SITC/Moffitt Cancer Center Advances in Cancer Immunotherapy Meeting December 7, 2013

Clinical Studies on PD-1/PD-L1 Antibodies

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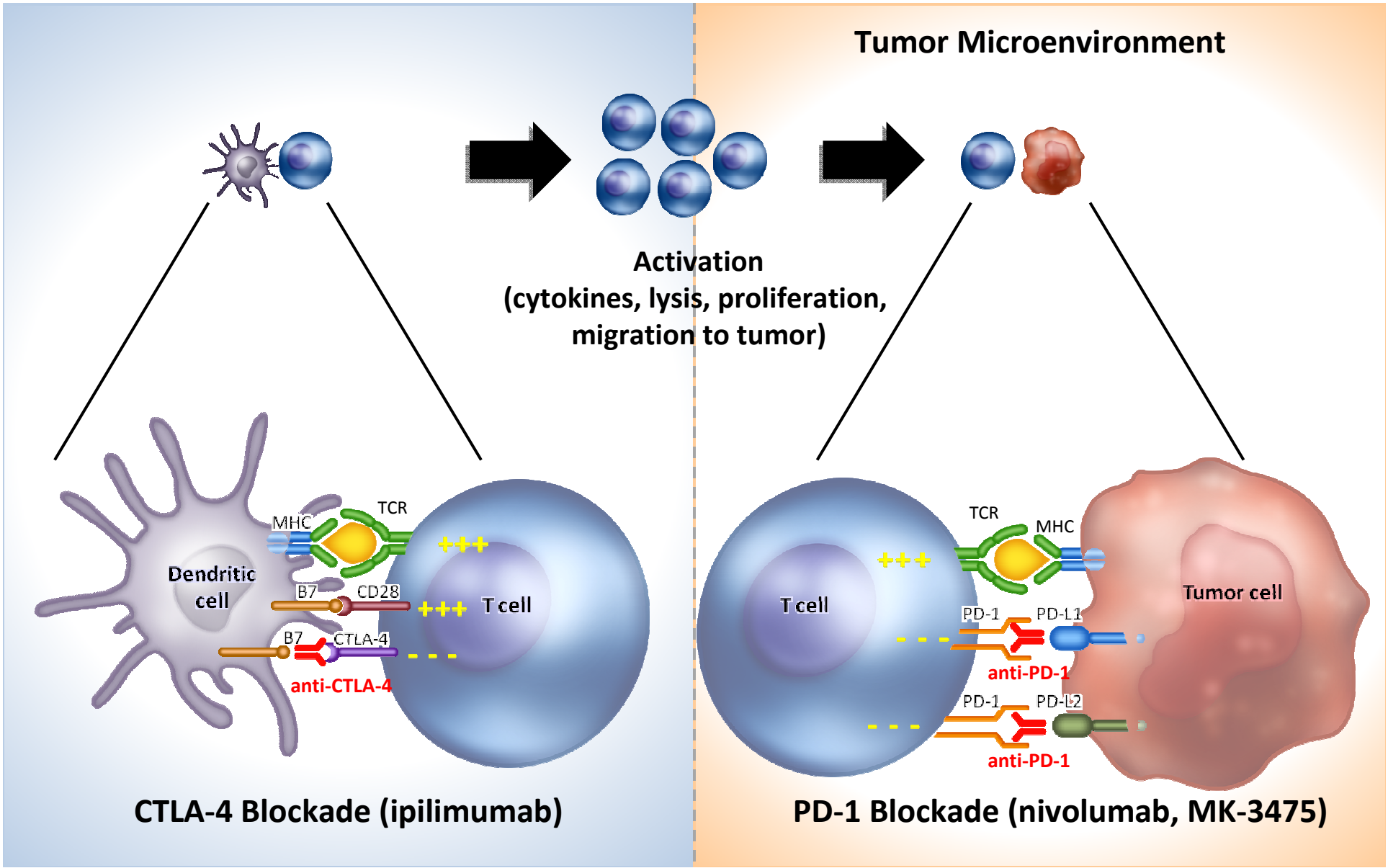
Disclosures

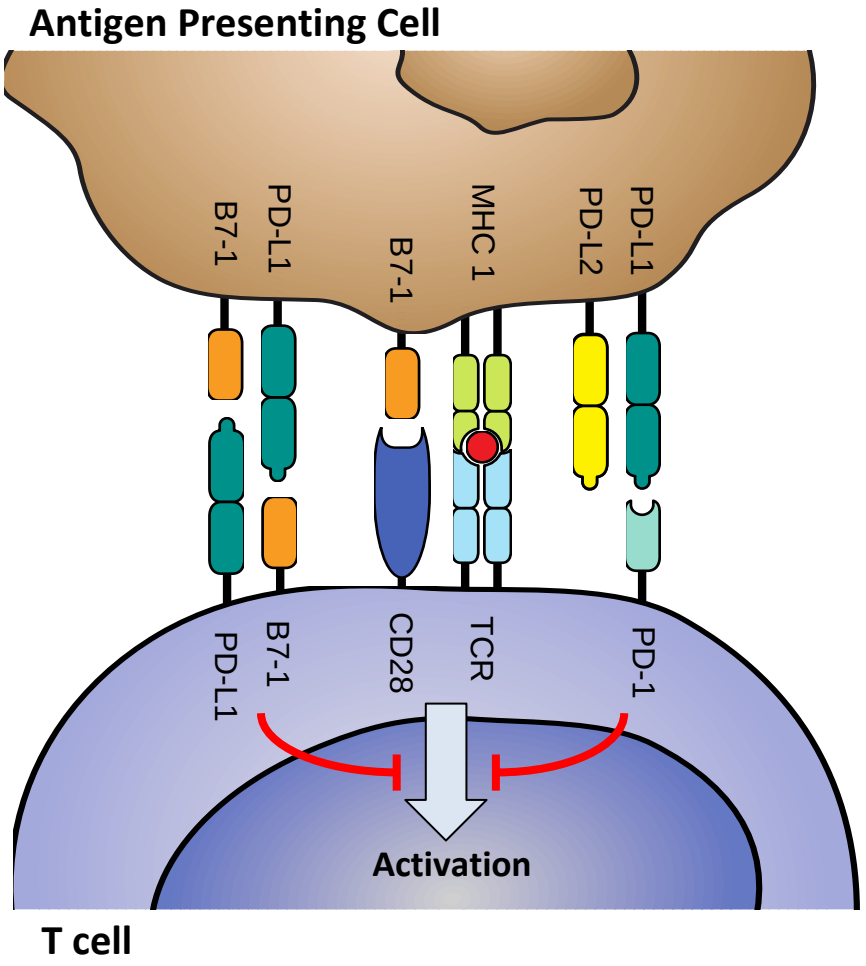
- I have accepted honoraria for advisory boards and DSMBs from BMS, Merck, GSK and Genentech of less than $10,000 dollars per year
- My institution, but not me personally, receives funds from BMS, Merck, GSK and Genentech for the performance of trials
- I am not a member of any speaker’s bureau
- I have no other relevant disclosures

Blocking CTLA-4 and PD-1



PD-1/PD-L1 Pathway: Biology

- PD-1 is an inhibitory receptor expressed on activated T cells
- Ligation of PD-1 by PD-L1 or PD-L2 inhibits T cell activation
  - Additional PD-L1/B7.1 interaction can inhibit T cells independently of PD-1
- **Tumors express PD-L1 to evade immune surveillance**
  - PD-L1 expression is observed in ***nearly all*** tumor types
    - Often associated with poor prognosis *
- Inhibiting the PD-L1/PD-1 interaction can restore anti-tumor T cell activity



* Thompson et al. 2006; Hamanishi et al. 2007; Okazaki and Honjo 2007; Hino et al. 2010

Keir, ME et al 2008. Annu. Rev. Immunol. 26:677

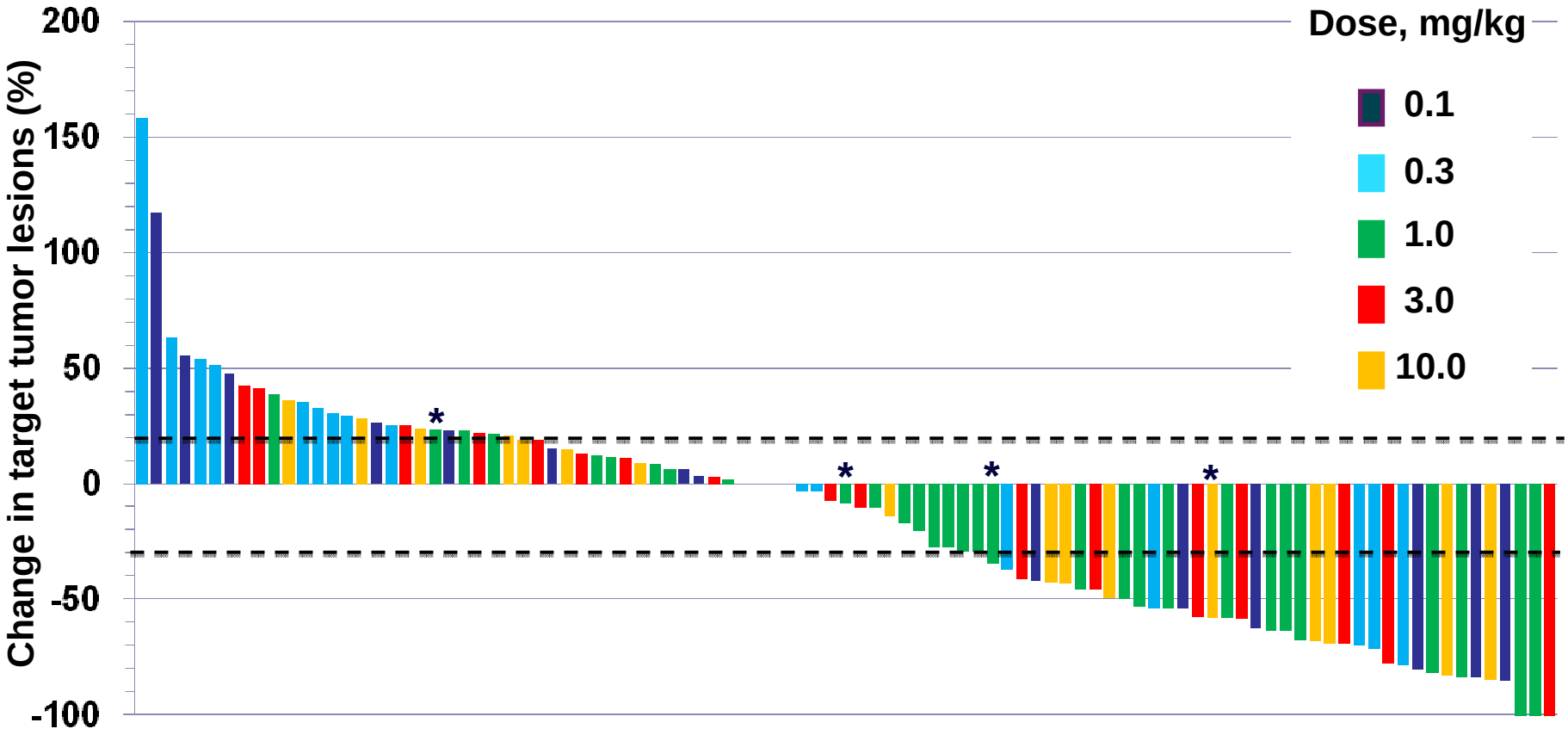
Agents in Development

- PD-1
  - **Nivolumab (BMS) IgG4**
  - **MK-3475 (Merck) IgG4**
  - CT-011 (Curetech) IgG1
  - PD-L2-FC fusion protein (Amplimmune)
- Anti-PD-L1
  - MDX-1105 (BMS) IgG4
  - **MPDL3280 (Genentech) modified IgG1**
  - **MEDI-4736 (Medimmune-AZ) IgG4**

Response Endpoints in Melanoma Patients Receiving Nivolumab Therapy

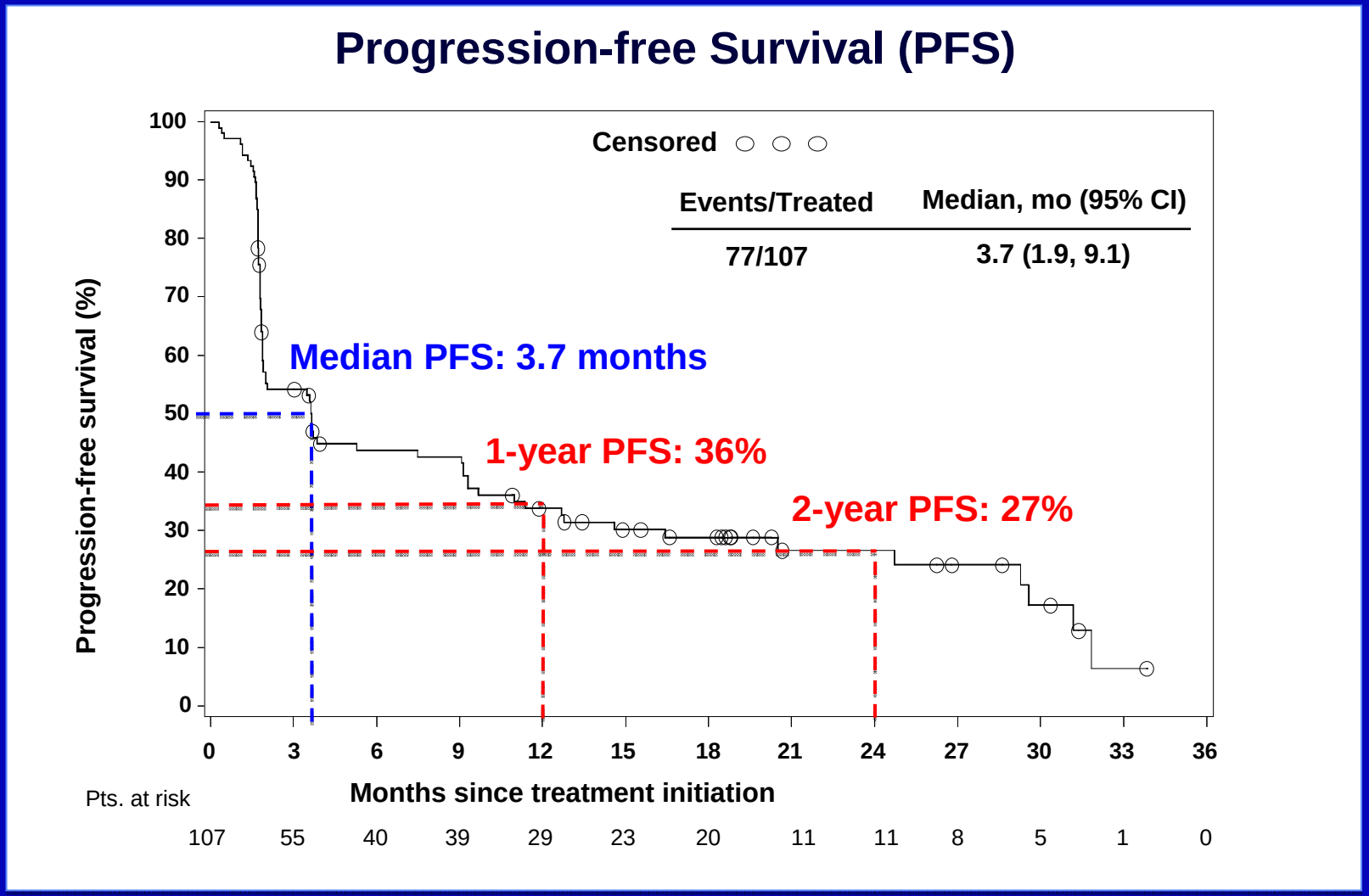
Dose, mg/kg	ORR %, (n/N)	Stable Disease Rate ≥24 wk, %, (n/N)	Duration of Response (Weeks)	
			Median (range)	Individual Responses
All doses	31 (33/107)	7 (7/107)	104 (18.4 to 117.0+)	–
0.1	35 (6/17)	0	NR (24.1 to 48.7+)	24.1, 24.1, 34.3, 44.1+, 48.1+, 48.7+,
0.3	28 (5/18)	6 (1/18)	NR (18.4 to 66.3+)	18.4, 44.4+, 64.6+, 65.1+, 66.3+
1	31 (11/35)	14 (5/35)	104 (32.4, 108.1+)	32.4, 32.4, 43.0+, 64.1+, 74.1+, 80.1+, 82.1+, 99.4, 100.9+, 104.1, 108.1+
3	41 (7/17)	6 (1/17)	75 (40.1+ to 115.4+)	40.1+, 40.4, 48.1, 56.1, 95.7, 106.7+, 115.4+
10	20 (4/20)	0	112 (73.9 to 117.0+)	73.9, 78.3+, 111.7, 117.0+

Best Change In Target Lesions to First RECIST Progression in Nivolumab Phase I study

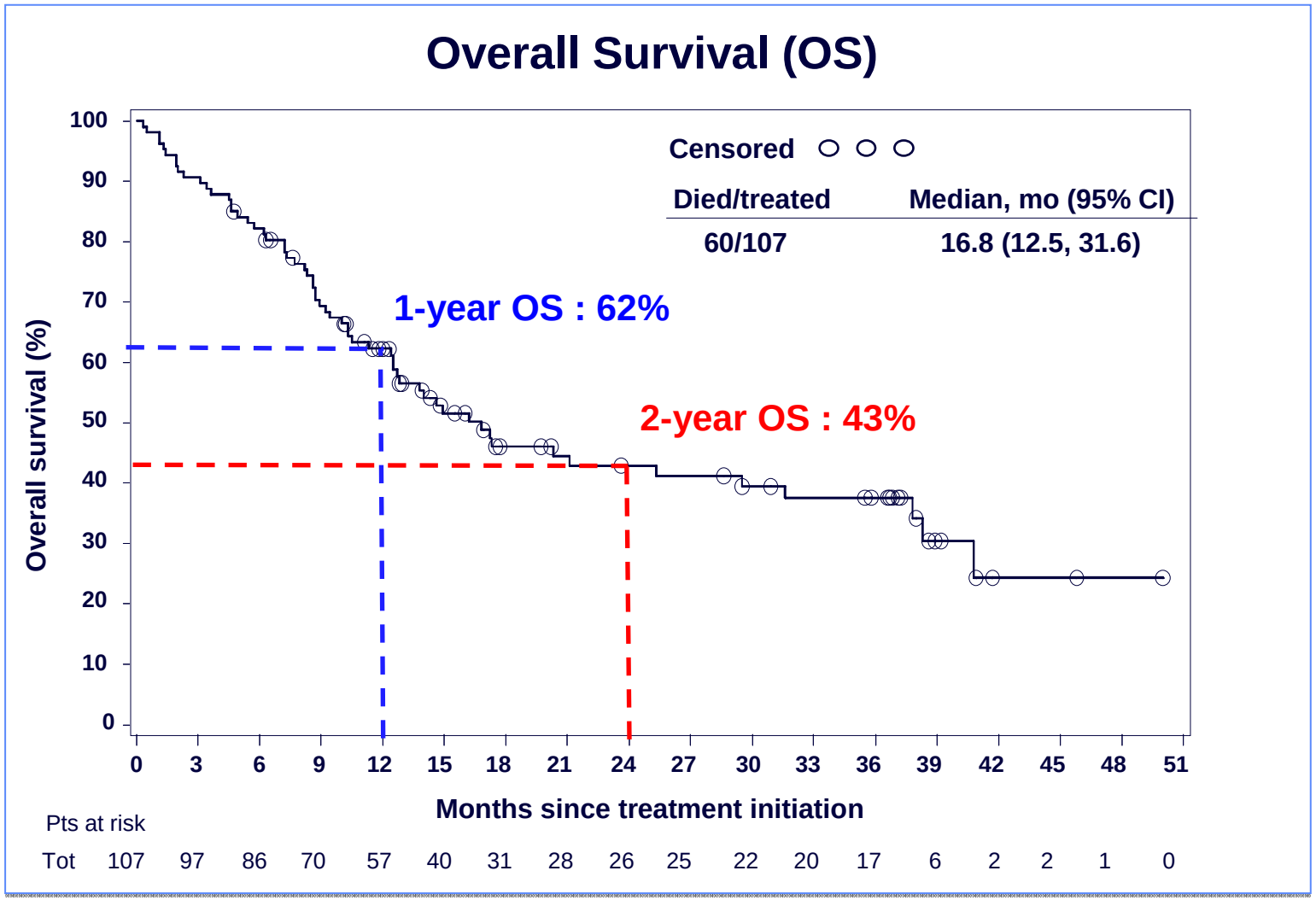


Horizontal line at −30% = threshold for defining objective response (partial tumor regression) in absence of new lesions or non-target disease according to RECIST. Horizontal line at +20% indicates the threshold for determination of progressive disease according to RECIST.

Progression-free Survival for Patients with Melanoma Treated with Nivolumab

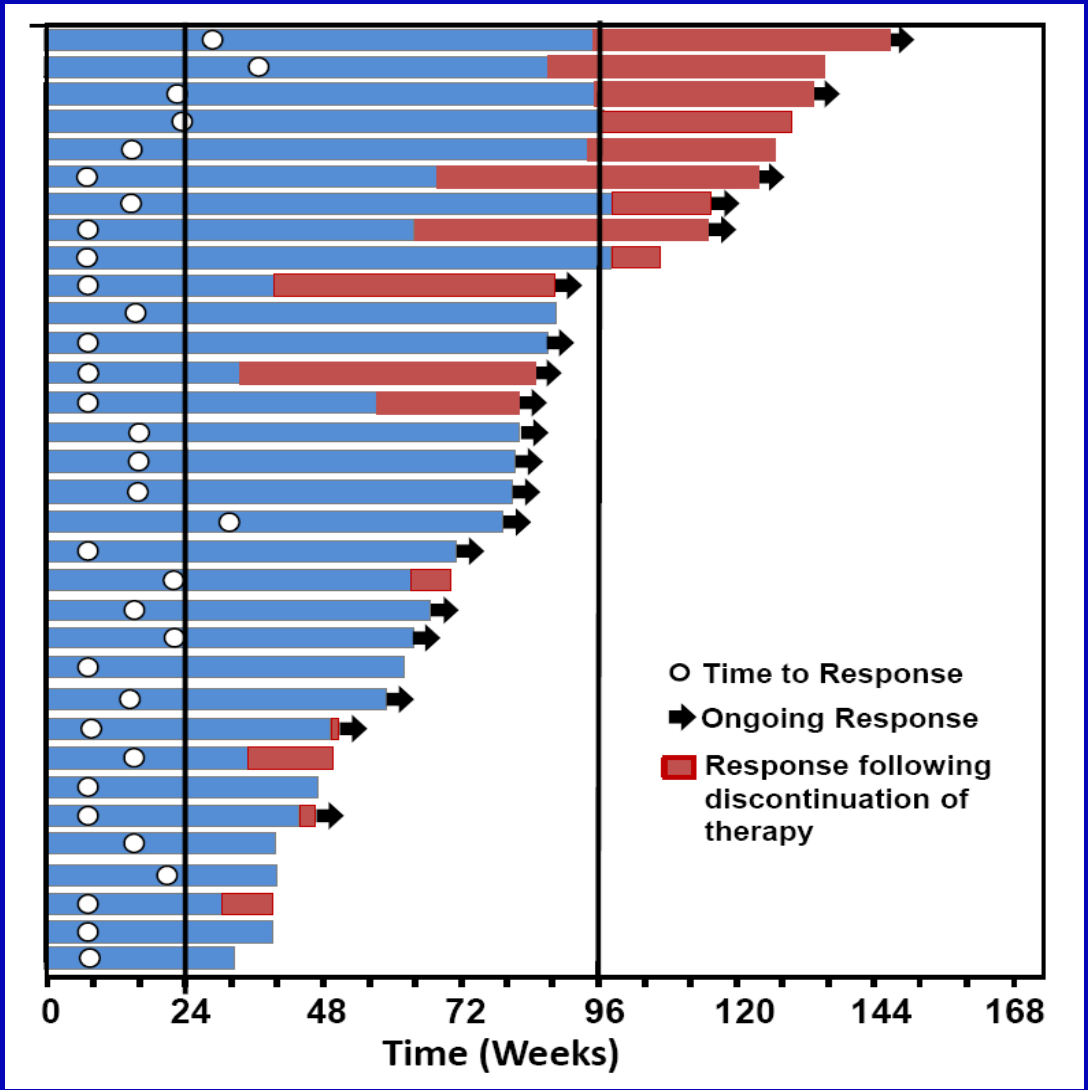


Overall Survival for Patients with Melanoma Treated with Nivolumab



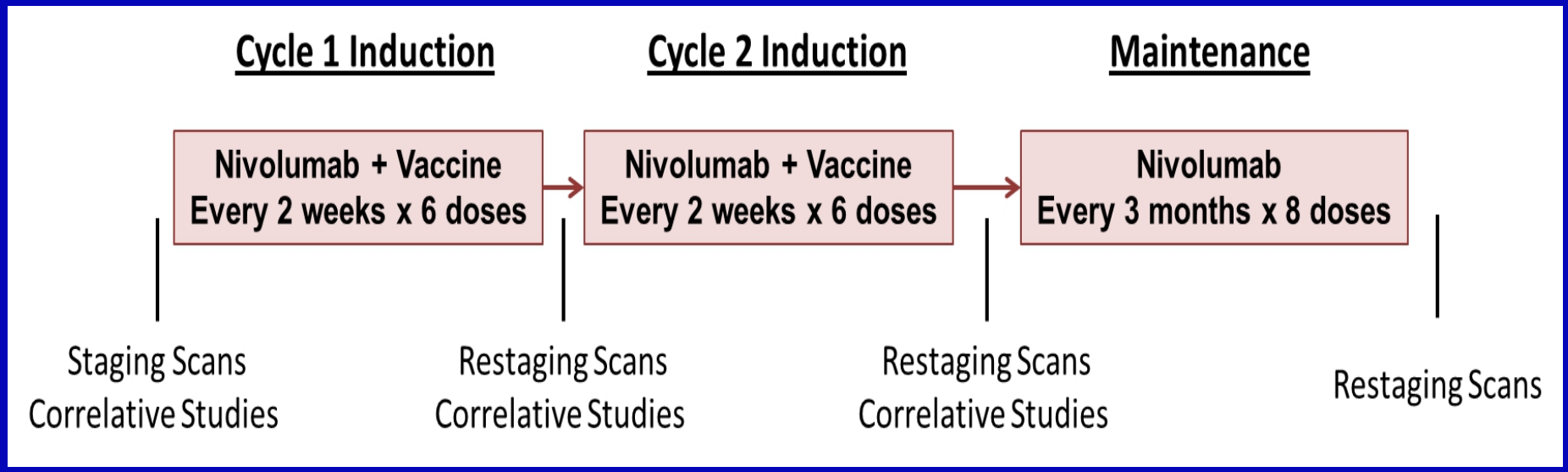
Median Survival = 16.8 months

Response Characteristics in Patients with Melanoma Receiving Nivolumab



- For 17 responding patients who discontinued therapy for reasons other than disease progression, 71% (12/17) responded for ≥16 weeks since end of therapy
- 67% (8/12) remained in response from 16-56 weeks at time of data analysis

Nivolumab with peptide vaccine phase I study: Schema



IPI NAÏVE (Cohorts 1-3)

Cohort 1

Dose of PD1: 1mg/kg

Peptide vaccine: yes

HLA A201 positive: yes

Cohort 2

Dose of PD1: 3 mg/kg

Peptide vaccine: yes

HLA A201 positive: yes

Cohort 3

Dose of PD1: 10mg/kg

Peptide vaccine: yes

HLA A201 positive: yes

IPI REFRACTORY (Cohorts 4-6)

Cohort 4

Dose of PD1: 3 mg/kg

Peptide vaccine: yes

HLA A201 positive: yes

IPI Toxicity: Grade 1 or 2 only

Cohort 5

Dose of PD1: 3 mg/kg

Peptide vaccine: yes

HLA A201 positive: yes

IPI Toxicity: Grade 3, no infliximab

Cohort 6

Dose of PD1: 3 mg/kg

Peptide vaccine: No

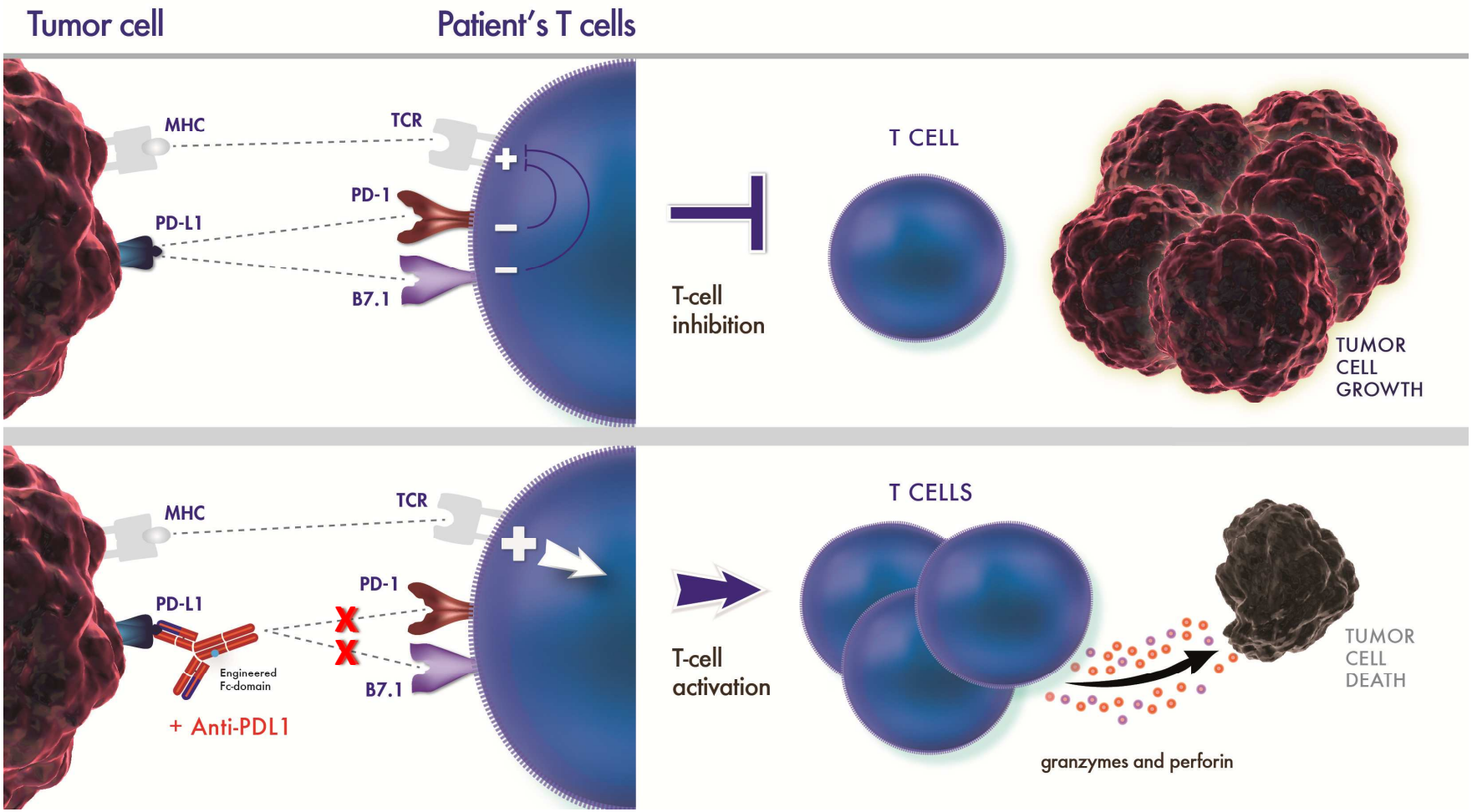
HLA A201 positive: No

IPI Toxicity: Grade 1 or 2 only

Clinical Efficacy

Dose of Nivolumab	Objective Response	Objective Response Rate, % (95% CI)	Response Duration, weeks	Stable Disease ≥ 24 weeks	Progression-Free Survival Rate at 24 weeks
Ipilimumab naïve patients					
1 mg/kg HLA A2+	3/10	30% (6.7 - 65.3%)	140+, 128+, 76+	2/10	50%
3 mg/kg HLA A2+	4/13	31% (9.1 - 61.4%)	84+, 36, 24, 24	1/13	39%
10 mg/kg HLA A2+	1/11	9% (0.2 - 41.3%)	84+	4/11	45%
Ipilimumab refractory patients					
3 mg/kg HLA A2+	3/10	30% (6.7 - 65.3%)	60+, 60+, 60+,	2/10	50%
3 mg/kg HLA A2+ with grade 3 irAE	1/5	20% (0.5 - 71.6%)	36+	2/5	60%
3 mg/kg HLA unrestricted	10/38	26% (13.4 - 43.1%)	48+, 36+, 36+, 36+, 36+, 24+, 24+,24+, 24+, 12+	7/38	44%
All Cohorts	22/87	25% (16.6 - 35.8%)	12+ to 140+	18/87	46%

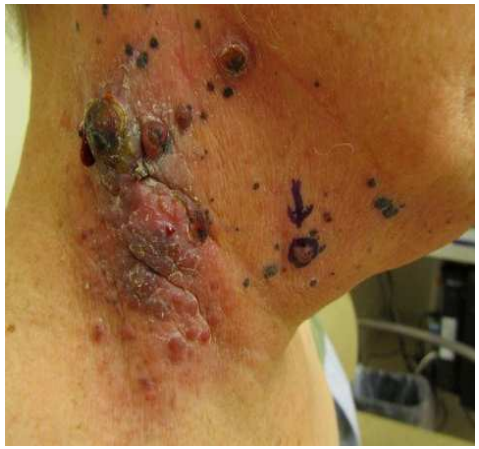
MPDL3280A (Anti-PDL1) Inhibits the Binding of PD-L1 to PD-1 and B7.1: Hamid et al



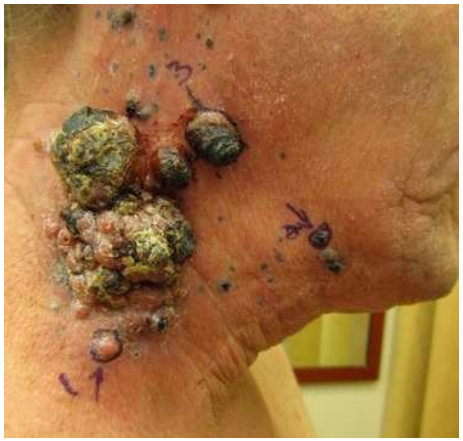
- Blocking PD-L1 restores T-cell activity, resulting in tumor regression in preclinical models
- Binding to PD-L1 leaves PD-1/PD-L2 interaction intact

Salvage of BRAF-Positive Metastatic Melanoma Patient with MPDL-3280A After Progression on Vemurafenib

Baseline

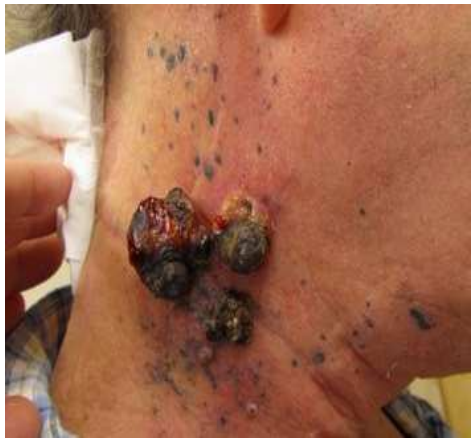


Week 6

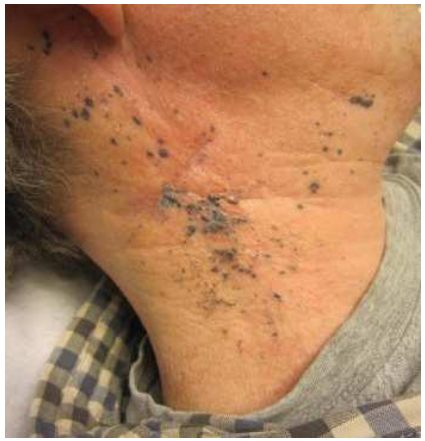


31% increase in target lesions **(RECIST PD)**

Week 12

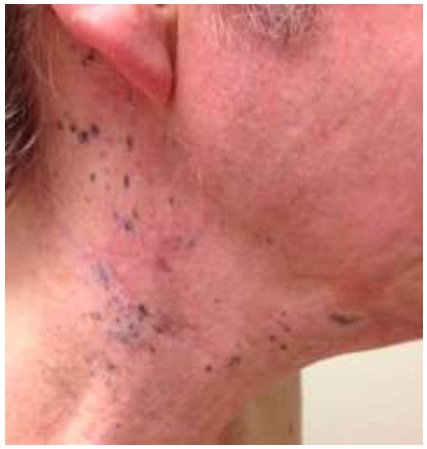


Week 18



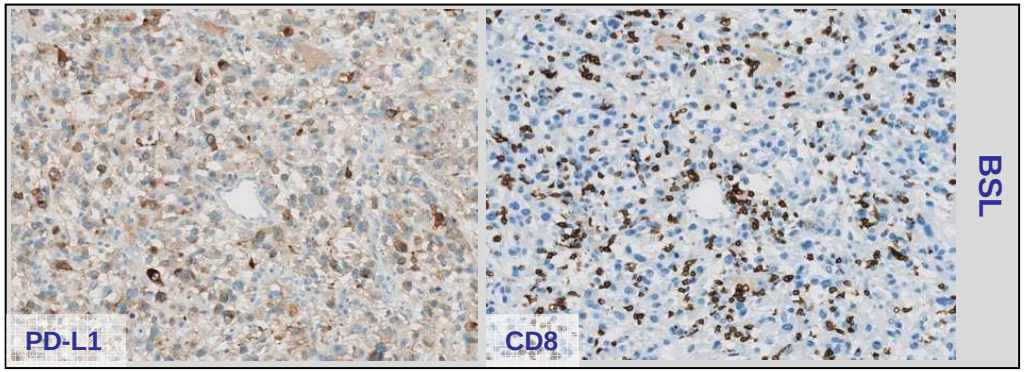
Post Resection

Week 46

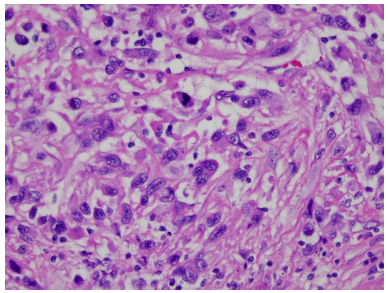


Dana Farber Cancer Institute (Ibrahim/Hodi)

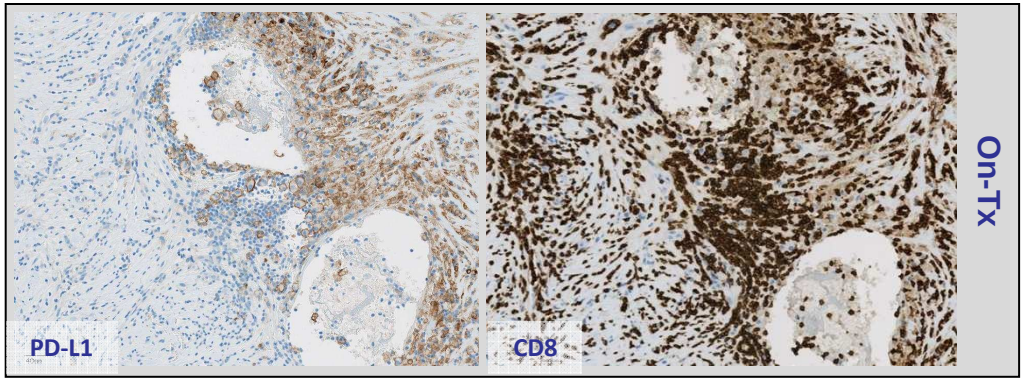
Serial biopsy in a PD-L1+ RCC patient with a rapid response to MPDL3280A:



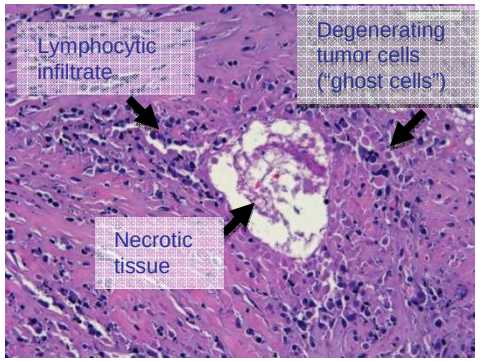
Biomarkers at baseline:
PD-L1+
Frequent CD8+ T-cells



Baseline H&E: RCC

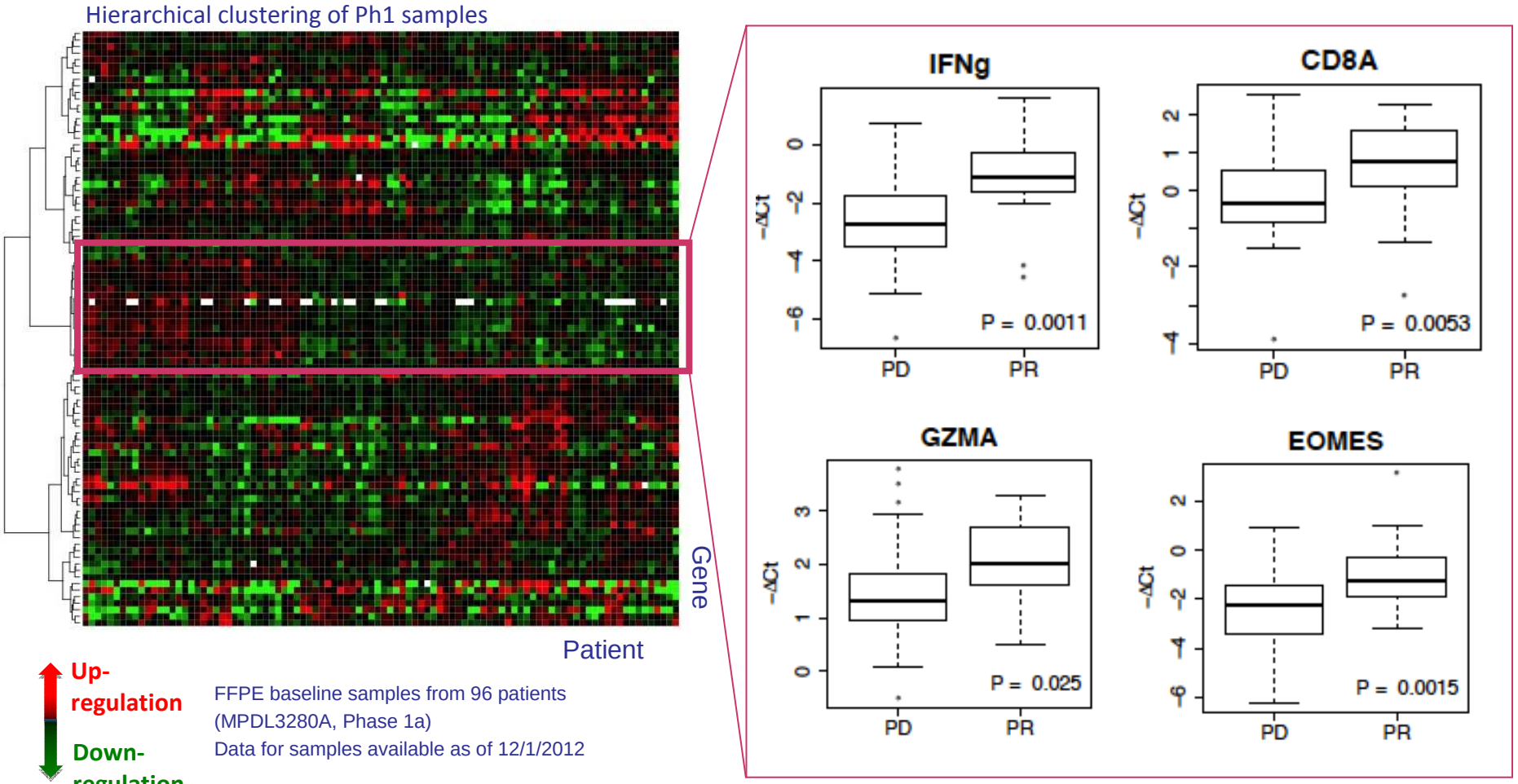


Biomarkers at week 4:
PD-L1+
Dense CD8+ T-cell infiltrate



On-treatment H&E: dense lymphocytic infiltrate and *no viable* tumor cells seen

Anti-tumor response to MPDL3280A is associated with Th1 T cell gene signature



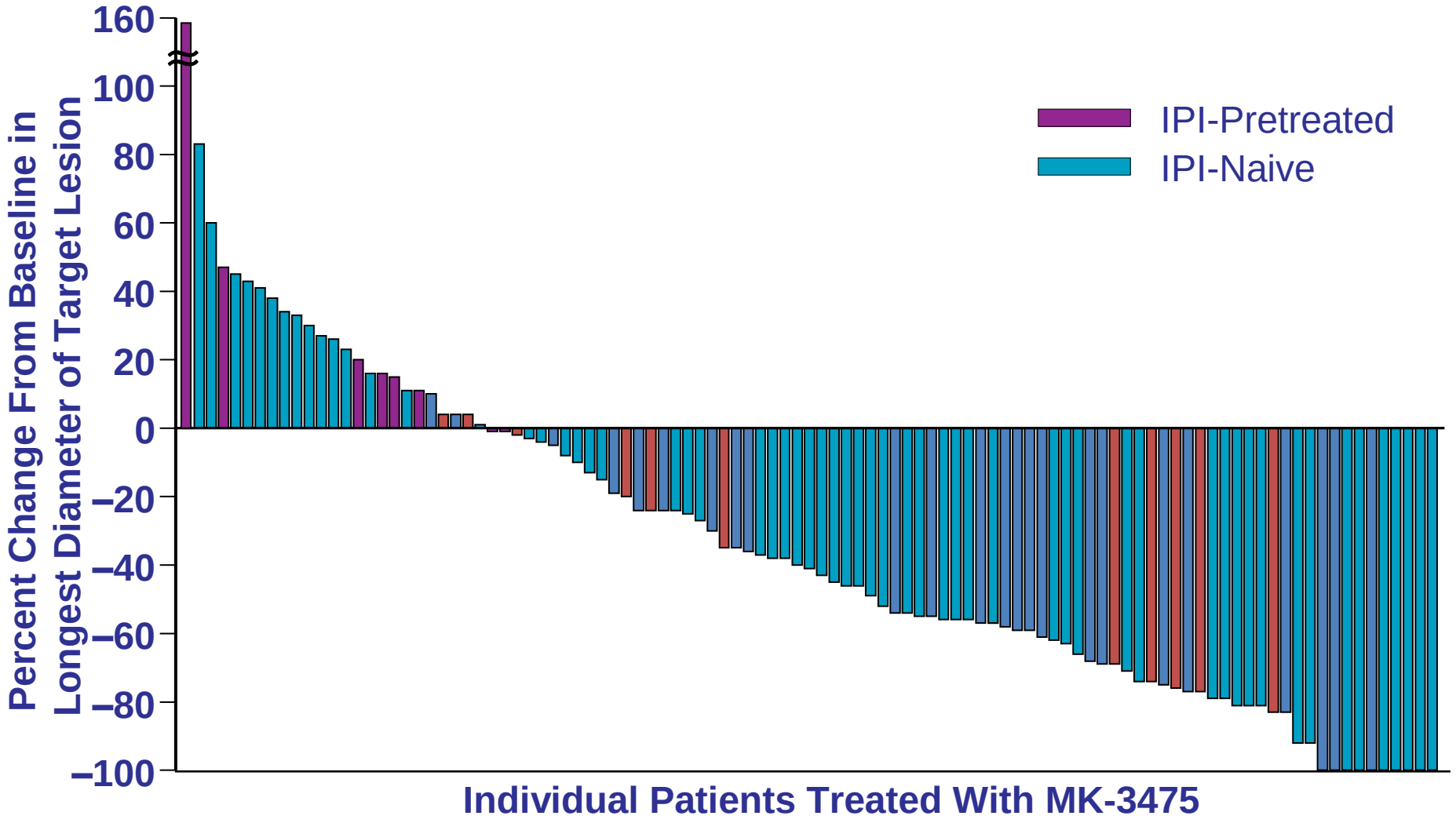
Higher expression of cytotoxic Th1 T-cell markers in tumor tissue is associated with MPDL3280A activity

Conclusions: MPDL-3280A activity

- Preliminary tumor PD-L1 IHC status is associated with anti-tumor response to MPDL3280A
- Patients with higher baseline signatures of cytotoxic Th1 T-cell markers appear to respond favorably to MPDL3280A in initial analysis
- MPDL3280A therapy appears to restore anti-tumor immunity
  - Evidence of adaptive PD-L1 tumor expression and active immune infiltration in responders
- These data provide mechanistic insights into anti-PDL1 biology and immunotherapy
- The relationship between PD-L1 status and OS is being prospectively studied

Efficacy of PD-1 ab MK-3475 Waterfall plot: Ribas et al

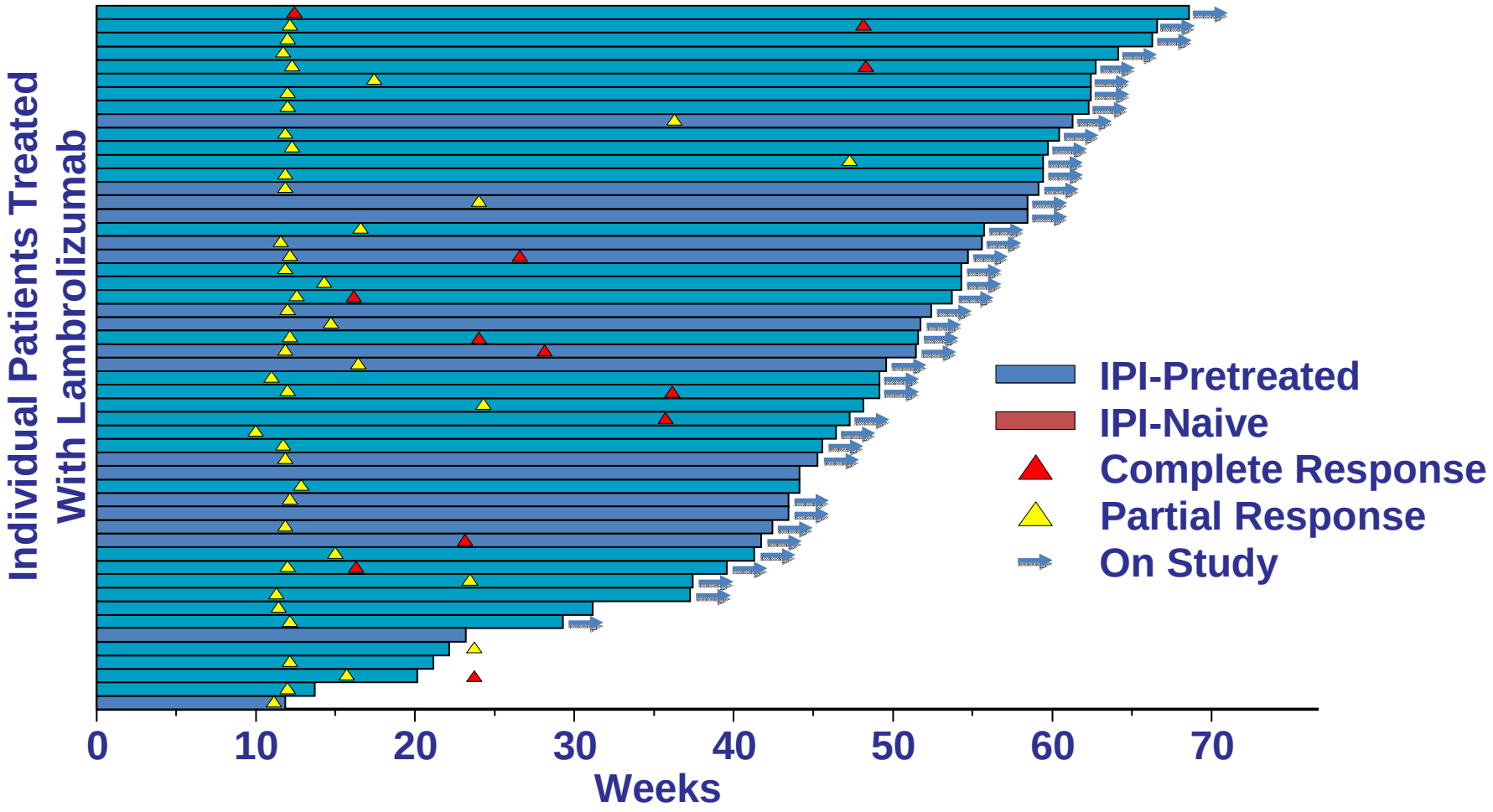
(Independent Central Review per RECIST 1.1)



Presented by: Antoni Ribas

Time to Response and On-Study Duration for MK-3475

(Independent Central Review per RECIST 1.1)



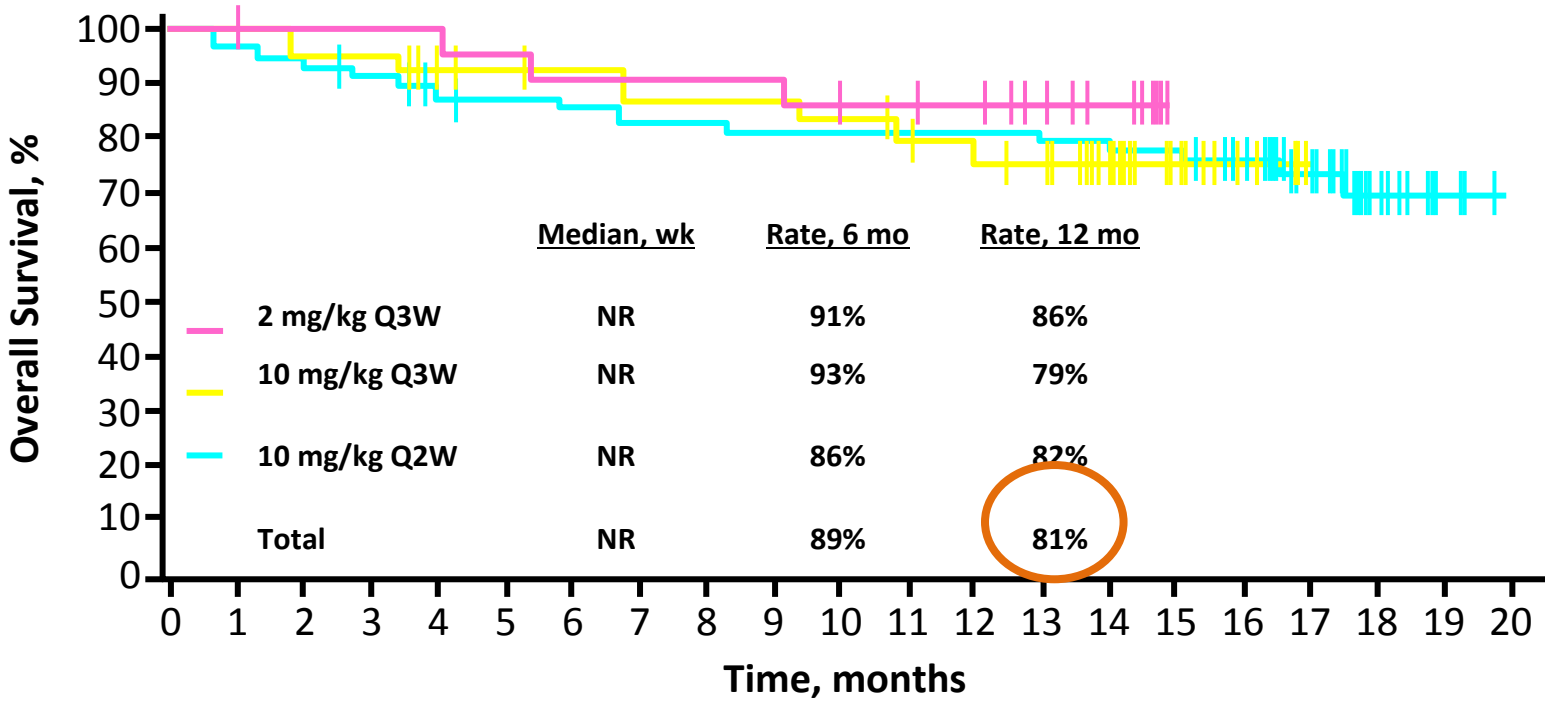
The median duration of response had not been reached at the time of analysis, with median follow-up time of 11 months.

Updated Antitumor Activity

MK-3475 Dose	Prior IPI Treatment	RECIST 1.1, Independent Review					
		N	CR, % (95% CI)	ORR, % (95% CI)	DCR, % (95% CI)	Response Duration[a] Range, weeks	Response Ongoing,[b] %
Total		116	9 (4–15)	41 (32–51)	61 (52–70)	8+ – 65+	88
10 mg/kg Q2W	Naive	37	14 (5–29)	49 (32–66)	68 (50–82)	8+ – 65+	78
	Treated	14	14 (2–43)	57 (29–82)	64 (35–87)	12+ – 62+	88
	Total	51	14 (6–26)	51 (37–65)	67 (52–79)	8+ – 65+	81
10 mg/kg Q3W	Naive	19	5 (0.1–26)	37 (16–62)	47 (24–71)	11 – 51+	86
	Treated	26	0 (0–13)	27 (12–48)	69 (48–86)	24+ – 60+	100
	Total	45	2 (0.1–12)	31 (18–47)	58 (42–72)	11 – 60+	93
2 mg/kg Q3W	Naive	20	10 (1–32)	40 (19–64)	55 (32–77)	12+ – 48+	100

DCR, disease control rate (ie, confirmed response + stable disease as best response).
"+" indicates censored observation. (Patients were censored for response duration at the time of their last non-PD disease assessment.)
Analysis cut-off date: July 26, 2013.
[a]Median duration of response was not reached for any dosing cohort (median follow-up [treatment] duration for responders, 14.5 months).
[b]Defined for this analysis as no assessment of PD by independent central review.

Kaplan-Meier Estimates of Overall Survival



n at risk

2 mg/kg Q3W	22	21	21	21	21	20	19	19	19	19	17	17	16	11	8	0	0	0	0	0	0
10 mg/kg Q3W	56	56	53	53	49	48	47	44	44	44	42	39	38	32	24	16	7	0	0	0	0
10 mg/kg Q2W	57	55	53	51	47	46	45	44	44	43	43	43	43	42	41	40	36	25	13	3	0

- **Median OS not reached for any dosing cohort**
- **Results were similar in IPI-naive and IPI-treated patients**

Analysis cut-off date: July 26, 2013.

Summary of Treatment-Related AEs

	10 mg/kg Q2W n = 57	10 mg/kg Q3W n = 56	2 mg/kg Q3W n = 22	Total N = 135
Time on therapy, days, median (range)	**296 (1- 596)**	**148 (1 - 505)**	**127 (1 - 442)**	**163 (1-596)**
Any grade treatment-related AE	**93%**	**75%**	**68%**	**82%**
Grade 3-4 treatment-related AE	**25%**	**4%**	**9%**	**13%**
Serious treatment-related AE	**18%**	**4%**	**5%**	**10%**
Treatment-related AE leading to discontinuation	**14%**	**5%**	**5%**	**9%**

- Treatment-related AEs with incidence ≥10%: fatigue (37%), pruritus (26%), rash (22%), diarrhea (21%), arthralgia (17%), vitiligo (14%), headache (13%), nausea (12%), asthenia (11%), myalgia (11%), AST increase (10%)
- Grade 3-4 treatment-related AEs that occurred in >1 patient were AST increase, fatigue, rash,[a] and renal failure (n = 2 each)
- Most treatment-related AEs were successfully managed with treatment discontinuation, supportive care, and, occasionally, glucocorticoids

Analysis cut-off date: July 26, 2013.
[a]Includes 1 case each of "rash" and "rash erythematous."

MK-3475 Summary

- 9% CR and 41% ORR per RECIST v1.1 across all doses
  - 14% CR and 51% ORR in the 10 mg/kg Q2W cohort
  - 10% CR and 40% ORR in the 2 mg/kg Q3W cohort
- Tumor size reduction begins early and may continue beyond 6 months of treatment
  - Some responses occurred as late as 48 weeks
  - ORR for all dose cohorts improved over time
- High percentage of durable responses will translate into a marked survival benefit
  - Median PFS for the overall population was 36 weeks
  - 81% OS rate at 12 months; median OS not reached for any dose cohort
- MK-3475–related adverse events can be successfully managed with early identification and management
- Clinical development of MK-3475 is ongoing in melanoma, non-small cell lung cancer, breast cancer, head and neck cancer, gastric cancer, bladder cancer, myeloma, myelodysplastic syndrome, and lymphoma

Summary: Efficacy of Anti-PD-L1

	N	ORR	CR	PFS-24 weeks
Hamid (MPDL3280A)	38	28%	?	43%
*Brahmer (BMS-936559)	52	17%	6%	42%

**N Engl J Med* 2012; 366:2455-65

Presented by: Walter J. Urba, MD, PhD

Summary: Efficacy of Anti-PD-1

	N	ORR	CR	OS	
				1 yr	2 yr
MK-3475 (Ribas #9009)	135	37%	7%	na	na
Nivolumab (Weber #9011)	87	25%	2%	na	na
Nivolumab (Sznol #9006)	107	31%	?	62%	43%

Presented by: Walter J. Urba, MD, PhD

Summary: Anti-PD-1 after ipilimumab

	N	ORR
$^{+}ipi^{T}$	30	20%
$^{*}ipi^{T}$	63	26%
$^{@}ipi^{T}$	39	44%

* Weber et al. ASCO #9011
+ Wolchok et al. ASCO #9012
@Ribas et al. ASCO #9009

Presented by: Walter J. Urba, MD, PhD

Summary: PD-1 Pathway Blockade Toxicity

- Qualitatively similar immune-related adverse events to ipilimumab
- Significantly less grade 3/4 toxicity than IPI
- Less diarrhea, colitis
- Pneumonitis can be more severe
- Fewer patients required steroids/hospitalization
- Fewer patients discontinued therapy

Pneumonitis associated with PD-1 pathway blockade

Clinical trial	Tumor histology	Any grade % (n/N)	Grade 3-4 % (n/N)
Nivo monotherapy	Multiple	4 (12/306)	1 (4/306)*
Nivo + ipilimumab**	MEL	5 (4/86)	1 (1/86)
Nivo ± peptide vaccine***	MEL	3 (3/90)	2 (2/90)
Anti-PD-L1 (BMS-963559) monotherapy	Multiple	1 (3/284)	0

Data analysis in Feb/March 2013. *3 pts with grade 3-4 pneumonitis expired (1 CRC, 2 NSCLC). **J Wolchok, ***J Weber, ASCO 2013.

- Pneumonitis rates were similar across 4 clinical trials
- Treatment algorithms for early detection and management were implemented (dose delay/discontinuation, immunosuppression)

Summary: PDL-1 Expression and Response Rate Evaluating PD-L1 status as a candidate biomarker

	N	PDL1 + Positive	PDL1 - Negative
Nivolumab (Topalian, NEJM, 2012)	**42**	**9/25 (36%)**	**0/17 (0%)**
Nivolumab (Weber #9011)	**44**	**8/12 (67%)**	**6/32 (19%)**
MPDL3280A (Hamid #9010)	**30**	**4/15 (27%)**	**3/15 (20%)**
Nivolumab/ Ipilimumab (Callahan #3003)	**27**	**4/10 (40%)**	**8/17 (47%)**
Nivolumab (Grosso #3016)	**34**	**7/16 (44%)**	**3/18 (17%)**

Presented by: Walter J. Urba, MD, PhD

Summary: Ipilimumab and Nivolumab Clinical Experience in Patients with Advanced Melanoma

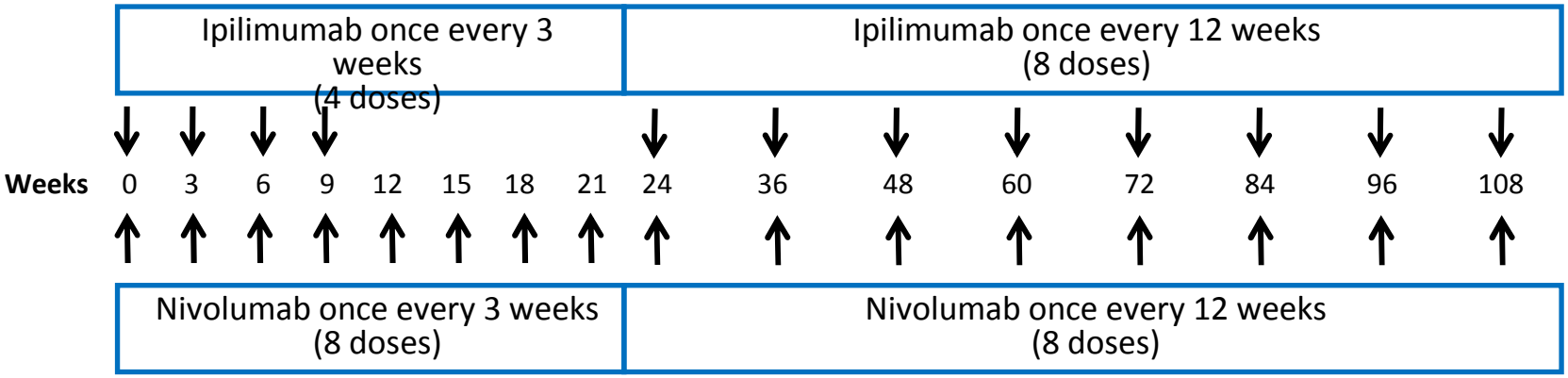
- **Ipilimumab:** 3 mg/kg every 3 wk, 4 doses (Phase 3)
  - ORR: 11%; 2 patients with CR[1]
  - Median OS: 10.1 mo;[1] 4-year survival rate (Phase 2 studies): 18%[2]
  - Grade 3-4 related AEs: 23%; included diarrhea (5%) and colitis (5%)[1]

- **Nivolumab**: 0.1 mg/kg to 10 mg/kg every 2 wk, ≤48 doses (Phase 1b)
  - ORR: 41%; 1 patient with CR (3 mg/kg)[3]
  - Median OS: 16.8 mo;[4] 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 May10 [Epub ahead of print]. [3]Topalian et al. N Engl J Med 2012;2443-54. [4]Sznol et al. ASCO 2013, oral presentation, abs CRA9006.

Phase I Study Concurrent PD-/IPI: 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**

Clinical Activity: Concurrent PD-1/IPI Regimen

Dose (mg/kg)		Response Evaluable Patients n	CR n	PR n	Objective Response Rate % [95% CI]	Aggregate Clinical Activity Rate % [95% CI]	≥80% Tumor Reduction at 12 wk n (%)
Nivolumab	Ipilimumab						
0.3	3	14	1	2	21 [5-51]	50 [23-77]	4 (29)
1	3	17	3	6	53 [28-77]	65 [38-86]	7 (41)
3	1	15	1	5	40 [16-68]	73 [45-92]	5 (33)
3	3	6	0	3	50 [12-88]	83 [36-100]	0
Concurrent		52	5	16	40 [27-55]	65 [51-78]	16 (31)

- With concurrent treatment of nivolumab + ipilimumab, 40% (range 21-53%) of patients had confirmed objective responses
- About one third of patients (31%) had rapid and deep tumor regressions

Presented by: Jedd D. Wolchok, MD, PhD

Clinical Activity: Concurrent PD-1/IPI Regimen

Dose (mg/kg)		Response Evaluable Patients n	CR n	PR n	Objective Response Rate % [95% CI]	Aggregate Clinical Activity Rate % [95% CI]	≥80% Tumor Reduction at 12 wk n (%)
Nivolumab	Ipilimumab						
0.3	3	14	1	2	21 [5-51]	50 [23-77]	4 (29)
1	3	17	3	6	53 [28-77]	65 [38-86]	7 (41)
3	1	15	1	5	40 [16-68]	73 [45-92]	5 (33)
3	3	6	0	3	50 [12-88]	83 [36-100]	0
Concurrent		52	5	16	40 [27-55]	65 [51-78]	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, 7 at 12 weeks and 2 at their first assessment, which was after week 12
- ≥80% tumor reductions appear infrequently (<10%) in the nivolumab and ipilimumab monotherapy experiences

Safety Summary: Concurrent PD-1/IPI

Concurrent Treatment

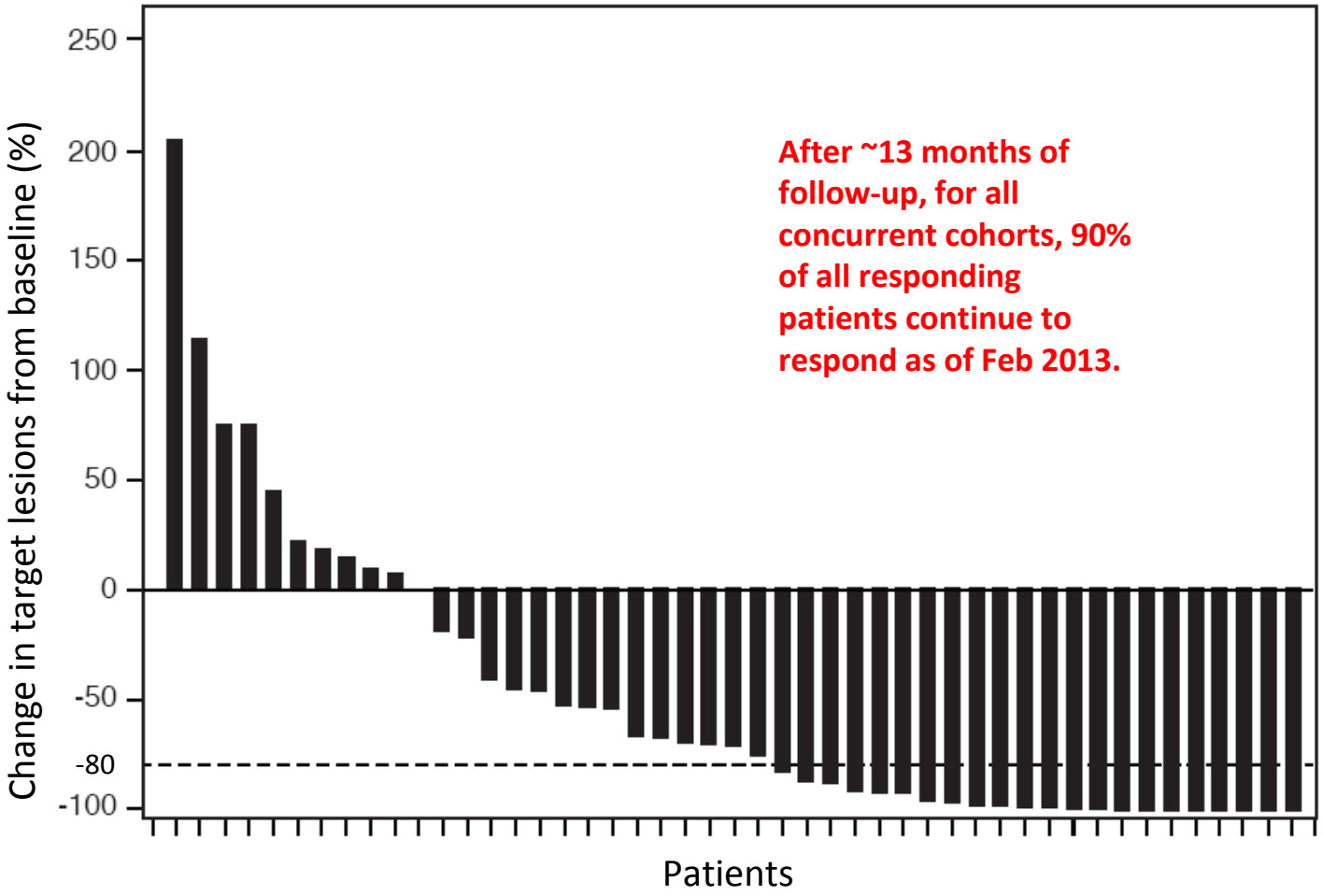
- Grade 3-4 related adverse events occurred in 28 of 53 patients (53%), representing mostly tissue-specific inflammation
  - The most common were asymptomatic lab abnormalities: elevations of lipase (13% of patients), AST (13%), and ALT (11%)
- The 3 mg/kg nivolumab + 3 mg/kg ipilimumab cohort exceeded the MTD
  - 3 of 6 patients had DLTs of asymptomatic grade 3-4 elevated lipase that persisted ≥3 weeks
    - Therefore, 1 mg/kg nivolumab + 3 mg/kg ipilimumab was chosen to move forward
    - Eleven patients (21%) discontinued treatment due to related adverse events

Sequenced Treatment

- Grade 3-4 related adverse events occurred in 6 of 33 patients (18%)
  - The most common was asymptomatic elevation of lipase (2 patients, 6%)
- Three patients (9%) discontinued treatment due to related adverse events

- **Related adverse events were managed using standard protocol algorithms**
- **No treatment-related deaths were reported**

Best Responses in All Evaluable Patients in Concurrent PD-1/IPI Cohorts



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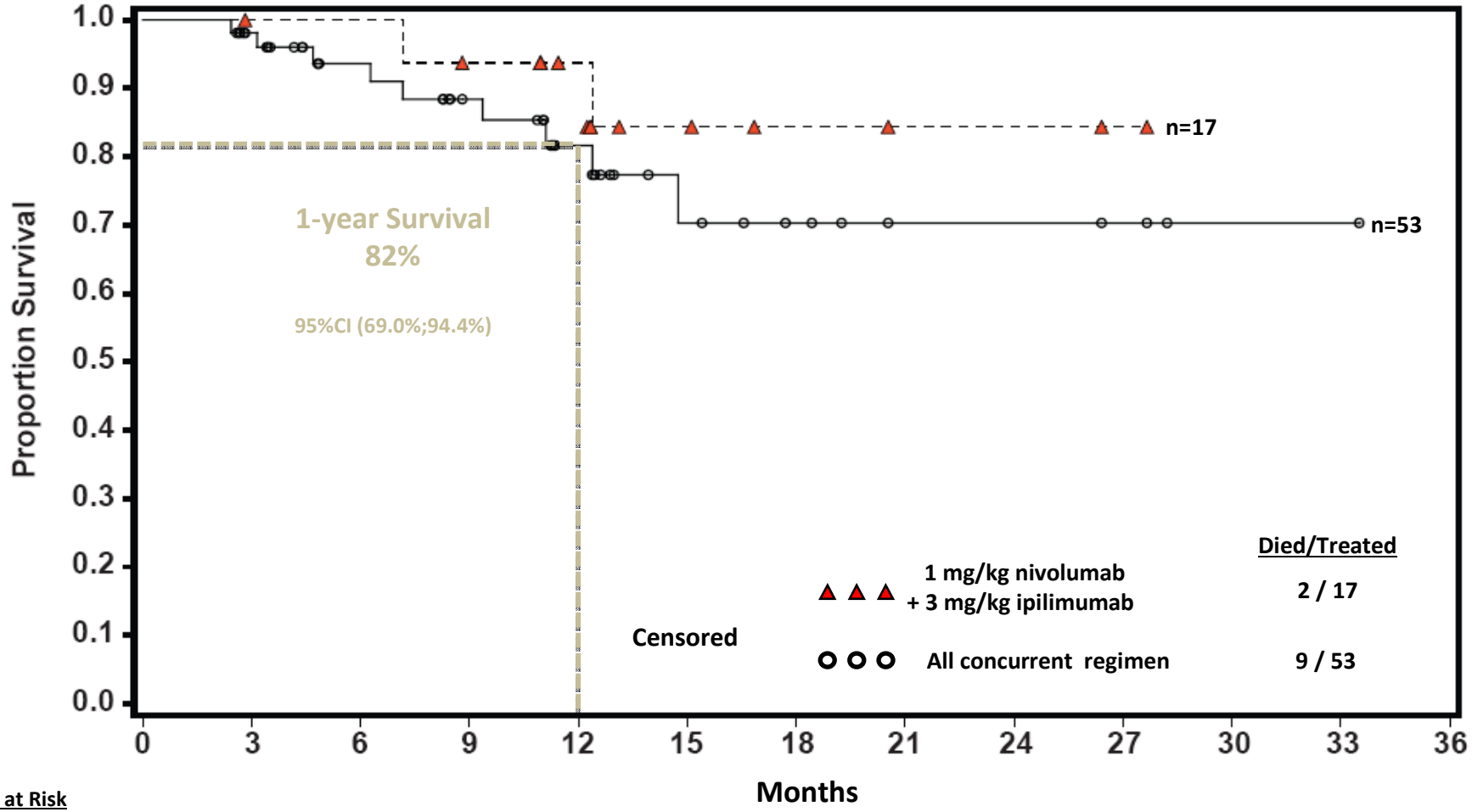
Preliminary Survival of Patients Treated with the Concurrent PD-1/IPI Regimen



Patients at Risk

1 mg + 3 mg	17	16	16	14	10	5	3	2	2	1	0	0	0
All concurrent	53	47	36	29	19	10	7	4	4	3	1	1	0

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Power and pitfalls of PD-1/PD-L1 blockade

Advantages

- Superior therapeutic index to ipi? → Phase III trials
- Biomarker PD-L1 predictive? It is straightforward and can also serve as target[1]
- Ready for combinations?
  - Ipilimumab
  - Vaccines, adoptive cell Rx
  - Molecularly-targeted drugs
  - Several antibodies, immunoconjugates to test

Challenges

- Target expression is induced by T cell → γ-IFN
- Biomarker likely complex and not limited to PD-L1, hard to assay
- Which PD-1 axis blocker is optimal, depend on context?
- Follow-up is relatively short
- Combinations require complex collaborations (science, legal, financial)

1. Chen et al Clin Cancer Res 2012