Society for Immunotherapy of Cancer (SITC)

Immunotherapy for the Treatment of GU Malignancies

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University of Texas MD Anderson Cancer Center

Advances in Cancer Immunotherapy™ - Texas
June 19, 2015

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Presenter Disclosure Information

Sumit Subudhi, MD, PhD

The following relationships exist related to this presentation:

Valeant, Role (Speaker)

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Objectives

- **To understand the current roles of immuno-therapies in the standard-of-care.**
- **To understand how to integrate promising immunotherapies into the standard-of-care.**
- **To understand the challenges of immune-based therapeutic combinations.**

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Immunotherapy Strategies

- **Bacterial stimulants**
- **Cytokines**
- **Vaccines**
- **Immune checkpoint therapy**

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Where are We Now?

- **Bladder**
  - **Bacterial stimulant (BCG)**
- **Kidney/Renal**
  - **Cytokines (IL-2, IFN-α)**
- **Prostate**
  - **Vaccine (Sipuleucel-T)**

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Bacterial products as cancer immunotherapy?

William Coley

- **Coley's toxin**
  - **Consisted of Streptococcus pyogenes**
  - **Cured 1st patient in 1891**
  - **TNF-alpha**

NR 5Y 5-10 10-20 >20 yr

SUMMARY OF PATIENTS TREATED WITH COLEY'S TOXINS BEFORE 1940

Type of cancer	Total	A	B	C	D	E
Soft-tissue sarcomas	104	38	12	17	15	22
Lymphosarcomas (lymphomas)	50	24	7	4	7	8
Osteosarcoma	3	2	1	0	0	0
Ovarian carcinoma	4	1	2	0	0	1
Cervical carcinoma	2	0	1	0	0	1
Testicular	18	10	2	3	2	1
Renal	6	3	0	1	1	1
Multiple myeloma	1	0	0	1	0	0
Colorectal carcinoma	2	1	1	0	0	0
Breast carcinoma	14	8	4	2	0	0
Melanoma	6	2	3	0	1	0

Starnes. Nature 1992; 357: 6373

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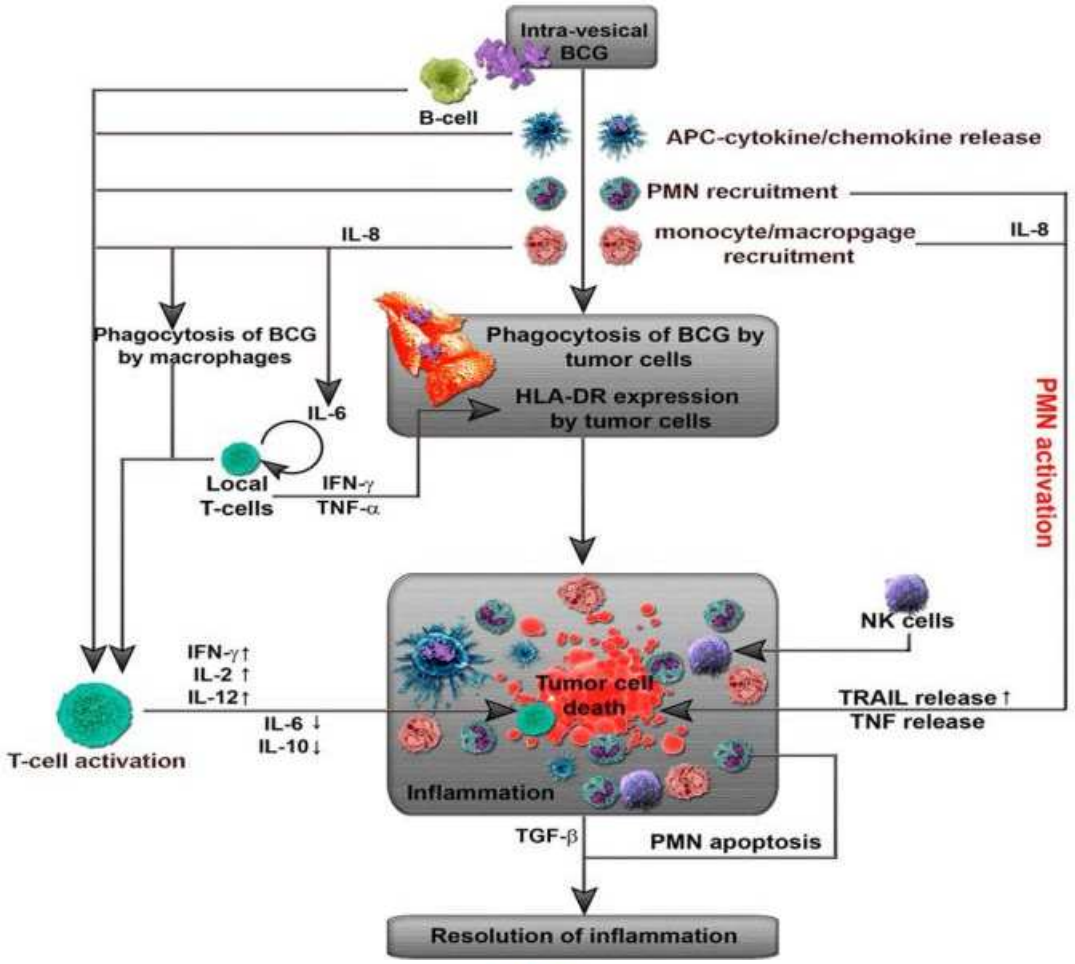
Bacillus Calmette-Guerin (BCG)

Since 1970s…minimal progress…



Jinesh G & Kamat A, Oncoimmunology, 2012

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Cytokines

- **IL-2**
  - **Stimulate CD8+ T cells (CTLs) and natural killer cell responses**
- **IFN-α and IFN-β (Interferons)**
  - **Increases MHC class I expression**
  - **Direct anti-proliferative effects on tumor cells**

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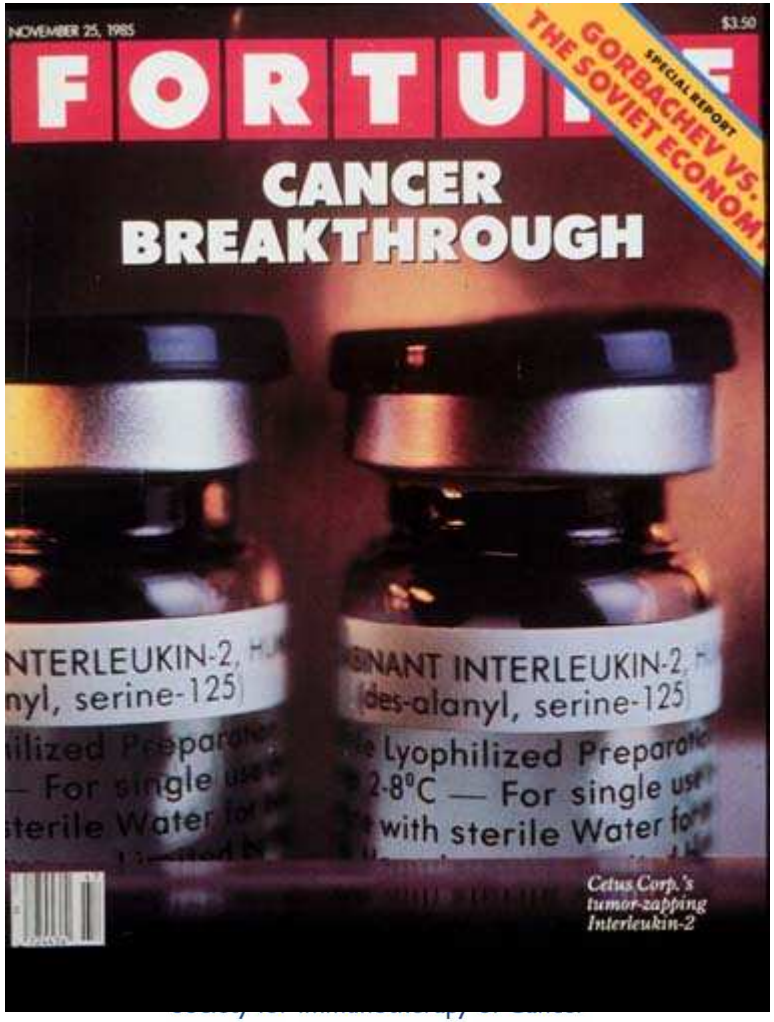
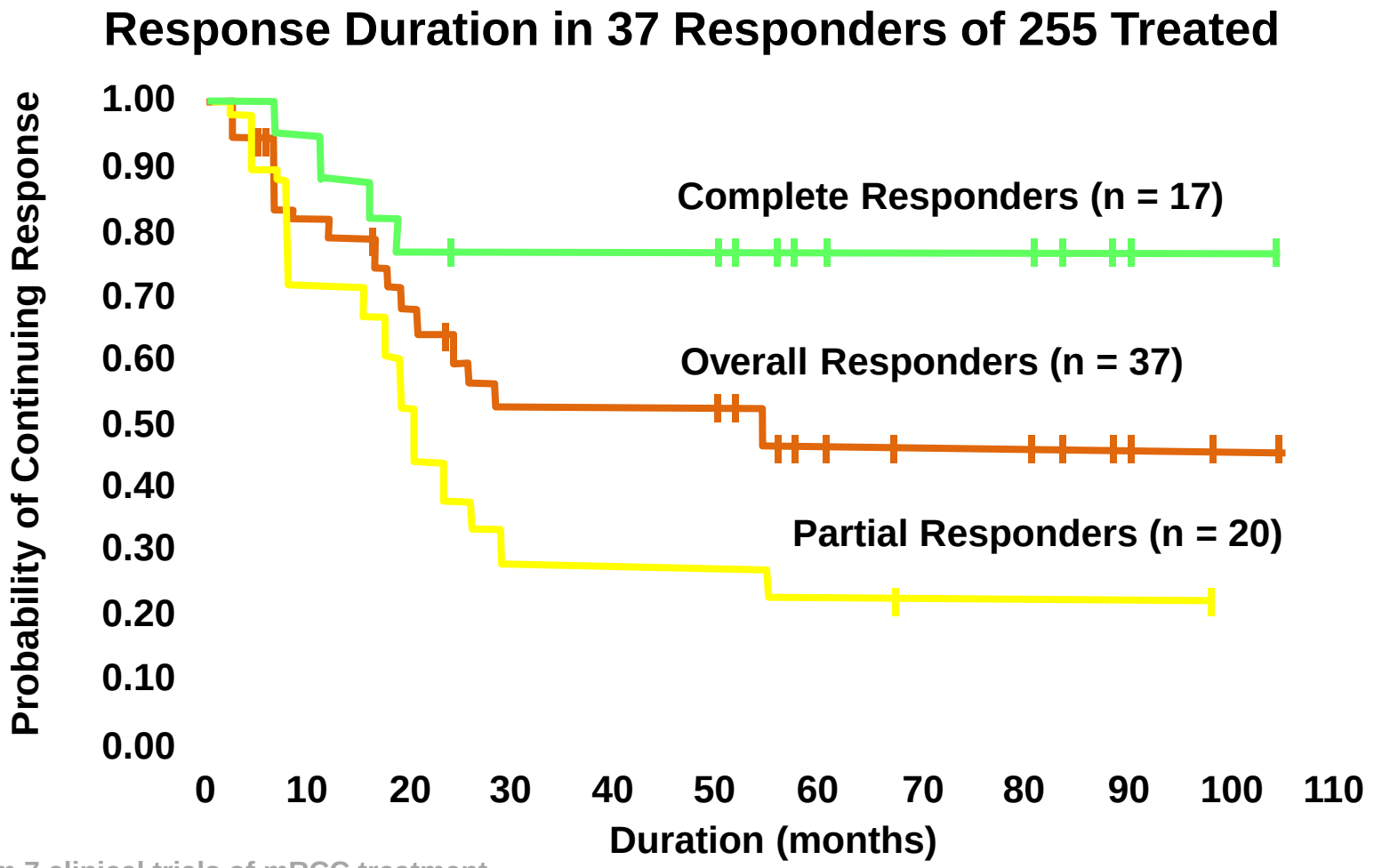
1985: Cancer Breakthrough (IL-2)

November 25, 1985

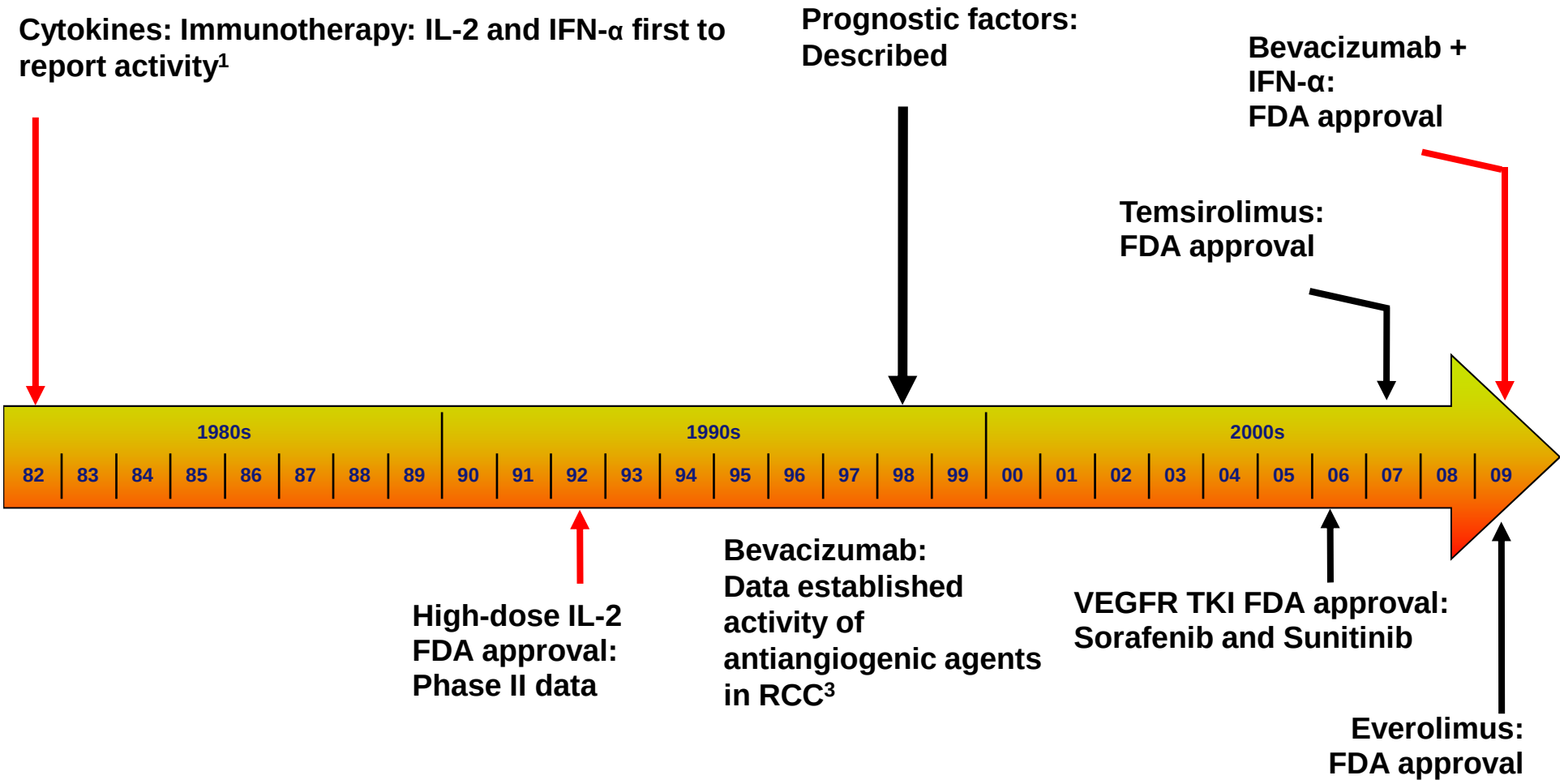


High-Dose IL-2



Data from 7 clinical trials of mRCC treatment.

Treatment of RCC



IFN-α = interferon-α; IL-2 = interleukin-2; TKI = tyrosine kinase inhibitor; VEGFR = VEGF receptor

1. Snow M, et al. *Urology.* 1982;20:177; 2. Latif F, et al. *Science.* 1993;260:1317–1320; 3. Yang J, et al. *N Engl J Med*. 2003;349:427–434.

Courtesy of Robert Motzer, MD

Systemic treatment for clear cell RCC

Setting		Phase III	Alternative
1st-Line Therapy	Good or intermediate risk*	Sunitinib Bevacizumab + IFN-α Pazopanib	HD IL-2
	Poor risk*	Temsirolimus	Sunitinib
2nd-Line Therapy	Prior cytokine	Axitinib Sorafenib	Sunitinib or bevacizumab
	Prior VEGFR inhibitor	Everolimus Axitinib	Clinical Trials
	Prior mTOR inhibitor	Clinical Trials	

***MSKCC risk status**

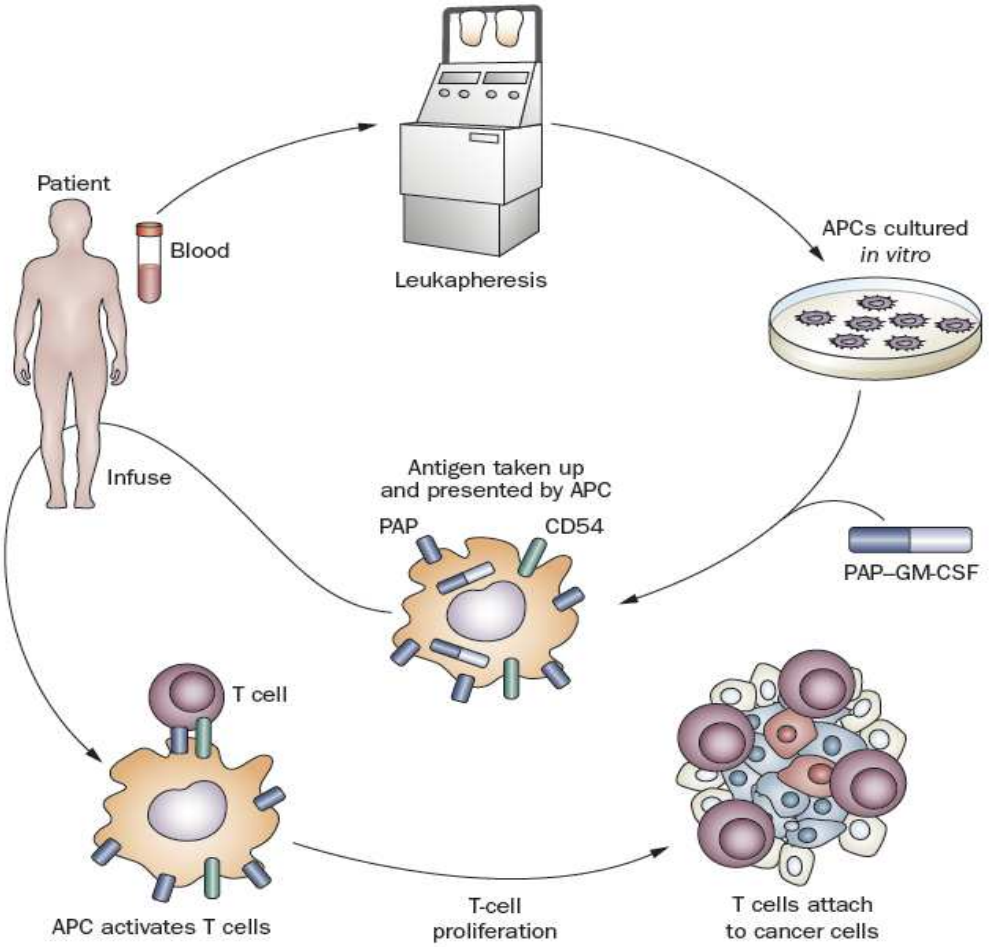
Atkins. ASCO 2006 Plenary session; Figlin. *Clin Adv Hematol Oncol*. 2007;5:35; Escudier. *Drugs*. 2007;67:1257; Cho. *Clin Cancer Res*. 2007;13:761s; Atkins. *Clin Cancer Res*. 2005;11:3714.

Cytokine Therapies in Phase III Trials

	Regimen	No. of Pts	% Response	Survival Benefit
Motzer et al[1]	IFN IFN + Retinoid	145 139	6% 12%	No
Gordon et al[2]	IFN IFN + Thalidomide	169 175	8% 3%	No
Negrier et al[3]	IL-2 IFN IL-2 + IFN	138 147 140	7% 8% 19%	No
Yang et al[4]	High dose IL-2 Low dose IL-2 SQ IL-2	96 92 93	21% 11% 10%	No

Autologous Dendritic Cell-Based Vaccine

Sipuleucel-T (Provenge)



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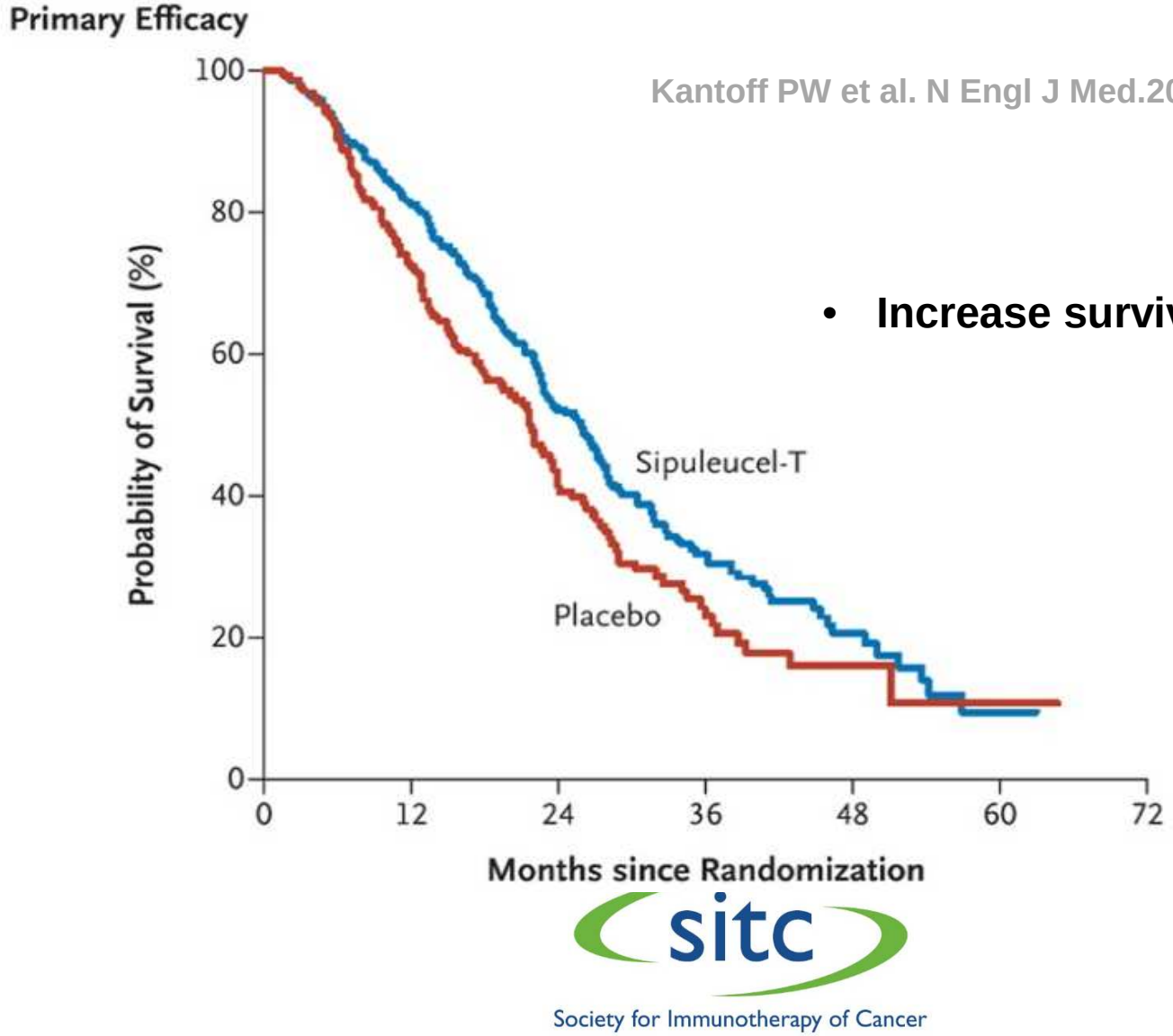
Sipuleucel-T Improves Survival



Kantoff PW et al. N Engl J Med.2010 Jul 29;363(5):411-22.

- **Increase survival by 4.1 months**

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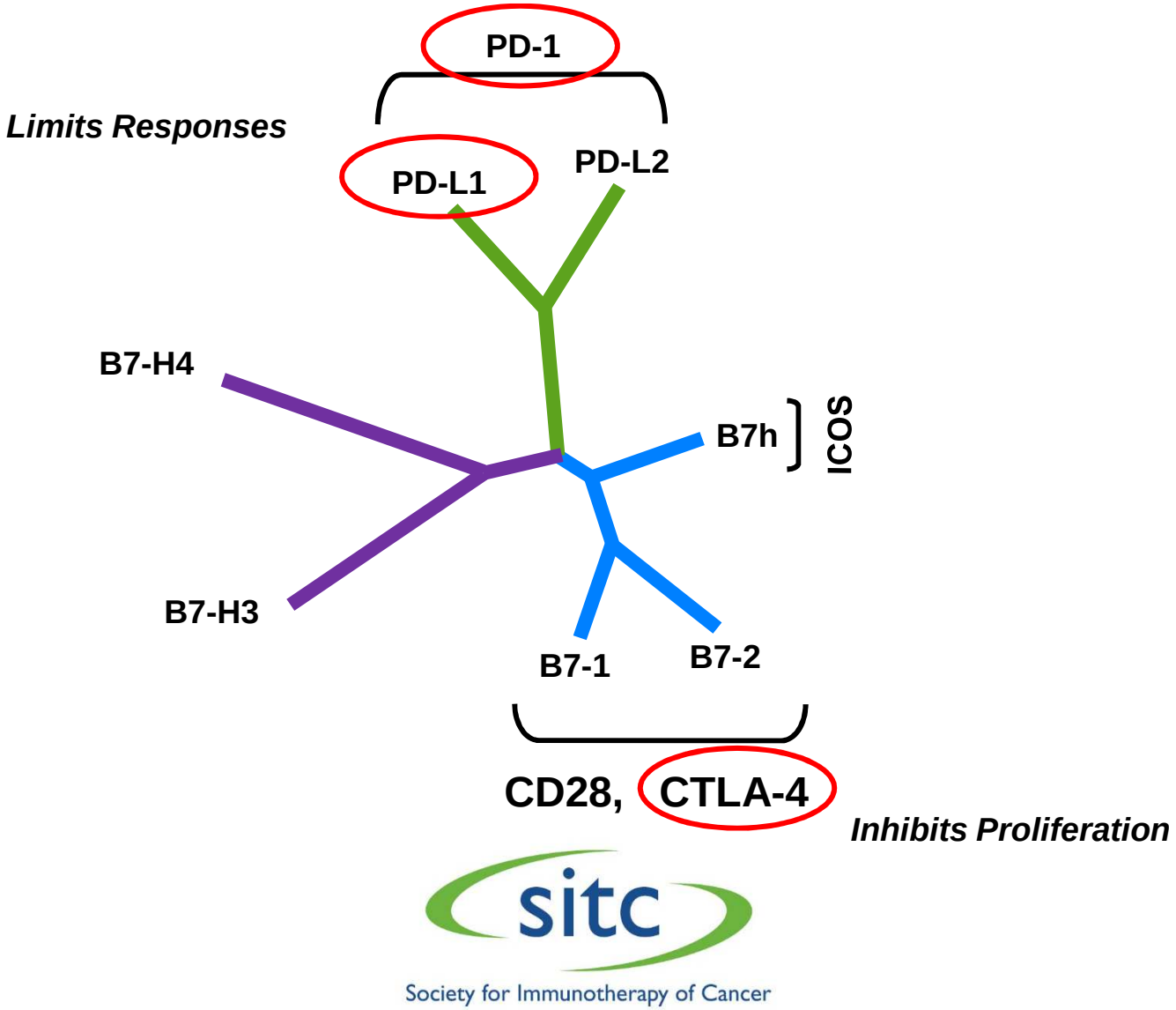
Immune Checkpoints



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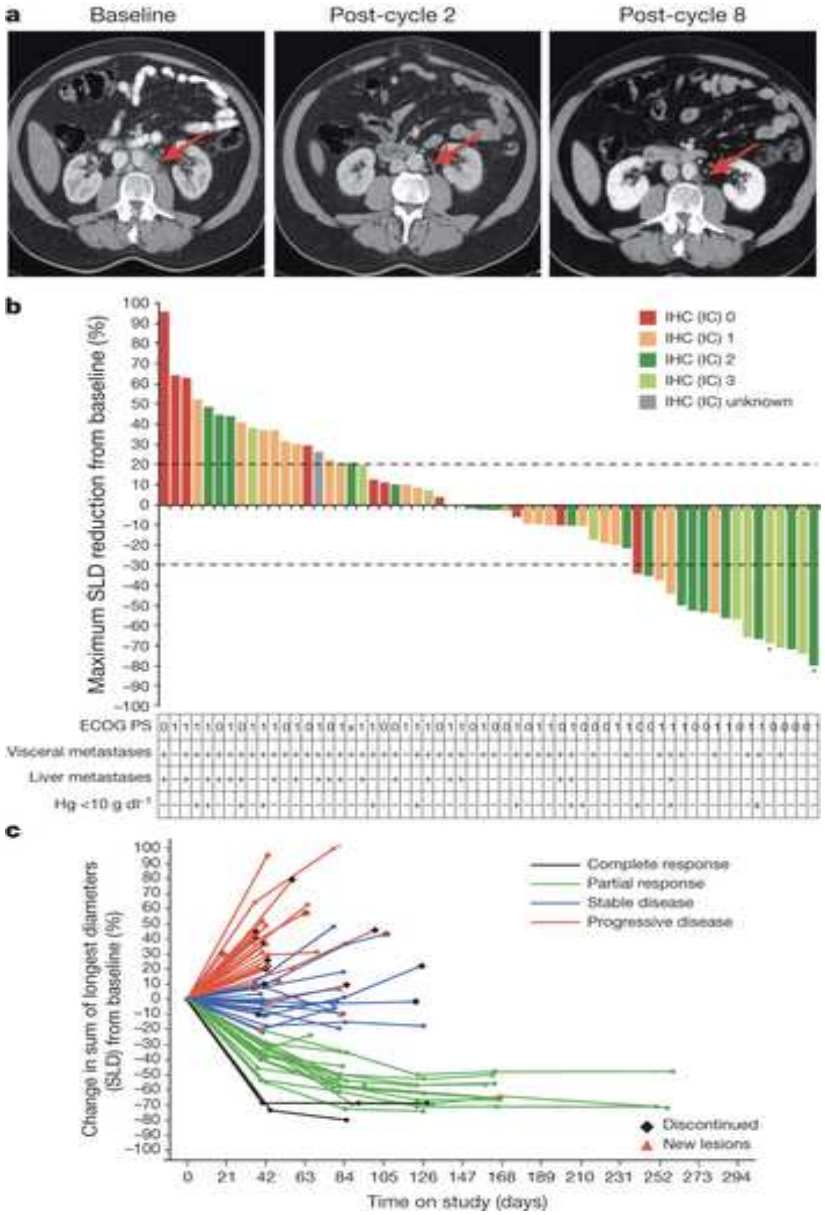
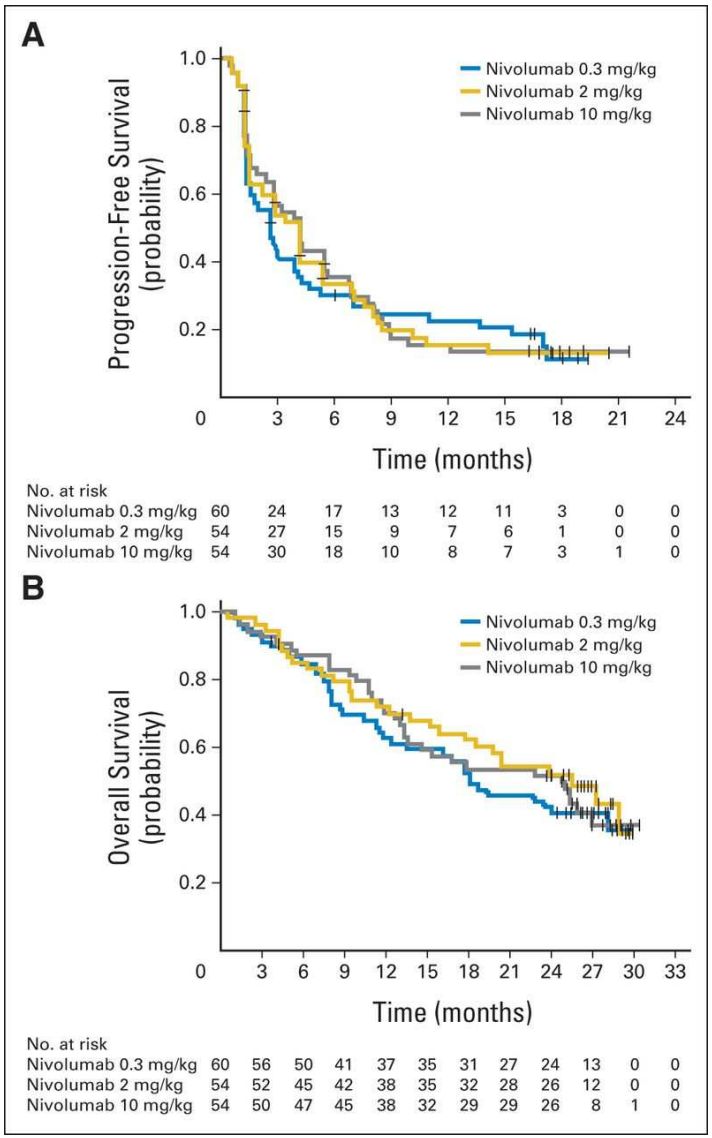
MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer



- **Response rate: 43% in IHC 2-3 PD-L1 staining; 16% in IHC 0-1 PD-L1 staining**

Powles et al. Nature 515 (2014)

Nivolumab (anti-PD-1) for mRCC



Total:168 patients

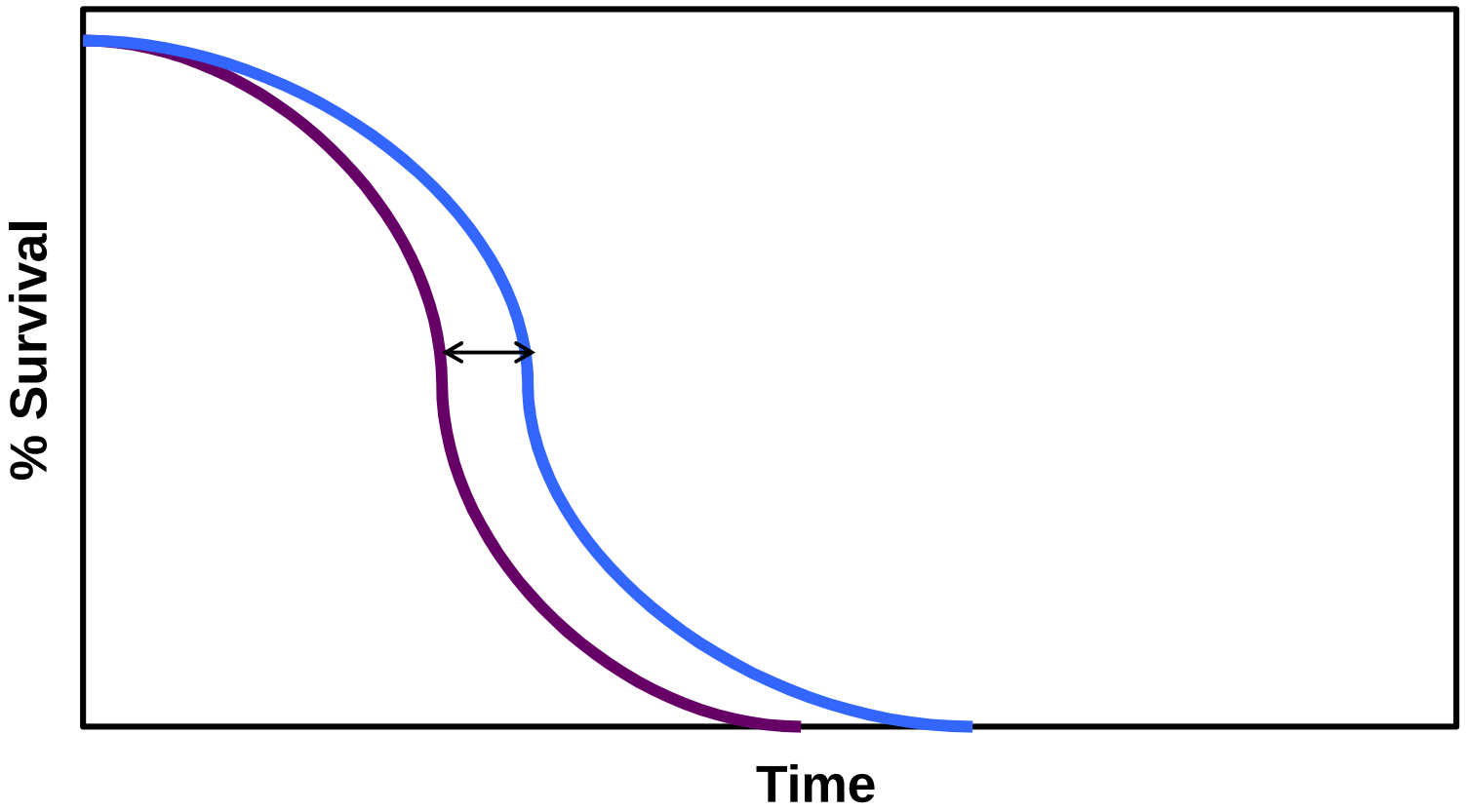
Median PFS: 2.7, 4.0, and 4.2 mo

ORRs: 20%, 22%, and 20%

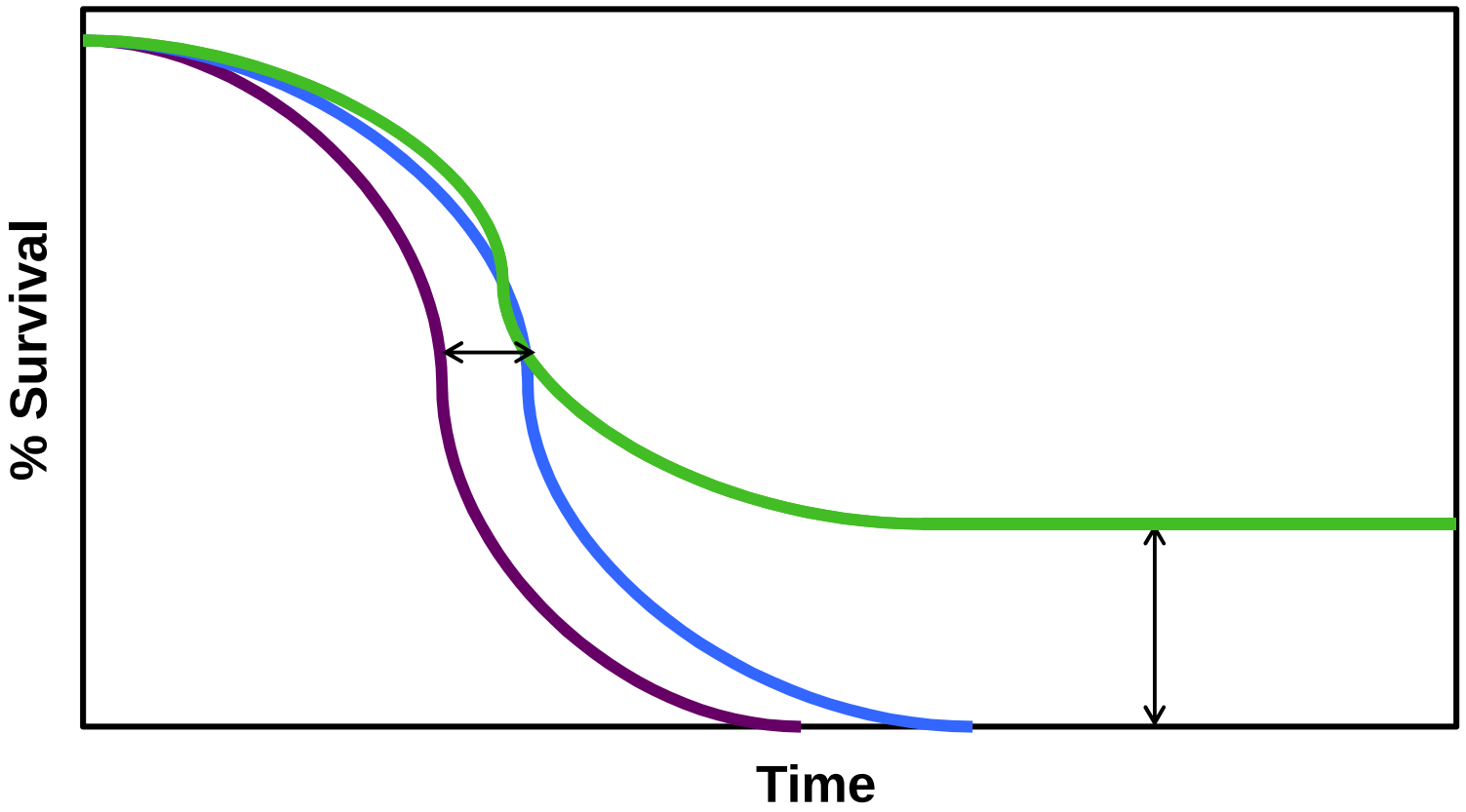
Median OS: 18.2, 25.5, 24.7 mo

Robert J. Motzer et al. JCO doi:10.1200/JCO.2014.59.0703

Standard survival curve



Improving survival with immunotherapy

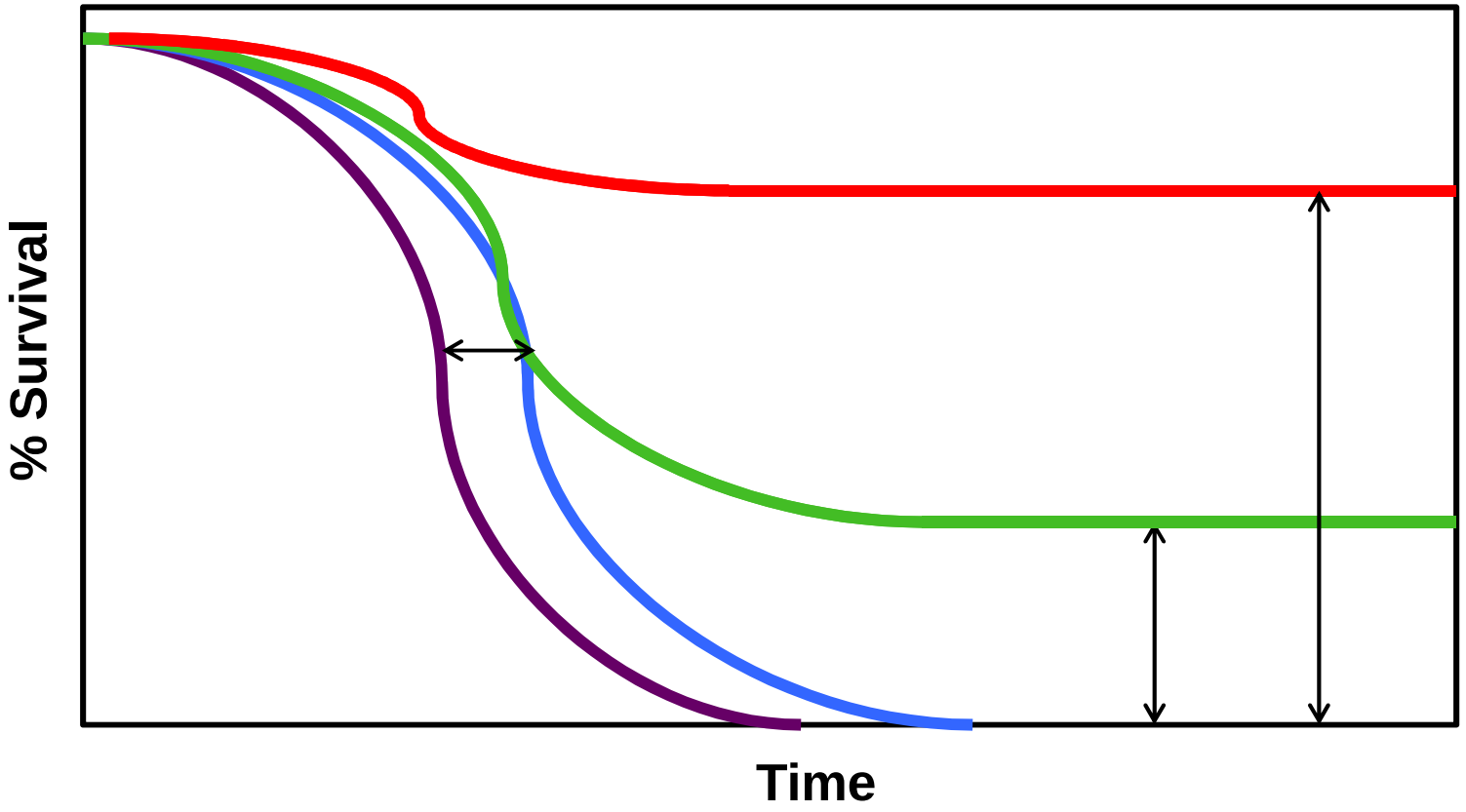


Control

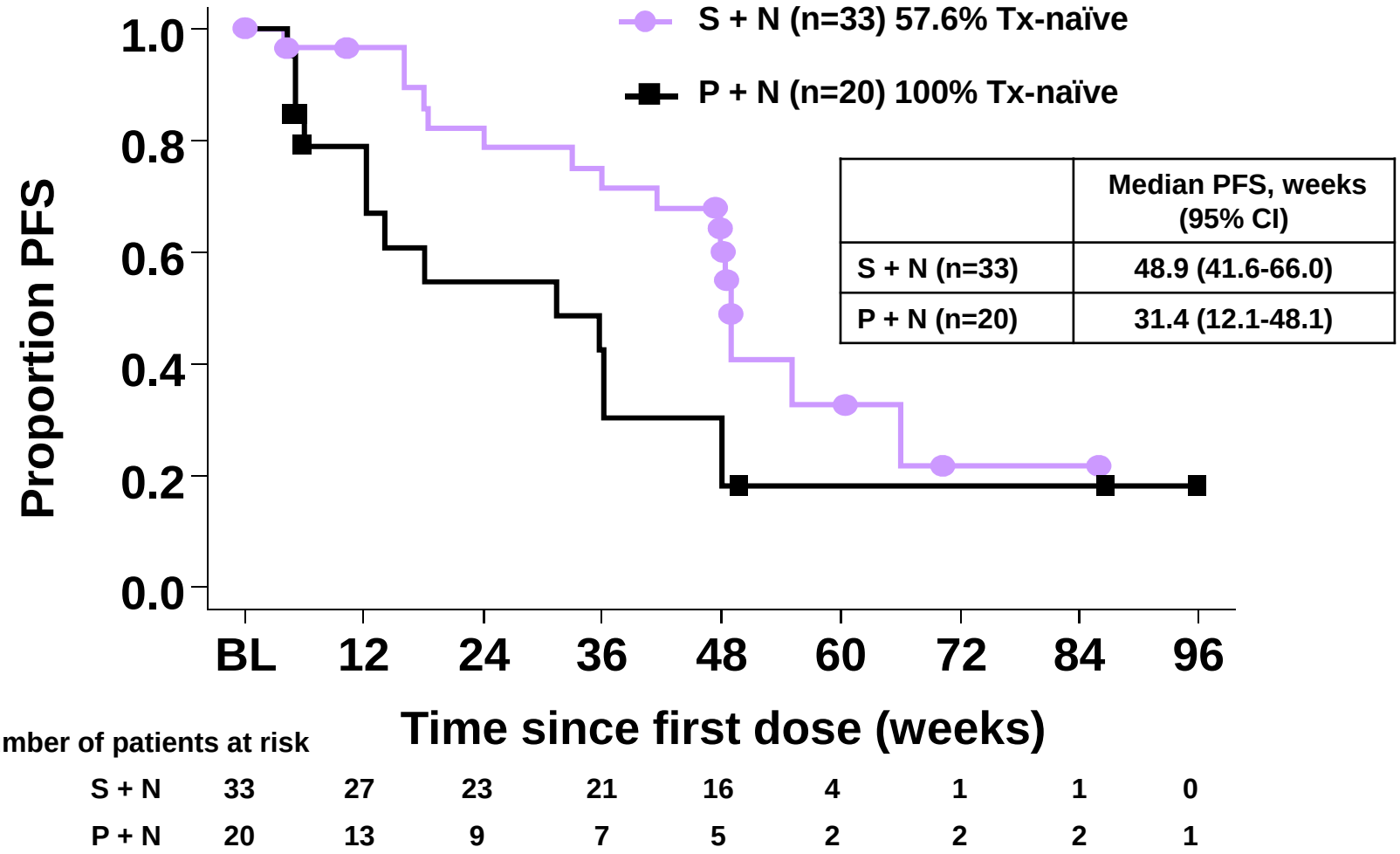
Standard or Other Therapy

Immunotherapy (anti-CTLA-4)

Improving survival with combination therapy



Nivolumab in combination with sunitinib or pazopanib in mRCC



	Median PFS, weeks (95% CI)
S + N (n=33)	48.9 (41.6-66.0)
P + N (n=20)	31.4 (12.1-48.1)

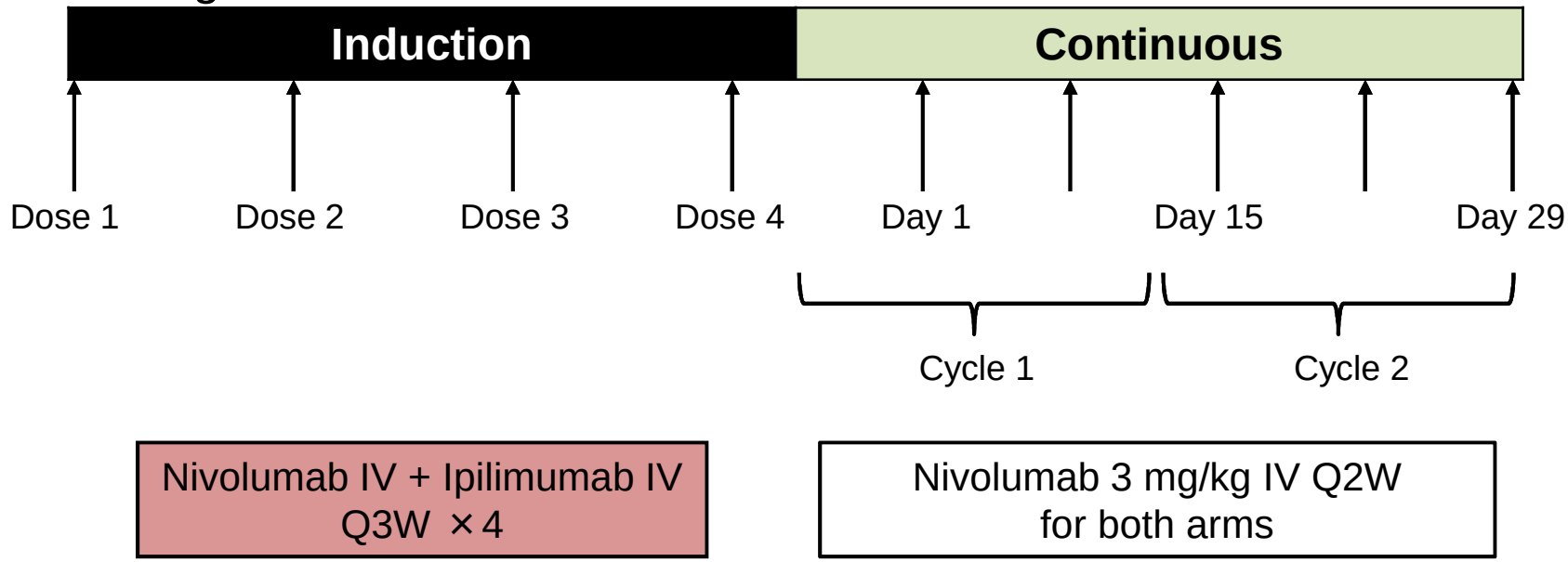
Number of patients at risk

S + N	33	27	23	21	16	4	1	1	0
P + N	20	13	9	7	5	2	2	2	1

Amin, et al. ASCO 2014, Abstract 5010

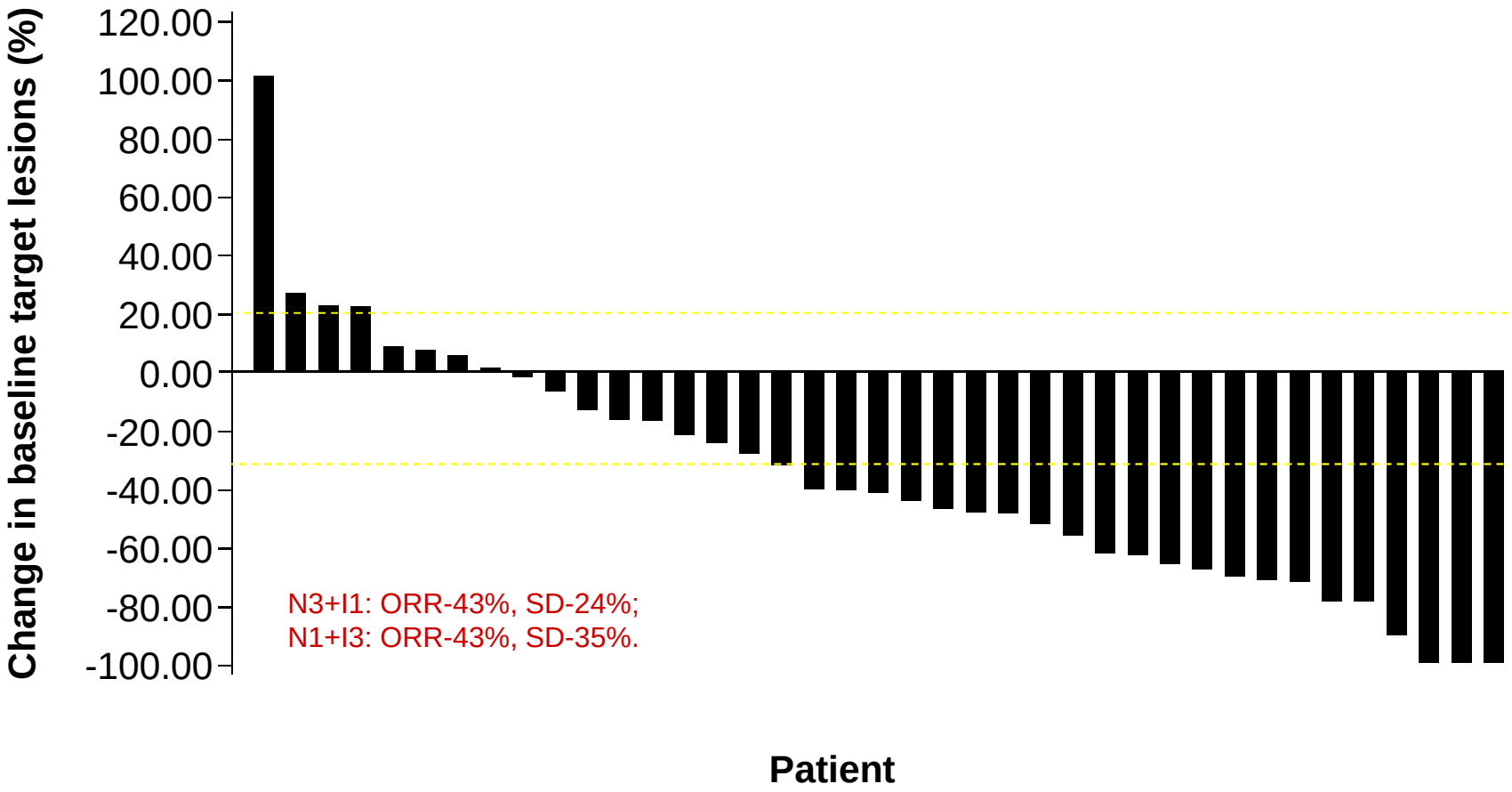
Concurrent regimen of nivolumab and ipilimumab in mRCC

☐ Dosing schedule:

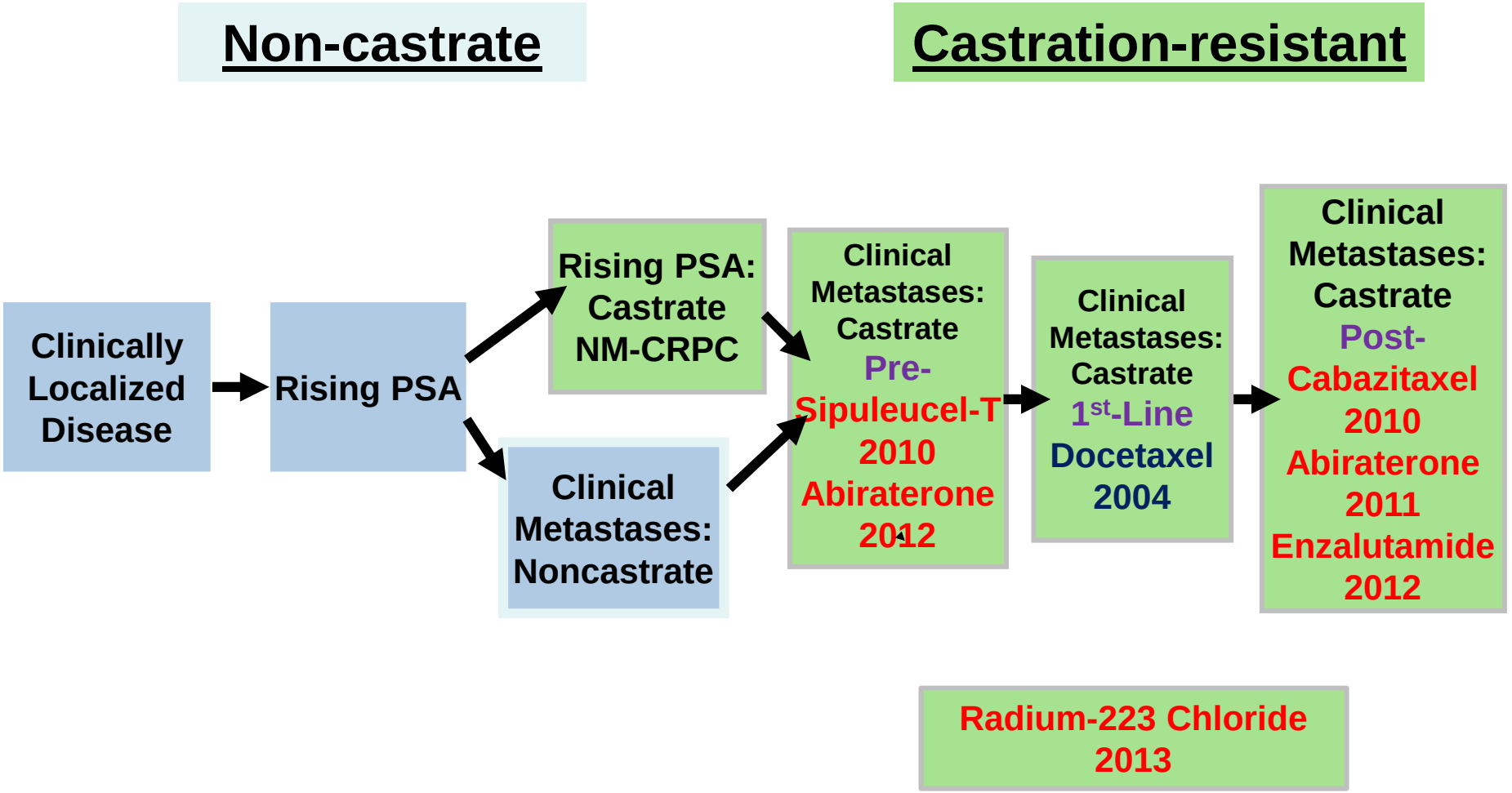


Hammers et al. ASCO 2014

Maximum tumor burden change in baseline target lesions

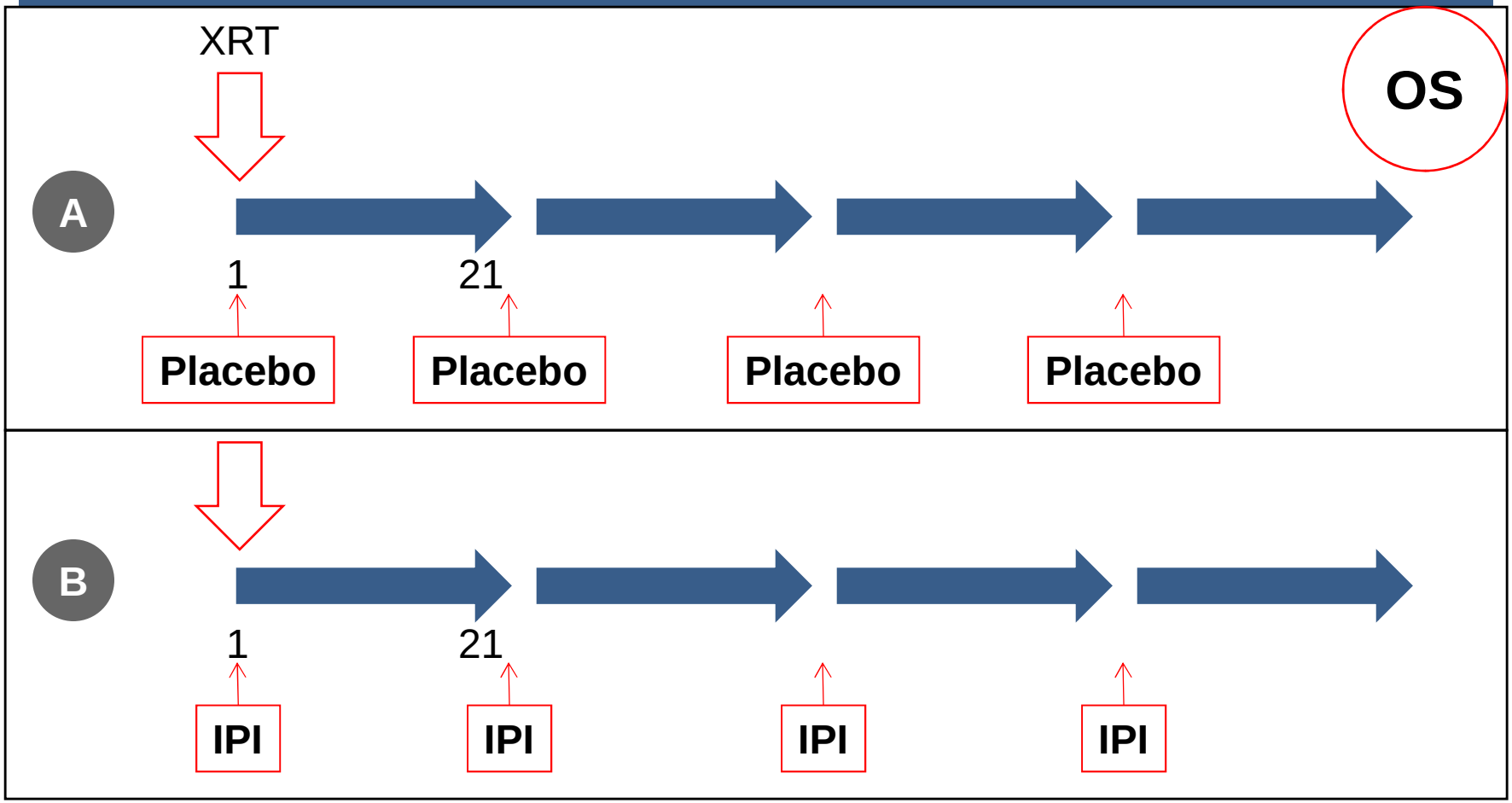


Clinical states model of prostate cancer



Modified from Scher and Heller. *Urology* 2000.

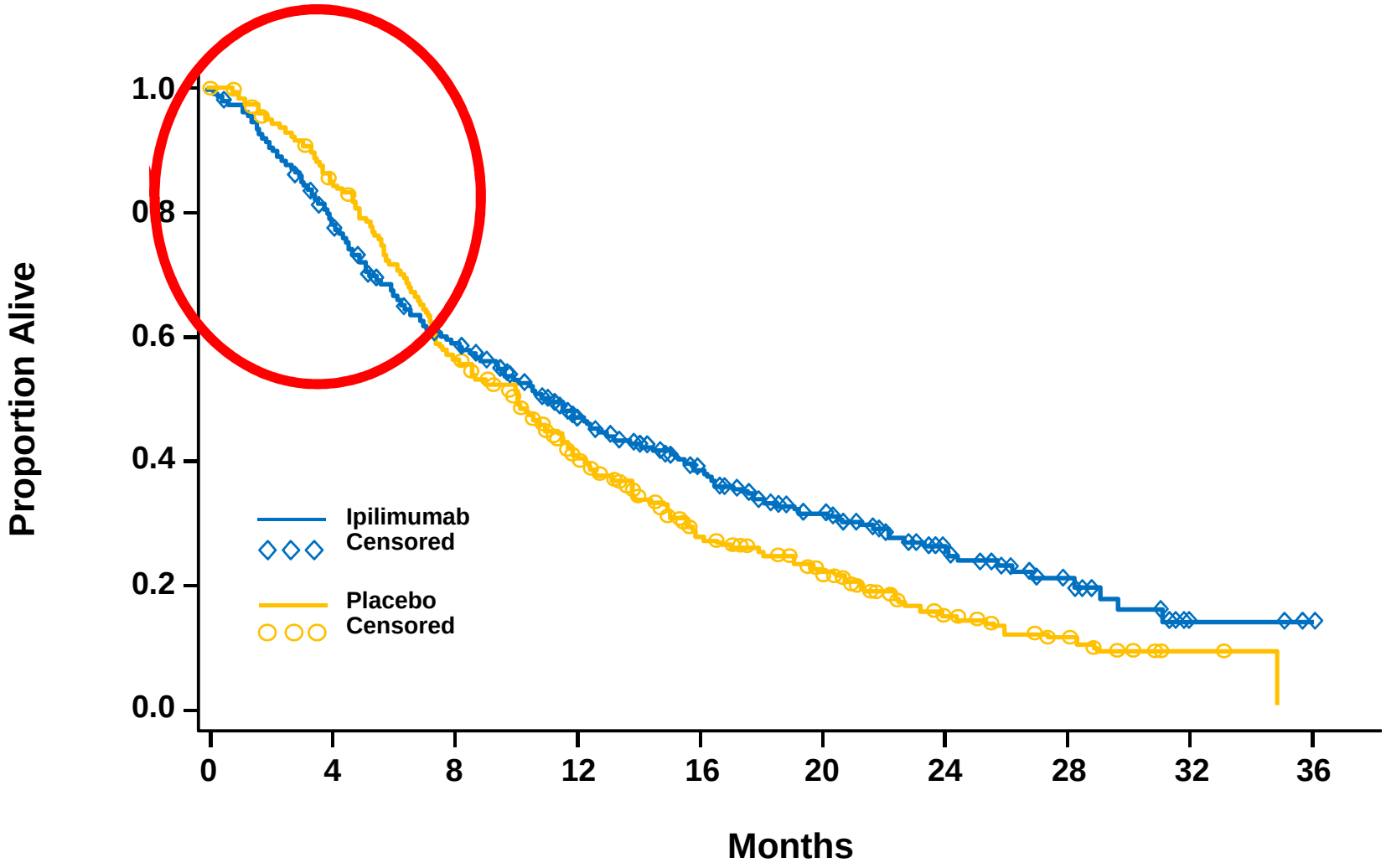
A randomized, double-blind, phase III trial comparing Ipilimumab vs. placebo following radiotherapy in subjects with castration-resistant prostate cancer that have received prior treatment with Docetaxel



NCT00861614; BMS
Estimated Enrollment: 800
Study Start Date: May 2009
Estimated Study Completion Date: September 2013
Estimated Primary Completion Date: September 2013 (Final data collection date for primary outcome measure)

… then q3 months until PD

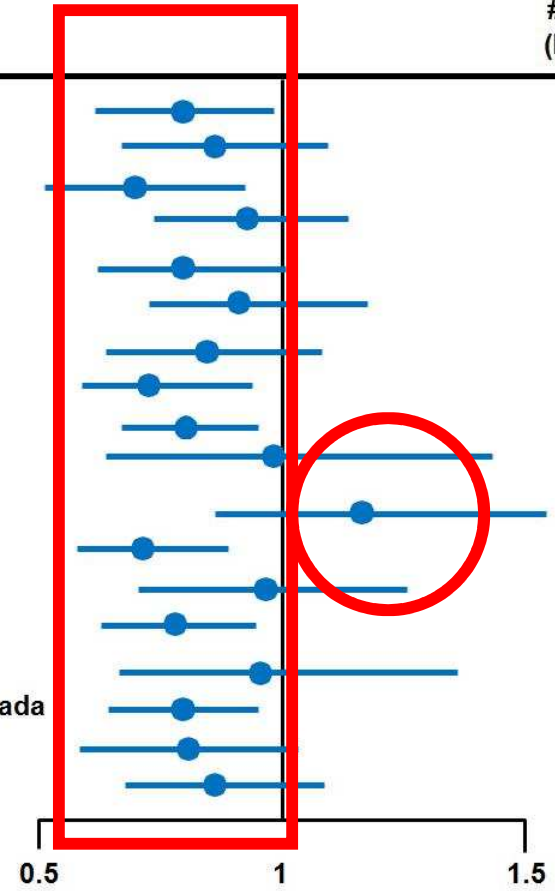
Ant-CTLA-4 (ipilimumab) + radiation therapy in castration-resistant prostate cancer (CRPC)



Kwon, ED et al. Lancet Oncol. 2014 Jun;15(7):700-12

Overall survival: Pre-specified subgroups

Subgroup		# Death / # Randomized (Ipilimumab vs Placebo)	Hazard Ratio (95% CI)
Age	<70	138/215 vs 172/234	0.81 (0.64, 1.01)
	≥70	131/184 vs 133/166	0.88 (0.69, 1.13)
ECOG status	0	98/167 vs 123/168	0.72 (0.55, 0.94)
	1	171/232 vs 182/232	0.94 (0.76, 1.16)
Alkaline phosphatase	<1.5 x ULN	142/243 vs 166/243	0.78 (0.62, 0.97)
	≥1.5 x ULN	127/156 vs 139/157	0.95 (0.75, 1.21)
Gleason score	≤7	111/174 vs 140/190	0.86 (0.67, 1.11)
	>7	134/191 vs 149/186	0.76 (0.60, 0.96)
LDH	Normal	205/326 vs 237/325	0.82 (0.68, 0.99)
	Elevated	52/58 vs 50/53	1.00 (0.68, 1.47)
Visceral metastases	Yes	94/113 vs 93/114	1.20 (0.90, 1.60)
	No	173/280 vs 206/275	0.73 (0.59, 0.89)
Hemoglobin	<11 g/dL	98/111 vs 103/113	0.98 (0.74, 1.29)
	≥11 g/dL	171/288 vs 202/287	0.79 (0.64, 0.97)
Region	USA/Canada	57/86 vs 65/93	0.99 (0.69, 1.42)
	Non-USA/Canada	212/313 vs 240/307	0.79 (0.66, 0.96)
Average daily worst pain at baseline	<4	88/152 vs 106/150	0.81 (0.61, 1.07)
	≥4	147/197 vs 152/186	0.88 (0.70, 1.11)



Favor Ipilimumab ← 95% CI → Favor Placebo

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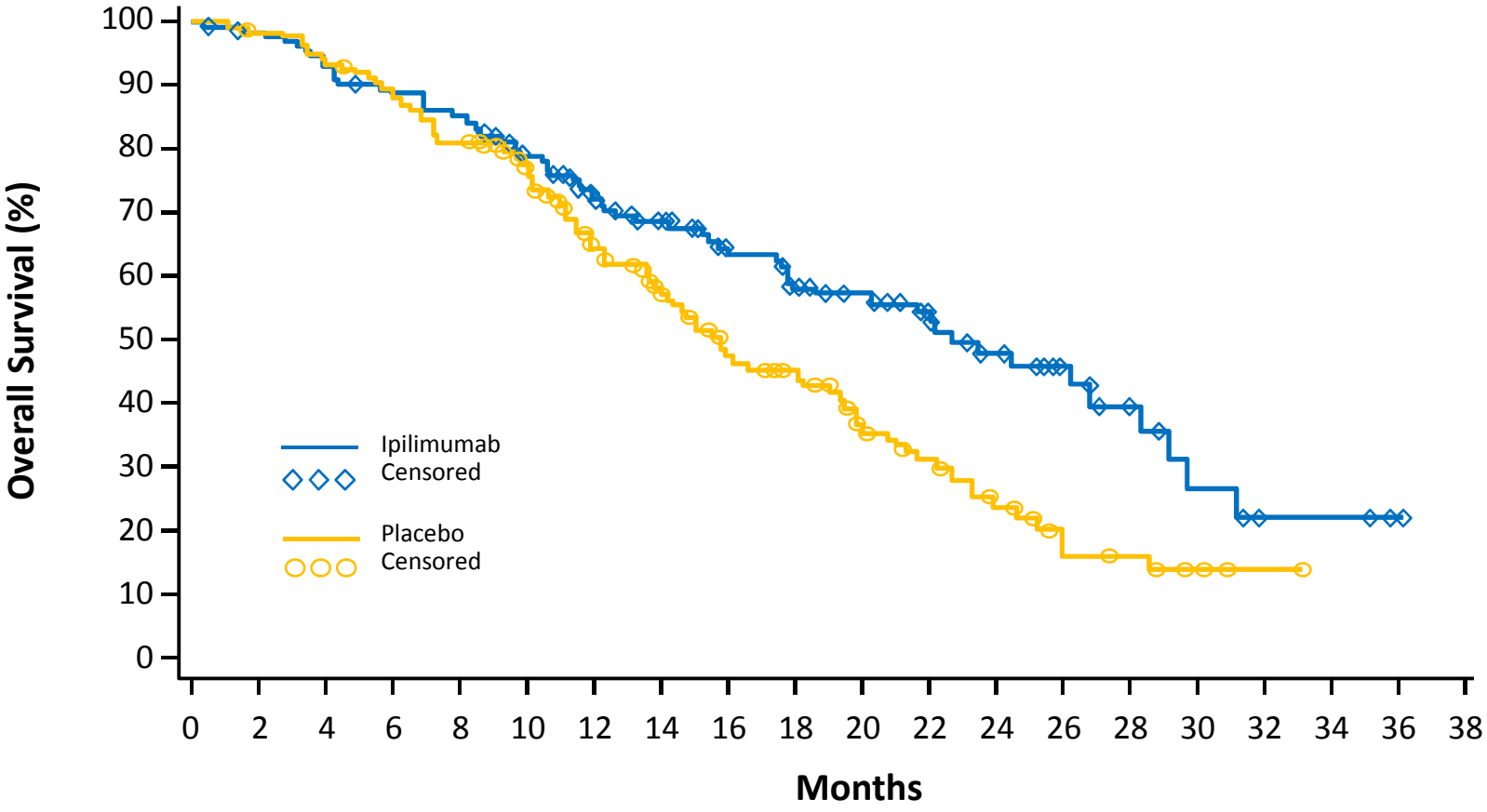
Exploratory subgroup analysis of OS in CRPC patients treated with Ipilimumab



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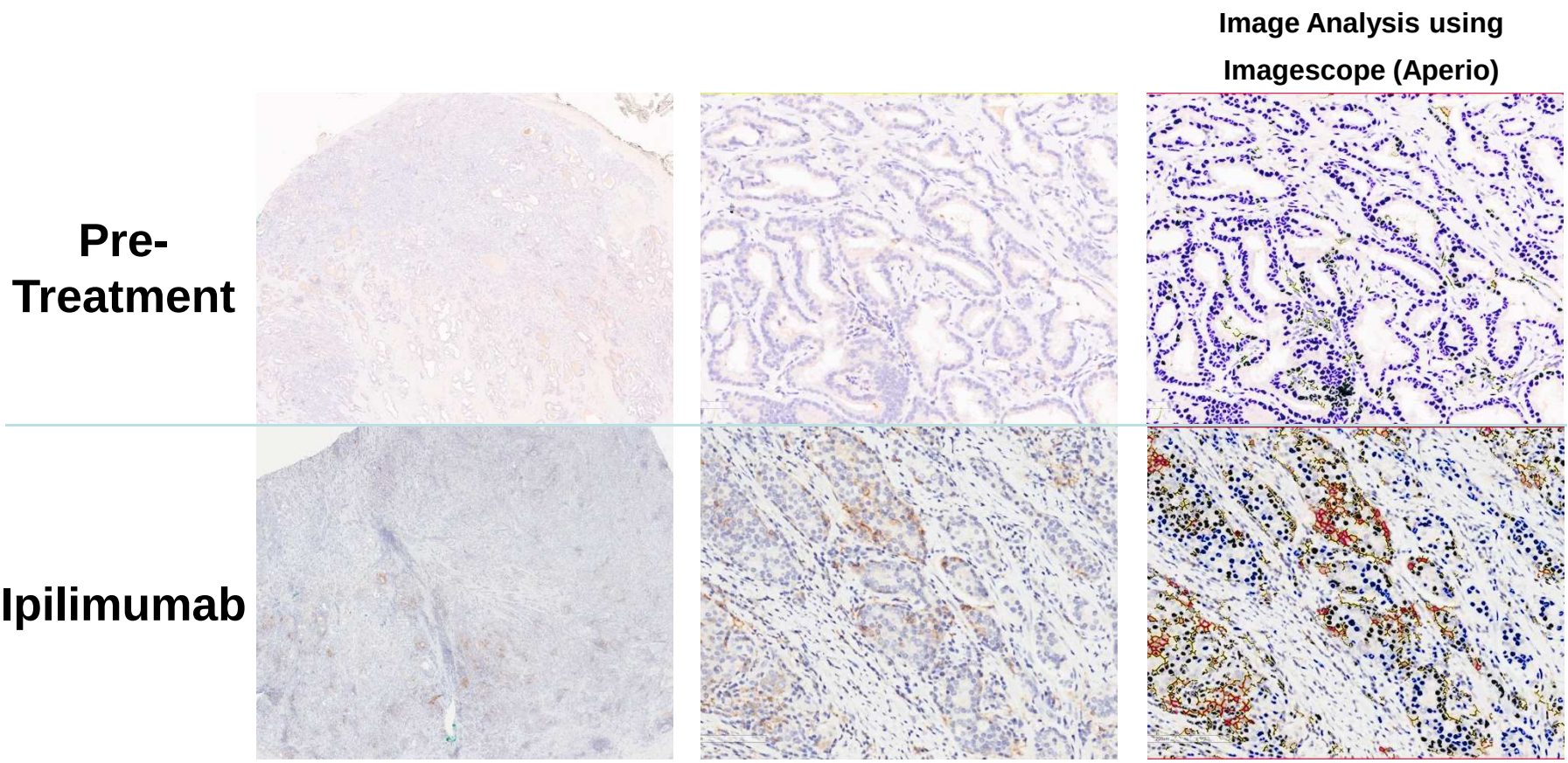
PD-L1 IHC staining



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Challenges and Limitations

- **Subset of patients benefit**
- **Measuring disease burden / treatment response**
  - **Immune-related response criteria (irRC)**
- **Toxicities**
  - **Immune-related adverse events (irAEs)**

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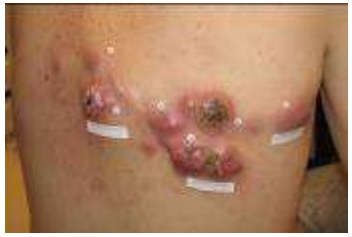
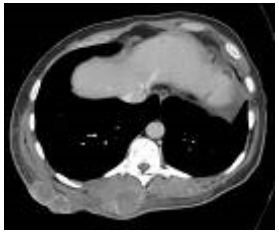
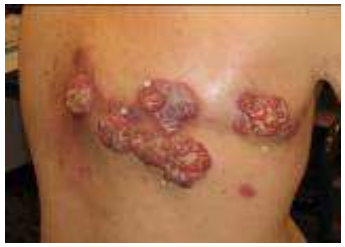
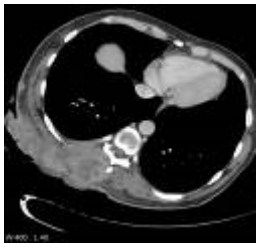
Delayed immune responses

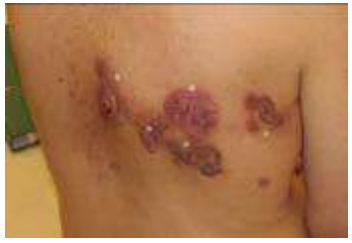
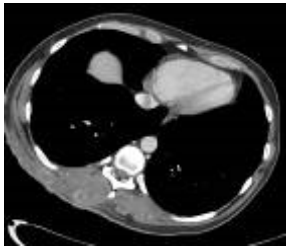
Screening

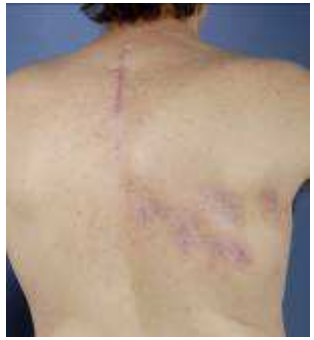
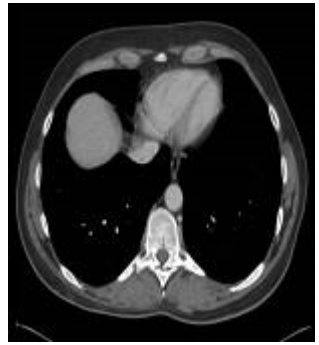
Week 12
Initial increase in
total tumour burden (mWHO PD)

Week 16
Responding

Week 72
Durable & ongoing response

Courtesy of K. Harmankaya

Immune-related toxicities

1. **Pneumonitis—Shortness of breath**
2. **Colitis—Diarrhea, abdominal pain**
3. **Hepatitis—Fatigue, abdominal pain**
4. **Hypophysitis—Headache, vision change, fatigue, low blood pressure**
5. **Dermatitis—Rash**

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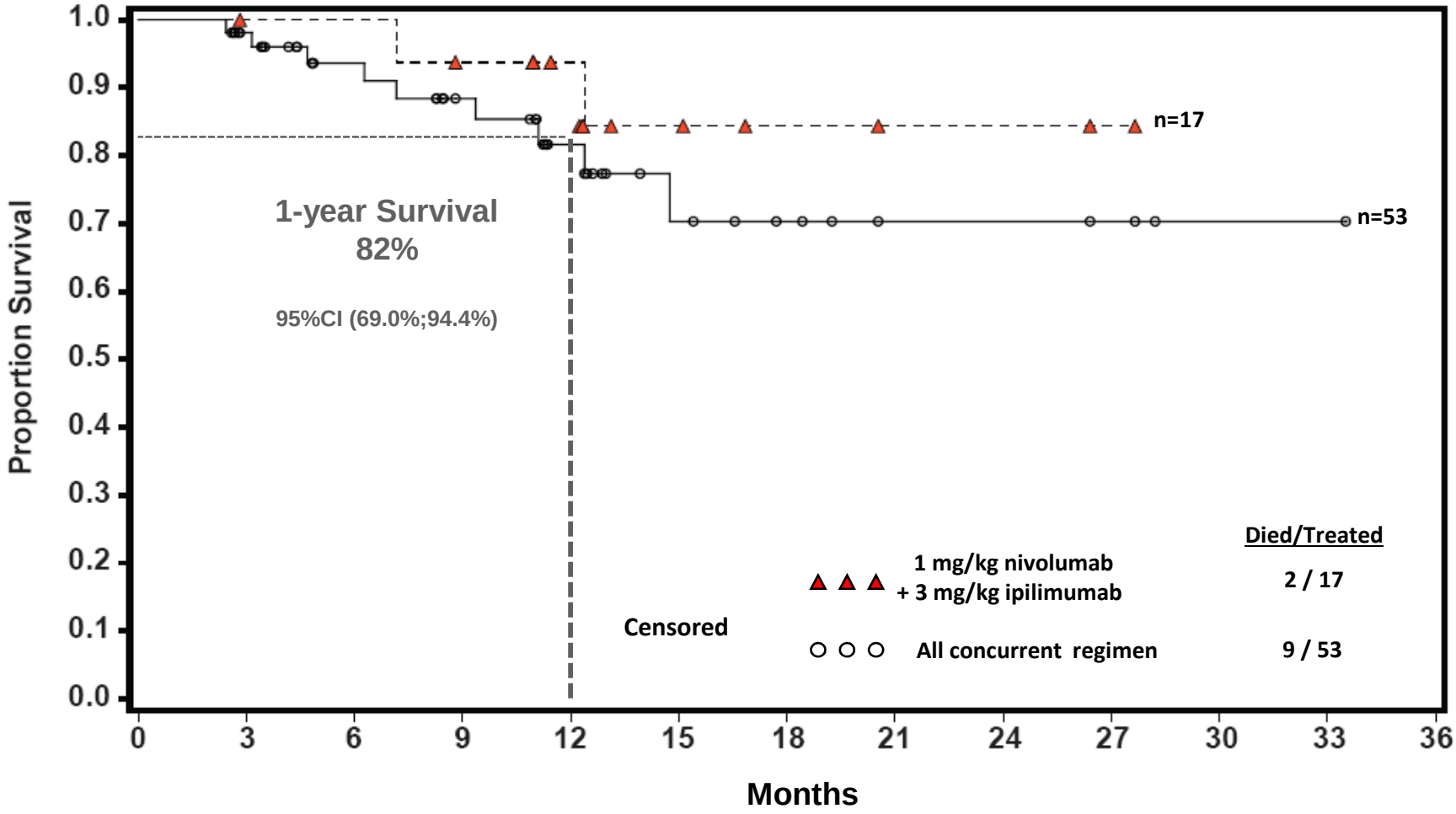
Ipilimumab plus nivolumab in melanoma



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

Wolchok, Hodi, BMS

2013: Breakthrough of the Year

December 20, 2013

Lessons and Take Home Messages

- **IL-2 therapy provides long-term survival but with low response rates and significant toxicities.**
- **Vaccines prolong survival without measurable response.**
- **Targeting individual immune checkpoints have modest activity.**
- **Combination therapies provide higher response rates with pending survival data.**
- **Immune-related toxicities have to be managed early.**

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Novel immunotherapy targets