Society for Immunotherapy of Cancer (SITC)

IMMUNOTHERAPY FOR TREATMENT OF GENITOURINARY MALIGNANCIES

Leonard J. Appleman MD PhD
University of Pittsburgh

Advances in Cancer Immunotherapy™ - Pittsburgh
July 31, 2015

Society for Immunotherapy of Cancer

OBJECTIVES

- Consider the role of cytokine therapy for renal cell carcinoma in the 21st Century

- Review the emerging data with checkpoint inhibitors in GU malignancies

- Discuss the clinical data regarding active specific immunotherapy for prostate cancer

sitc

Society for Immunotherapy of Cancer

RENAL CELL CARCINOMA

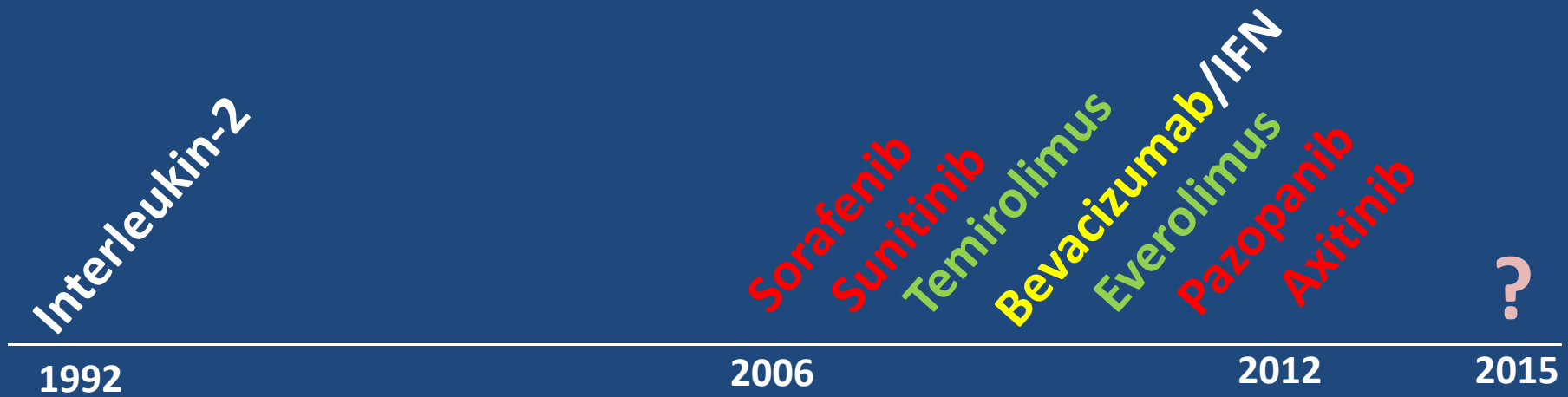
CYTOKINE THERAPY in RCC

High dose Interleukin-2

- Approved for RCC in 1992- 1st agent for this cancer
- Inpatient Therapy: 600,000 IU/kg IV q8 hrs; up to 14 doses. 4-6 cycles over 4-8 months.
- Highly Toxic: Vascular leak, hypotension, cardiac, pulmonary, hepatic, renal, CNS toxicity. *Mostly reversible*
- Durable complete remissions- 5-10%

HD IL-2: is there a role in modern times?

Renal Cell Carcinoma: Approved Agents 2015



VEGFR TKI

mTOR inhibitor

Cytokine

Neutralizing anti-VEGF mAb

Published OnlineFirst November 25, 2014; DOI: 10.1158/1078-0432.CCR-14-1520

Personalized Medicine and Imaging

Clinical Cancer Research

The High-Dose Aldesleukin "Select" Trial: A Trial to Prospectively Validate Predictive Models of Response to Treatment in Patients with Metastatic Renal Cell Carcinoma

David F. McDermott[1], Su-Chun Cheng[2], Sabina Signoretti[3], Kim A. Margolin[4], Joseph I. Clark[5], Jeffrey A. Sosman[6], Janice P. Dutcher[7], Theodore F. Logan[8], Brendan D. Curti[9], Marc S. Ernstoff[10], Leonard Appleman[11], Michael K.K. Wong[12], Nikhil I. Khushalani[12], Leslie Oleksowicz[13], Ulka N. Vaishampayan[14], James W. Mier[1], David J. Panka[1], Rupal S. Bhatt[1], Alexandra S. Bailey[1], Bradley C. Leibovich[15], Eugene D. Kwon[15], Fairooz F. Kabbinavar[16], Arie S. Belldegrun[16], Robert A. Figlin[17], Allan J. Pantuck[16], Meredith M. Regan[2], and Michael B. Atkins[18]

Contemporary Multicenter Experience: 1st line therapy

IL-2 Select: population

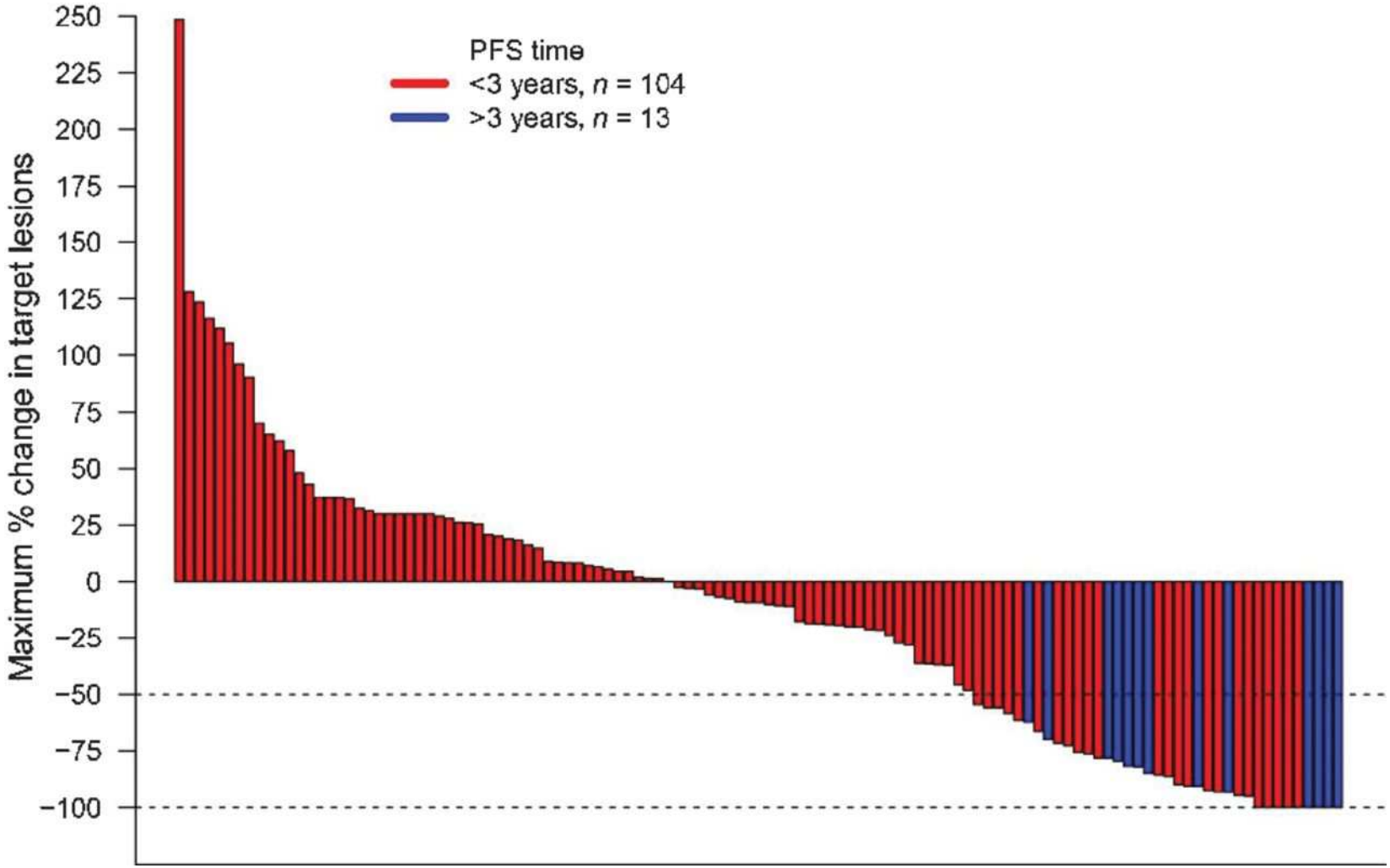
Table 1. Patient clinical characteristics of all treated patients

Characteristics	$n = 120$
Median age, y (range)	56 (28–70)
ECOG performance status[a] 0/1, %	72/24[b]
Prior nephrectomy, %	99
MSKCC risk factors, *n* (%)	
0 (favorable)	23 (19)
1–2 (intermediate)	84 (70)
≥3 (poor)	13 (11)
UCLA SANI Score, *n* (%)	
Low	10 (8)
Intermediate	102 (85)
High	8 (7)

[a]Criteria as described in Oken et al. (42).

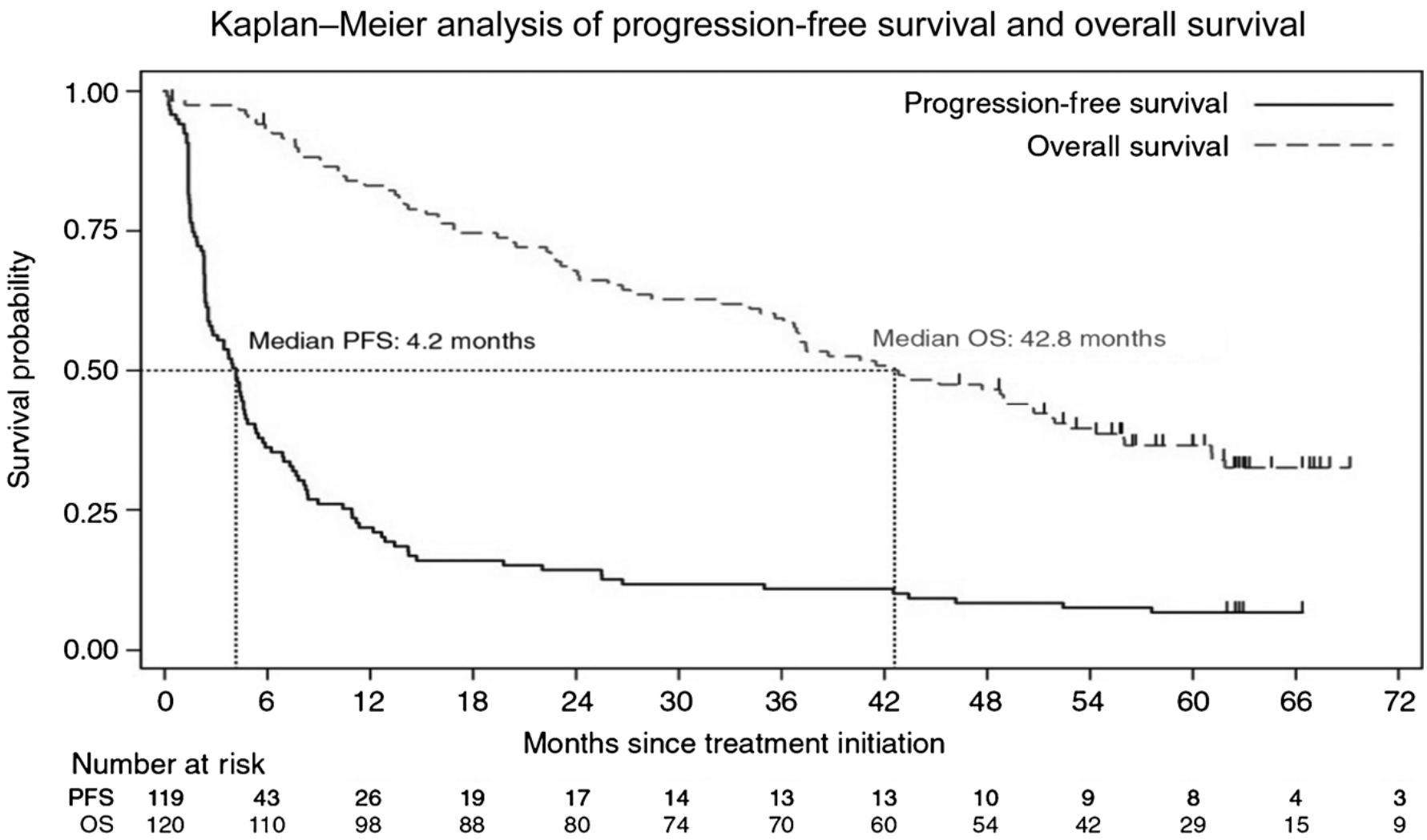
[b]4% missing data.

Characteristics of tumor regression in patients with mRCC receiving HD IL2 therapy by investigator assessment



David F. McDermott et al. Clin Cancer Res 2015;21:561-568

Clinical Cancer Research
AACR American Association for Cancer Research



David F. McDermott et al. Clin Cancer Res 2015;21:561-568

Overall survival in 21st Century mRCC First-line studies

STUDY/Rx	Fav(%)	Int (%)	Poor (%)	Median OS (months)
IL-2 SELECT	19	70	11	**42.8**
Motzer 2007, 2009 (Sunitinib)	38	56	6	**26.4**
Heng (TKI, bev)	21	46	24	**22**
COMPARZ 2014 (Sun/Paz)	25	56	14	**29**

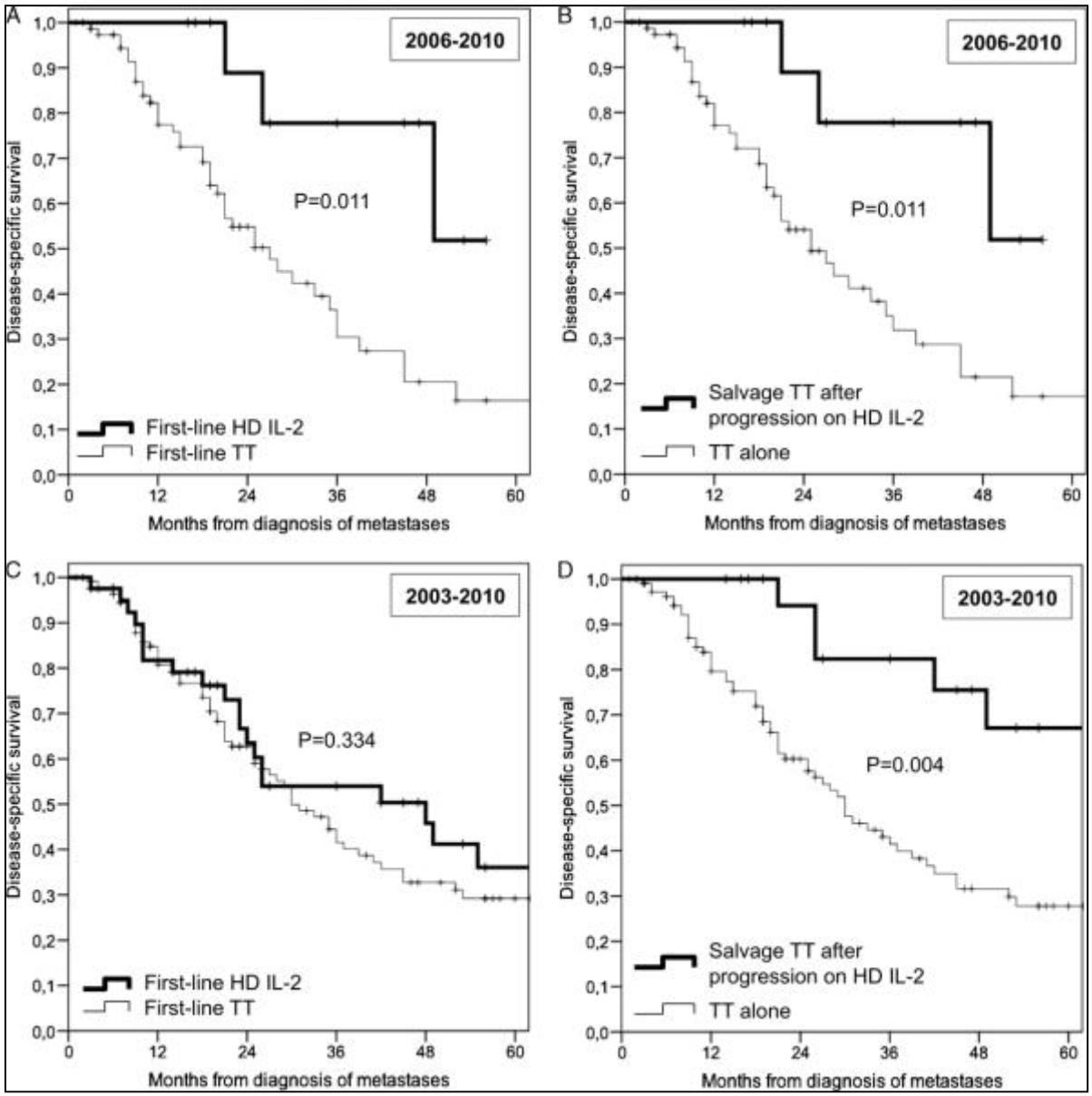
ORIGINAL ARTICLE

Salvage-Targeted Kidney Cancer Therapy in Patients Progressing on High-Dose Interleukin-2 Immunotherapy

The UCLA Experience

Frédéric D. Birkhäuser, MD,† Allan J. Pantuck, MD,* Edward N. Rampersaud, MD,* Xiaoyan Wang, PhD,‡ Nils Kroeger, MD,* Frédéric Pouliot, MD,* Nazy Zomorodian, MSN,* Joseph Riss, PhD,* Gang Li, PhD,‡ Fairooz F. Kabbinavar, MD,* and Arie S. Belldegrun, MD**

Salvage-Targeted Kidney Cancer Therapy in Patients Progressing on High-Dose Interleukin-2 Immunotherapy: The UCLA Experience



Birkhauser, F; Pantuck, A; Rampersaud, E.; Wang, X; Kroeger, N.; Pouliot, F.; Zomorodian, N.; Riss, J.; Li, G.; Kabbinavar, F.; Belldegrun, A.

Cancer Journal. 19(3):189-196, May/June 2013.
DOI:
10.1097/PPO.0b013e318292e8a4

FIGURE 3 . DSS by Kaplan Meier analysis: A, Comparison of patients treated with first-line HD IL-2 (n = 12) and with first-line TT (n=78) between 2006 and 2010. B, Comparison of patients treated with salvage TT after progression on HD IL-2 (n = 12) and with TT alone (n = 77) between 2006 and 2010. C, Comparison of patients treated with first-line HD IL-2 (n = 41) and with first-line TT (n = 115) between 2003 and 2010. D, Comparison of patients treated with salvage TT after progression on HD IL-2 (n = 21) and with TT alone (n = 109) between 2003 and 2010.

Birkhauser *et al*.

	Hazard Ratio	95% CI for Hazard Ratio	*P* - Value
Effect of salvage TT after progression on HD IL-2 vs. TT alone	0.32	(0.14–0.69)	0.004
Overall effect of UISS M (at diagnosis of metastatic disease)			0.004
Effect of UISS M intermediate-risk vs. low-risk	2.41	(1.26–4.60)	0.008
Effect of UISS M high-risk vs. low-risk	4.21	(1.72–10.30)	0.002
Effect of asymptomatic vs. symptomatic	0.67	(0.38–1.18)	0.165
Effect of female vs male	0.73	(0.39–1.39)	0.343
Effect of age at nephrectomy, yrs	0.99	(0.97–1.02)	0.602

Salvage-Targeted Kidney Cancer Therapy in Patients Progressing on High-Dose Interleukin-2 Immunotherapy: The UCLA Experience.
Birkhauser, Frederic; Pantuck, Allan; Rampersaud, Edward; Wang, Xiaoyan; Kroeger, Nils; Pouliot, Frederic; Zomorodian, Nazy; Riss, Joseph; Li, Gang; Kabbinavar, Fairooz; Belldegrun, Arie

Cancer Journal. 19(3):189-196, May/June 2013.
DOI: 10.1097/PPO.0b013e318292e8a4

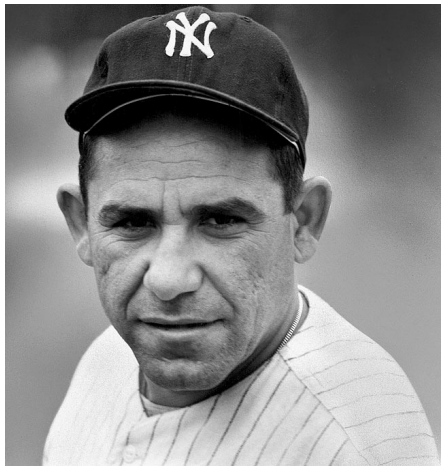
TABLE 2 Multivariate Cox Regression Analysis Comparing the Groups Salvage TT After Progression on HD IL-2 and TT Alone From 2003-2010

HD IL-2 for RCC in modern times
First-line therapy

- *HD IL-2 vs VEGFR TKI:* HD IL-2 is toxic but offers 5-10% durable remission off therapy and perhaps additional survival benefit in progressors. *Consider offering as an option to young, fit patients likely to benefit.*

"When you come to a fork in the road, take it"

- Yogi Berra



- *HD IL-2 vs checkpoint inhibitor therapy:*

  -Stay tuned.

Checkpoint inhibitors in RCC

PNAS

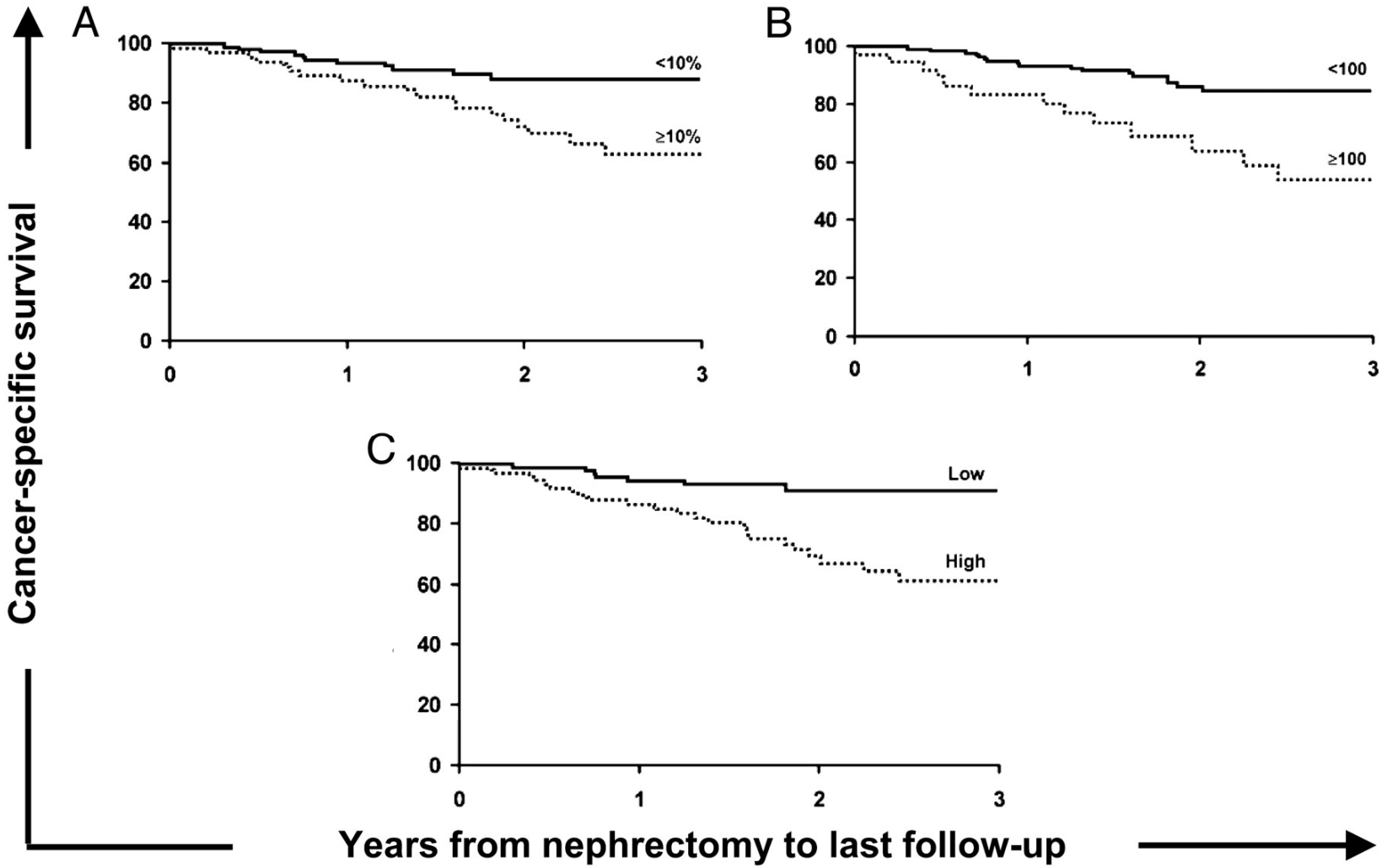
Costimulatory B7-H1 in renal cell carcinoma patients: Indicator of tumor aggressiveness and potential therapeutic target

R. Houston Thompson*†, Michael D. Gillett*†, John C. Cheville‡, Christine M. Lohse§, Haidong Dong¶, W. Scott Webster*, Kent G. Krejci*, John R. Lobo*, Shomik Sengupta*, Lieping Chen∥, Horst Zincke*, Michael L. Blute*, Scott E. Strome**, Bradley C. Leibovich*††, and Eugene D. Kwon*¶‡‡§§

Departments of *Urology, ‡Laboratory Medicine and Pathology, §Health Sciences Research, ¶Immunology, and **Otolaryngology, Mayo Medical School, Mayo Clinic, Rochester, MN 55905; and ∥Department of Dermatology and Oncology, Johns Hopkins University School of Medicine, Baltimore, MD 21287

Edited by James P. Allison, Memorial Sloan-Kettering Cancer Center, New York, NY, and approved October 25, 2004 (received for review August 27, 2004)

Associations of B7-H1 expression with death from RCC in 196 clear cell RCC specimens.



R. H. Thompson et al. PNAS 2004;101:17174-17179

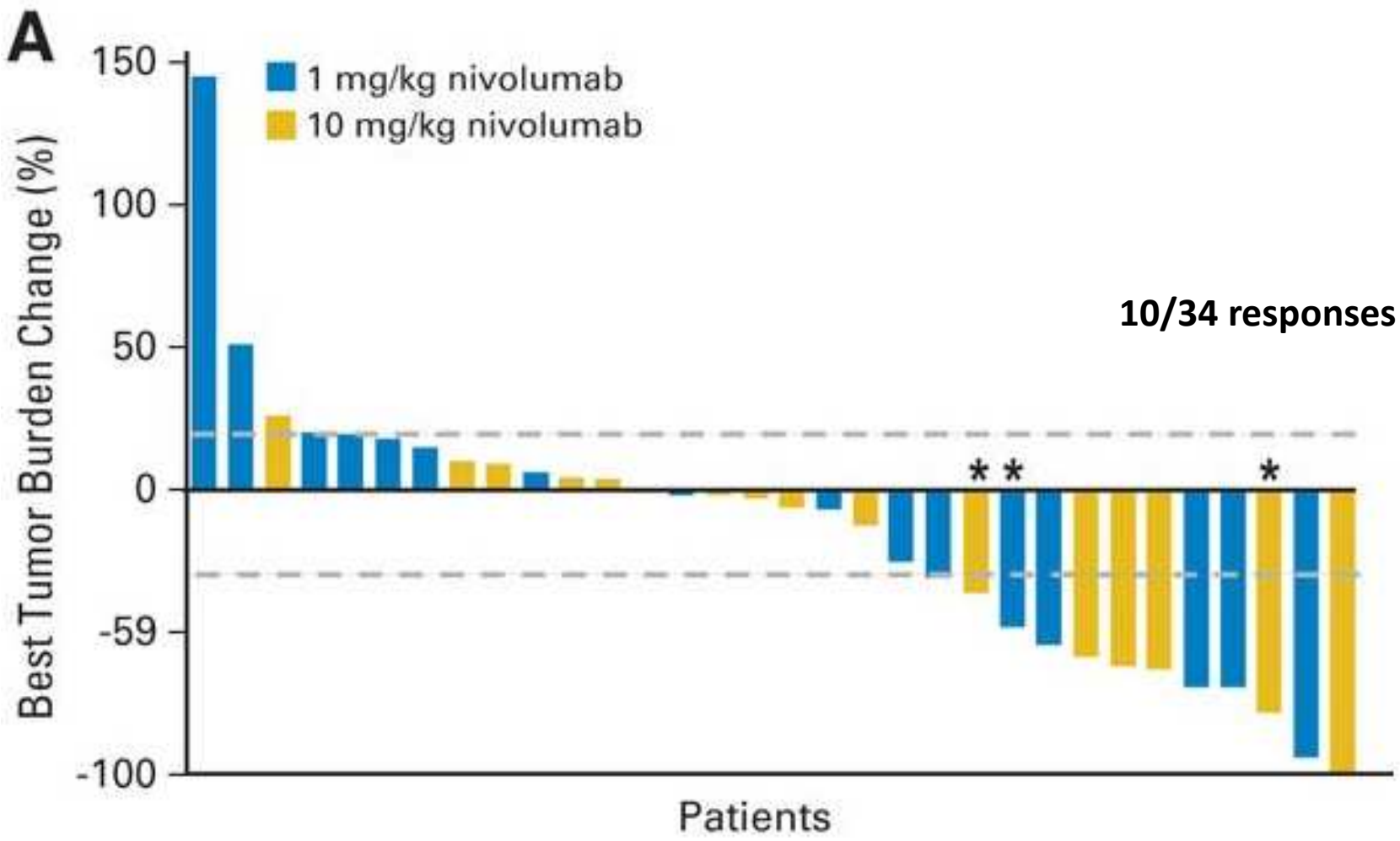
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Survival, Durable Response, and Long-Term Safety in Patients With Previously Treated Advanced Renal Cell Carcinoma Receiving Nivolumab

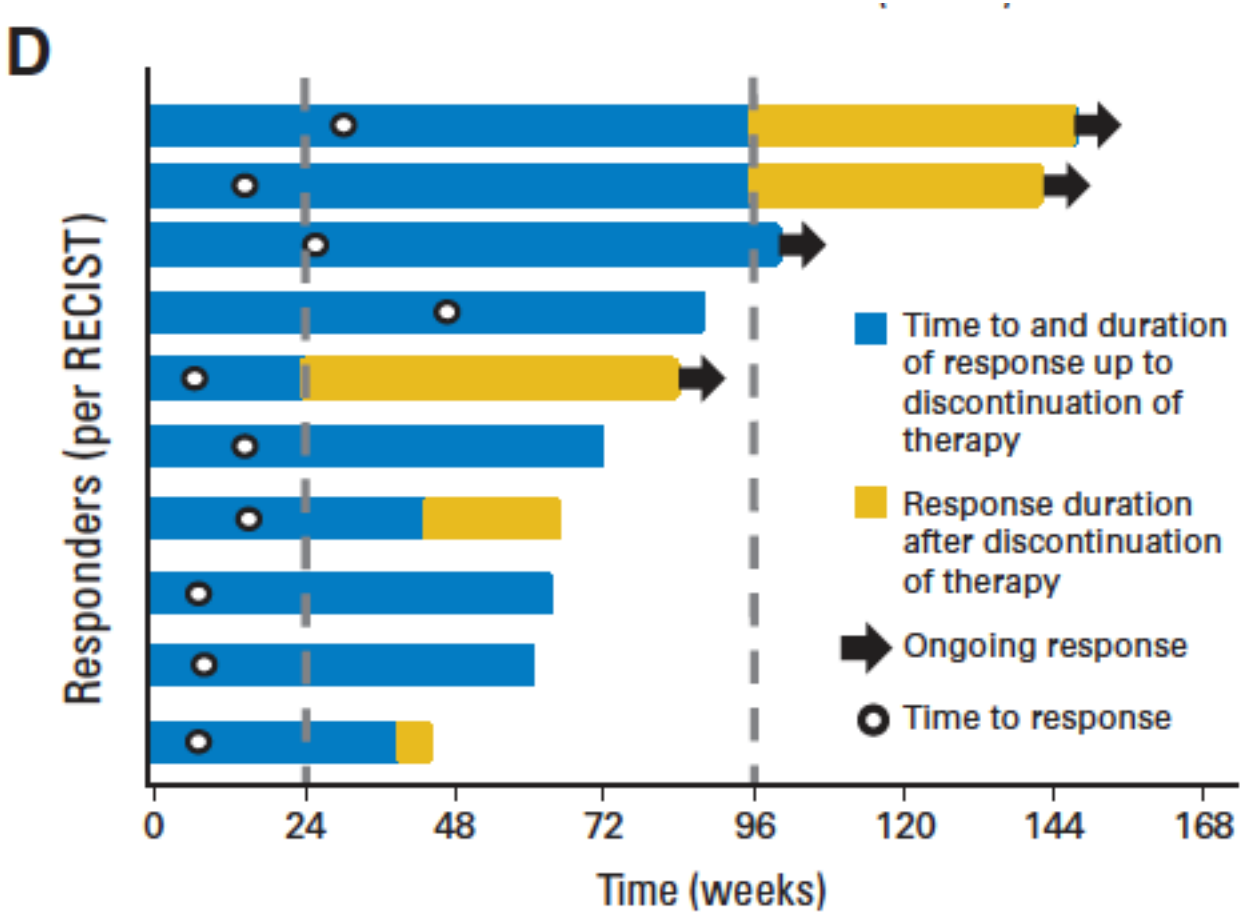
David F. McDermott, Charles G. Drake, Mario Sznol, Toni K. Choueiri, John D. Powderly, David C. Smith, Julie R. Brahmer, Richard D. Carvajal, Hans J. Hammers, Igor Puzanov, F. Stephen Hodi, Harriet M. Kluger, Suzanne L. Topalian, Drew M. Pardoll, Jon M. Wigginton, Georgia D. Kollia, Ashok Gupta, Dan McDonald, Vindira Sankar, Jeffrey A. Sosman, and Michael B. Atkins

Characteristics of tumor regression in patients with renal cell carcinoma receiving nivolumab therapy.



10/34 responses

David F. McDermott *et al.* JCO 2015;33:2013-2020



David F. McDermott *et al.* JCO 2015;33:2013-2020

VOLUME 33 · NUMBER 13 · MAY 1 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Nivolumab for Metastatic Renal Cell Carcinoma: Results of a Randomized Phase II Trial

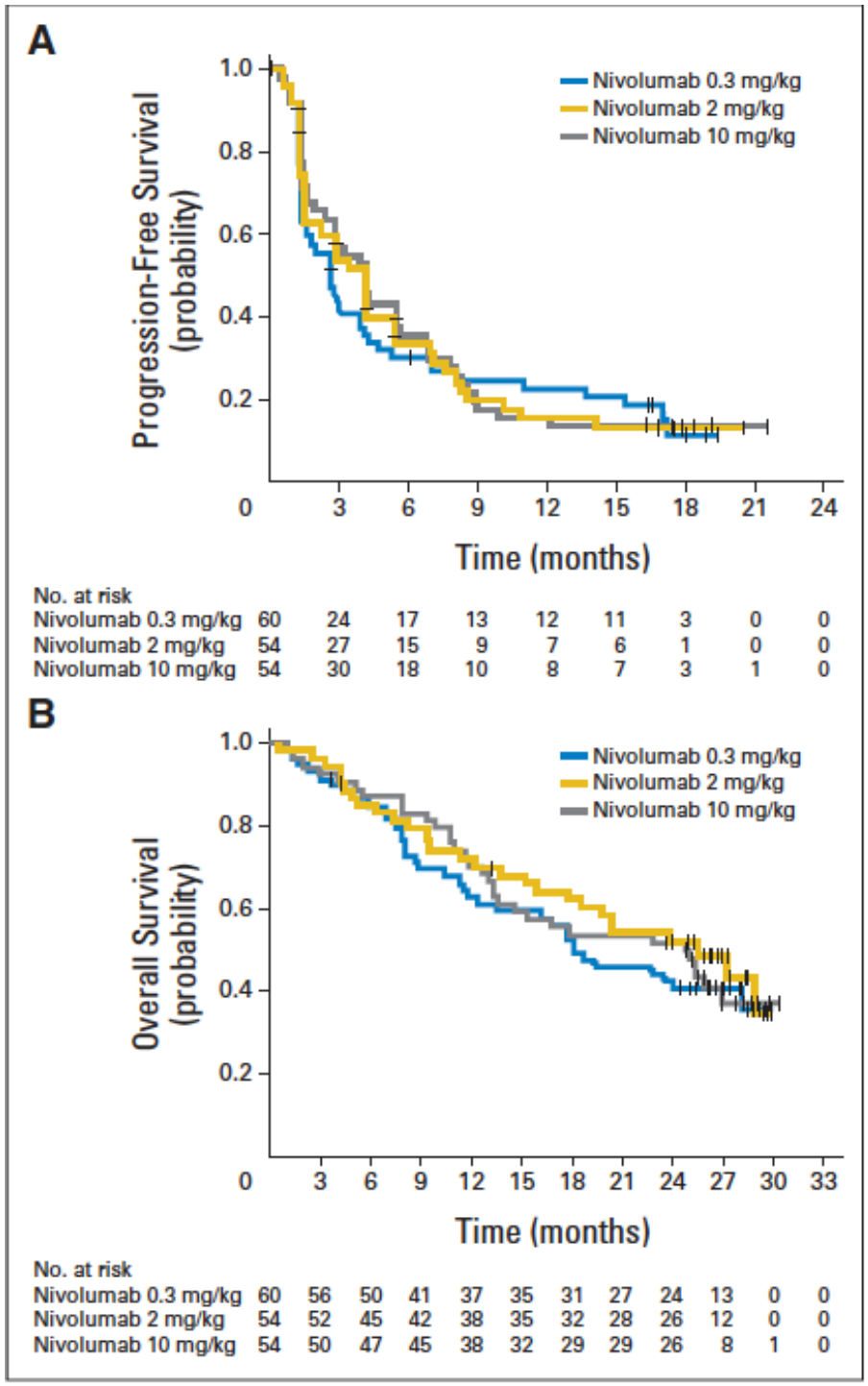
Robert J. Motzer, Brian I. Rini, David F. McDermott, Bruce G. Redman, Timothy M. Kuzel, Michael R. Harrison, Ulka N. Vaishampayan, Harry A. Drabkin, Saby George, Theodore F. Logan, Kim A. Margolin, Elizabeth R. Plimack, Alexandre M. Lambert, Ian M. Waxman, and Hans J. Hammers

Robert J. Motzer, Memorial Sloan-Kettering Cancer Center, New York; Saby George, Roswell Park Cancer Institute, Buffalo, NY; Brian I. Rini, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; David F. McDermott, Beth Israel Deaconess Medical Center, Dana-Farber/Harvard Cancer Center, Boston, MA; Bruce G. Redman

Randomized Phase II of Nivolumab in RCC
BEST RESPONSE FOR ALL DOSE LEVELS

Response	Num (%)
Complete response	2/168 (1.2%)
Partial Response	33/168 (20%)
Stable Disease	69/168 (41%)
Progressive Disease	49/168 (35%)
Not Evaluable	5/168 (3%)

Motzer *et al*. JCO



Motzer *et al*. JCO

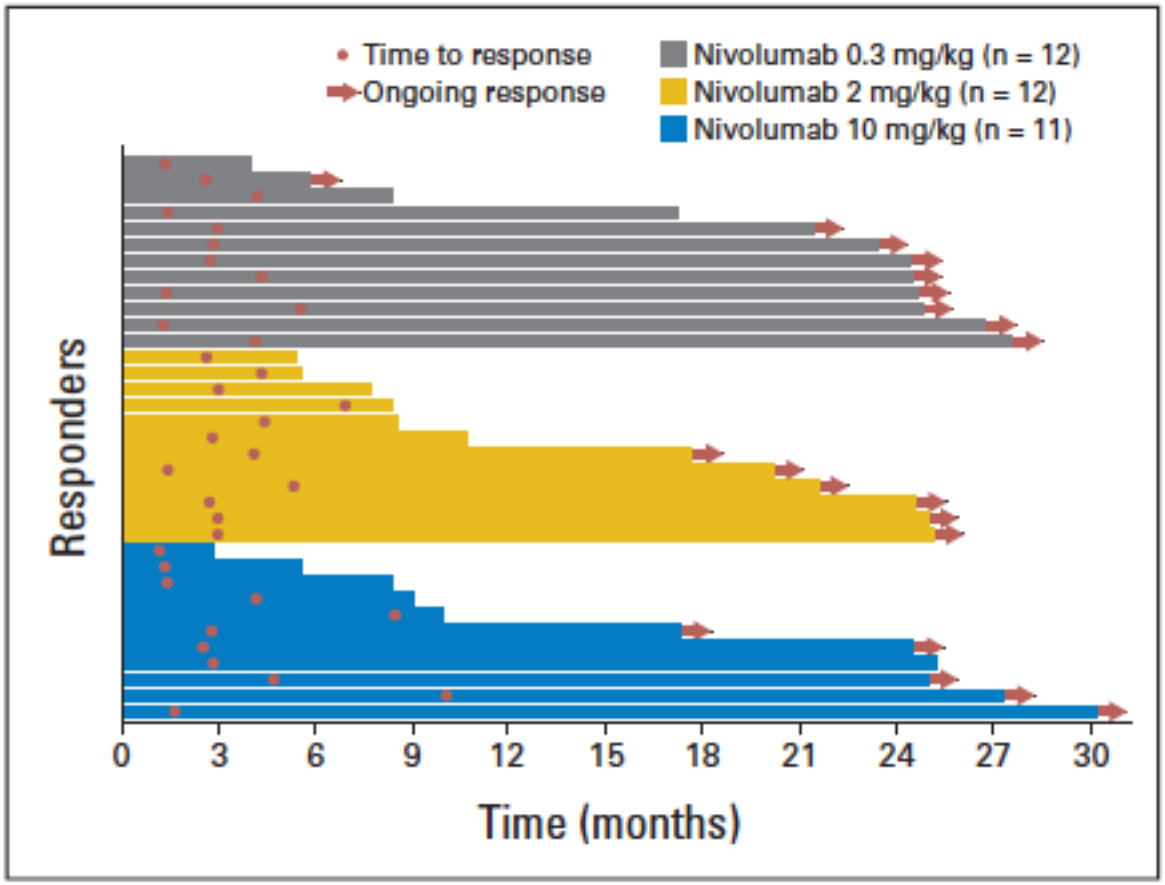


Fig 3. Duration of response in patients who achieved objective response by dose treatment arm. Based on data cutoff date of March 5, 2014.

Motzer *et al*. JCO

ClinicalTrials.gov

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Trial record **1 of 2** for: nivolumab RCC everolimus

Previous Study | Return to List | Next Study

Study of Nivolumab (BMS-936558) vs. Everolimus in Pre-Treated Advanced or Metastatic Clear-cell Renal Cell Carcinoma (CheckMate 025)

July 20, 2015 Press Release: "An open-label, randomized Phase III study evaluating nivolumab versus everolimus in previously-treated patients with advanced or metastatic renal cell carcinoma (RCC) was stopped early because an assessment conducted by the independent Data Monitoring Committee (DMC) concluded that the study met its endpoint, demonstrating ***superior overall survival in patients receiving [nivolumab] compared to the control arm***.

PD-1 inhibition in RCC: How much of a “tail” are we going to see on the survival and progression-free survival curves?

Will it compare to HD IL-2 in similar populations?

Poster #: 4516

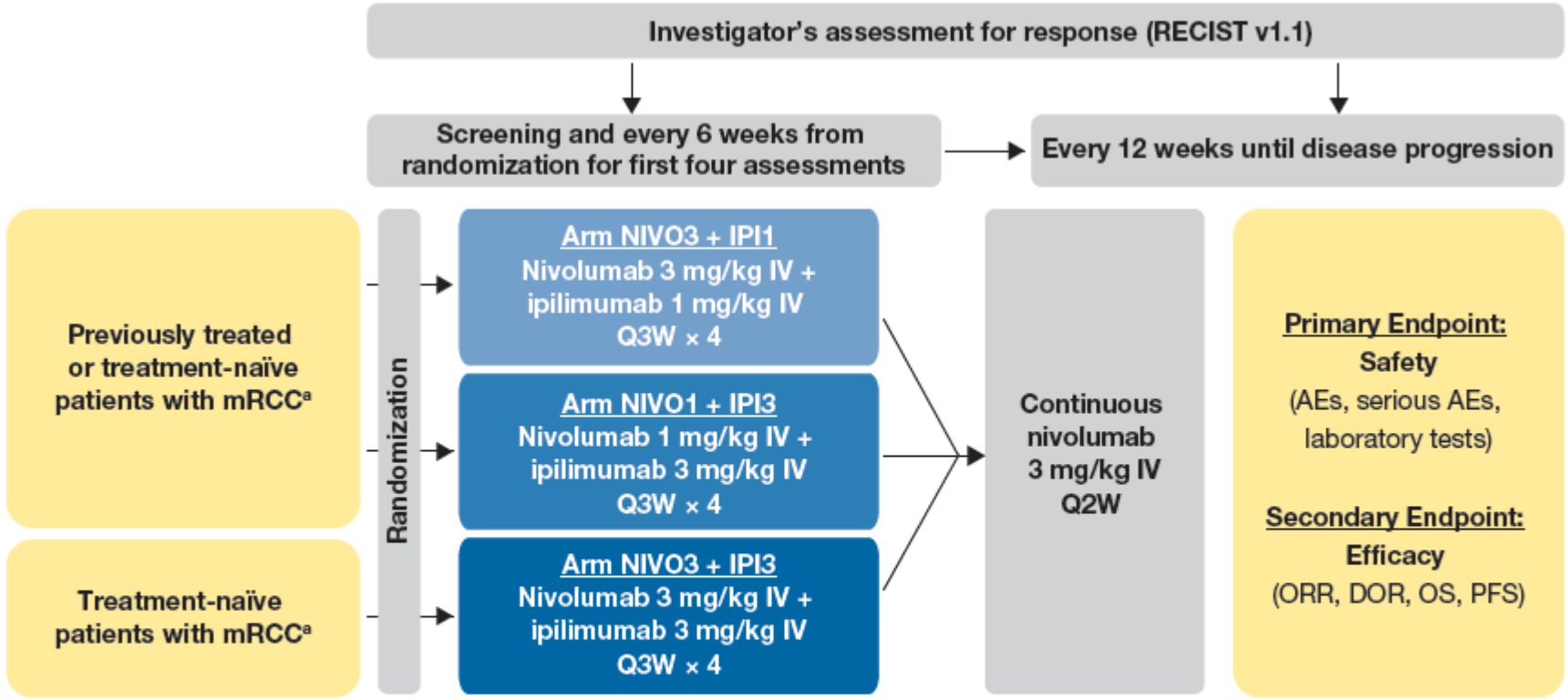
Expanded Cohort Results From CheckMate 016: A Phase I Study of Nivolumab in Combination With Ipilimumab in Metastatic Renal Cell Carcinoma (mRCC)

Hans J. Hammers,[1] Elizabeth R. Plimack,[2] Jeffrey R. Infante,[3] Brian I. Rini,[4] David F. McDermott,[5] Marc S. Ernstoff,[4] Martin H. Voss,[6] Padmanee Sharma,[7] Sumanta K. Pal,[8] Albiruni Razak,[9] Christian Kollmannsberger,[10] Daniel Y.C. Heng,[11] Jennifer Spratlin,[12] Yun Shen,[13] Paul Gagnier,[13] Asim Amin[14]

[1]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; [2]Fox Chase Cancer Center, Philadelphia, PA, USA; [3]Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN, USA; [4]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [5]Beth Israel Deaconess Medical Center, Dana-Farber/Harvard Cancer Center, Boston, MA, USA; [6]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [7]MD Anderson Cancer Center, University of Texas, Houston, TX, USA; [8]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [9]Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada; [10]British Columbia Cancer Agency, Vancouver, British Columbia, Canada; [11]Tom Baker Cancer Center, University of Calgary, Calgary, Alberta, Canada; [12]Cross Cancer Institute, University of Alberta, Edmonton, Alberta, Canada; [13]Bristol-Myers Squibb, Princeton, NJ, USA; [14]Levine Cancer Institute, Charlotte, NC, USA

Email: hhammer2@jhmi.edu

Methods
Figure 1. Study design

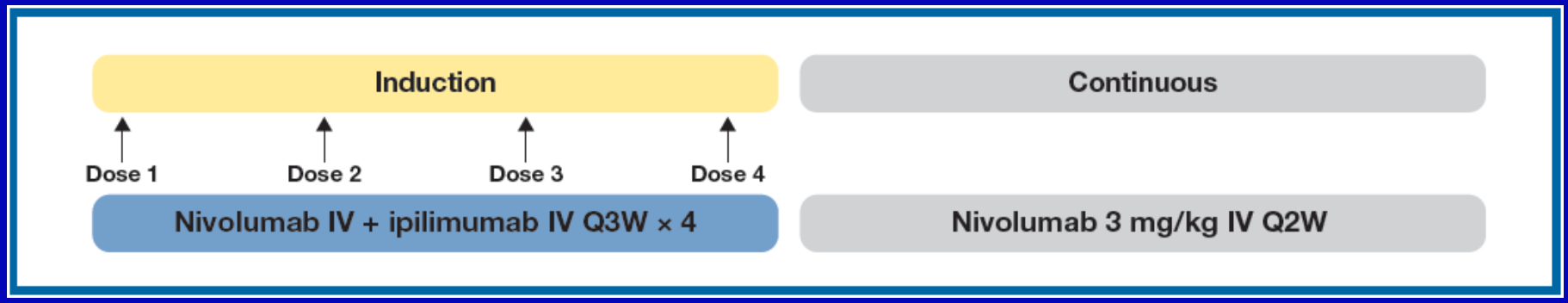


[a]For expansion cohorts NIVO3 + IPI1 and NIVO1 + IPI3 and for NIVO3 + IPI3, one prior adjuvant or neoadjuvant therapy for localized or locally advanced RCC is allowed provided recurrence occurred ≥6 months after the last dose of the adjuvant or neoadjuvant therapy. Interferon alpha or interleukin-2 (IL-2) as prior therapy is allowed

AE = adverse event; DOR = duration of response; IPI1 = ipilimumab 1 mg/kg; IPI3 = ipilimumab 3 mg/kg; IV = intravenous; NIVO1 = nivolumab 1 mg/kg; NIVO3 = nivolumab 3 mg/kg; ORR = objective response rate; PFS = progression-free survival; Q2W = every 2 weeks; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors

Methods
Figure 2. Dosing schedule

- At induction visits, patients received two infusions. The first infusion was always nivolumab (1 or 3 mg/kg), and the second was always ipilimumab, which was started ≥30 minutes after completion of the nivolumab infusion (Figure 2)



Results
Safety

- Treatment-related AEs are presented in Table 4
- Treatment in the nivolumab 3 + ipilimumab 3 arm was stopped due to toxicity
- No grade 5 treatment-related AEs were observed in any treatment arm

Results: Table 4. Treatment-related AEs[a] (≥20% of patients)

	NIVO3 + IPI1		NIVO1 + IPI3		NIVO3 + IPI3	
	N = 47		N = 47		N = 6	
Preferred term, n (%)	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Total patients with an event	39 (83.0)	16 (34.0)	44 (93.6)	30 (63.8)	6 (100.0)	5 (83.3)
Fatigue	23 (48.9)	0	30 (63.8)	3 (6.4)	6 (100.0)	0
Rash	12 (25.5)	0	10 (21.3)	0	3 (50.0)	0
Pruritus	12 (25.5)	0	13 (27.7)	0	2 (33.3)	0
Nausea	11 (23.4)	0	20 (42.6)	0	3 (50.0)	0
Diarrhea	11 (23.4)	1 (2.1)	20 (42.6)	7 (14.9)	2 (33.3)	1 (16.7)
Chills	10 (21.3)	0	4 (8.5)	0	3 (50.0)	0
Hypothyroidism	9 (19.1)	0	13 (27.7)	0	5 (83.3)	0
Pyrexia	9 (19.1)	2 (4.3)	7 (14.9)	0	4 (66.7)	1 (16.7)
Arthralgia	9 (19.1)	0	10 (21.3)	0	3 (50.0)	0
Increased lipase	8 (17.0)	6 (12.8)	16 (34.0)	12 (25.5)	2 (33.3)	2 (33.3)
Myalgia	7 (14.9)	0	9 (19.1)	1 (2.1)	3 (50.0)	0
Headache	6 (12.8)	0	9 (19.1)	1 (2.1)	4 (66.7)	2 (33.3)
Increased alanine aminotransferase (ALT)	6 (12.8)	2 (4.3)	13 (27.7)	9 (19.1)	3 (50.0)	0
Increased aspartate aminotransferase (AST)	5 (10.6)	2 (4.3)	13 (27.7)	4 (8.5)	3 (50.0)	0
Decreased appetite	5 (10.6)	0	14 (29.8)	0	3 (50.0)	0
Hyperhidrosis	4 (8.5)	0	0	0	3 (50.0)	0
Increased blood creatinine	4 (8.5)	0	6 (12.8)	0	2 (33.3)	0
Dyspnea	4 (8.5)	0	4 (8.5)	0	2 (33.3)	0
Hyperthyroidism	3 (6.4)	1 (2.1)	8 (17.0)	0	3 (50.0)	0

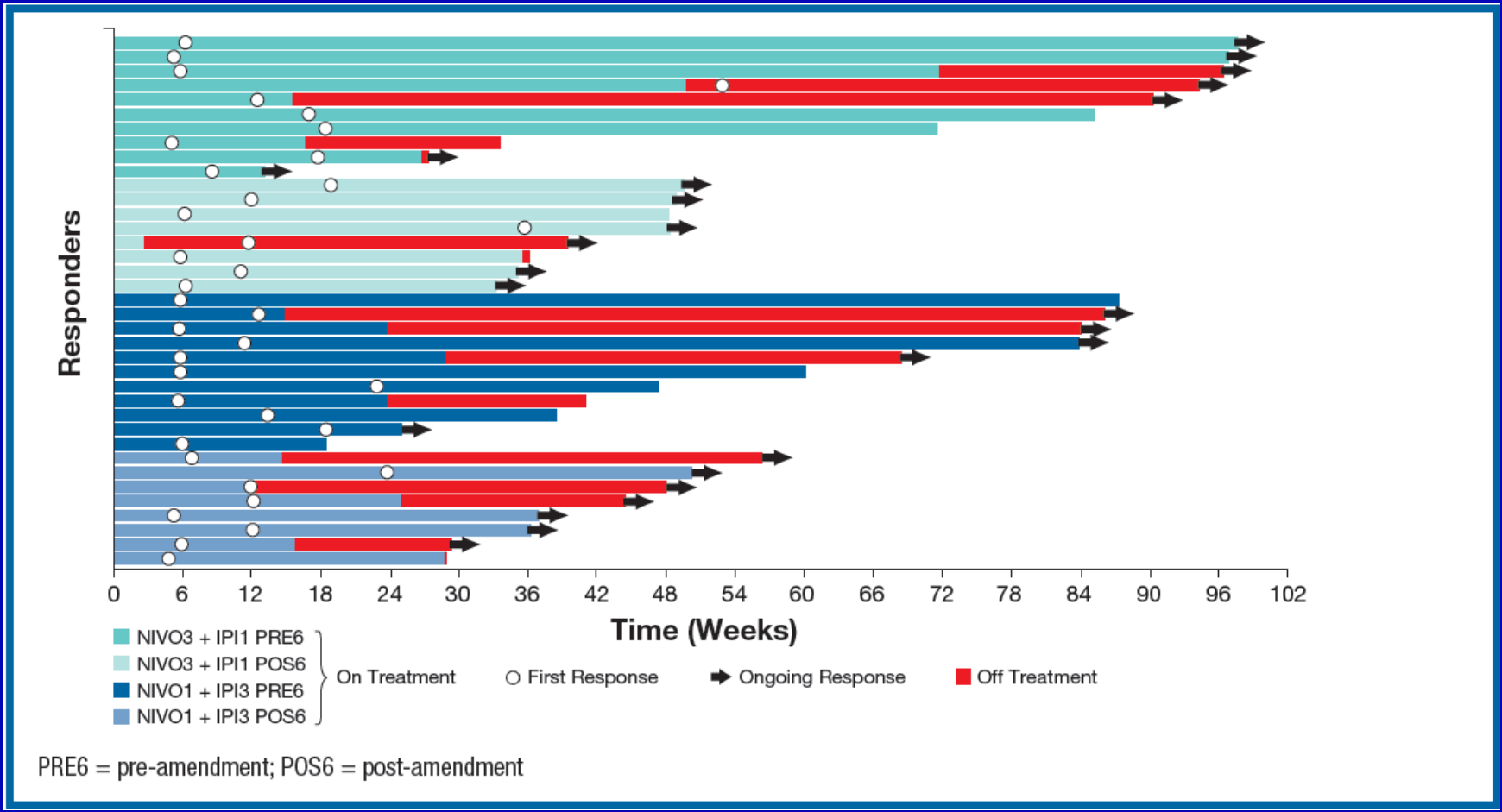
Results: Efficacy
Table 6. Antitumor activity

- **ORR and best overall response are shown in Table 6**

	NIVO3 + IPI1	NIVO1 + IPI3	NIVO3 + IPI3
	N = 47	N =47	N = 6
Confirmed ORR[a], n (%) 95% CI	18 (38.3) 24.5–53.6	19 (40.4) 26.4–55.7	0
Best overall response[b], n (%) Complete response Partial response Stable disease Progressive disease	 4 (8.5) 14 (29.8) 17 (36.2) 10 (21.3)	 1 (2.1) 18 (38.3) 17 (36.2) 7 (14.9)	 0 0 5 (83.3) 1 (16.7)

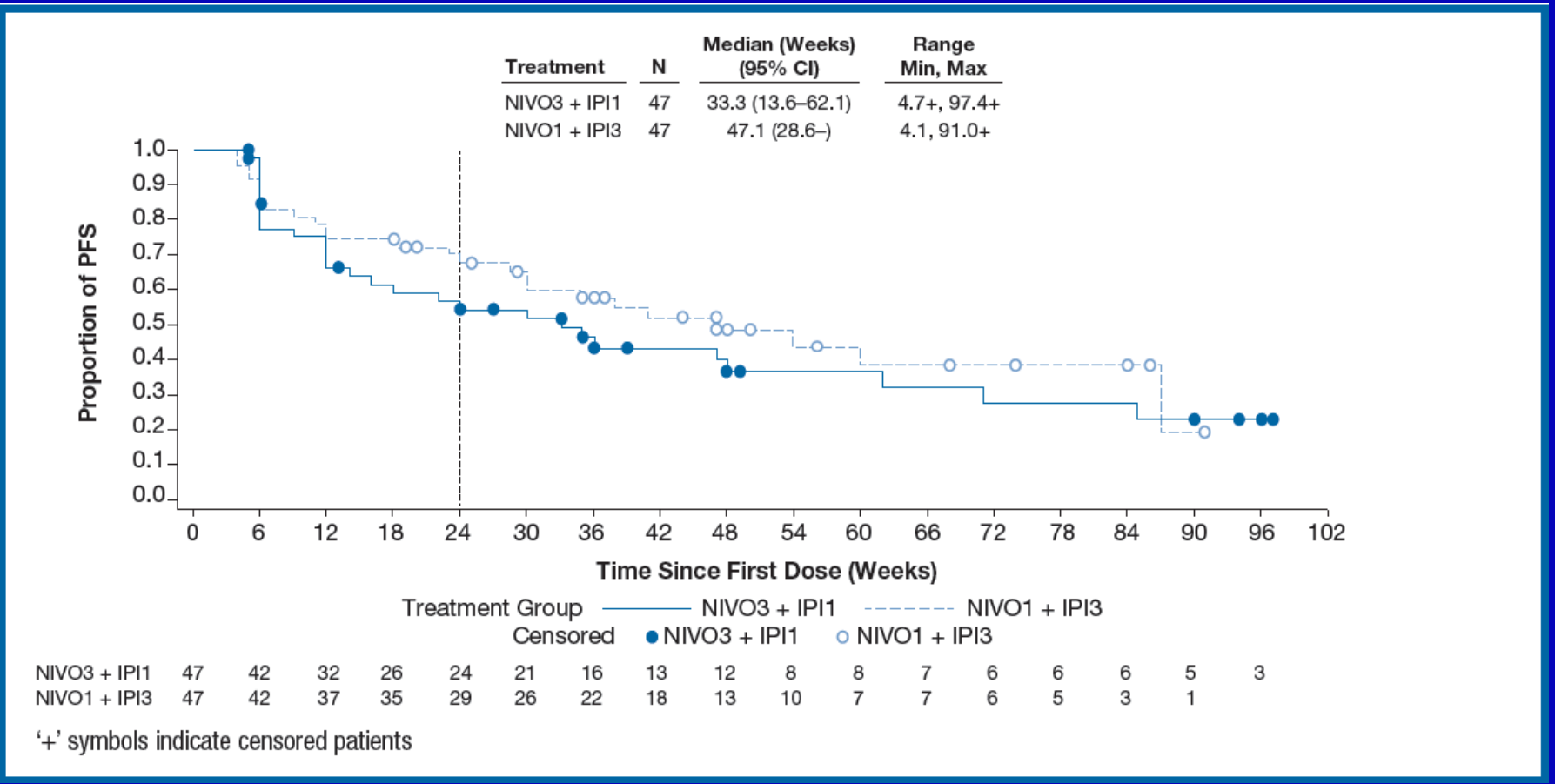
[a]Confirmed response only; [b]No unconfirmed complete responses were reported in either arm; unconfirmed partial responses were reported in one patient (2.1%) in the NIVO3 + IPI1 arm and in two patients (4.3%) in the NIVO1 + IPI3 arm. Best overall response was not determinable in one patient (2.1%) in the NIVO3 + IPI1 arm and in two patients (4.3%) in the NIVO1 + IPI3 arm.

Results: Figure 3. Time to and duration of response



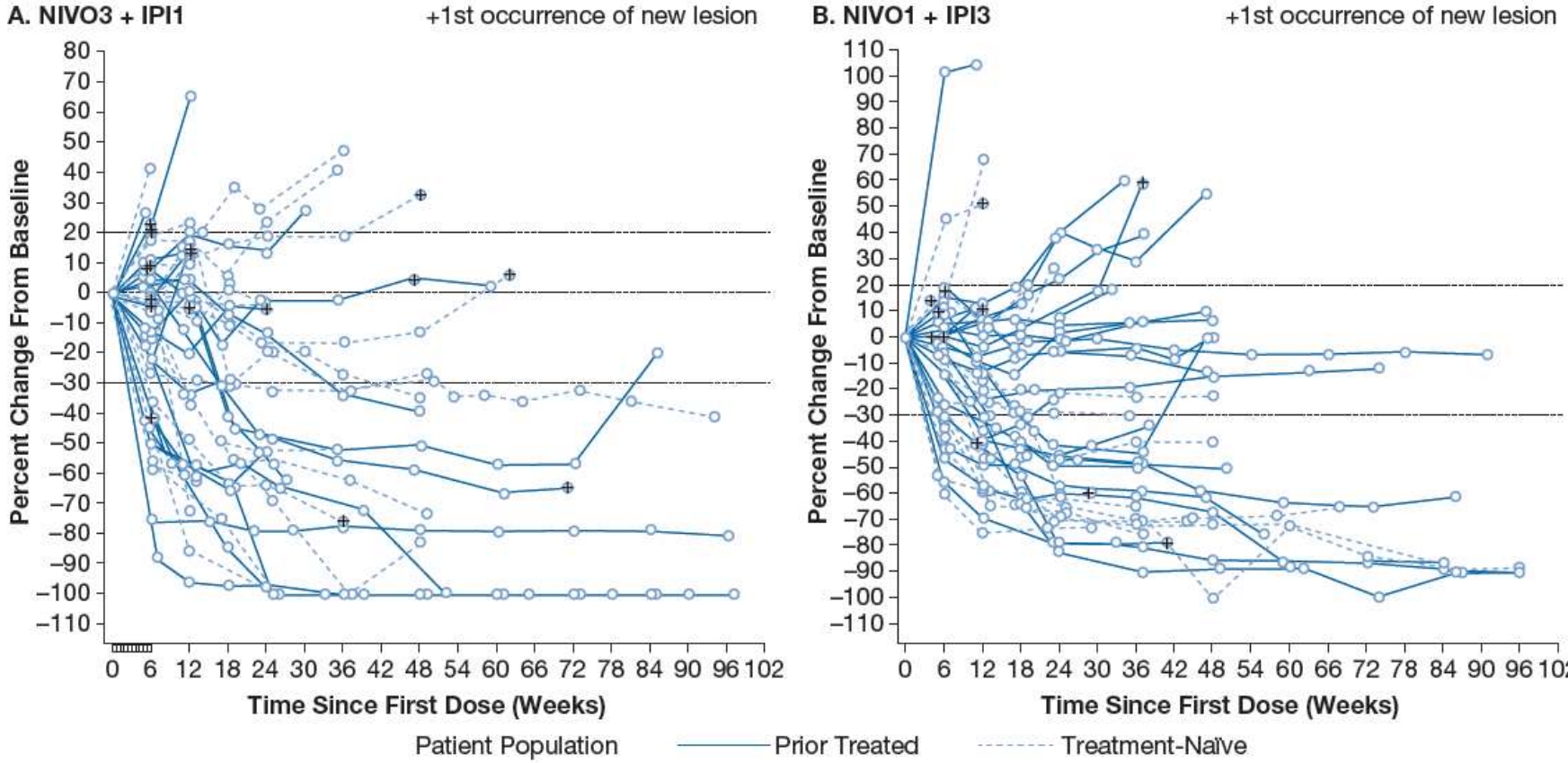
Results
Figure 4. Progression-free survival

- **The PFS rate (95% CI) at 24 weeks was 54% (39–68) in the nivolumab 3 + ipilimumab 1 arm (N = 47) and 68% (52–79) in the nivolumab 1 + ipilimumab 3 arm (N = 47) (Figure 4)**



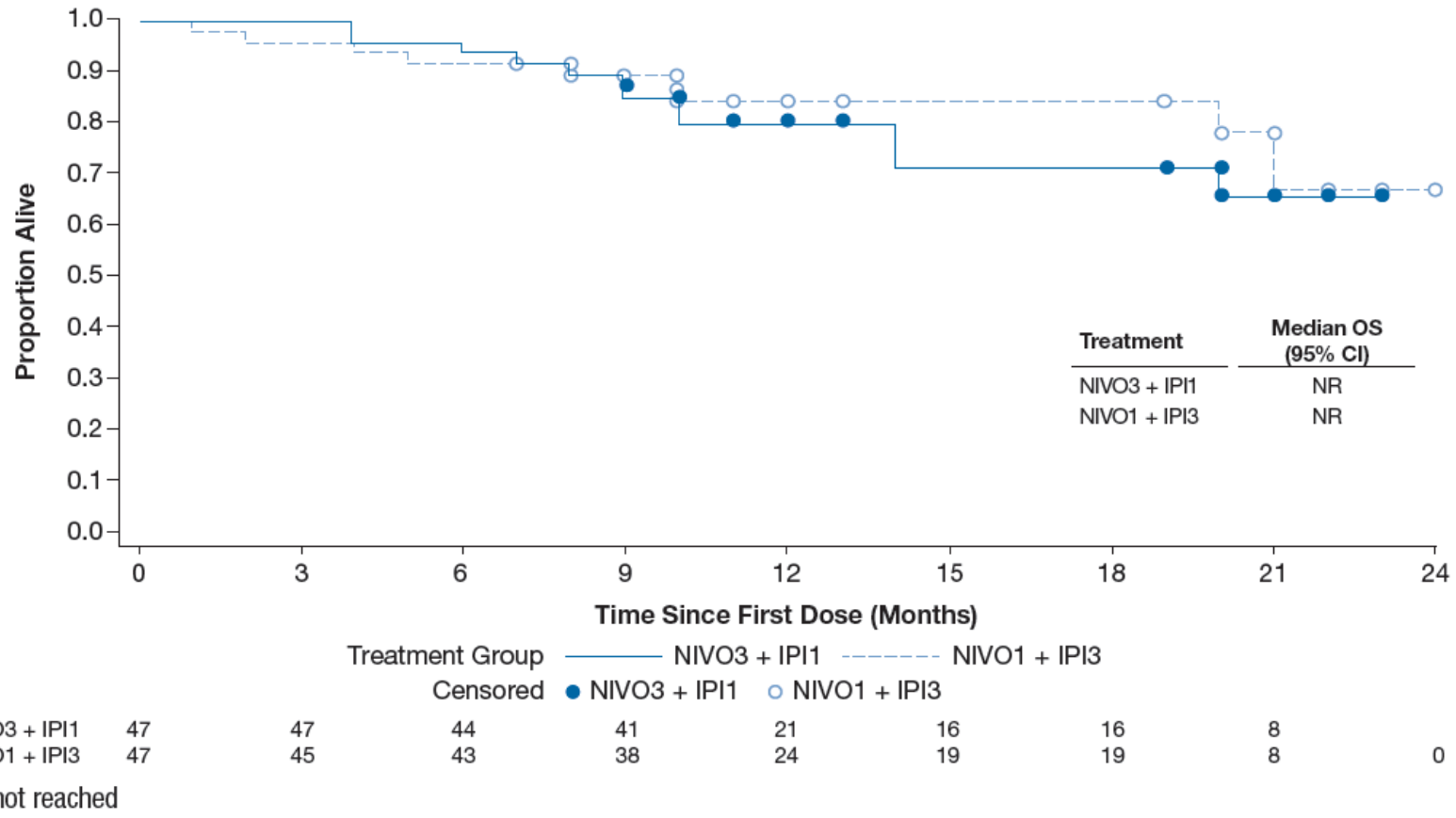
Results
Figure 5. Tumor burden

- Figures 5A and 5B show changes in tumor burden over time in the nivolumab 3 + ipilimumab 1 and nivolumab 1 + ipilimumab 3 arms



Results
Figure 6. Overall survival

- Median OS was not reached in either the nivolumab 3 + ipilimumab 1 arm or in the nivolumab 1 + ipilimumab 3 arm (Figure 6)



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Home > Find Studies > Search Results > Study Record Detail Text Size

Trial record **3 of 3** for: ipilimumab nivolumab RCC

Previous Study | Return to List | Next Study

Nivolumab Combined With Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma (CheckMate 214)

This study is currently recruiting participants. (see Contacts and Locations)

Verified May 2015 by Bristol-Myers Squibb

Sponsor:
Bristol-Myers Squibb

Collaborator:
Ono Pharmaceutical Co. Ltd

Information provided by (Responsible Party):
Bristol-Myers Squibb

ClinicalTrials.gov Identifier:
NCT02231749

First received: September 1, 2014
Last updated: July 17, 2015
Last verified: May 2015
History of Changes

Nivo 3 mg/kg; Ipi 1 mg/kg x4 then Nivo

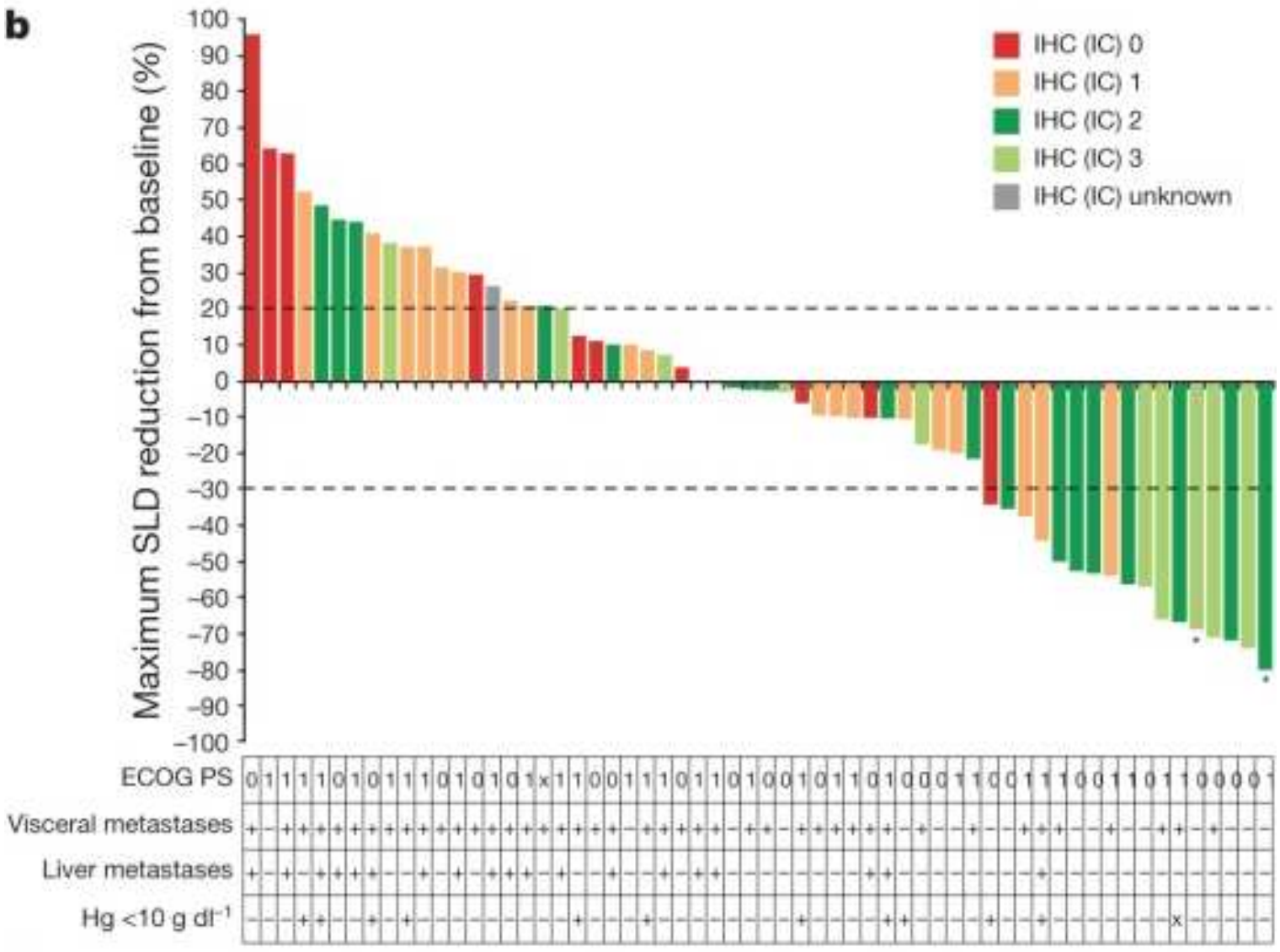
Primary Outcomes:

1. Progression-free survival
2. Overall survival

BLADDER CANCER

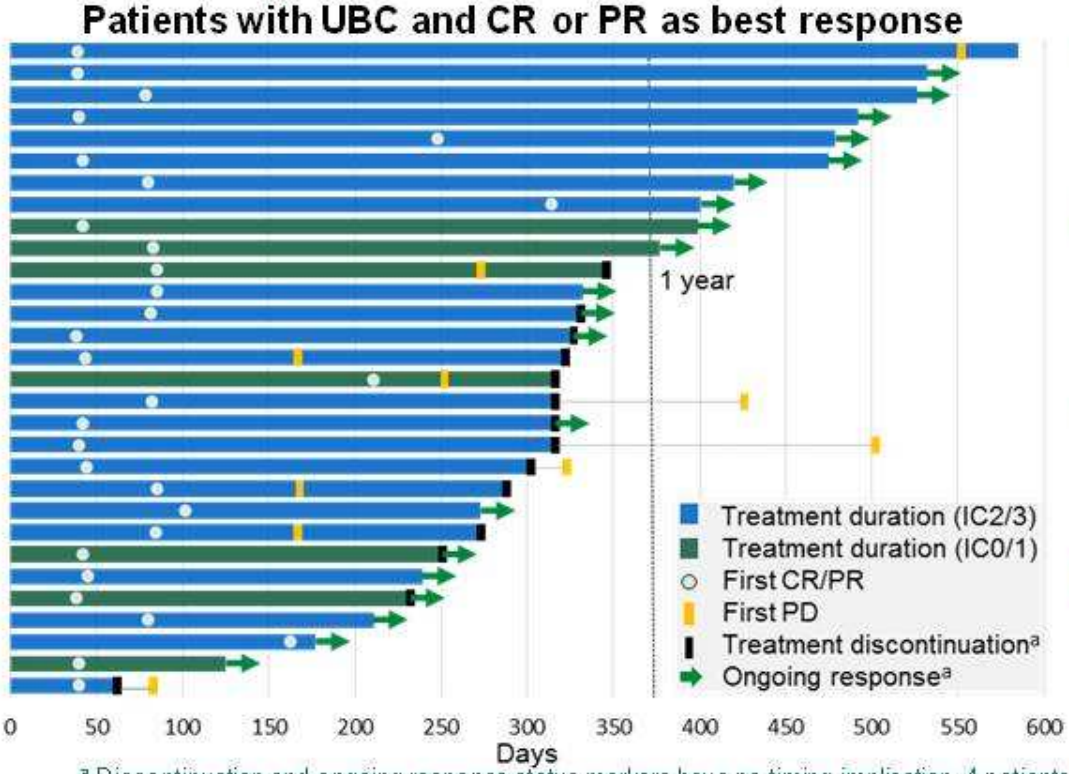
- Intravesical BCG has a role in high-risk non-muscle-invasive disease, with or without intereferon
- Advanced/Metastatic disease is aggressive, with median survival about 1-2 years. Some responsive to platinum-based chemotherapy
- Targeted agents largely disappointing. Unmet need for further therapy

MPDL3280A anti-tumour activity in patients with UBC.



T Powles *et al. Nature* **515**, 558-562 (2014) doi:10.1038/nature13904; Used with permission

Atezolizumab (MPDL3280A): Duration of Treatment and Response in UBC



- Median duration of response has not yet been reached in either IC group (range, 0+ to 43 mo)
- Median time to response was 62 days
  - IC2/3 patients: range, 1+ to 10+ mo
  - IC0/1 patients: range, 1+ to 7+ mo
- 20 of 30 responding patients had ongoing responses at the time of data cutoff
- 10 patients have been treated for over 1 year, including 3 retreated following protocol amendment

[a] Discontinuation and ongoing response status markers have no timing implication. 4 patients discontinued treatment after cycle 16 prior to 1 year per original protocol. Responses plotted are investigator assessed and have not all been confirmed by the data cutoff (Dec 2, 2014).

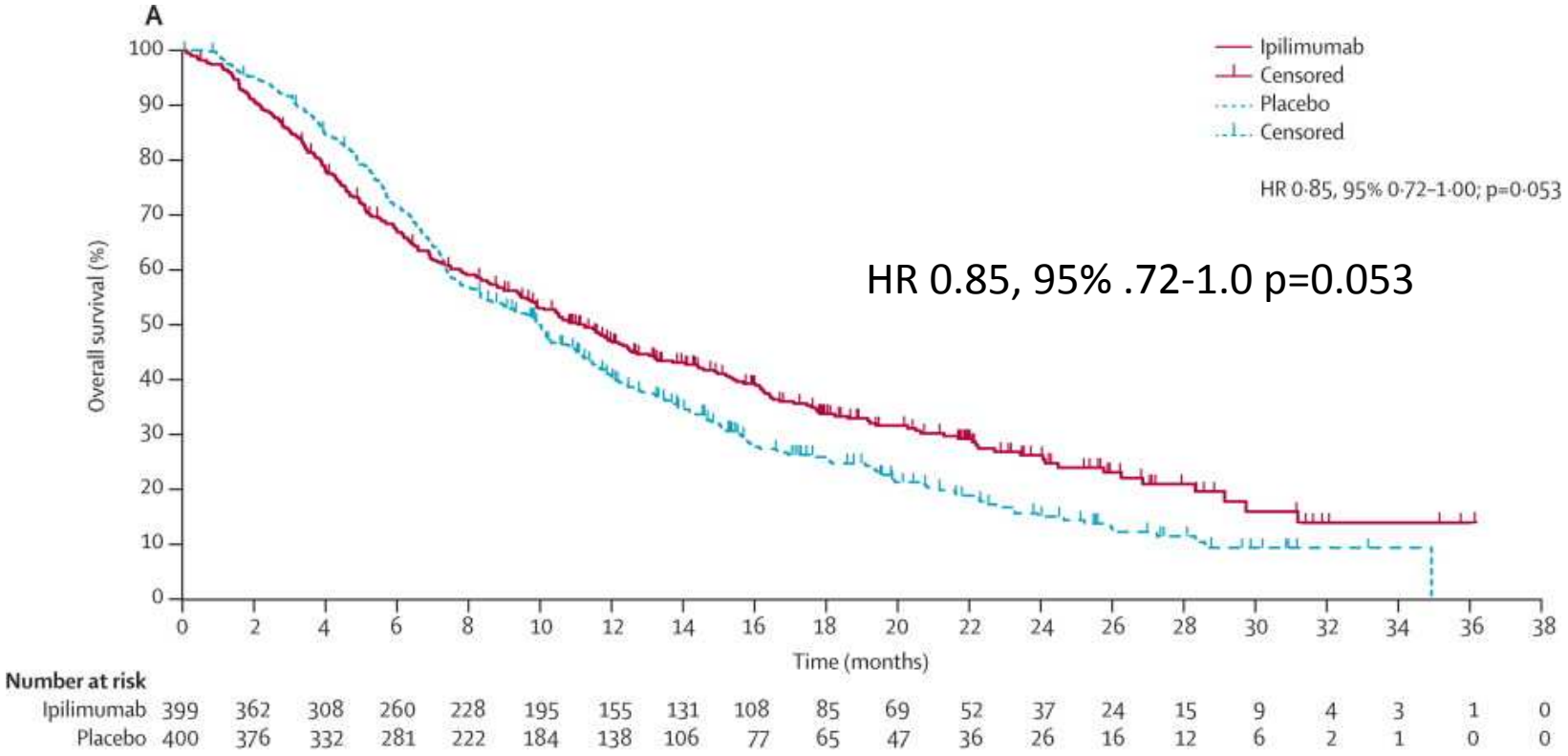
Presented By Daniel Petrylak at 2015 ASCO Annual Meeting

What about prostate cancer??

Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial

*Eugene D Kwon, Charles G Drake, Howard I Scher, Karim Fizazi, Alberto Bossi, Alfons J M van den Eertwegh, Michael Krainer, Nadine Houede, Ricardo Santos, Hakim Mahammedi, Siobhan Ng, Michele Maio, Fabio A Franke, Santhanam Sundar, Neeraj Agarwal, Andries M Bergman, Tudor E Ciuleanu, Ernesto Korbenfeld, Lisa Sengelev, Steinbjorn Hansen, Christopher Logothetis, Tomasz M Beer, M Brent McHenry, Paul Gagnier, David Liu, Winald R Gerritsen, for the CA184-043 Investigators**

Overall survival



HR 0.85, 95% .72-1.0 p=0.053

Median overall survival was 11·2 months (95% CI 9·5–12·7) for ipilimumab and 10·0 months (95% CI 8·3–11·0) for placebo

ED **Kwon** , CG Drake , HI Scher , K Fizazi , A Bossi , AJ M van den Eertwegh.

Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial

The Lancet Oncology, Volume 15, Issue 7, 2014, 700 - 712

http://dx.doi.org/10.1016/S1470-2045(14)70189-5

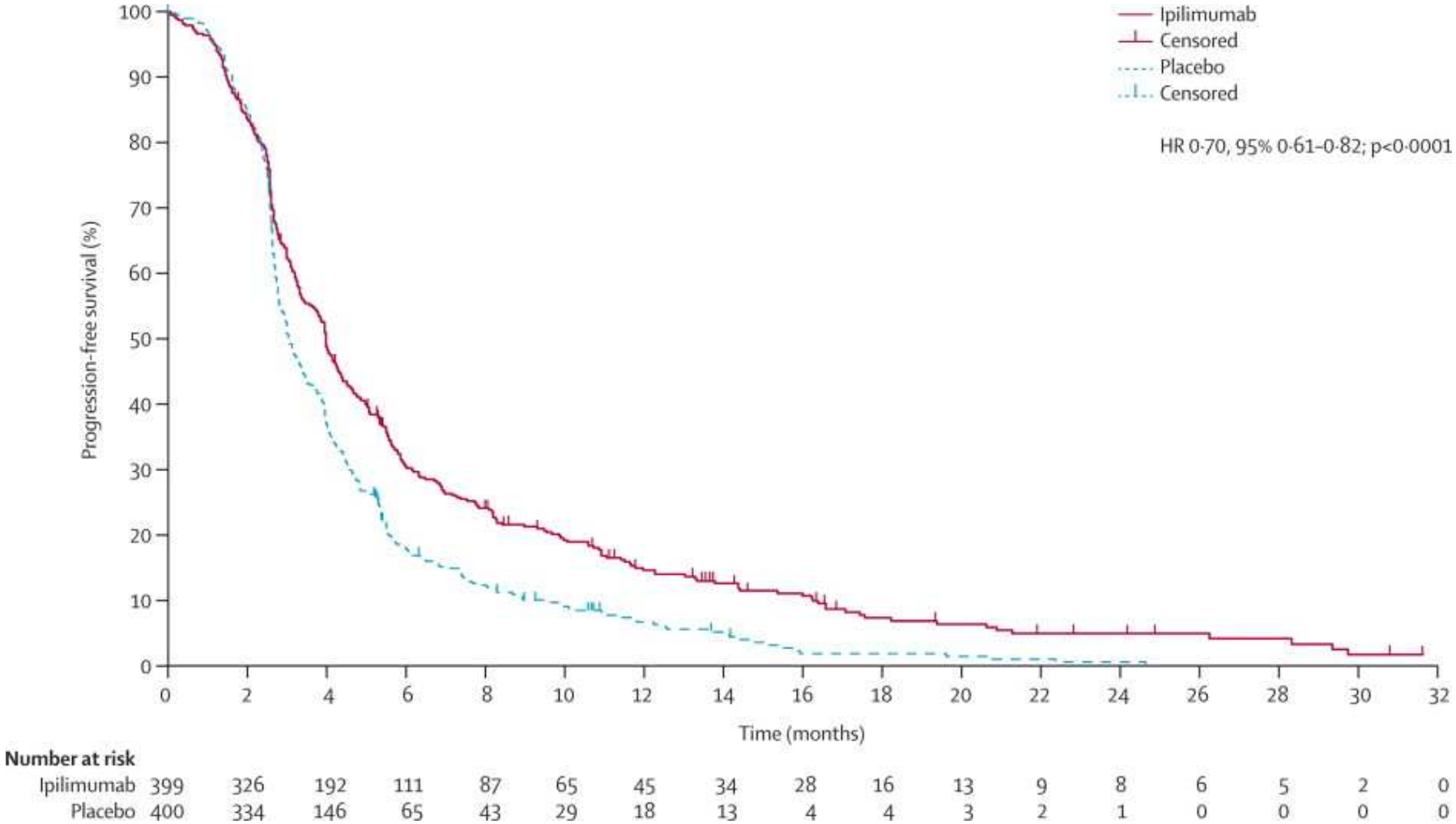


Figure 4 Progression-free survival in the intention-to-treat population

Eugene D Kwon , Charles G Drake , Howard I Scher , Karim Fizazi , Alberto Bossi , Alfons J M van den Eertwegh , Mi...

Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial

The Lancet Oncology, Volume 15, Issue 7, 2014, 700 - 712

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

Castration-refractory metastatic prostate cancer: Zero out of 17 patients responded

The NEW ENGLAND JOURNAL of MEDICINE

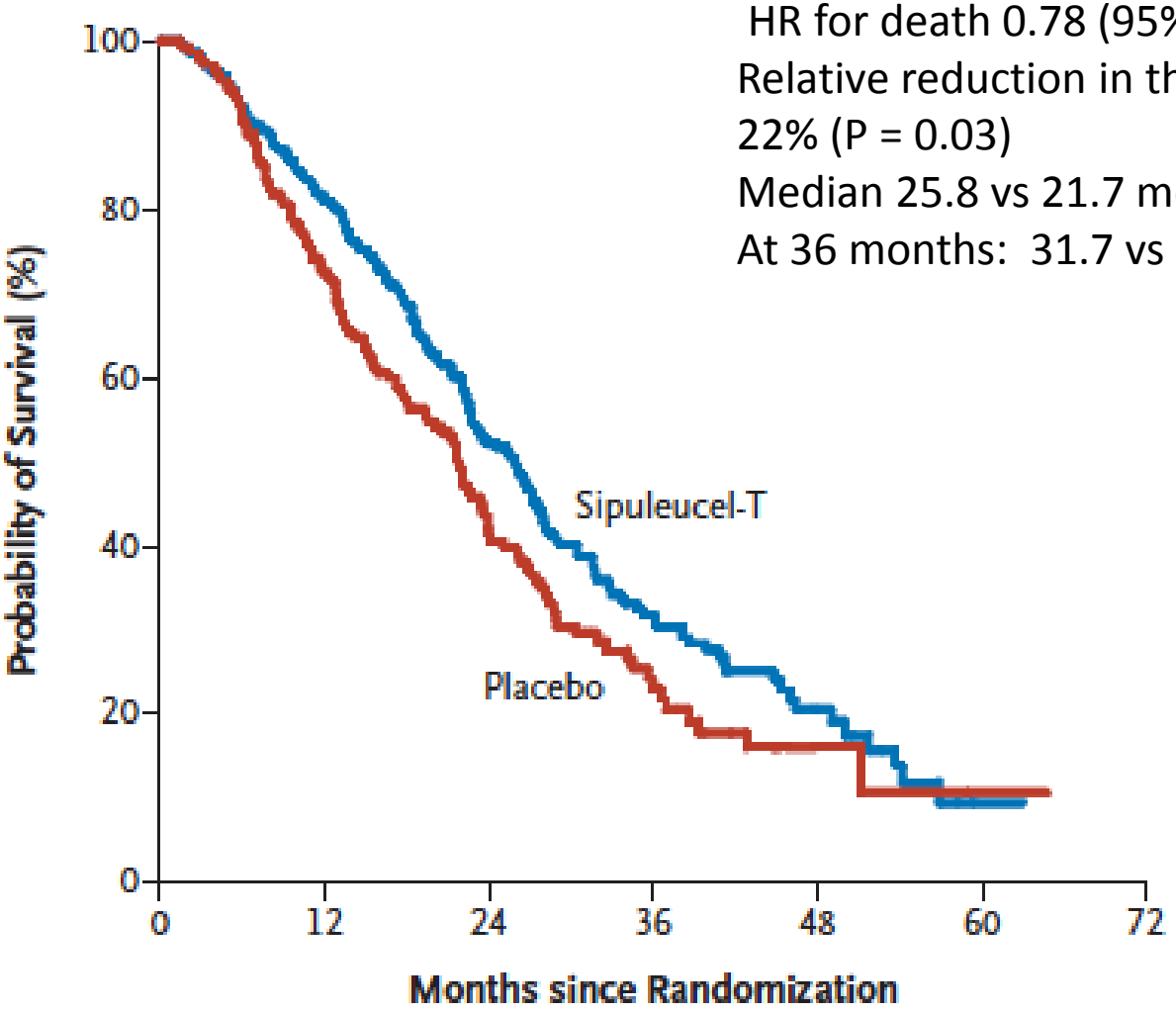
ESTABLISHED IN 1812 JULY 29, 2010 VOL. 363 NO. 5

Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer

Philip W. Kantoff, M.D., Celestia S. Higano, M.D., Neal D. Shore, M.D., E. Roy Berger, M.D., Eric J. Small, M.D., David F. Penson, M.D., Charles H. Redfern, M.D., Anna C. Ferrari, M.D., Robert Dreicer, M.D., Robert B. Sims, M.D., Yi Xu, Ph.D., Mark W. Frohlich, M.D., and Paul F. Schellhammer, M.D., for the IMPACT Study Investigators*

Prostatic acid phosphatase---GM-CSF Fusion protein loaded onto autologous DCs
512 subjects randomized 2:1 sipuleucel-T vs placebo
3 pheresis/infusions q2 weeks

Primary Efficacy



No. at Risk						
Sipuleucel-T	341	274	129	49	14	1
Placebo	171	123	55	19	4	1

HR for death 0.78 (95% CI, 0.61 to 0.98),
Relative reduction in the risk of death of 22% (P = 0.03)
Median 25.8 vs 21.7 months
At 36 months: 31.7 vs 23% surviving

Kantoff *et al.* NEJM

Kantoff et al. NEJM

- No difference in time to radiographic or clinical progression
- PSA response: 2.6 vs. 1.3%

VOLUME 28 · NUMBER 7 · MARCH 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Overall Survival Analysis of a Phase II Randomized Controlled Trial of a Poxviral-Based PSA-Targeted Immunotherapy in Metastatic Castration-Resistant Prostate Cancer

Philip W. Kantoff, Thomas J. Schuetz, Brent A. Blumenstein, L. Michael Glode, David L. Bilhartz, Michael Wyand, Kelledy Manson, Dennis L. Panicali, Reiner Laus, Jeffrey Schlom, William L. Dahut, Philip M. Arlen, James L. Gulley, and Wayne R. Godfrey

From the Dana-Farber Cancer Institute, Harvard Medical School, Boston; Theron Biologics, Cambridge, MA; Trial

See accompanying editorial on page 1085

Randomized Phase II: 82 vs 40 patients.

Poxvirus encoding PSA plus B7.1, ICAM and LFA-3 costimulatory molecules

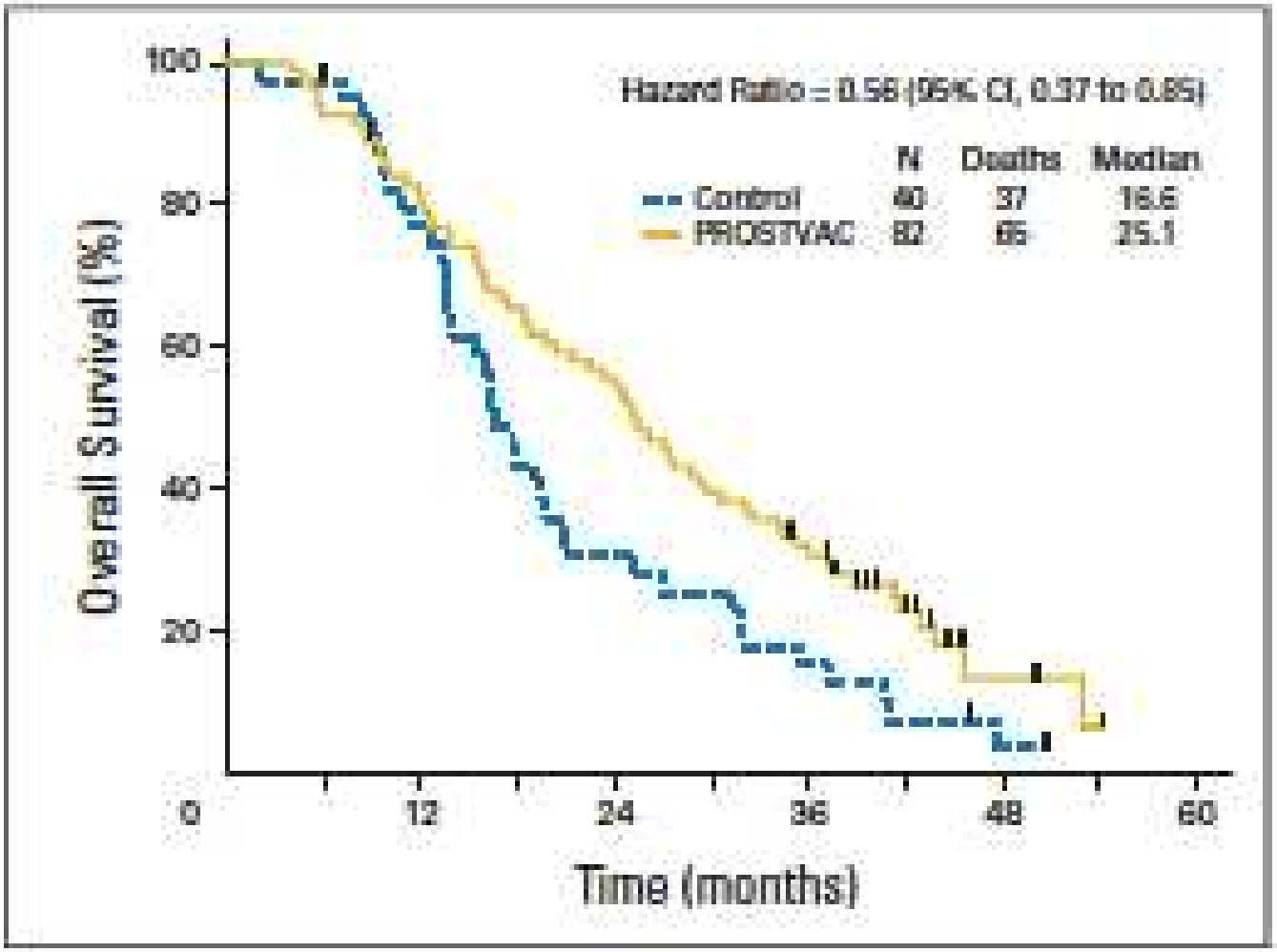


Fig 4. Overall survival. Kaplan-Meier estimator for PROSTVAC (a vaccine containing two recombinant viral vectors [vaccinia and fowlpox] and three immune co-stimulatory molecules [B7.1, ICAM-1, and LFA3]) arm is shown as a solid gold line and estimator for the control arm is a dashed blue line. The small vertical tic marks show the censoring times. The estimated median overall survival is 25.1 months for the PROSTVAC arm and 16.6 months for the control arm.

CONCLUSIONS

- HD IL-2 is toxic, but may have a role for select patients with metastatic RCC
- PD-1 inhibition has activity in mRCC and TCC
- PD-1/CTLA-4 dual inhibition is highly active in mRCC
- Role of checkpoint inhibition in prostate cancer remains to be defined
- Vaccines have prolonged survival without objective response in prostate cancer.

Future Directions

- Understanding the biology of T cell costimulation and anergy

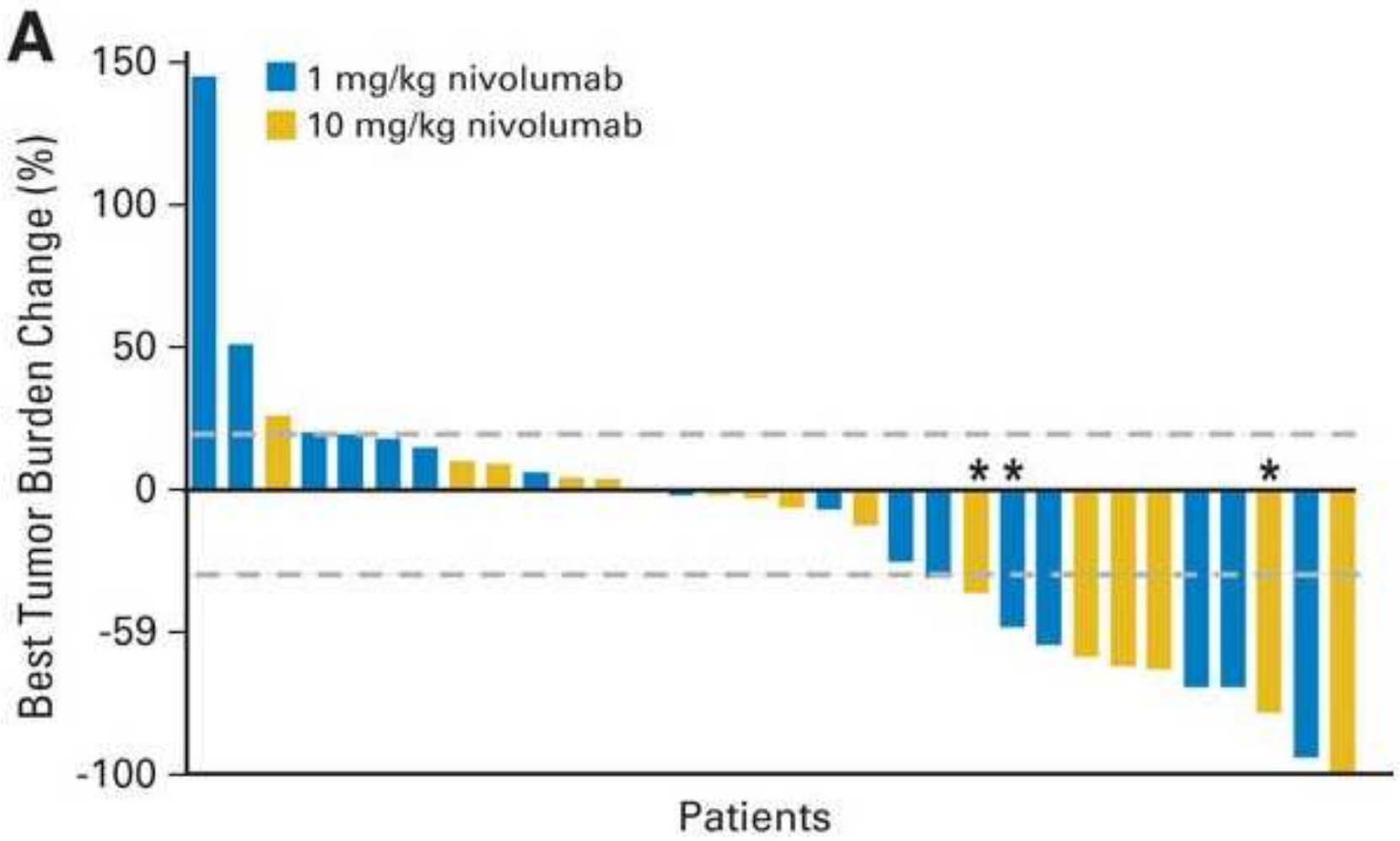
- Combination therapies
  - IL-2 plus checkpoint inhibition
  - PD-1/CTLA-4 blockade for prostate cancer
  - Vaccines/checkpoint inhibitors

- **Identification of tumor antigens**


SPALDING

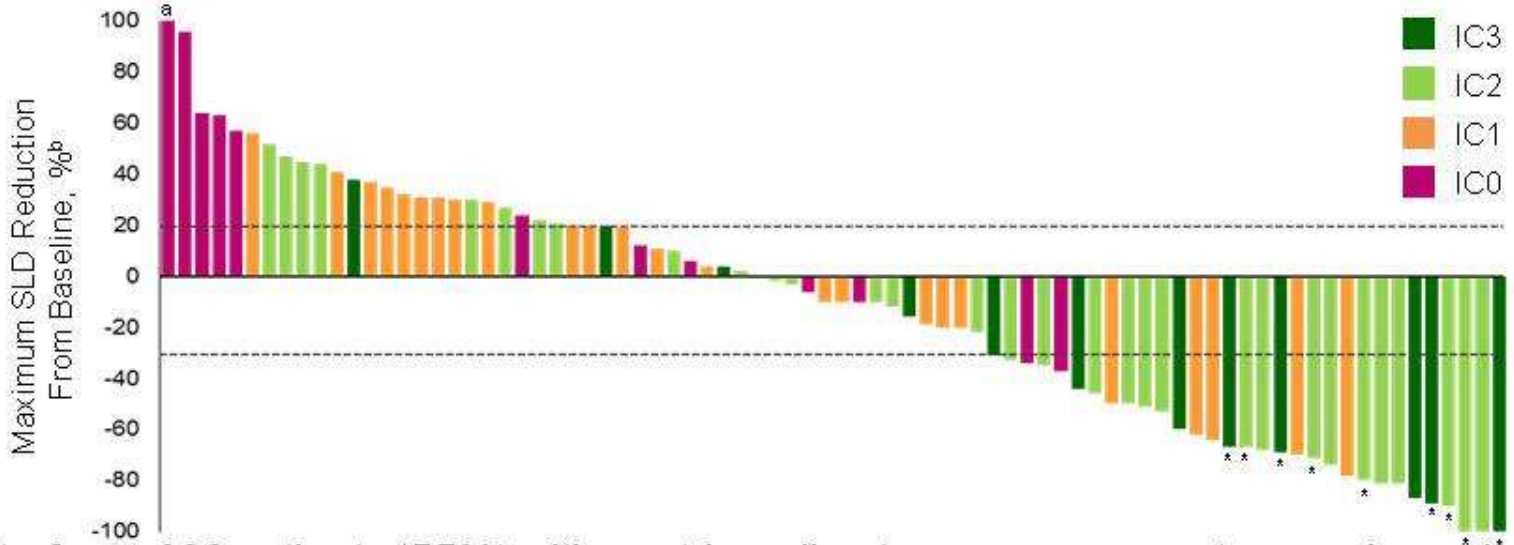
THANK YOU

Characteristics of tumor regression in patients with renal cell carcinoma receiving nivolumab therapy.



David F. McDermott *et al.* JCO 2015;33:2013-2020

Atezolizumab (MPDL3280A): Response in UBC by IC status

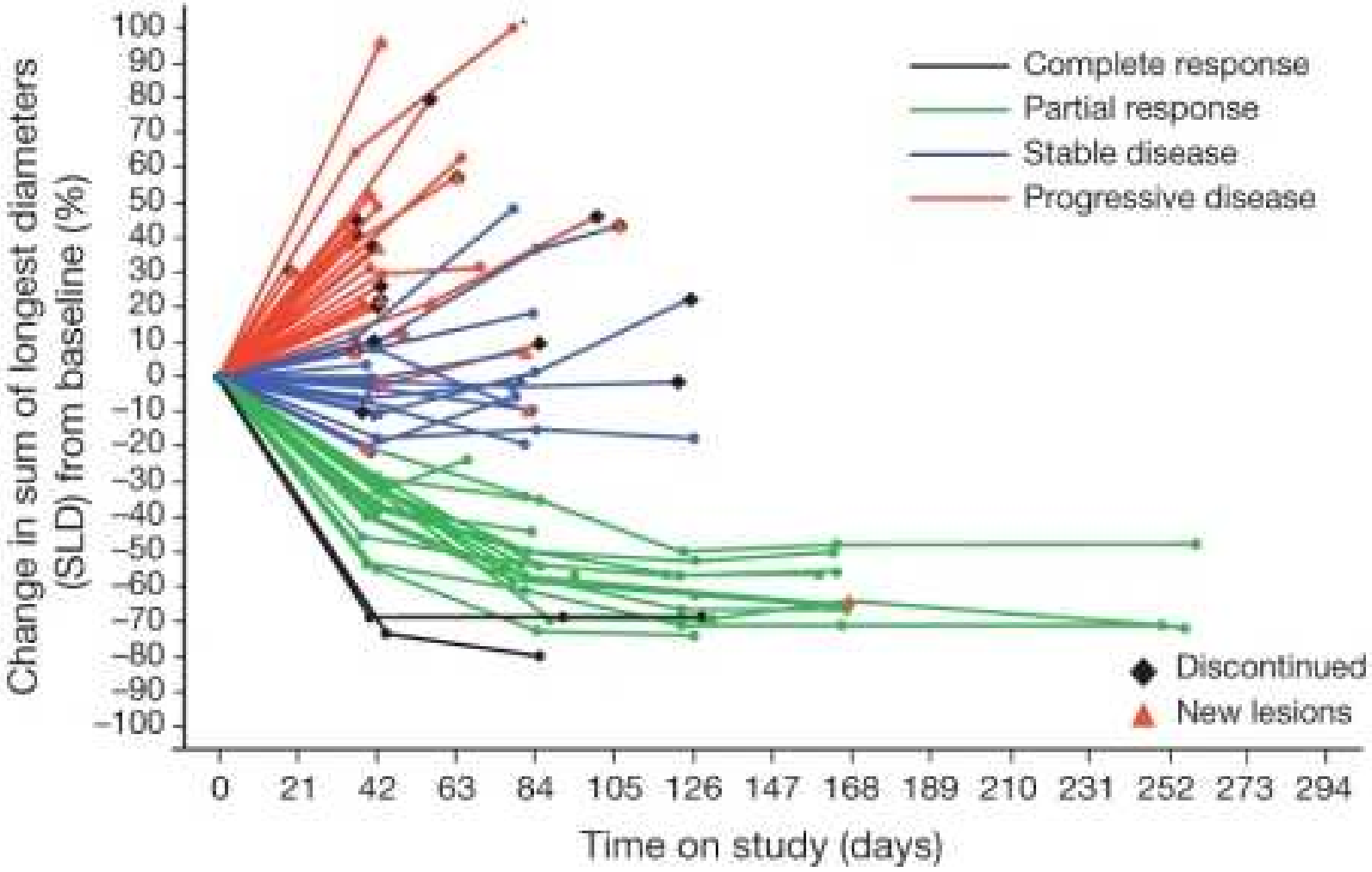


- Forty-four of 80 patients (55%) with post-baseline tumor assessments experienced a reduction in tumor burden
- Decreased circulating inflammatory marker (CRP) and tumor markers (CEA, CA-19-9) were also observed in patients responding to atezolizumab

[a] Change in SLD > 100%. [b] Seven patients without post-baseline tumor assessments not included. Asterisks denote 9 CR patients, 6 of whom have been confirmed by data cutoff date (Dec 2, 2014) and 7 of whom had < 100% reduction due to lymph node target lesions. All lymph nodes returned to normal size per RECIST v1.1.

Presented By Daniel Petrylak at 2015 ASCO Annual Meeting

MPDL3280A anti-tumour activity in patients with UBC.



nature

T Powles *et al. Nature* **515**, 558-562 (2014) doi:10.1038/nature13904; Used with permission