Memorial Sloan Kettering Cancer Center

LUDWIG CANCER RESEARCH

Combination Checkpoint Blockade

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Disclosures: Jedd D. Wolchok, MD, PhD

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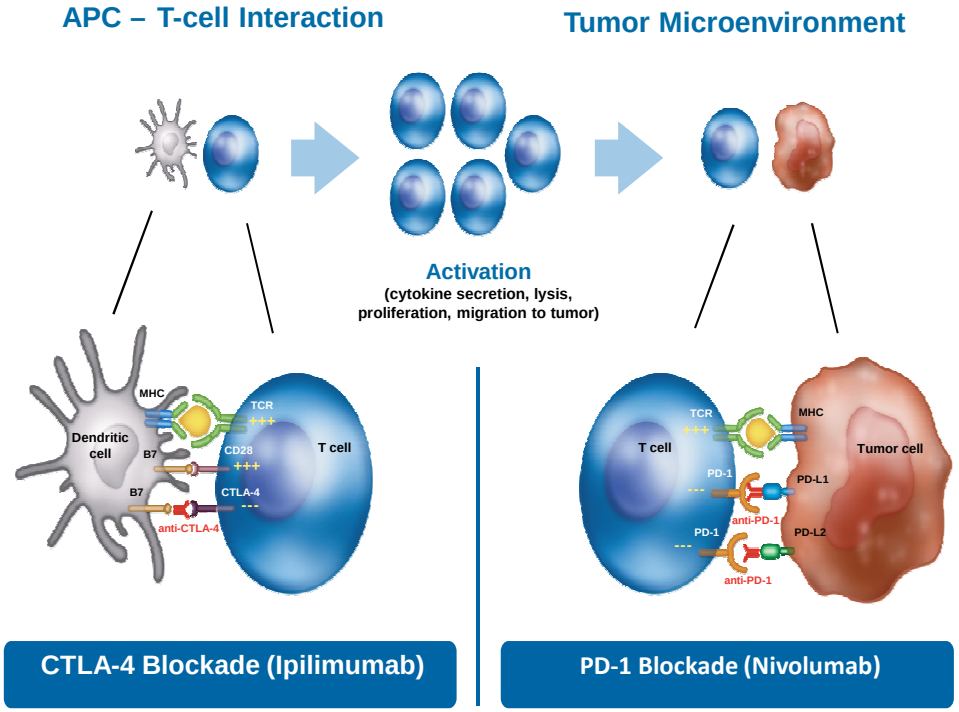
Biologic Rationale for Combined PD-1 and CTLA-4 Blockade

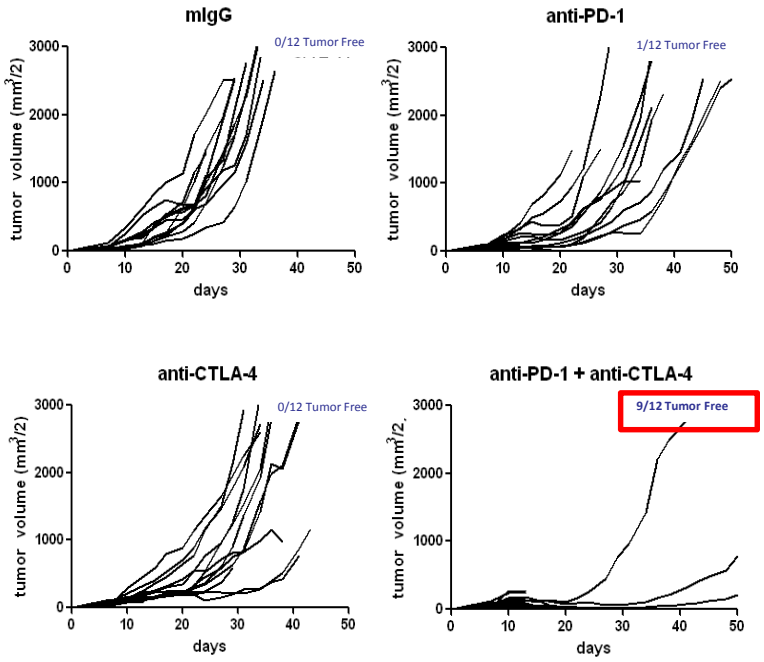
- Ipilimumab (IPI) monotherapy in melanoma improves OS (~20% of treated patients alive ≥3 years)[1]
- Phase III studies of nivolumab (NIVO) monotherapy in advanced melanoma:[2,3]
  - 1-year OS rate of 73% and ORR of 40% in untreated melanoma (BRAF wild-type)
  - ORR of 32% after progression on IPI, or IPI and a BRAF inhibitor if BRAF mutation-positive



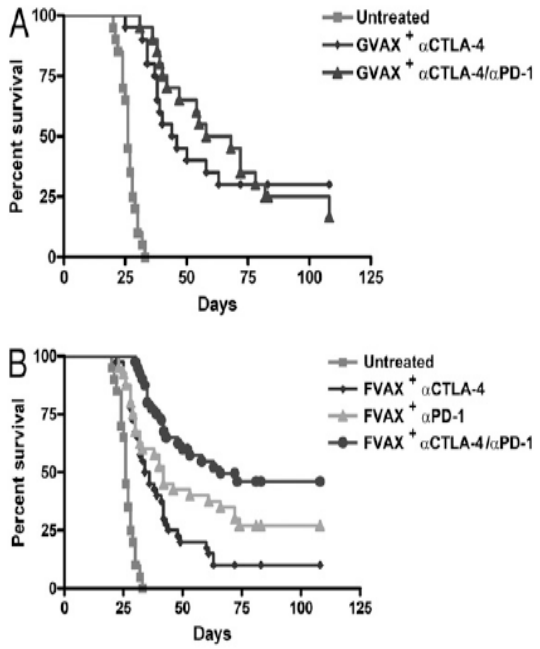
1. Schadendorf et al. *J Clin Oncol* 2015 Feb 9 [Epub ahead of print]; 2. Robert et al. *N Engl J Med* 2015;372:320-330; 3. Weber et al. *Lancet Oncol* 2015;16:375-384.

Antitumor Activity of Anti-CTLA-4 and Anti-PD-1 Antibodies in Murine Tumor Models

MC38 Colon Cancer
Antibody Rx Only[1,2]



B16BL6 Melanoma
Antibody Rx + Cellular Vaccine[3]



1. Korman et al. *J Immunol* 2007;178:48.37. 2. Selby et al. ASCO 2013, abs 3061. 3. Curran et al. *Proc Natl Acad Sci USA* 2010;107:4275-4280.

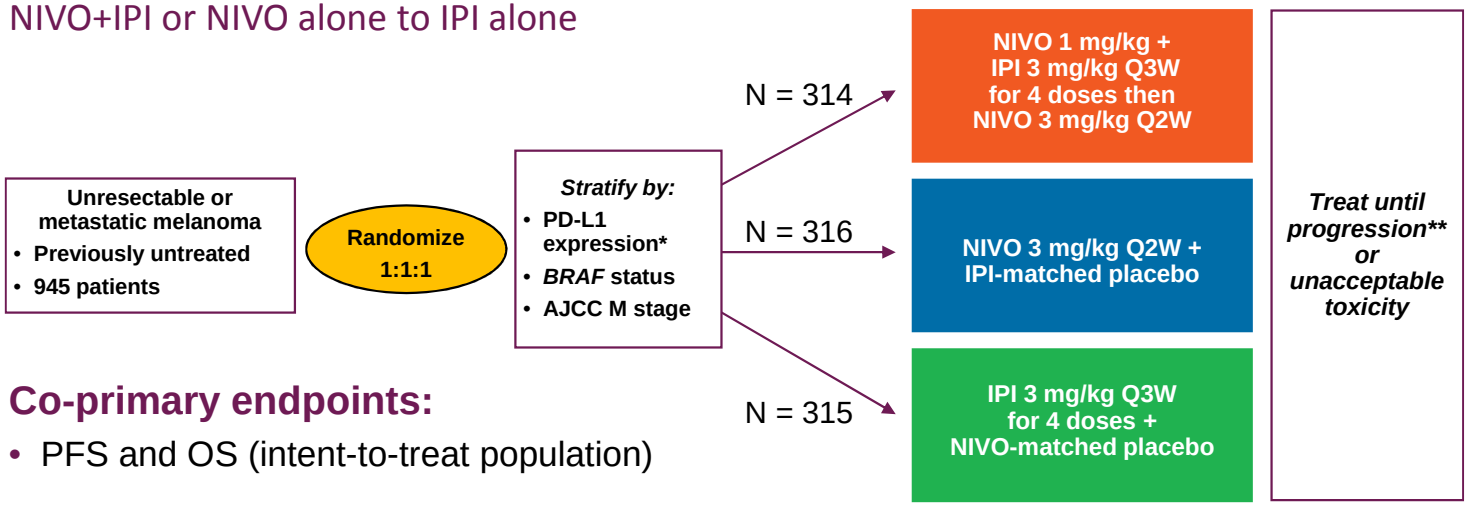
Clinical Experience With Nivolumab Plus Ipilimumab Combination

- Phase I study of nivolumab (NIVO) plus ipilimumab (IPI) in advanced melanoma[1,2]:
  - Objective response rate (ORR) up to 53% (complete response [CR] rate of 18%)
  - 2-year overall survival (OS) rate up to 88%
- Phase II study of NIVO+IPI in untreated melanoma[3]:
  - ORR of 59% with the combination vs 11% for IPI alone; CR rate of 22% with the combination
  - Treatment-related grade 3–4 adverse events (AEs): 54% for the combination vs 24% for IPI
- In the above studies, response rates were similar regardless of PD-L1 expression[1-3]

1. Wolchok et al. *N Engl J Med* 2013;369:122–33; 2. Oral presentation by Dr. Mario Sznol at the ASCO 2014 Annual Meeting; 3. Postow et al. *N Engl J Med* 2015;372:2006–17.

CheckMate 067: Study Design

Randomized, double-blind, phase 3 study to compare NIVO+IPI or NIVO alone to IPI alone



Co-primary endpoints:

- PFS and OS (intent-to-treat population)

Secondary and other endpoints:

- ORR by RECIST v1.1
- Predefined tumour PD-L1 expression level as a predictive biomarker of efficacy
- Safety profile (in patients who received ≥1 dose of study drug)

*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.

Larkin et al. *N Engl J Med* 2015;373:23–34; Previously presented by Dr. James Larkin at the ECC 2015 Annual Meeting

Key Eligibility Criteria

- Histologically confirmed stage III (unresectable) or stage IV melanoma
- No prior systemic therapy for unresectable or metastatic melanoma
  - Prior adjuvant therapy allowed
- Age ≥18 years
- ECOG performance status of 0 or 1
- Tumour tissue available for assessment of PD-L1 expression
- Known *BRAF* V600 mutational status
- No active brain metastases, ocular melanoma, or autoimmune disease

Larkin et al. *N Engl J Med 2015;373:23–34*; Previously presented by Dr. Jedd Wolchok at the ASCO 2015 Annual Meeting

Baseline Patient Characteristics

	NIVO+IPI (N = 314)	NIVO (N = 316)	IPI (N = 315)
Median age, years (range)	61 (18–88)	60 (25–90)	62 (18–89)
Age ≥65 years, %	41	37	42
Age ≥75 years, %	11	12	14
Sex — Male, %	66	64	64
ECOG performance status of 0,* %	73	75	71
M stage — M1c, %	58	58	58
LDH — >ULN, %	36	35	37
LDH — >2x ULN, %	12	12	10
Brain metastases	4	3	5
PD-L1 expression ≥5%, ** **%**	22	25	24
***BRAF* V600 mutant, %**	32	32	31

- Median follow-up ranged from 12.2 to 12.5 months across treatment groups

*Remaining patients had an ECOG PS of 1, except for one patient with a PS of 2 (NIVO) and one unreported (NIVO+IPI)
**Pre-treatment tumour specimens were centrally assessed by PD-L1 immunohistochemistry using a validated BMS/Dako assay

LDH = lactate dehydrogenase; ULN = upper limit of normal

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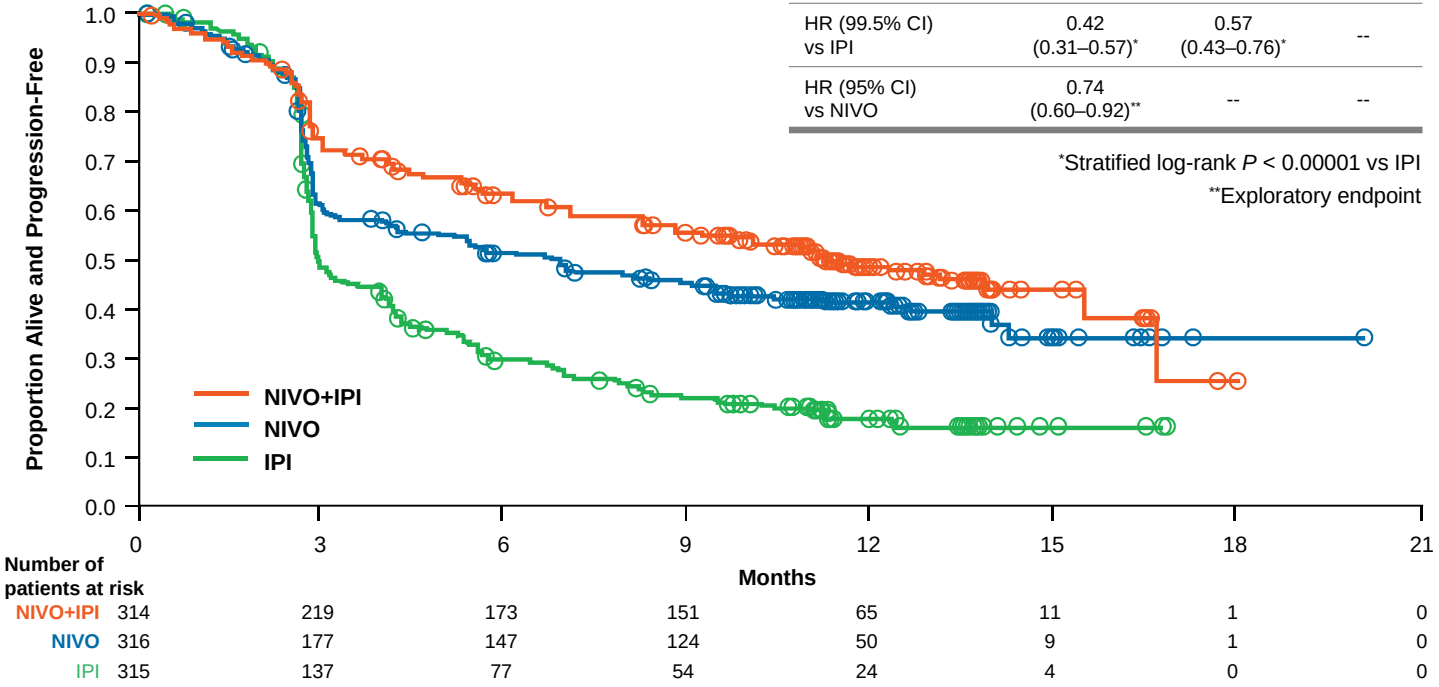
PFS (Intent-to-Treat)

	NIVO+IPI (N = 314)	NIVO (N = 316)	IPI (N = 315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs IPI	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	--
HR (95% CI) vs NIVO	0.74 (0.60–0.92)**	--	--

*Stratified log-rank $P < 0.00001$ vs IPI

**Exploratory endpoint



Number of patients at risk								
NIVO+IPI	314	219	173	151	65	11	1	0
NIVO	316	177	147	124	50	9	1	0
IPI	315	137	77	54	24	4	0	0

CI = confidence interval; HR = hazard ratio

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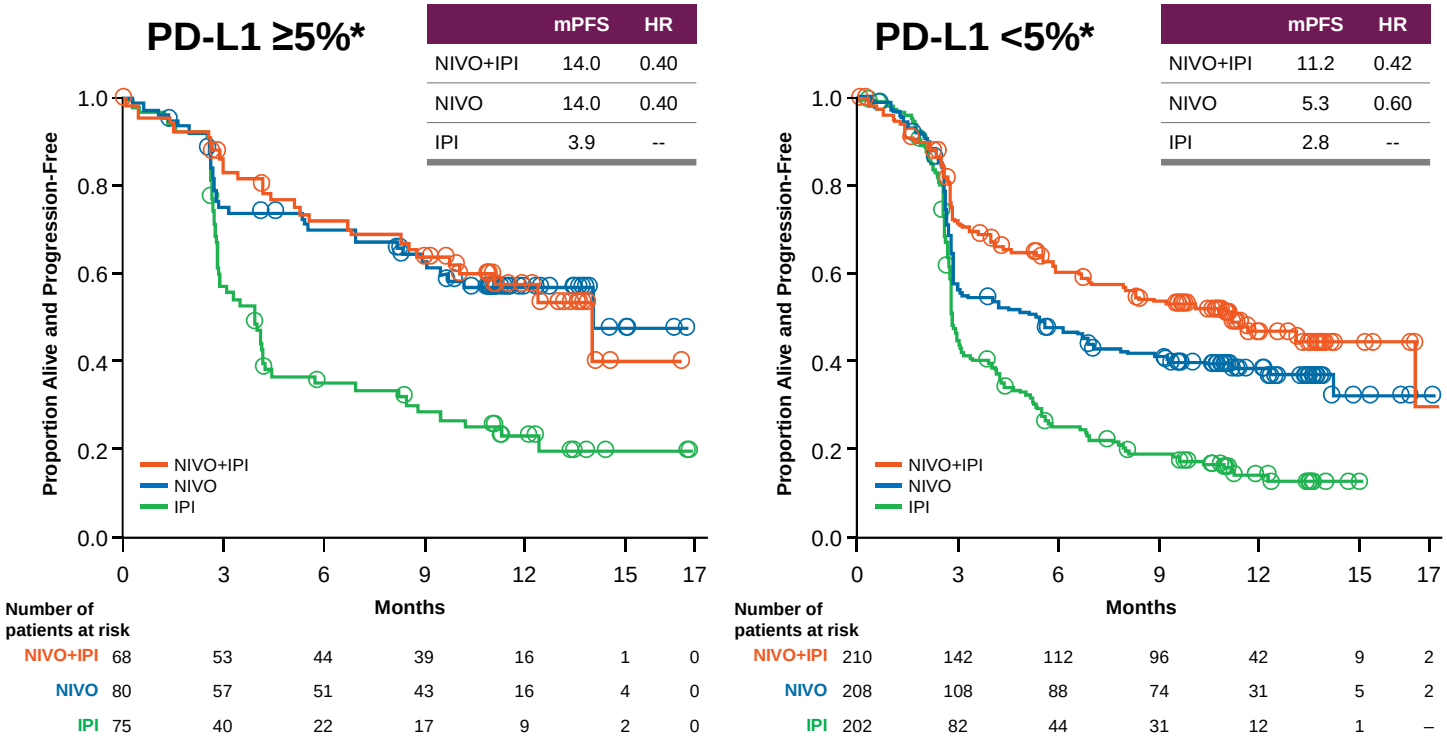
PFS by PD-L1 Expression Level (5%)



*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumour cells in a section of at least 100 evaluable tumour cells

HR = hazard ratio; mPFS = median PFS

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Response to Treatment

	NIVO+IPI (N = 314)	NIVO (N = 316)	IPI (N = 315)
ORR, % (95% CI)*	57.6 (52.0–63.2)	43.7 (38.1–49.3)	19.0 (14.9–23.8)
Two-sided *P* value vs IPI	<0.001	<0.001	--
Best overall response , (%)			
Complete response	11.5	8.9	2.2
Partial response	46.2	34.8	16.8
Stable disease	13.1	10.8	21.9
Progressive disease	22.6	37.7	48.9
Unknown	6.7	7.9	10.2
Duration of response (months)			
Median (95% CI)	NR (13.1–NR)	NR (11.7–NR)	NR (6.9–NR)

*By RECIST v1.1.

CI = confidence interval; NR = not reached

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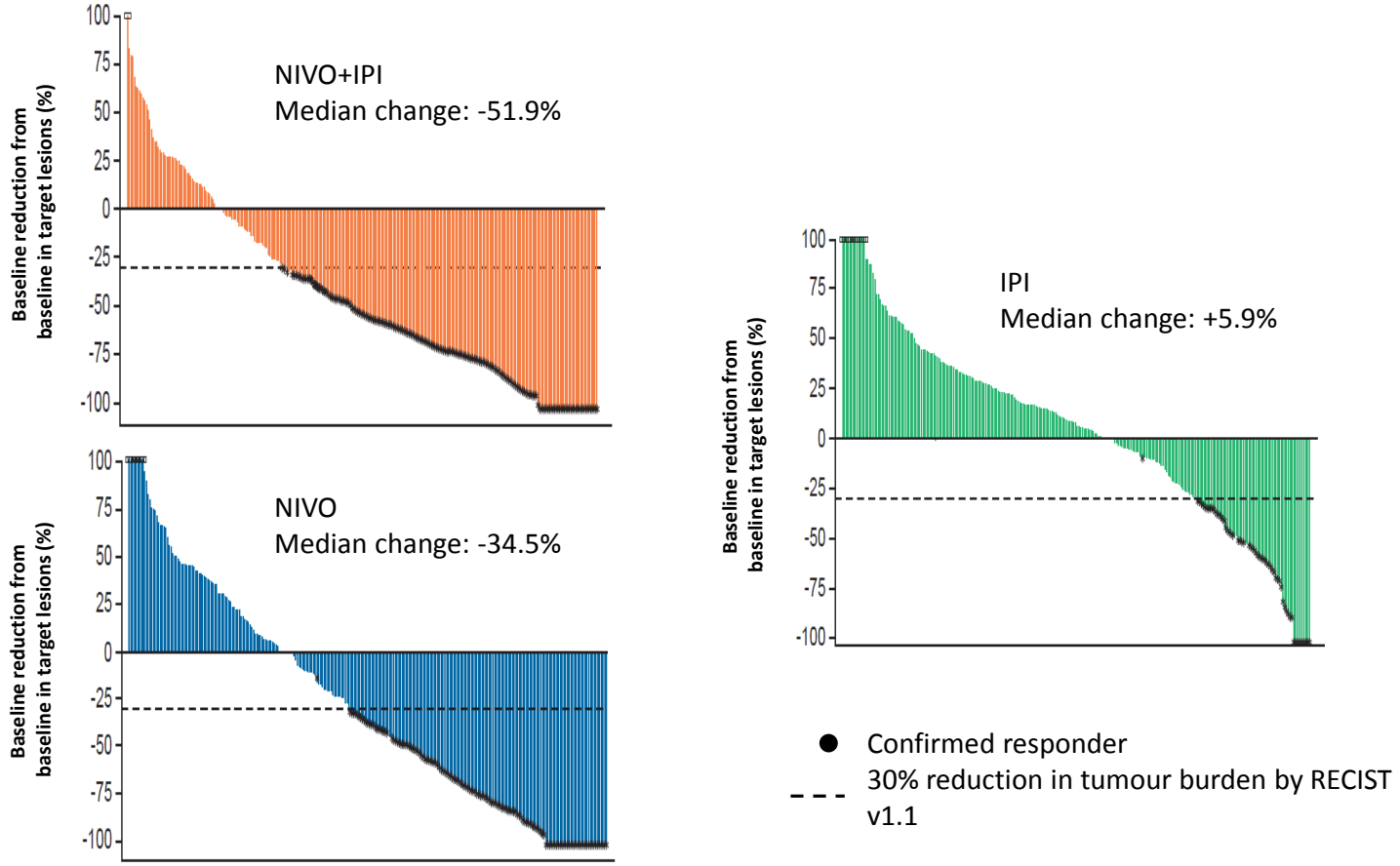
Tumour Burden Change From Baseline



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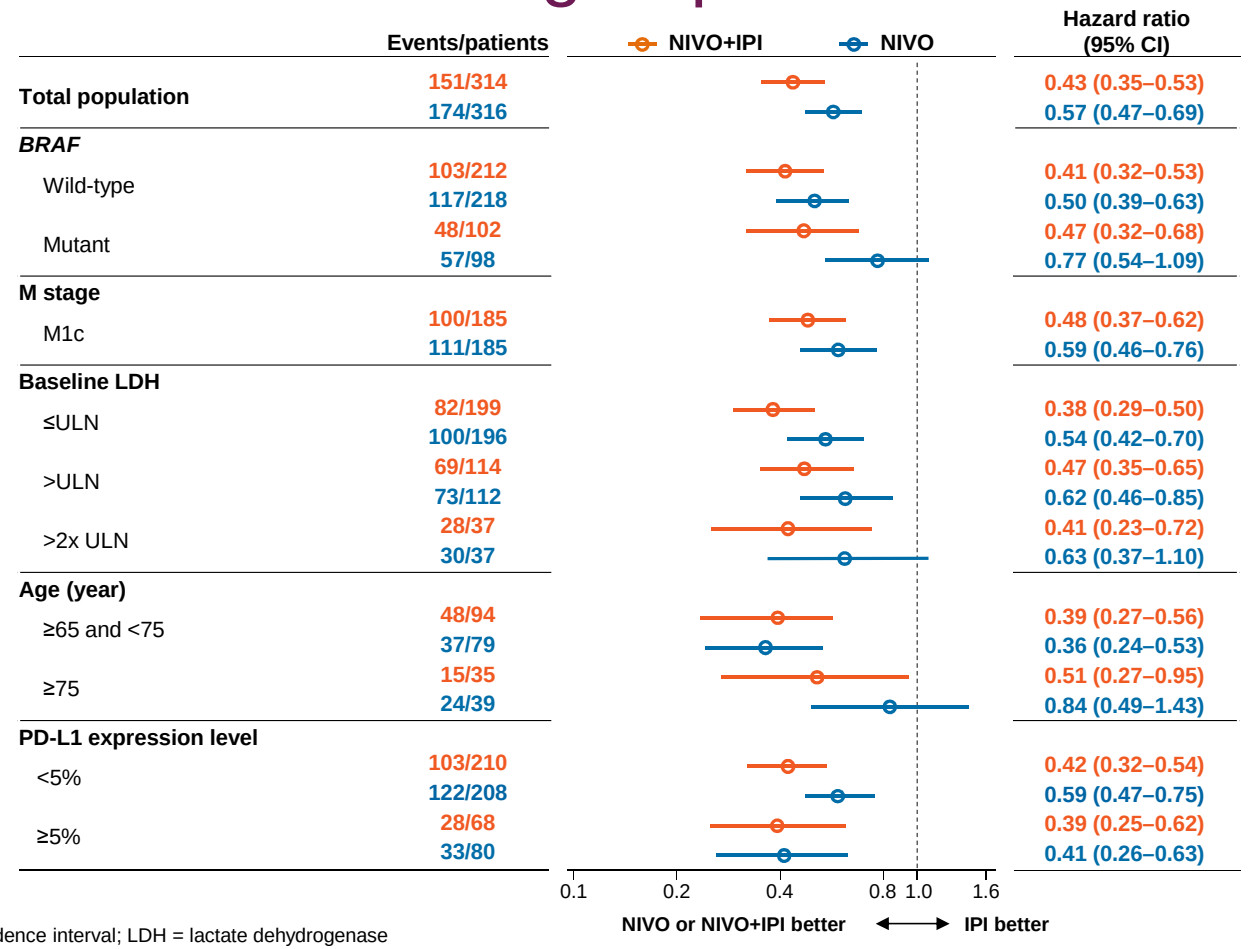
PFS in Patient Subgroups



CI = confidence interval; LDH = lactate dehydrogenase

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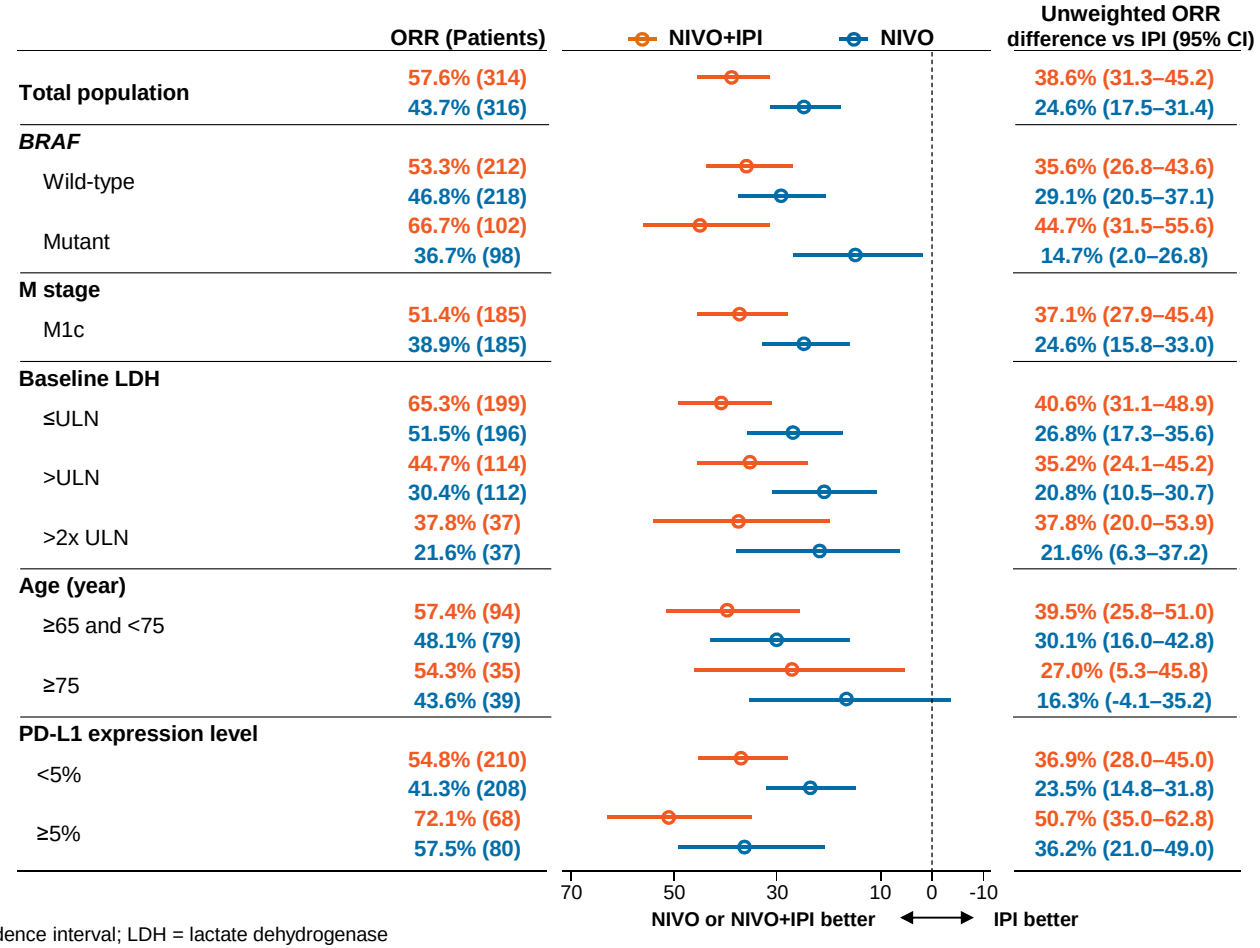
ORR in Patient Subgroups



CI = confidence interval; LDH = lactate dehydrogenase

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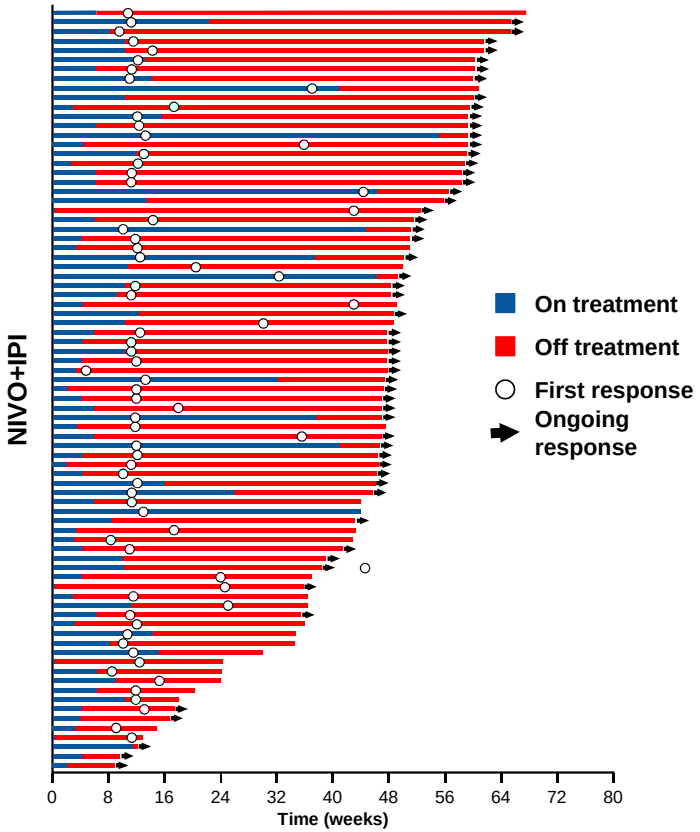
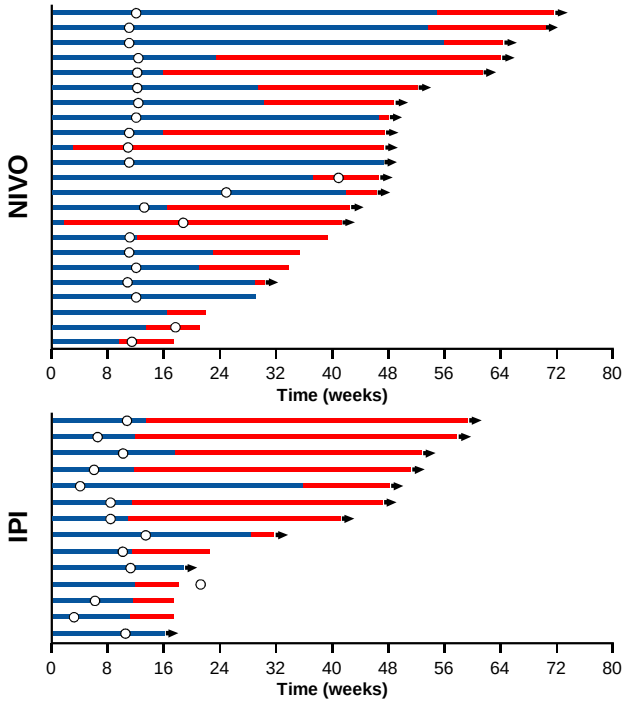
Time to and Durability of Response in Patients Who Discontinued Due to Toxicity

- A total of 38% (120/314) of patients who received NIVO+IPI discontinued due to toxicity





- 68% (81/120) of patients who discontinued NIVO+IPI due to drug-related toxicity experienced a complete or partial response

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Safety Summary by Key Subgroups

Patients Reporting Event, %	NIVO+IPI (N = 313)		NIVO (N = 313)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Treatment-related AE	96	55	82	16
Age ≥65 and <75 years	95	50	81	22
Age ≥75 and <85 years	97	48	83	21
M1c disease	94	54	79	14
PD-L1 expression ≥5%	97	53	85	16
Patients with complete response	100	58	93	32
Treatment-related AE leading to discontinuation	36	29	8	5
Treatment-related death*	0		<1	

- Treatment-related AEs reported with IPI were consistent with prior experience

*One death in the NIVO group was reported as neutropaenia

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Treatment-Related Select AEs Reported in ≥10% of Patients

Patients Reporting Event, %	NIVO+IPI (N = 313)		NIVO (N = 313)		IPI (N = 311)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Skin	59	6	42	2	54	3
Pruritus	33	2	19	0	36	<1
Rash	28	3	22	<1	21	2
Rash maculo-papular	12	2	4	<1	12	<1
Gastrointestinal	46	15	20	2	37	12
Diarrhoea	44	9	19	2	33	6
Colitis	12	8	1	1	12	9
Hepatic	30	19	6	3	7	2
Elevated ALT	18	8	4	1	4	2
Elevated AST	15	6	4	1	4	1
Endocrine	30	5	14	1	11	2
Hypothyroidism	15	<1	9	0	4	0

- Immune modulators were used to manage AEs in 83% in the NIVO+IPI group, 47% of patients in the NIVO group, and 56% in the IPI group

ALT = alanine aminotransferase; AST = aspartate aminotransferase

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Grade ≥2 Treatment-Related Select AEs Across Organ Categories

Number of organ categories impacted, n (%)*	All treated patients		
	NIVO+IPI (N = 313)	NIVO (N = 313)	IPI (N = 311)
0	91 (29)	236 (75)	171 (55)
1	125 (40)	61 (20)	112 (36)
2	77 (25)	14 (5)	24 (8)
3	15 (5)	2 (1)	4 (1)
>3	5 (2)	0 (0)	0 (0)

- A higher proportion of patients who received the combination experienced at least two grade 2–4 AEs across organ categories during treatment

*Organ categories: skin, gastrointestinal, endocrine, hepatic, pulmonary, renal

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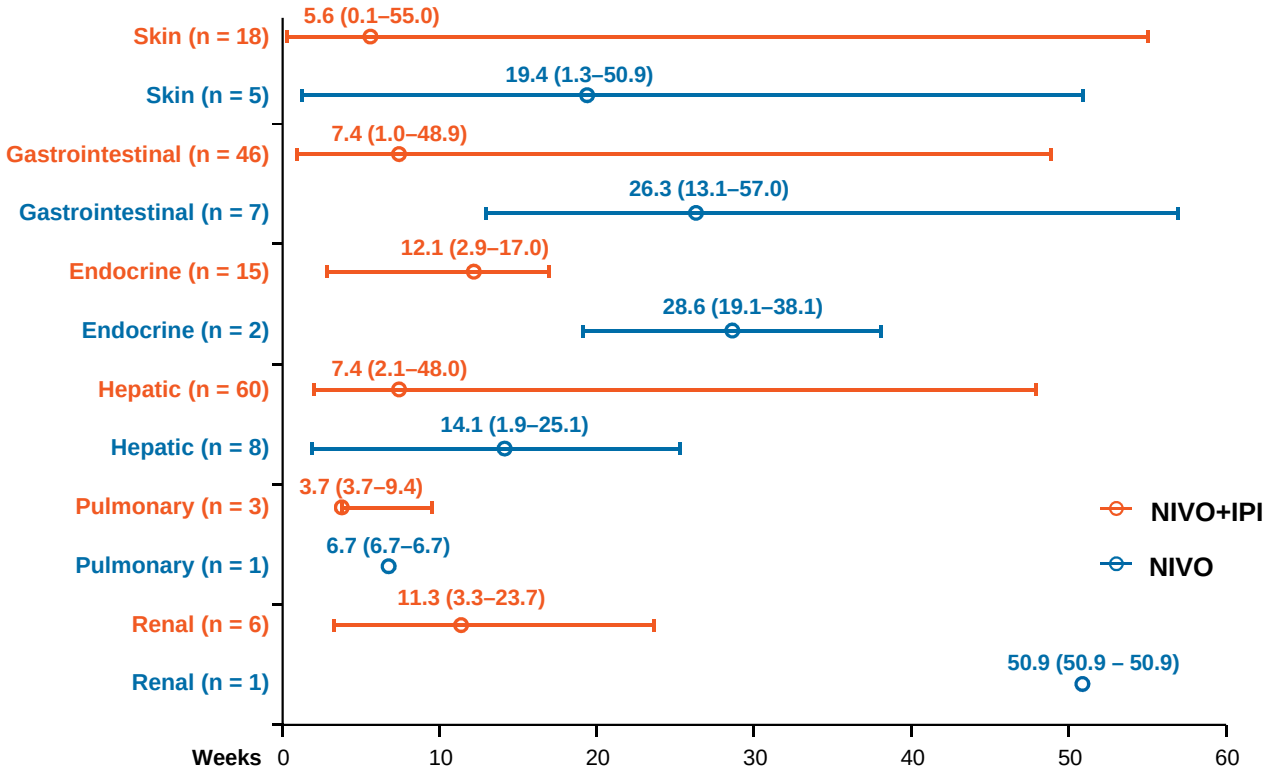
Time to Onset of Grade 3–4 Treatment-Related Select AEs



Circles represent medians; bars signify ranges

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Resolution to Baseline of Grade 3–4 Treatment-Related Select AEs in Patients Treated With Immune Modulators

Select AEs organ category*	NIVO+IPI (N = 313)		NIVO (N = 313)	
	Patients with resolution of select AEs, n (%)	Median time to resolution, weeks (range)	Patients with resolution of select AEs, n (%)	Median time to resolution, weeks (range)
Skin	12 (86)	3.4 (0.7–53.0+)	3 (75)	2.1 (0.9–24.3+)
Gastrointestinal	41 (98)	3.0 (0.3–33.1+)	3 (50)	NE (0.9–31.4+)
Endocrine	5 (46)	NE (1.6–46.6+)	0 (0)	NE (14.4+–39.6+)
Hepatic	38 (100)	4.1 (0.3–26.0)	6 (100)	7.0 (2.0–27.1)
Pulmonary	2 (100)	4.2 (1.1–7.3)	1 (100)	2.3 (2.3–2.3)
Renal	3 (100)	1.7 (0.4–3.6)	0	-

- The majority of grade 3–4 select AEs resolved, with the exception of endocrinopathies

*Includes events reported between the first dose and 30 days after the last dose of study therapy

NE = not evaluable

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Conclusions

- NIVO alone and NIVO+IPI significantly improved PFS and ORR vs IPI alone in patients with previously untreated melanoma
  - NIVO+IPI resulted in numerically longer PFS and a higher ORR vs NIVO alone
  - PFS and ORR benefit was observed across predefined subgroups, including patients with elevated LDH and stage M1c
- Safety profile of the combination was consistent with earlier experience
  - Incidence of AEs was highest in the combination group and lowest in the NIVO alone group
  - The safety profile of NIVO+IPI across subgroups of patients, including those ≥65 years of age, was consistent with the overall population
  - The majority of grade 3–4 AEs resolved within 4 weeks with the use of immune modulators according to established guidelines
- Overall, NIVO+IPI provided a favorable benefit-risk profile in treatment-naïve advanced melanoma patients, including those with poor prognostic factors

Acknowledgments

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