Therapeutic Checkpoint Blockade

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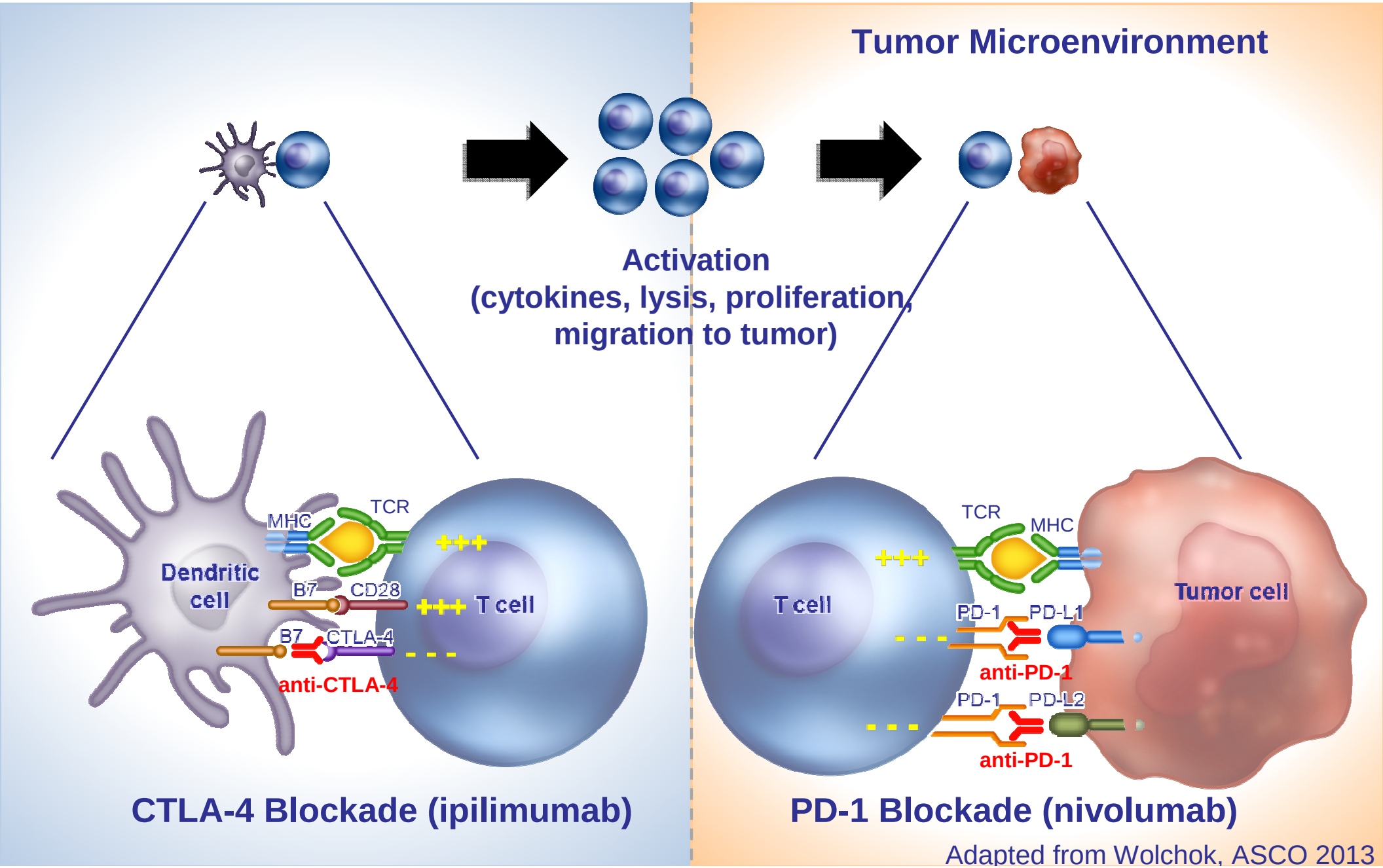
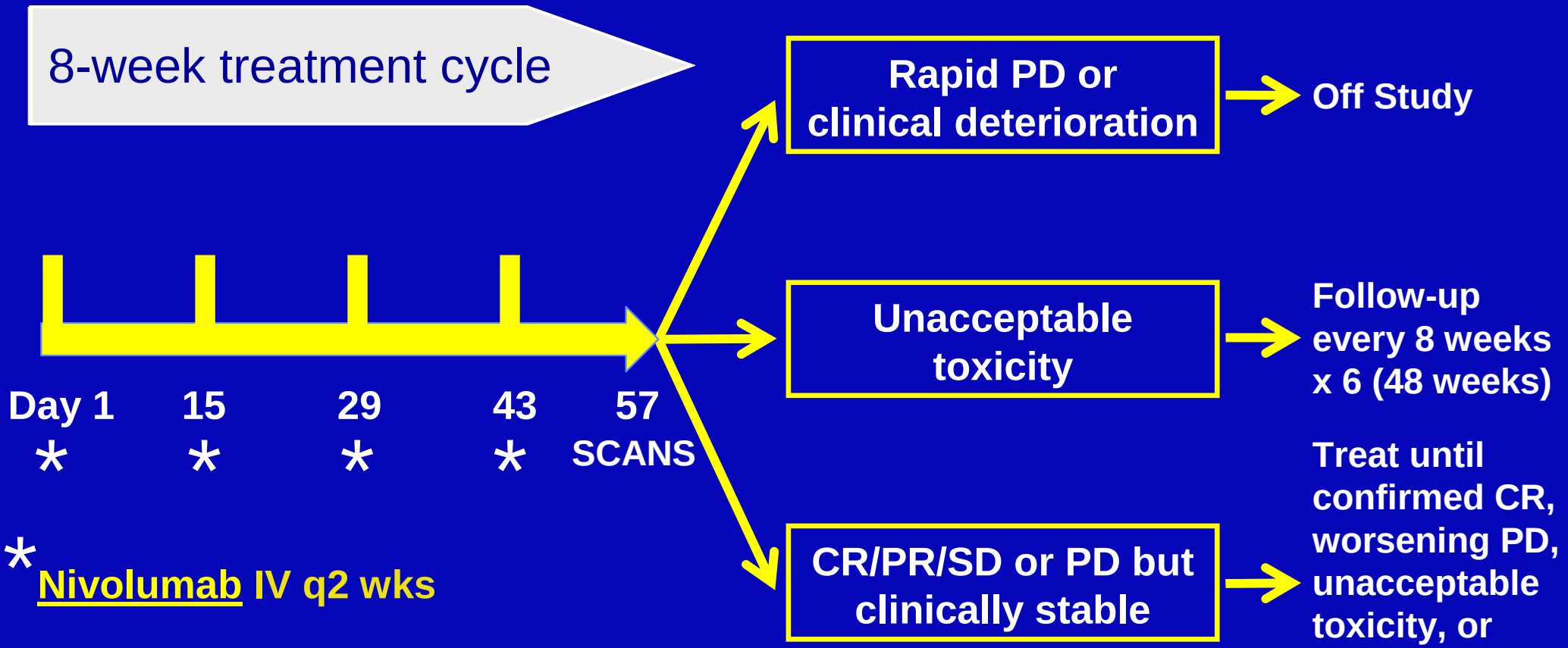
Blocking CTLA-4 and/or PD-1



Adapted from Wolchok, ASCO 2013

Phase I Nivolumab Study Design



Eligibility: Advanced MEL, mRCC, NSCLC, CRC, or CRPC with PD after 1-5 systemic therapies

CR = complete response; CRC = colorectal cancer; CRPC = castrate-resistant prostate cancer; MEL = melanoma; mRCC = metastatic renal cell carcinoma; NSCLC = non-small cell lung cancer; PD = progressive disease; PR = partial response; SD = stable disease

Brahmer et al. NEJM

Nivolumab Study Design

1 Dose escalation

NSCLC, MEL, RCC, CRC, CRPC
(1 - 3 - 10 mg/kg)

MEL expansion (1, 3, 10 mg/kg)
N=16/dose level

NSCLC, RCC, CRC, CRPC expansion
(10 mg/kg)
N=16 per histology

2 Cohort expansion

NSCLC, non-SCC (1, 3, 10 mg/kg)
N=16/dose, 48 patients randomized

NSCLC, SCC(1, 3, 10 mg/kg)
N=16/dose, 48 patients randomized

MEL (0.1, 0.3, 1 mg/kg)
N=16/dose, 48 patients randomized

RCC (1 mg/kg)
16 patients randomized

Characteristics of 306 treated patients:

- **Median age = 63 years**
- **ECOG PS=0 (42%) or 1 (56%)**
- ***47% had received ≥3 prior systemic therapies***

Clinical activity of Nivolumab

Tumor type (dose, mg/kg)	No. pts	Objective response rate[a]	Median[b] duration of response (wks)	Medain PFS[c] (months)	Median OS[c,d] (months)
NSCLC (1-10)	129	17%	74	2.3	9.6
Melanoma (0.1-10)	107	31%	104	3.7	16.8
RCC (1 or 10)	34	30%	56	7.3	>22

- All patients initiated treatment 2008-2012, ≥14 months before data analysis in March 2013
- OR = CR/PR by RECIST 1.0
- No ORs observed in 19 CRC or 17 CRPC patients

[a] Tumors and responses were assessed after each cycle per modified RECIST v1.0. Confidence intervals for ORRs and stable disease rates were calculated using the Clopper-Pearson method.

[b] Time from first response to documented progression, death, or last tumor assessment (for censored data denoted by +)

[c] Time-to-event endpoints (PFS, OS, duration of response) were estimated using the Kaplan-Meier method.

[d] Survival data were collected retrospectively.

Objective Response Rates by Dose Level

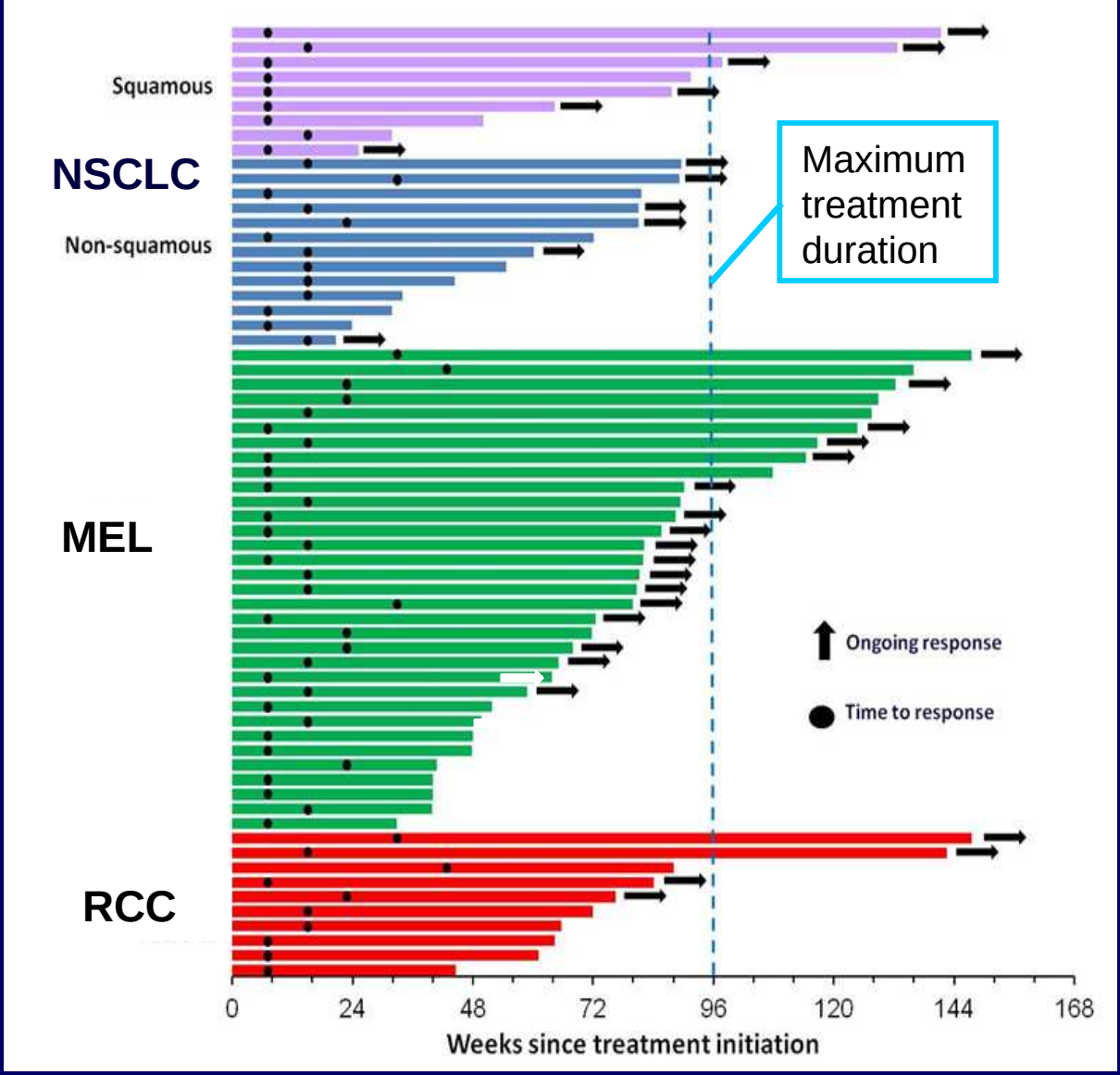
% (CI_{90})	Dose Level (mg/kg Q2W)				
	0.1	0.3	1	3	10
Objective Response Rate (ORR)					
Melanoma N = 107	**35** (n = 6) N = 17	**28** (n = 5) N = 18	**31** (n = 11) N = 35	**41** (n = 7) N = 17	**20** (n = 4) N = 20
NSCLC - SQ N=54	--	--	**0** N = 13	**22** (n = 4) N = 18	**24** (n = 5) N = 21
NSCLC - NSQ N=74	--	--	**5** (n = 1) N = 18	**26** (n = 5) N = 19	**19** (n = 7) N = 37
RCC N=34	--	--	**28** (n = 5) N = 18	--	**31** (n = 5) N = 16

Response evaluation by standard RECIST

8 patients had a persistent reduction in baseline target lesions in the presence of new lesions but were not classified as responders for the ORR calculation.

Efficacy population; cutoff July 1, 2011

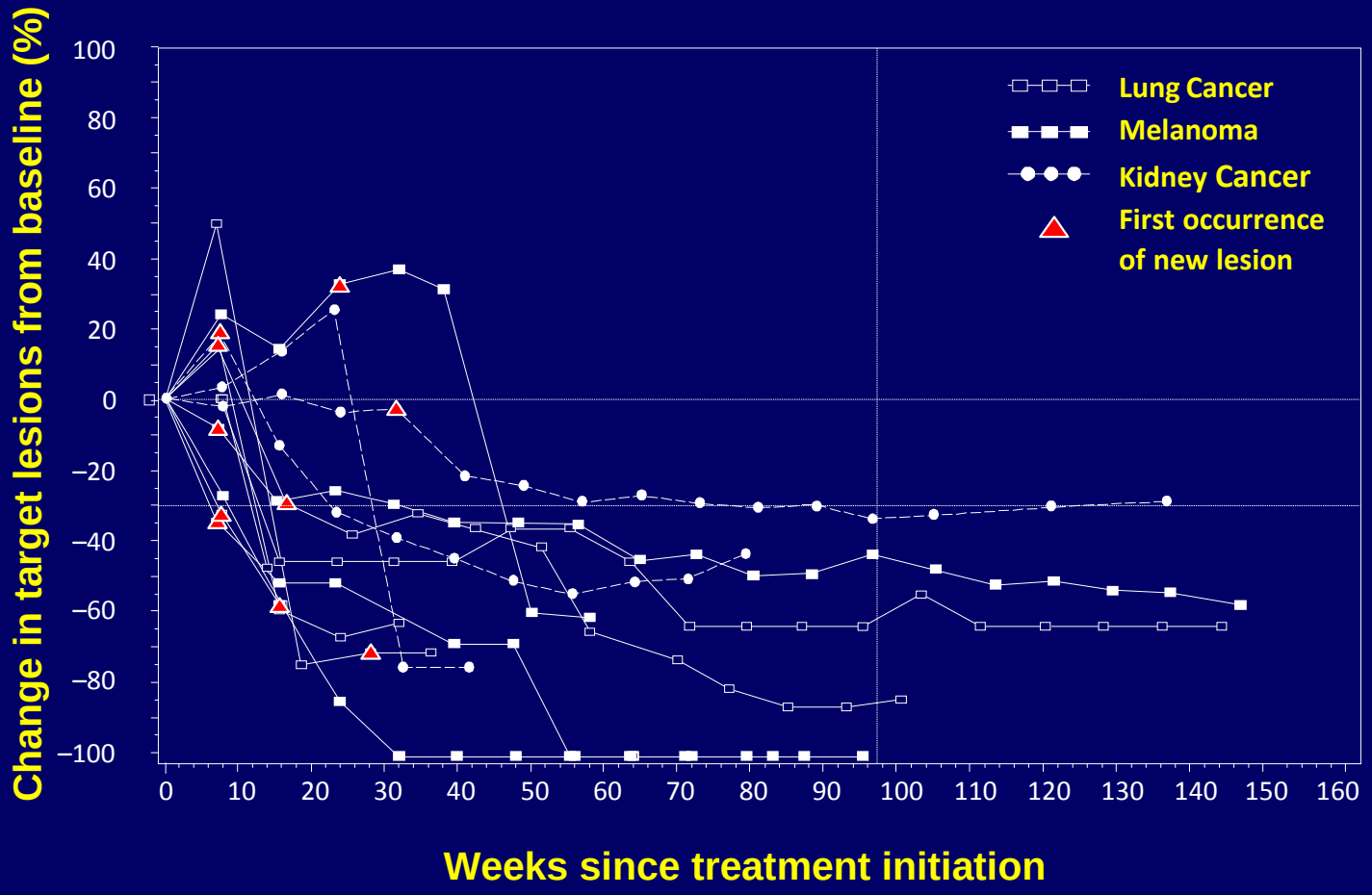
Durability of objective responses induced by nivolumab in patients with advanced NSCLC, MEL and RCC



Sixty-five of 306 patients had ORs (CR/PR):

- ❑30 of 65 (**46%**) responses were evident at first tumor evaluation (8 weeks)
- ❑42 of 65 (**65%**) patients had responses lasting >1 year
- ❑35 of 65 (**54%**) responses were ongoing at time of data analysis
- ❑Responses persisted off-drug

Unconventional “immune-related” responses in 13 patients with NSCLC, MEL and RCC



- 13 of 270 pts (**5%**) with NSCLC/MEL /RCC had unconventional responses
- irResponse durability and persistence off-drug were similar to conventional RECIST responses

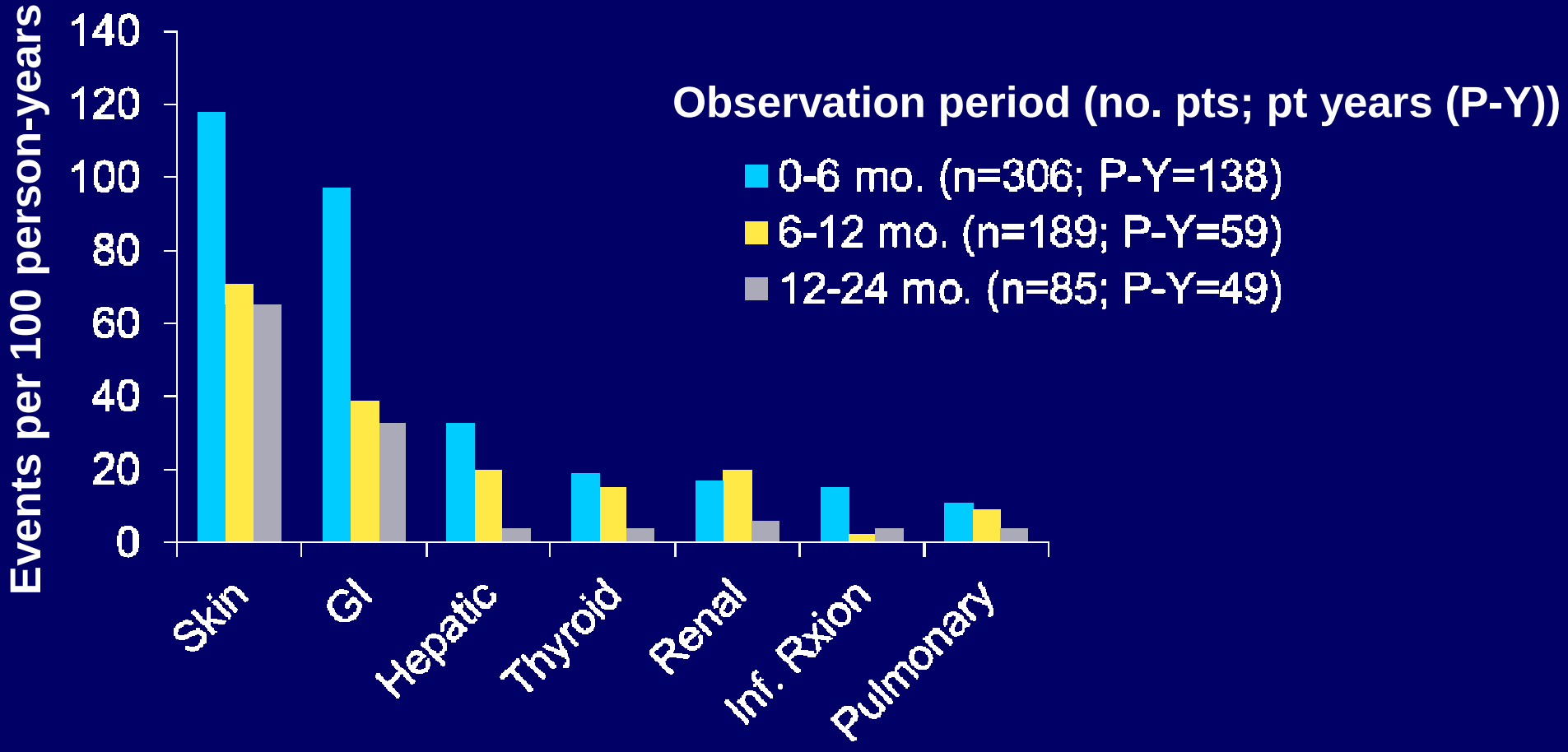
Treatment-related select adverse events ("immune-related") in ≥ 3% of 306 patients

Select AE	All grades n (%)	Grade 3-4 n (%)
Any select AE	140 (46)	19 (6)
Rash	45 (15)	0
Diarrhea	41 (13)	3 (1)
Pruritis	32 (11)	1 (0.3)
Pneumonitis*	12 (4)	4 (1)
Infusion reaction	12 (4)	0
TSH ↑, hypothyroidism	11 (4)	1 (0.3)
ALT ↑	11 (4)	1 (0.3)
AST ↑	9 (3)	0

Select AEs in <3% of pts included colitis, hypophysitis, nephritis and diabetes mellitus.

*There were 3 (1%) deaths associated with pneumonitis

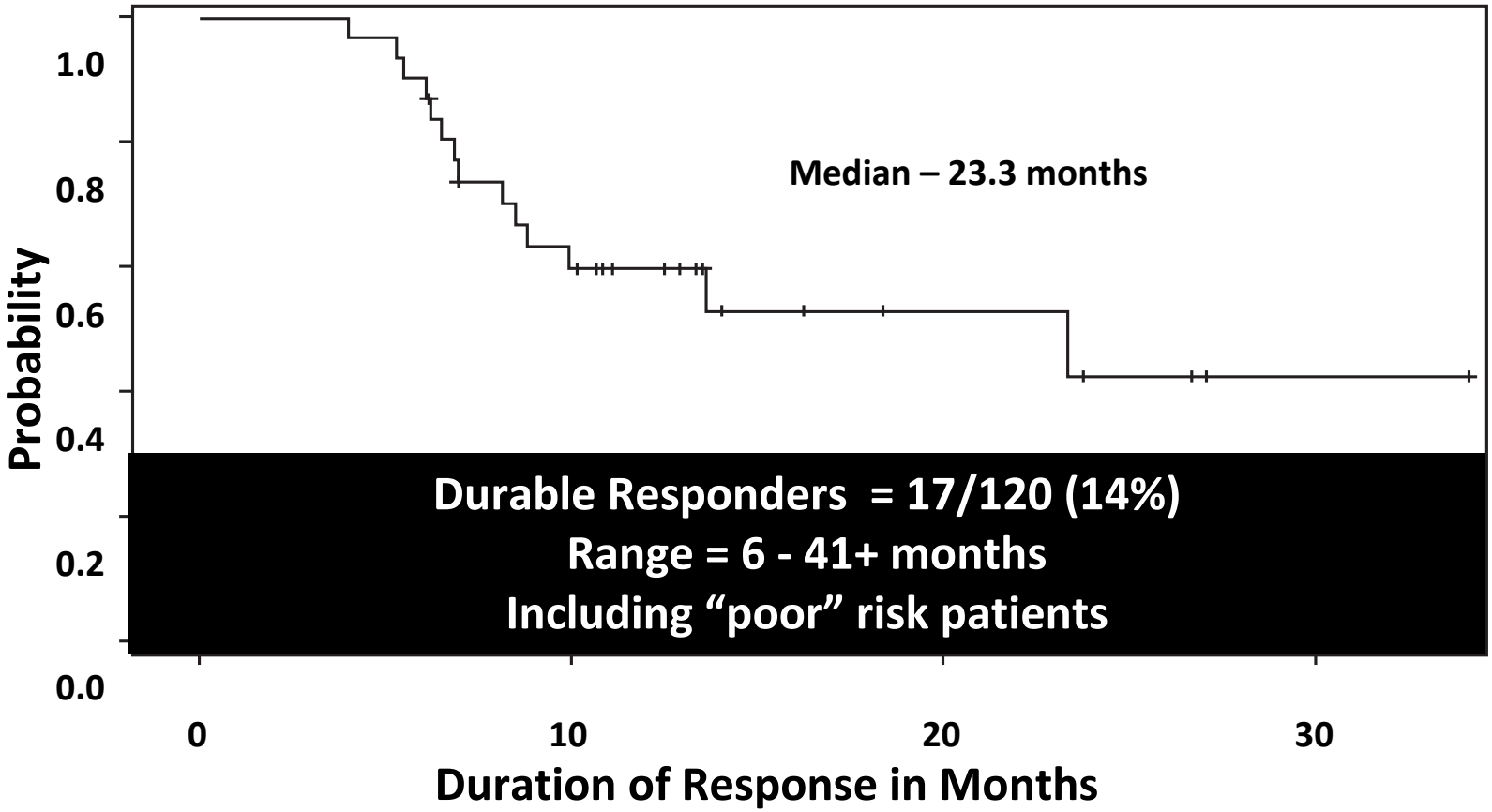
Exposure-adjusted select ("immune-related") adverse events: toxicity is not cumulative



- Multiple occurrences of all-cause select AEs in individual pts are included in this exposure-adjusted analysis.
- Drug-related AE's: all grades, 75%; grade 3-4, 17% of pts
- Drug-related select AE's: all grades, 46%; grade 3-4, 6% of pts

Renal Cell Carcinoma

High dose IL-2 can induce durable responses



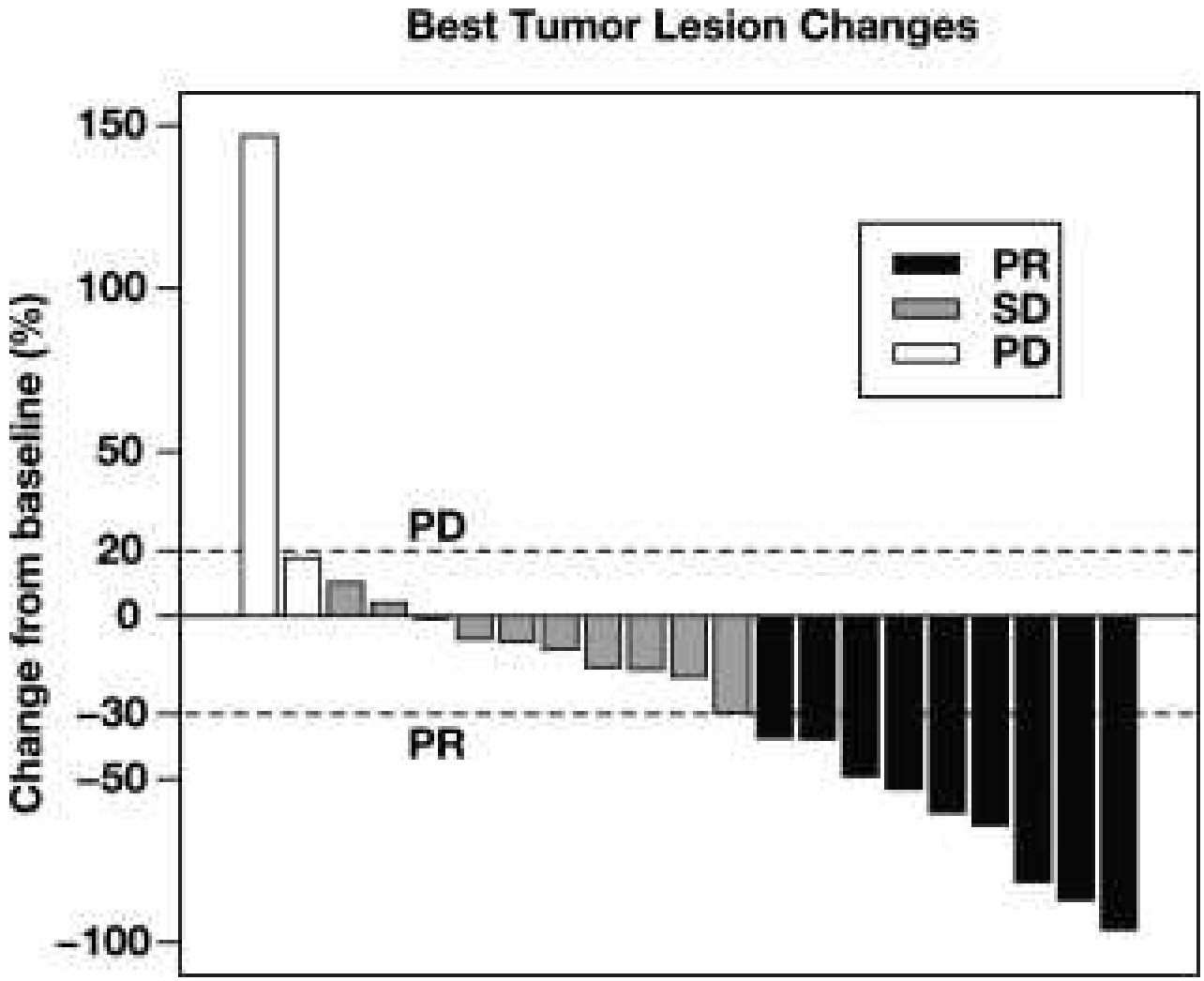
- 15-20% Objective response rate, 5-7% durable CRs
- Significant toxicity: better selection criteria imperative
- No targeted therapy produces response durations like HD IL-2

Objective Tumor Regressions With Ipilimumab Monotherapy in Metastatic RCC

	No. Patients	Doses of Ipilimumab	Response Duration
Cohort A loading dose of 3 mg/kg, then1 mg/kg	21		
PR	**1 (5%)**	**5**	**18 months**
Cohort B: all doses at 3 mg/kg			
Previous IL2	26		
PR	**2 (8%)**	**4, 4**	**7, 8 months**
No previous IL2	14		
PR	**3 (21%)**	**3, 6, 4**	**12, 17, 21 months**

Yang et al. *J Immunother.* 2007

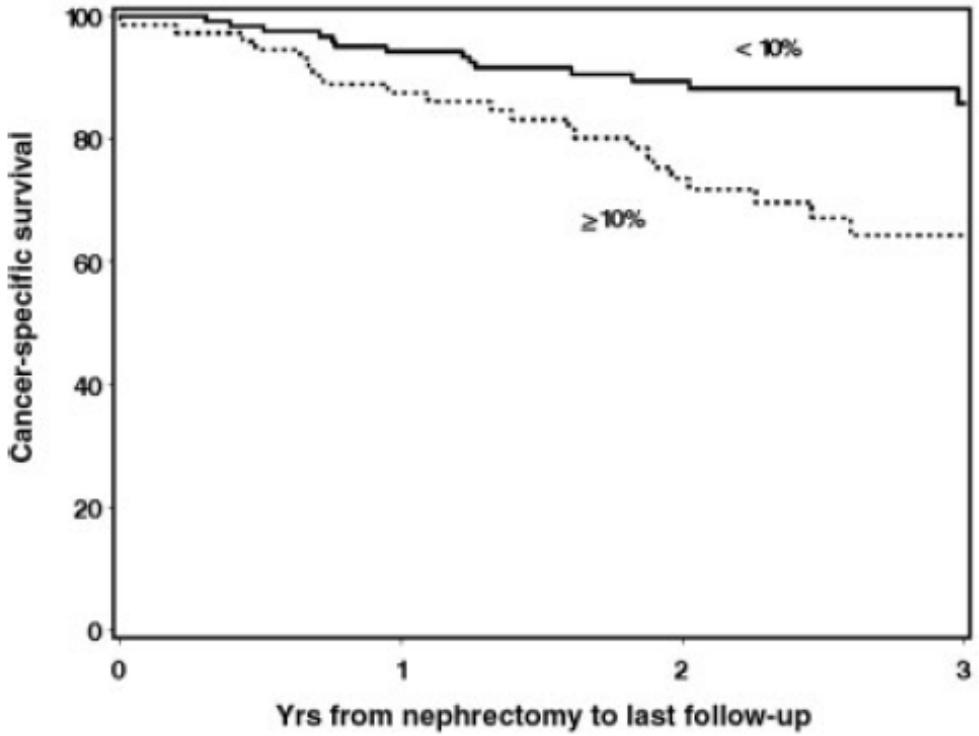
Phase 1 dose - escalation trial of tremelimumab plus sunitinib in patients with metastatic renal cell carcinoma



* Study terminated early due to renal toxicity

Rini et al. *Cancer* 2010

Prognostic Relevance of PD-1 Pathway in RCC



<10% PD-L1 expression

--- ≥10% PD-L1 expression (+)

- RCC: can constitutively express PD-L1 (15-66%)
- Tumoral PD-L1 expression may be associated with:
  - Impaired antitumor immunity
  - More aggressive disease
  - Shorter survival

Thompson Clin Cancer Res 2005
Thompson Clin Cancer Res 2007
Frigola Clin Cancer Res 2011
Krambeck Clin Cancer Res 2007

Efficacy of nivolumab monotherapy in patients with RCC

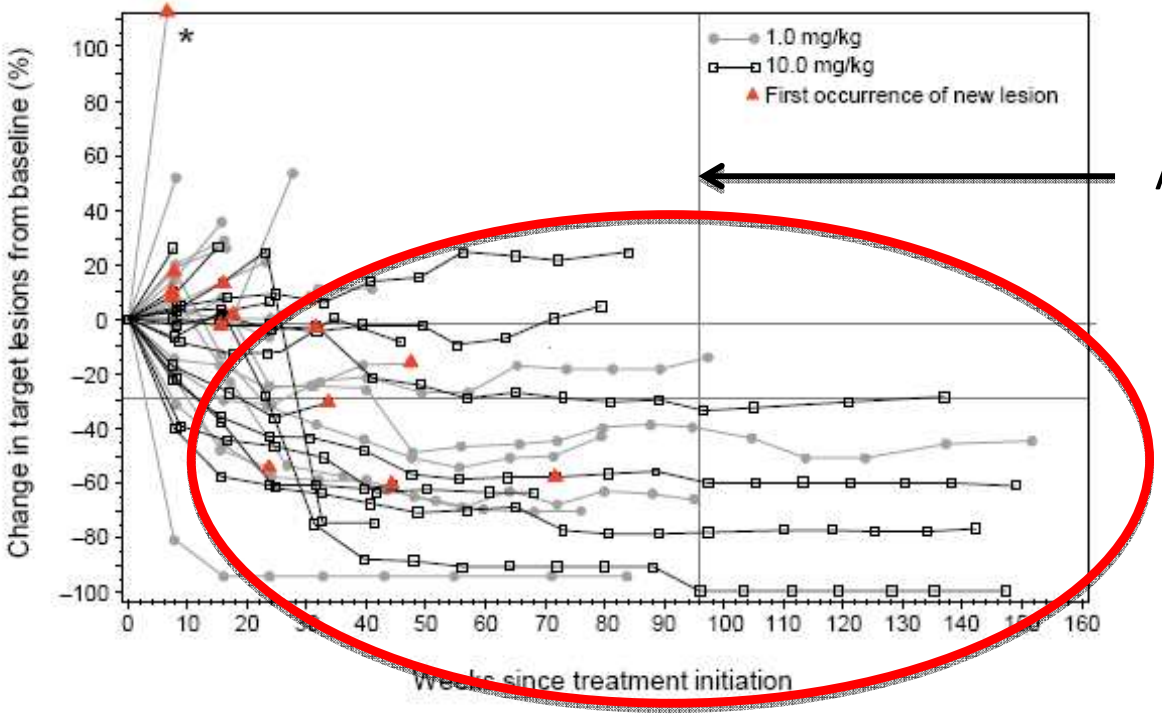
Dose, mg/kg	Objective response rate	Median duration of response Weeks (range)	Stable disease rate %		Median PFS, Months (95% CI)	Median OS, Months (95% CI)
			≥24 weeks	≥48 weeks		
All doses	29.4%	56	26.5%	5.9%	7.3	>22
1	27.8%	56	22.2%	5.6%	4.7	NR
10	31.3%	56	31.3%	6.3%	8.0	18.8

McDermott et al. ASCO 2012/2013

Update: Phase I Nivolumab: RCC cohort (n=34)

- Generally tolerable: fatigue, rash, pruritus, diarrhea
  - 3 deaths: pneumonitis (non-RCC)

- Preliminary efficacy in heavily pre-treated patients:
  - 29% objective responses
  - Median PFS 7.3 months

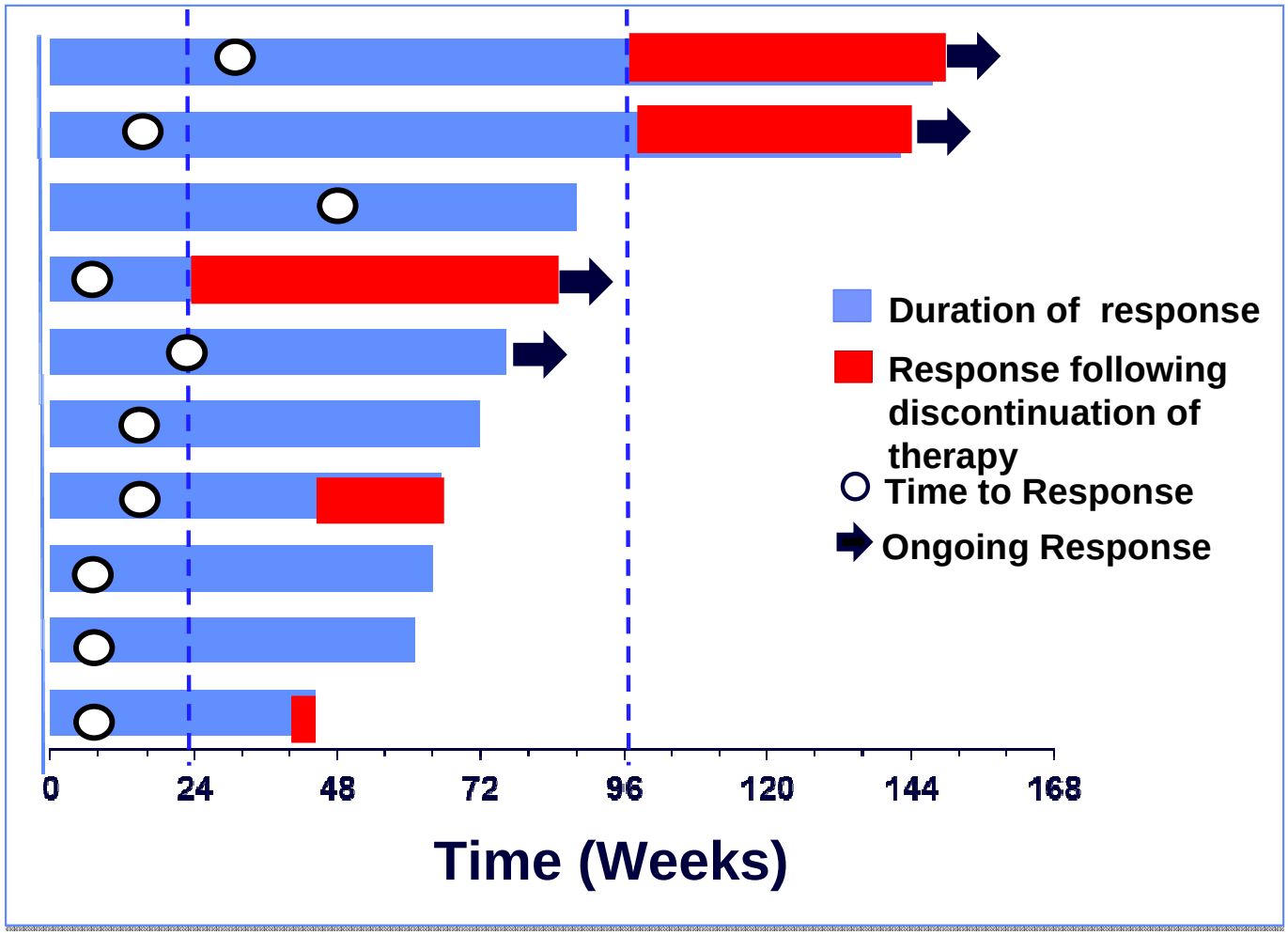


All stopped therapy

Durability of Response Even Off Drug

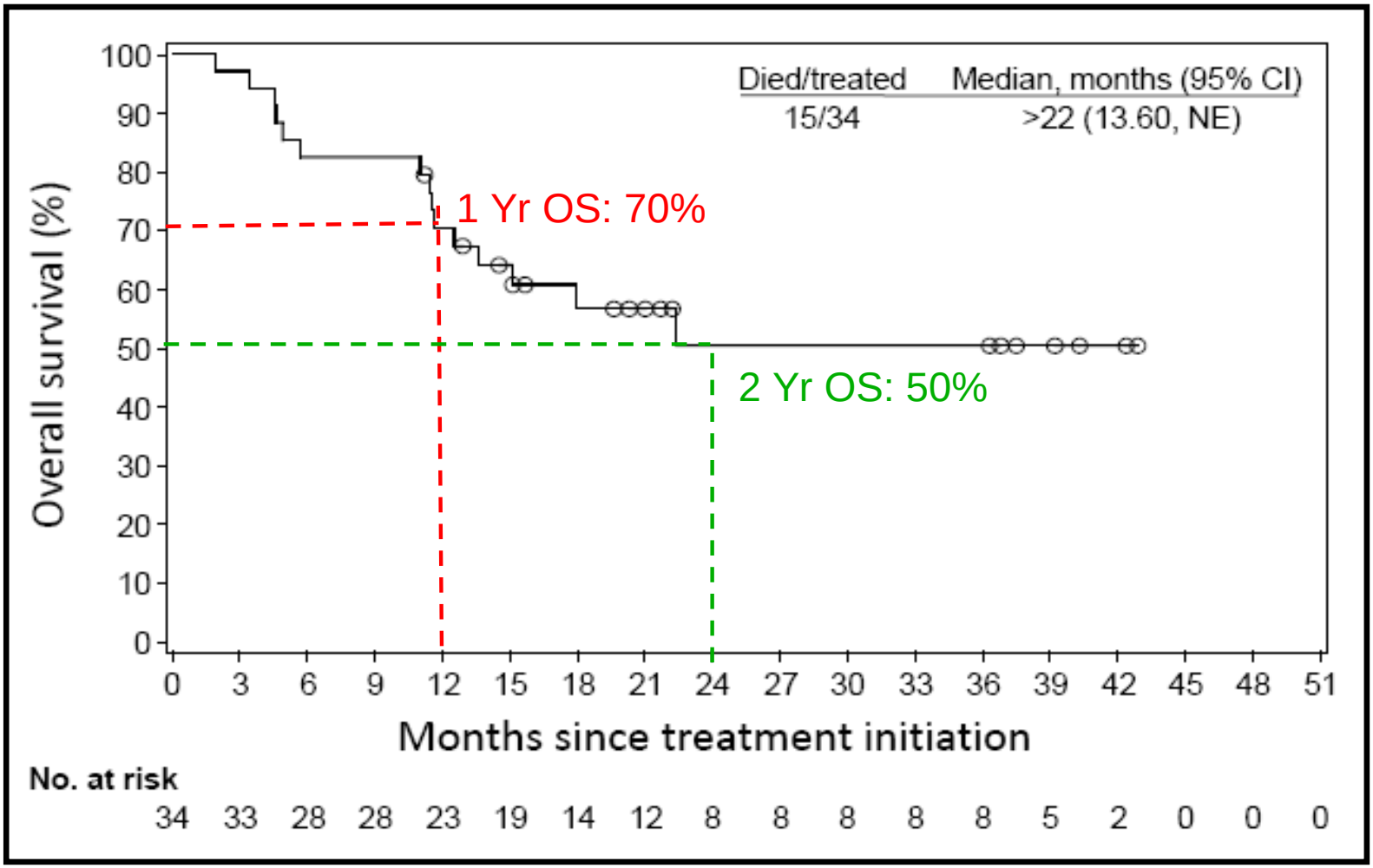
Drake ASCO 2013

Characteristics of Responses



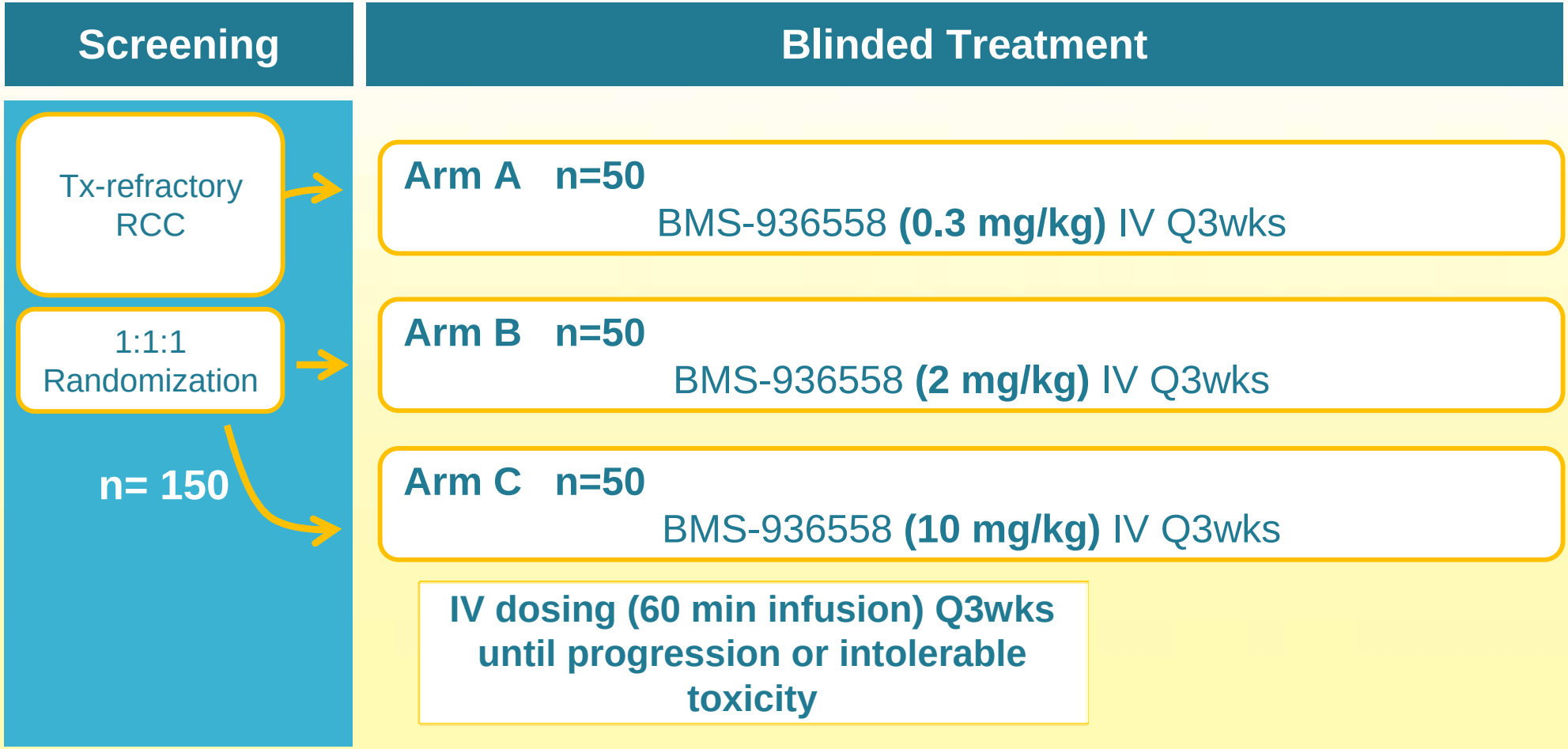
- Median time to response: 8 weeks (first tumor assessment)
- 4 patients had persistent responses ≥ 16 weeks off therapy

Survival Data with Nivolumab in RCC

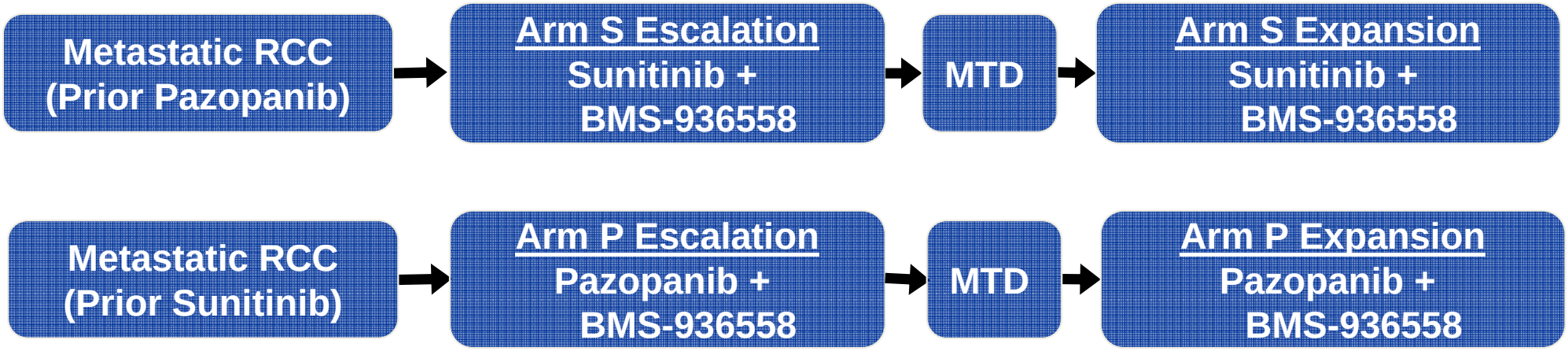


Drake ASCO 2013

Completed Randomized Phase II Study Design



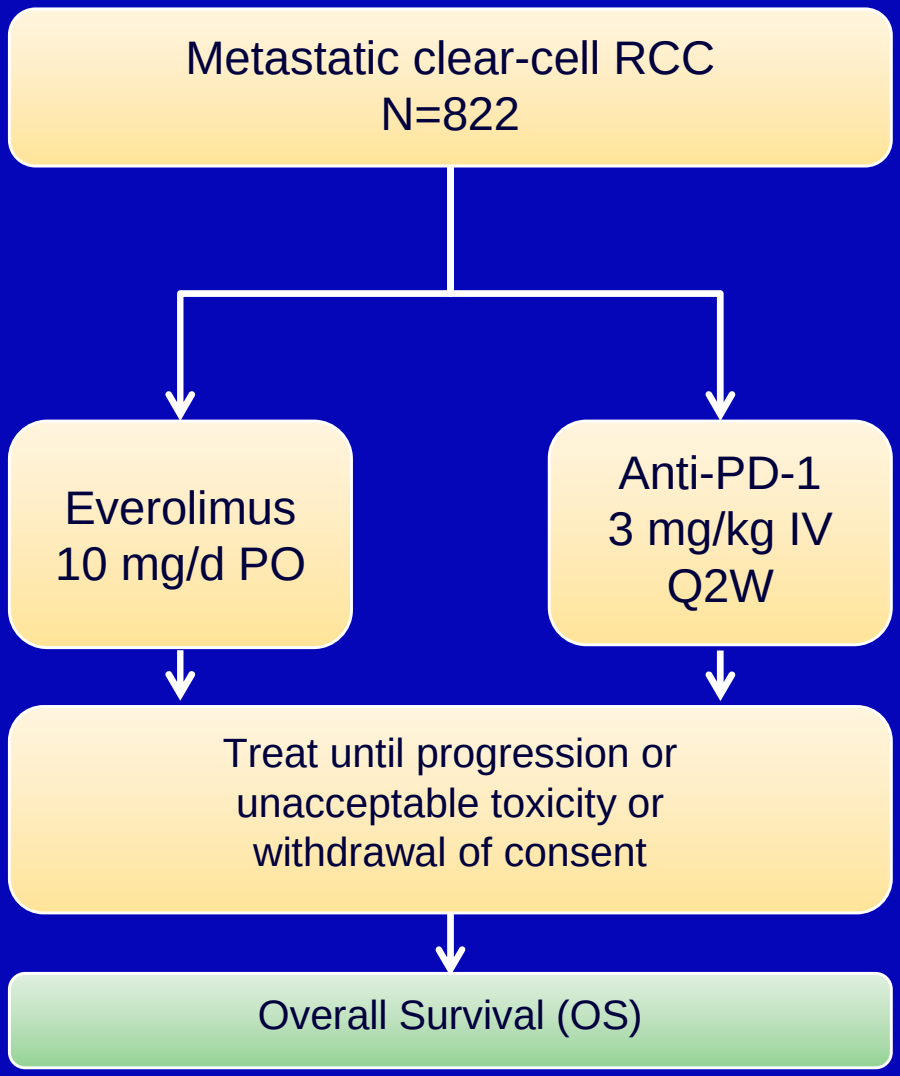
Phase 1 Study Combining Anti-PD-1 (BMS-936558) With Sunitinib or Pazopanib in Patients with Metastatic RCC



Ipilimumab + Nivolumab Arms Added

Primary end points: Safety,Tolerability, MTD

Phase 3 study of anti-PD-1 versus everolimus in patients with previously treated mRCC (NCT01668784)



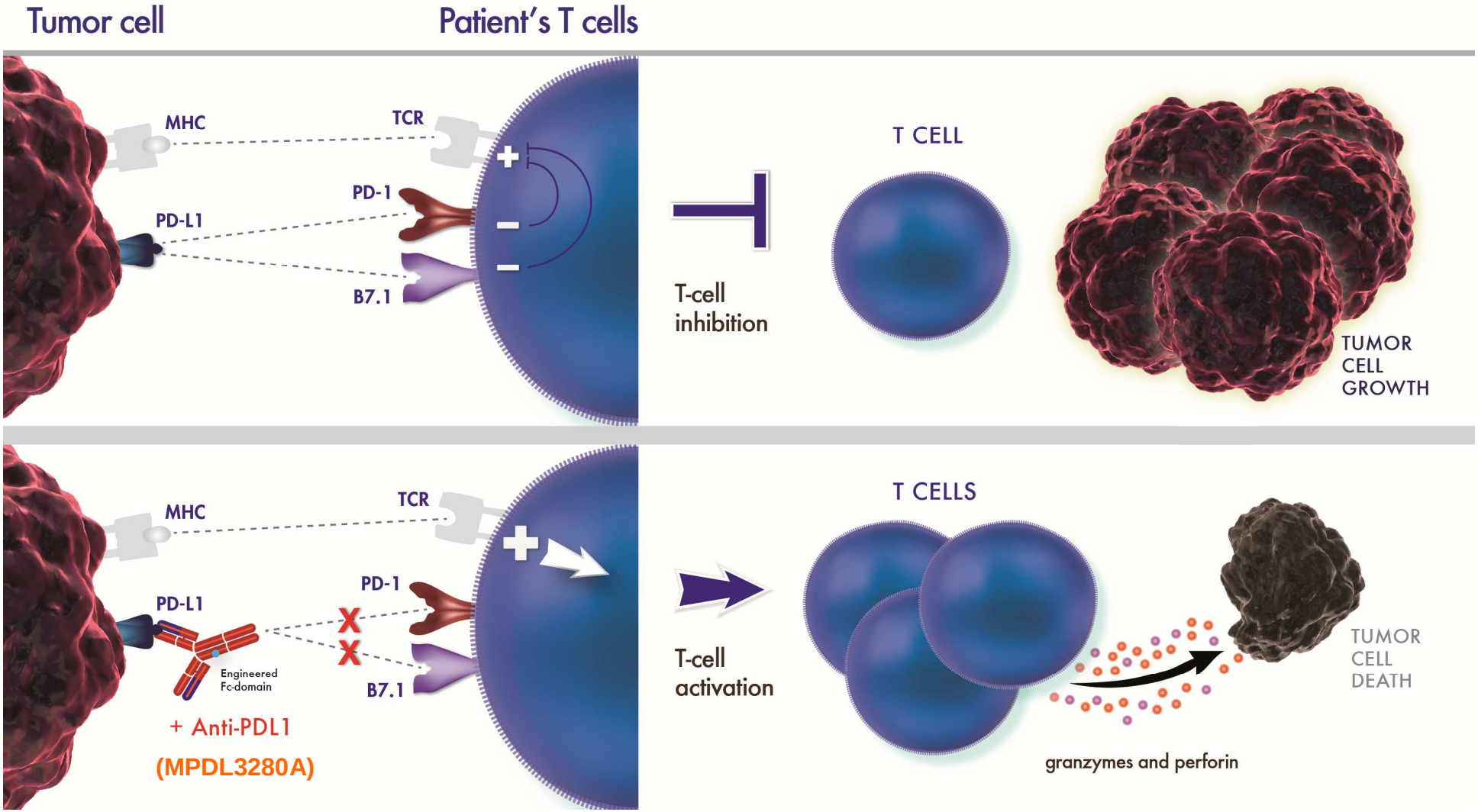
Start Date: October 2012
Estimated Study Completion Date: February 2016
Estimated Primary Completion Date: February 2016
Status: Recruiting

Primary Endpoints
- OS

Secondary Endpoints
- PFS
- ORR
- Duration of objective response
- Duration of overall survival
- Safety
- Disease related symptom progression rate

Key Eligibility Criteria
- Confirmed RCC with clear-cell component
- 1/2 prior anti-angiogenic therapies in advanced/metastatic setting
- ≤3 prior systemic treatment regimens and evidence of progression on or after last treatment and within 6 months of enrollment
- Karnofsky Performance Score ≥70%
- No CNS metastasis

MPDL3280A (Anti-PDL1) Inhibits the Binding of PD-L1 to PD-1 and B7.1



- Blocking PD-L1 restores T-cell activity, resulting in tumor regression in preclinical models
- Binding to PD-L1 leaves PD-1/PD-L2 interaction intact and may enhance efficacy and safety

D. Cho ASCO 2013

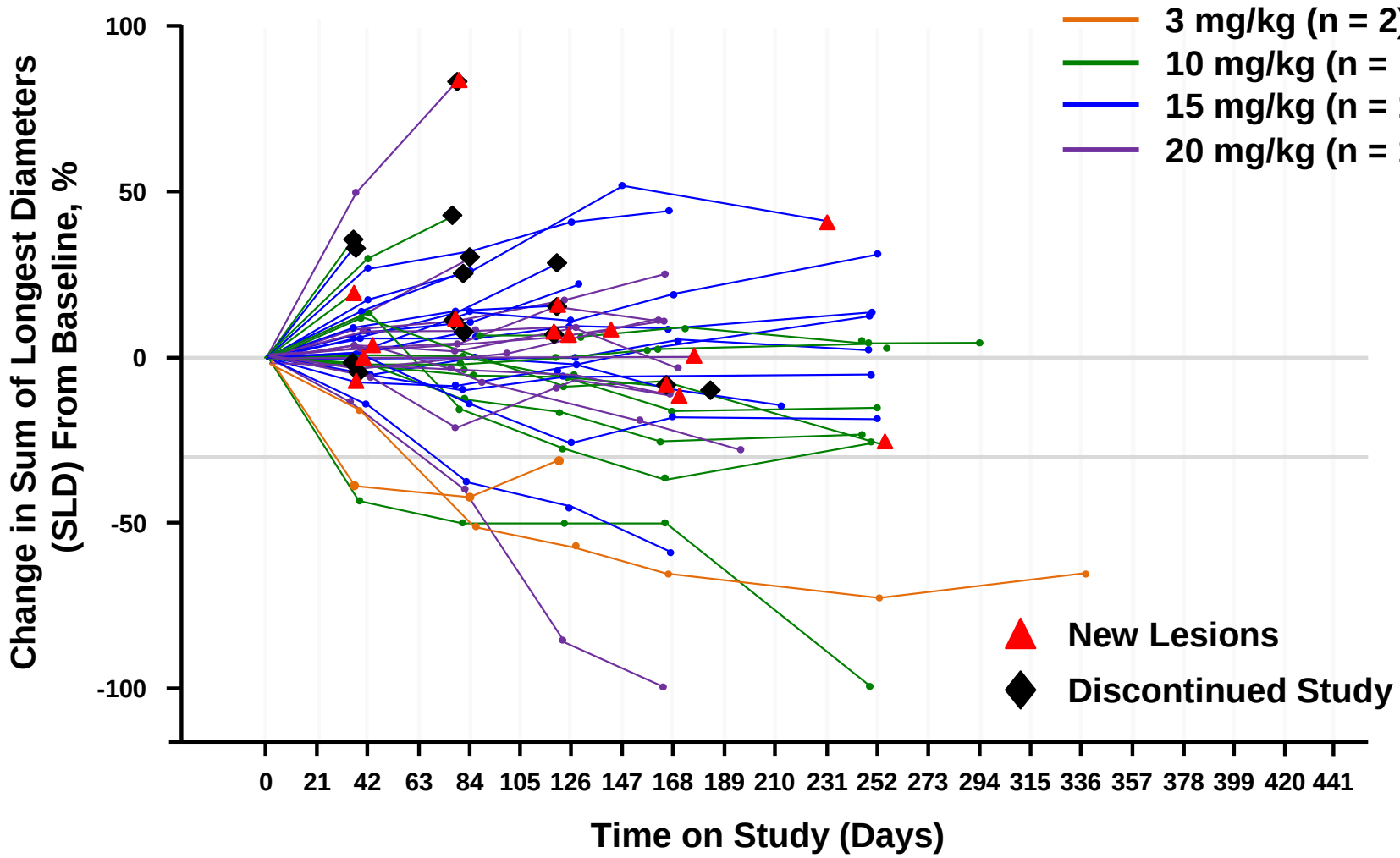
MPDL3280A Phase 1a Efficacy Summary

Investigator Assessed

	RECIST 1.1 Response Rate (ORR)	SD of 24 Weeks or Longer	24-Week PFS
Overall population (N = 140)	21%	16%	45%
RCC* (n = 47)	13%	32%	53%
Clear cell (n = 40)	13%	35%	57%
Non-clear cell (n = 6)	17%	0	20%

* 1 patient with unknown histology. Includes sarcomatoid and papillary RCC.
All patients first dosed prior to August 1, 2012; data cutoff February 1, 2013.
ORR includes unconfirmed PR/CR and confirmed PR/CR.

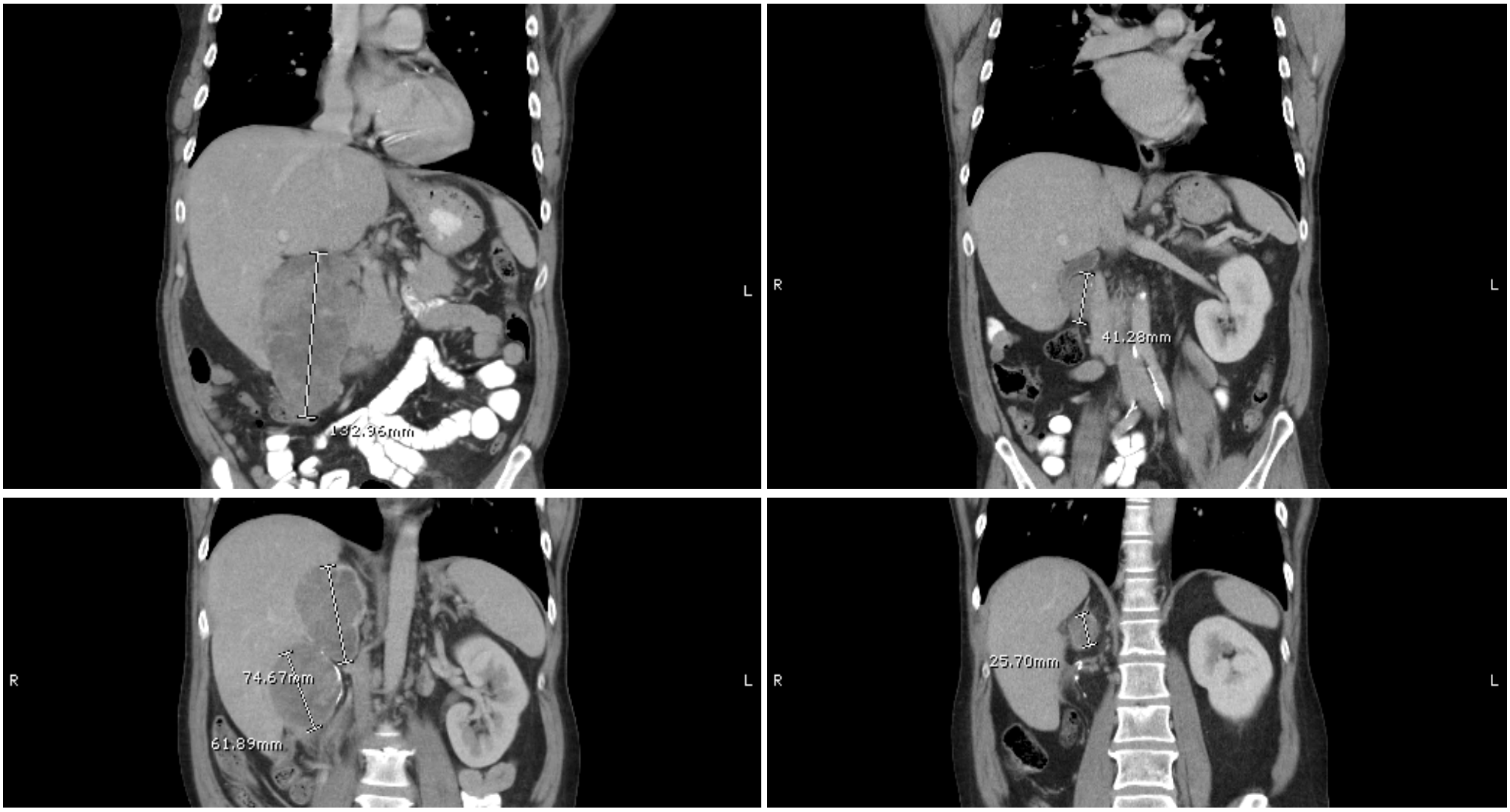
MPDL3280A Phase 1a Tumor Burden Over Time (RCC)



Patients first dosed at 3-20 mg/kg prior to August 1, 2012 with at least 1 post-baseline evaluable tumor assessment; data cutoff Feb 1, 2013.

PD-L1–Positive RCC Patient With Response to MPDL3280A

Baseline | **After 16 weeks**



45-year-old male with RCC, s/p nephrectomy, HD IL-2, PD-L1 positive

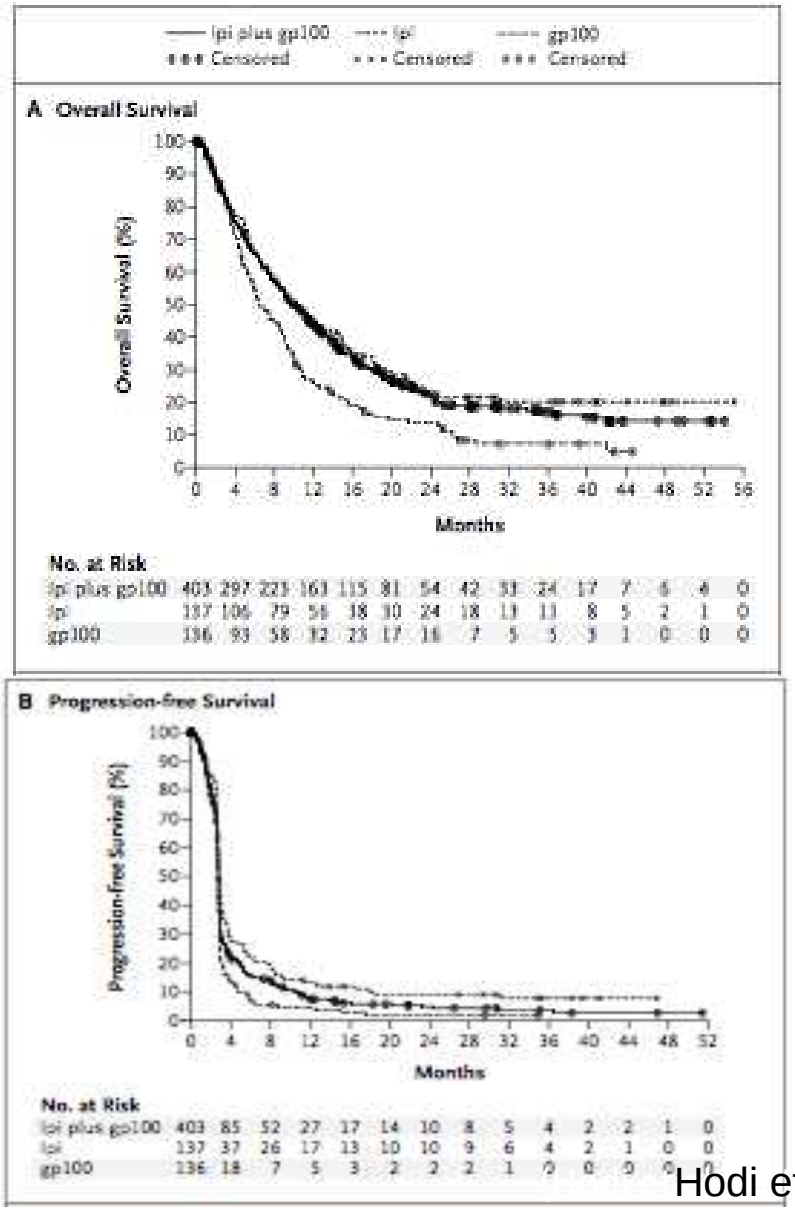
Images include data from after Feb 1, 2013.
Yale School of Medicine (Sznol/Herbst).

PRESENTED AT: ASCO Annual '13 Meeting

Metastatic Melanoma

Ipilimumab improves OS in metastatic melanoma

- Vaccine vs. ipilimumab vs. vaccine/ipilimumab
- OS: 6.4 vs. 10.1 vs. 10 months
- FDA approved 3/2011



Hodi et al. NEJM

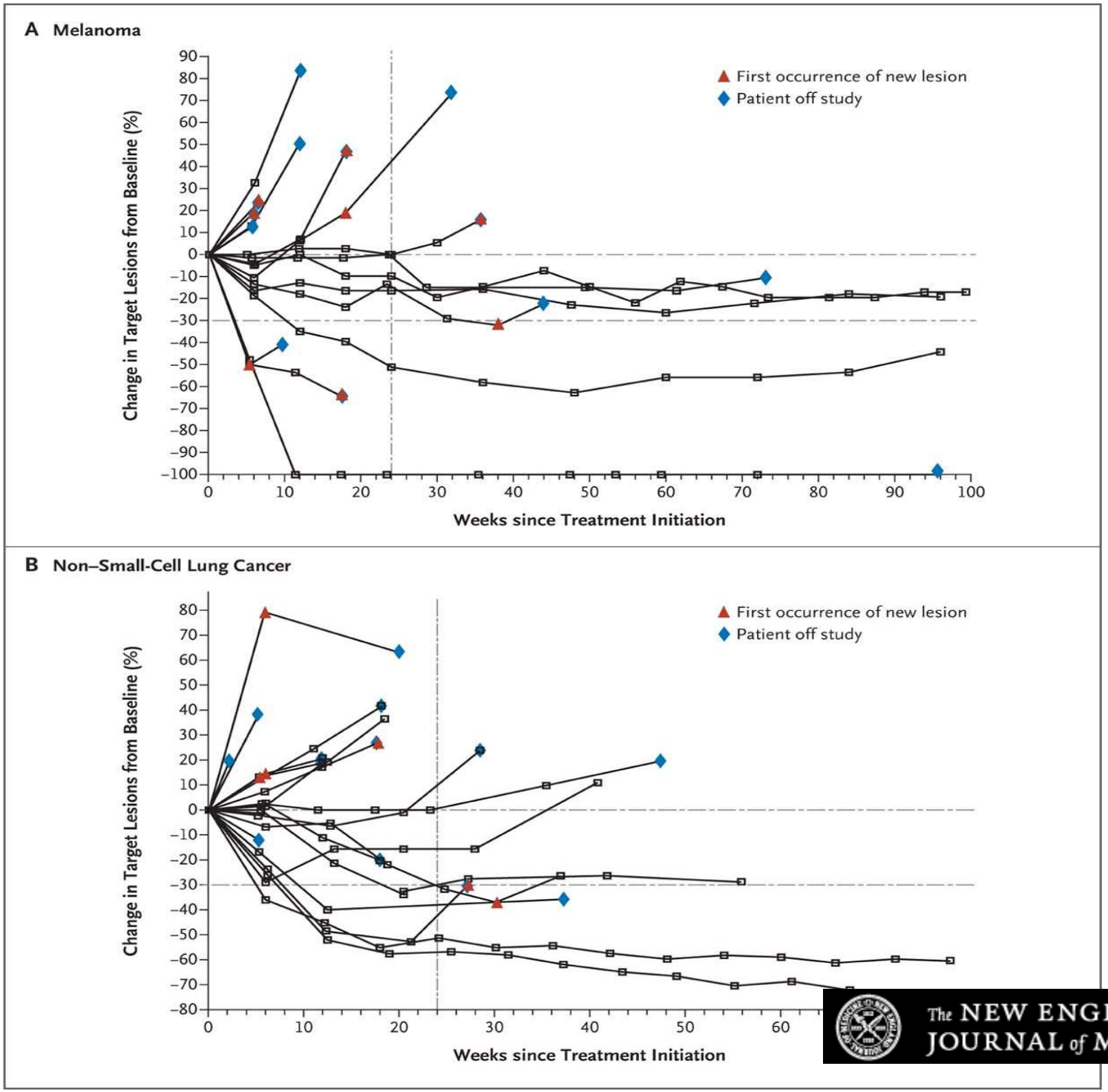
Ipilimumab and Nivolumab Clinical Experience in Patients with Advanced Melanoma

- **Ipilimumab:** 3 mg/kg every 3 wk, 4 doses (Phase 3)
  - ORR: 11%; 2 patients with CR[1]
  - Median overall survival: 10.1 mo; 4-year survival rate: 18%[2]
  - Grade 3-4 related AEs: 23%; included diarrhea (5%) and colitis (5%)[1]

- **Nivolumab**: 3 mg/kg every 2 wk, ≤48 doses (Phase 1b)
  - ORR: 41%; 1 patient with CR[3]
  - Median overall survival: 16.8 mo; 2-year survival rate: 43%[4]
  - Grade 3-4 related AEs: 14%; included diarrhea (1%), pneumonitis (1%), and hypophosphatemia (1%)[3]

[1]Hodi et al. NEngl J Med. 2010;363:711-23. [2]Wolchok et al. Ann Oncol 2013. [3]Topalian et al. N Engl J Med 2012;2443-54. [4]Sznol et al. ASCO 2013, oral presentation, abs 9006.

Nivolumab monotherapy in melanoma



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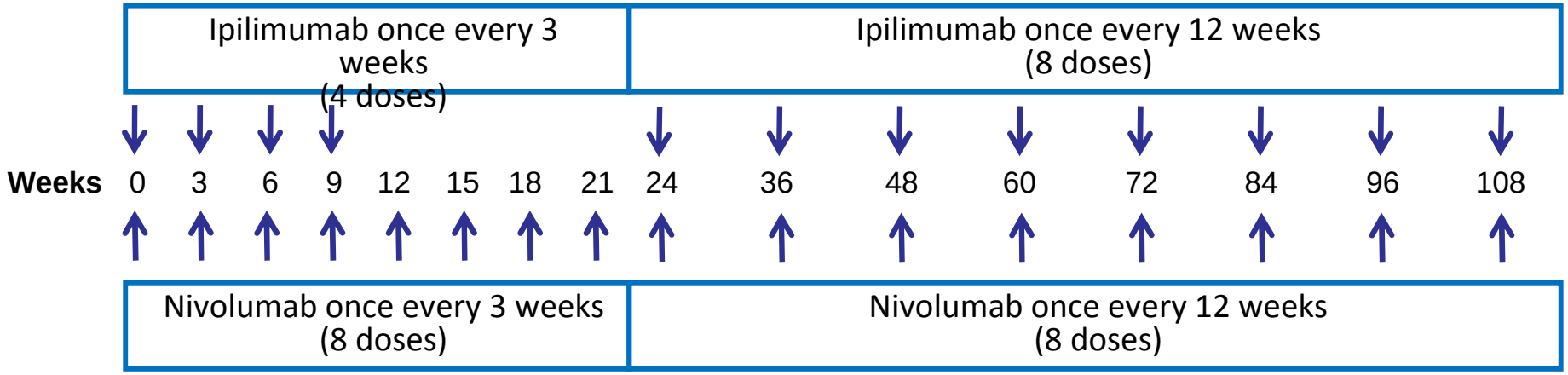
Phase I Study: Dose Cohorts

Cohort	Nivolumab Dose (mg/kg)	Ipilimumab Dose (mg/kg)
Concurrent regimen		
	0.3	3
	1	3
	3	1
	3	3
Sequenced regimen		
	1	Prior
	3	Prior

Phase I Study: Schedule

Concurrent Cohorts



- First tumor assessment at 12 weeks

Sequenced Cohorts

- Following prior ipilimumab, patients received nivolumab every 2 weeks for a maximum of 48 doses
- First tumor assessment at 8 weeks

- **Tumor assessments by mWHO and immune-related response criteria**
- **Data as of Feb 2013 for 86 patients**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Adv

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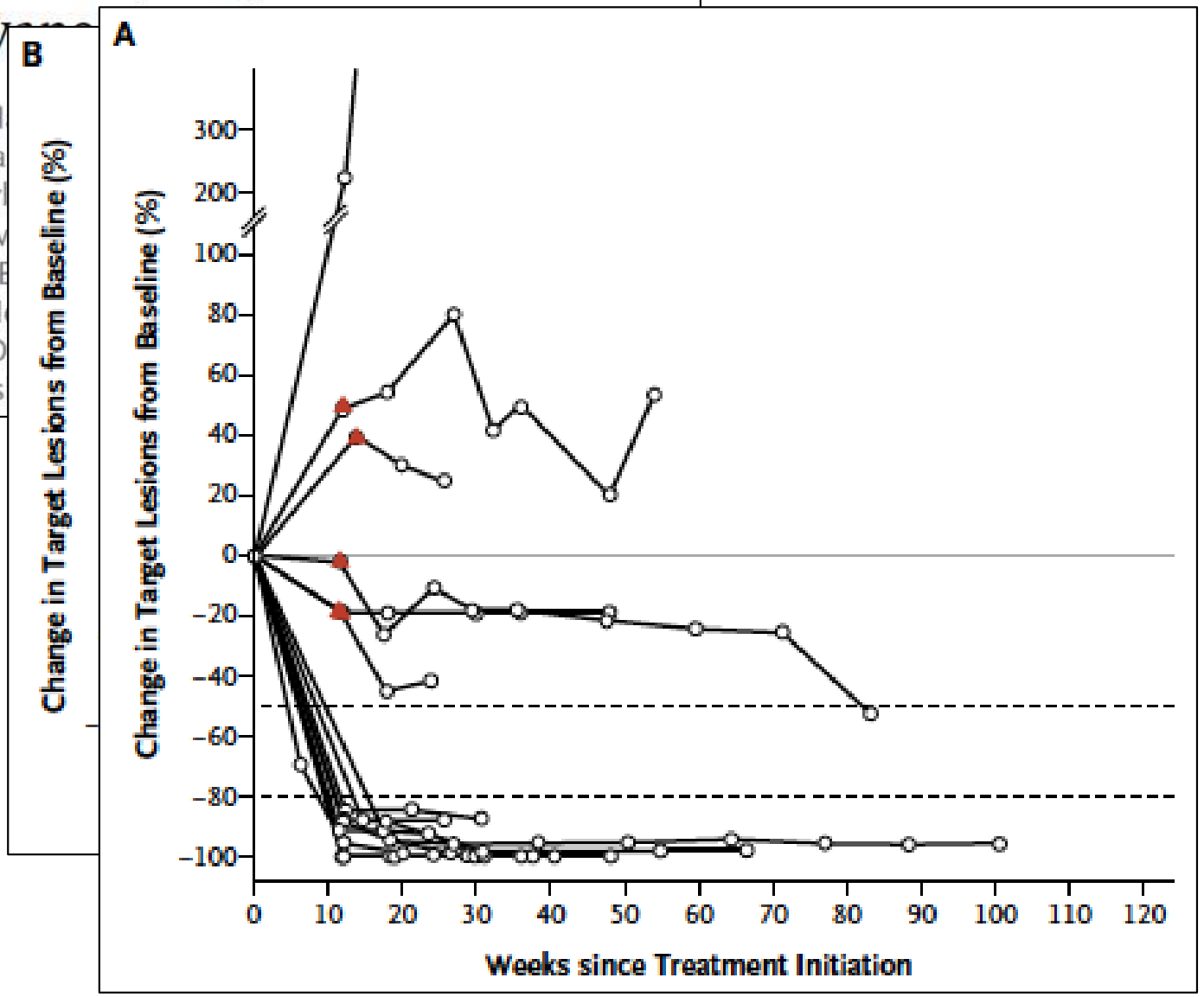
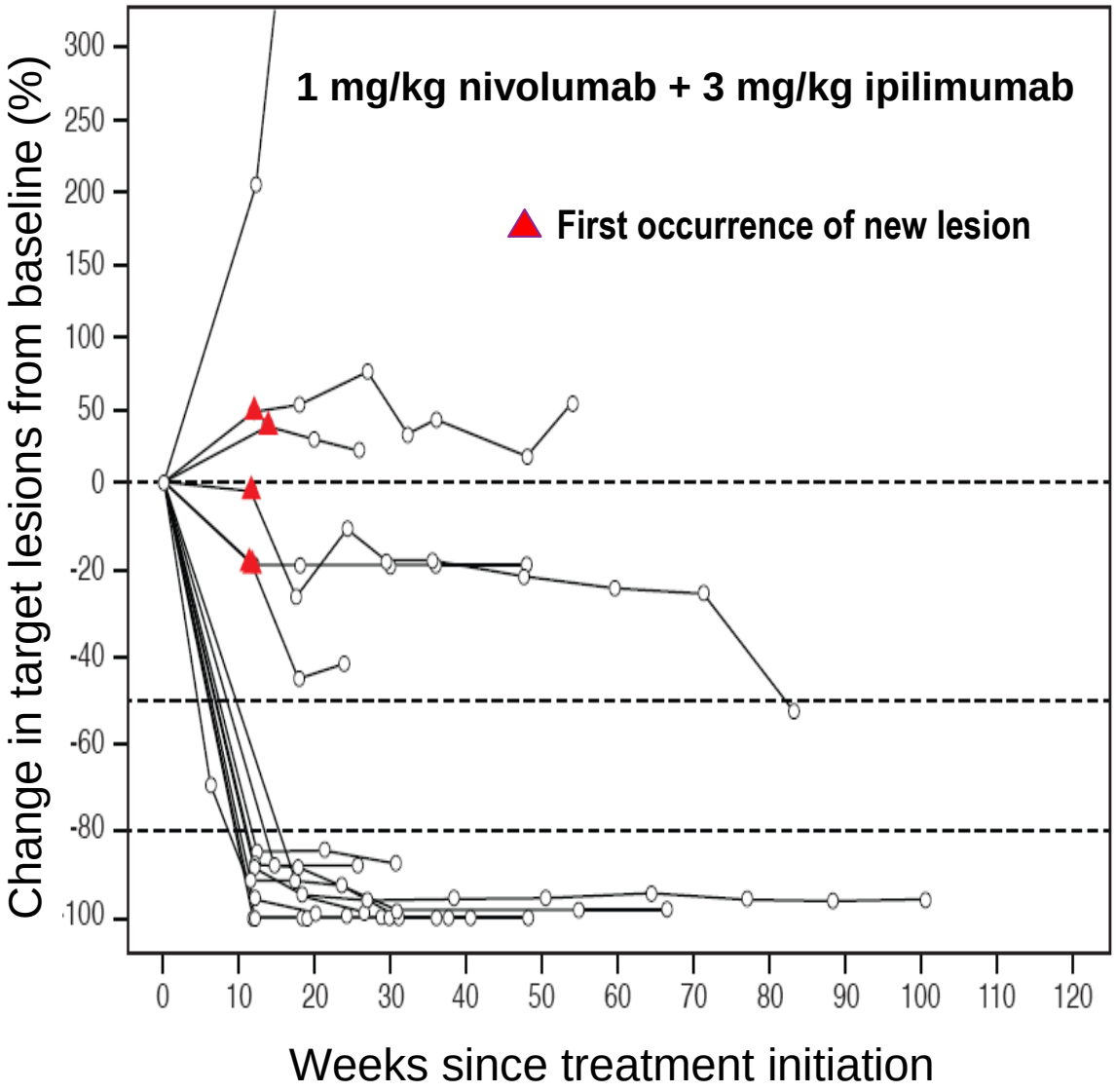
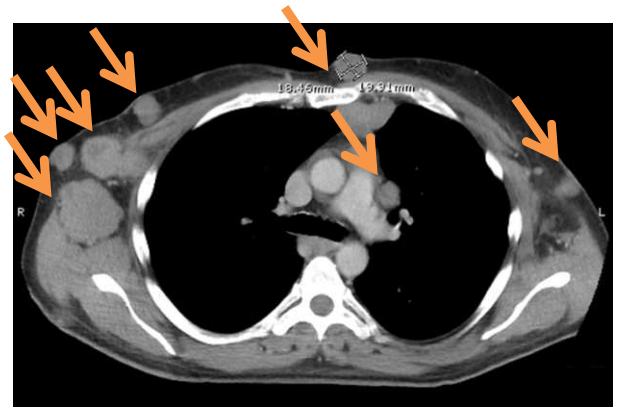
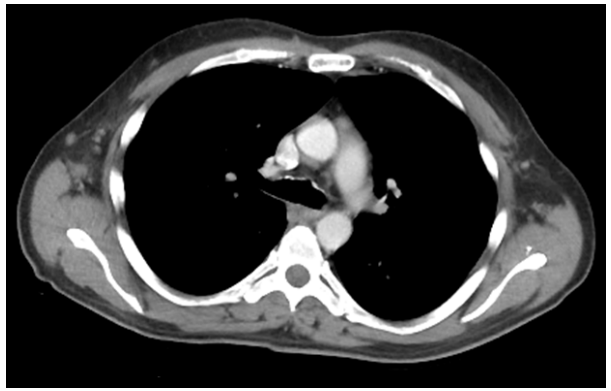


Rapid and Durable Changes in Target Lesions





Pre-treatment



12 weeks

- A 52-year-old patient presented with extensive nodal and visceral disease
- Baseline LDH was elevated (2.3 x ULN); symptoms included nausea and vomiting
- Within 4 wk, LDH normalized and symptoms resolved
- At 12 wk, there was marked reduction in all areas of disease as shown

Clinical Activity: Concurrent Regimen

Dose (mg/kg)		Response Evaluable Patients n	CR n	PR n	Objective Response Rate [95% CI]	≥80% Tumor Reduction at 12 wk n (%)
Nivolumab	Ipilimumab					
0.3	3	14	1	2	21 [5-51]	4 (29)
1	3	17	3	6	53 [28-77]	7 (41)
3	1	15	1	5	40 [16-68]	5 (33)
3	3	6	0	3	50 [12-88]	0
Concurrent		52	5	16	40 [27-55]	16 (31)

- With 1 mg/kg nivolumab + 3 mg/kb ipilimumab, 53% of patients had confirmed objective responses (3 CRs and 6 PRs)
- All 9 of these had ≥80% tumor reduction at the first scheduled 12-week tumor assessment
- ≥80% tumor reductions appear infrequently (<10%) in the nivolumab and ipilimumab monotherapy experiences

Treatment-Related Adverse Events (≥10% of all patients)

Treatment-Related Adverse Event Number of Patients (%)	Concurrent All Cohorts (n=53)		Sequenced All Cohorts (n=33)	
	All Gr	Gr 3-4	Al Gr	Gr 3-4
Any adverse event	49 (93)	28 (53)	24 (73)	6 (18)
Rash	29 (55)	2 (4)	3 (9)	0
Pruritus	25 (47)	0	6 (18)	0
Fatigue	20 (38)	0	3 (9)	0
Diarrhea	18 (34)	3 (6)	3 (9)	0
Nausea	11 (21)	0	1 (3)	0
Pyrexia	11 (21)	0	1 (3)	0
↑ AST	11 (21)	7 (13)	0	0
↑ ALT	11 (21)	6 (11)	1 (3)	0
↑ Lipase	10 (19)	7 (13)	4 (12)	2 (6)
↑ Amylase	8 (15)	3 (6)	1 (3)	1 (3)
Cough	7 (13)	0	2 (6)	0
Vomiting	6 (11)	1 (2)	0	0
Vitiligo	6 (11)	0	0	0
Headache	6 (11)	0	0	0

PD-1 Pathway Agents in Development

Agent	Structure	Stage of Development
Nivolumab	Fully human PD-1 IgG4 Ab	Ph III RCC Ph III NSCLC Ph III melanoma
BMS-936559	Fully human PD-L1 IgG4 Ab	Ph I
CT-011	Humanized PD-1 IgG1 Ab	Ph II melanoma Ph II RCC
MPDL-3280A (Genentech)	Fully human PD-L1 mutated IgG1 Ab (effectorless)	Ph I, (II)
Lambrolizumab (Merck)	Humanized PD-1 IgG4 Ab	Ph I, (II)
Medi-4736	Fully human PD-L1 IgG4 Ab	Ph 1
AMP-224	PD-L2 IgG1 fusion protein	Ph I

Conclusions

- Inhibiting various elements of the PD-1 / PD-L1/2 pathway has clinical activity across solid tumors
  - Durable responses (?off therapy) are possible
  - Issues of dose and schedule are not completely understood
- Ongoing clinical trials will further define the utility of these agents in each specific disease
- Combination checkpoint inhibition holds particular promise balanced against toxicity