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Immunotherapy for the Treatment of Genitourinary Cancers

Brendan D. Curti, MD

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Disclosures

- Earle A. Chiles Research Institute accepted grants from BMS, MedImmune, Prometheus and Merck to cover costs of clinical trials.
- I am neither employed nor do I have equity interests in any company or entity whose products/drugs will be discussed today.
- Unpaid consultant for BMS, Agonox, Ubivac, Nektar
- Travel: BMS, Agonox, Prometheus, Nektar
- Research Support: NIH (R21CA190790, R21CA176705), Prostate Cancer Foundation, Safeway Foundation, Kuni Foundation, Prometheus Pharmaceuticals, Galectin Therapeutics, Viralytics
- Speakers Bureau: Prometheus
- I will be discussing non-FDA approved treatments during my talk.

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Learning Objectives

- Gain an understanding of the different immunotherapy modalities (cytokines, T-cell checkpoint antibodies and vaccine therapy) used in the treatment of genitourinary malignancy.
- Review recent clinical data targeting PD-1 and PD-L1 in renal, bladder and prostate malignancies.
- Discuss biomarker and immunological monitoring of GU patients treated with immunotherapy.
- Survey areas of active clinical immunotherapy clinical trials in GU malignancy.

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Overview

- Immunotherapy 1.0 (Interleukin-2)
- Immunotherapy 1.1 (Sipuleucel-T)
- Immunotherapy 2.0 (PD-1 therapy)
- Immune monitoring 1.0 and 2.0
- Immunotherapy 2.X (Clinical Trials and Notable Ideas in Development)

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Payne *et al. Journal for ImmunoTherapy of Cancer* 2014, **2**:13
http://www.immunotherapyofcancer.org/content/2/1/13

Journal for ImmunoTherapy of Cancer

RESEARCH ARTICLE Open Access

Durable responses and reversible toxicity of high-dose interleukin-2 treatment of melanoma and renal cancer in a Community Hospital Biotherapy Program

Roxanne Payne[1], Lyn Glenn[1], Helena Hoen[1], Beverley Richards[1], John W Smith II[2], Robert Lufkin[2], Todd S Crocenzi[1], Walter J Urba[1] and Brendan D Curti[1*]

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Major Selection Criteria for IL-2

- Metastatic renal cancer or melanoma
- Normal pulmonary and cardiac function as assessed by PFTs and ETT
- “Relatively” normal renal and hepatic function
- Controlled brain metastases
- No active infection
- No active autoimmune disease requiring steroids (vitiligo and autoimmune hypothyroidism OK)

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IL-2 Treatment

- IL-2 = 600,000 international units per kg IVB x 14 planned doses.
- Manage clinical consequences of immune activation.
- Second cycle given after 2 week break. Scans repeated one month later.
- More IL-2 for lucky responders (up to 3 courses (6 cycles) maximum).

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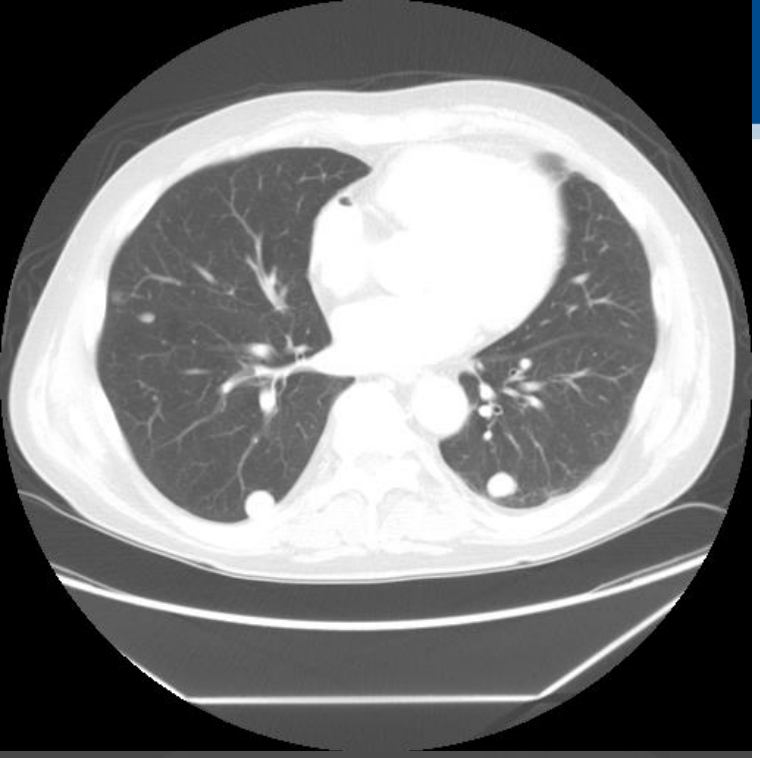
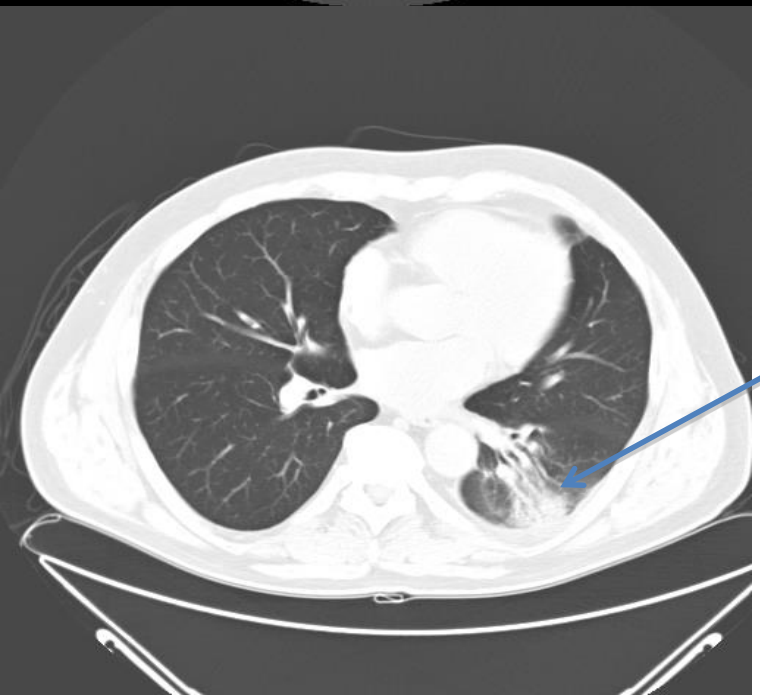
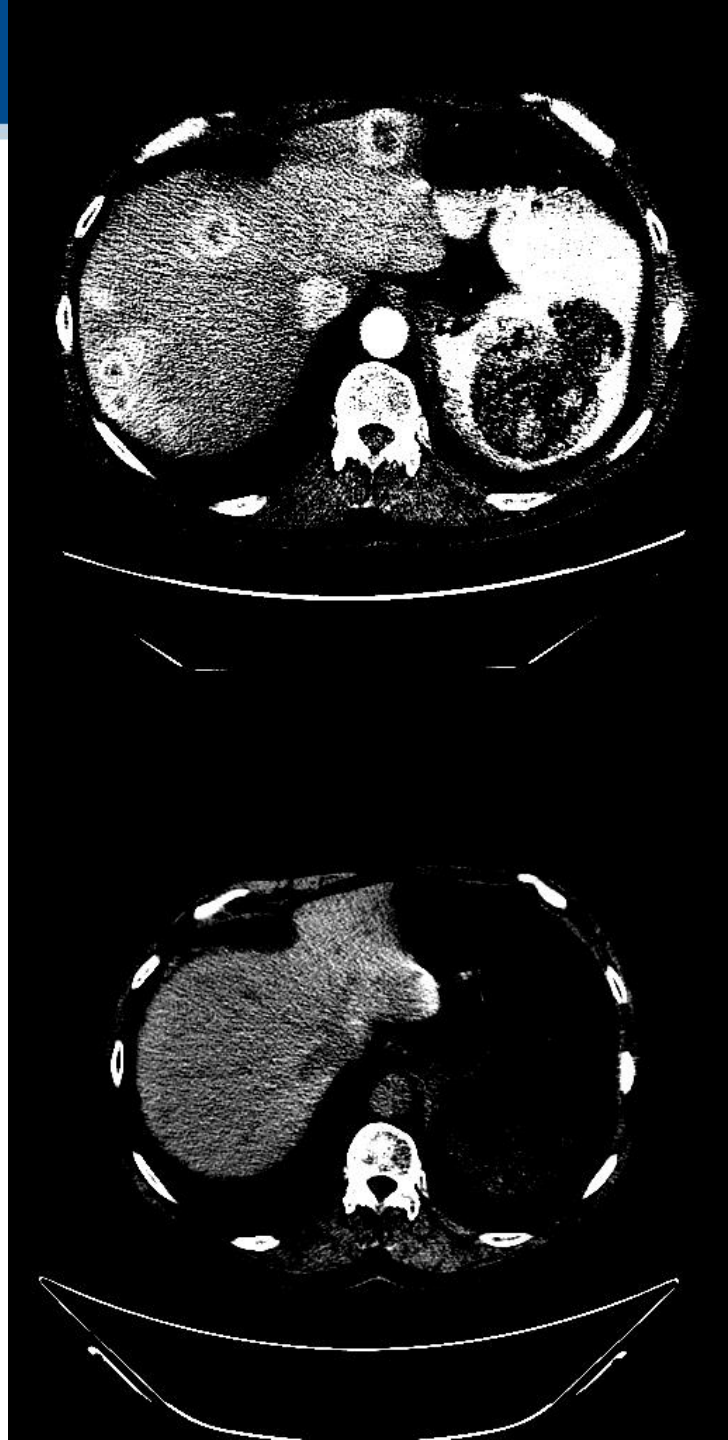


Pt 4 – Renal CA
CT PR
PET CR

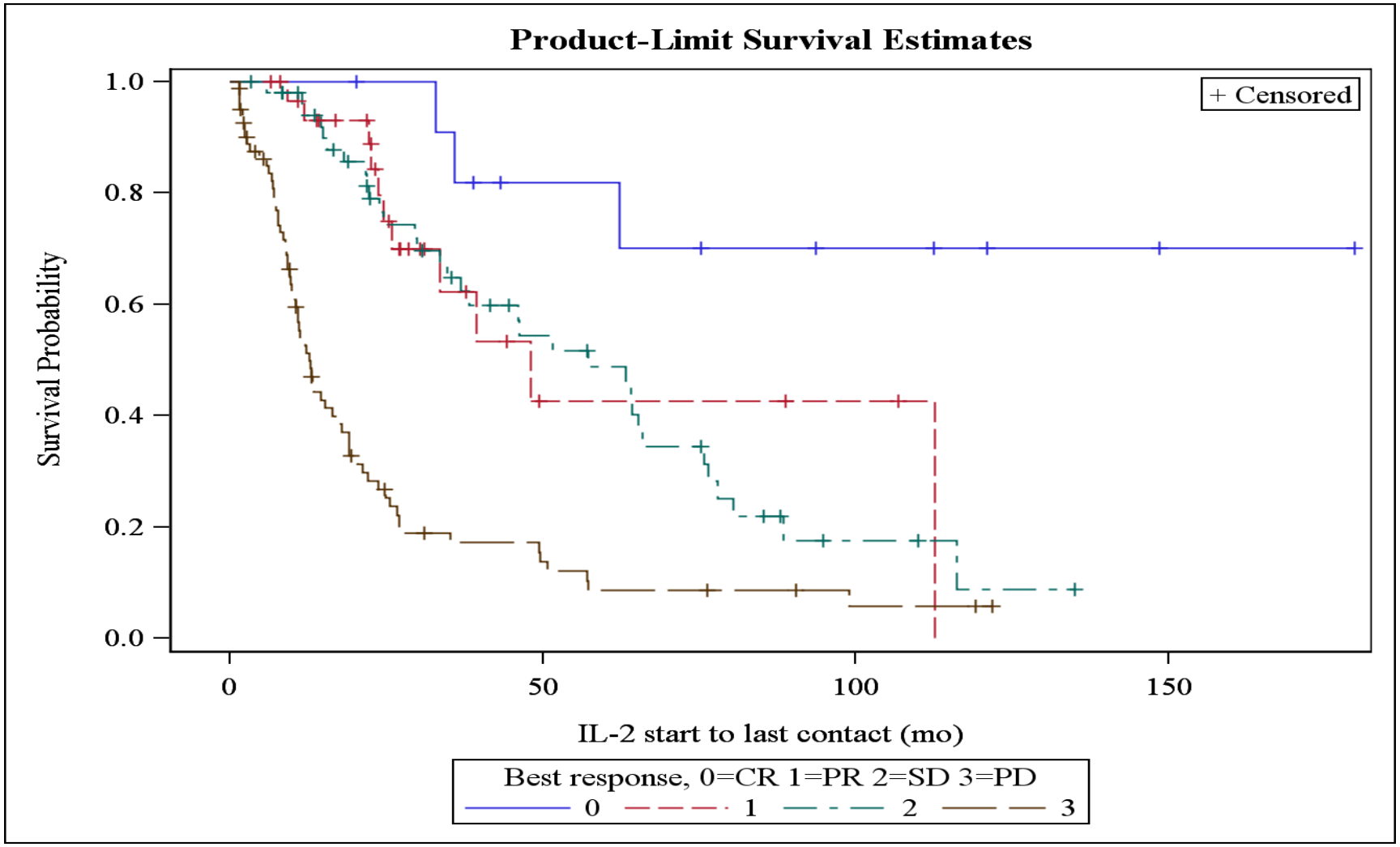


Lesion tx'd with SBRT

After



High-dose IL-2: RCC Survival



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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 5, 2015 VOL. 373 NO. 19

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, T.K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gauler, T. Ueda, Y. Tomita, F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J.S. Simon, L.-A. Xu, I.M. Waxman, and P. Sharma, for the CheckMate 025 Investigators*

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Patient Characteristics and Previous Treatments

MSKCC risk group — no. (%)†			
Favorable	145 (35)	148 (36)	293 (36)
Intermediate	201 (49)	203 (49)	404 (49)
Poor	64 (16)	60 (15)	124 (15)
Karnofsky performance status — no. (%)‡			
<70	2 (<1)	1 (<1)	3 (<1)
70	22 (5)	30 (7)	52 (6)
80	110 (27)	116 (28)	226 (28)
90	150 (37)	130 (32)	280 (34)
100	126 (31)	134 (33)	260 (32)
Previous systemic cancer therapy for metastatic renal-cell carcinoma — no. (%)§			
Sunitinib	246 (60)	242 (59)	488 (59)
Pazopanib	119 (29)	131 (32)	250 (30)
Axitinib	51 (12)	50 (12)	101 (12)

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Overall Survival of Nivolumab Versus Everolimus

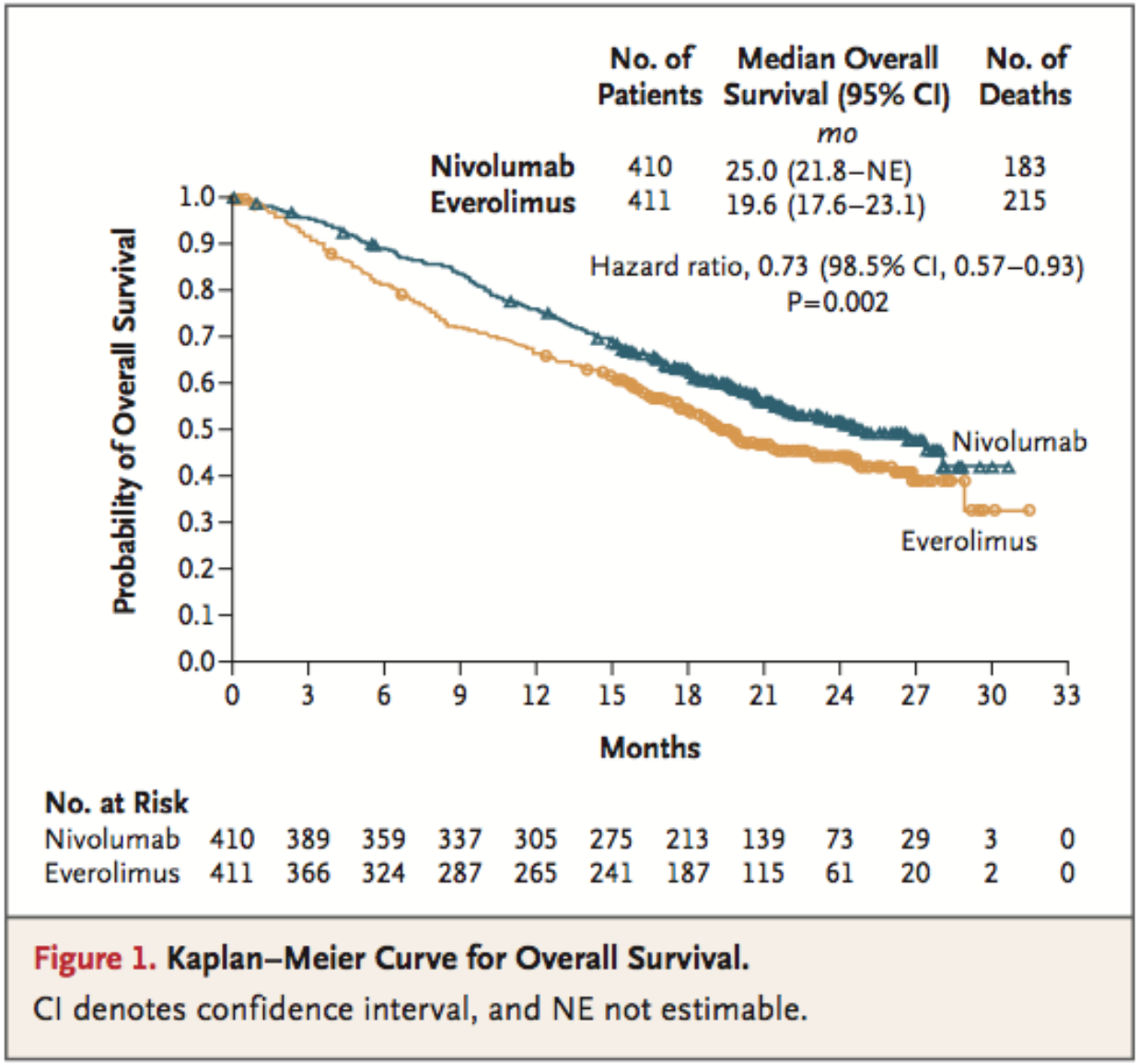

Figure 1. Kaplan–Meier Curve for Overall Survival.

CI denotes confidence interval, and NE not estimable.

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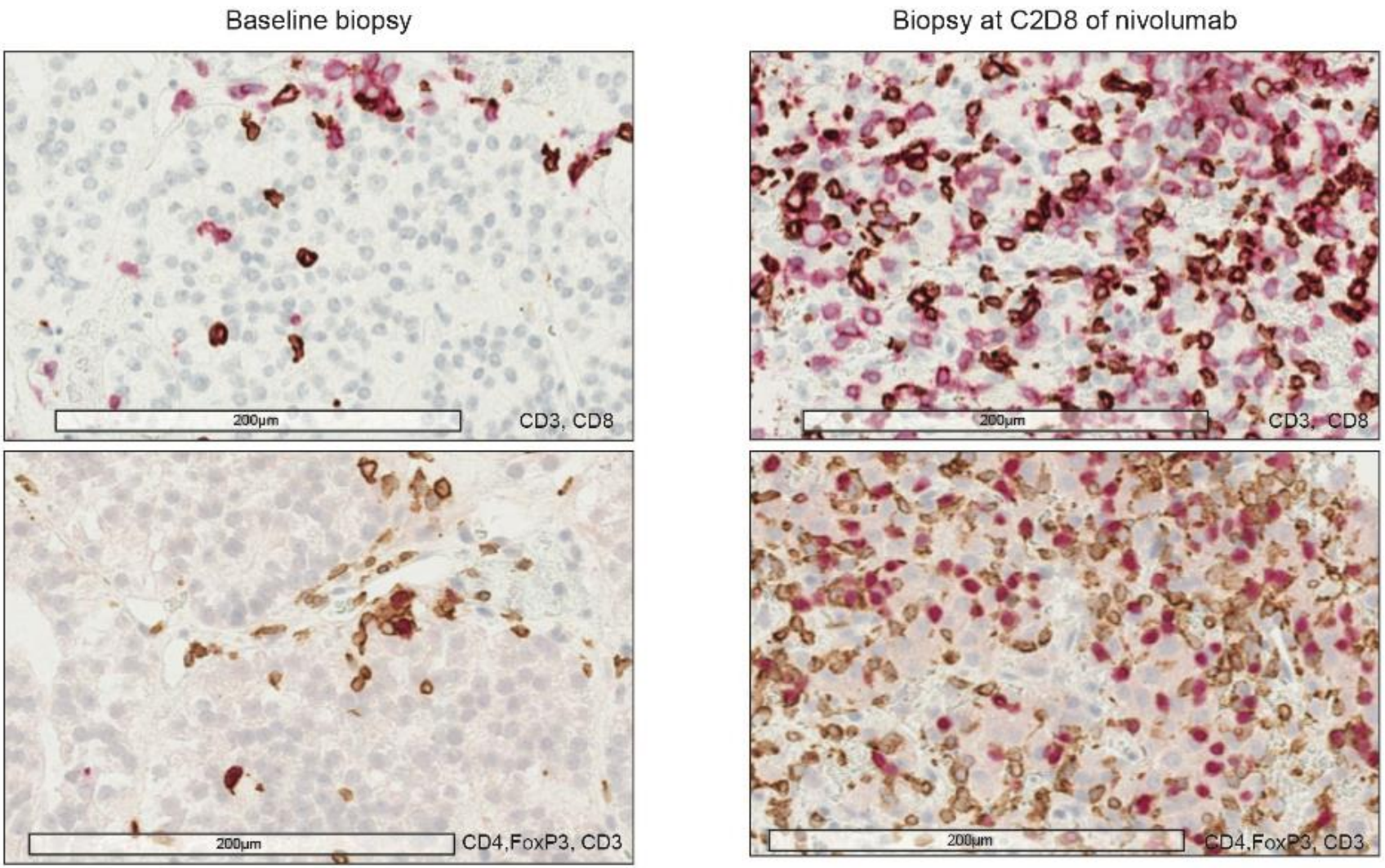
RCC PD-L1 Expression Before Treatment

Table 1. (Continued.)

Characteristic	Nivolumab Group (N=410)	Everolimus Group (N=411)	Total (N=821)
Patients with quantifiable PD-L1 expression — no. (%)	370 (90)	386 (94)	756 (92)
PD-L1 expression level¶			
≥1%	94 (25)	87 (23)	181 (24)
<1%	276 (75)	299 (77)	575 (76)
≥5%	44 (12)	41 (11)	85 (11)
<5%	326 (88)	345 (89)	671 (89)
Patients without quantifiable PD-L1 expression — no. (%)	40 (10)	25 (6)	65 (8)

IHC for CD3, CD4, CD 8, FoxP3 Before and After Nivolumab



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Choueiri et al., Clin Cancer Res May 2016

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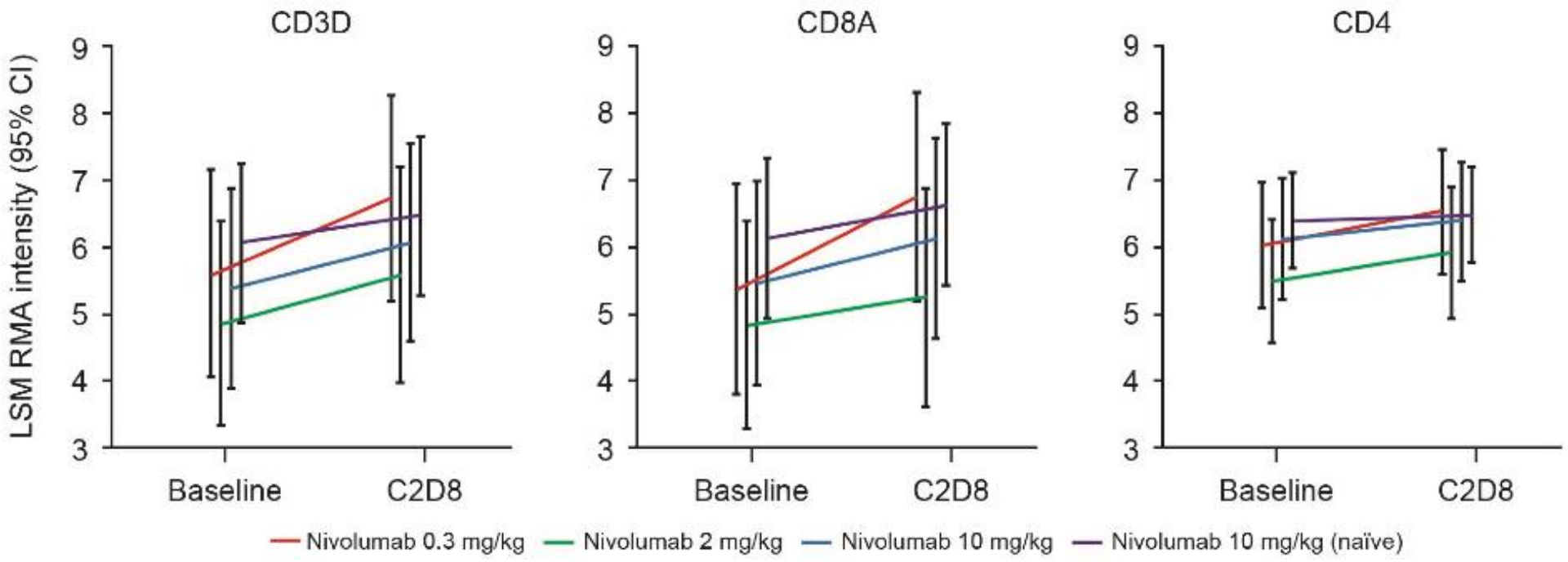
Percentage of T Cell Phenotypes in Biopsy Specimens: Baseline vs C2D8



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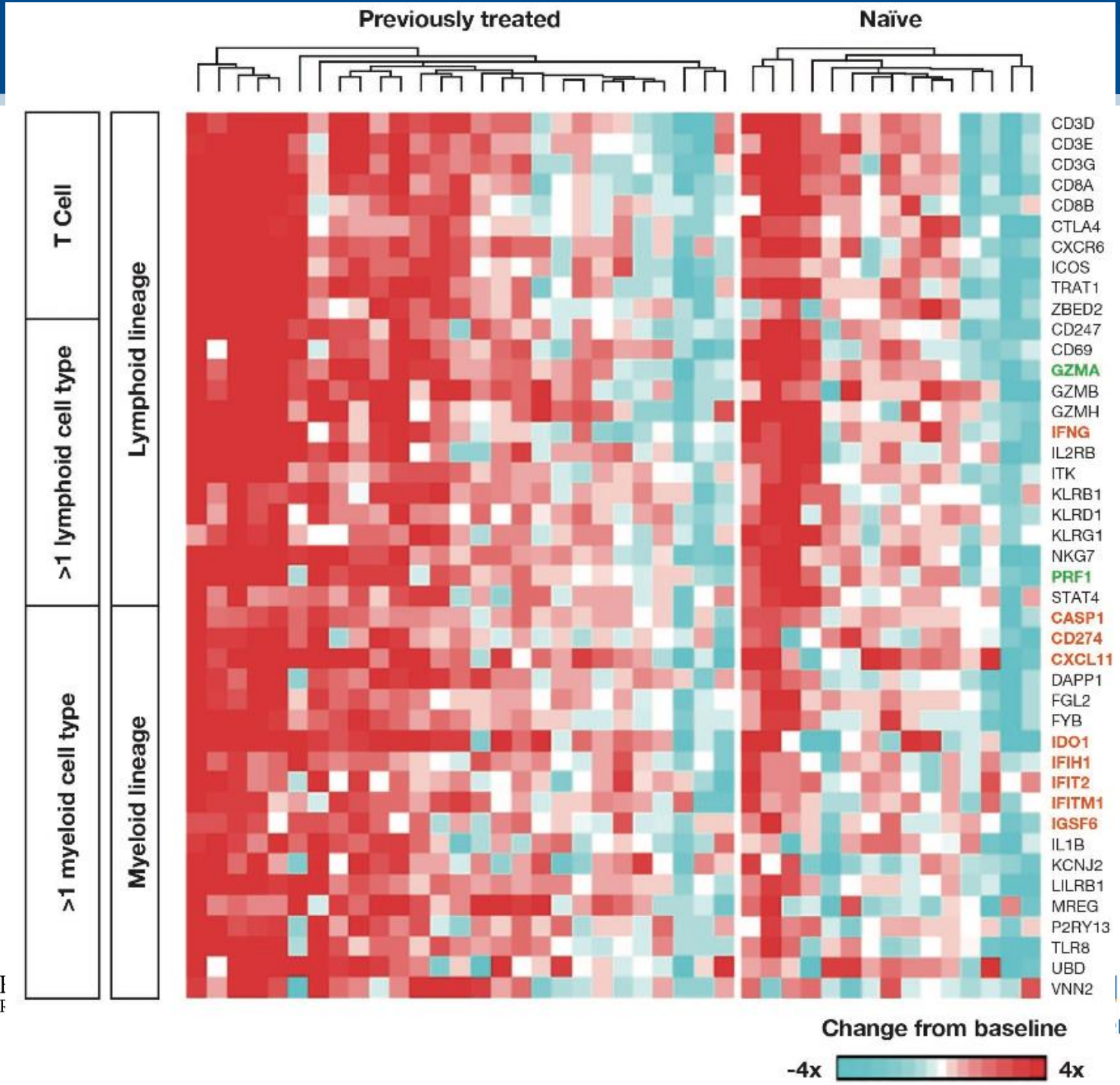

Previously treated
Naïve
T Cell
>1 lymphoid cell type
Lymphoid lineage
>1 myeloid cell type
Myeloid lineage
CD3D
CD3E
CD3G
CD8A
CD8B
CTLA4
CXCR6
ICOS
TRAT1
ZBED2
CD247
CD69
GZMA
GZMB
GZMH
IFNG
IL2RB
ITK
KLRB1
KLRD1
KLRG1
NKG7
PRF1
STAT4
CASP1
CD274
CXCL11
DAPP1
FGL2
FYB
IDO1
IFIH1
IFIT2
IFITM1
IGSF6
IL1B
KCNJ2
LILRB1
MREG
P2RY13
TLR8
UBD
VNN2
Change from baseline
-4x
4x

VOLUME 34 · NUMBER 8 · MARCH 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Atezolizumab, an Anti–Programmed Death-Ligand 1 Antibody, in Metastatic Renal Cell Carcinoma: Long-Term Safety, Clinical Activity, and Immune Correlates From a Phase Ia Study

David F. McDermott, Jeffrey A. Sosman, Mario Sznol, Christophe Massard, Michael S. Gordon, Omid Hamid, John D. Powderly, Jeffrey R. Infante, Marcella Fassò, Yan V. Wang, Wei Zou, Priti S. Hegde, Gregg D. Fine, and Thomas Powles

Listen to the podcast by Dr Rini at www.jco.org/podcasts

PD-L1 Expression on RCC Tumor Cells and Response

Table 3. Efficacy of Atezolizumab in Patients With Clear-Cell Renal Cell Carcinoma by PD-L1 IC Expression Status

PD-L1 IC Status	ORR		Median (range) DOR, months	Median (95% CI) PFS, months	Median (95% CI) OS, months	1-Year OS Rate, % (95% CI)	2-Year OS Rate, % (95% CI)
	No. (%)	95% CI, %*					
All† (n = 62)	9 (15)	7 to 26	17.4 (7.6 to ≥ 26.9)	5.6 (3.9 to 8.2)	28.9 (20.0 to NR)	81 (70% to 92%)	58 (43 to 73)
IC1/2/3 (n = 33)‡§	6 (18)	7 to 35	14.9 (7.6 to ≥ 20.2)	5.6 (2.8 to 9.0)	NR (20.0 to NR)	81 (67% to 96%)	65 (45 to 86)
IC0‖ (n = 22)	2 (9)	1 to 29	NR (≥ 16.6 to ≥ 26.9)	4.5 (1.3 to 8.1)	28.8 (16.3 to 28.9)	80 (62% to 98%)	51 (27 to 74)
IC unknown (n = 7)	1 (14)	0 to 58	8.3 (8.3-8.3)	11.1 (4.3 to NR)	NR (11.7 to NR)	80 (45% to 100%)	53 (5 to 100)

Abbreviations: DOR, duration of response; IC, tumor-infiltrating immune cell; IHC, immunohistochemistry; NR, not reached; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PD, progressive disease; PFS, progression-free survival.

*Investigator-assessed confirmed responses per RECIST v1.1; data cutoff, December 2, 2014.

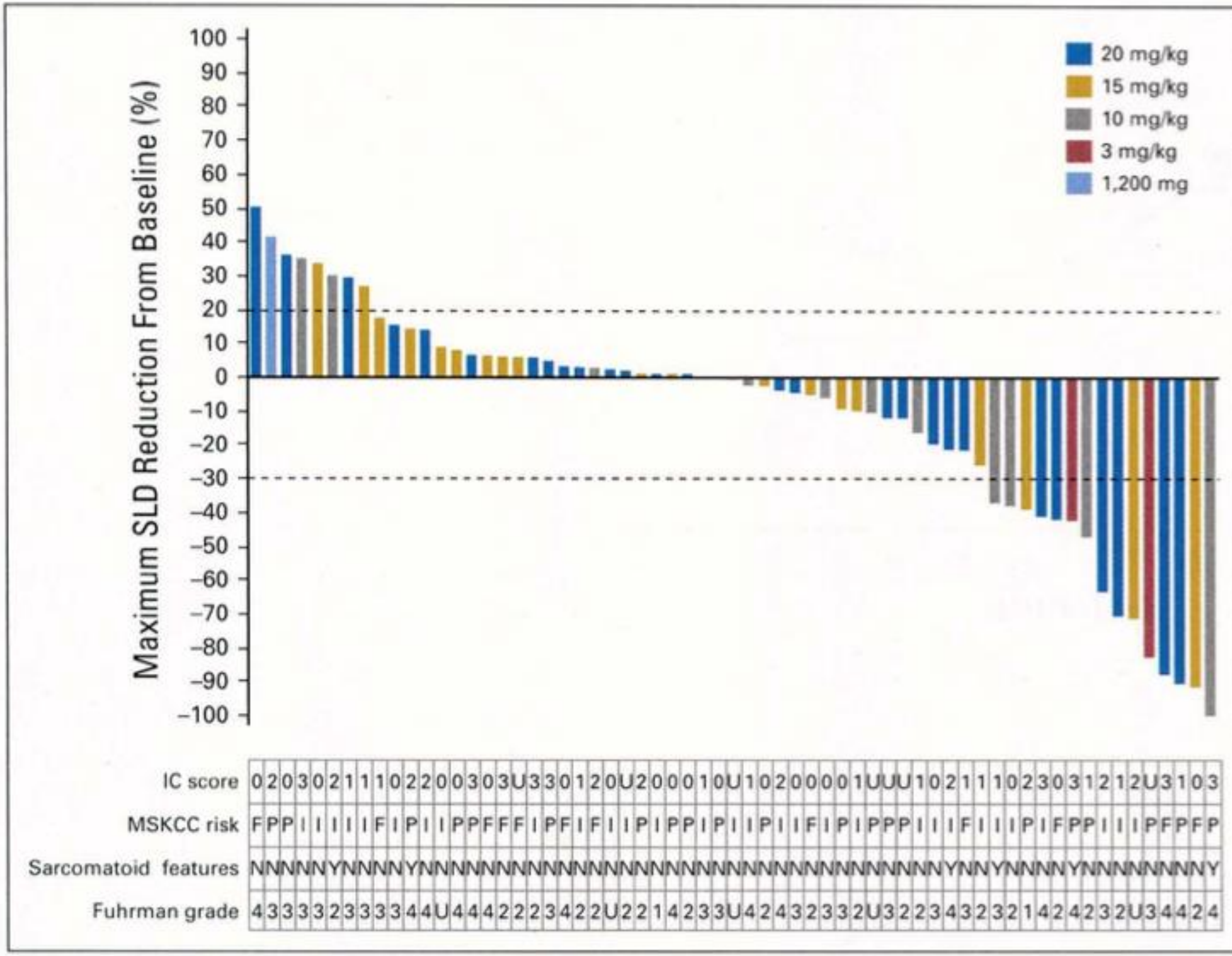
†n = 63 for PFS and OS analyses.

‡IC1/2/3 = IC ≥ 1%.

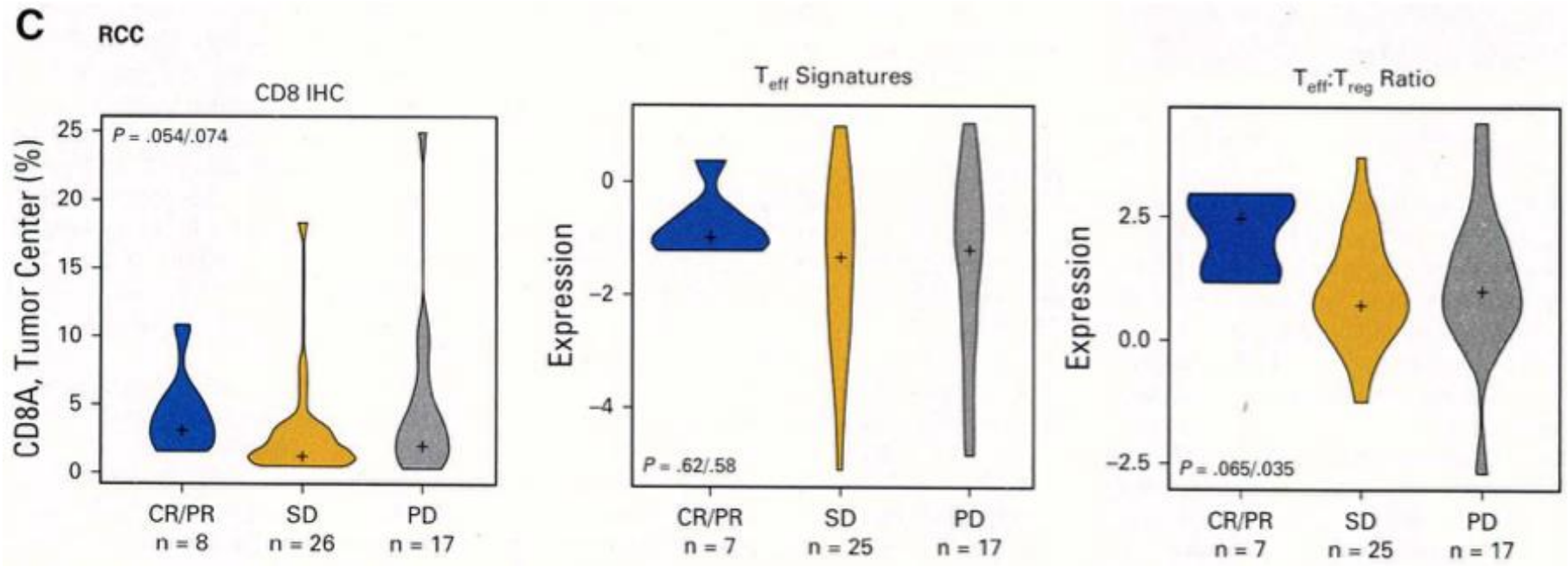
§n = 34 for PFS and OS analyses.

‖IC0 = IC less than 1%. Two patients had missing or unevaluable scans.

Atezolizumab Activity By Dose Level in Renal Cell Carcinoma



Violin Plots of T Cell Measures Related to Overall Survival



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

Thomas Powles[1], Joseph Paul Eder[2], Gregg D. Fine[3], Fadi S. Braiteh[4], Yohann Loriot[5], Cristina Cruz[6], Joaquim Bellmunt[7], Howard A. Burris[8], Daniel P. Petrylak[2], Siew-leng Teng[3], Xiaodong Shen[3], Zachary Boyd[3], Priti S. Hegde[3], Daniel S. Chen[3] & Nicholas J. Vogelzang[9]

558 | NATURE | VOL 515 | 27 NOVEMBER 2014

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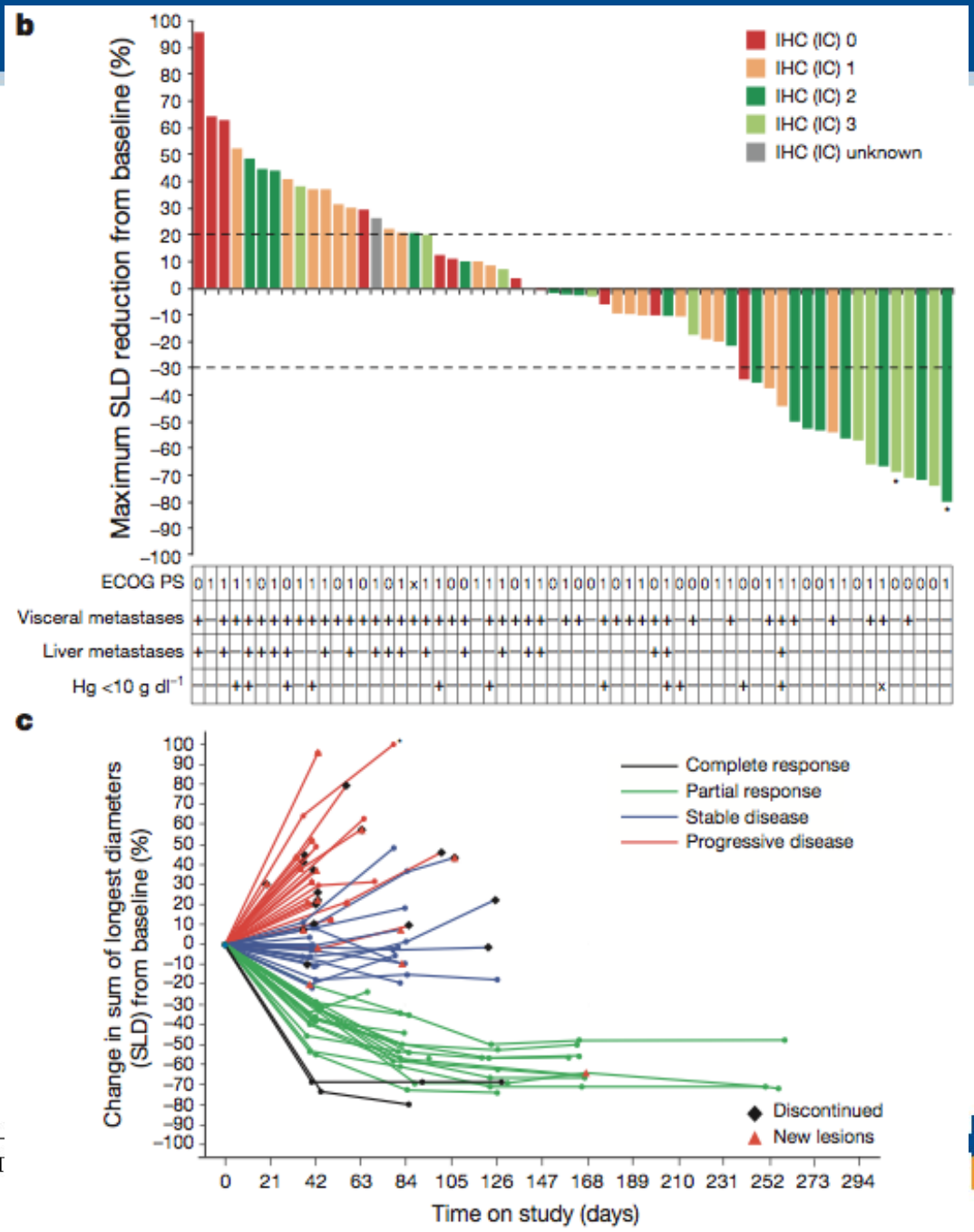
PD-L1 Expression on TIL in Metastatic Bladder Cancer

Tumour-infiltrating immune cells and objective response rates

	Objective response rate *n* (%)	Stable disease *n* (%)	Progressive disease *n* (%)
IHC 2/3 (*n* = 30)	13 (43.3) (95% CI: 25.5–62.6)	8 (26.7)	8 (26.7)
IHC 3 (*n* = 10)	5 (50.0) (95% CI: 22.2–77.8)	2 (20.0)	3 (30.0)
IHC 2 (*n* = 20)	8 (40.0) (95% CI: 20.9–63.9)	6 (30.0)	5 (25.0)
IHC 0/1 (*n* = 35)	4 (11.4) (95% CI: 4.0–26.3)	13 (37.1)	13 (37.1)
IHC 1 (*n* = 23)	3 (13.0) (95% CI: 3.7–31.7)	8 (34.8)	8 (34.8)
IHC 0 (*n* = 12)	1 (8.3) (95% CI: 0.4–34.9)	5 (41.7)	5 (41.7)



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Sipuleucel-T Immunotherapy

- Autologous cellular product derived from the patient's peripheral blood mononuclear cells (PBMC).
- Can be used in men with asymptomatic or minimally symptomatic CRPC with metastatic disease.

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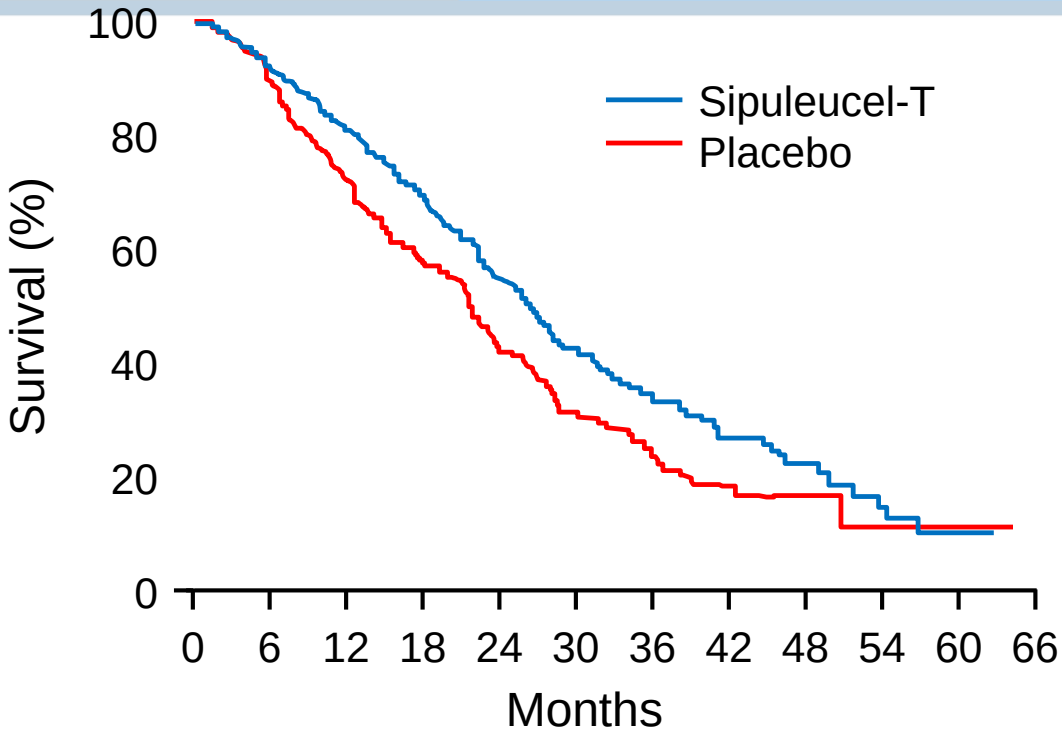
Survival: Sipuleucel-T vs Placebo



And by the way, PSAs did not decrease.

	Placebo	Sip-T	HR; *P*
N	171	341	
Median OS, mo	21.7	25.8	0.78; 0.03

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Kantoff PW, et al. *N Engl J Med*. 2010;363:411-422.

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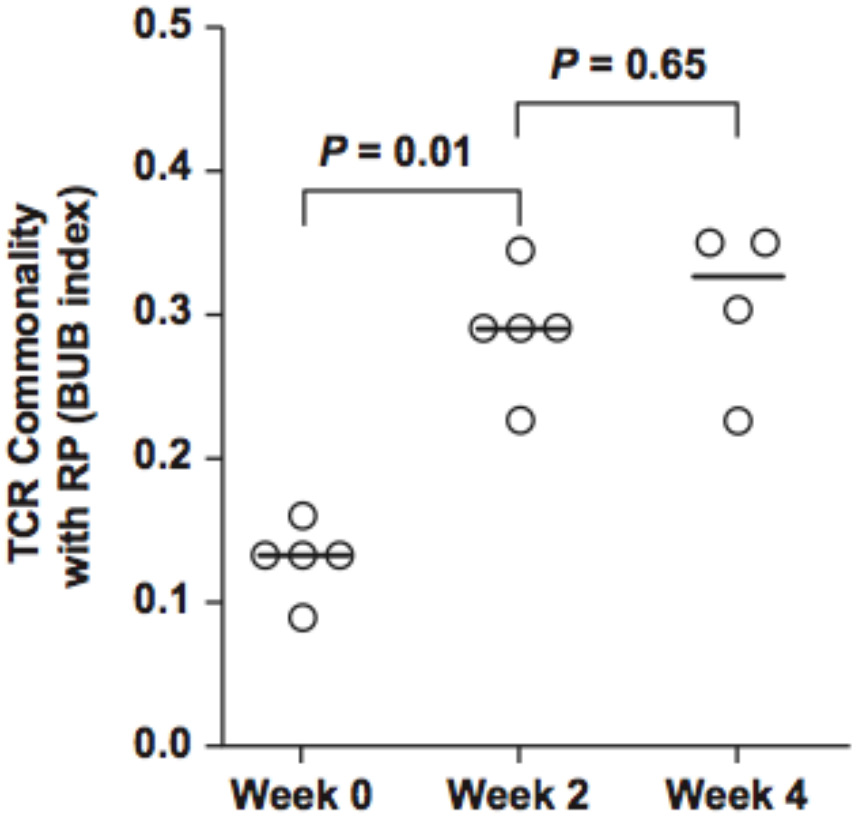
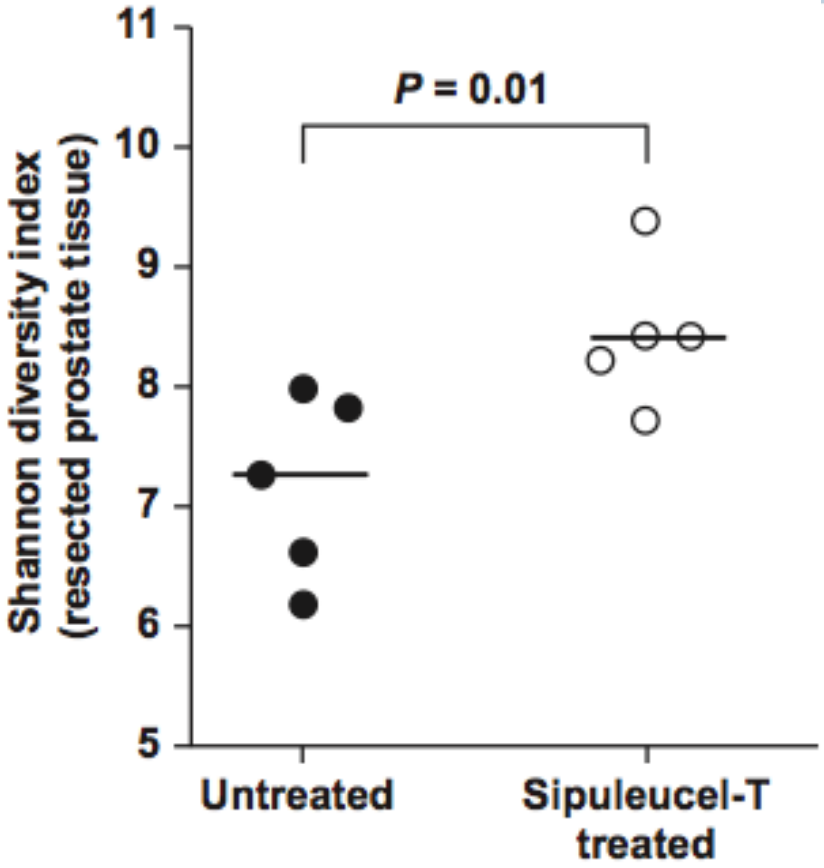
So what immunological effects might Sipuleucel-T have?





= T cell receptor; RP = radical prostatectomy; BUB = Baroni-Urbani and Buser.

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www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 33

Research Paper: Immunology

Early evidence of anti-PD-1 activity in enzalutamide-resistant prostate cancer

Julie N. Graff[1,2], Joshi J. Alumkal[1], Charles G. Drake[3], George V. Thomas[4], William L. Redmond[5], Mohammad Farhad[5,6], Jeremy P. Cetnar[1], Frederick S. Ey[1], Raymond C. Bergan[1], Rachel Slottke[1] and Tomasz M. Beer[1]

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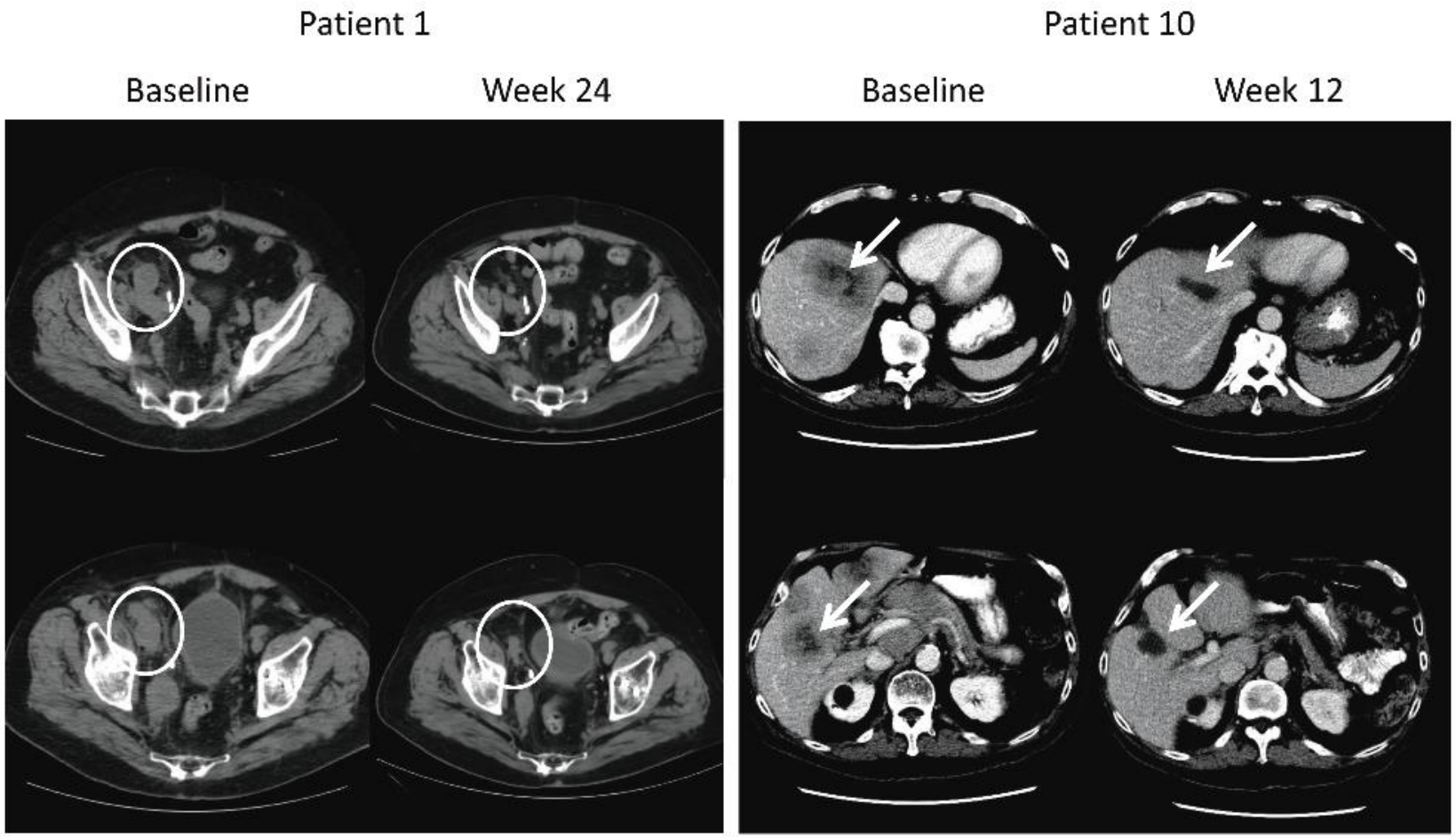
Clinical Response of Enzalutamide + Anti-PD-1



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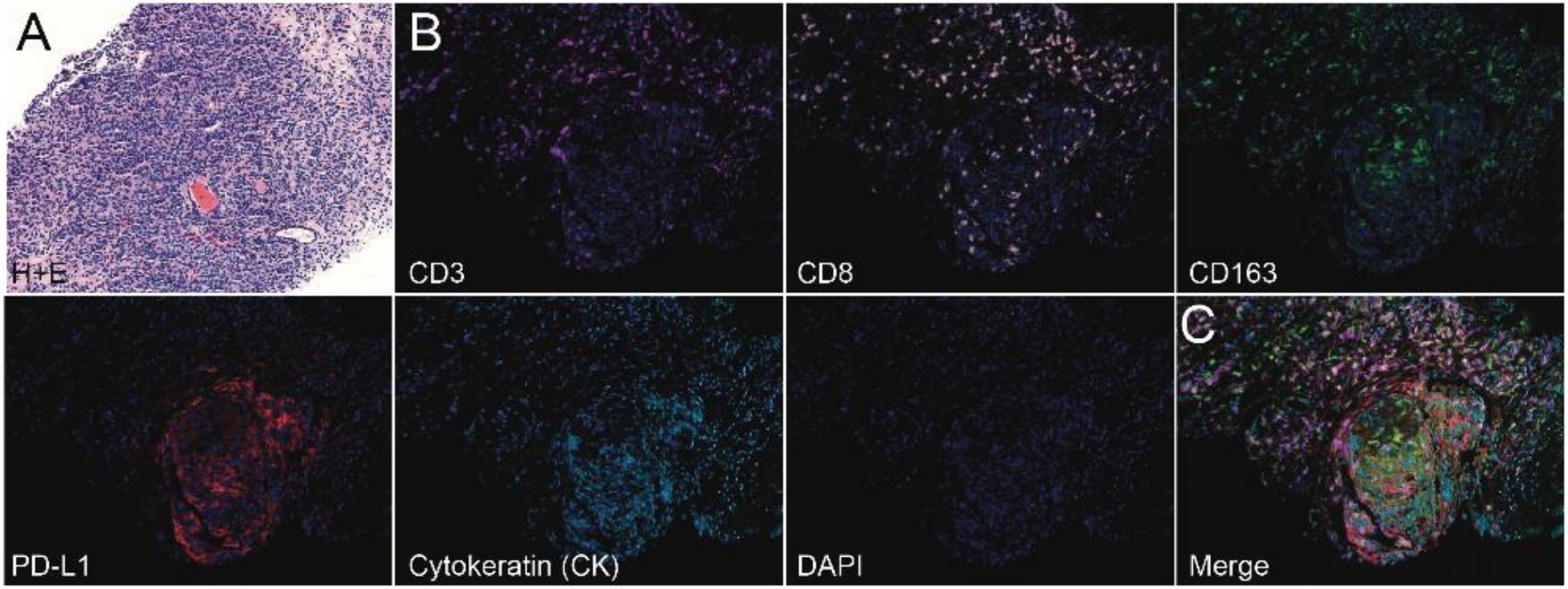
Multispectral imaging of Lymph node in Metastatic Prostate Cancer – Pre-anti-PD-1



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Selected GU Clinical Trials at EACRI

- A Phases 3 Randomized, Double Blind, Multi-center Study of Adjuvant Nivolumab versus Placebo in Subjects with High Risk Invasive Urothelial Carcinoma
- MEDI4736 in Combination with Tremelimumab in Subjects with Advanced Solid Tumors
- Phase II Randomized Study of High Dose IL-2 Versus SBRT and IL-2 in Patients with Metastatic Renal Cancer
- A Phase 1, Dose-Finding and Signal-Seeking Study of the Safety and Efficacy of Intravenous CAVATAK (Coxssackie virus A21) Alone and in Combination with Pembrolizumab in . . . Metastatic Bladder Cancer

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Conclusions

- Immunotherapy can enhance survival in patients with advanced GU malignancy.
  - Immunotherapy 1.x works as does 2.x
  - Tails on survival curves exist (but lots of room for improvement)
- T cell responses to cancer immunotherapy are important across all tumor types
- PD-1 expression in the tumor (and/or TIL) important, but best threshold/assay debatable.

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