Nivolumab ± Ipilimumab in Treatment of Patients With Metastatic Colorectal Cancer With and Without High Microsatellite Instability: CheckMate 142 Interim Results

Abstract 3501

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Introduction

- **Although approximately 15% of early colorectal cancers (CRCs) display a high degree of microsatellite instability (MSI-H), indicating a deficient DNA mismatch repair system (dMMR),[1,2] MSI-H status is found in approximately 4% of metastatic CRC[3]**
- **MSI-H CRC is known to have an exceptionally high mutation burden[4]**
- **Increased presence of tumor-specific neoantigens in hypermutated tumors is associated with an increased quantity of tumor-infiltrating lymphocytes (TILs) and overexpression of immune checkpoint receptors and ligands, such as programmed death-1 (PD-1) and PD-1 ligand 1 (PD-L1)[5]**

1. Aaltonen LA, et al. *N Engl J Med*. 1998;338:1481–1487.
2. Popat S, et al. *J Clin Oncol*. 2005;23:609–618.
3. Goldstein J, et al. *Ann Oncol*. 2014;25:1032–1038.
4. Dienstmann R, et al. *J Clin Oncol*. 2014;32:Abstract 3511.
5. Strickland KC, et al. *Oncotarget*. 2016;7:13587–13598.

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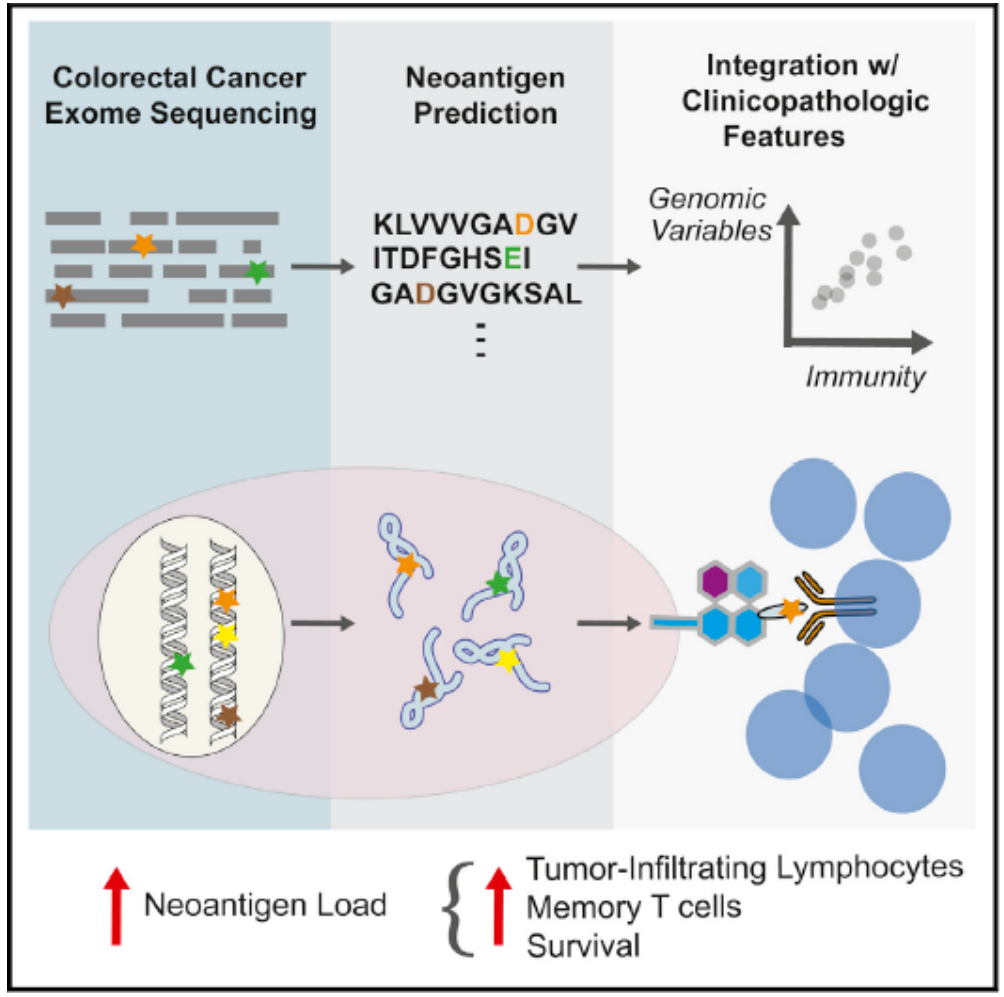
Hypermutation and Immuno-Oncology: Rationale for Evaluating Nivolumab ± Ipilimumab in CRC

- **In CRC, MSI-H is associated with increases in immune infiltration and expression of immune checkpoint regulators[1,2]**
- **Elevated neoantigen load in CRC is associated with improved survival[2]**
- **For these reasons, checkpoint inhibitor blockade, including PD-1 blockade and cytotoxic T-lymphocyte antigen 4 (CTLA-4) blockade, is expected to be particularly effective in MSI-H CRC**



1. Llosa NJ, et al. *Cancer Discov*. 2015;5:43–51.
2. Giannakis M, et al. *Cell Reports*. 2016;15:857–865.

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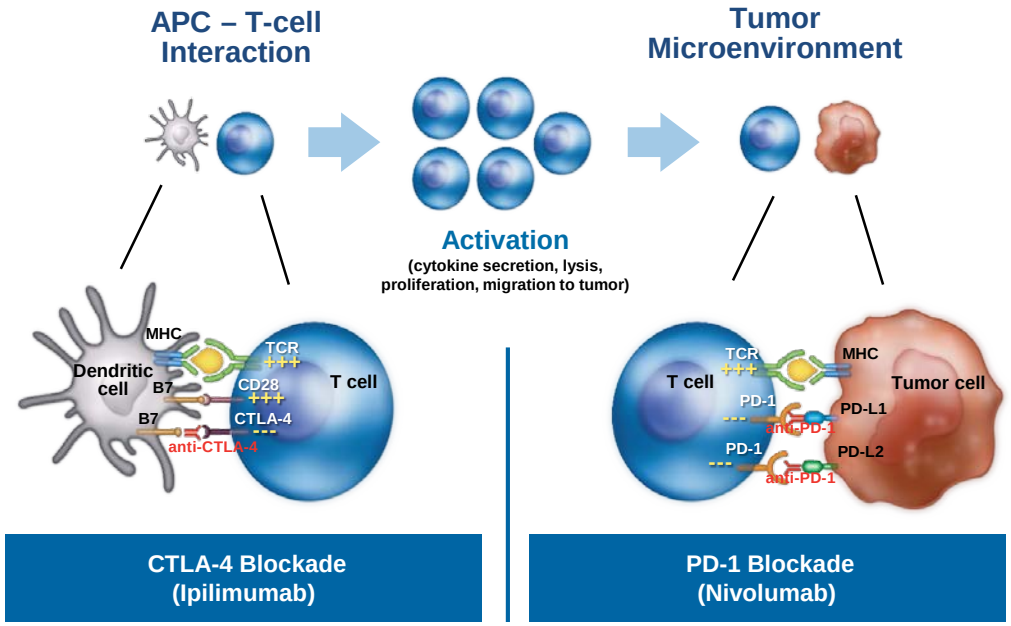
Ipilimumab and Nivolumab Mechanisms of Action

- PD-1 expression on TILs is associated with decreased cytokine production and effector function[1]
- Nivolumab is a fully human IgG4 immune checkpoint inhibitor antibody
  - Binds PD-1 receptors on T cells
  - Disrupts PD-L1/PD-L2 signaling to restore antitumor immunity[2-4]
- Nivolumab and the anti-CTLA-4 antibody, ipilimumab, enhance T-cell antitumor activity through distinct but complementary mechanisms[1-3,5]
- The combination of nivolumab and ipilimumab has demonstrated deep and durable responses in solid tumors[6,7]



1. Hamid O, et al. *Exp Opin Biol Ther.* 2013;13:847–861.
2. Brahmer JR, et al. *J Clin Oncol.* 2010;28:3167–3175.
3. Wang C, et al. *Cancer Immunol Res.* 2014;2:1–11.
4. Topalian SL, et al. *N Engl J Med.* 2012;366:2443–2454
5. Pardoll D, et al. *Nat Rev Cancer*. 2012;12:252-264.
6. Wolchok J, et al. *N Engl J Med*. 2013;369:122–133.
7. Postow MA, et al. *N Engl J Med*. 2015;372:2006–2017.

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Eligibility Criteria

- **Inclusion criteria**
  - **Histologically confirmed CRC**
  - **Recurrent or metastatic disease measurable by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1**
  - **Adults aged ≥18 years with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1**
  - **Disease progression after ≥1 prior therapy regimen (patients with MSI-H) or the latest treatment (all patients), or intolerance or refusal to take chemotherapy**
- **Exclusion criteria**
  - **Central nervous system involvement**
  - **History of malignancy within 3 years**
  - **Active or history of autoimmune disease**
  - **Need for treatment with immunosuppressive medications including corticosteroids**
  - **Prior treatments targeting T-cell costimulation or immune checkpoint pathways**

MSI-H (by polymerase chain reaction): ≥ 30% markers with instability
MSI-H/dMMR (by immunohistochemistry): loss of ≥ 1 marker

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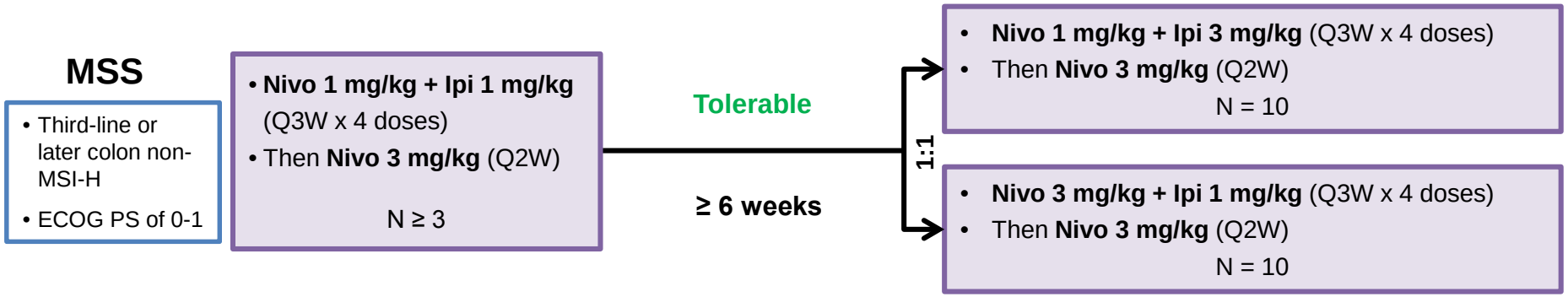
Phase 2 CheckMate 142 Study Design: Microsatellite Stable (MSS) Cohort



Independent safety arm in MSS (third or later line) and to inform Nivo + Ipi dose in patients with MSI-H

Ipi = ipilimumab; Nivo = nivolumab; Q2W = every 2 weeks; Q3W = every 3 weeks

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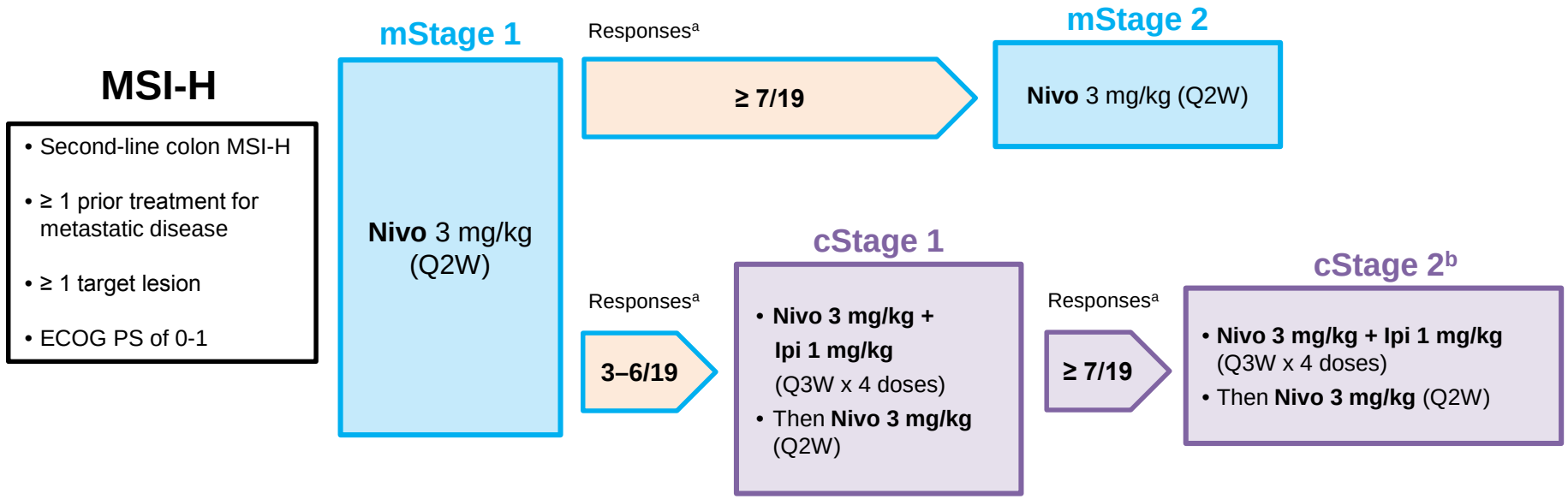
Phase 2 CheckMate 142 Study Design: MSI-H Cohort



[a]In patients with centrally confirmed MSI-H status
[b]Currently enrolling
cStage 1 = combination therapy stage 1; cStage 2 = combination therapy stage 2; Ipi = ipilimumab; mStage 1 = monotherapy stage 1; mStage 2 = monotherapy stage 2; Nivo = nivolumab; Q2W = every 2 weeks; Q3W = every 3 weeks

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Study Endpoints

- **Primary endpoint**
  - **Investigator-assessed objective response rate (ORR) using RECIST v1.1 in patients with MSI-H**
- **Secondary endpoint**
  - **Independent radiology review committee-assessed ORR**
- **Exploratory endpoints**
  - **Safety and tolerability**
  - **Progression-free survival (PFS)**
  - **Overall survival (OS)**
  - **Investigator-assessed ORR in patients with MSS**
  - **Biomarkers**

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Demographics

	MSI-H		MSS	
	Nivolumab 3 mg/kg (n = 70)[a]	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 30)[b]	Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg (n = 10)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 10)
Median age, years (range)	53 (26–79)	60 (33–81)	49 (35–65)	52 (38–69)
Age < 65 years, n (%)	54 (77.1)	22 (73.3)	9 (90.0)	9 (90.0)
Male, n (%)	42 (60.0)	15 (50.0)	7 (70.0)	8 (80.0)
Race, n (%)				
White	61 (87.1)	25 (83.3)	10 (100)	10 (100)
Black	7 (10.0)	1 (3.3)	0	0
Asian	1 (1.4)	2 (6.7)	0	0
Other	1 (1.4)	2 (6.7)	0	0
ECOG PS, n (%)[c]				
0	30 (42.9)	10 (33.3)	4 (40.0)	3 (30.0)
1	39 (55.7)	20 (66.7)	6 (60.0)	7 (70.0)

[a]Monotherapy stages 1 and 2 combined; [b]Combination therapy stages 1 and 2 combined; [c]One patient with an ECOG PS of 1 at randomization had deteriorated to a score of 3 by the time of treatment initiation

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Disease Characteristics and Prior Therapy

	MSI-H		MSS	
	Nivolumab 3 mg/kg (n = 70)[a]	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 30)[b]	Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg (n = 10)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 10)
Disease stage at diagnosis, n (%)				
I–II	15 (21.4)	2 (6.7)	1 (10.0)	1 (10.0)
III	24 (34.3)	16 (53.3)	5 (50.0)	1 (10.0)
IV	30 (42.9)	12 (40.0)	4 (40.0)	8 (80.0)
Mutation status, n (%)				
KRAS/BRAF wild type	26 (37.1)	6 (20.0)	2 (20.0)	5 (50.0)
BRAF mutated	11 (15.7)	6 (20.0)	0	0
KRAS mutated	23 (32.9)	14 (46.7)	6 (60.0)	3 (30.0)
Unknown	10 (14.3)	4 (13.3)	2 (20.0)	2 (20.0)
Prior treatments, n (%)				
1	9 (12.9)	2 (6.7)		
2	21 (30.0)	15 (50.0)	–	–
≥ 3	39 (55.7)	13 (43.3)		
Prior radiotherapy, n (%)	26 (37.1)	7 (23.3)	–	–

[a]Monotherapy stages 1 and 2 combined; [b]Combination therapy stages 1 and 2 combined

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MSI-H Patient Disposition

	MSI-H	
	Nivolumab 3 mg/kg (n = 70)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 30)
Continuing treatment, n (%)	47 (67.1)	18 (60.0)
Not continuing treatment, n (%)	23 (32.9)	12 (40.0)
Reasons for not continuing, n (%)		
Disease progression	19 (27.1)	6 (20.0)
Study drug toxicity	2 (2.9)	4 (13.3)
Withdrew consent/other	1 (1.4)	1 (3.3)
Not reported	1 (1.4)	1 (3.3)

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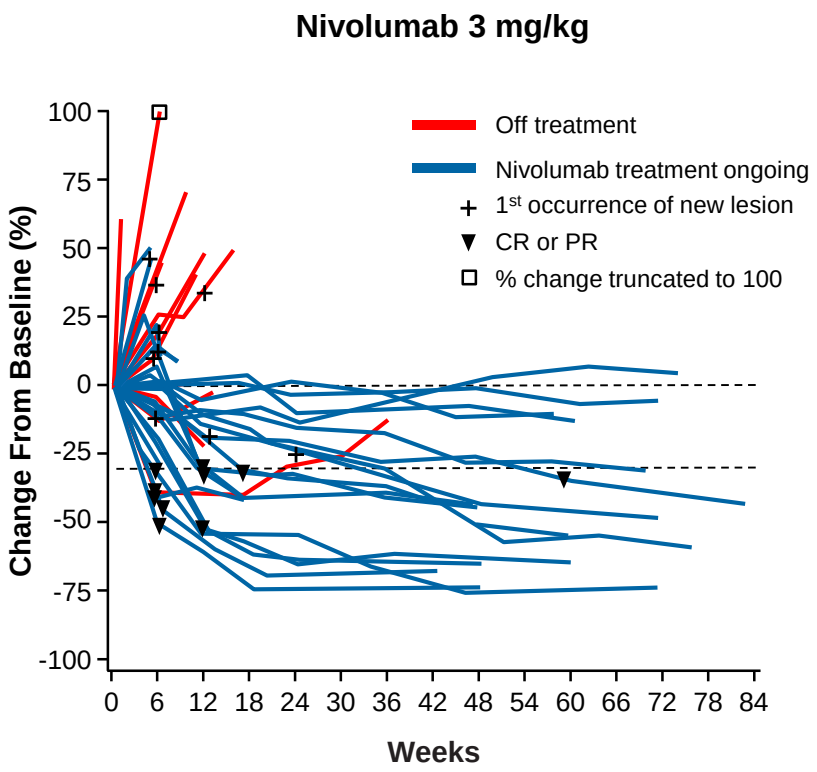
Investigator-Assessed Best Overall Response in Patients With MSI-H Receiving Nivolumab Monotherapy

	Nivolumab 3 mg/kg (n = 47)[a]
ORR, n (%) (95% exact CI)	**12 (25.5) (15.4, 38.1)**
Complete response	**0**
Partial response	**12 (25.5)**
Stable disease	**14 (29.8)**
Progressive disease	**17 (36.2)**
Unable to determine	**4 (8.5)**
Median time to response, mo (range)	**2.12 (1.3–13.6)**
Median duration of response, mo (range)	**NE (0.0[b]–15.2[b])**

[a]Patients with ≥ 12 weeks of follow-up
[b]Includes censored observations
CR = complete response; NE = not estimable; PR = partial response



Horizontal reference line indicates 30% reduction

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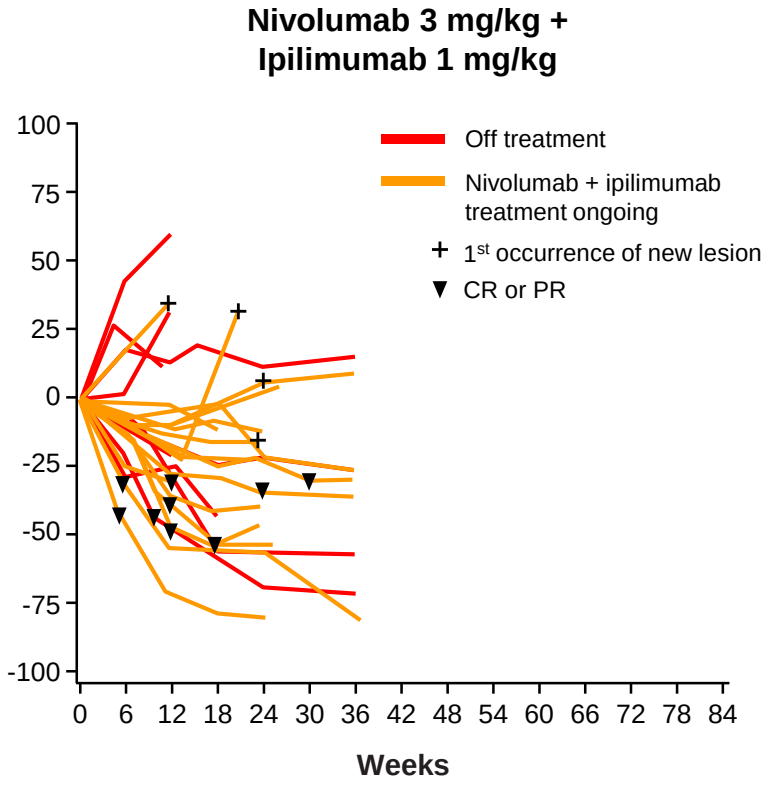
Investigator-Assessed Best Overall Response in Patients With MSI-H Receiving Nivolumab + Ipilimumab

	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 27)[a]
ORR, n (%) (95% exact CI)	**9 (33.3) (18.6, 50.9)**
Complete response	**0**
Partial response	**9 (33.3)**
Stable disease	**14 (51.9)**
Progressive disease	**3 (11.1)**
Unable to determine	**0**
Median time to response, mo (range)	**2.73 (1.2–6.9)**
Median duration of response, mo (range)	**NE (NE–NE)**

[a]Patients with ≥ 12 weeks of follow-up
[b]Includes censored observations
CR = complete response; NE = not estimable; PR = partial response



Horizontal reference line indicates 30% reduction

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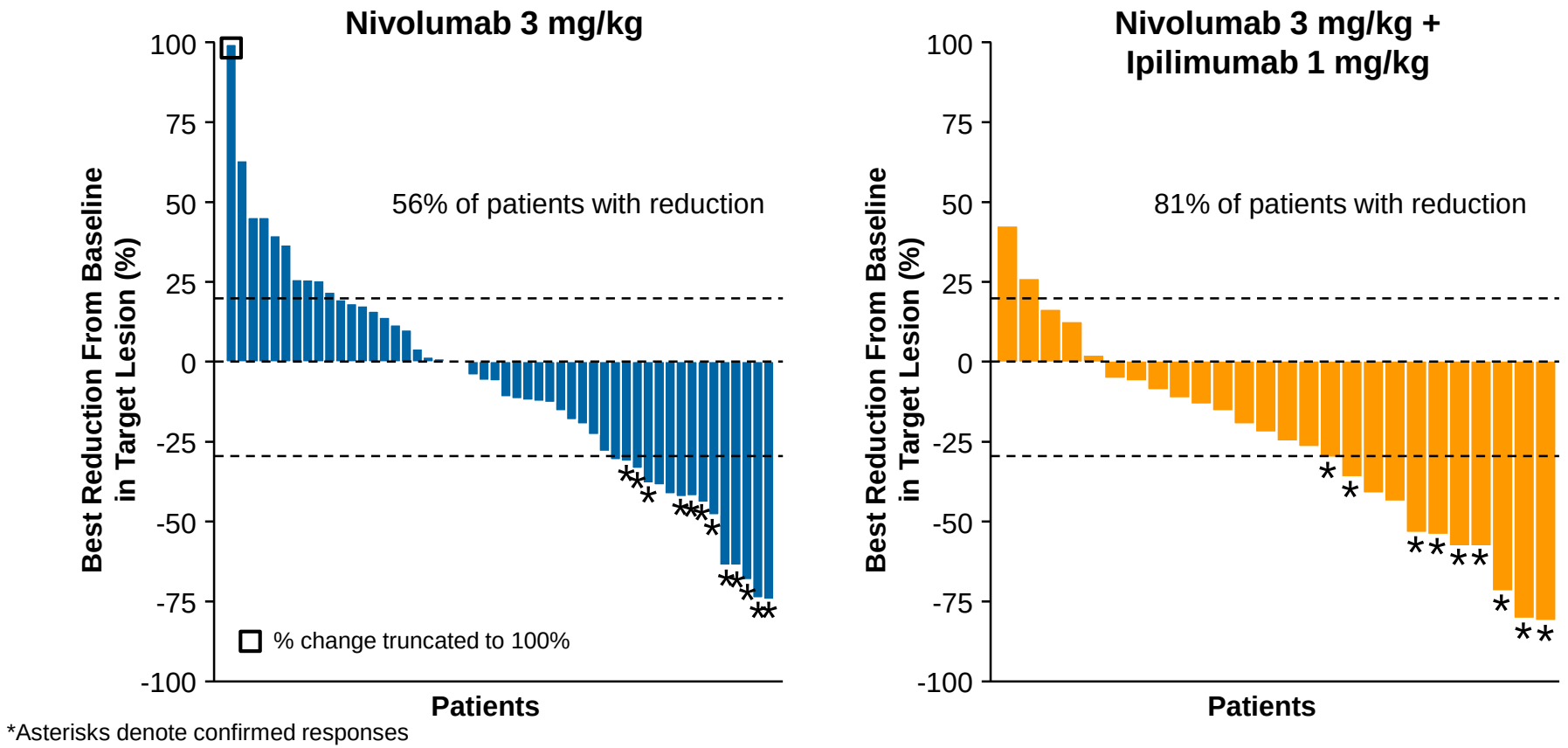
Best Reduction in Target Lesion Size in Patients With MSI-H



*Asterisks denote confirmed responses

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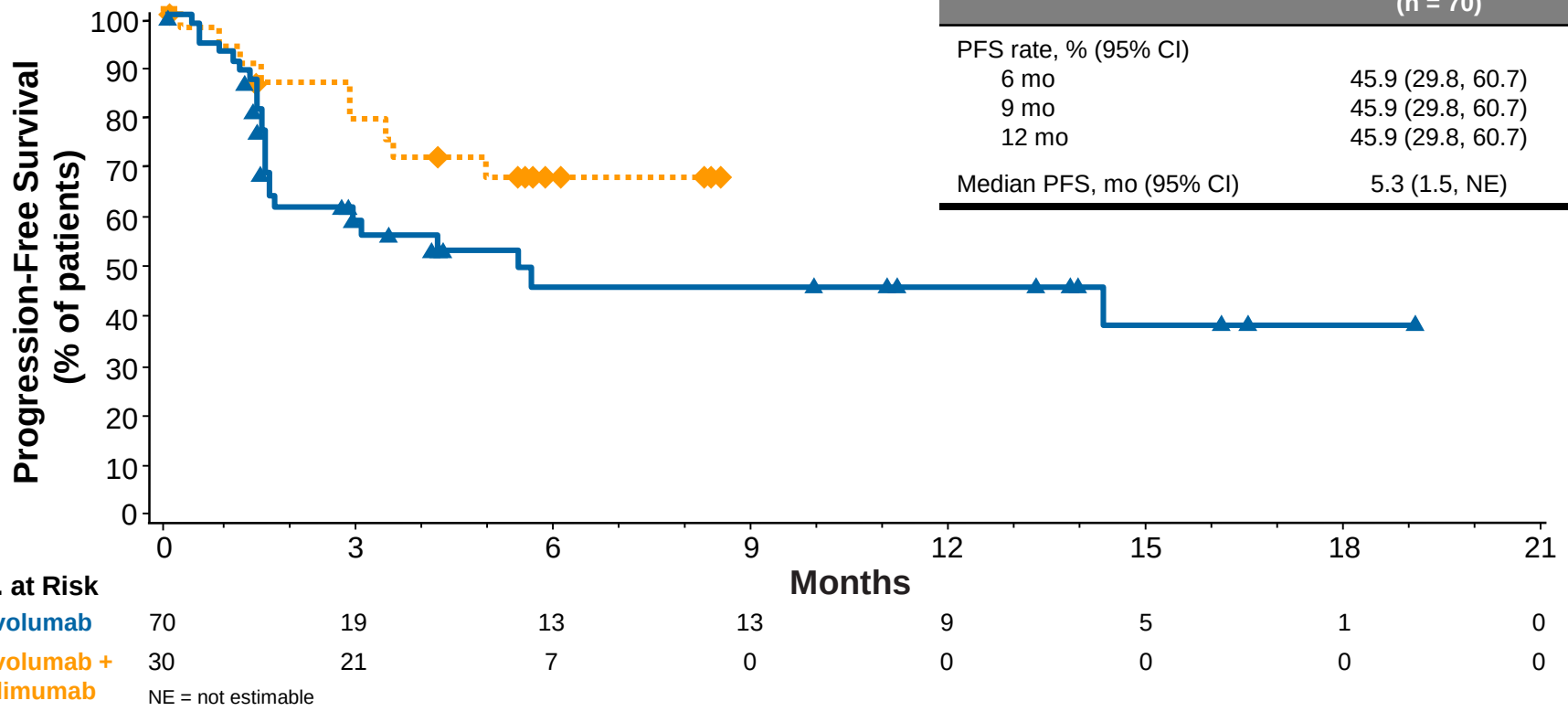
Investigator-Assessed PFS in Patients With MSI-H



	Nivolumab 3 mg/kg (n = 70)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 30)
PFS rate, % (95% CI)		
6 mo	45.9 (29.8, 60.7)	66.6 (45.5, 81.1)
9 mo	45.9 (29.8, 60.7)	NE
12 mo	45.9 (29.8, 60.7)	NE
Median PFS, mo (95% CI)	5.3 (1.5, NE)	NE (3.4, NE)

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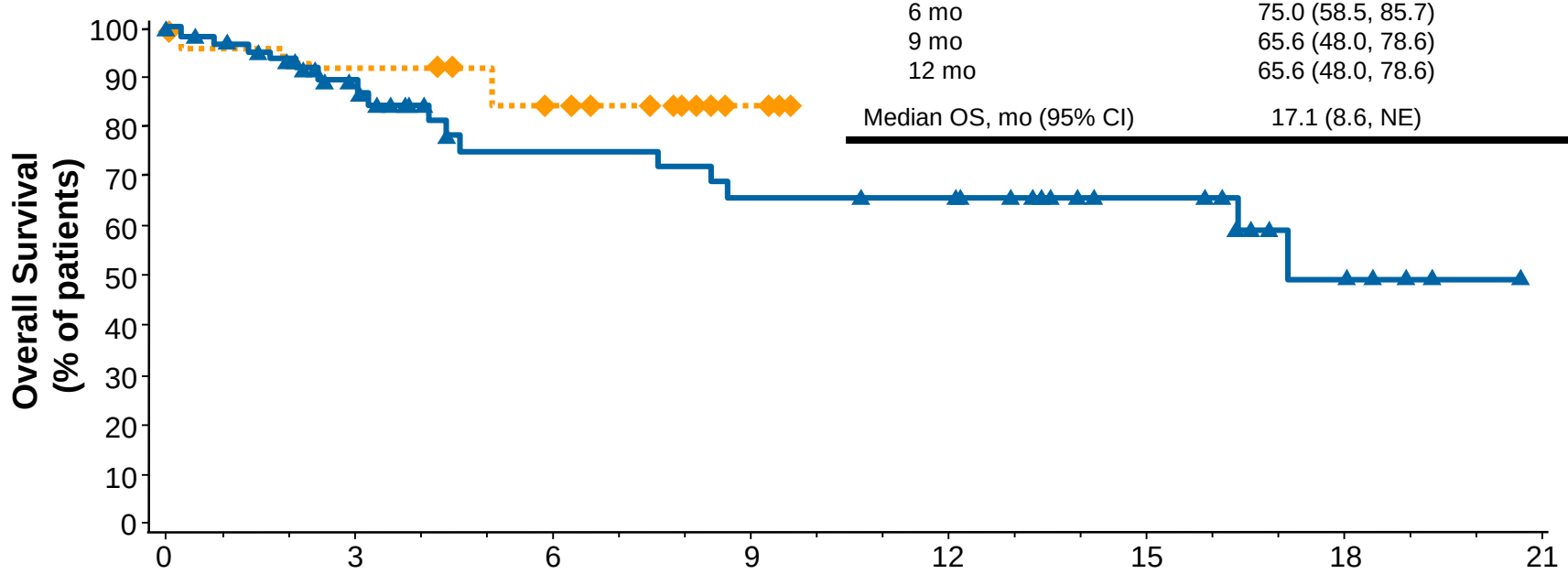
OS in Patients With MSI-H

	Nivolumab 3 mg/kg (n = 70)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 30)
OS rate, % (95% CI)		
6 mo	75.0 (58.5, 85.7)	85.1 (65.0, 94.2)
9 mo	65.6 (48.0, 78.6)	85.1 (65.0, 94.2)
12 mo	65.6 (48.0, 78.6)	NE
Median OS, mo (95% CI)	17.1 (8.6, NE)	NE (NE, NE)



No. at Risk							
Nivolumab	70	34	24	21	20	12	5	0
Nivolumab + Ipilimumab	30	26	21	4	0	0	0	0

NE = not estimable

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Summary of Efficacy in Patients With MSS

	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg (n = 10)	Nivolumab 3 mg/kg + ipilimumab 1 mg/kg (n = 10)
ORR, n (%)	1 (10)	0
Median PFS, mo (95% CI)	2.28 (0.62, 4.40)	1.31 (0.89, 1.71)
Median OS, mo (95% CI)	11.53 (0.62, NE)	3.73 (1.22, 5.62)

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Treatment-Related Adverse Events in ≥15% of Patients With MSI-H

Event, %	Nivolumab 3 mg/kg (N = 70)		Nivolumab 3 mg/kg + ipilimumab 1 mg/kg (N = 30)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any event	41 (58.6)[a]	10 (14.3)	25 (83.3)	8 (26.7)
Fatigue	13 (18.6)	1 (1.4)	6 (20.0)	0
Diarrhea	10 (14.3)	1 (1.4)	13 (43.3)	0
Pruritus	8 (11.4)	0	5 (16.7)	1 (3.3)
Nausea	5 (7.1)	0	6 (20.0)	0
Pyrexia	3 (4.3)	0	7 (23.3)	0
Any event leading to discontinuation	4 (5.7)	2 (2.9)	4 (13.3)	4 (13.3)

[a]One Grade 5 event of sudden death

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Treatment-Related Adverse Events in ≥15% of Patients With MSS

Event, %	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg (N = 10)		Nivolumab 3 mg/kg + ipilimumab 1 mg/kg (N = 10)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any event	8 (80.0)	7 (70.0)	8 (80.0)	3 (30.0)
Diarrhea	4 (40.0)	1 (10.0)	2 (20.0)	0
Asthenia	3 (30.0)	2 (20.0)	1 (10.0)	0
Nausea	3 (30.0)	1 (10.0)	2 (20.0)	0
Pyrexia	3 (30.0)	0	2 (20.0)	0
Vomiting	3 (30.0)	1 (10.0)	1 (10.0)	0
Fatigue	2 (20.0)	0	2 (20.0)	1 (10.0)
Dry skin	2 (20.0)	0	0	0
Cough	0	0	2 (20.0)	0
Any event leading to discontinuation	5 (50.0)	5 (50.0)	2 (20.0)	2 (20.0)

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Conclusions

- **Nivolumab monotherapy demonstrated encouraging activity in patients with MSI-H status at this interim analysis; the combination of nivolumab + ipilimumab also demonstrated promising preliminary activity**
- **Responses to nivolumab monotherapy and the nivolumab + ipilimumab combination were durable in patients with MSI-H**
- **Nivolumab and the combination of nivolumab + ipilimumab demonstrated tolerable safety profiles in relation to clinical benefit and were consistent with observations in other solid tumors**
- **Results are encouraging and support continued evaluation of nivolumab monotherapy and nivolumab + ipilimumab in patients with MSI-H metastatic CRC and potentially other tumors with mismatch repair defects**

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