Immunotherapy for Genitourinary Cancers

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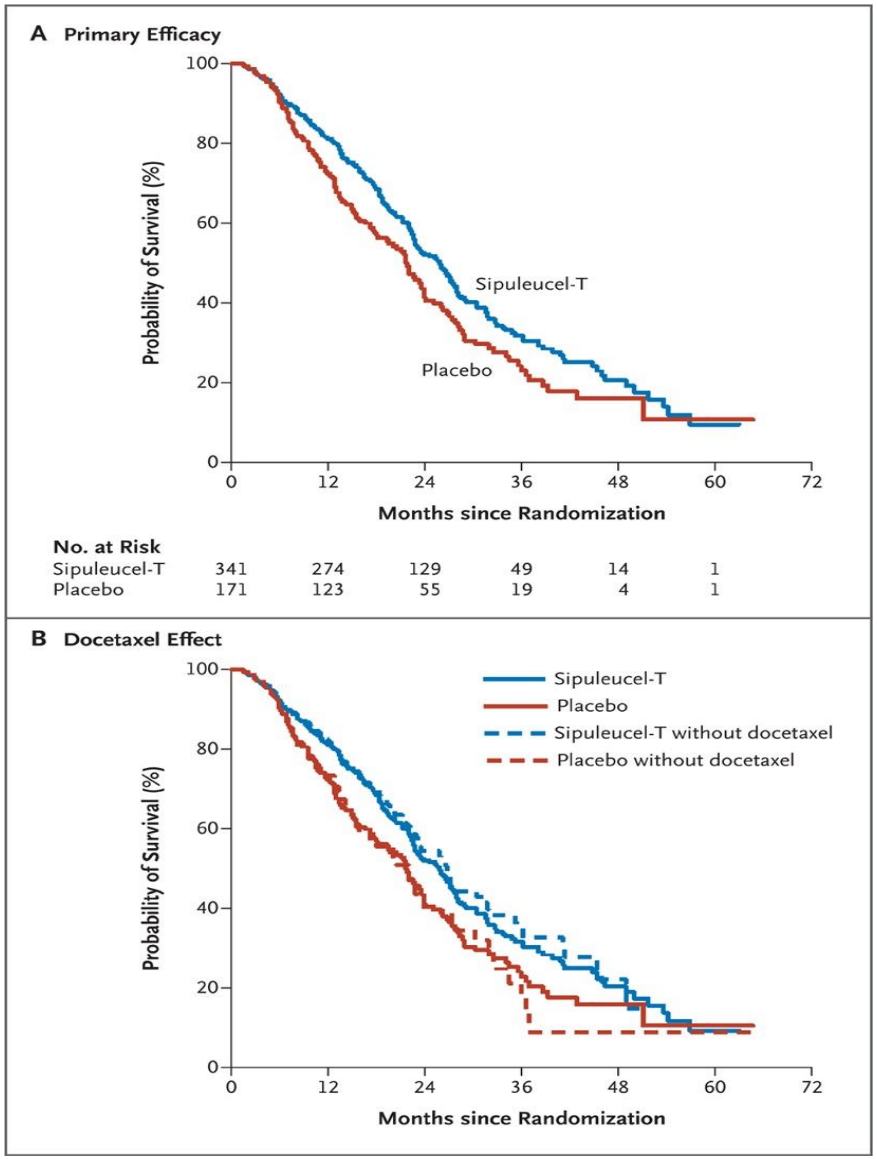
Disclosures

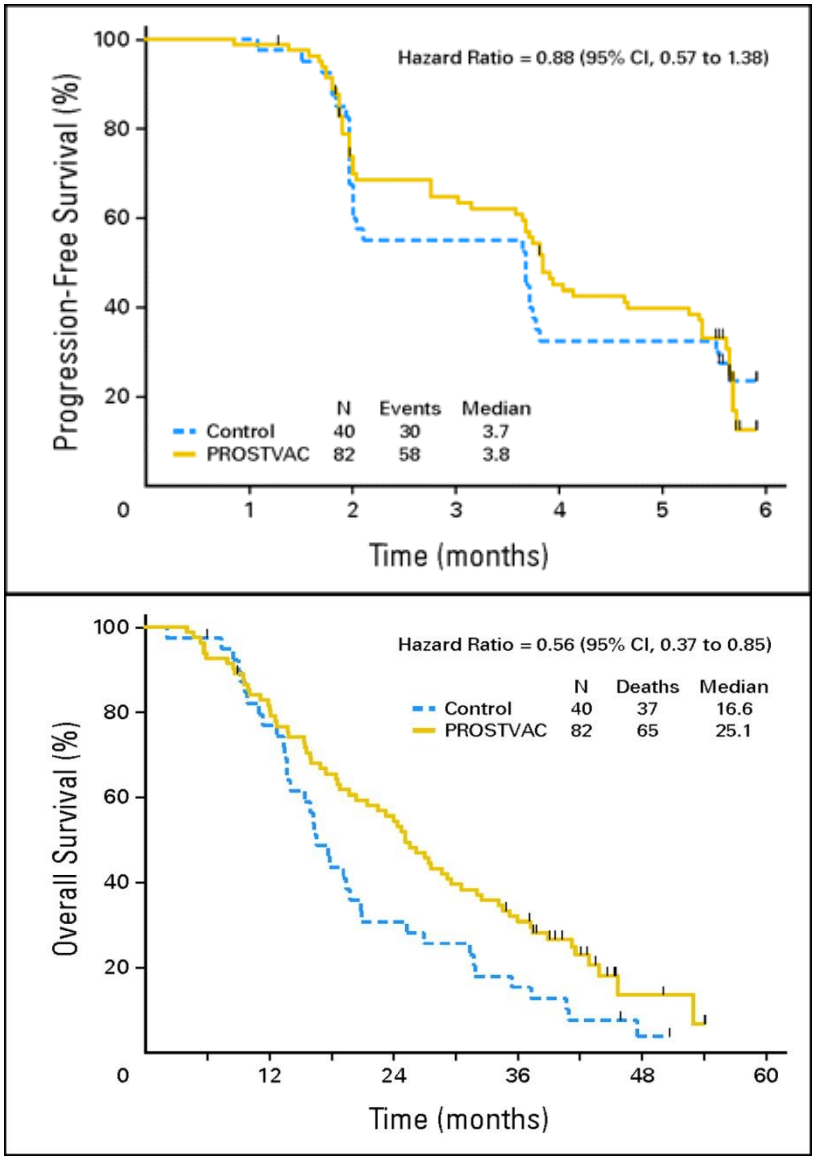
- Advisory Board: Bayer Pharmaceuticals

- No non-FDA approved treatments will be discussed

Vaccines in Prostate Cancer



Kantoff, et al, NEJM 2010.



Kantoff, el al, JCO 2010

Therapy must be…

- ***Exportable***: "off the shelf"
- ***Reportable***: need appropriate endpoints
- ***Translatable***: biologic effect*
- ***Time Table***: Anticipated time-to-effect
- ***Radiographic assessment:*** pseudoprogression?

*Immune read-out associated with treatment effect?

Immunotherapies: Prostate

Successes (many)

- Sipuleucel-T* +/- chemo; GM-CSF; AR directed agents
- ProstVAC*
- Anti-CTLA-4 (Ipilimumab)**
- Anti-PD-1 (Nivolumab)****?**
- Ipi + Nivolumab [combo]**?**
- Vaccines + cytokines/RT/chemo/adjuvants
- CAR+ (armored) T cells +/- chemo

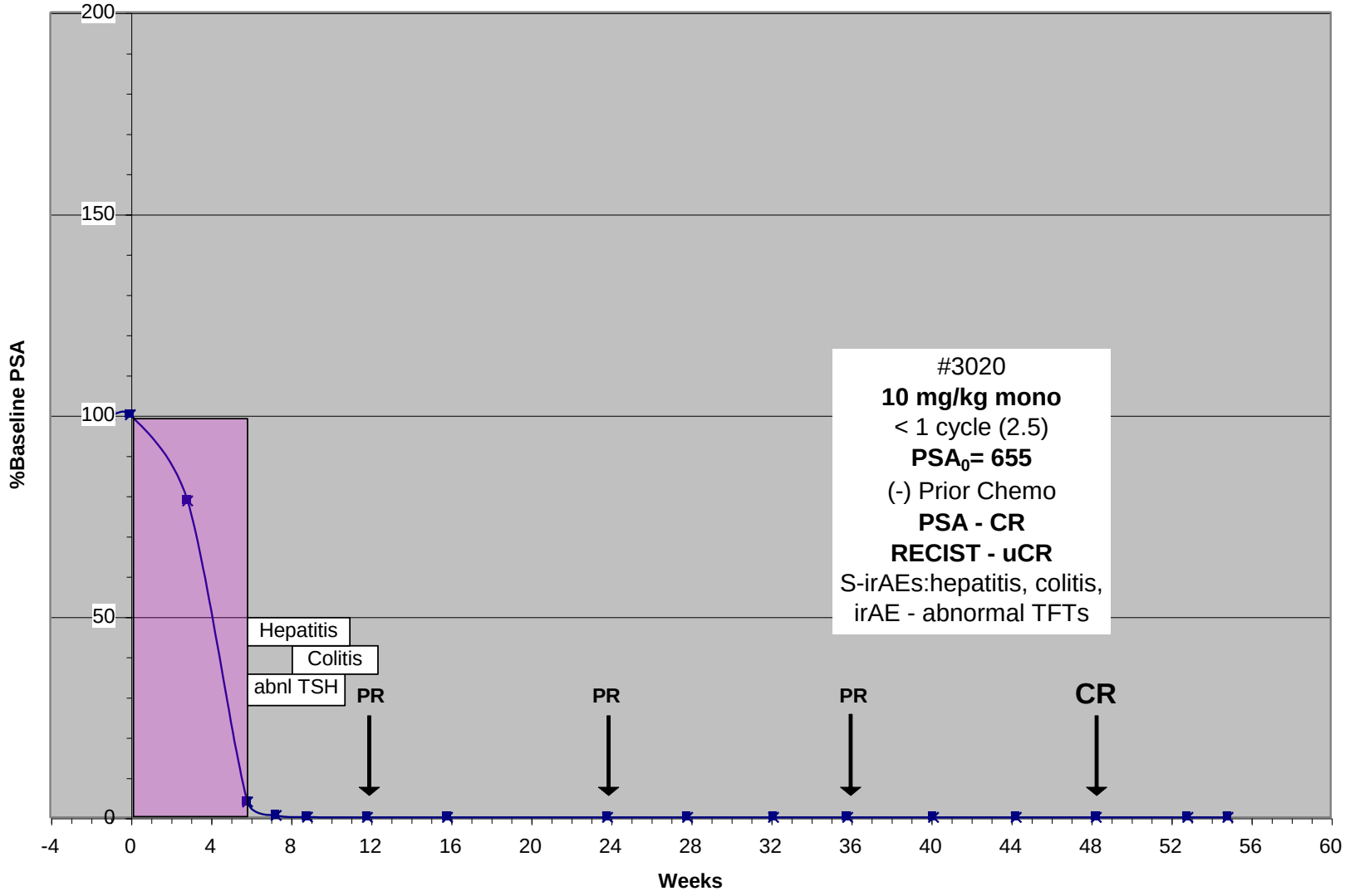
Failures (many)

- G-Vax
- Protein
- Peptide
- DNA (xenogeneic)
- ? Carriers/Adjuvants: KLH, Alhydrogel, QS21

*** Is overall survival sufficient in the absence of clinical benefit, ie (anti-tumor effects(s)?**

**** Can immunotherapies be specific for certain histologic types of cancers?**

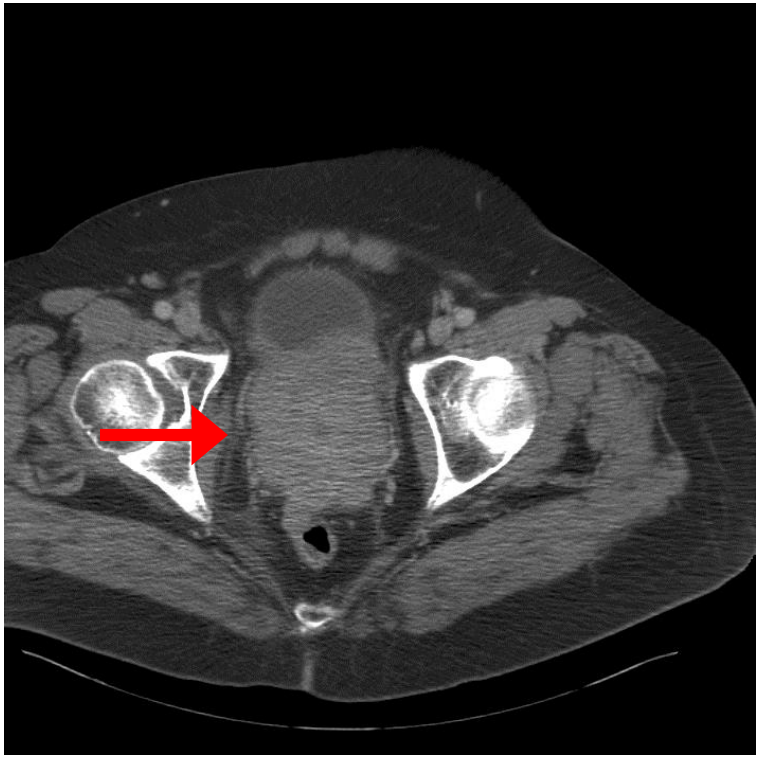
Subject 3020, 10 mg/kg monotherapy



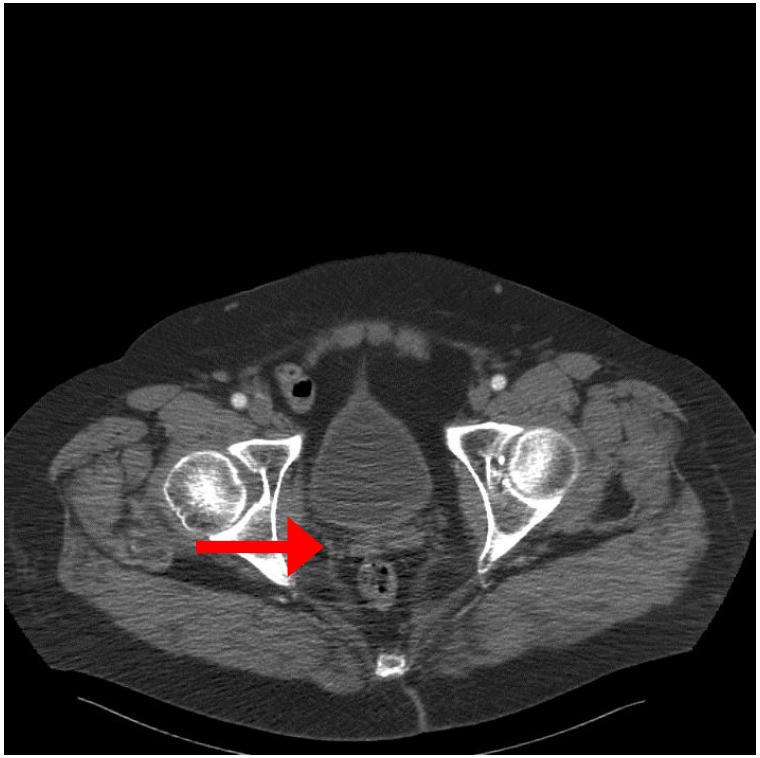
Beer, et al, ASCO 2008

Subject 3020:
Resolution of Prostate Mass

Screening

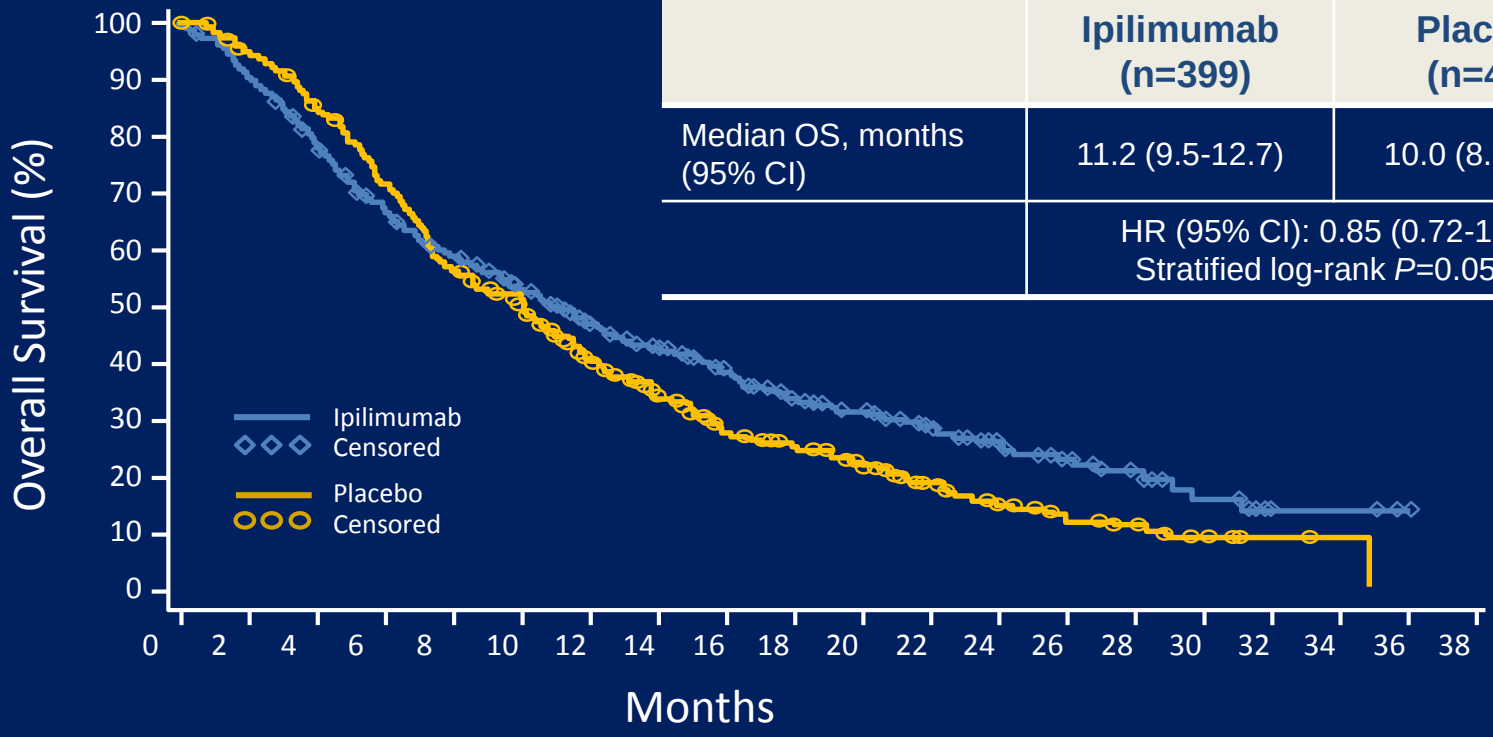


14 months



Phase 3 Study of Ipilimumab in Post-Docetaxel mCRPC (CA184-043)[1]

Primary Endpoint: OS (Intent to Treat [ITT] Population)



	Ipilimumab (n=399)	Placebo (n=400)
Median OS, months (95% CI)	11.2 (9.5-12.7)	10.0 (8.3-11.0)
	HR (95% CI): 0.85 (0.72-1.00) Stratified log-rank *P*=0.0530	

Safety

- Adverse event (AE) profile was consistent with that previously reported for ipilimumab*
  - The most frequent severe immune-related AEs were diarrhea and colitis

*See poster presentation at this meeting: Beer et al. Abstract ID: 52.

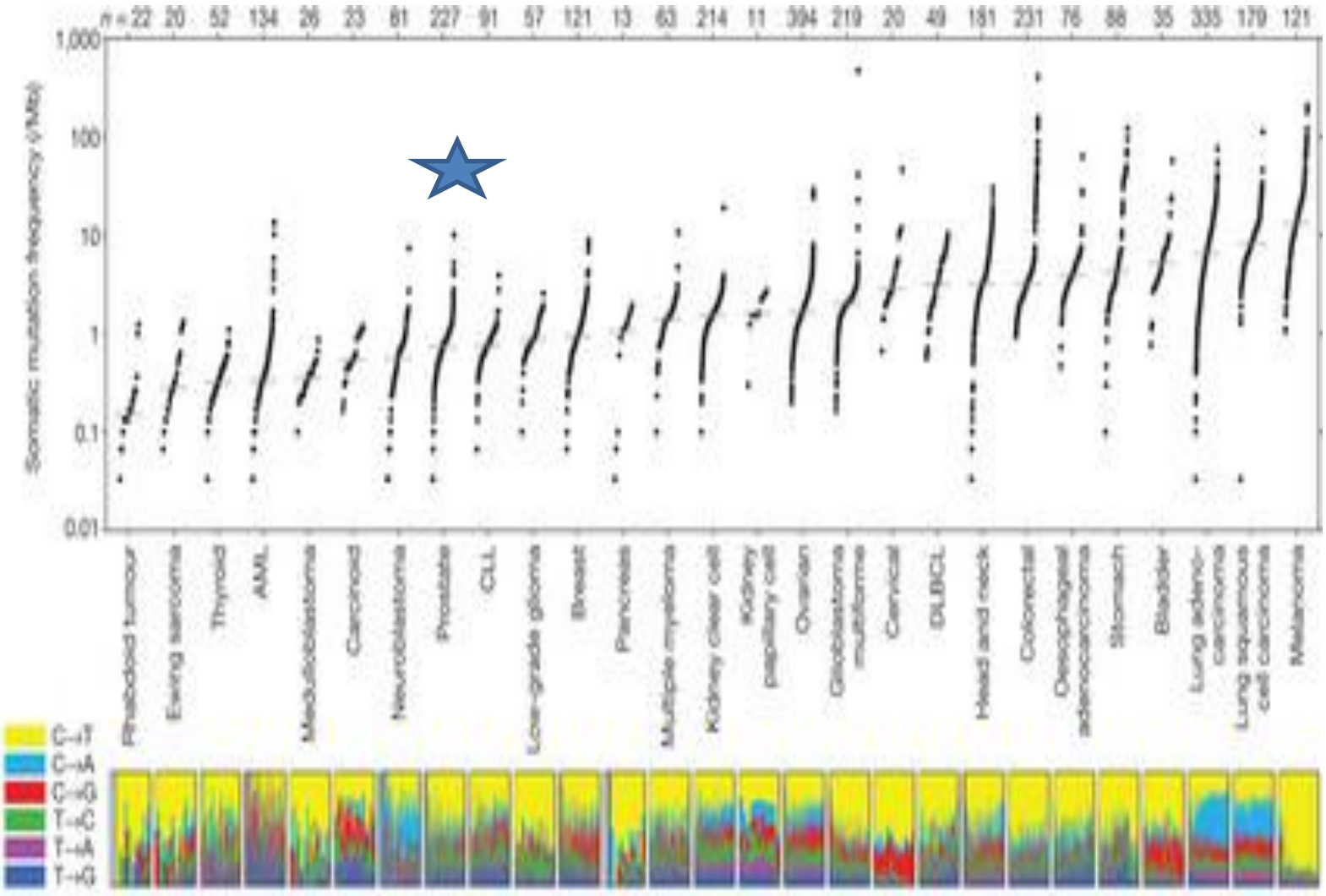
[1]Gerritsen WR et al. Paper presented at: European Cancer Congress 2013; Amsterdam, The Netherlands. Abstract 2850.

Kwon, et al Lancet Onc 2014

Lessons learned: Prostate cancer vaccine trials

- **Prostate *not* an "immunologic solid tumor" c/w melanoma, renal, lung, bladder**
- ***Not* significantly hyper-mutated**
- **↑ doses of vaccine ≠ augmentation of immunogenicity, ie, lower doses likely more immunogenic**
- **Abs were generated with specificity for the immunogen; no biologic effect seen**
- ***no* potentiation of T cell responses**
- ***Immunologic signals - not immediate; ? Boosters**
- ***Limited efficacy* of checkpoint inhibitors, anti-CTLA-4, anti- PD1**
- **No evidence of disease pseudoprogression before response.**
- **No abscopal effects**

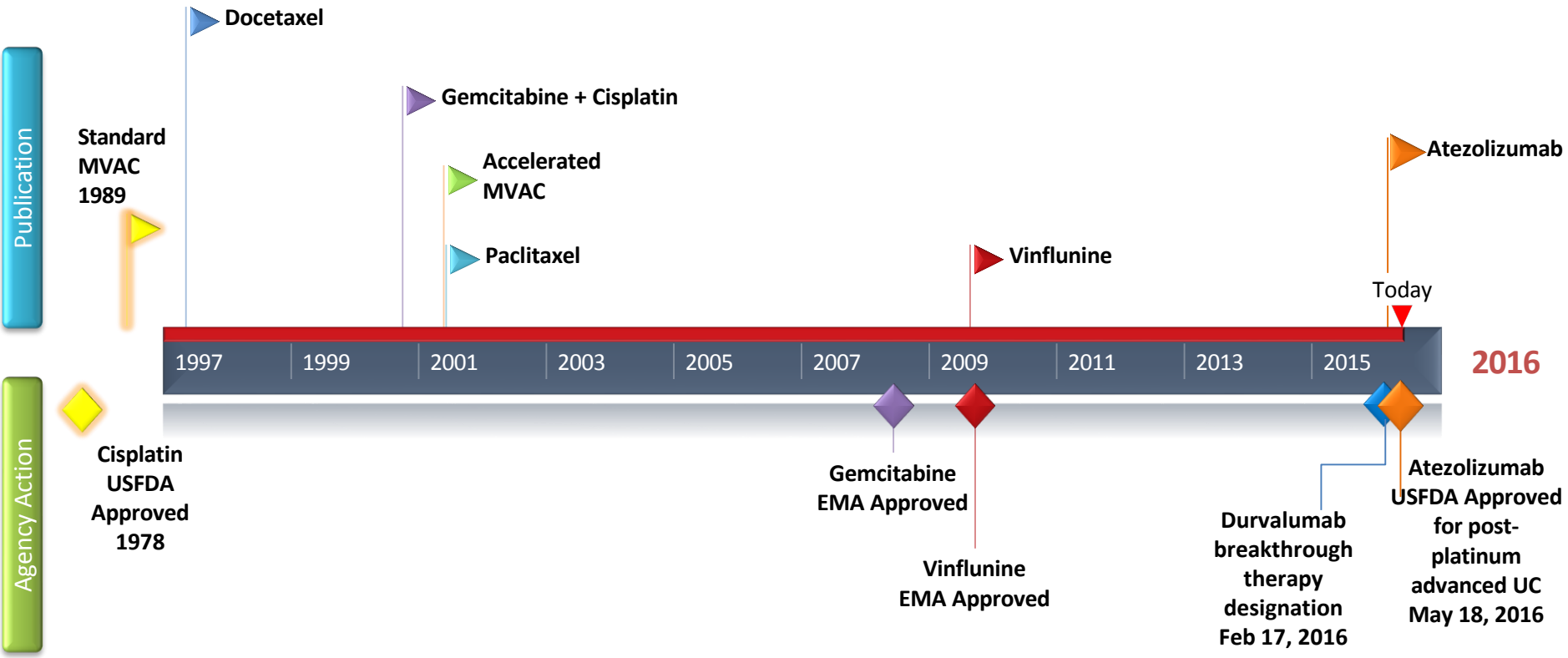
Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs.



Each dot corresponds to a tumour–normal pair, with vertical position indicating the total frequency of somatic mutations in the exome.

Lawrence, et al Nature 2013

Evolution of Systemic Therapy for Urothelial Cancer



Sternberg CN, Yagoda A, et al. *Cancer* 1989; **64**(12): 2448-58. McCaffrey JA, et al. *J Clin Oncol* 1997; **15**(5): 1853-7
von der Maase H, et al. *J Clin Oncol* 2005; **23**(21): 4602-8. Sternberg CN, et al. *J Clin Oncol* 2001; **19**(10): 2638-46.
Vaughn DJ, et al. *J Clin Oncol* 2002; **20**(4): 937-40. Bellmunt J, et al. *J Clin Oncol* 2009; **27**(27): 4454-61.
Rosenberg JE, et al. *Lancet* 2016. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. http://www.ema.europa.eu/ema/

Immunotherapies: Bladder/Renal

- Intravesical BCG, IFN
- Nivolumab [MPDL3280A]
- Atezolizumab
- Oncolytic virus: CG0070 – adenovirus + GM-CSF

- HD IL-2
- IFN-α
- Nivolumab
- Ipilimumab
- Atezolizumab
- Varlilumab (CDX-1127, anti-CD27)
- MGA217 (B7H3)
- SNG-CD70A (CD70)
- LAG-3
- Lirilumab (anti-Kir)

Bladder cancer:
ASCO 2016 - a banner year!

- # 4502: Durvalumab phase I
- # 4501: Nivolumab phase I/II
- # LBA4500: Atezolizumab 1st line
- # 4515: Atezolizumab 2nd line
- # 104: Atezolizumab biomarkers

Durvalumab (PD-L1 antibody) Phase 1 Expansion cohort

Study 1108: Dose-escalation and Dose-expansion Study in Patients with Advanced Solid Tumors

- Ongoing Phase I study of durvalumab monotherapy (N=1038) has shown a tolerable safety profile with early and durable antitumor activity in several tumor types[1–4]

Primary endpoint
Safety and tolerability

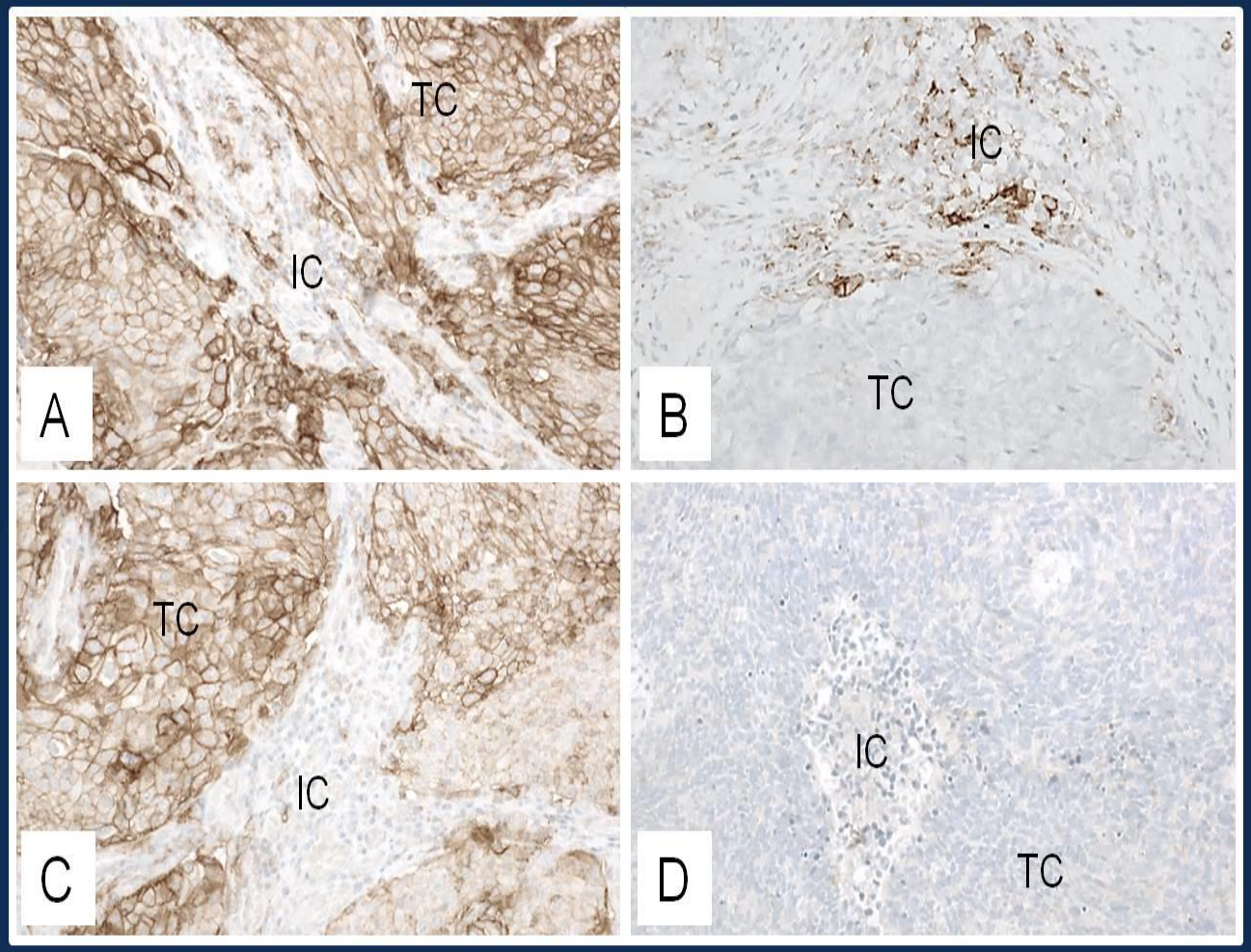
Key secondary endpoints
ORR per RECIST v1.1; DCR; DoR; PFS; OS

Exploratory endpoint
PD-L1 expression on tumor cells and tumor infiltrating immune cells

- Tumor assessments conducted at Weeks 6, 12, 16 then every 8 weeks during treatment period
- After one year of treatment, patients entered follow-up
- Upon evidence of progressive disease, patients were offered retreatment with durvalumab

1. Segal N, et al. Ann Oncol 2014;25(Suppl 4):iv365 (Abstract 1058PD [poster]); 2. Lutzky J, et al. J Clin Oncol 2014;32:5s(Suppl) Abstract 3001 [oral]; 3. Rizvi N, et al. J Clin Oncol 2015;33(Suppl) Abstract 8032 [Poster]; 4. Segal NH et al. J Clin Oncol 2015;33(Suppl) Abstract 3011 [Poster].

PD-L1 Scoring Criteria



(A) Tumor biopsy with PD-L1 immunostaining ≥25% TC and ≥25% IC (TC+/IC+); (B) <25% TC and ≥25% IC (TC–/IC+); (C) ≥25% TC and <25% IC (TC+/IC–); and (D) <25% TC and <25% IC (TC–/IC–).

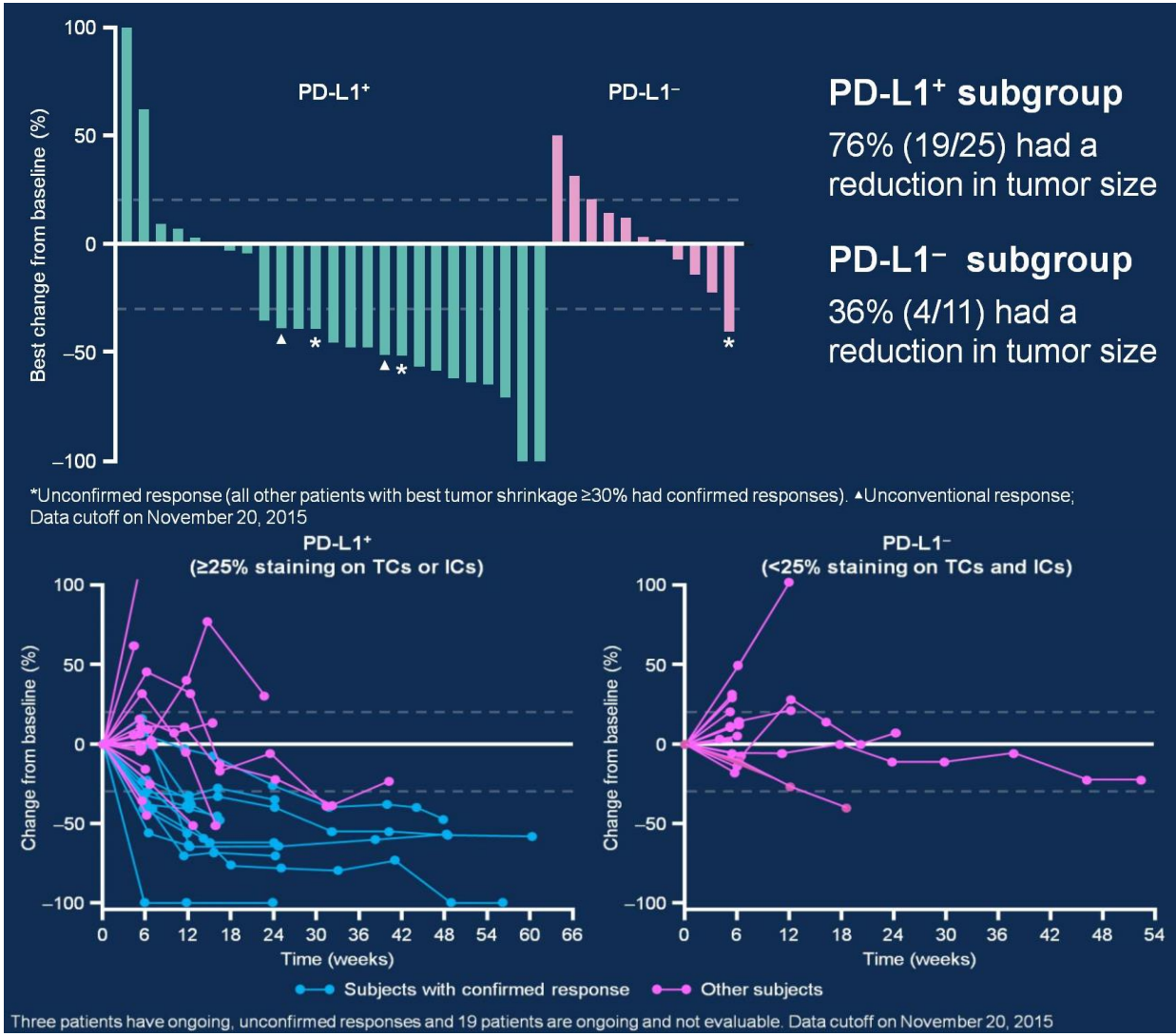
Confirmed ORR and DCR12 by PD-L1 Localization

PD-L1 expression by location	PD-L1 status definition	ORR[a]		DCR12[b]	
		(%) n/N	95% CI	(%) n/N	95% CI
all evaluable patients		31 (13/42)	18–47	48 (20/42)	32–64
TCs or ICs	PD-L1$^+$ (≥25% TCs or ICs)	46 (13/28)	28–66	57 (16/28)	37–76
	PD-L1$^-$ (<25% TCs and ICs)	0 (0/14)	0–23	29 (4/14)	8–58
TCs	PD-L1$^+$	47 (7/15)	21–73	53 (8/15)	27–79
	PD-L1$^-$	22 (6/27)	9–42	44 (12/27)	26–65
ICs	PD-L1$^+$	56 (10/18)	31–79	67 (12/18)	41–89
	PD-L1$^-$	13 (3/24)	3–32	33 (8/24)	16–55

PD-L1 status determined from the most recently collected tissue sample (prior to first dose of study treatment) with a quantifiable result; [a]ORR was defined as confirmed complete or partial response per RECIST v1.1 in response-evaluable; [b]DCR12 was defined as confirmed complete or partial response or stable disease for ≥12 weeks per RECIST v1.1. Data cutoff on November 20, 2015

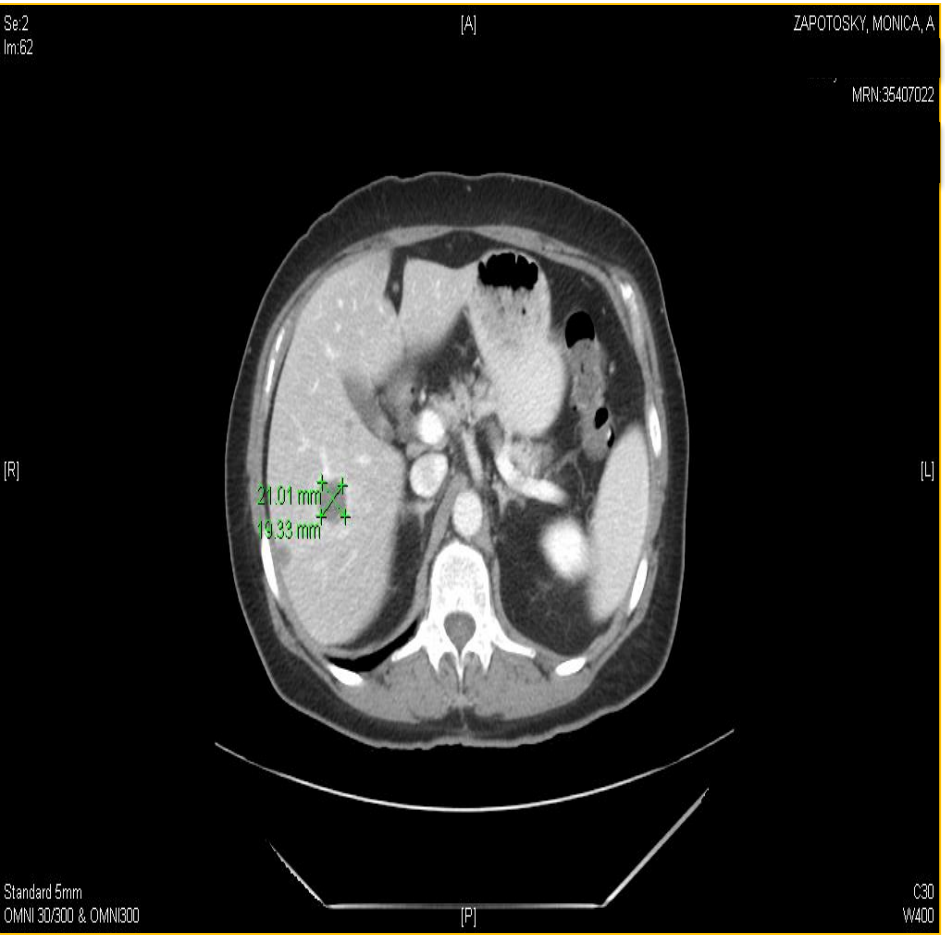
Durvalumab expansion cohort

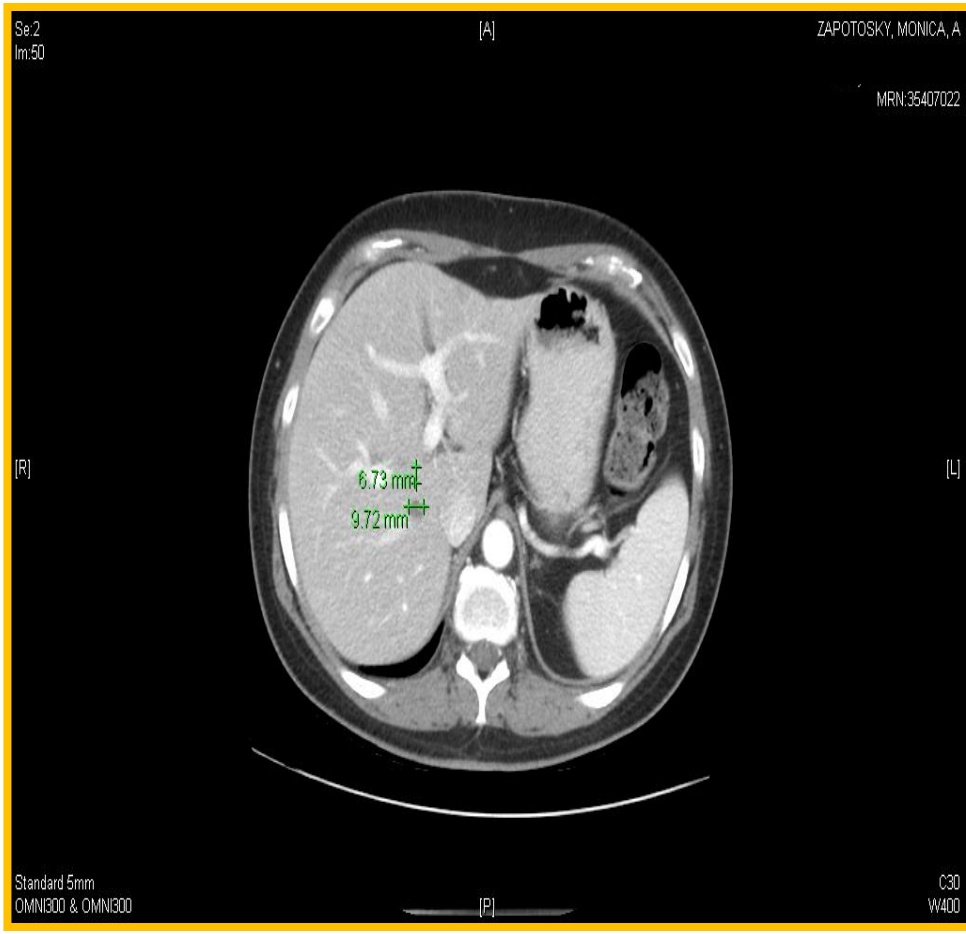
- High ORR in PD-L1 positive tumors
- Limited/no activity in PD-L1 negative but small #s
- Possibly best PD-L1 assay based on high ORR in positive patients



Atezolizumab in cisplatin-ineligible bladder cancer

- No “standard” though gemcitabine and carboplatin is community standard
- Atezolizumab is first FDA-approved PD-L1 inhibitor
  - Approved for locally advanced or metastatic urothelial carcinoma previously treated with platinum-based chemotherapy





Bladder Ca with sarcomatoid features s/p ITP now s/p Nivolumab

IMvigor210 Study: Cohort 1

IMvigor210:
- Inoperable locally advanced or metastatic urothelial carcinoma
- Predominantly UC histology
- Tumor tissue evaluable for PD-L1 testing[a]

→ **Cohort 1** (N = 119): 1L cisplatin ineligible → Atezolizumab 1200 mg IV q3w until RECIST v1.1 progression

→ Cohort 2: Platinum-treated mUC → Atezolizumab 1200 mg IV q3w until loss of clinical benefit

Cohort 1–specific inclusion criteria
- No prior treatment for mUC (> 12 mo since perioperative chemo)
- ECOG PS 0-2
- Cisplatin ineligibility[1] based on ≥ 1 of the following:
  - Renal impairment: GFR < 60 and > 30 mL/min[b]
  - ≥ Grade 2 hearing loss or peripheral neuropathy
  - ECOG PS 2

Primary endpoint
- Confirmed ORR: RECIST v1.1 (per central IRF)

Key secondary endpoints
- DOR, PFS, OS, safety

IRF, independent review facility. ClinicalTrials.gov ID: NCT02108652.
[a] PD-L1 prospectively assessed by a central laboratory, with patients and investigators blinded. [b] Cockcroft-Gault formula. 1. Galsky *J Clin Oncol* 2011.

Efficacy

Response to Atezolizumab (IRF RECIST v1.1)

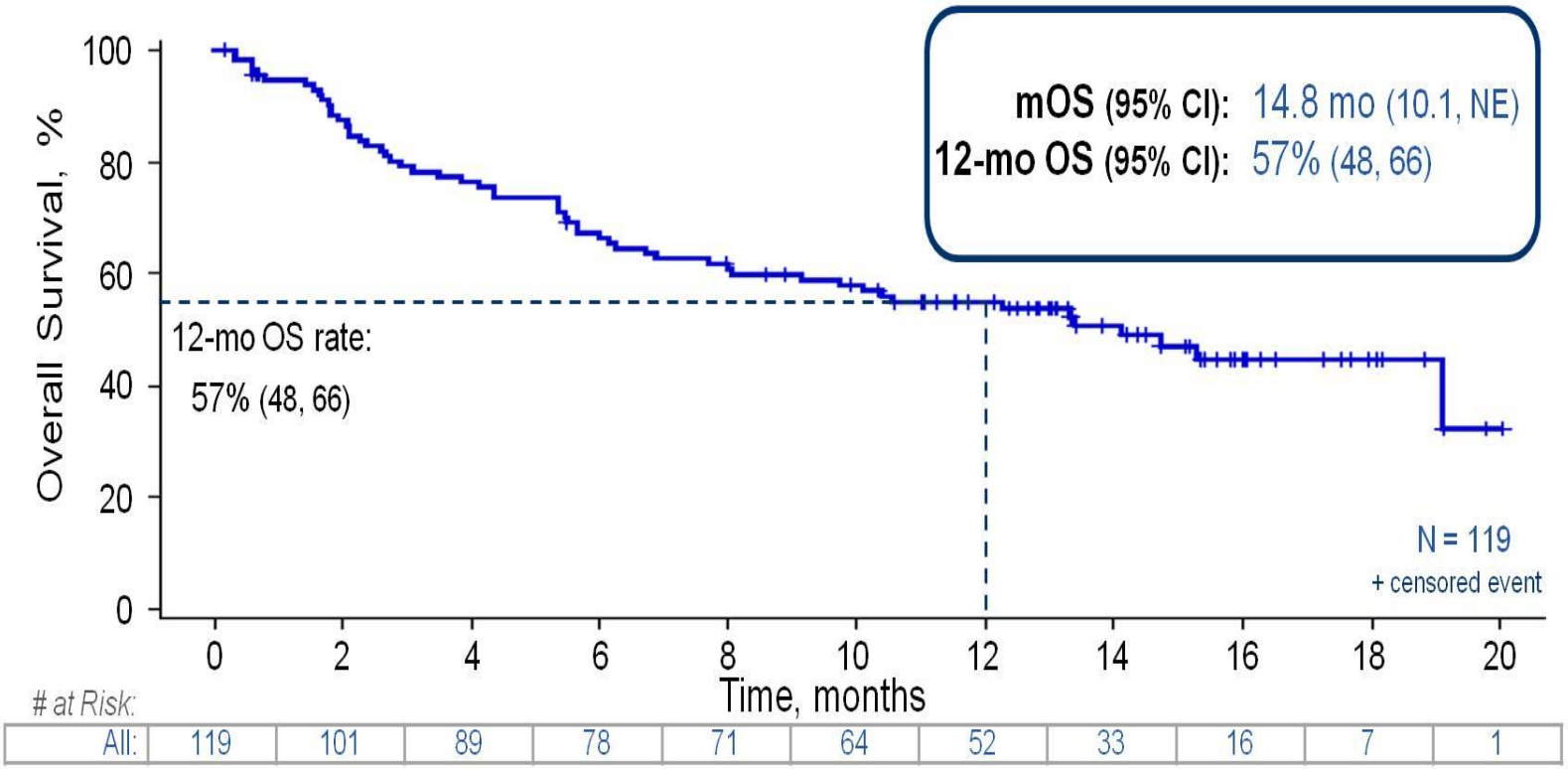
	IC2/3 (n = 32)	IC1/2/3 (n = 80)	All Patients (N = 119)	IC1 (n = 48)	IC0 (n = 39)
ORR[a] (95% CI)	28% (14, 47)	25% (16, 36)	24% (16, 32)	23% (12, 37)	21% (9, 36)
CR	**6%**	**6%**	**7%**	**6%**	**8%**
PR	22%	19%	17%	17%	13%

- Patients in this analysis had a median of follow-up duration of 14.4 mo (range, 0.2-20.1 mo)
- Confirmed complete responses were observed in all PD-L1 subgroups

[a] Includes 19 patients with missing/unevaluable responses. All treated patients had measurable disease at baseline per investigator-assessed RECIST v1.1. PD-L1 IC status: IC2/3 (≥ 5%), IC1 (≥ 1% and < 5%), IC0 (< 1%). Data cutoff: March 14, 2016.

Efficacy

Overall Survival (Median and Landmark 12-Month OS)

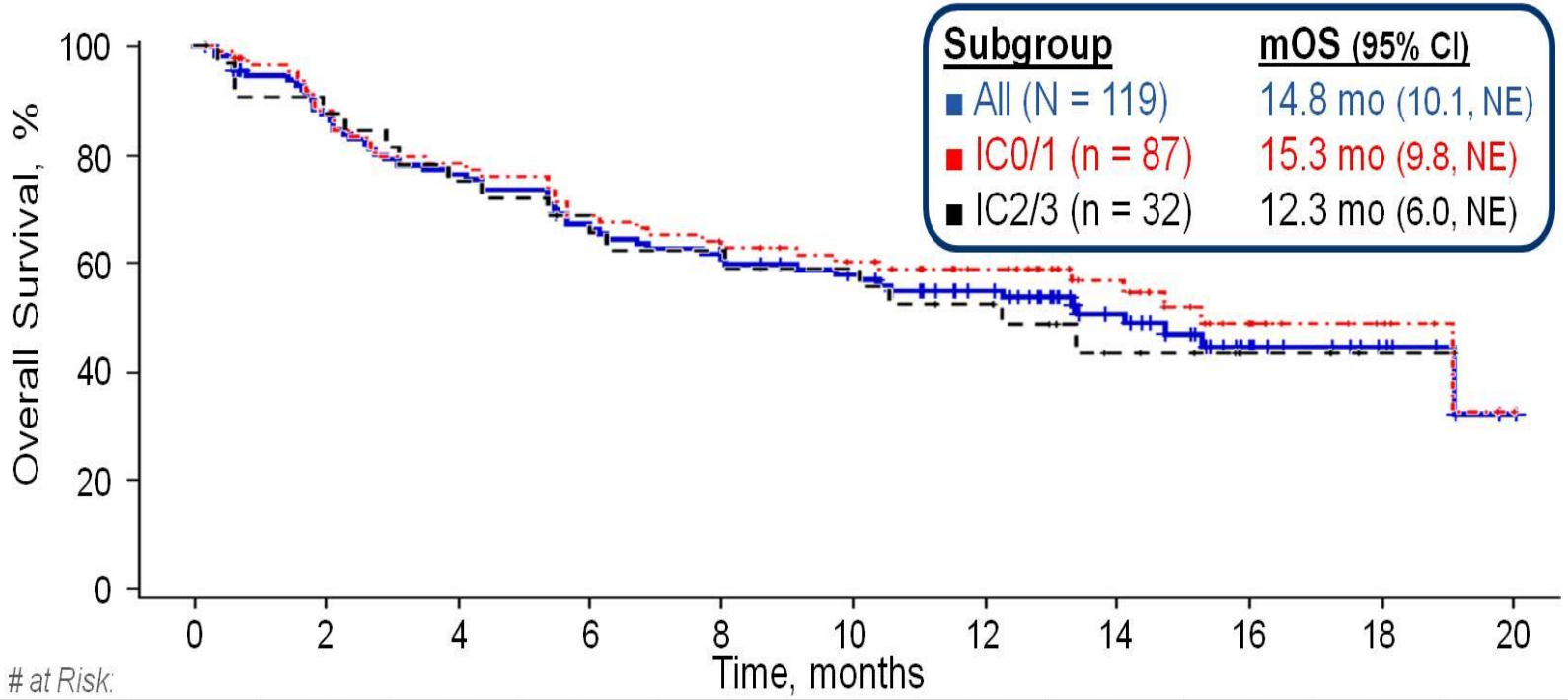


- With a median follow-up of 14.4 months,[a] the event rate is 47%
- Atezolizumab compares favorably with historic data from cisplatin-ineligible patients, both from clinical trials and real-world studies[1,2]

[a] Range, 0.2 to 20.1 mo. Data cutoff: March 14, 2016. 1. De Santis *J Clin Oncol* 2012. 2. Galsky ECC 2015 [poster 115].

Efficacy

Overall Survival (Median OS) by PD-L1 Status



 # at Risk:

All:	119	101	89	78	71	64	52	33	16	7	1
IC0/1:	87	73	65	57	52	46	37	26	13	6	1
IC2/3:	32	28	24	21	19	18	15	7	3	1	0

- With a median follow-up of 14.4 months,[a] the event rate is 47%

[a] Range, 0.2 to 20.1 mo. Data cutoff: March 14, 2016.

IMvigor210 Cohort 2: Study Design

Basis for Accelerated Approval

- Locally advanced or metastatic urothelial carcinoma
- Predominantly TCC histology
- Tumor tissue for PD-L1 testing[a]

→ **Cohort 1** (N = 119)
1L cisplatin ineligible → *Cohort 1 presented earlier this morning*[1]

→ **Cohort 2** (N = 310)
Platinum-treated mUC → Atezolizumab
1200 mg IV q3w
until loss of benefit

Cohort 2–specific inclusion criteria

- Progression during/following platinum (no restrictions on # prior lines of therapy)
- ECOG PS 0-1
- CrCl ≥ 30 mL/min

Median follow-up: 17.5 months
(range, 0.2 to 21.1+ mo)

Co-primary endpoints:

- ORR (confirmed) per RECIST v1.1 by central review
- ORR per immune-modified RECIST by investigator

Key secondary endpoints

- DOR, PFS, OS, safety

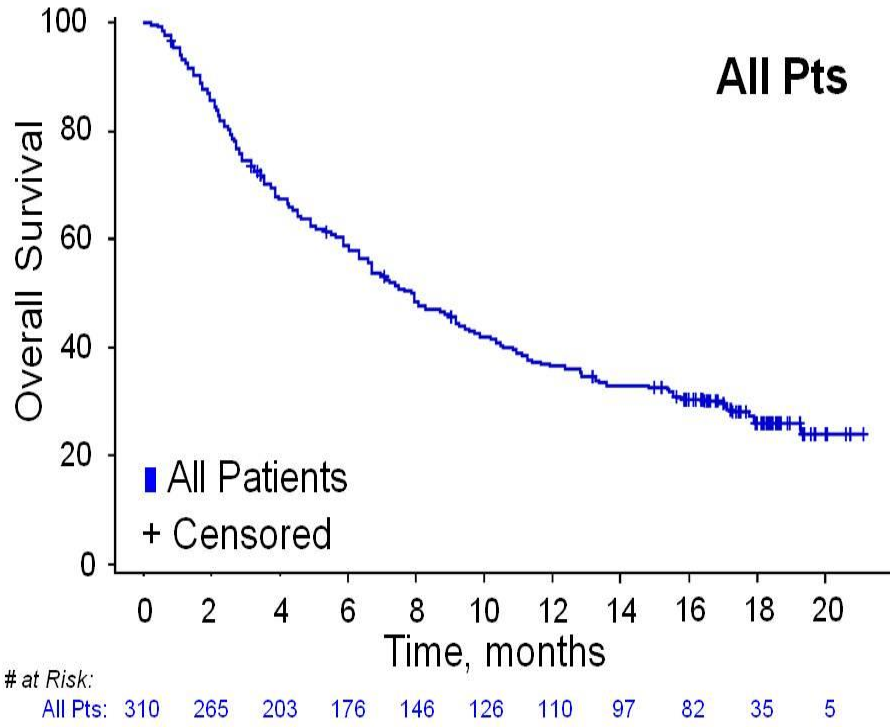
Key exploratory endpoints

- Biomarkers (*To be presented later this morning in the Clinical Science Symposium*[2])

TCC, transitional cell carcinoma. [a] Patients and investigators blinded to PD-L1 IHC status. Trial Identifier: NCT02108652.
1. Balar ASCO 2016 [abstract LBA4500]. 2. Rosenberg ASCO 2016 [abstract 104]. ("*Immunotherapy: Now We're Getting Personal*" session)

Efficacy

Overall Survival



Subgroup	Median OS (95% CI)		
	IC2/3	IC0/1	All
All pts (N = 310)	11.9 mo (9.0, 17.9)	6.7 mo (5.4, 8.0)	7.9 mo (6.7, 9.3)
2L only (n = 120)	NE (10.9, NE)	7.1 mo (5.0, 9.2)	9.0 mo (7.2, 11.3)

Subgroup	12-mo OS (95% CI)		
	IC2/3	IC0/1	All
All pts (N = 310)	50% (40, 60)	31% (24, 37)	37% (31, 42)
2L only (n = 120)	61% (44, 77)	29% (19, 39)	38% (29, 47)

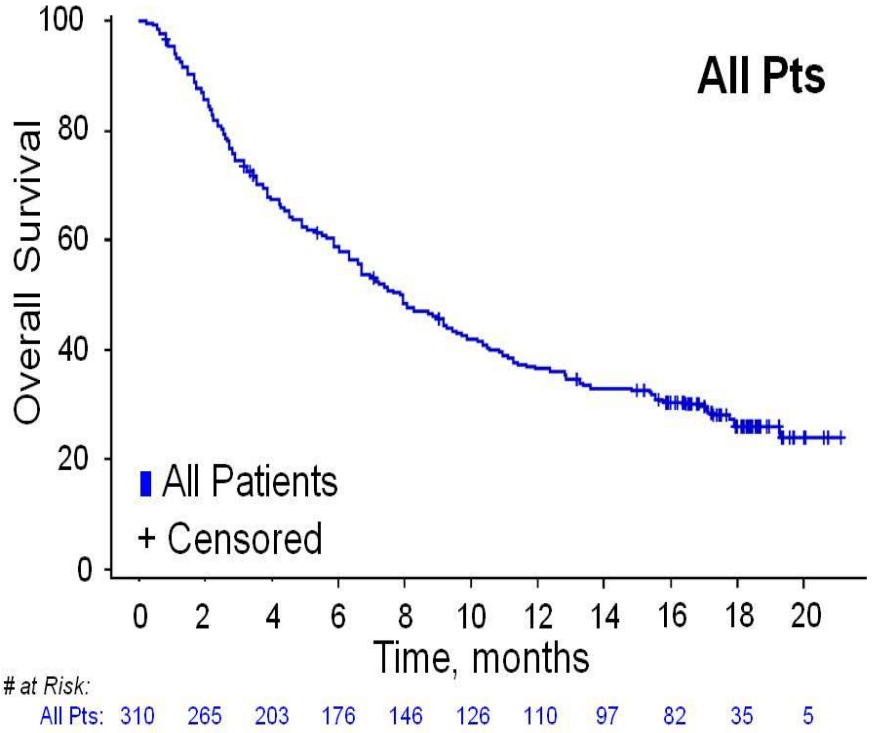
- Longer OS observed in patients with higher PD-L1 IC status
- 12-mo OS compares favorably with historic estimates of ≈ 20%[1]

Median follow-up (range):
All pts: 17.5 mo (0.2 to 21.1+ mo)
2L only: 17.3 mo (0.5 to 21.1+ mo)

NE, not estimable. [a] One prior line of therapy for mUC and no (neo)adjuvant therapy. Data cutoff: March 14, 2016. 1. Agarwal *Clin Genitourin Cancer* 2014.

Efficacy

Overall Survival



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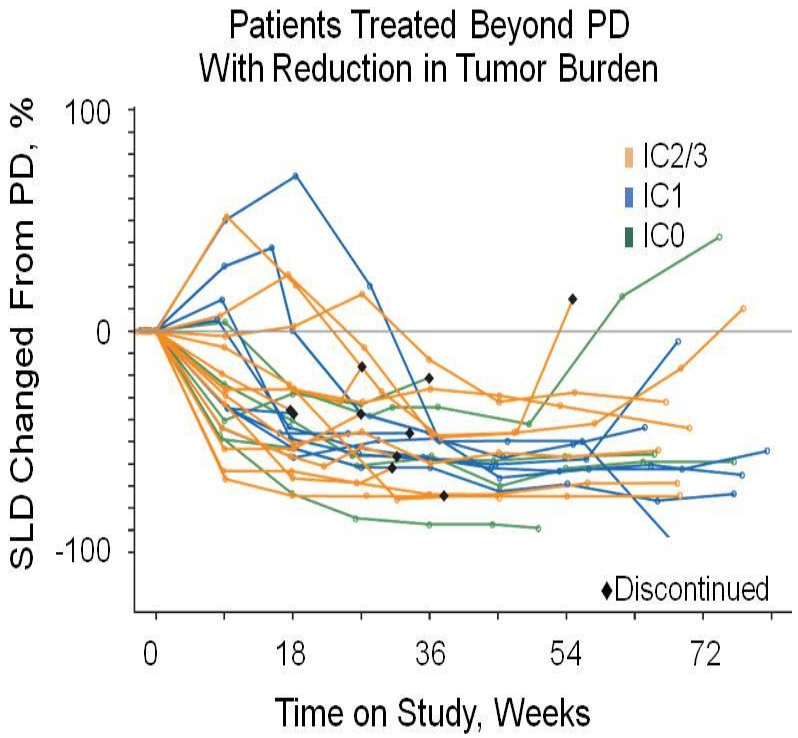
Outcome of Patients Treated Beyond Progression

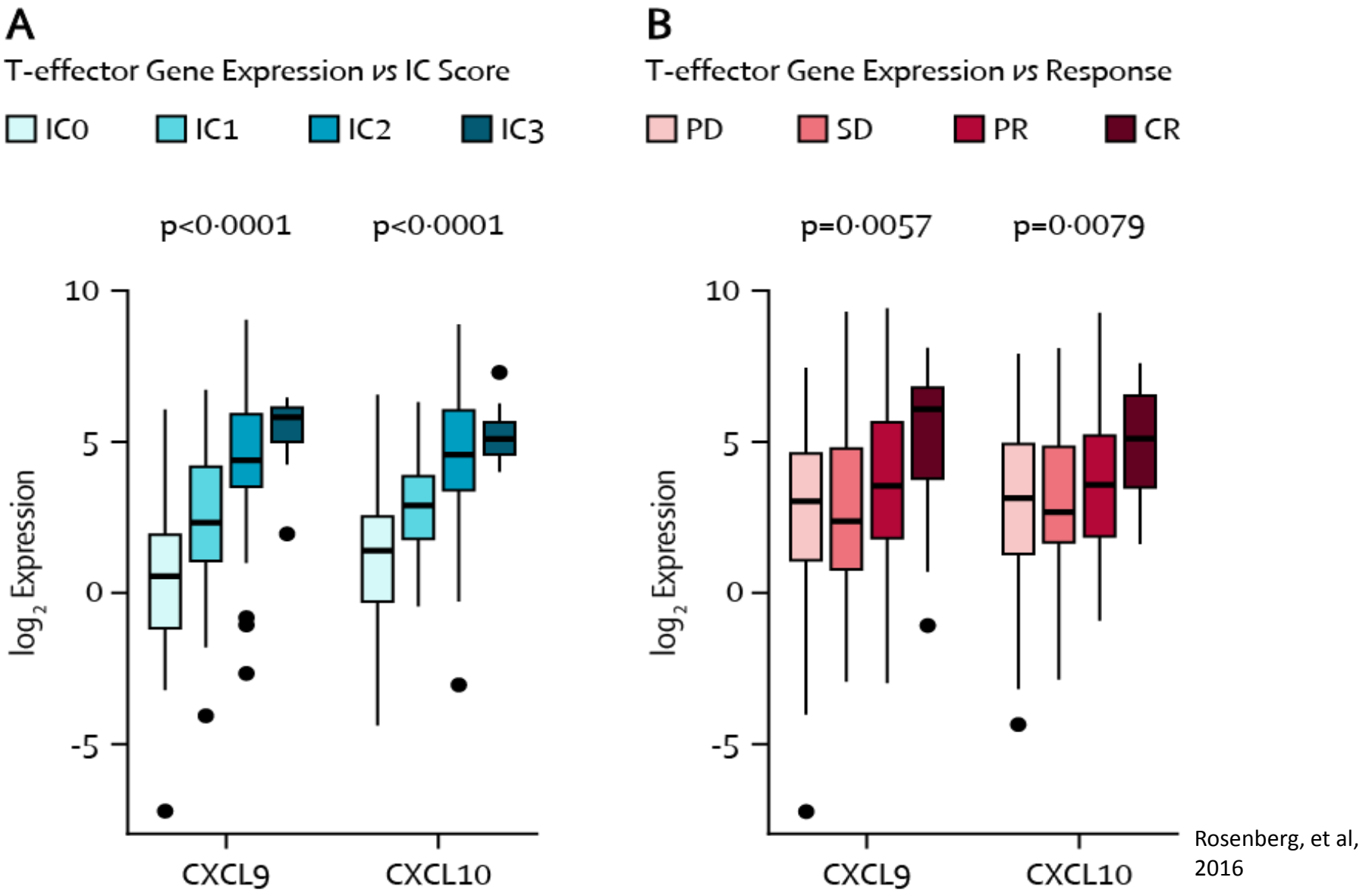
- Subsequent reductions in target lesion SLD were seen in patients treated with atezolizumab beyond progression, highlighting the potential the potential for non-classical responses



- In patients treated beyond PD
  - 19% (26/134) had SLD reductions ≥ 30% in target lesions
  - 28% (38/134) had disease stabilization (> -30% to +20% SLD change)
  - mOS was 11.4 mo in all patients treated beyond progression
  - 12-mo OS was 50% in all patients treated beyond progression
  - The safety of atezolizumab was consistent with that in the ITT population

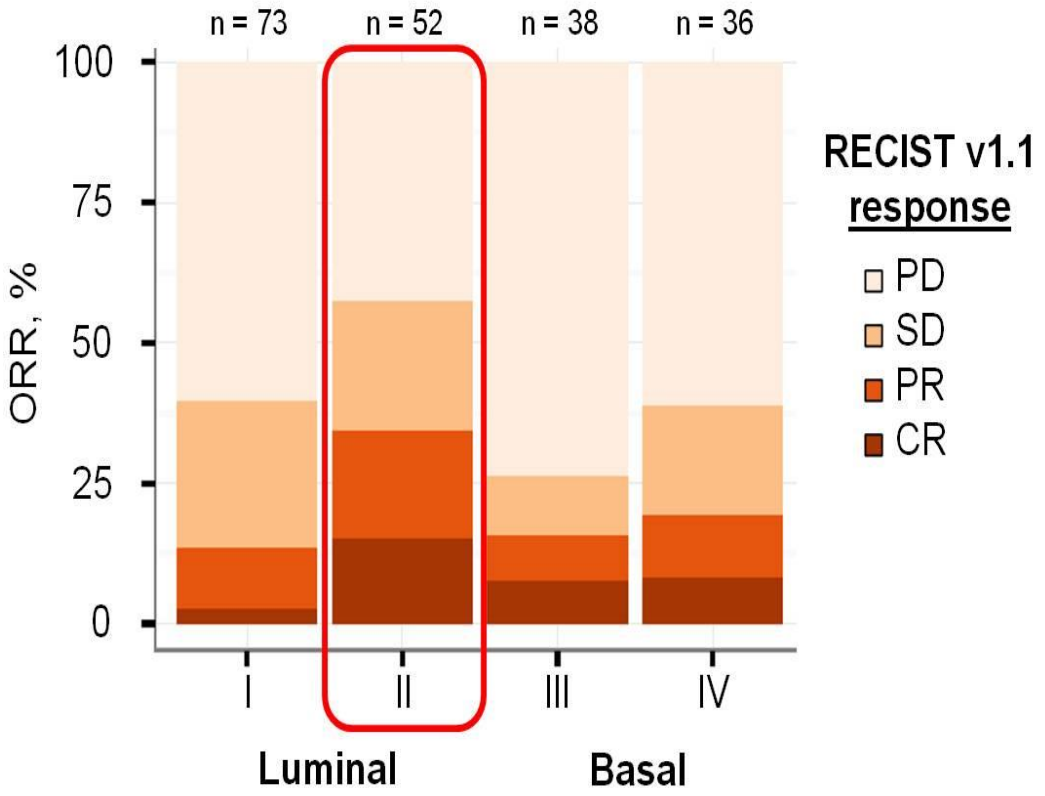
Patients without post-PD baseline tumor assessments (n = 29) are not included in plot. Data cutoff: March 14, 2016.

High levels of immune response genes are associated with both PD-L1 staining and treatment response



Rosenberg, et al, 2016

TCGA Subtype II Is Associated With Higher ORR

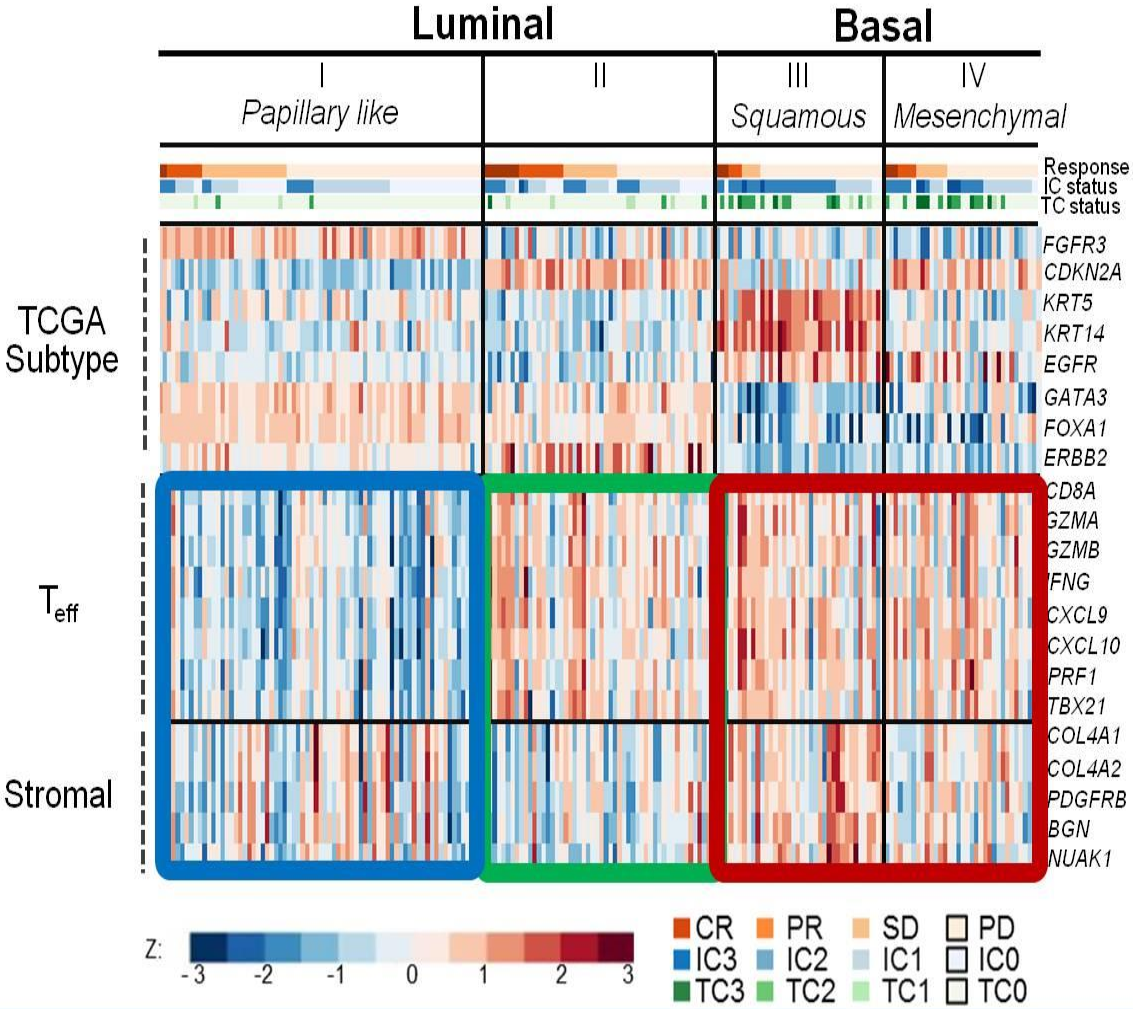


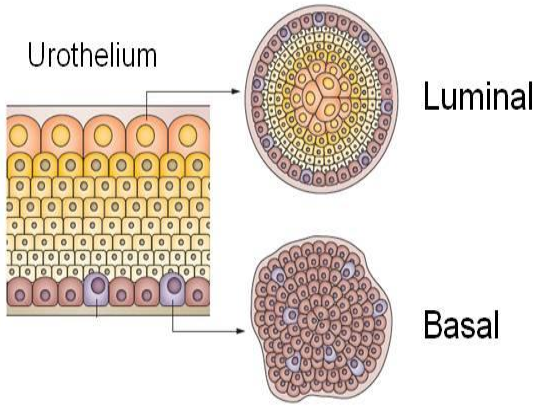
- Gene expression data used to classify IMvigor210 tumor samples recapitulated TCGA subtypes[1,2]
- Responses occurred in all subtypes, but ORR was significantly higher in luminal II vs other subtypes ($P = 0.0072$)
- What might be the drivers of this subtype-specific response?

TCGA, The Cancer Genome Atlas. Data cutoff: March 14, 2016.

1. Cancer Genome Atlas Research Network *Nature* 2014. 2. Rosenberg *Lancet* 2016.

IMvigor210: TCGA Subtype in mUC

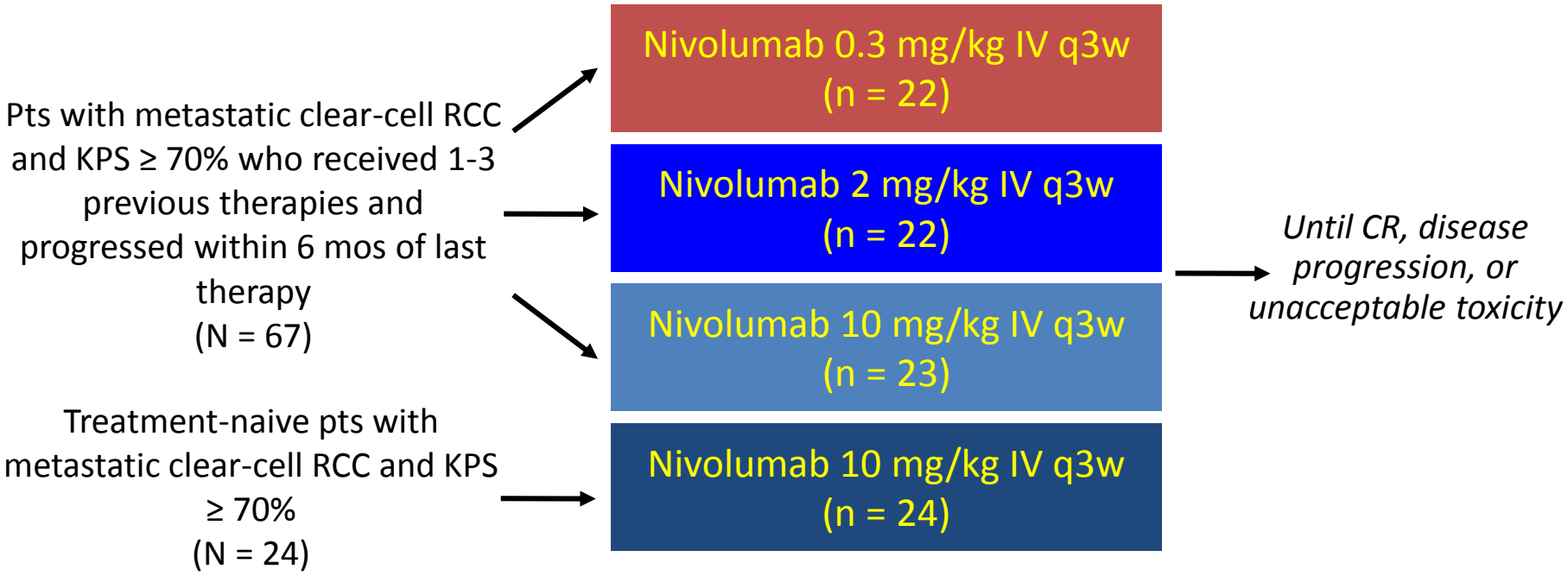




- Luminal I tumors have low T_{eff} expression
- Luminal II tumors have high T_{eff} and low stromal gene expression
- Basal tumors have high T_{eff} and high stromal gene expression

Data cutoff: March 14, 2016.

Nivolumab in mRCC: Study Design

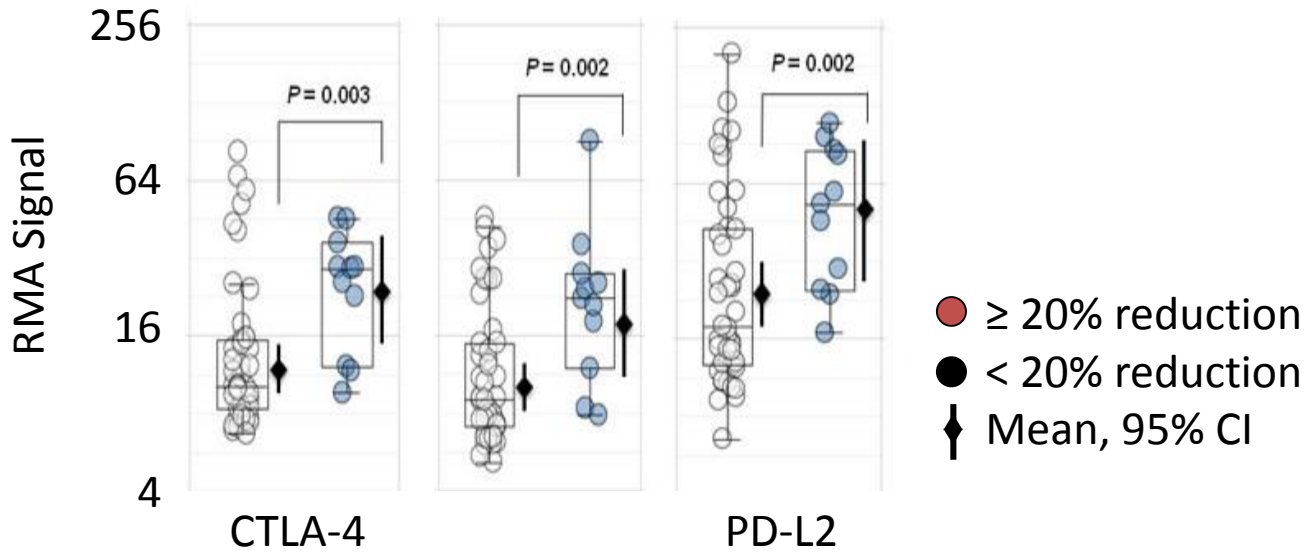


- Primary endpoint: PD effects on tumor-infiltrating T cells and serum chemokines
- Secondary endpoints: response, safety, tolerability
- Exploratory endpoints: associations of PD-L1 expression, serum cytokines, gene expression, TCR repertoire, in relation to efficacy

Choueiri TK, et al. ASCO 2015. Abstract 4500.

Nivolumab in mRCC: Immune Checkpoint Expression and Tumor Burden

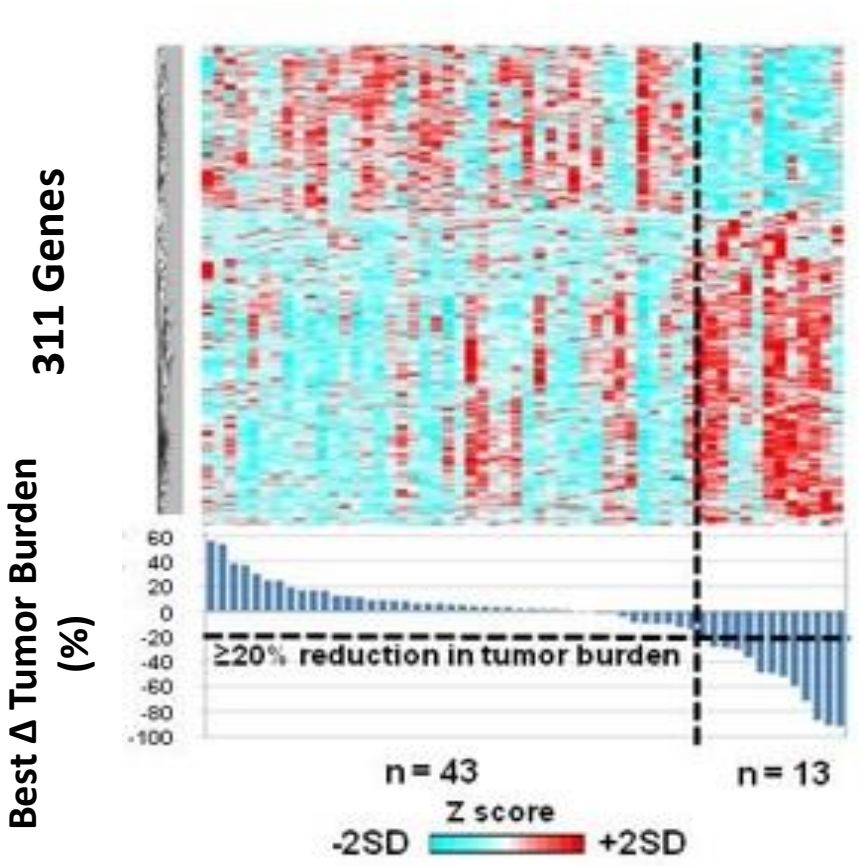
- Increased expression of 3 immune checkpoint genes during treatment found to correlate with ≥ 20% reduction in tumor burden
- Expression of these genes may signal process of immune editing even in presence of nivolumab



Choueiri TK, et al. ASCO 2015. Abstract 4500. Reprinted with permission.

Nivolumab in mRCC: Baseline GEPs Correlate With Response

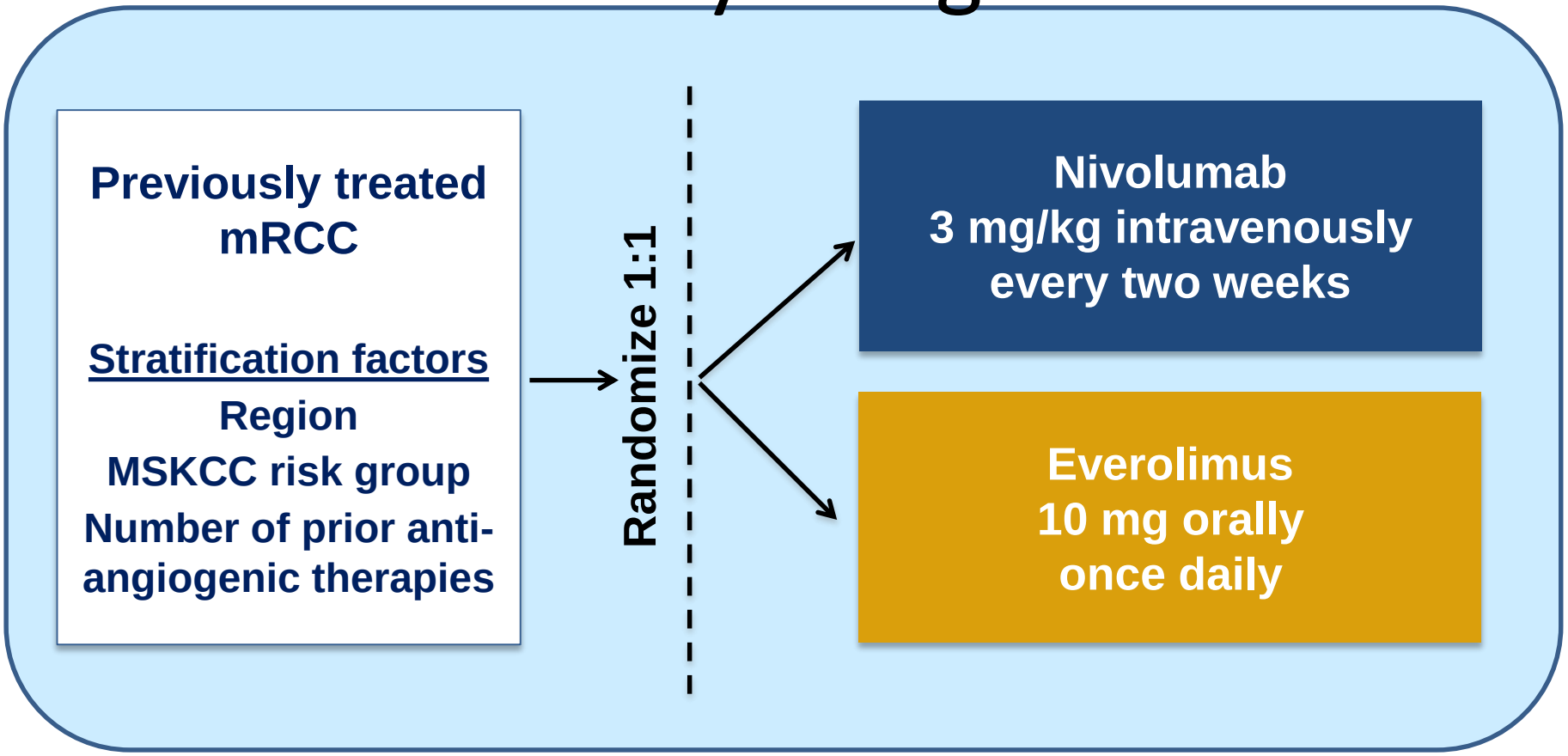
- Response (≥ 20% reduction in tumor burden) associated with:
  - **Lower baseline expression** of genes involved in protein localization, lung morphogenesis, and downregulated by ipilimumab[2] in melanoma
  - **Higher baseline expression** of genes of myeloid and lymphoid lineage, immune system genes, upregulated by ipilimumab in melanoma



Choueiri TK, et al. ASCO 2015. Abstract 4500. 2. Ji RR, et al. Cancer Immunol Immunother. 2102;61:1019-1031. Reprinted with permission.

CheckMate 025:
A randomized, open-label, phase III study of nivolumab versus everolimus in advanced renal cell carcinoma

Study design



- Patients were treated until progression or intolerable toxicity occurred
- Treatment beyond progression was permitted if drug was tolerated and clinical benefit was noted

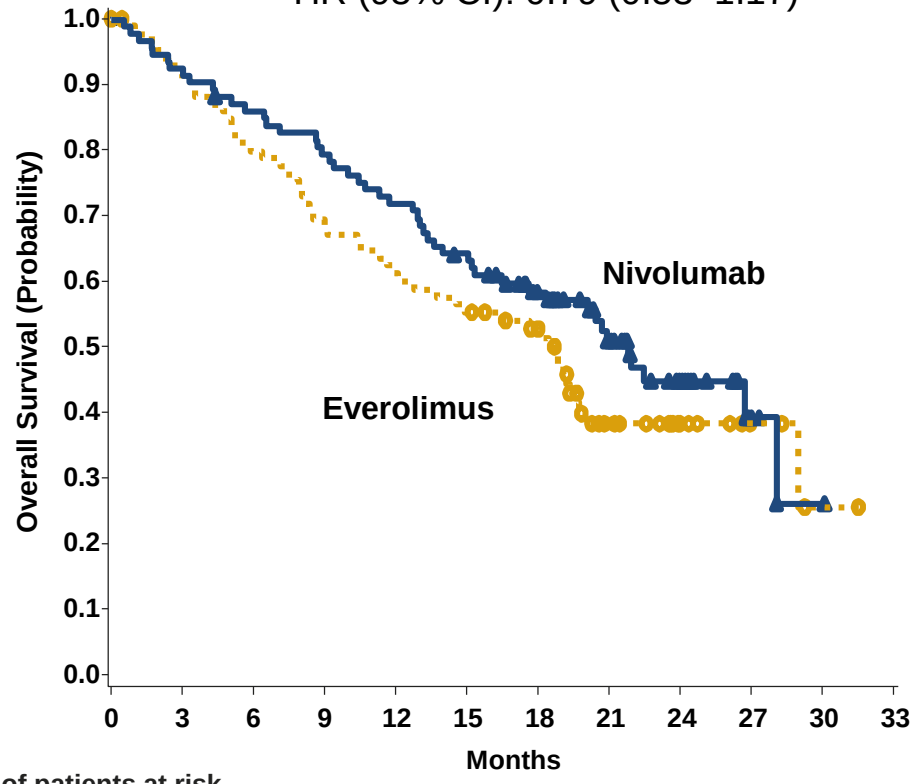
Motzer, et al, NEJM, 2015

Overall survival by PD-L1 expression

PD-L1 ≥1% (n = 24%)

Median OS, months (95% CI)	
Nivolumab	21.8 (16.5–28.1)
Everolimus	18.8 (11.9–19.9)

HR (95% CI): 0.79 (0.53–1.17)



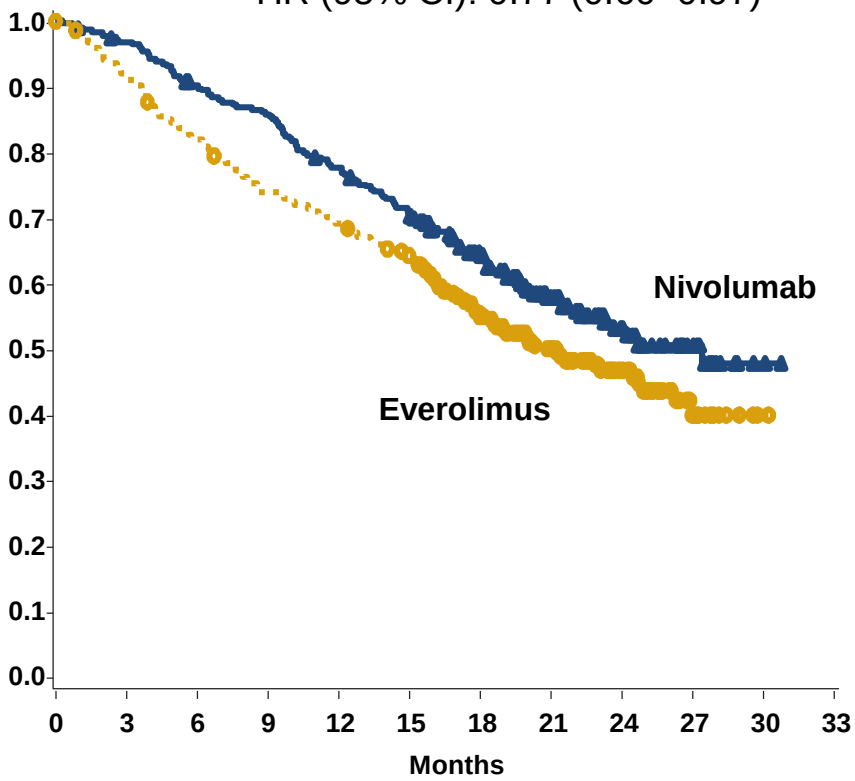
No. of patients at risk

Nivolumab	94	86	79	73	66	58	45	31	18	4	1	0
Everolimus	87	77	68	59	52	47	40	19	9	4	1	0

PD-L1 <1% (n = 76%)

Median OS, months (95% CI)	
Nivolumab	27.4 (21.4–NE)
Everolimus	21.2 (17.7–26.2)

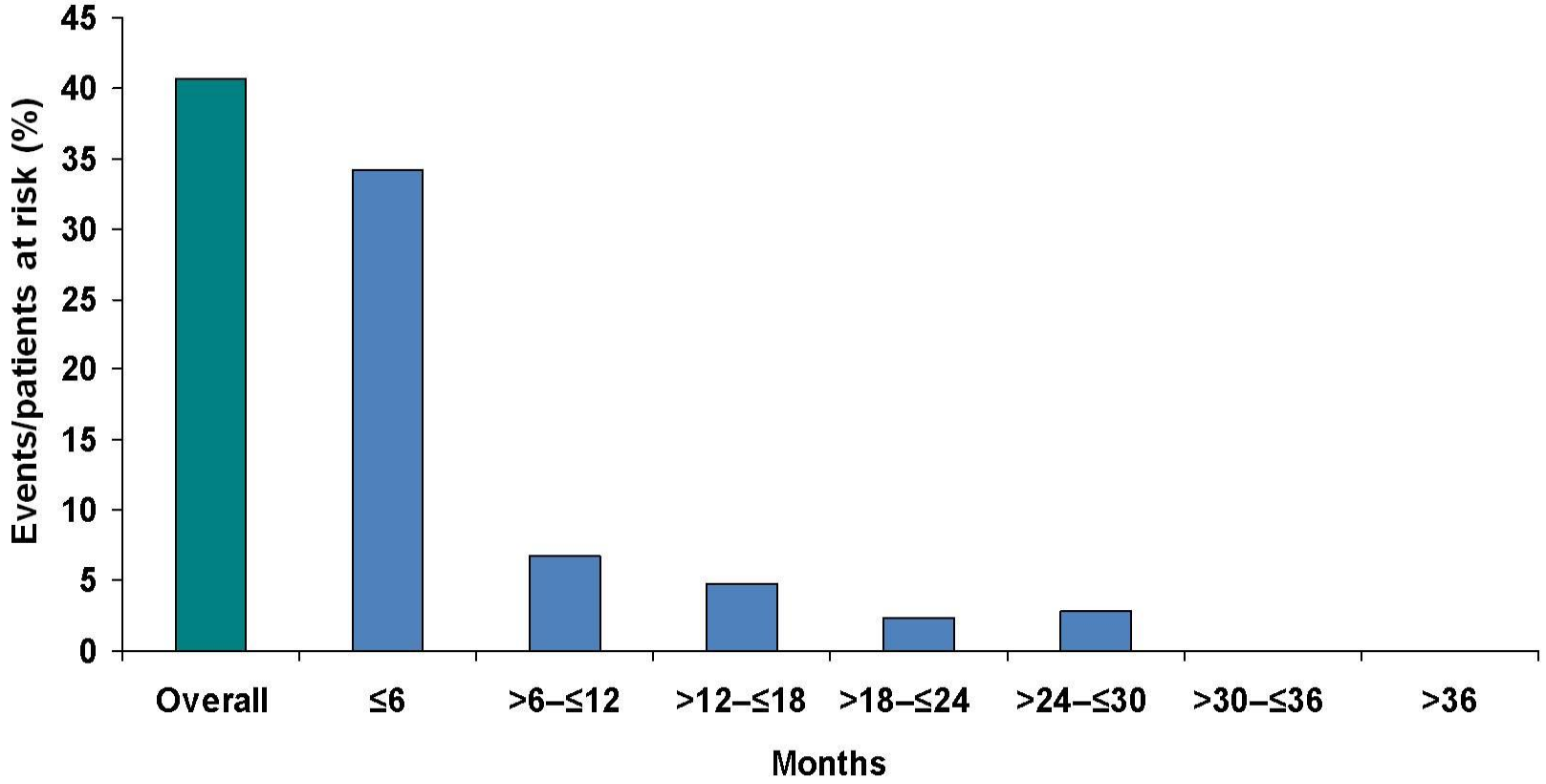
HR (95% CI): 0.77 (0.60–0.97)



	276	265	245	233	210	189	145	94	48	22	2	0
	299	267	238	214	200	182	137	92	51	16	1	0

Low rates of immune related AE's with long-term nivolumab therapy

Emergence of select treatment-related AEs (any grade) over time in phase II study



- Select treatment-related AEs included endocrine, gastrointestinal, hepatic, pulmonary, renal, and skin

Conclusions on Checkpoint Inhibitors:

- Patients who have a response may represent a prevalent “immune-responsive” subset of who benefit from either cytokines or checkpoint inhibitors
- PD-1 ligand 1 (PD-L1) expression, in tumor cells or infiltrating immune cells - associated with benefit from PD-1 or PD-L1 inhibitors.

- PD-L1 expression in renal-cell cancer tissue did not delineate the patients who were more likely to benefit.

- the most effective duration of therapy with nivolumab and whether the therapy should continue beyond progression remains unknown

❖ **Are we leaning toward customized immunotherapy, ie, fitting a particular cancer to the drug?**

Unresolved Issues…

- Not all solid tumors respond equally. Why is prostate the exception?
- Timing of immune modulation is critical
- T ½ for Ipilimumab long c/w nivolumab
- Can immune system be primed?
- Importance of establishing concordant immune endpoints; are they relevant for all cancers?
- Do immune endpoints correlate with change in tumor biology?
- Candidate selection; cancer localization