Presentation 1050O
Abstract 7843

Nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC): Results of a phase I trial

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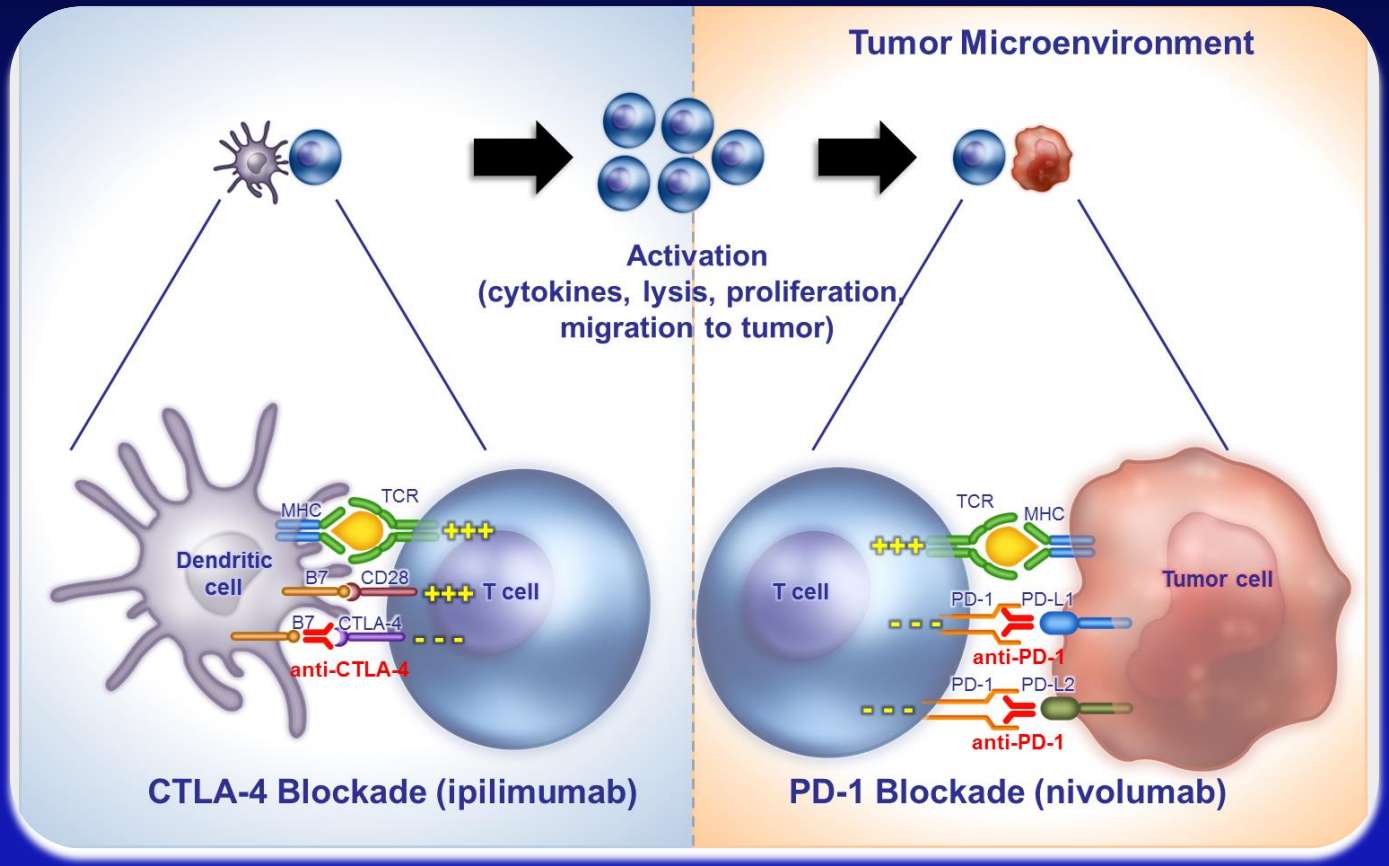
Background: Nivolumab and ipilimumab

- Therapeutic options for advanced/stage IV RCC include cytokine therapies and targeted therapies
  - Prognosis remains poor, with a 5-year survival rate <5%[1,2]
- Nivolumab is a fully human anti-PD-1 immune checkpoint inhibitor[3,4]
  - Has shown antitumor activity in mRCC, melanoma, and NSCLC[3]
- Ipilimumab is a fully humanized IgG1 antibody to CTLA-4
  - Approved therapy for metastatic melanoma[5]
  - Provides responses in patients with mRCC with an acceptable safety profile[5–7]
- In a phase I advanced melanoma study, nivolumab + ipilimumab showed encouraging clinical activity and acceptable safety[8]

CTLA-4 = cytotoxic T-lymphocyte antigen; PD-1 = programmed death-1; PD-L1 = programmed death-1 ligand 1.

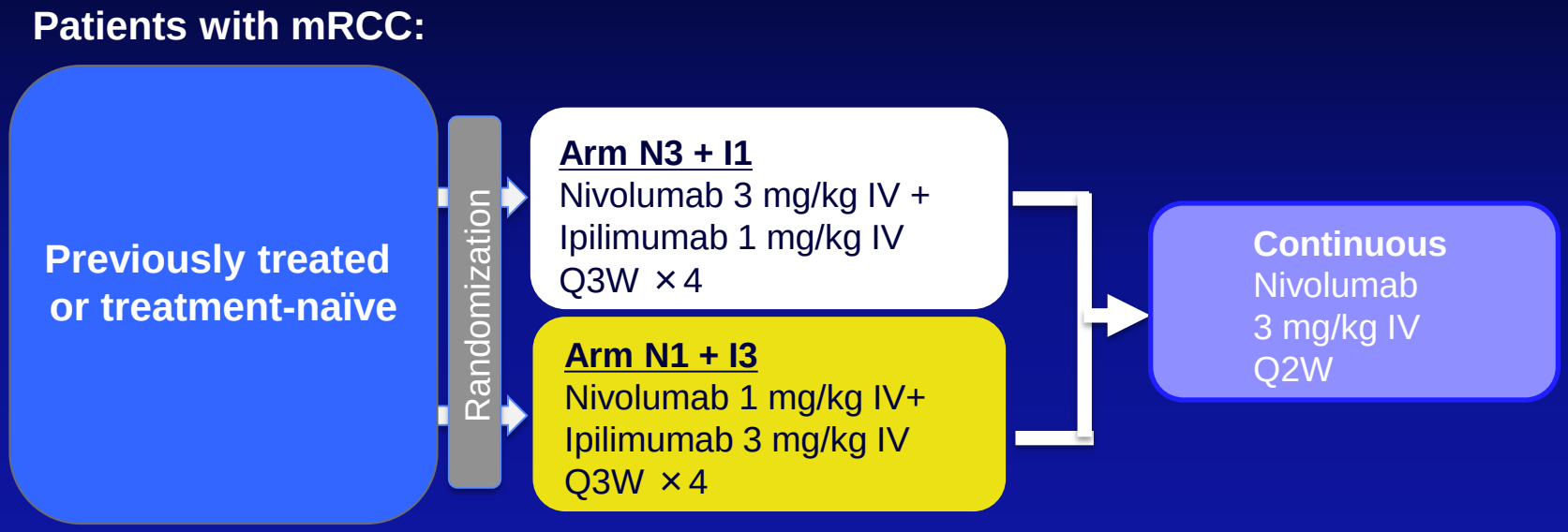
1. Logan JE, et al. Rev Urol. 2012;14:65–78; 2. Hutson TE. Proc Bayl Univ Med Cent. 2005;18:337–40; 3. Topalian SL, et al. N Engl J Med. 2012;366:2443–54; 4. Brahmer JR, et al. J Clin Oncol. 2010;28:3167–75; 5. Yervoy® [prescribing information]. Bristol-Myers Squibb Company, 2011; 6. Data on file, 2008. 7. Yang JC, et al. J Immunother. 2007;30:825–30; 8. Wolchok JD, et al. N Engl J Med. 2013;369:122–33.

Mechanism of action



MHC = major histocompatibility complex; TCR = T-cell receptor.

CA209-016 (NCT01472081): Phase I study design (N + I cohort)

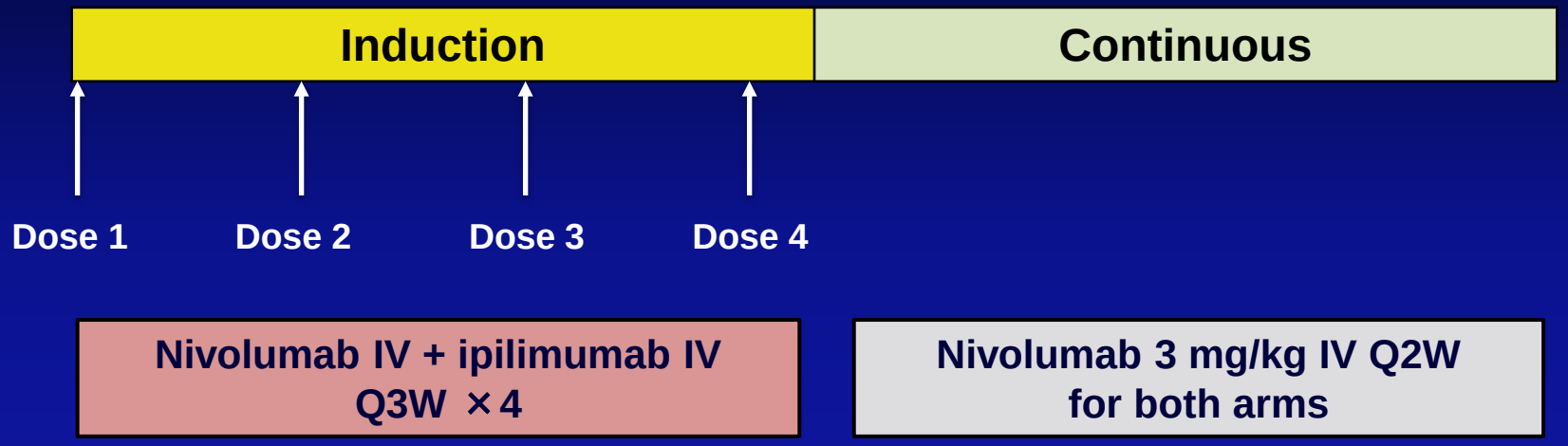


- **Primary endpoint: Safety (AEs, laboratory tests)**
- **Secondary endpoint: Efficacy (ORR, duration of response, PFS)**
- **Exploratory endpoint: Response by tumor PD-L1 status**
- **Study assessments: Tumor response (RECIST v1.1) evaluated at screening, every 6 weeks (first 4 assessments), then every 12 weeks until disease progression**

ORR = objective response rate.
TKI cohort presented by Amin A, et al. ESMO 2014, Abstract 7506, 1052PD.

Treatment administration

- Dosing schedule



- At induction visits, patients received two infusions
  - First infusion was always nivolumab (1 or 3 mg/kg)
  - Ipilimumab (1 or 3 mg/kg) infusion was started ≥30 min after completion of nivolumab infusion

Key inclusion and exclusion criteria

Inclusion

- mRCC with clear-cell component
- Age ≥18 years
- Measurable disease (RECIST v1.1)
- Favorable/intermediate-risk MSKCC
- KPS ≥80%
- Previously treated or treatment-naïve: no limit on number of prior therapies
- Available tumor tissue (archival or recent)

Exclusion

- Prior therapy with anti-PD-1, -L1, or -L2; anti-CD137; anti-CLTA-4 antibody, or other similar agent

L1/L2 = ligand 1/2.

Baseline patient characteristics

Characteristic	N3 + I1 (n = 21)	N1 + I3 (n = 23)
Age, y, mean (SD)	53.2 (8.26)	53.5 (11.24)
Sex, male, n (%)	17 (81.0)	21 (91.3)
MSKCC risk category, n (%) Favorable Intermediate Poor	 5 (23.8) 16 (76.2) 0	 5 (21.7) 18 (78.3) 0
Radiotherapy, n (%)	7 (33.3)	8 (34.8)
Systemic treatments, n (%) Anti-angiogenic Cytokine mTOR inhibitor	17 (81.0) 10 (47.6) 12 (57.1) 5 (23.8)	18 (78.3) 15 (65.2) 6 (26.1) 7 (30.4)
Prior lines of therapy, n (%) 0 1 2 >2	 4 (19.0) 11 (52.4) 3 (14.3) 3 (14.3)	 5 (21.7) 11 (47.8) 1 (4.3) 6 (26.1)

- **All patients had prior nephrectomy except for one in the N3 + I1 arm, and two in N1 + I3 arm**

Treatment-related select AE categories

Category, n (%)	N3 + I1 (n = 21)		N1 + I3 (n = 23)	
	All	Grade 3/4	All	Grade 3/4
Endocrinopathy	3 (14.3)	0	8 (34.8)	0
Adrenal insufficiency	1 (4.8)	0	2 (8.7)	0
Hypothyroidism	3 (14.3)	0	6 (26.1)	0
Hyperthyroidism	0	0	2 (8.7)	0
Autoimmune thyroiditis	0	0	1 (4.3)	0
Gastrointestinal disorder	6 (28.6)	1 (4.8)	9 (39.1)	4 (17.4)
Diarrhea	6 (28.6)	1 (4.8)	8 (34.8)	3 (13.0)
Colitis	1 (4.8)	0	2 (8.7)	2 (8.7)
Hepatic	1 (4.8)	0	9 (39.1)	6 (26.1)
AST increased	0	0	9 (39.1)	3 (13.0)
ALT increased	1 (4.8)	0	9 (39.1)	6 (26.1)
Blood bilirubin increased	0	0	1 (4.3)	1 (4.3)

Treatment-related select AE categories (cont.)

Category, n (%)	N3 + I1 (n = 21)		N1 + I3 (n = 23)	
	All	Grade 3/4	All	Grade 3/4
Infusion reaction	2 (9.5)	0	2 (8.7)	0
Infusion-related reaction	2 (9.5)	0	1 (4.3)	0
Hypersensitivity	0	0	1 (4.3)	0
Pneumonitis	1 (4.8)	0	2 (8.7)	0
Renal disorder	2 (9.5)	0	3 (13.0)	0
Blood creatinine increased	2 (9.5)	0	3 (13.0)	0
Acute renal failure	0	0	1 (4.3)	0
Skin disorder	8 (38.1)	0	9 (39.1)	0

- **No high-grade pulmonary AEs, including pneumonitis, were observed**

Concomitant immune-modulating medication for AE management

n (%)	N3 + I1 (n = 21)	N1 + I3 (n = 23)
Total patients using medication[a]	6 (28.6)	17 (73.9)
Medication		
Infliximab	1 (4.8)	1 (4.3)
Topical steroids	1 (4.8)	1 (4.3)
Systemic steroids	6 (28.6)	16 (69.6)

[a]Patients may have received more than one medication.

Treatment-related AEs leading to discontinuation

	N3 + I1 (n = 21)	N1 + I3 (n = 23)
	All	**All**
Patients with an event, n (%)	2 (9.5)	6 (26.1)
Event, n (%)		
Amylase increased	1 (4.8)	0
Lipase increased	1 (4.8)	2 (8.7)
ALT increased	0	2 (8.7)
Diarrhea	0	1 (4.3)
Pneumonitis	0	1 (4.3)

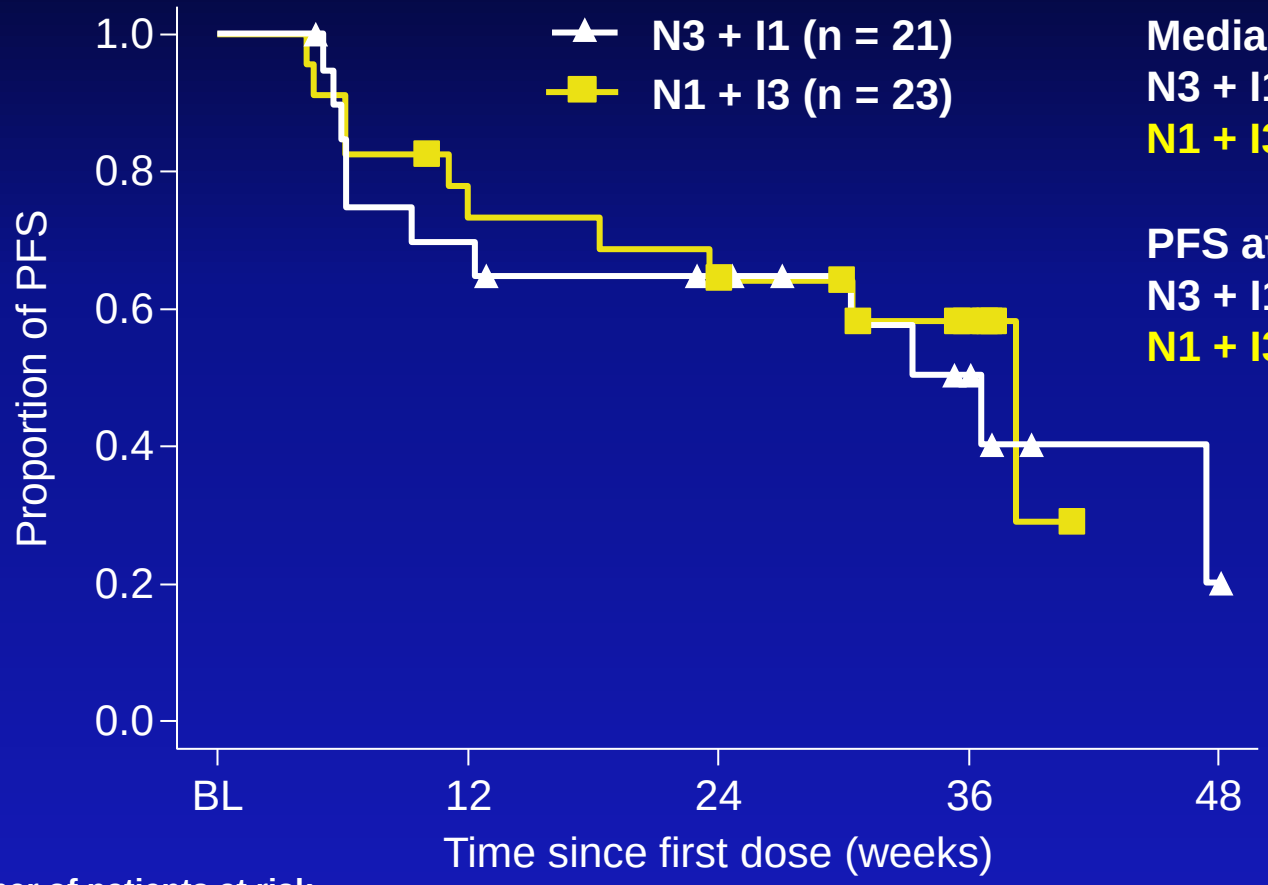
- **Rates of discontinuation appeared higher in the N1 + I3 arm**

Antitumor activity

	N3 + I1 (n = 21)	N1 + I3 (n = 23)
Confirmed ORR, n (%) 95% CI	9 (43) 21.8–66.0	11 (48) 26.8–69.4
Median duration of response (DOR), weeks (range)[a]	31.1 (4.1+–42.1+)[b]	NR (12.1+–35.1+)[c]
Ongoing responses, % (n/N)	78 (7/9)	82 (9/11)
Best objective response, n (%)[d] Complete response Partial response Stable disease Progressive disease Unable to determine	 0 9 (43) 5 (24) 5 (24) 1 (5)	 1 (4) 10 (43) 8 (35) 3 (13) 1 (4)

[a]Due to the high percentage of ongoing responses, median duration of response may be misleading; [b]Median follow-up 36.1 weeks; [c]Median follow-up 40.1 weeks; [d]Excludes unconfirmed responses.
DOR defined as time between date of first response and date of disease progression or death (whichever occurs first).

Progression-free survival



Median PFS, weeks (95% CI):
N3 + I1: 36.6 (6.0, --)
N1 + I3: 38.3 (18.3, --)

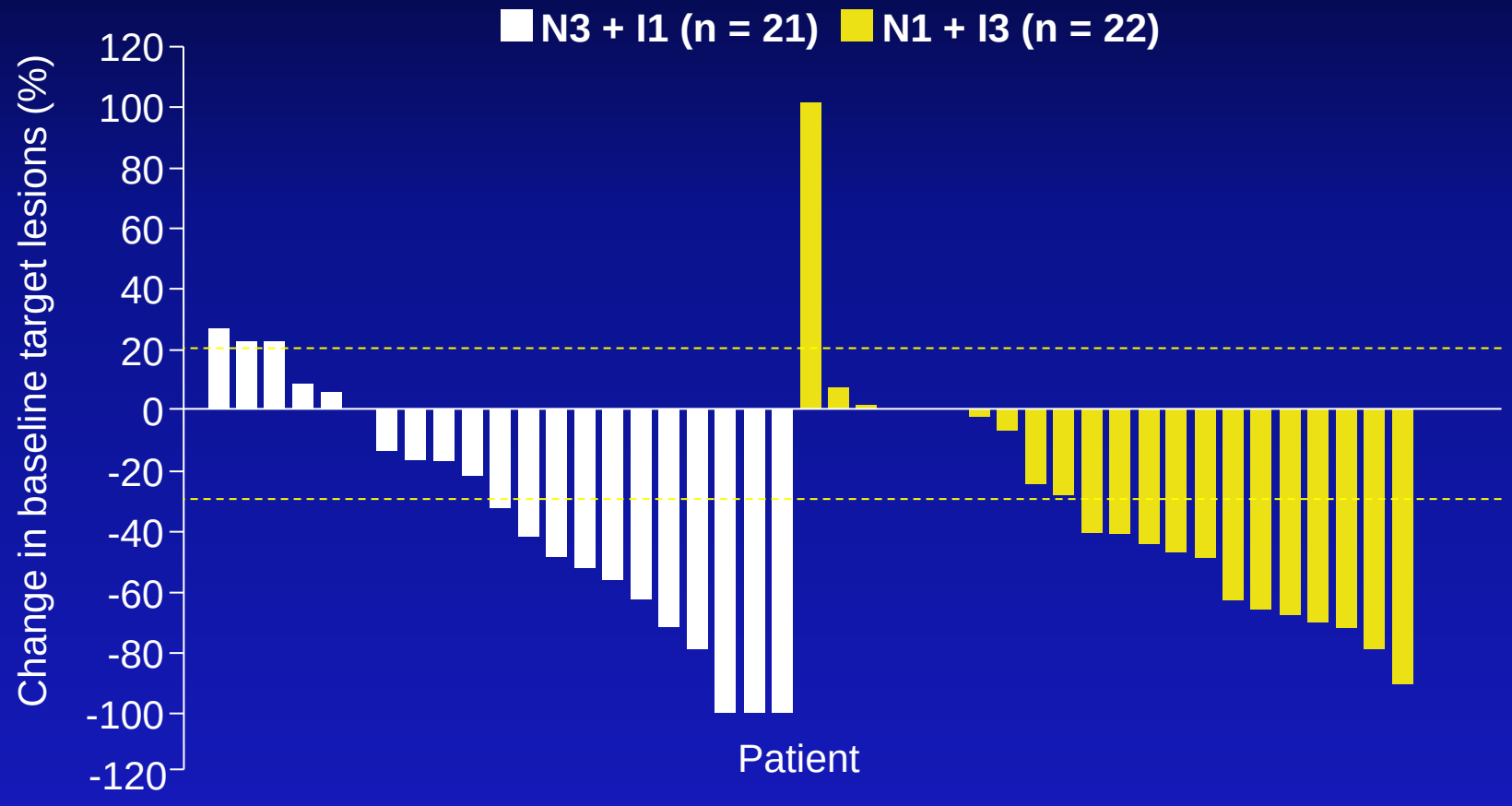
PFS at 24 weeks
N3 + I1 = 65% (95% CI: 40–82)
N1 + I3 = 64% (95% CI: 41–80)

Number of patients at risk

N3 + I1	21	14	11	6	1
N1 + I3	23	17	14	7	0

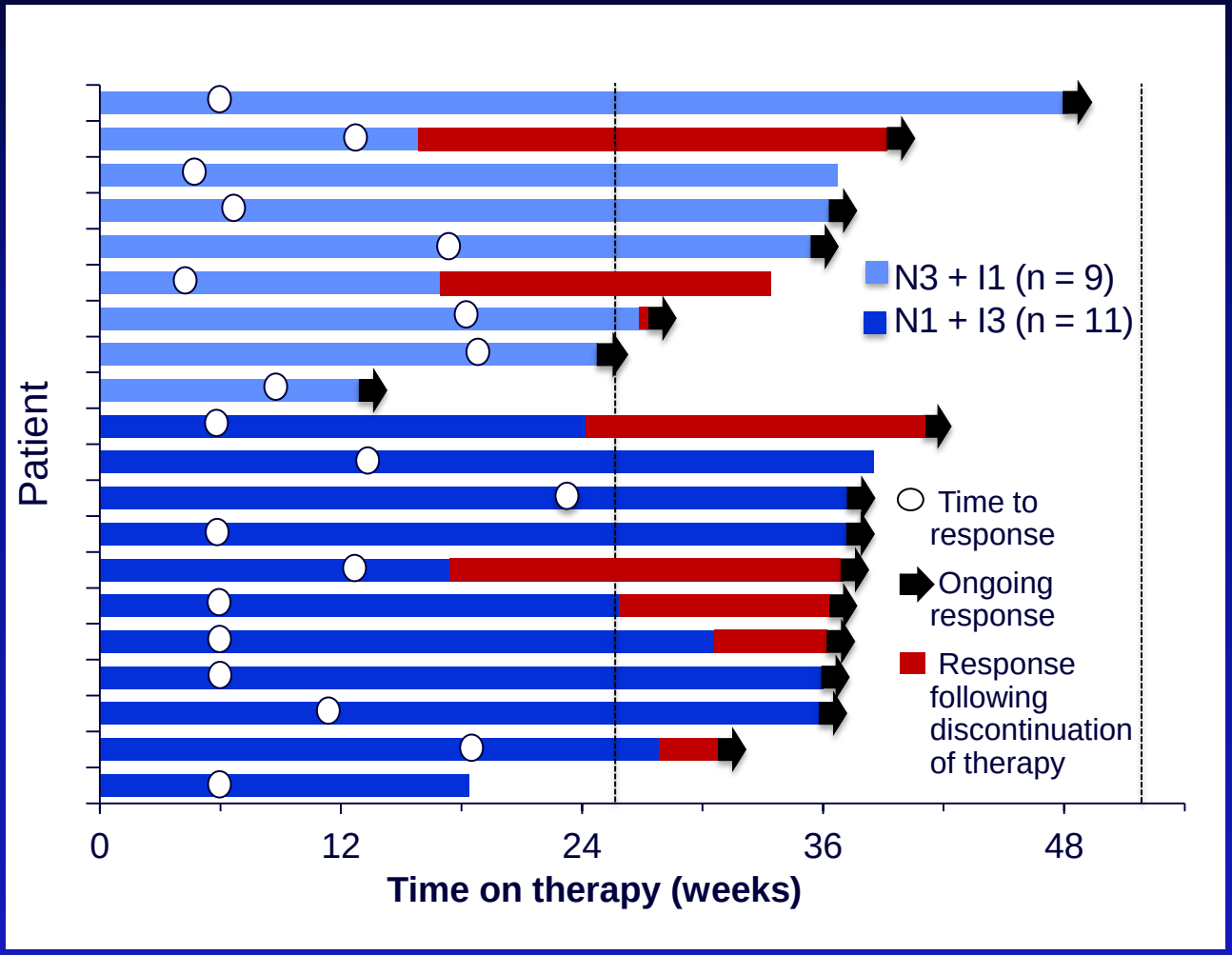
Symbols represent censored observation. Number of patients at risk listed is number at risk before entering the time period.

Maximum tumor burden reduction in baseline target lesions



Positive change in tumor burden indicates tumor growth; negative change indicates tumor reduction.

Time to response and duration of response



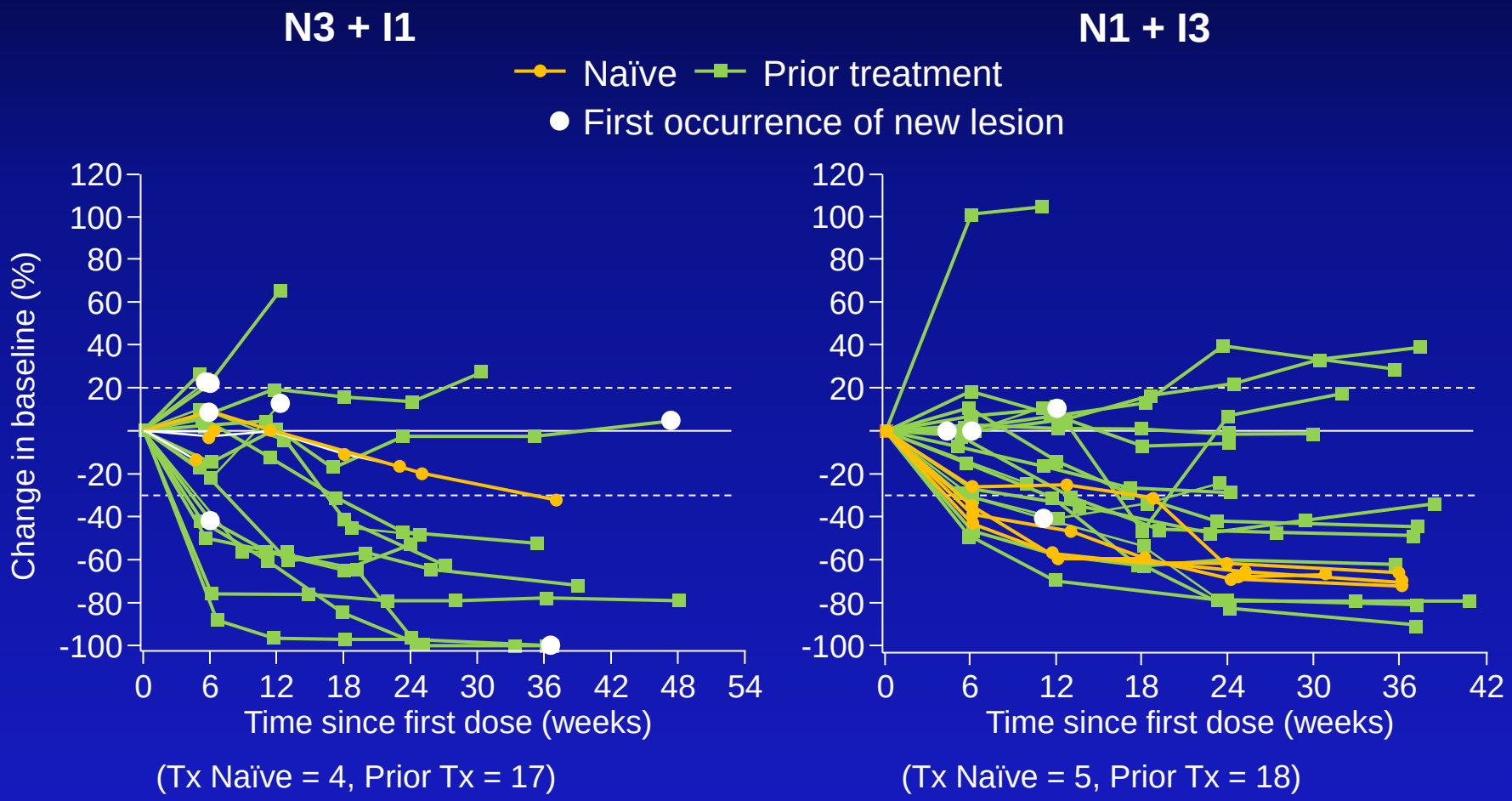
Responders at first assessment (6 weeks):
N3 + I1 = 4/9 (44.4%)
N1 + I3 = 6/11 (54.5%)

Ongoing responders:
N3 + I1 = 7/9 (77.8%)
N1 + I3 = 9/11 (81.8%)

Patients discontinuing treatment (not due to progression) who continued to respond:
N3 + I1 = 3/9 (33.3%)
N1 + I3 = 5/11 (45.5%)

Change from baseline in target tumor burden

Target tumor burden percent change from baseline over time



Positive change in tumor burden indicates tumor growth; negative change indicates tumor reduction.

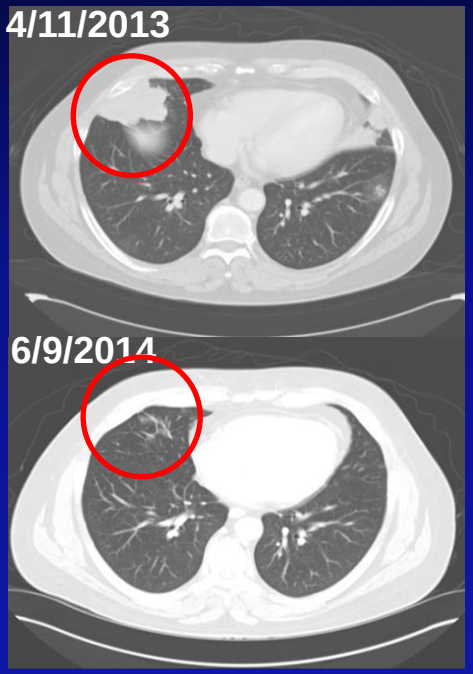
ORR by baseline PD-L1 expression

- **Tumor tissue collection was retrospective; 36 evaluable samples[a]**
  - **PD-L1 expression was measured using the Dako immunohistochemistry assay**

PD-L1 cutoff	PD-L1 status	ORR[b], n/N (%)
1% tumor membrane staining	+	8/16 (50.0)
	-	11/20 (55.0)
5% tumor membrane staining	+	1/4 (25.0)
	-	18/32 (56.3)

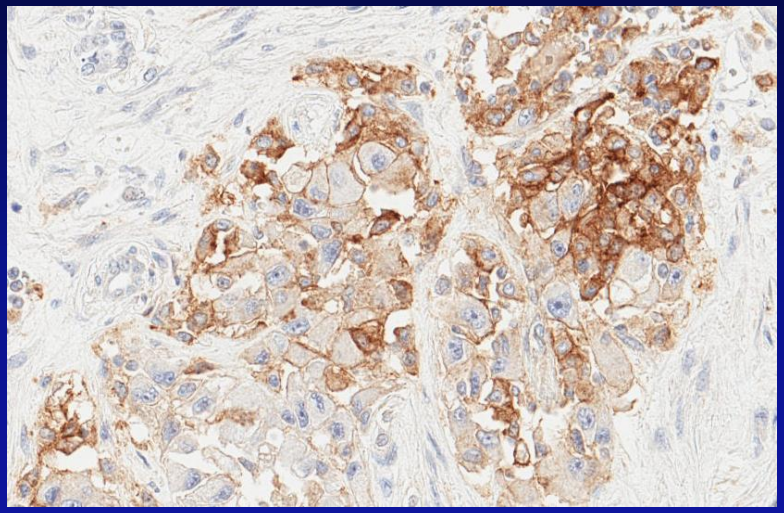
[a]44 samples available; [b]ORR of PD-L1 evaluable patients; ORR includes complete or partial responders determined by RECIST.

Complete response with nivolumab and ipilimumab combination treatment



April 11, 2013:
Right middle lobe pleural-based lung mass measured 4.1 × 6.2 cm

June 9, 2014:
No mass noted in right middle lobe



PD-L1 staining of patient tumor tissue

- Patient had Fuhrman grade 4, unclassified RCC with clear-cell component, with no sarcomatoid features
- After treatment with high-dose IL-2, CT scans showed significant increase in pulmonary nodules
- After treatment with nivolumab + ipilimumab, CT scans showed resolution of both pulmonary nodules and a lesion adjacent to the liver. Maintenance therapy was continued without any toxicity with CT scans showing ongoing response

Conclusions

- Combination therapy with nivolumab and ipilimumab demonstrated acceptable safety and evidence of antitumor activity in mRCC:
  - Grade 3/4 events were manageable using recommended treatment algorithms
  - The ORR suggests greater activity than reported previously with nivolumab or ipilimumab monotherapy in RCC[1–4]
  - Responses appear durable even after discontinuation of study drug

- The encouraging antitumor activity reported with this combination is the basis for a planned phase III combination trial in first-line mRCC

1. Topalian SL, et al. N Engl J Med. 2012;366:2443–54; 2. Motzer R, et al. ASCO 2014. Abstract 4504; 3. Choueiri T, et al. ASCO 2014. Abstract 5012; 4. Yang JC, et al. J Immunother. 2007;30:825–30.

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- **Martin H. Voss, MD**; Memorial Sloan Kettering Cancer Center, USA

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Related presentations

- **Sunday September 28th**
  - Poster Discussion, #1052PD, 13:00-14:00 , Room: Valencia

    Amin A, et al. Nivolumab (N) (anti-PD-1; BMS-936558, ONO 4538) in combination with sunitinib (S) or Pazopanib (P) in patients (pts) with metastatic renal cell carcinoma
- **Monday, September 29th**
  - Proffered Paper session , #810O, 11:00 - 12:30, Room : Sevilla

    Motzer R, et al. Randomized, dose-ranging phase II trial of nivolumab for metastatic renal cell carcinoma (mRCC)