Efficacy and safety of nivolumab plus ipilimumab in previously treated metastatic urothelial carcinoma

First results from the phase I/II CheckMate 032 study

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Presenter disclosure information

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The following relationships exist related to this presentation:

- Jounce Therapeutics, board membership, consultancy, stock/stock options
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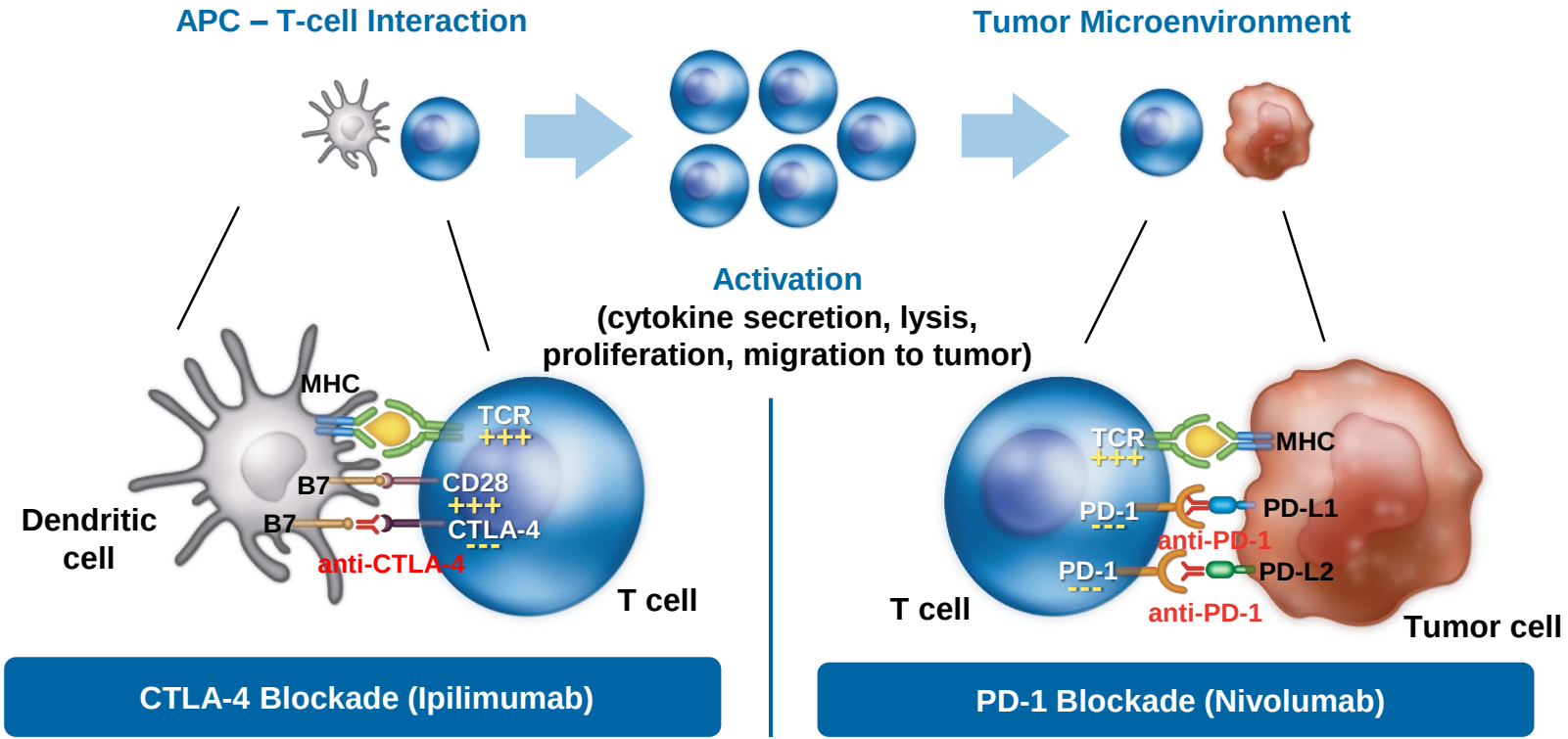
- Neon Therapeutics, consultancy, stock/stock options
- AstraZeneca, consultancy
- Amgen, consultancy
- Bristol-Myers Squibb, consultancy

Introduction

- In previously treated patients with metastatic urothelial carcinoma (mUC), chemotherapy yields poor efficacy outcomes and is associated with significant toxicity[1]
- Phase I/II and II studies of nivolumab monotherapy have recently shown notable antitumor activity in patients with previously treated mUC[2,3]
  - ORR of 19.6% and a median OS of 8.7 months, with efficacy seen in all PD-L1 expression subgroups in the phase II study[3]
- Preclinical and clinical data indicate that the combination of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) can improve antitumor activity in advanced melanoma, NSCLC, and mRCC[4-8]
- This is the first study to assess the clinical activity of NIVO + IPI for previously treated patients with mUC

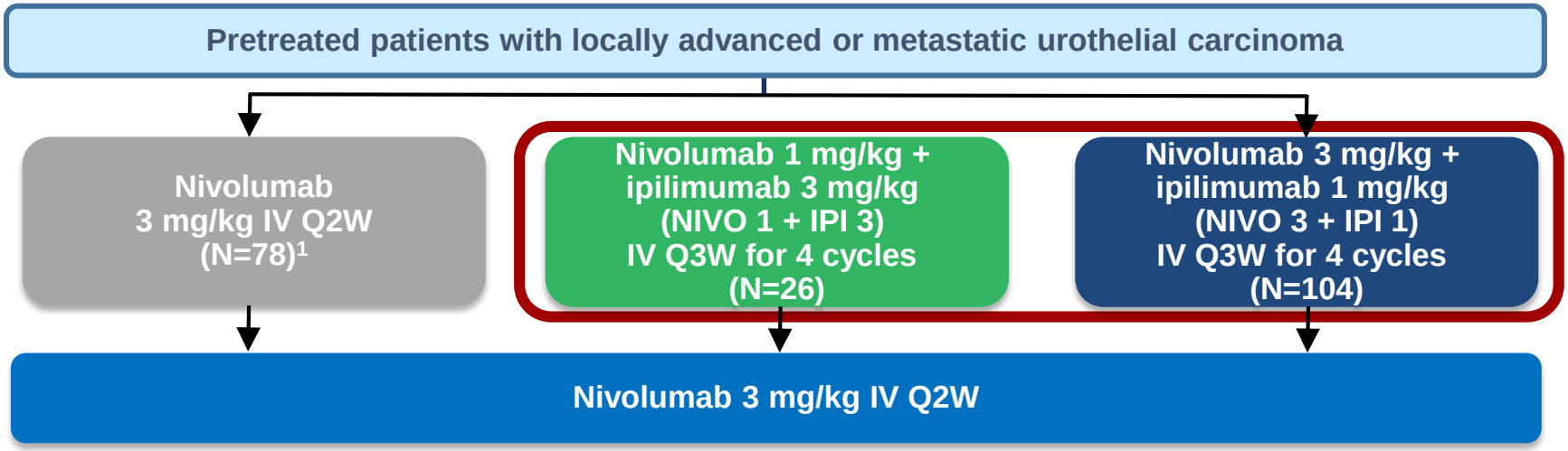
1. Raggi D, et al. *Ann Oncol* 2016;27:49–61. 2. Sharma P, et al. *Lancet Oncol* 2016 Oct 7 [Epub ahead of print]. 3. Galsky MD, et al. ESMO 2016 Congress. Presentation LBA31_PR. 4. Shi LZ, et al. *Nat Commun* 2016;7:12335. 5. Larkin J, et al. *N Engl J Med* 2015:373:23-34. 6. Wolchok JD, et al. *N Engl J Med* 2013:369:122-33. 7. Hellman MD, et al. J Clin Oncol 34, 2016 (suppl; abstr 3001). 8. Hammers HJ, et al. ESMO 2016 Congress. Abstract 2970.

Biologic rationale for combined PD-1 and CTLA-4 blockade in patients with mUC



CheckMate 032: Study design

Open-label, multicenter, phase I/II study (NCT01928394)



- Treatment beyond progression was permitted if treatment was tolerated and prespecified clinical benefit was noted
- Tumor measurements: CT or MRI every 6 weeks (±1 week) from first dose for the first 24 weeks, then every 12 weeks (±1 week)

1. Sharma P, et al. *Lancet Oncol* 2016 Oct 7 [Epub ahead of print].

Eligibility criteria

- Confirmed urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra
- Patients with mUC or surgically unresectable UC who had progressive disease despite ≥1 prior lines of chemotherapy (including a platinum-containing regimen) for metastatic disease or recurrence within 1 year of completing prior platinum-based neoadjuvant or adjuvant therapy
- ECOG performance status of 0 or 1
- Measurable disease (RECIST v1.1)

Study endpoints

- Primary
  - Investigator-assessed confirmed ORR by RECIST v1.1
- Secondary
  - Safety
  - Duration of response
  - Progression-free survival
  - Overall survival
- Exploratory
  - Biomarkers (PD-L1, PD-1, tumor immune cells, tumor genomic profiling, circulating cytokines)
  - Other (immunogenicity, pharmacokinetics, quality of life)

Patient baseline characteristics

Characteristic	NIVO 1 + IPI 3 (N=26)	NIVO 3 + IPI 1 (N=104)
Median age, years (range)	64 (38–83)	63 (39-83)
Age ≥65 years, %	50.0	45.2
Male, %	76.9	77.9
No. of prior regimens, %[a]		
1	42.3	34.6
2–3	42.3	44.2
>3	15.4	19.2
ECOG PS, %		
0	26.9	38.5
1	73.1	61.5
Site of metastasis, %		
Liver	38.5	35.6
Visceral	88.5	88.5
Lymph node	11.5	10.6
CNS	7.7	0
Tumor PD-L1 expression, %		
<1	30.8	51.9
≥1	38.5	28.8
Not quantifiable	30.8	19.2

[a]1.9% of patients in the NIVO 3 + IPI 1 arm did not report number of prior regimens

Patient disposition and treatment exposure

	NIVO 1 + IPI 3 (N=26)	NIVO 3 + IPI 1 (N=104)
Patients continuing treatment, %	46.2	14.4
Median follow-up, months	7.8	16.7
Minimum follow-up, months	3.9	14.5
Treatment exposure		
Doses received (NIVO, IPI), median (range)	6 (1–53), 4 (1–4)	4 (1–39), 4 (1–8)
Nivolumab maintenance, %	50	40
Reasons for discontinuation, %		
Disease progression	38.5	64.4
Study drug toxicity	7.7	13.5
Withdrawal of consent	0	1.0
Patients receiving subsequent systemic therapy, %	7.7	22.1

Treatment-related and select treatment-related AEs in ≥5% of patients

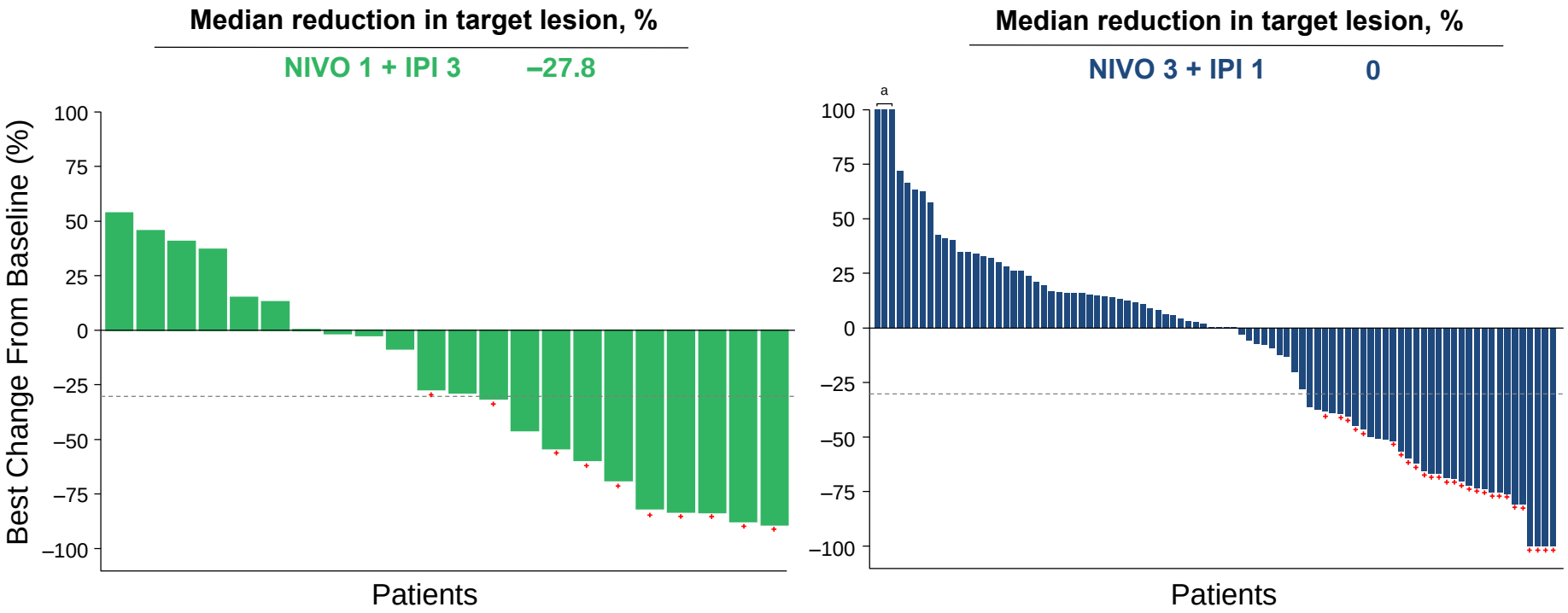
Event, %	NIVO 1 + IPI 3 (N=26)		NIVO 3 + IPI 1 (N=104)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
All treatment-related AEs	76.9	30.8	84.6	31.7
Treatment-related AEs leading to discontinuation	7.7	7.7	13.5	12.5
Select (immune-mediated) treatment-related AEs				
Pruritus	42.3	0	28.8	1.0
Rash, maculopapular	26.9	0	16.3	1.0
Diarrhea	26.9	7.7	23.1	4.8
Hypothyroidism	15.4	0	13.5	0
Hyperthyroidism	0	0	12.5	0
Pneumonitis	7.7	3.8	4.8	0
Colitis	3.8	0	5.8	3.8
Elevated ALT	0	0	17.3	5.8
Elevated AST	0	0	11.5	3.8

One treatment-related death reported in the NIVO 3 + IPI 1 group (pneumonitis)

Antitumor activity

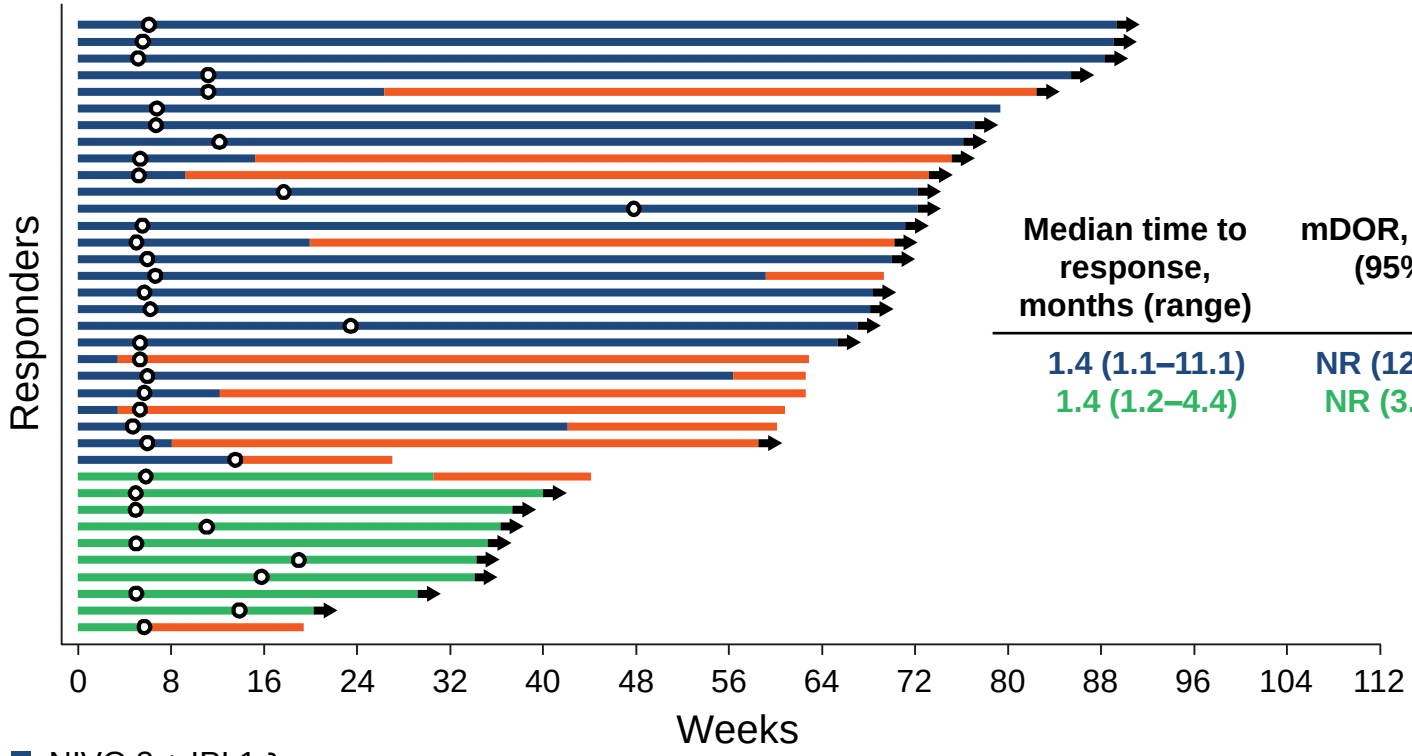
Outcome, %	NIVO 1 + IPI 3 (N=26)	NIVO 3 + IPI 1 (N=104)
Confirmed ORR, %	38.5	26.0
95% CI	20.2–59.4	17.9–35.5
Best overall response, %		
Complete response	3.8	2.9
Partial response	34.6	23.1
Stable disease	19.2	25.0
Progressive disease	26.9	41.3

Tumor change from baseline in target lesion



[a]Indicates changes truncated to 100%
Symbols in red indicate responders
Dashed lines indicate RECIST 1.1 response

Time to response and durability of response

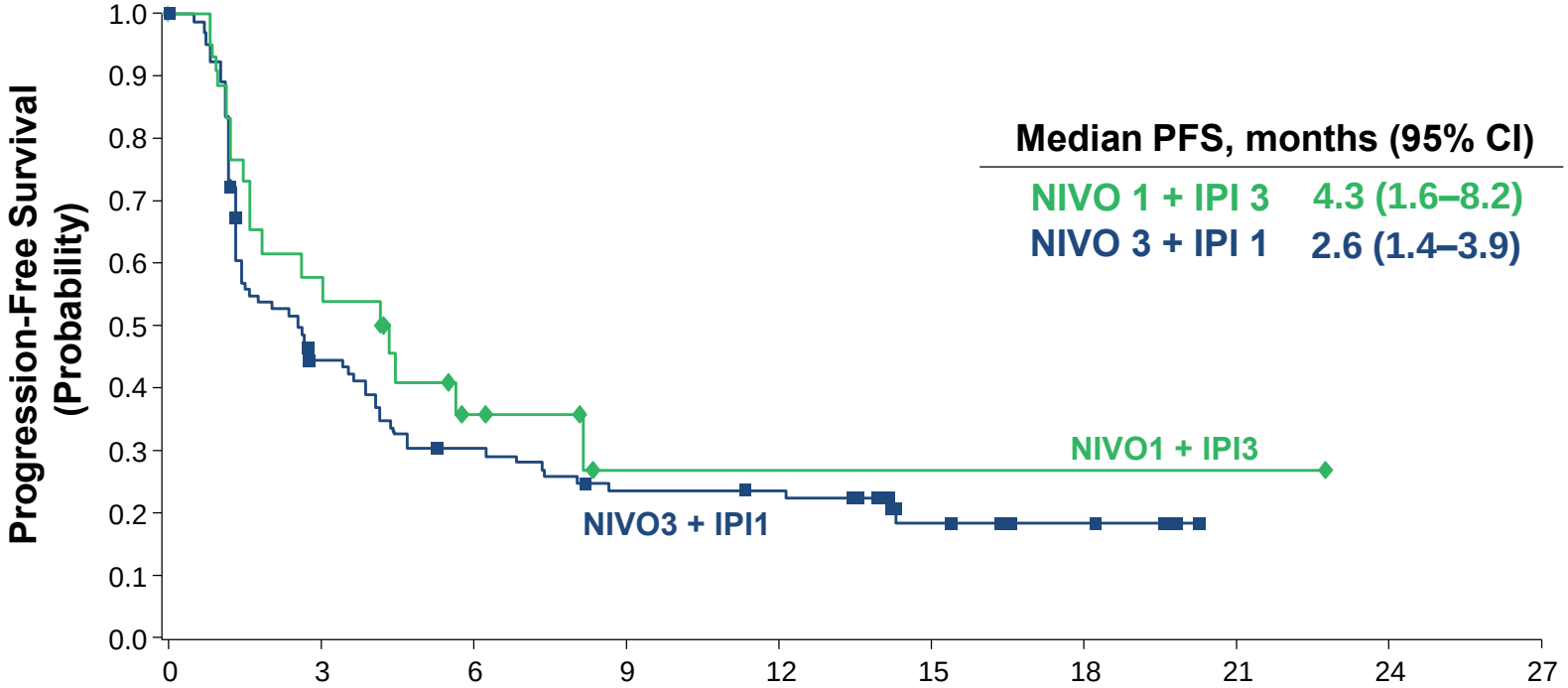


	Median time to response, months (range)	mDOR, months (95% CI)	Ongoing response (%)
NIVO 3 + IPI 1	1.4 (1.1–11.1)	NR (12.8–NR)	70
NIVO 1 + IPI 3	1.4 (1.2–4.4)	NR (3.2–NR)	80

NIVO 3 + IPI 1
NIVO 1 + IPI 3
On treatment
First response
Ongoing response
Off treatment

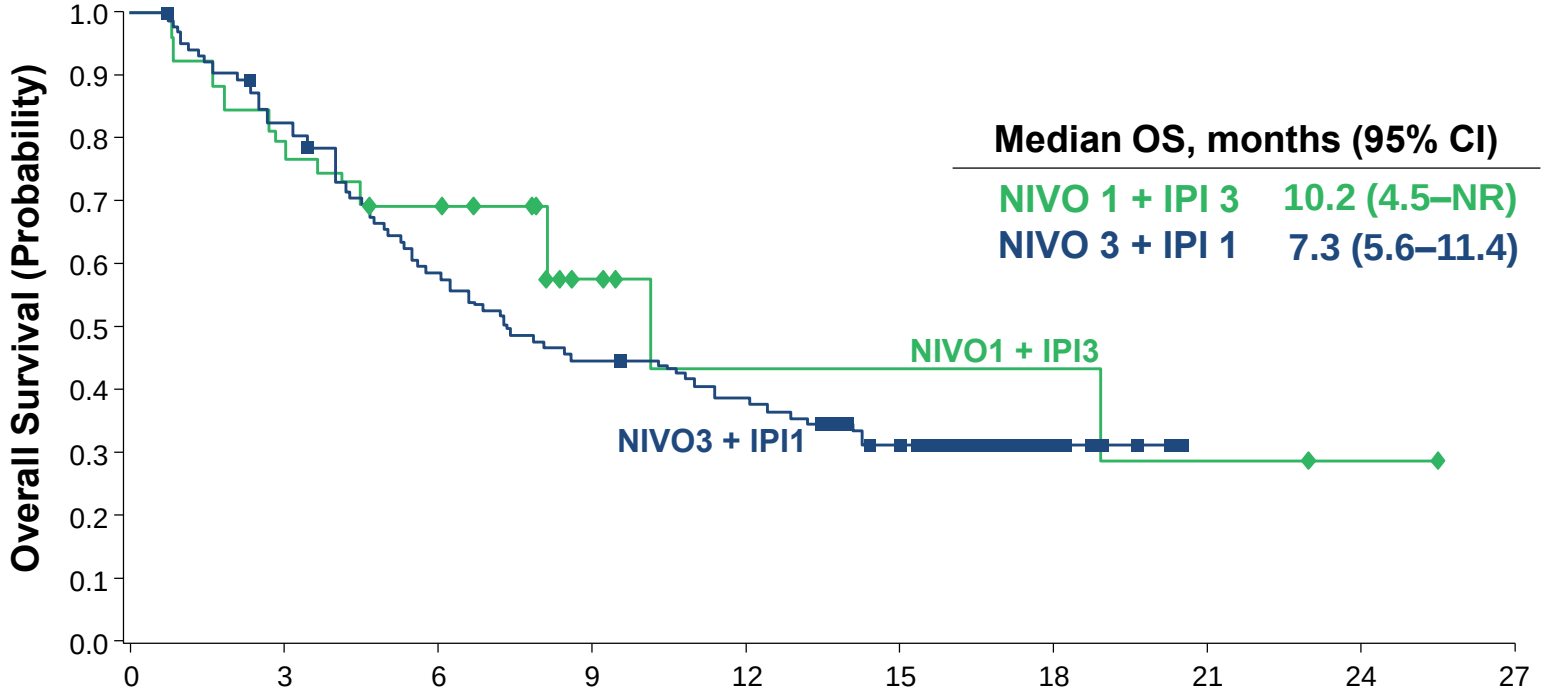
Bars indicate survival

Progression-free survival



No. at risk										
NIVO 1 + IPI 3	26	15	6	1	1	1	1	1	0	0
NIVO 3 + IPI 1	104	41	27	20	19	8	4	0	0	0

Overall survival



No. at risk										
NIVO 1 + IPI 3	26	21	17	7	3	3	3	2	1	0
NIVO 3 + IPI 1	104	84	59	45	38	27	8	0	0	0

Lessons and take-home messages

- NIVO 1 + IPI 3 led to higher rates of response and median OS than NIVO 3 + IPI 1, NIVO monotherapy,[1,2] and historical control[3]
  - Efficacy with NIVO 3 + IPI 1 did not appear to differentiate from NIVO monotherapy
- The safety profile was consistent between both combination therapy arms
- These results support further development of NIVO 1 + IPI 3 for mUC

1. Sharma P, et al. *Lancet Oncol* 2016 Oct 7 [Epub ahead of print]. 2. Galsky MD, et al. ESMO 2016 Congress. Presentation LBA31_PR.
3. Domingo-Domenech J, et al. *Exp Rev Prec Med Drug Devel* 2016;1361–68.

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