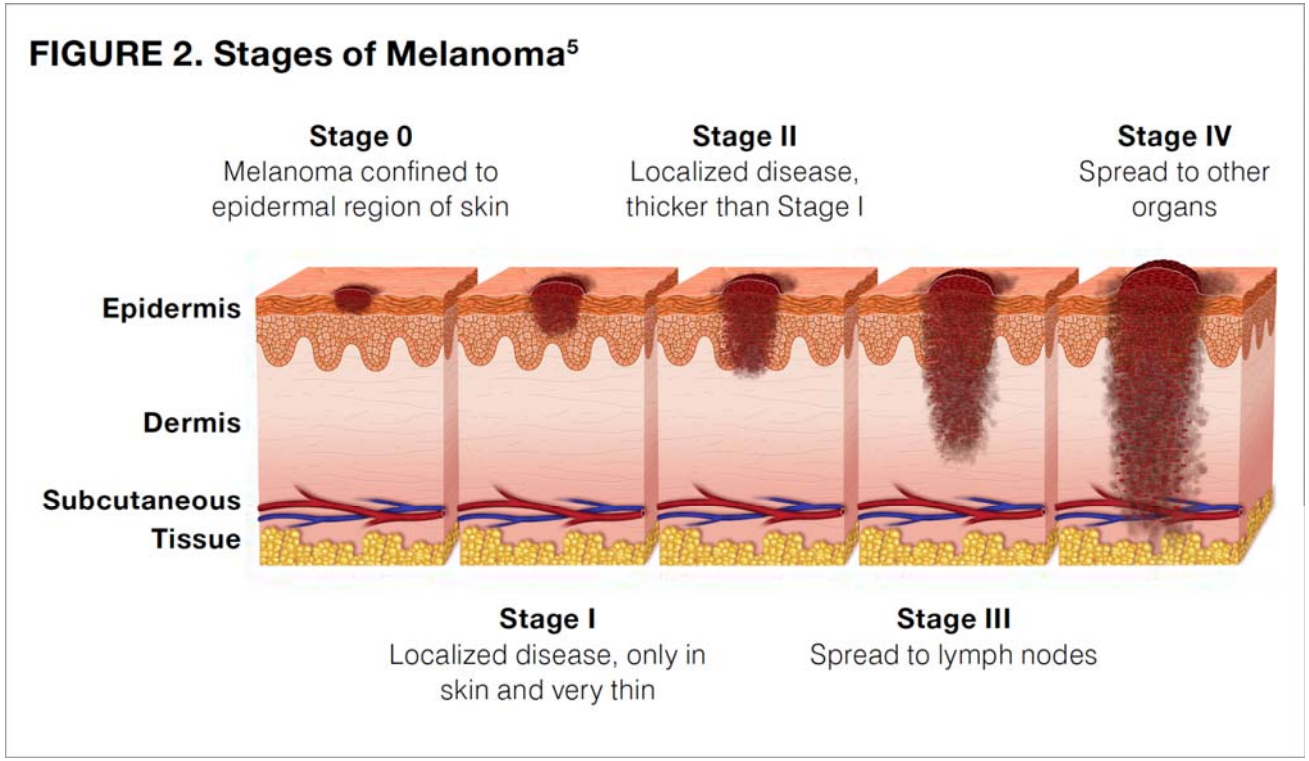
Learning Objectives

- Review the up-to-date information on risk factors, incident, screening, diagnosis and prevention recommendations for melanoma
- Describe therapeutic interventions and adjuvant therapies for melanoma
- Identify medical options for treating advanced stage melanoma including innovative research

What is melanoma?

- Fifth most common cancer in the US in men and women
- Survival rates depend on the stage at the time of diagnosis
- Incidence of melanoma is increasing faster than any other potentially preventable cancers
- Screening

Melanoma Staging



Risk Factors

- The development of melanoma is multifactorial and appears to be related to multiple risk factors
  - Very fair skinned
    - Particularly those with fair or red hair
  - Tendency to sun burn
  - Excessive childhood sun exposure
    - EX: blistering childhood sun burns
  - Age:
    - The incidence steadily rises with age
    - The highest incidence is in those over 80

Clinical Presentation

- Breslow thickness
- Ulceration status (present or absent)
- Dermal mitotic rate (mm^2)
- Assess deep and peripheral margin status
- Microsatellitosis(present or absent)
- Pure desmoplasia if present
- Lymphovascular/ angiolymphatic invasion
- Neurotropism/perineural invasion

Primary Treatment of the Early Stage Melanomas

- Stage 0: In situ melanoma
  - Wide local excision
- Stage IA (T1a): <0.8mm, no ulceration
  - Wide local excision, sentinel lymph node biopsy in special circumstances
  - Risk of positive SLN <5%
- Stage IB (T1b): <0.8mm, with ulceration or 0.8-1mm
  - Wide local excision, consider SLN biopsy
  - Risk if positive SLN 5-10%

Primary Treatment of the Early Stage Melanomas

- Stage IIB: 2-4mm with ulceration or >4mm without ulceration
- Stage IIC: >4mm with ulceration
- IIB/IIC:
  - Adjuvant Pembrolizumab vs locoregional radiation therapy
- Stage III: Nodal involvement
  - Wide local incision, Adjuvant Nivolumab or Pembrolizumab, BRAF mutation testing, Dabrafenib or Trametinib
  - Positive sentinel lymph nodes treatment: complete lymph node dissection vs ultrasound surveillance

Case Study: Metastatic Melanoma

- 52 year-old female lifeguard presented with skin lesion on left arm, progressively increasing in size over the last 3 months
- Past medical history: Hypertension
- Underwent surgery and SLN followed by lymphadenectomy
- Pathology consistent with malignant melanoma involving 2/6 lymph nodes
- PDL1 expression over 5%
- Performance status Ecog: 0

What treatment option would you prescribe in the adjuvant setting?

1. Observation
2. Nivolumab
3. Pembrolizumab
4. Ipilimumab

Stage IIB/IIC Melanoma Risk of Recurrence

- Retrospective Study From Memorial Sloan Kettering Cancer Center
- Study design: a retrospective review of 738 adult patients from a prospectively maintained, single-institution database, with resected pathologic stage II primary cutaneous melanoma (AJCC 7th ed.). All patients were treated at Memorial Sloan Kettering Cancer Center between January 1993 and December 2013. Patients underwent pathological nodal staging by sentinel lymph node biopsy or elective lymph node dissection. Median follow-up of patients with stage IIB and stage IIC melanoma was 50.2 and 46.2 months respectively.[3]
- Resected Stage IIB: 32% (n=73/226) Rate of Recurrence[3]

Risk of Recurrence: Distant Metastases

Stage IIB: Of the 73 patients with recurrence, 30% (n=22) had distant metastasis as their first recurrence[3]

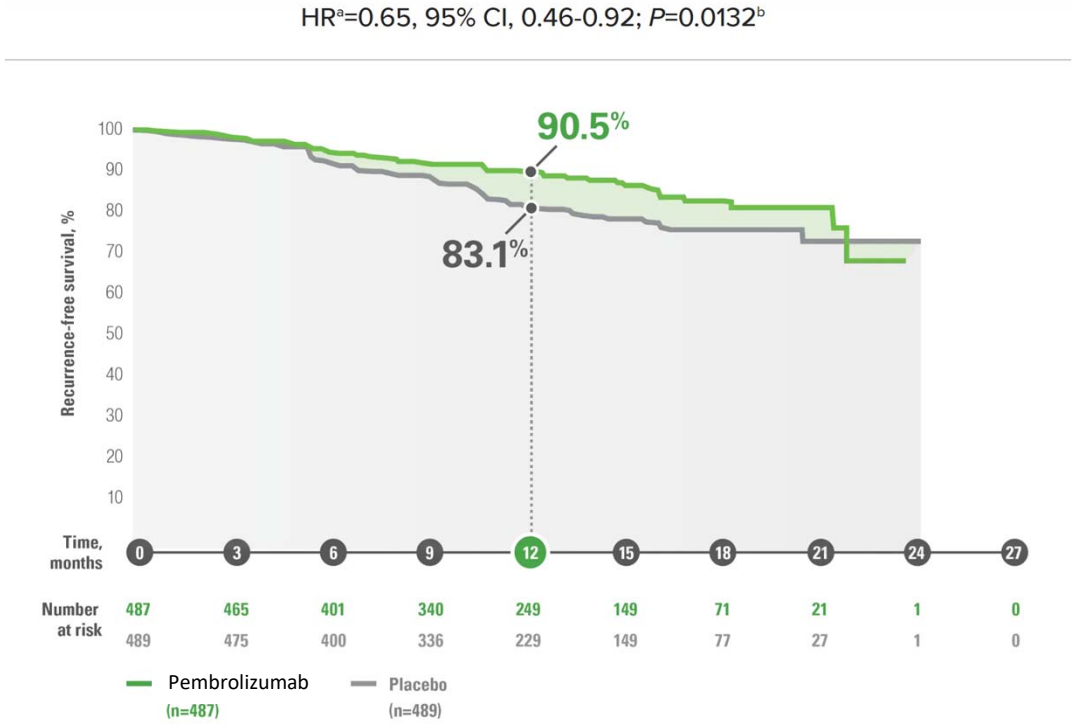
The sites of first recurrence for remaining patients were local/in-transit (47%) and regional nodal (23%).[3]

Resected Stage IIC: 46% (n=52/112) Rate of Recurrence[3]

Stage IIC: Of the 52 patients with recurrence, 52% (n=27) had distant metastasis as their first recurrence[3]

The sites of first recurrence for remaining patients were local/in-transit (29%) and regional nodal (19%).[3]

Clinical Findings from KEYNOTE-716 (Stage IIB/IIC)



Kaplan-Meier Estimates of Recurrence-Free Survival (RFS) With Pembrolizumab vs Placebo in KEYNOTE-716[2]

Adjuvant Pembrolizumab Keynote-716

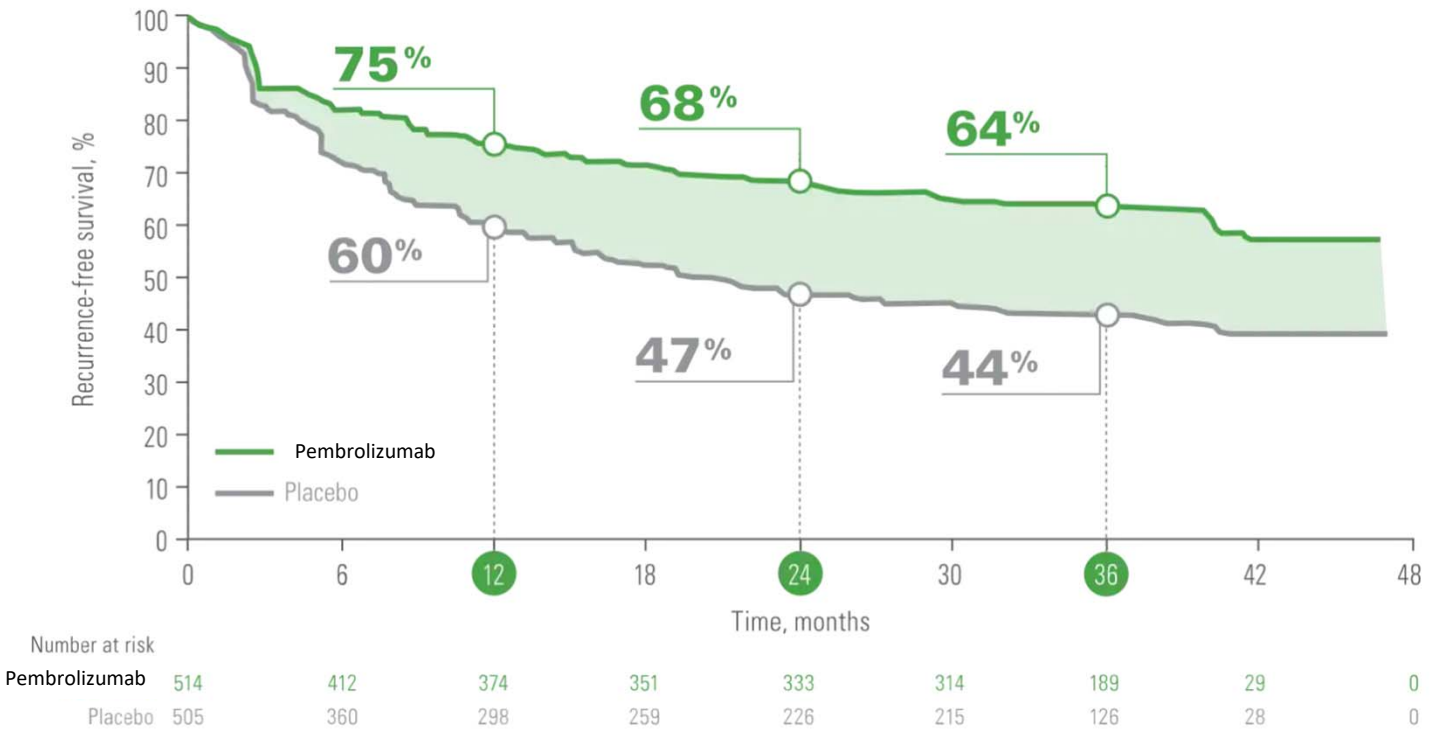
- Reduction in the risk of disease recurrence or death with Pembrolizumab compared with placebo HR=0.65, 95% CI, 0.46-0.92; *P*=0.0132

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) (Adjuvant Treatment of Stage III Melanoma)

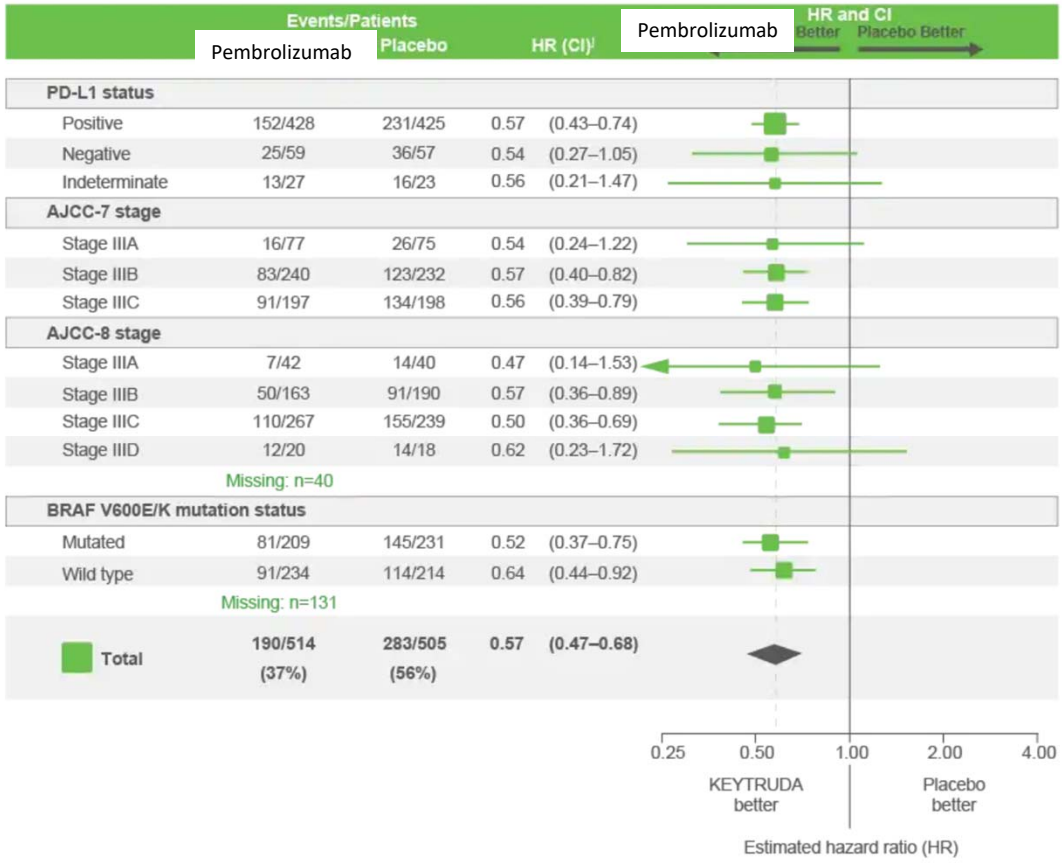
- Category 1 Treatment Option NCCN Guidelines® recommend pembrolizumab as an option for adjuvant treatment of select patients with resected stage III cutaneous melanoma regardless of BRAF mutation status (category 1).[6,h]
- Pembrolizumab is a category 1 option for patients with AJCC 7th edition stage IIIA with sentinel lymph node (SLN) metastasis > 1mm or stage IIIB/C confined to the lymph nodes.

Stage III: 3-Year Clinical Findings from KEYNOTE-054

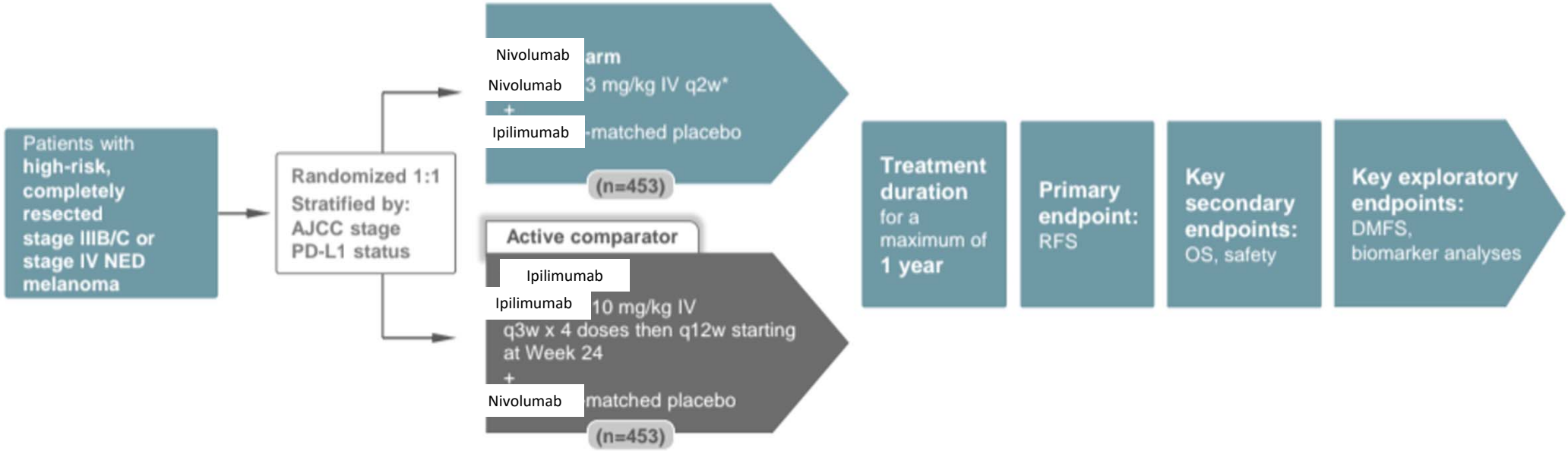
HR[i]=0.56 (95% CI, 0.47–0.68)



3-Year Subgroup Analyses of KEYNOTE-054



Stage III: Checkmate 238: 5-year follow-up of nivolumab in the adjuvant treatment of melanoma



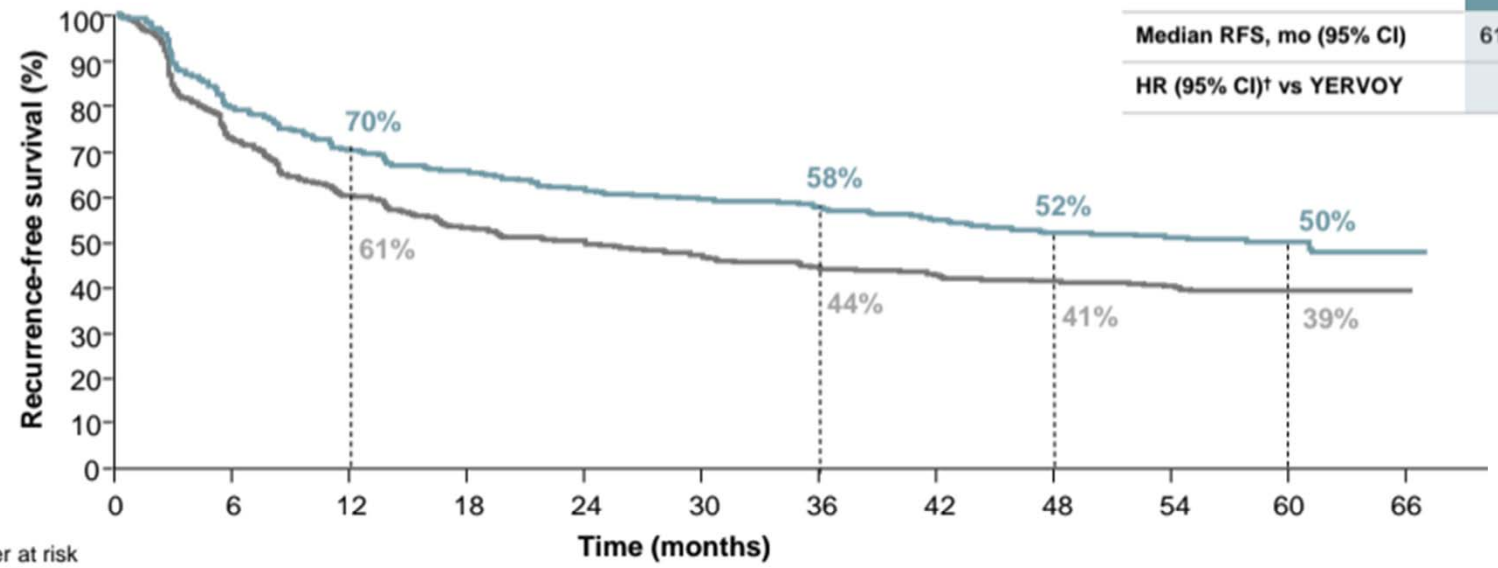
Patient Baseline Characteristics

	(nivolumab) (n=453)	(ipilimumab) (n=453)
Median age, years (range)	56 (19–83)	54 (18–86)
Male, n (%)	258 (57.0)	269 (59.4)
Stage IIIB–C, n (%)	368 (81.2)*	366 (80.8)
Macroscopic lymph node involvement (% of stage IIIB–IIIC)	217 (59.0)	214 (58.5)
Ulceration (% of stage IIIB–IIIC)	155 (42.1)	137 (37.4)
Stage IV, n (%)	82 (18.1)	87 (19.2)
M1c without brain metastases (% of stage IV)	14 (17.1)	15 (17.2)
Tumor PD-L1 expression ≥5%,† n (%)	153 (33.8)	154 (34.0)
***BRAF* mutation, n (%)**	187 (41.3)	194 (42.8)
LDH ≤ULN, n (%)	413 (91.2)	411 (90.7)
Melanoma subtype, n (%)		
Cutaneous	388 (85.7)	377 (83.2)
Mucosal	16 (3.5)	13 (2.9)
Acral	16 (3.5)	18 (4.0)

*Two additional patients had stage IIIA disease. †PD-L1 IHC 28-8 pharmDx assay.
LDH=lactate dehydrogenase; PD-L1=programmed death ligand 1; ULN=upper limit of normal.
Weber J et al. Oral presentation at SMR 2021.

Nivolumab: RFS Analysis in the ITT population over 5 years

	Nivolumab (n=453)	Ipilimumab (n=453)
Median RFS, mo (95% CI)	61.0 (42.5–NR)*	24.1 (16.6–35.1)
HR (95% CI)† vs YERVOY	0.72 (0.60–0.86)	



Number at risk

Nivolumab	453	354	311	283	262	245	234	220	202	176	94	4
Ipilimumab	453	316	253	220	201	185	173	165	152	134	78	1

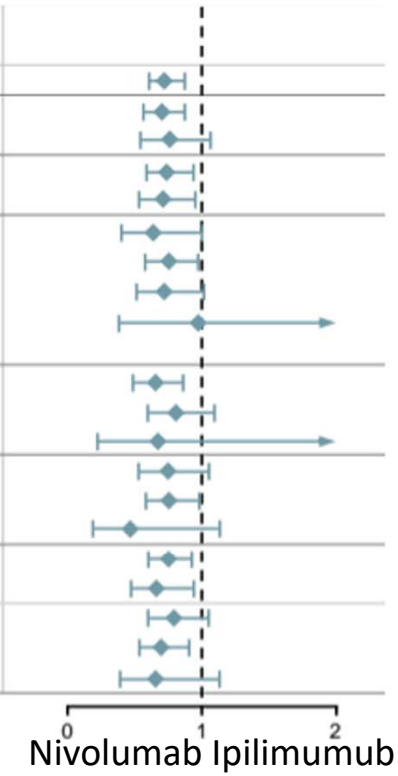
*Median not stable.[1] †Stratified.[1]

CI=confidence interval; HR=hazard ratio; ITT=intent to treat; mo=month; NR=not reached; RFS=recurrence-free survival.

1. Weber J et al. Oral presentation at SMR 2021. 2. Weber J et al. Oral presentation at ESMO 2020. Abstract 1076O. 3. Weber J et al. Oral presentation at ESMO 2019. Abstract 2801. 4. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. 5. Weber J et al. *N Engl J Med.* 2017;377(19):1824-1835.

Nivolumab: RFS HR in pre-specified subgroup analysis

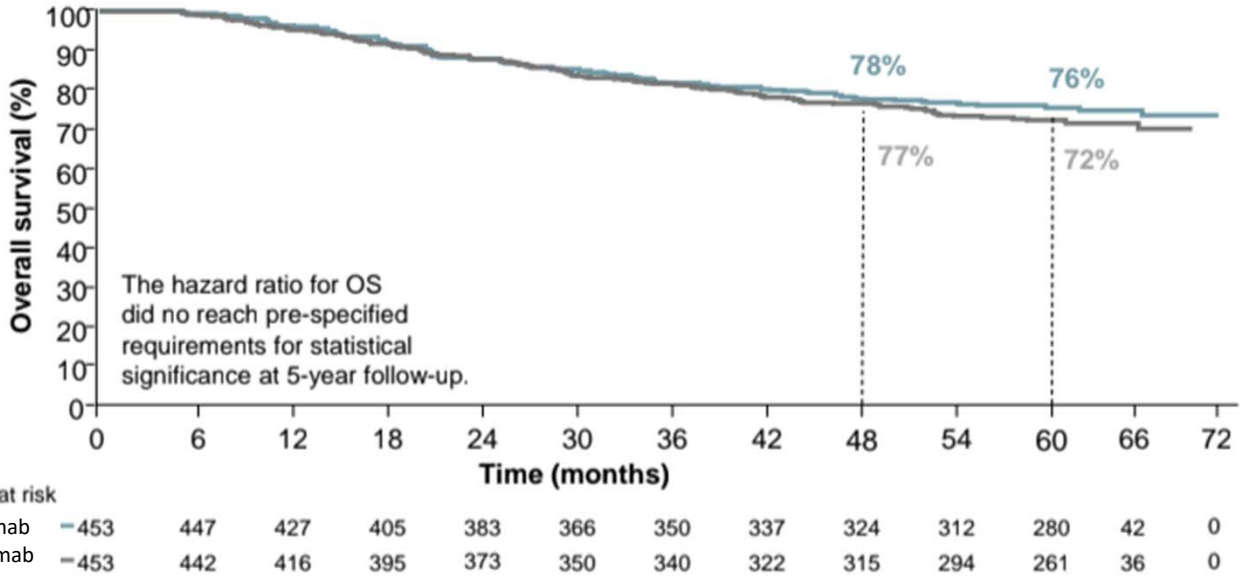
Subgroup		Nivolumab (3mg/kg) No. of events (No. of subjects)	Ipilimumab (10mg/kg) No. of events (No. of subjects)	Unstratified HR (95% CR)
Overall	Overall	218 (453)	257 (453)	0.73 (0.61–0.87)
Age	<65 years	147 (333)	184 (339)	0.70 (0.57–0.88)
	≥65 years	71 (120)	73 (114)	0.76 (0.55–1.06)
Sex	Male	131 (258)	157 (269)	0.74 (0.59–0.93)
	Female	87 (195)	100 (184)	0.71 (0.54–0.95)
Stage	IIIB	65 (166)	74 (147)	0.72 (0.52–1.01)
	IIIC	111 (202)	131 (219)	0.76 (0.59–0.97)
	IV M1a–M1b	32 (62)	43 (66)	0.64 (0.40–1.01)
	IV M1c	9 (20)	9 (21)	0.98 (0.39–2.47)
	Not reported	1 (1)	0 (0)	–
Stage III: ulceration	Absent	81 (201)	115 (213)	0.65 (0.49–0.87)
	Present	89 (155)	83 (137)	0.81 (0.60–1.09)
	Not reported	6 (14)	7 (16)	0.67 (0.22–2.02)
Stage III: lymph node involvement	Microscopic	58 (128)	72 (134)	0.75 (0.53–1.06)
	Macroscopic	109 (217)	122 (214)	0.75 (0.58–0.98)
	Not reported	9 (25)	11 (18)	0.47 (0.19–1.13)
PD-L1 status†	<5% or indeterminate	161 (300)	183 (299)	0.75 (0.61–0.93)
	≥5%	57 (153)	74 (154)	0.66 (0.47–0.94)
***BRAF* mutation status‡**	Mutant	90 (187)	106 (194)	0.80 (0.60–1.05)
	Wild-type	100 (197)	125 (212)	0.69 (0.53–0.90)
	Not reported	28 (69)	26 (47)	0.66 (0.39–1.13)



*Stratified HR=0.72 (95% CI: 0.60–0.86). †PD-L1 IHC 28-8 pharmDx assay. ‡V600E/K.
CI=confidence interval; HR=hazard ratio; no=number; PD-L1=programmed cell death ligand 1; RFS=recurrence-free survival.
Weber J et al. Oral presentation at SMR 2021. [

Nivolumab: OS in the ITT population

	Nivolumab (n=453)	Ipilimumab (n=453)
Median OS, mo (95% CI)	NR	NR
HR (95% CI)* vs YERVOY	0.86 (0.66–1.12)	



Number at risk

Nivolumab	453	447	427	405	383	366	350	337	324	312	280	42	0
Ipilimumab	453	442	416	395	373	350	340	322	315	294	261	36	0

- At the 60-month analysis, there were 228 total events (108 for Nivolumab and 120 for Ipilimumab vs the 302 events anticipated[1]
- Current total events yield ~75% power to detect a significant difference between Nivolumab and Ipilimumab

*Stratified.[1]

CI=confidence interval; HR=hazard ratio; ITT=intent to treat; mo=month; NR=not reached; OS=overall survival.

1. Weber J et al. Oral presentation at SMR 2021. 2. Ascierto PA et al. *Lancet Oncol.* 2020;21:1465-1477.

Select Safety Results in Checkmate 238

Adverse Reactions occurring in ≥ 10% of patients treated with Nivolumab

		Nivolumab 3 mg/kg (n=452)		Ipilimumab 10 mg/kg (n=453)	
		Any grade	Grades 3–4	Any grade	Grades 3–4
Discontinuation due to adverse events, %		9	-	42	-
Grade 3–4 adverse events, %		-	25.4	-	55.2
General disorders, %	Fatigue*	57	0.9	55	2.4
Gastrointestinal disorders, %	Diarrhea	37	2.4	55	11
	Nausea	23	0.2	28	0
	Abdominal pain†	21	0.2	23	0.9
	Constipation	10	0	9	0
Skin and subcutaneous tissue disorders, %	Rash‡	35	1.1	47	5.3
	Pruritus	28	0	37	1.1
Musculoskeletal and connective tissue disorders, %	Musculoskeletal pain§	32	0.4	27	0.4
	Arthralgia	19	0.4	13	0.4
Nervous system disorders, %	Headache	23	0.4	31	2.0
	Dizziness‖	11	0	8	0
Infections, %	Upper respiratory tract infection¶	22	0	15	0.2
Respiratory, thoracic, and mediastinal disorders, %	Cough/productive cough	19	0	19	0
	Dyspnea/exertional dyspnea	10	0.4	10	0.2
Endocrine disorders, %	Hypothyroidism#	12	0.2	7.5	0.4

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[1]
*Includes asthenia.[1] †Includes abdominal discomfort, lower abdominal pain, upper abdominal pain, and abdominal tenderness.[1] ‡Includes dermatitis also described as acneiform, allergic, bullous, or exfoliative and rash described as generalized, erythematous, macular, papular, maculopapular, pruritic, pustular, vesicular, or butterfly, and drug eruption.[1] §Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, spinal pain, and pain in extremity.[1] ‖Includes postural dizziness and vertigo.[1] ¶Includes upper respiratory tract infection, including viral respiratory tract infection, lower respiratory tract infection, rhinitis, pharyngitis, and nasopharyngitis.[1] #Includes secondary hypothyroidism and autoimmune hypothyroidism.[1]

Case Study: Metastatic Melanoma

- 67-year-old retired male airline pilot presents with SOB and fatigue and numerous hardened black lumps on the left arm
- Past medical history: hypertension and osteoarthritis
- Pathology: Metastatic melanoma
- Ecog: 1
- PET Scan: Metastases involving the lung, liver, bone and lymph
- LDH: 8156, LFT: 1.5x normal

Which of the following treatment options is most appropriate?

1. Nivolumab
2. Nivolumab Relatlimab
3. Pembrolizumab
4. Ipilimumab

SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE[a,b,c]

Metastatic or unresectable disease

FIRST-LINE THERAPY[d]

- Preferred regimens
  - Combination checkpoint blockade (preferred)
    - Nivolumab/ipilimumab (category 1)[e,f,g,h]
    - Nivolumab and relatlimab-rmbw (category 1)[e]
  - Anti-PD-1 monotherapy[e,f,i]
    - Pembrolizumab (category 1)
    - Nivolumab (category 1)
- Other recommended regimens
  - Combination targeted therapy if *BRAF* V600-activating mutation[j,k,l,m,n]
    - Dabrafenib/trametinib (category 1)
    - Vemurafenib/cobimetinib (category 1)
    - Encorafenib/binimetinib (category 1)
  - Pembrolizumab/low-dose ipilimumab[o] (category 2B)

Disease progression, intolerance, and/or projected risk of progression with *BRAF*-targeted therapy

SECOND-LINE OR SUBSEQUENT THERAPY[p]

- Systemic therapy
  - Preferred regimens
    - Anti-PD-1 monotherapy[e,f]
      - Pembrolizumab
      - Nivolumab
    - Nivolumab/ipilimumab[e,f,g]
    - Nivolumab and relatlimab-rmbw[q]
    - Pembrolizumab/low-dose ipilimumab for progession following anti-PD-1 therapy[e,f]
    - Combination targeted therapy with *BRAF* V600-activating mutation[k,l,m]
      - Dabrafenib/trametinib
      - Vemurafenib/cobimetinib
      - Encorafenib/binimetinib
  - Other recommended regimens
    - Ipilimumab[e]
    - High-dose IL-2[r]
  - Useful in certain circumstances
    - For activating mutations of *KIT*
      - KIT inhibitor therapy (eg, imatinib, dasatinib, nilotinib, ripretinib)
    - For *ROS1* fusions
      - Crizotinib, entrectinib
    - For *NTRK* fusions
      - Larotrectinib, entrectinib
    - For *BRAF* fusions and non-V600 mutations[s]
      - Trametinib
    - For *NRAS*-mutated tumors (for progression following immune checkpoint inhibitor therapy)
      - Binimetinib[t] (category 2B)
    - Combination therapy
      - Pembrolizumab/lenvatinib[u]
      - Ipilimumab[e]/intralesional T-VEC (category 2B)
    - Combination BRAF/MEK + PD(L)-1 checkpoint inhibitors (eg, dabrafenib/trametinib + pembrolizumab or vemurafenib/cobimetinib + atezolizumab)
    - Cytotoxic agents[v]
- Consider best supportive care for poor performance status (See NCCN Guidelines for Palliative Care)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

See footnotes on next page

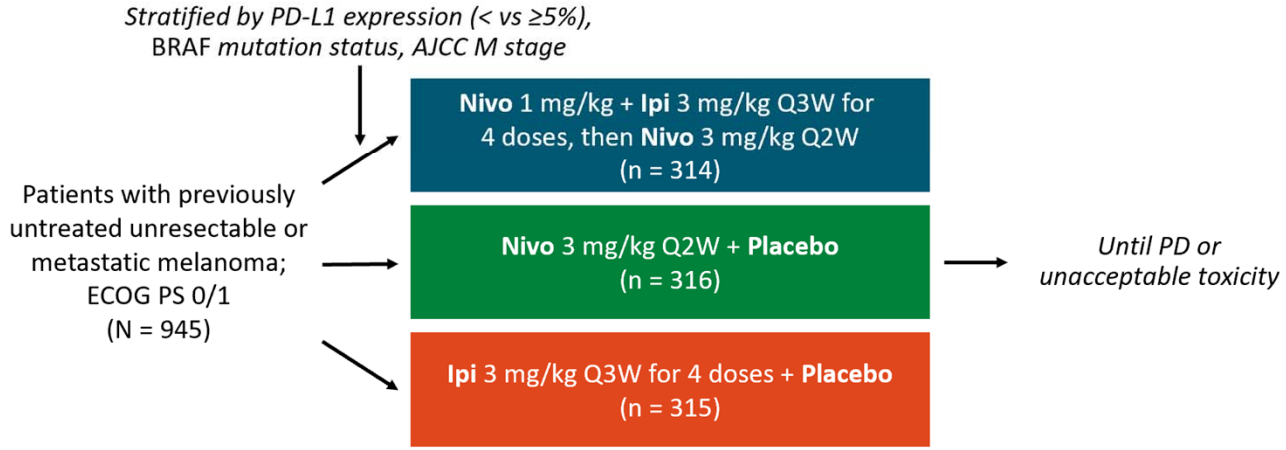
Checkmate 067: 7.5-year follow-up of Nivolumab + Ipilimumab in 1L metastatic melanoma

- Nivolumab, as a single agent or in combination with Ipilimumab, is indicated for the treatment of adult patients with unresectable or metastatic melanoma, including BRAF MT and WT patients

CheckMate 067: Long-term Survival and HRQoL With First-line Nivolumab ± Ipilimumab in Advanced Melanoma at 7.5-Yr Follow-up

CheckMate 067 7.5-Yr Follow-up: Study Design

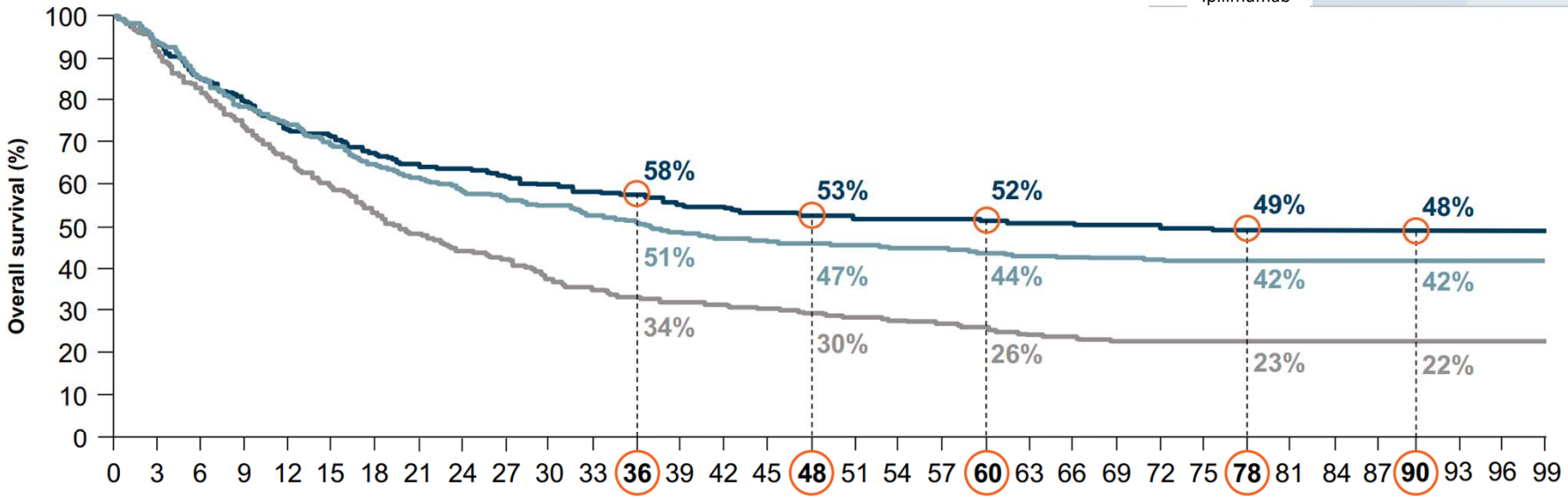
- International, randomized, double-blind phase III trial (data cutoff for current analysis: November 12, 2021; minimum follow-up: 90 mo)



- **Coprimary endpoints:** PFS and OS (nivo-containing arms vs ipi-only arm)
- **Secondary endpoints:** ORR, HRQoL, MSS, treatment-free analyses

OS analysis in the ITT population through 7.5 years[1-3]

	Nivolumab + Ipilimumab	Nivolumab (n=316)	Ipilimumab (n=315)
Median OS, mos (95% CI)[2]	72.1 (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.9–24.6)
HR (95% CI) vs Ipilimumab	0.53 (0.44–0.65)	0.63 (0.52–0.77)	–



No. at risk

314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	158	157	156	154	153	150	147	145	144	143	141	138	129	58	7	0
316	292	265	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	137	134	132	130	128	126	124	123	121	120	118	107	54	4	0
315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	75	70	68	64	64	63	63	63	63	62	57	24	5	0

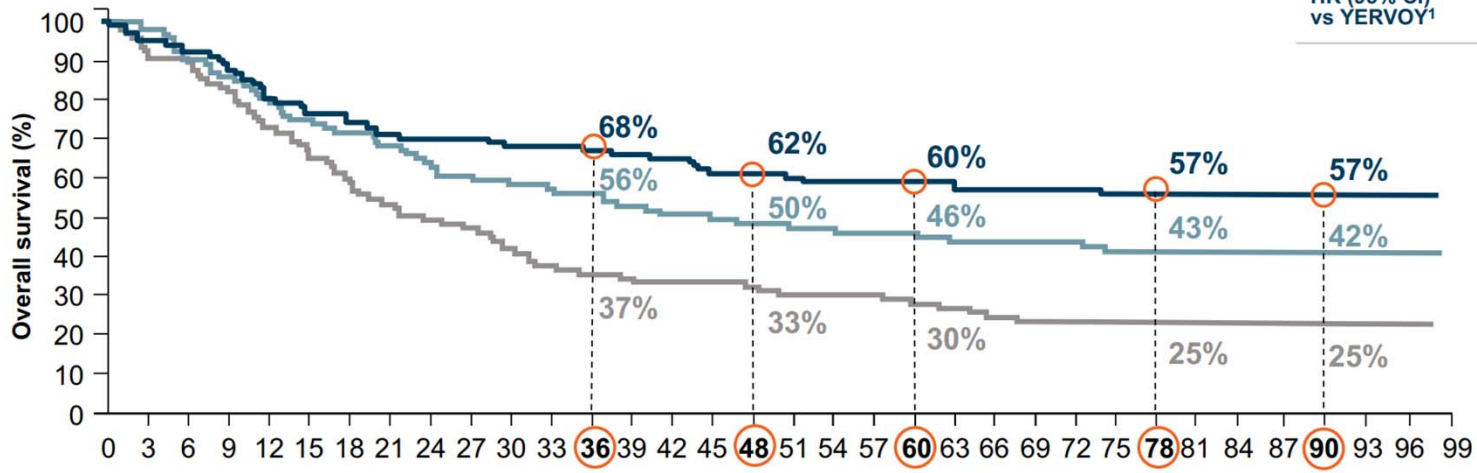
CI=confidence interval; HR=hazard ratio; ITT=intent to treat; mo=month; NR=not reached; OS=overall survival.

1. Data on file. NIVO 0151. Princeton, NJ: Bristol-Myers Squibb Company. 2. Hodi et al. Poster presentation at: ASCO 2022. 3. Wolchok JD, et al. Oral presentation at ASCO 2021. Abstract 9506. 4. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company.

OS in patients with *BRAF* MT tumors through 7.5 years[1-3]

	Nivolumab + Ipilimumab	Nivolumab (n=23)	Ipilimumab (n=28)
Median OS, mos (95% CI)[1]	NR (50.7–NR)	45.5 (26.4–93.6)	24.6 (17.9–31.0)
HR (95% CI) vs YERVOY[1]	0.43 (0.29–0.63)	0.65 (0.46–0.93)	–

BRAF MT subgroup: OS at 7.5 years[1-3]



No. at risk

103	99	96	91	83	80	77	74	73	73	71	71	70	69	67	63	63	61	60	60	60	58	58	57	56	56	56	56	56	56	52	2	2	0
98	93	86	81	75	69	67	64	57	56	55	53	52	48	47	45	44	43	42	42	41	40	40	40	39	38	38	38	38	37	34	0	0	0
100	91	88	81	71	64	58	53	49	47	41	37	36	33	33	33	30	29	29	28	27	25	23	21	21	21	21	21	21	20	20	7	0	0

Patients were stratified by *BRAF* status at baseline.[4]

OS analysis of this pre-specified subpopulation was not powered to detect statistical differences.[5]

1L=first-line; CI=confidence interval; HR=hazard ratio; mo=month; MT=mutant; NR=not reached; OS=overall survival; WT=wild-type.

1. Data on file. NIVO 0151. Princeton, NJ: Bristol-Myers Squibb Company. 2. Hodi et al. Poster presentation at: ASCO 2022. 3. Wolchok JD, et al. Oral presentation at ASCO 2021. Abstract 9506. 4. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2019;381 (16): 1535-1546. 5. Hodi FS, Chiarion-Sileni V, Gonzalez R, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (Checkmate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *Lancet Oncol*. 2018; 19(11):1480-1492.

CheckMate 067 7.5-Yr Follow-up: OS (Coprimary Endpoint)

OS	Nivo + Ipi (n = 314)	Nivo (n = 316)	Ipi (n = 315)
Median OS, mo (95% CI)	72.1 (38.2-NR)	36.9 (28.2-58.7)	19.9 (16.8-24.6)
HR (95% CI) vs ipi	0.53 (0.44-0.65)	0.63 (0.52-0.77)	--
HR (95% CI) vs nivo*	0.84 (0.68-1.04)	--	--
OS rate, %			
▪ 60 mo	52	44	26
▪ 72 mo	50	43	23
▪ 90 mo	48	42	22

OS Rate by *BRAF* Status, %	Nivo + Ipi	Nivo	Ipi
BRAF mutant	57	42	25
BRAF wild-type	43	41	21

- OS remains durable in patients regardless of *BRAF* status
- 4 deaths attributed to melanoma progression

Hodi. ASCO 2022. Abstr 9522.

CheckMate 067 7.5-Yr Follow-up: PFS (Coprimary Endpoint) and Melanoma-Specific Survival

PFS	Nivo + Ipi (n = 314)	Nivo (n = 316)	Ipi (n = 315)
Median, mo (95% CI)	11.5 (8.9-20.0)	6.9 (5.1-10.2)	2.9 (2.8-3.1)
HR (95% CI) vs ipi	0.42 (0.35-0.51)	0.53 (0.44-0.64)	--
HR (95% CI) vs nivo*	0.79 (0.65-0.97)	--	--
PFS rate, %			
▪ 60 mo	37	29	7
▪ 72 mo	36	29	7
▪ 90 mo	33	27	7

MSS*†	Nivo + Ipi (n = 314)	Nivo (n = 316)	Ipi (n = 315)
Median, mo (95% CI)	NR (71.9-NR)	49.4 (35.1-NR)	21.9 (18.1-27.4)
HR (95% CI) vs ipi	0.48 (0.39-0.60)	0.61 (0.49-0.75)	--
HR (95% CI) vs nivo*	0.79 (0.63-1.00)	--	--
MSS rate, %			
▪ 60 mo	57	49	30
▪ 72 mo	56	48	27
▪ 90 mo	55	47	26

Hodi. ASCO 2022. Abstr 9522.

Incidence and resolution of immune-related adverse reactions in the (nivolumab) + (ipilimumab) arm[1-3*]

	Any-grade IRAEs		Grade 3–5 IRAEs	
	Incidence, (n)	Resolution	Incidence, (n)	Resolution
Pneumonitis	(20) 6%	100%	(4) 1%	100%
Diarrhea/colitis	(79) 25%	95%	(49) 16%	98%
Hepatitis	(45) 14%	91%	(38) 12%	92%
Nephritis and renal dysfunction	(8) 3%	88%	(7) 2%	86%
Rash	(72) 23%	89%	(12) 4%	100%
Hypersensitivity	(2) 1%	50%	(0) 0%	NA
Endocrinopathies				
Hypophysitis	(26) 8%	50%	(9) 3%	78%
Adrenal insufficiency	(13) 4%	15%	(5) 2%	20%
Hypothyroidism/thyroiditis	(6) 2%	100%	(1) 0.3%	100%
Hyperthyroidism	(7) 2%	86%	(1) 0.3%	100%
Diabetes mellitus	(0) 0%	NA	(0) 0%	NA

IRAE analyses were limited to subjects who received immune-modulating medication for treatment of the event, with the exception of endocrine events.[2]

*Resolution was defined as improvement to Grade 0 or baseline grade per investigator assessment for all clustered events in a given category that occurred in a patient.[3]

IRAE=immune-related adverse event; NA=not available.

1. OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. 2. Data on file. NIVO 450. Princeton, NJ: Bristol-Myers Squibb Company; 2019.
3. Hodi FS, et al. *Lancet Oncol*. 2018;19(11):1480-1492 [supplementary appendix].

CheckMate 067 7.5-Yr Follow-up: Conclusions

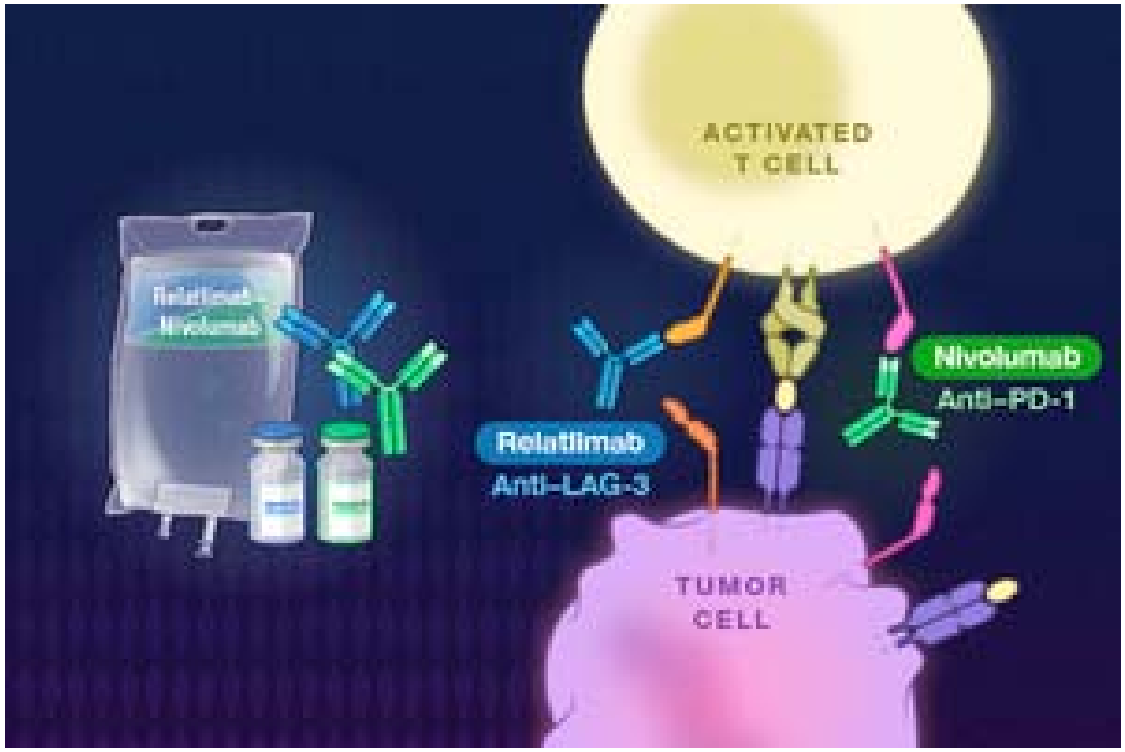
- In this analysis after 7.5 yr of follow-up, first-line nivo + ipi demonstrated durable survival benefits in patients with advanced melanoma
  - 7.5-yr OS rates: nivo + ipi, 48%; nivo only, 42%; ipi only, 22%
  - Nivo + ipi exhibited greater improvements in MSS and DoR vs nivo only and ipi only
- Patients receiving nivo + ipi had longer treatment-free intervals and lower likelihood of receiving subsequent systemic tx
- HRQoL outcomes comparable to 5-yr analysis with no sustained deterioration during treatment, after treatment discontinuation, or during treatment-free period

RELATIVITY-047: (nivolumab and relatlimab-rmbw) for the treatment of patients with unresectable or metastatic melanoma

RESEARCH SUMMARY

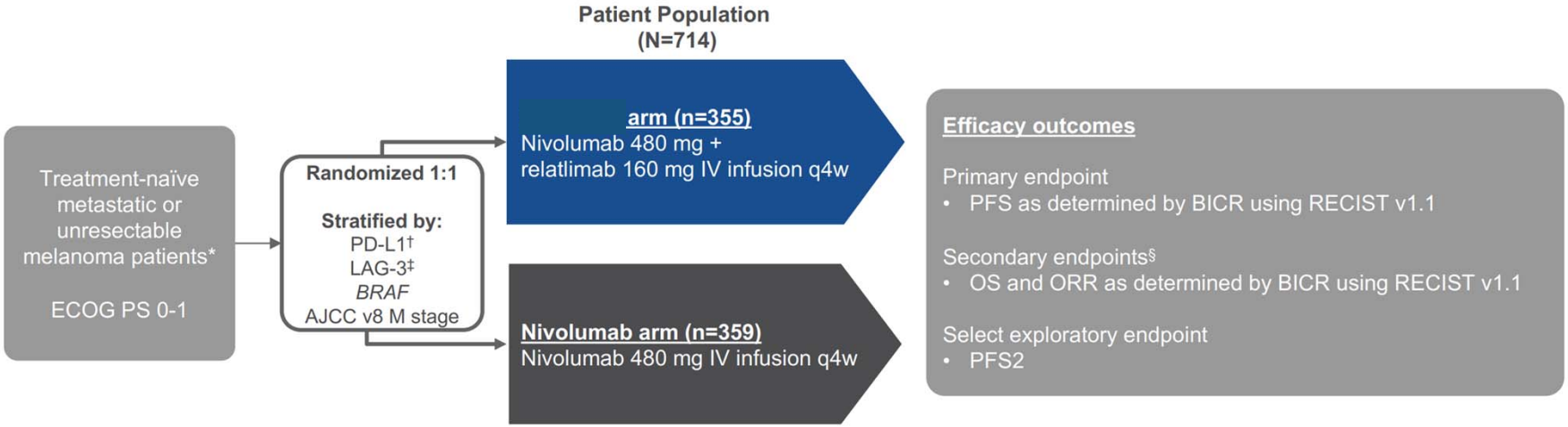
Relatlimab and Nivolumab vs. Nivolumab in Untreated Advanced Melanoma

Tawbi HA et al. DOI: 10.1056/NEJMoa2109970


ACTIVATED
T CELL
Nivolumab
Anti–PD-1
Relatlimab
Anti–LAG-3
TUMOR
CELL

Study Design

RELATIVITY-047: First phase 3 trial confirming the benefits of an anti–LAG-3 therapy in combination with the PD-L1 inhibitor, nivolumab[1,2]



Median duration of treatment for Opdualag at 19.3-month follow-up was 8.3 months.[3] Treat until disease progression or unacceptable toxicity.[1]

Inclusion criteria[1,2]:

- Histologically confirmed unresectable stage III or stage IV melanoma
- Expression of LAG-3 and PD-L1 that could be evaluated in tumor tissue

Exclusion criteria[1]:

- Patients with active autoimmune disease
- Medical conditions requiring systemic treatment with moderate- or high-dose corticosteroids or immunosuppressive medications
- Patients with uveal melanoma
- Patients with active or untreated brain or leptomeningeal metastases

*Patients were allowed to have received prior adjuvant and neoadjuvant melanoma therapy. Anti–PD-1, anti–CTLA-4, or *BRAF*-MEK therapy was allowed as long as there was at least 6 months between the last dose of therapy and date of recurrence; interferon therapy was allowed as long as the last dose was at least 6 weeks prior to randomization.[1] †PD-L1 expression (≥1% vs <1%) using PD-L1 IHC 28-8 pharmDx test.[1] ‡LAG-3 expression (≥1% vs <1%) using a clinical trial assay.[1] §The final analysis of OS was not statistically significant.[1]

AJCC=American Joint Committee on Cancer; BICR=blinded independent central review; *BRAF*=B-Raf proto-oncogene; CTLA-4=cytotoxic T-lymphocyte antigen 4; ECOG PS=Eastern Cooperative Oncology Group Performance Status; IHC=immunohistochemistry; IV=intravenous; ORR=overall response rate; OS=overall survival; PD-L1=programmed death ligand 1; PFS=progression-free survival; PFS2=second progression-free survival; q4w=every 4 weeks; RECIST=Response Evaluation Criteria In Solid Tumors.

Baseline characteristics across prespecified subgroups[1,2]

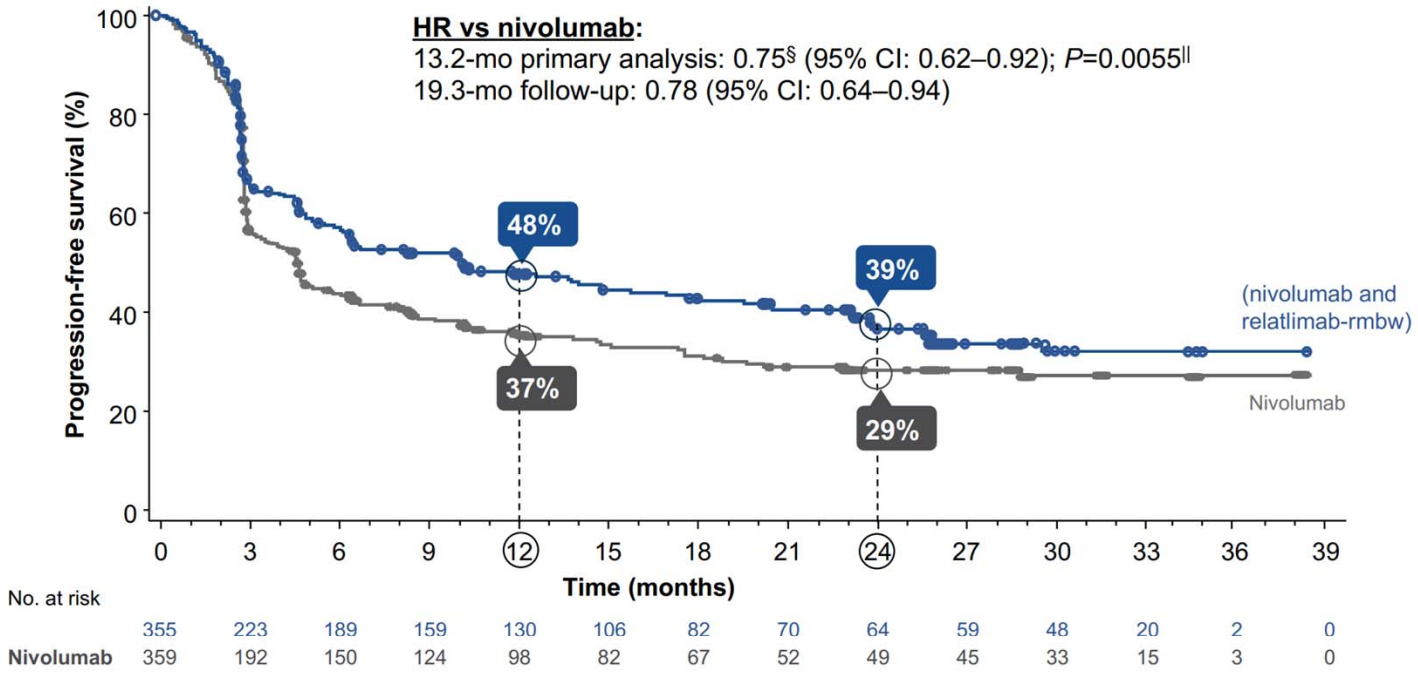
Characteristic		(nivolumab and relatlimab-rmbw) (n=355)	Nivolumab (n=359)
Median age, years		63	62
Female, n (%)		145 (40.8)	153 (42.6)
AJCC v8 M stage, n (%)	M0 M1A or B M1C M1D	35 (9.9) 162 (45.6) 151 (42.5) 6 (1.7)	23 (6.4) 195 (54.3) 127 (35.4) 11 (3.1)
ECOG PS, n (%)	0 1	236 (66.5) 119 (33.5)	242 (67.4) 117 (32.6)
Serum LDH level, n (%)	>ULN >2x ULN	130 (36.6) 32 (9.0)	128 (35.7) 31 (8.6)
Prior systemic therapy,* n (%)			
Adjuvant		31 (8.7)	26 (7.2)
Neoadjuvant		2 (0.6)	1 (0.3)
Unknown or other		0	2 (0.6)
Tumor burden, median (min–max), mm		59.0 (10–317)	54.5 (10–548)
Melanoma subtype classification	Cutaneous acral Cutaneous non acral Mucosal Other	41 (11.5) 249 (70.1) 23 (6.5) 42 (11.8)	41 (11.4) 254 (70.8) 28 (7.8) 36 (10.0)
Stratification factor, n (%)			
***BRAF* mutation status**	Mutant Wild-type	136 (38.3) 219 (61.7)	139 (38.7) 220 (61.3)
AJCC v8 M stage (metastasis stage with LDH level)	M0, M1, and normal LDH level M1 and elevated LDH level	232 (65.4) 123 (34.6)	237 (66.0) 122 (34.0)
PD-L1 expression	≥1% <1%	146 (41.1) 209 (58.9)	147 (40.9) 212 (59.1)
LAG-3 expression	≥1% <1%	268 (75.5) 87 (24.5)	269 (74.9) 90 (25.1)

*Most common therapy was interferon.[1,2]

AJCC=American Joint Committee on Cancer; ECOG PS=Eastern Cooperative Oncology Group Performance Status; LAG-3=lymphocyte-activation gene 3; LDH=lactate dehydrogenase; PD-L1=programmed death ligand 1; ULN=upper limit of normal.

PFS*†‡ in the ITT population[1,2,4]

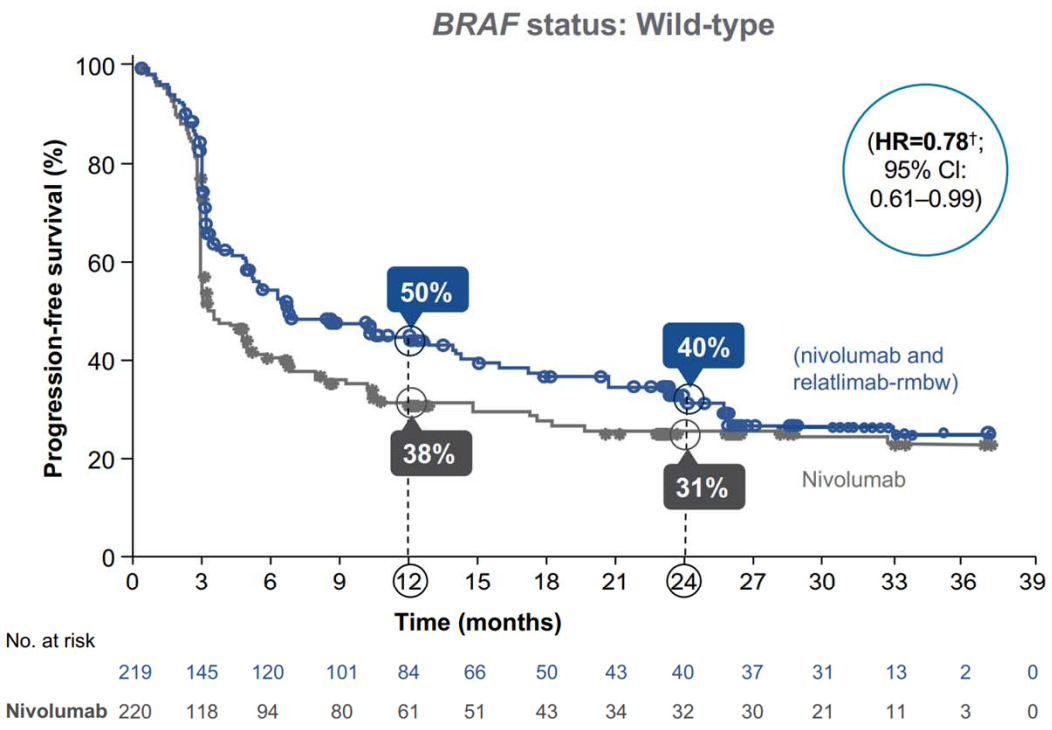
Progression-free survival at the 19.3-month median follow-up*†‡



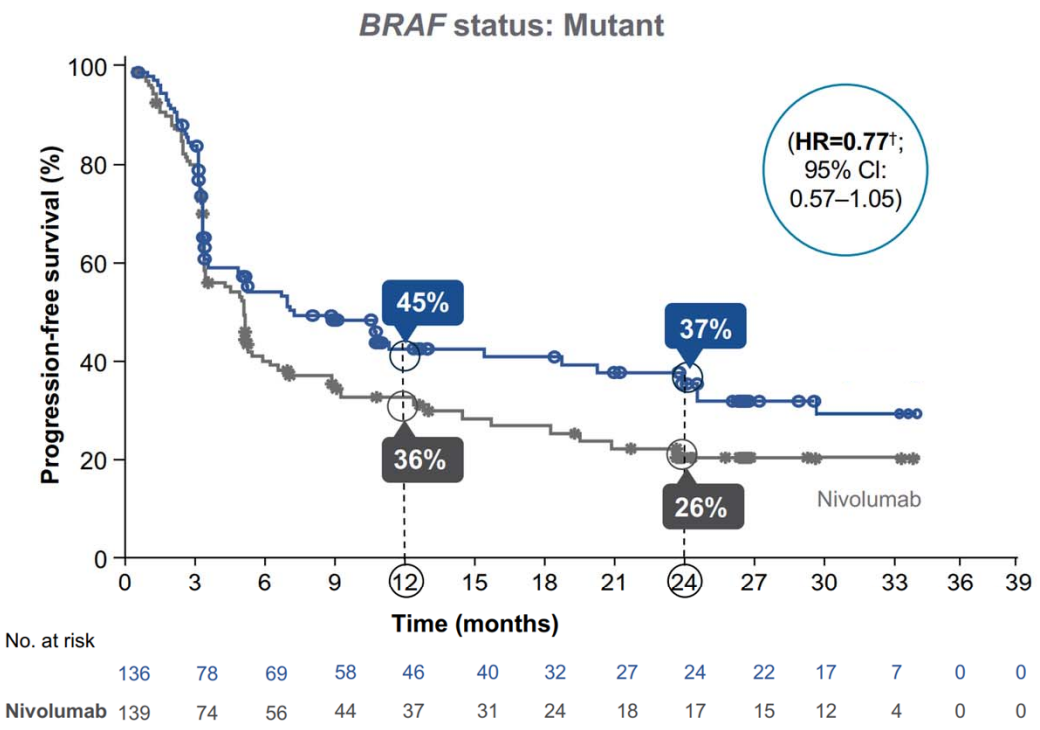
Symbols represent censored observations.[1]

*Assessed by BICR. †Final PFS analysis.[1] ‡Kaplan-Meier estimate.[1] §Based on stratified log Cox proportional hazard model.[1] ‖Based on stratified log-rank test.[1]
AJCC=American Joint Committee on Cancer; CI=confidence interval; HR=hazard ratio; ITT=intent to treat; LAG-3=lymphocyte-activation gene 3; M stage=melanoma stage; PD-L1=programmed death ligand 1; PFS=progression-free survival.

Progression-free survival* by *BRAF* mutation status at the 19.3-month median follow-up[5]



Symbols represent censored observations.[1]

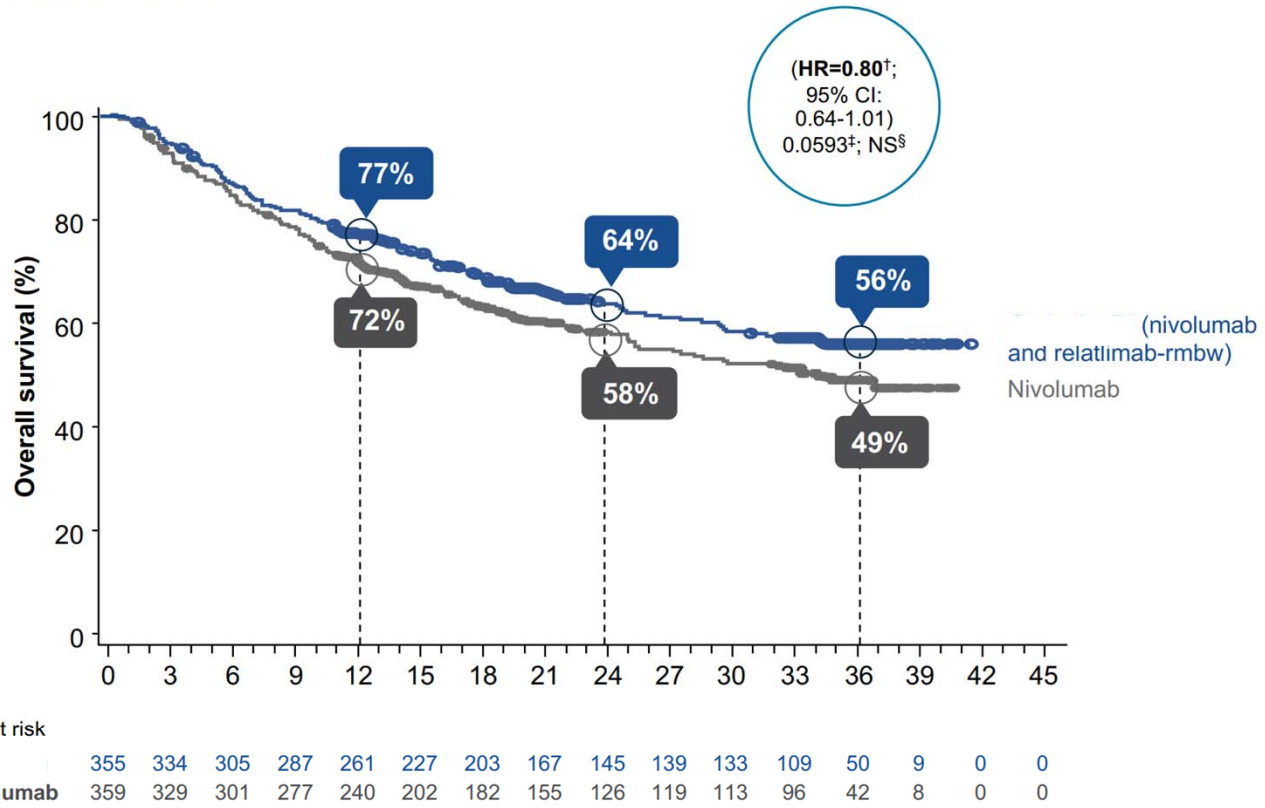


Symbols represent censored observations.

*Assessed by BICR.[5] †Based on unstratified Cox proportional hazard model.[5]
BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio.

Median OS* has not yet been reached vs 34.1 months for nivolumab monotherapy[1,4]

Overall survival* in RELATIVITY-047



Symbols represent censored observations.[1]

OS did not reach statistical significance.[1] Median follow-up was 19.3 months.[1,2]

*At the time of the final OS analysis, which was event-driven and occurred after the final PFS analysis.[1] †Based on stratified Cox proportional hazard model.[1] ‡Based on stratified log-rank test. §Not significant at alpha level 0.04302.[1]
CI=confidence interval; HR=hazard ratio; OS=overall survival.

Adverse reactions occurring in ≥15% of patients in RELATIVITY-047[1]

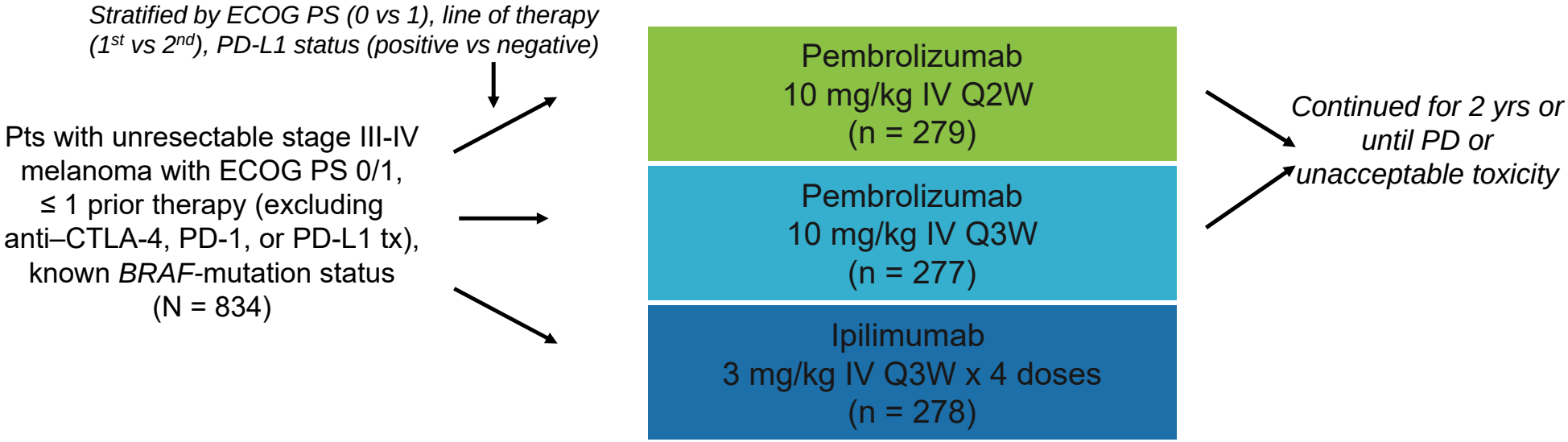
	[redacted] (nivolumab and relatlimab-rmbw) (n=355)	Nivolumab (n=359)	[redacted] (n=355)	Nivolumab (n=359)
Adverse Reaction*	**All Grades (%)**		**Grades 3/4 (%)**	
Musculoskeletal and Connective Tissue				
Musculoskeletal pain†	45	31	4.2	1.7
General				
Fatigue†	39	29	2	0.6
Skin and Subcutaneous Tissue				
Rash†	28	21	1.4	1.9
Pruritus	25	17	0	0.6
Gastrointestinal				
Diarrhea†	24	17	2	1.4
Nausea	17	14	0.6	0
Nervous System				
Headache†	18	12	0.3	0.3
Endocrine				
Hypothyroidism†	17	14	0	0
Metabolism and Nutrition Disorders				
Decreased Appetite	15	7	0.6	0.3
Respiratory, Thoracic, and Mediastinal Disorders				
Cough†	15	11	0.3	0

- Grade 3/4 increases greater than 1% vs nivolumab monotherapy were fatigue (1.4%) and musculoskeletal pain (2.5%)[1]
- Treatment-related discontinuation rates were 14.6% with Opdualag vs 6.7% with nivolumab[8]
  - Grade 1/2 discontinuation rate was 5.8% with Opdualag vs 3.6% with nivolumab
  - Grade 3/4 discontinuation rate was 8.5% with Opdualag vs 3.1% with nivolumab
- With 19.3 months median follow-up, there were no new or unexpected safety events observed with the combination of nivolumab plus relatlimab. The safety profile of nivolumab plus relatlimab remains consistent and in line with the analyses previously presented and included within the Opdualag PI[4]

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.
*Clinically relevant adverse reactions in <15% of patients who received Opdualag included vitiligo, adrenal insufficiency, myocarditis, and hepatitis.[1] †Includes multiple terms.[1]

KEYNOTE-006: Study Design

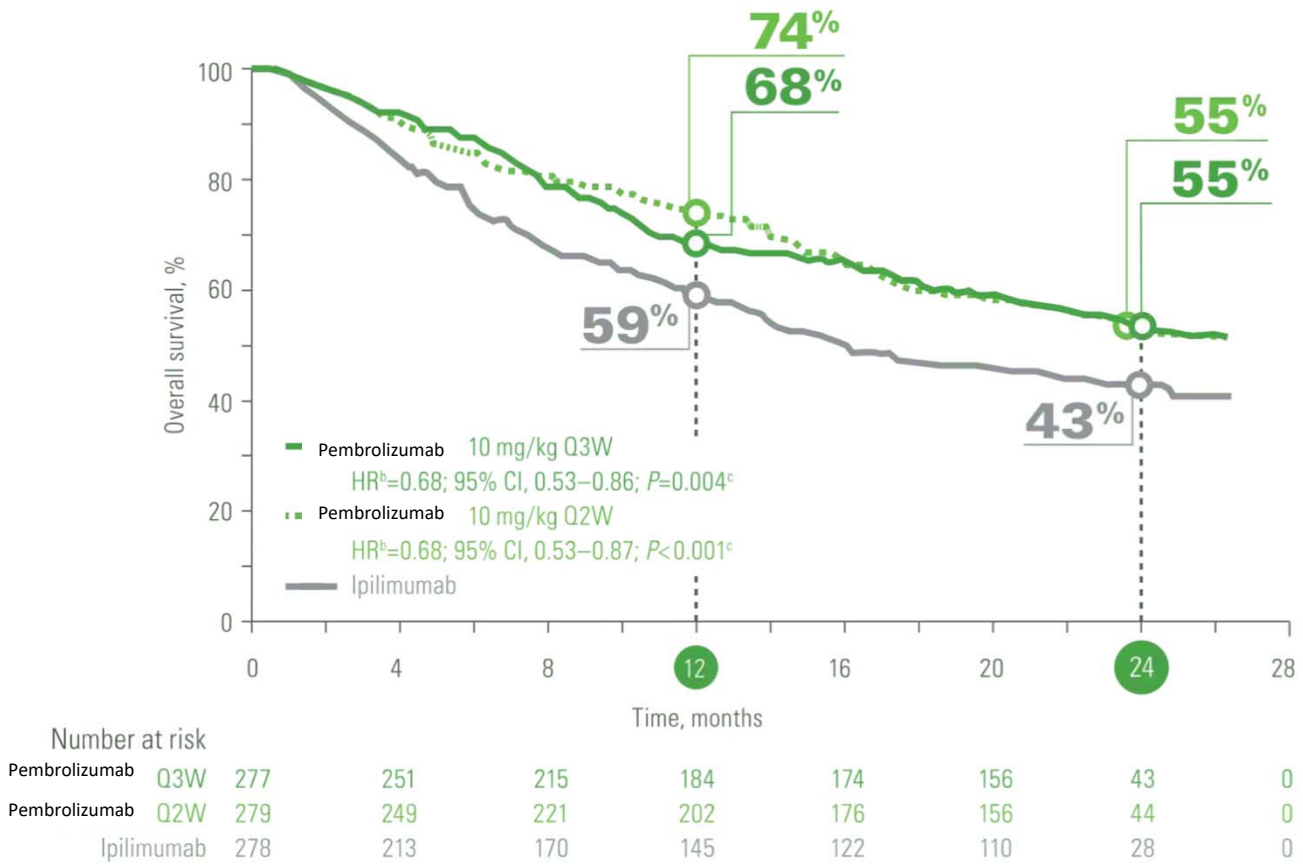
- International, randomized, open-label, active-controlled phase III study



- Endpoints: primary: PFS, OS; secondary: ORR, DoR, safety
- Long-term analysis: pembrolizumab arms pooled for analyses; protocol-specified time on pembrolizumab: ≥ 21.6 mos

Robert C, et al. ASCO 2017. Abstract 9504.

Clinical Findings from KEYNOTE-006



KEYNOTE-006: Baseline Characteristics

Characteristic	Pembrolizumab (n = 556)	Ipilimumab (n = 278)
Median age, yrs (range)	62 (18-89)	62 (18-88)
Male, %	60	58
ECOG PS 0, %	69	68
Elevated LDH, %	32	33
BRAF V600–mutation positive, %	35	38
PD-L1 positive, %	80	81
M1c disease, %	66	64
1 prior therapy, %	34	35

Robert C, et al. ASCO 2017. Abstract 9504.

KEYNOTE-006: Exposure and Adverse Events

AE	Pembrolizumab (n = 555)	Ipilimumab (n = 256)
Median exposure, mos (range)	5.70 (0.03-29.60)	2.10 (0.03-3.00)
Treatment-related AE, %	79	74
▪ Grade 3/4	17	19
▪ Led to death	< 1	0
▪ Led to discontinuation	10	9
Immune-mediated AE, %	26	19
▪ Grade 3/4	9	12
▪ Led to death	0	0
▪ Led to discontinuation	5	5

- Most common immune-mediated AEs (all incidence ≤ 11%): hypothyroidism, hyperthyroidism, colitis, skin disorders, pneumonitis

Robert C, et al. ASCO 2017. Abstract 9504.

KEYNOTE-006: Conclusions

- Superiority of pembrolizumab over ipilimumab confirmed in advanced melanoma with nearly 3-yr median follow-up
  - Prolonged PFS, OS with pembrolizumab
  - Favorable safety profile with pembrolizumab
- Favorable outcomes for pts who completed protocol-specified pembrolizumab treatment
  - 91% PFS after median follow-up 9.7 mos
- Investigators concluded that data from this study further support pembrolizumab as standard of care for advanced melanoma

Robert C, et al. ASCO 2017. Abstract 9504.

Thank You