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Society for Immunotherapy of Cancer

Cancer Immunotherapy 101

Immunotherapy for Genitourinary Cancers

August 19, 2016

Evan Y. Yu, M.D.
Professor of Medicine (Oncology)
University of Washington
Fred Hutchinson Cancer Research Center

Disclosures

- Consulting Fees: Agensys, Bayer, Dendreon, Genentech/Roche, Janssen, Merck
- Contracted Research: Agensys, Astellas, Bayer, Dendreon, Genentech/Roche, Imclone/Lilly, Merck

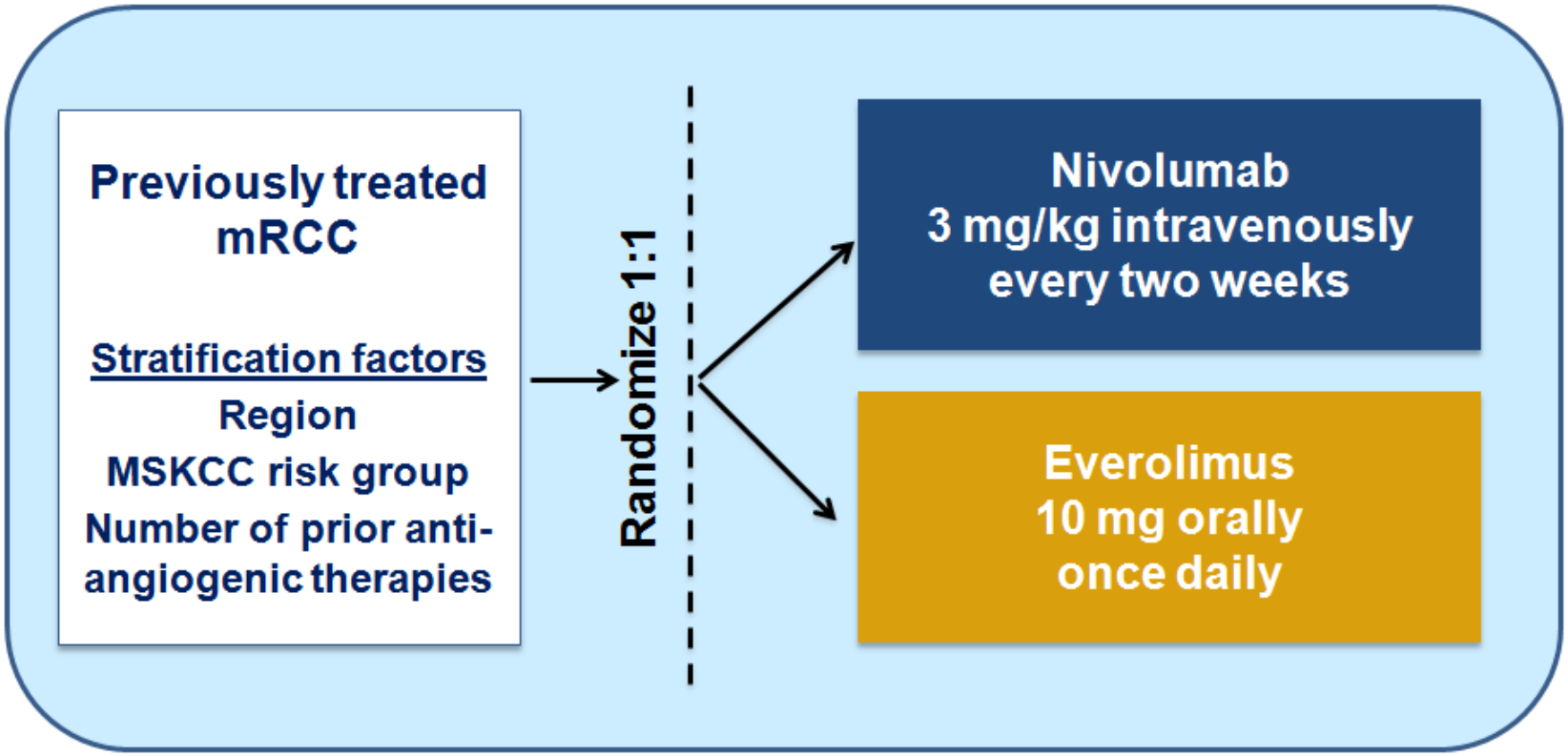
I will be addressing non-FDA approved therapies in this presentation.

Discussion Topics

- The cancers
  - Renal cell carcinoma
  - Urothelial carcinoma
  - Prostate carcinoma
- Standard of care therapies
- Ongoing key research topics
- Cases

Renal Cell Carcinoma

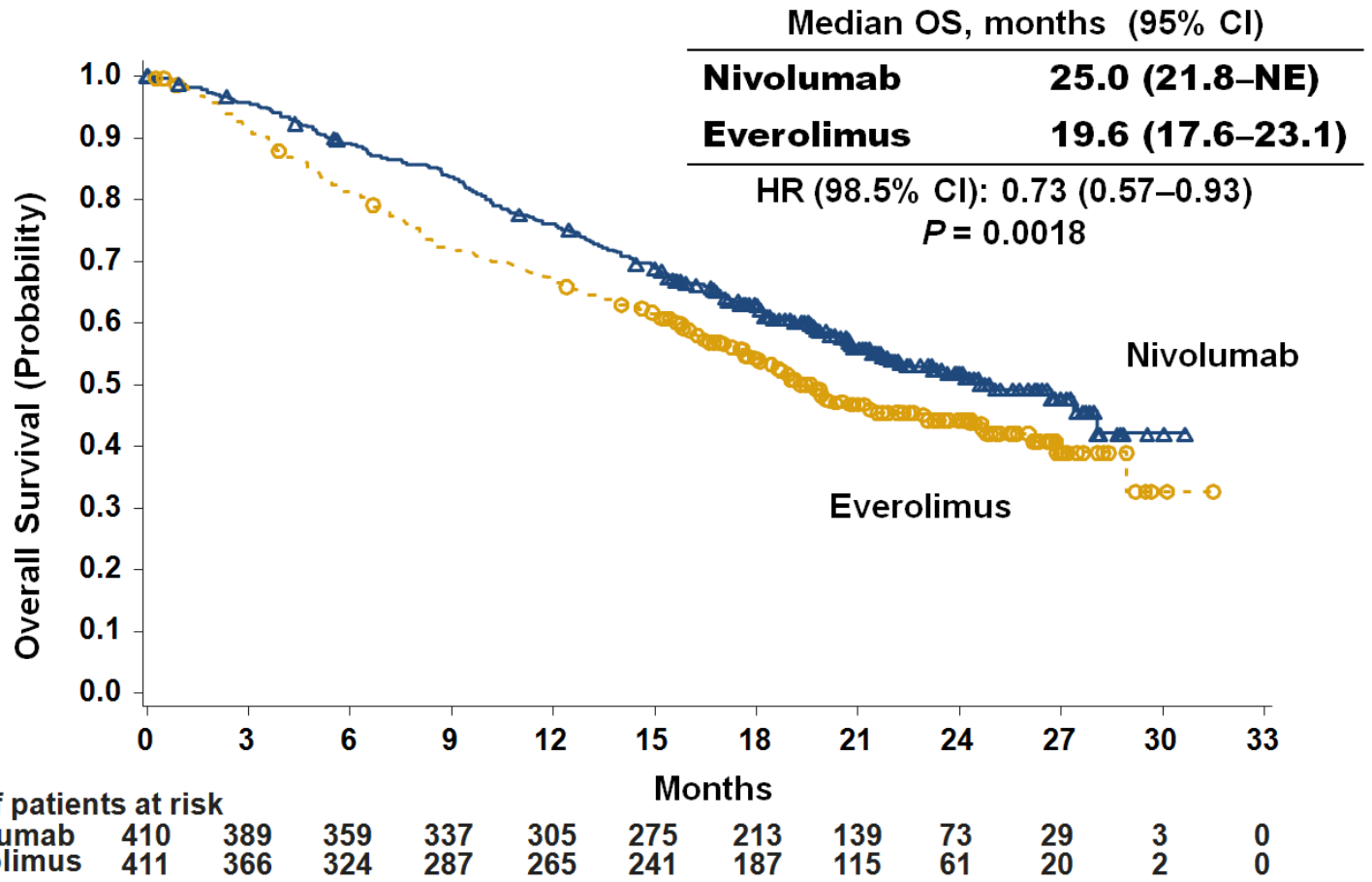
Second and Third Line for RCC



- Primary Endpoint: OS
- Secondary Endpoint: ORR, PFS, Aes, QOL, and OS by PD-L1 expression

Motzer RJ *et al*. N Engl J Med 2015; 373: 19: 1803-13.

Nivolumab is Superior for OS



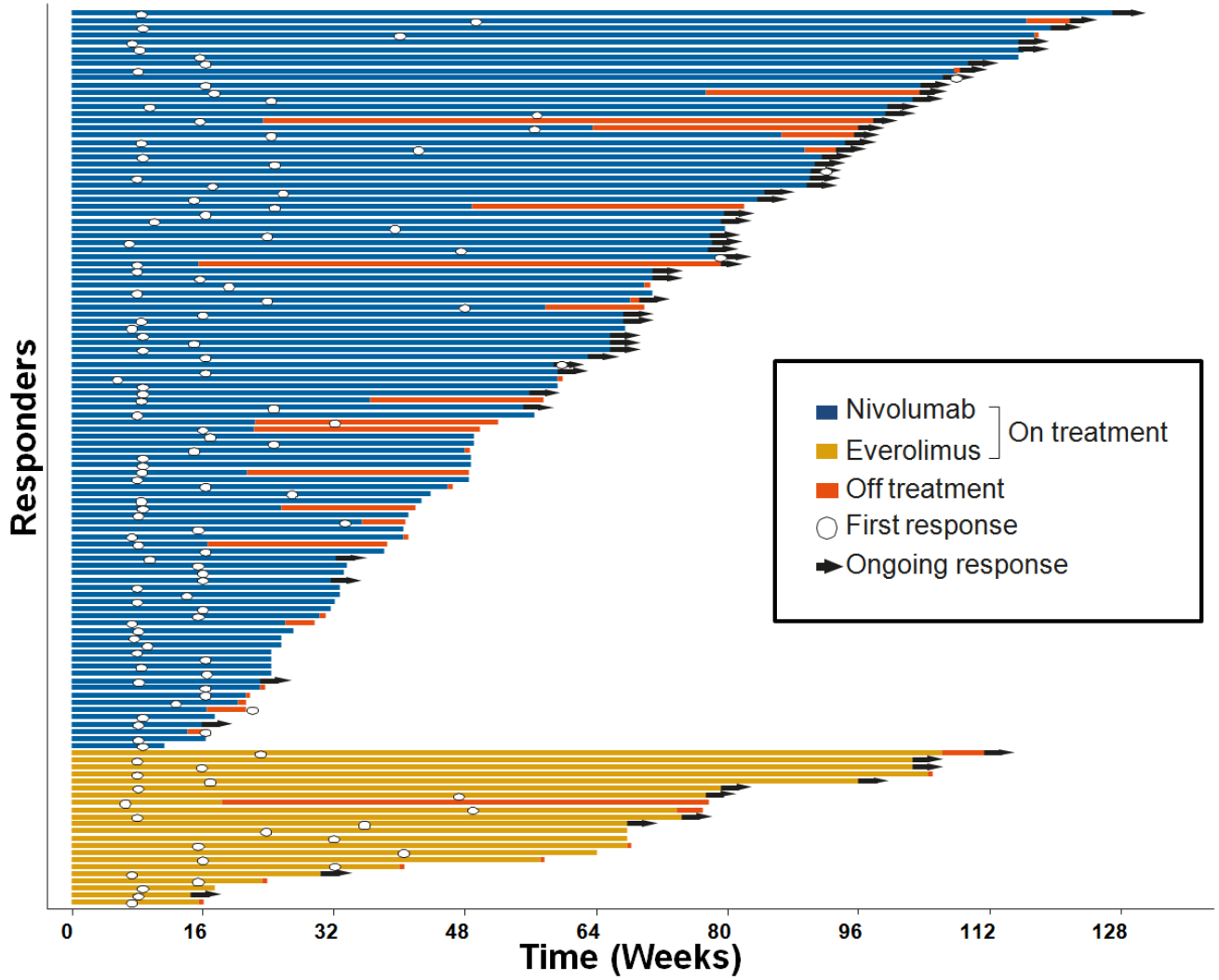
Motzer RJ *et al*. N Engl J Med 2015; 373: 19: 1803-13.

Response Rates

	Nivolumab N = 410	Everolimus N = 411
Objective response rate, %	25	5
Odds ratio (95% CI)	5.98 (3.68–9.72)	
P value	<0.0001	
Best overall response, %		
Complete response	1	1
Partial response	24	5
Stable disease	34	55
Progressive disease	35	28
Not evaluated	6	12
Median time to response, months (range)	3.5 (1.4–24.8)	3.7 (1.5–11.2)
Median duration of response, months (range)*	12.0 (0–27.6)	12.0 (0–22.2)
Ongoing response, n/N (%)	49/103 (48)	10/22 (45)

Motzer RJ *et al*. N Engl J Med 2015; 373: 19: 1803-13.

Durability of Response



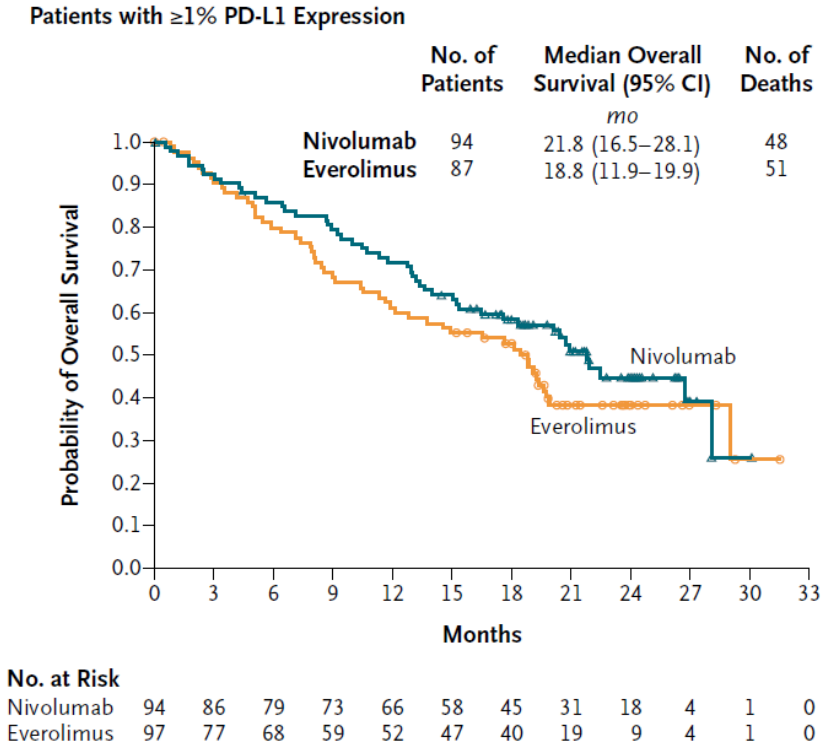
Motzer RJ *et al*. N Engl J Med 2015; 373: 19: 1803-13.

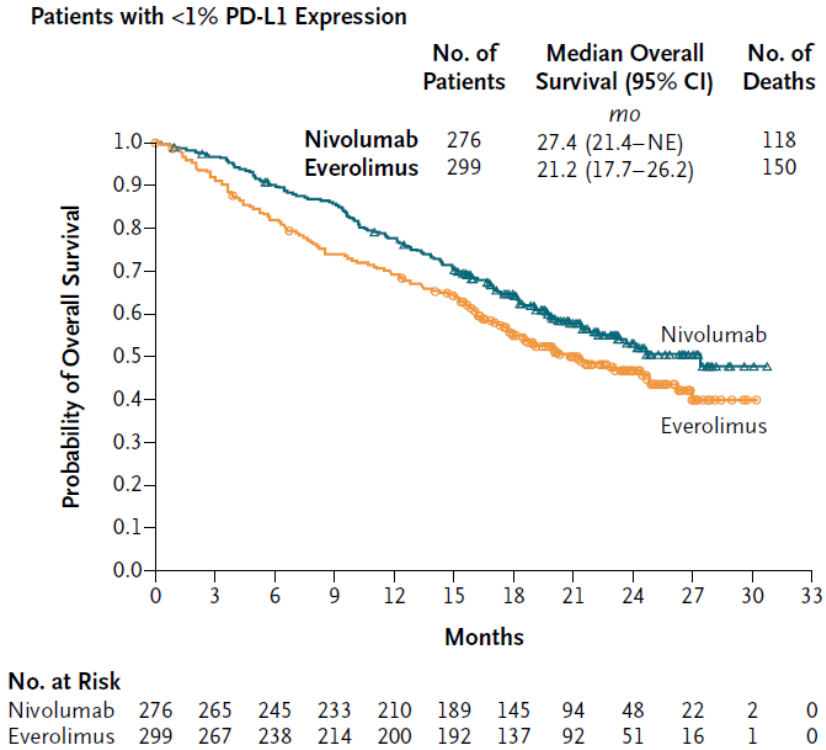
Adverse Events

	Nivolumab N = 406			Everolimus N = 397		
	Any grade	Grade 3	Grade 4[a]	Any grade	Grade 3	Grade 4[b]
Treatment-related AEs, %	79	18	1	88	33	4
Fatigue	33	2	0	34	3	0
Nausea	14	<1	0	17	1	0
Pruritus	14	0	0	10	0	0
Diarrhea	12	1	0	21	1	0
Decreased appetite	12	<1	0	21	1	0
Rash	10	<1	0	20	1	0
Cough	9	0	0	19	0	0
Anemia	8	2	0	24	8	<1
Dyspnea	7	1	0	13	<1	0
Edema peripheral	4	0	0	14	<1	0
Pneumonitis	4	1	<1	15	3	0
Mucosal inflammation	3	0	0	19	3	0
Dysgeusia	3	0	0	13	0	0
Hyperglycemia	2	1	<1	12	3	<1
Stomatitis	2	0	0	29	4	0
Hypertriglyceridemia	1	0	0	16	4	1
Epistaxis	1	0	0	10	0	0

Motzer RJ *et al*. N Engl J Med 2015; 373: 19: 1803-13.

PD-L1 Staining for RCC – Unclear Importance





- PD-L1 not helpful at this time

Motzer RJ *et al*. N Engl J Med 2015; 373: 19: 1803-13.

Summary of First-Line Therapy for RCC: Phase III Trial Results

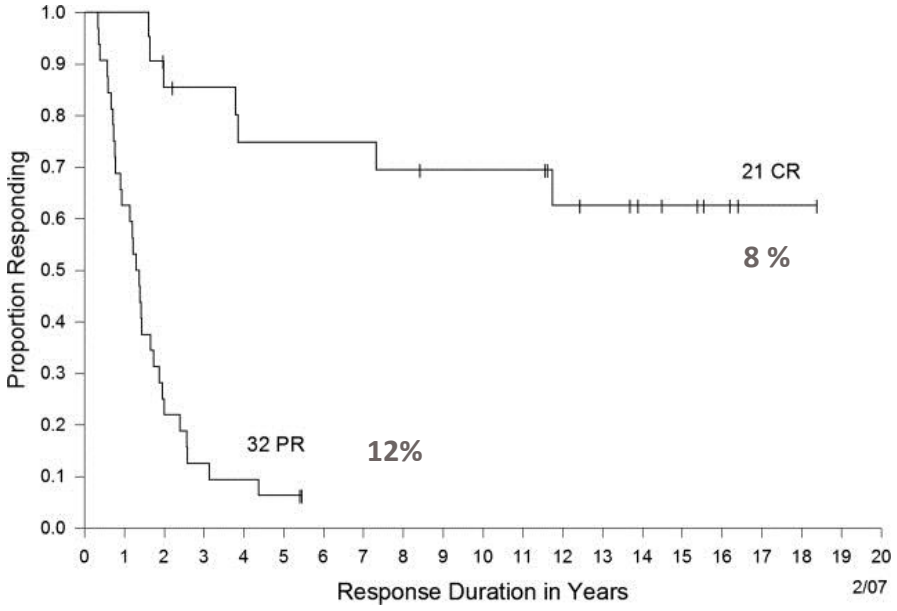
Agent	RR (%)	PFS (mos)	OS (mos)	Setting
IFN	12.4	NS	13	First-line, meta-analysis
High-dose IL-2	20.0	NS	19	First-line, NCI data
Sunitinib	31.0	11	26.4	First-line vs. IFN-α
Pazopanib	32.0	11.1	22.9	First-line vs. placebo
Bevacizumab (AVOREN/CALGB 90206)	31.0 25.5	10.2 8.5	23.3 18.3	First-line with IFN-α vs. IFN-α

Coppin, C *et al*. Cochrane Database of Systematic Reviews (2004) 3: CD001425; Klapper, JA *et al*. Cancer (2008) 113:293-301. Motzer, RJ *et al*. NEJM (2007) 356:115-24; Sternberg, CN *et al*. JCO (2010) 28:1061-68; Sternberg, CN *et al*. EJC (2013) 49:1287-96; Escudier, B *et al*. Lancet (2007) 370:2103-11. Escudier, B *et al*. JCO (2010) 28:2144-50; Rini BI *et al*. JCO (2008) 26:5422-28; Rini, BI *et al*. JCO (2010) 28-2137-43; NS = not stated.

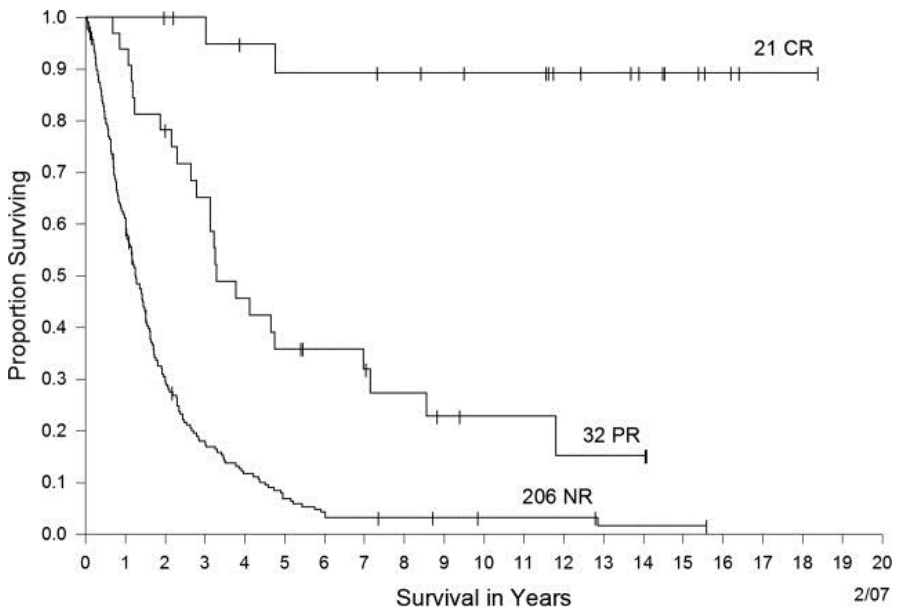
High-dose IL2 Outcomes

The Majority of CR's are Durable at >10 yrs

Response



Survival



Retrospective Analysis of 259 RCC patients treated at the NCI by HD IL-2 (1986-2006)

Klapper JA *et al*. *Cancer* (2008) 113:293.

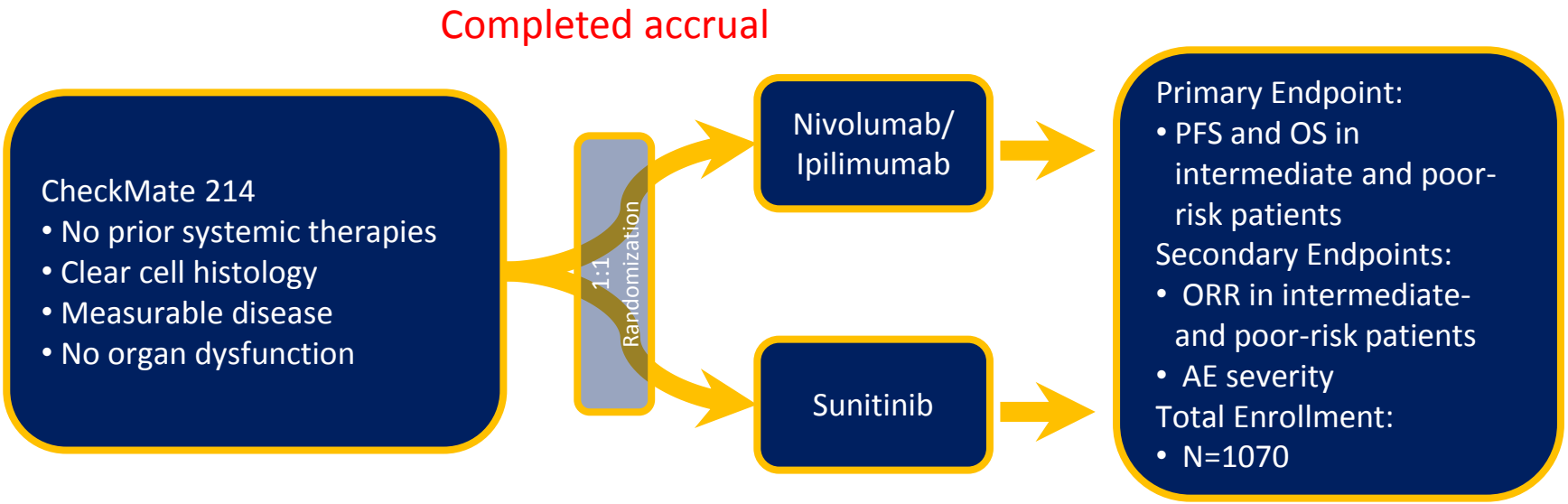
High-dose IL2 Selection Criteria

Highly selected patients:

- "Young" (no formal age limit but usually <65)
- No organ dysfunction
- Negative screening brain imaging, cardiac stress, +/- PFT's
- Excellent performance status
- Clear cell histology
- Prior cytoreductive nephrectomy
- Small volume, asymptomatic mets
- No prior systemic therapy

But we have no predictive biomarkers

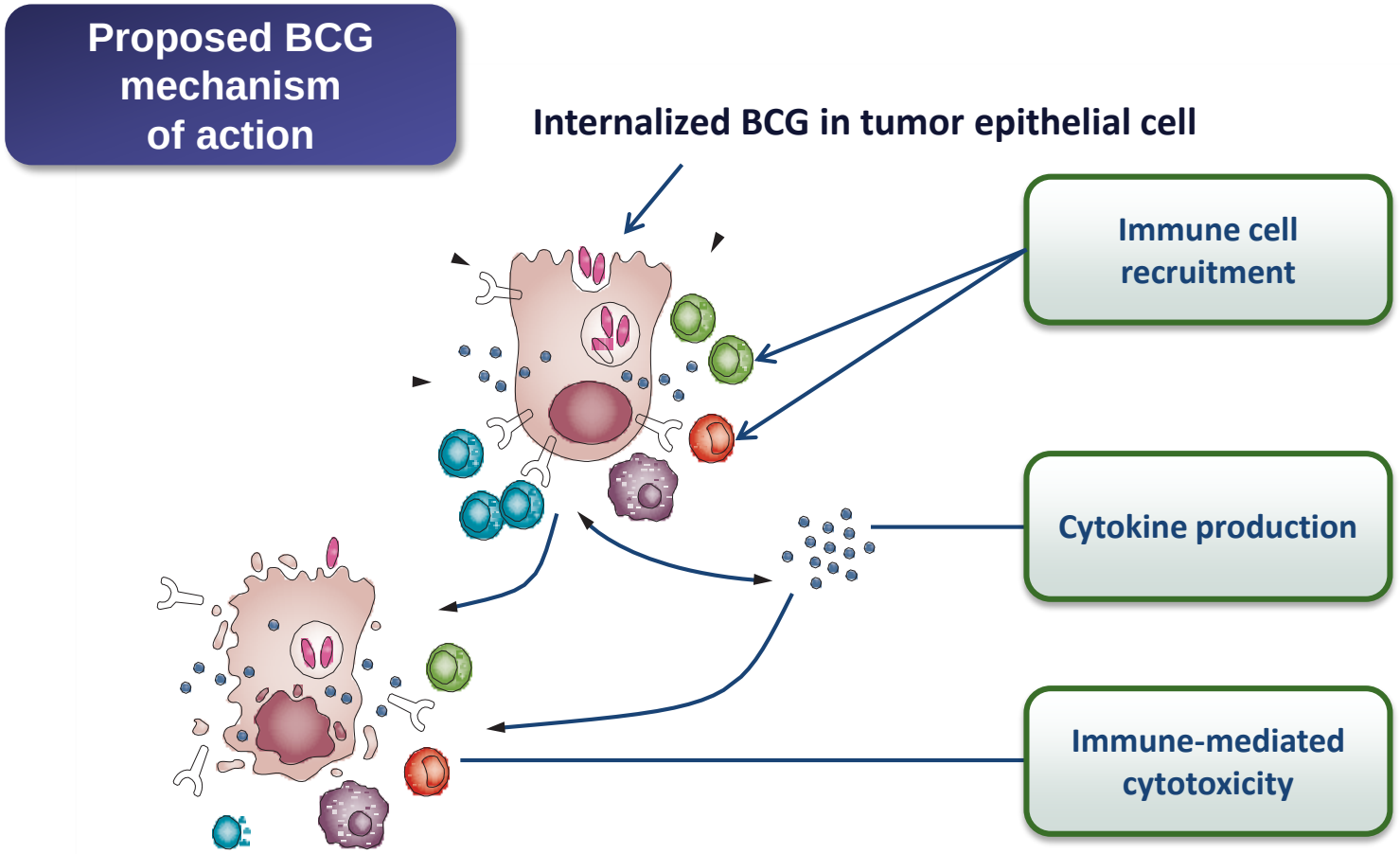
A Reasonable First-line Trial: Combining Anti-PD1 (Nivolumab) with Anti-CTLA4 (Ipilumumab)



- Other phase 3 checkpoint inhibitor trials
  - Atezolizumab + Bevacizumab vs. Sunitinib (still enrolling internationally. Closed in the US for concern Sunitinib arm will receive nivolumab on treatment failure)
  - Avelumab (anti-PD-L1) + Axitinib vs. Sunitinib (just opening)

Urothelial Carcinoma

BCG was FDA Approved in 1990



Adapted from: Redelman-Sidi G, et al. *Nat Rev Urol.* 2014;11:153-162.

LETTER

doi:10.1038/nature13904

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]

Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial

Jonathan E Rosenberg, Jean Hoffman-Censits, Tom Powles, Michiel S van der Heijden, Arjun V Balar, Andrea Necchi, Nancy Dawson, Peter H O'Donnell, Ani Balmanoukian, Yohann Loriot, Sandy Srinivas, Margitta M Retz, Petros Grivas, Richard W Joseph, Matthew D Galsky, Mark T Fleming, Daniel P Petrylak, Jose Luis Perez-Gracia, Howard A Burris, Daniel Castellano, Christina Canil, Joaquim Bellmunt, Dean Bajorin, Dorothee Nickles, Richard Bourgon, Garrett M Frampton, Na Cui, Sanjeev Mariathasan, Oyewale Abidoye, Gregg D Fine, Robert Dreicer

On May 18th, 2016, the FDA approved the use of atezolizumab in patients with locally advanced or metastatic urothelial carcinoma who:

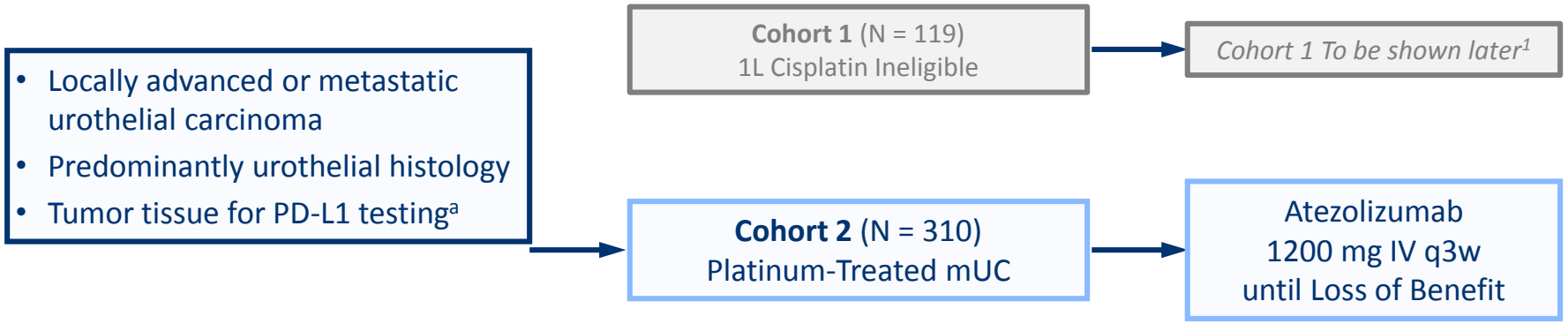
- Have disease progression during or following platinum-containing chemotherapy
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. This accelerated approval was based on the results of IMvigor 210 trial.

Testing of PD-L1 expression in tumor specimens is not required for the use of atezolizumab, but may guide in patient selection. The Ventana PD-L1 (SP142) Assay is approved for PD-L1 testing on tumor-infiltrating immune cells.

Powles T et al. *Nature* 2014; 515:558-62.
Rosenberg JE et al. *Lancet* 2016; 387:1909-20.

IMvigor 210 Study Design



Cohort 2-Specific Inclusion Criteria

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

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

- Intratumoral biomarkers

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

[a] Patients and investigators blinded to PD-L1 IHC status. Trial Identifier: NCT02108652.

1. Balar ASCO 2016 [abstract LBA4500].

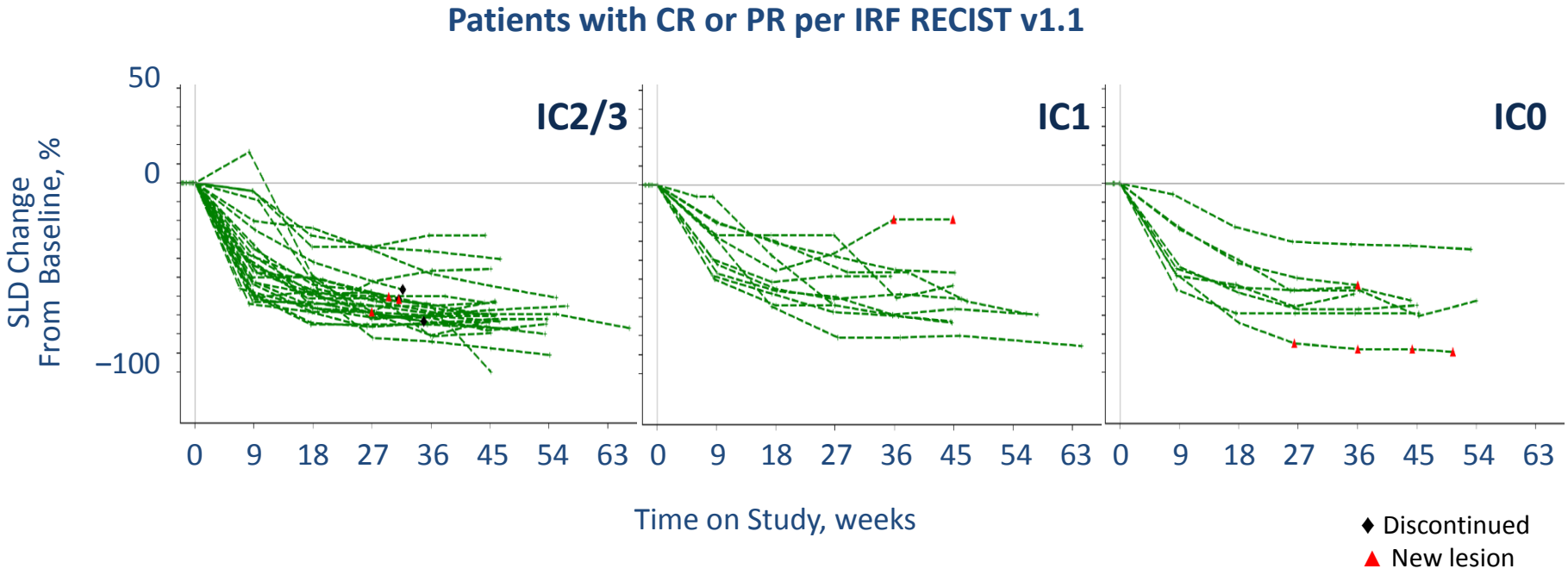
Atezolizumab Response Rates (by PD-L1 status)

	IC2/3 n = 100	IC1/2/3 n = 207	All[a] N = 310	IC1 n = 107	IC0 n = 103
ORR: confirmed IRF RECIST v1.1 (95% CI)	28% (19, 38)	19% (14, 25)	16% (12, 20)	11% (6, 19)	9% (4, 16)
CR rate: confirmed IRF RECIST v1.1 (95% CI)	**15% (9, 24)**	**9% (6, 14)**	**7% (4, 10)**	**4% (1, 9)**	**2% (0, 7)**

- Responses were seen in all IC subgroups, but ORR was enriched with higher PD-L1 status
- Complete responses accounted for nearly half of the observed responses
  - CRs were observed in all PD-L1 subgroups, with the highest rate in IC2/3 patients

[a] Includes 46 patients with missing/unevaluable responses. [b] CR + PR + SD ≥ 24-wk rate per IRF RECIST v1.1. Treated patients had measurable disease at baseline per investigator-assessed RECIST v1.1. Data cutoff: Mar. 14, 2016.

Duration of Response to Atezolizumab

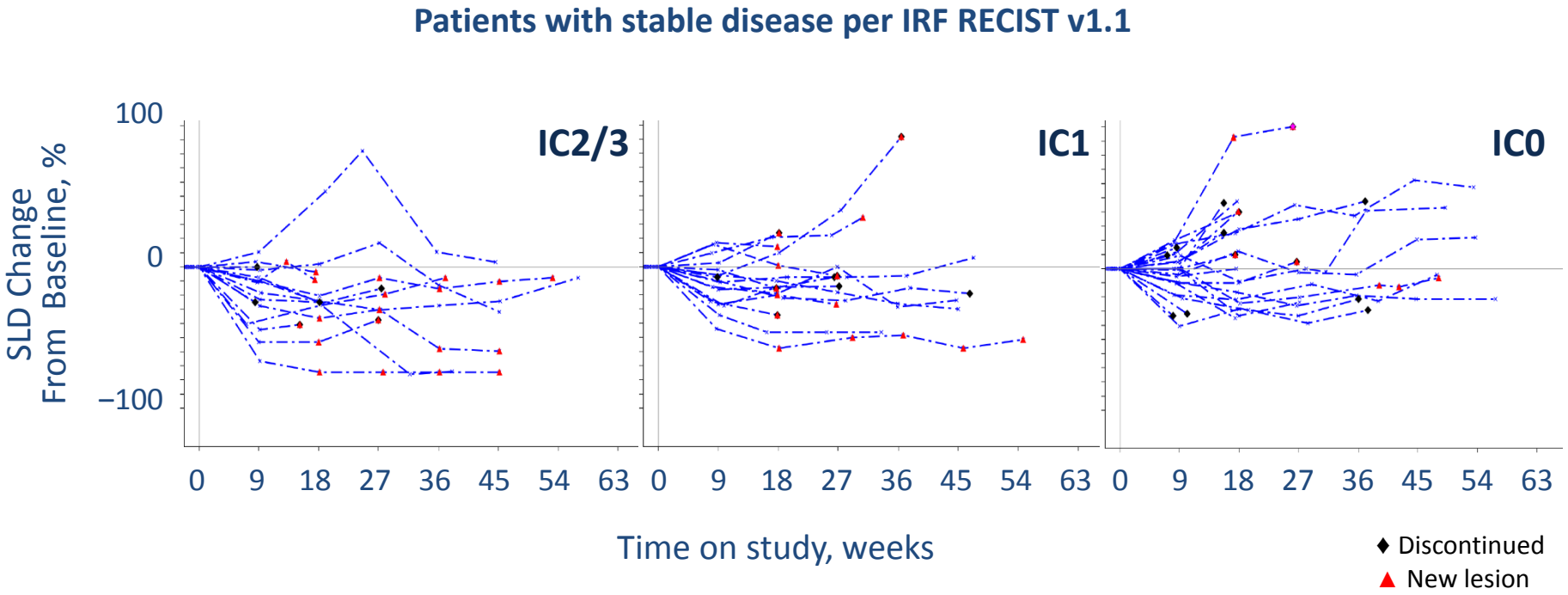


- Responses were durable, with mDOR not reached in any PD-L1 subgroup (range, 2.0+ to 13.7+ mo)
- Ongoing responses were seen in 38 of 45 responding patients (84%)
- Median follow-up time: 11.7 mo (range, 0.2+ to 15.2 mo)

Data cutoff: September 14, 2015.

Hoffman-Censits et al. GU ASCO 2016. Abstr 355.

Stable Disease with Atezolizumab

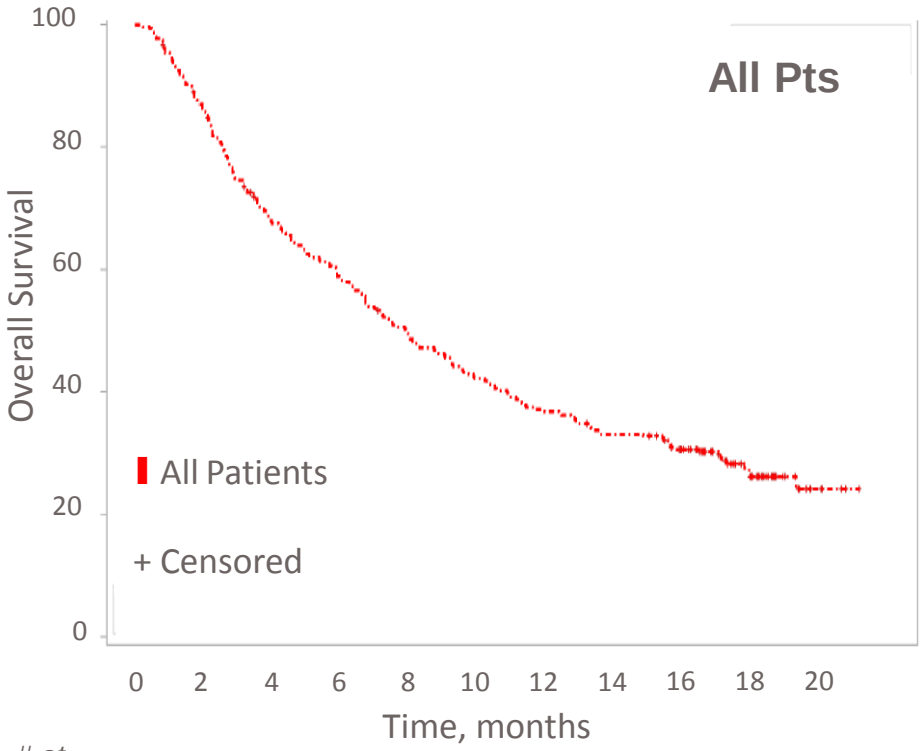


- Many non-responding patients experienced SD, suggesting that atezolizumab may provide clinical benefit to these patients
  - Disease control rate (CR + PR + SD ≥ 24-wk rate): 35% (IC2/3), 21% (IC1) and 19% (IC0)

Data cutoff: September 14, 2015.

Hoffman-Censits et al. GU ASCO 2016. Abstr 355.

Overall Survival with Atezolizumab



 # at Risk:

All pts: 310 265 203 176 146 126 110 97 82 35 5

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)

Subgroup	12-mo OS (95% CI)		
	IC2/3	IC0/1	All
All pts (N = 310)	50% (40, 60)	31% (24, 37)	37% (31, 42)

- Longer OS observed in patients with higher PD-L1 IC status
- mPFS (2.1 mo per RECIST v1.1; 2.6 mo per imRECIST) underscores a disconnect between PFS and OS

Median follow-up (range):
All Pts: 17.5 mo (0.2 to 21.1+ mo)

NE, not estimable. Data cutoff: Mar. 14, 2016.

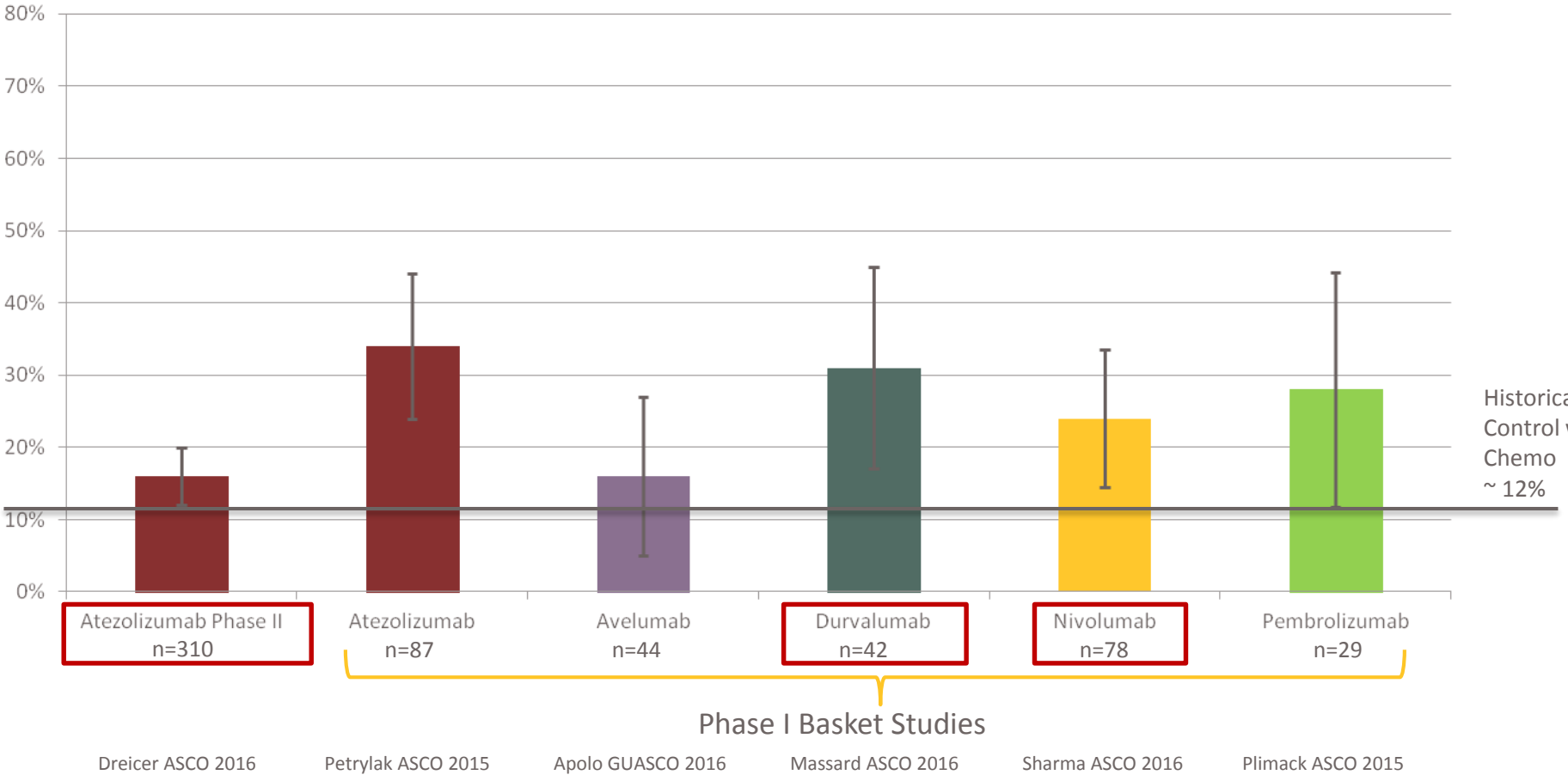
Immune-mediated Adverse Events

AE (N = 310)[a]	All Grade	Grade 3-4
Pneumonitis	2%	1%
AST increased	2%	1%
Dyspnea	1%	1%
ALT increased	1%	< 1%
Blood bilirubin increased	1%	< 1%
Rash	1%	< 1%
Hyperglycemia	1%	0%
Colitis	1%	1%
Diarrhea	1%	< 1%
Transaminases increased	1%	< 1%
Dry skin	1%	0%
Pruritus	1%	0%
Pyrexia	1%	0%

- 30% of patients received steroids for any purpose
- Immune-mediated AEs (imAEs) were observed at frequencies of 10% (all Grade) and 6% (G3-4)
- No patients were treated with non-corticosteroids immunomodulatory agents for imAEs (e.g. infliximab, tocilizumab, rituximab, IL-2)

[a] Occurring in ≥ 2 patients (all Grade). Additional G3-4 events (n = 1 each): Autoimmune hepatitis, Cytokine release syndrome, hepatitis, paraplegia, pericardial effusion, blood alkaline phosphatase increased, chronic kidney disease, hypotension, musculoskeletal pain, sepsis. Data cutoff: March 14, 2016.

Overall Response Rates of PD-1/PD-L1 Antibodies in Post-Platinum Setting



Slide courtesy of Betsy Plimack from ASCO 2016 Discussion

PD-L1 status as a Biomarker for Metastatic Urothelial Cancer

Author	Phase	Drug	Setting	Total n	Definition of PDL1 +	% of patients PDL1 "high" or "positive"	ORR in favorable biomarker group	ORR - all
Balar ASCO 16	II	Atezolizumab	First line cis ineligible	119	IC 2/3	27%	28%	24%
Dreicer ASCO 16	II	Atezolizumab	Post platinum	310	IC 2/3	32%	28%	16%
Sharma ASCO 16	I basket	Nivolumab	Post platinum	78	>=1% TC	37%	24%	24%
Massard ASCO 16	I basket	Durvalumab	Post platinum	42	>25% in TC or IC	67%	46%	31%
Plimack ASCO 15	I basket	Pembrolizumab	Post platinum	29	≥1% tumor or stroma	100%	28%	28%
Apolo GUASCO 2016	I basket	Avelumab	Post platinum	44	≥5% tumor cells*	16%	40%	16%
Petrylak ASCO 15	I basket	Atezolizumab	pre/post platinum	87	IC 2/3	45%	50%	34%

Slide courtesy of Betsy Plimack from ASCO 2016 Discussion

IMvigor 210 Cohort 1 Data from ASCO

	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%

Subgroup	ORR[a]	95% CI
Demographics and prior treatment		
Age ≥ 80 years (n = 25)	28%	12, 49
Perioperative chemo[b] (n = 22)	36%	17, 59
Primary tumor sites		
Bladder/urethra (n = 85)	17%	9, 26
Upper tract (n = 33)	42%	25, 61
Metastatic sites at baseline		
Lymph node only (n = 31)	32%	17, 51
Visceral[c] (n = 78)	15%	8, 25
Liver (n = 25)	12%	3, 31
Cisplatin ineligibility criteria		
Impaired renal function (n = 83)	27%	17, 37
ECOG PS2 (n = 24)	25%	10, 47
Renal impairment **and** ECOG PS2 (n = 8)	25%	3, 65

Key Demographics

- 28% with upper tract disease
- 70% with Cr Cl 30-60
- 20% ECOG 2

Balar AV et al. ASCO 2016; LBA4500.

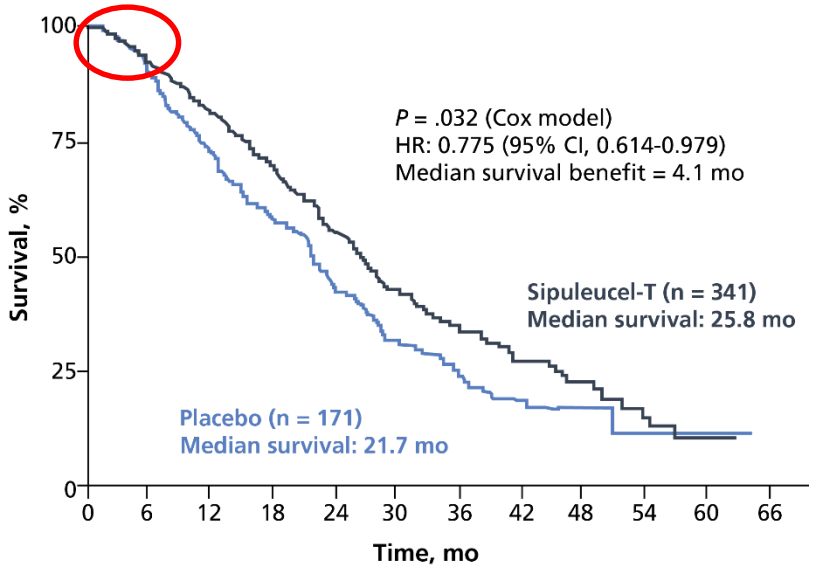
Next Steps and Key Data on the Horizon

- Will the Imvigor 210 Cohort 1 data lead to FDA approval in the first-line platinum ineligible setting since this is a vastly unmet need?
- KEYNOTE-052 trial – n=350 platinum ineligible patients with pembrolizumab just finishing accrual
- Confirmatory Phase 3 trials with atezolizumab and pembrolizumab are both post-platinum randomized vs. taxane
- Multiple trials with multiple agents in NMIBC with BCG refractory patients, neaodjuvant, adjuvant, and combinations

Prostate Carcinoma

Sipuleucel-T

- Short window of opportunity (must be asymptomatic metastatic castration-resistant prostate cancer)
- Patients should have reasonably indolent disease as survival curves don't split until the 6 month time point
- Only 1-3% with a significant PSA decline
- No improvement in PFS



Kantoff PW et al. *N Engl J Med.* 2010; 363:411-22.

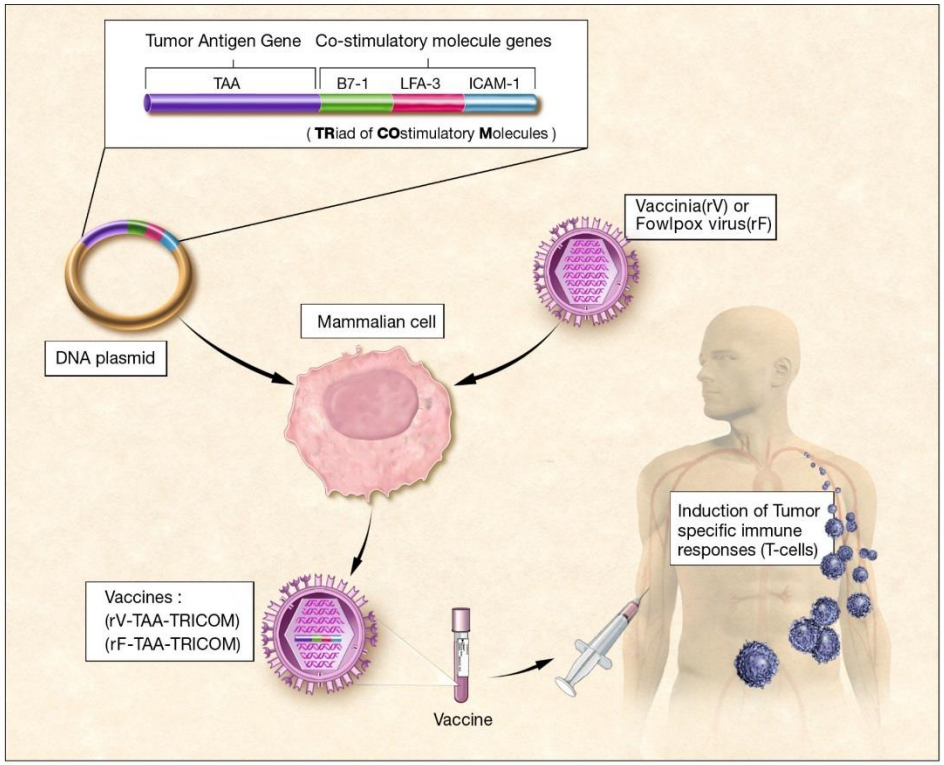
Survival Benefit with Sipuleucel-T is Greater for those who Start with a Lower Baseline PSA

IMPACT: OS by Baseline PSA

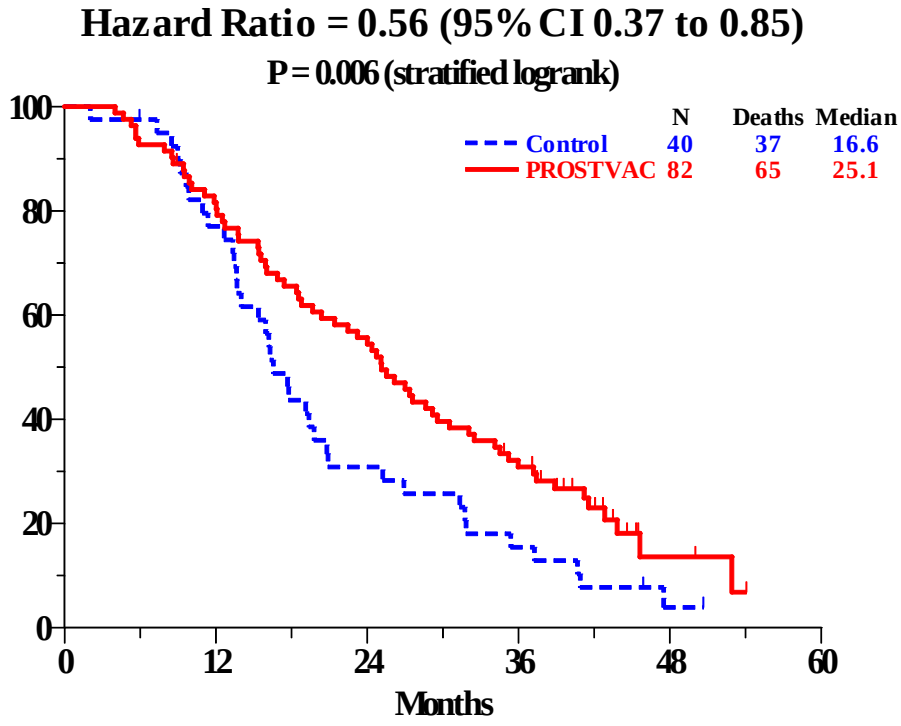
Median OS, mo	Baseline PSA (n= 128 for all categories)			
	≤22.1	>22.1–50.1	>50.1–134.1	>134.1
Sipuleucel-T	41.3	27.1	20.4	18.4
Control	28.3	20.1	15.0	15.6
Difference	**13.0**	**7.1**	**5.4**	**2.8**
HR (CI)	**0.51 (0.31-0.85)**	**0.74 (0.47-1.17)**	**0.81 (0.52-1.24)**	**0.84 (0.55-1.29)**

Schellhammer PF et al. *Urology.* 2013;81:1297-1302.

Prostvac



Mechanism diagram courtesy of Charles Drake

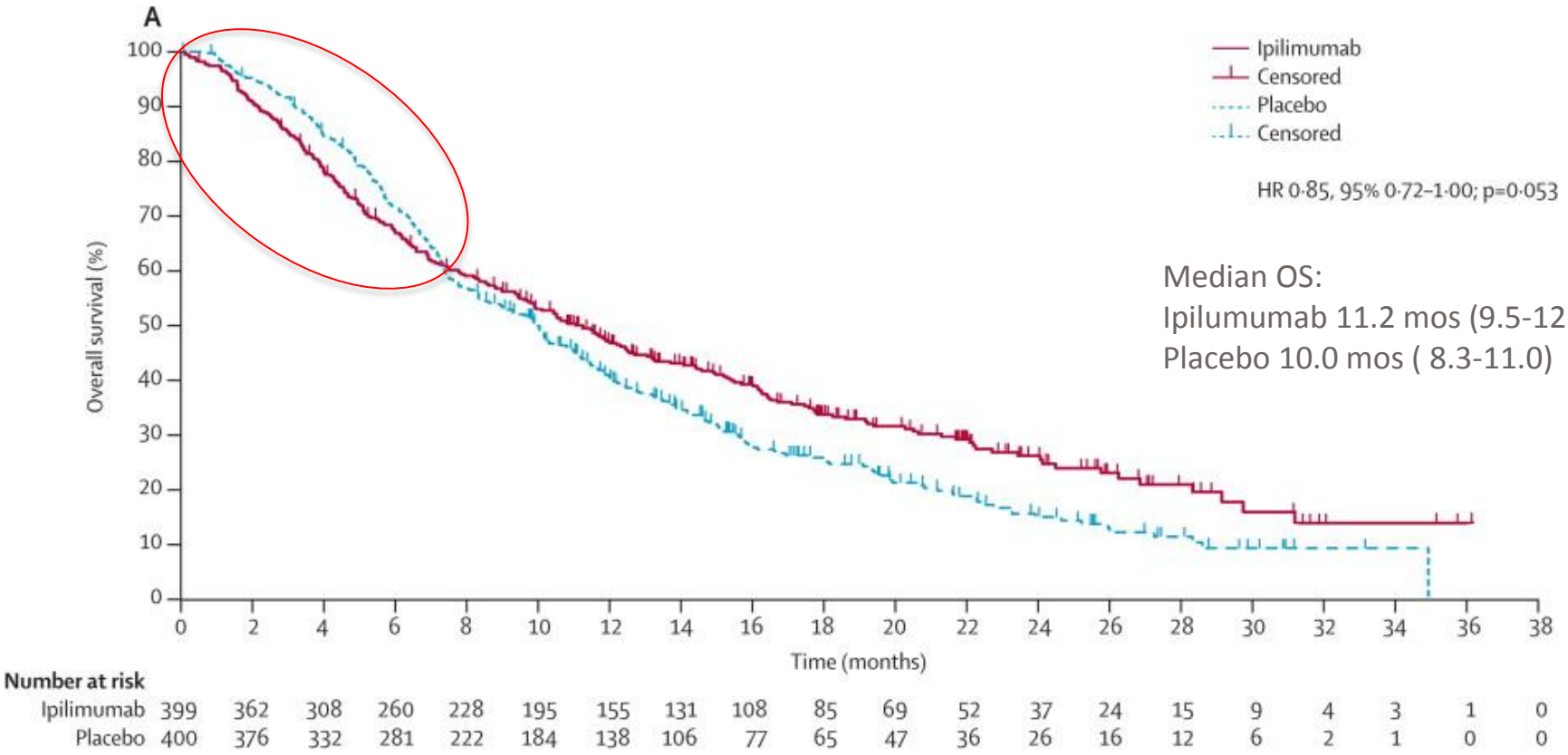


Prostvac Randomized Phase 2 OS Results

Phase 3 trial results are pending

Kantoff PW et al. *J Clin Oncol* 2010; 28:1099-1105.

Phase 3 Ipilumumab Post-Docetaxel OS Results



Median OS:
Ipilumumab 11.2 mos (9.5-12.7)
Placebo 10.0 mos (8.3-11.0)

Presence of visceral metastases had negative interaction with treatment effect
HR 1.644 (1.157-2.336; p=0.0056)

Kwon ED et al. *Lancet Oncol* 2014; 15:700-12.

Ipilumumab Pre-Chemotherapy Trial

- Unfortunately, the pre-chemotherapy trial has been reported to be negative as well
- Data not yet available
- Rationale for why this trial should have been positive
  - Patients with visceral metastases were excluded
  - Earlier disease setting might potentially be more ideal for immunotherapy to work
- Potential reasons to explain a negative trial
  - Unlike post-chemotherapy trial, there was no radiation therapy applied prior to ipilumumab; therefore, no potential for abscopal effect
  - Earlier disease setting might have led to more post-progression receipt of agents that further prolonged survival of control arm

Nivolumab Trial

- 296 patients with melanoma, non-small cell lung cancer, renal cell, colorectal or prostate cancer were treated with nivolumab
- 17 men with castration-resistant prostate cancer
- None had an objective response, although 1 patient had 28% reduction in measurable lesions
- 17 patients in entire cohort had PD-L1 negative IHC and none had an objective response while 9/25 (36%) patients with PD-L1 positive tumors had an objective response
  - 2 patients with prostate cancer analyzed for PD-L1 staining were both negative

Topalian SL et al. N Engl J Med. 2012; 366:2443-54.
Suzman DL and Antonarakis EA. Ther Adv Med Oncol 2014; 6:167-79.

PD-L1 Immunohistochemistry in Prostate Cancer

- Traditionally, it has been felt that PD-L1 positive staining by IHC in prostate cancer is rare
  - 3/20 (15%) primary prostate samples had focal areas of PD-L1 positivity (>5%) and only 2 had plasma membrane staining on malignant cells[1]
  - Used Johns Hopkins core with 5H1 clone
- In aggressive localized prostate cancers, 52.2% of training cohort (n=209) cases and 61.7% of test cohort (n=611) cases expressed moderate (IHC2) to high (IHC3) PD-L1 levels[2]
  - Correlation with Ki-67, Gleason and AR expression
  - Prognostic for biochemical recurrence
  - Used Ventana assay
- We need more studies evaluating staining in metastatic castration resistant prostate cancer tissues

Martin AM et al. Prostate Cancer Prostatic Dis. 2015; 18:325-32.
Gevensleben H et al. Clin Cancer Res 2015; Epub.

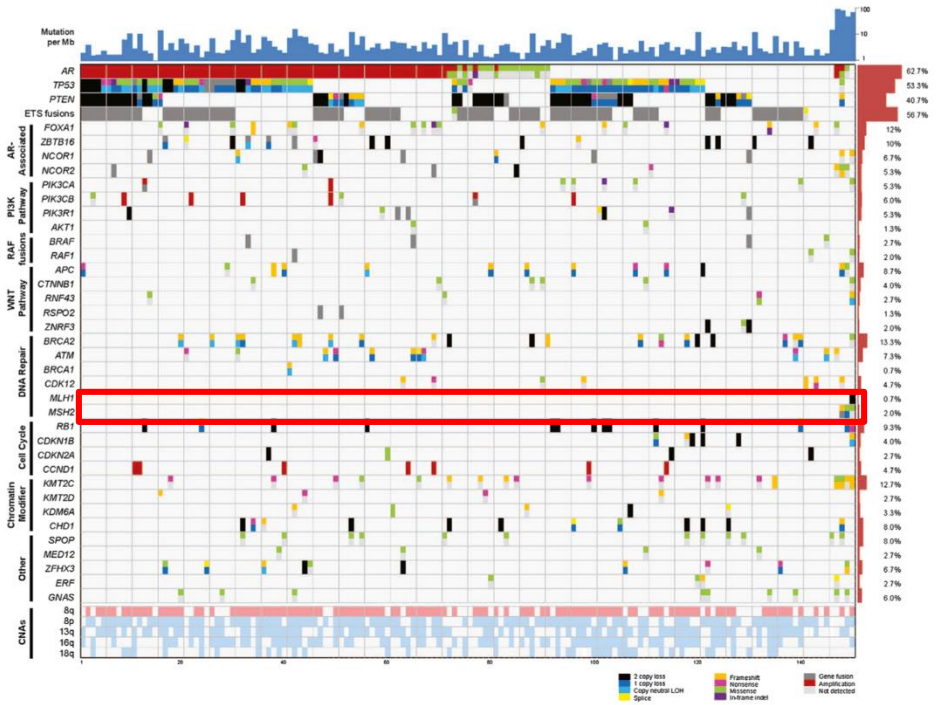
Mismatch Repair Alterations with MSI in Prostate Cancer

UW Rapid Autopsy

- 7/60 (11.7%) of advanced prostate cancers are hypermutated and all had mismatch repair gene mutations and MSI
- Hypermutation defined as >300 somatic protein altering mutations in metastatic tumors
- All mismatch repair alterations were in MSH2 or MSH6

SU2C mCRPC Biopsies

- 2.7% harbor MMR alterations in either MLH1 or MSH2, which are consistent with MSI



Pritchard CC et al. Nat Commun. 2014; 5:4988.

Robinson D et al. *Cell* 2015; 161:1215-28.

Summary of Immunotherapy Options for GU Malignancies

- Renal carcinoma
  - HD-IL2 may be used in first-line for select advanced patient populations
  - Nivolumab is FDA approved for patients with advanced RCC who have received prior anti-angiogenic therapy
  - Many front-line checkpoint inhibitor trials underway
- Urothelial carcinoma
  - Atezolizumab is FDA approved for patients with advanced urothelial carcinoma who have received prior platinum
  - Will other checkpoint inhibitors achieve FDA approval and will checkpoint inhibitors eventually become a first-line therapy?
- Prostate carcinoma
  - Sipuleucel-T is FDA approved for patients with asymptomatic mCRPC
  - Do checkpoint inhibitors have a future in this disease?

Does PD-L1 staining matter and if not, what should we use for patient selection?

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Thank you!

Better together.