Immunotherapy for Genitourinary Cancers

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Disclosures

- Consultant: Janssen, Medivation, Astellas, Asana, Genentech, Sanofi Aventis, Churchill Pharma, Ferring, Exelexis
- Research Funding: Genentech, Asana, Lily
- I will be discussing non FDA approved treatments

Immunotherapy for Genitourinary Cancers

- Long history of immune therapeutics
- Renal Cell Carcinoma:
  - Interleukin 2 (1992)
- Bladder Cancer: BCG (1998)
  - Standard of care of CIS, high grade T1
- Prostate Cancer: Sipuleucel-T (2010)

Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma

- The Cytokine Working Group phase III trial comparing interleukin-2 (IL-2) and interferon (IFN) to high-dose (HD) IL-2
- 192 patients enrolled
- ORR 23.2% for HD IL-2 versus 9.9% for IL-2/IFN (P = .018)
- Ten patients receiving HD IL-2 were progression-free at 3 years versus three patients receiving IL-2 and IFN
- The median response durations were 24 and 15 and median survivals were 17.5 and 13 months (P = .24)

McDermott DF, et al. J Clin Oncol. 2005;23:133

Bacillus Calmette-Guerin (BCG)

- Gold standard in the treatment of high-risk non-muscle-invasive bladder cancer, with initial response rates of approximately 70%
- While the mechanism of action remains to be fully elucidated, BCG works via activation of the immune system and induction of an inflammatory response
- BCG attaches to urothelial cells, followed by internalization
- These cells then upregulate MHC-II molecules and secrete cytokines, resulting in recruitment of immune cells, including lymphocytes, to the tumor environment

A very brief history of Immunotherapy for prostate Cancer

- Early (mostly) empiricism: GM-CSF
- Therapeutic vaccines
  - Sipuleucel-T
  - G-VAX (failed in phase III)
  - Prostvac (Phase III not yet reported)
- CTLA-4/Check point inhibition
  - Ipilimumab
  - PD1 and PDL1

Active Cellular Immunotherapy (Sipuleucel-T)

Patient's white blood cells harvested

Short-term culture with protein "cassette"

GM-CSF

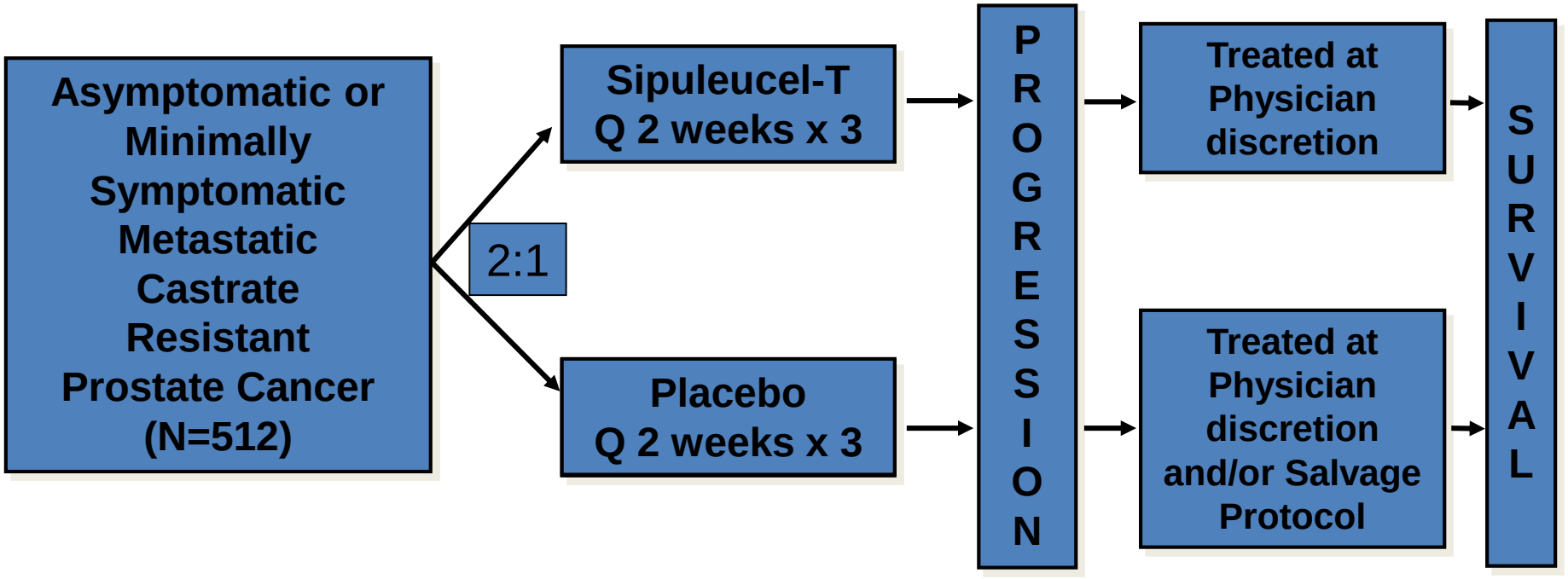
Prostatic acid phosphatase (PAP)

Shipping

Cells infused back into patient (IV)

Randomized Phase 3 IMPACT Trial

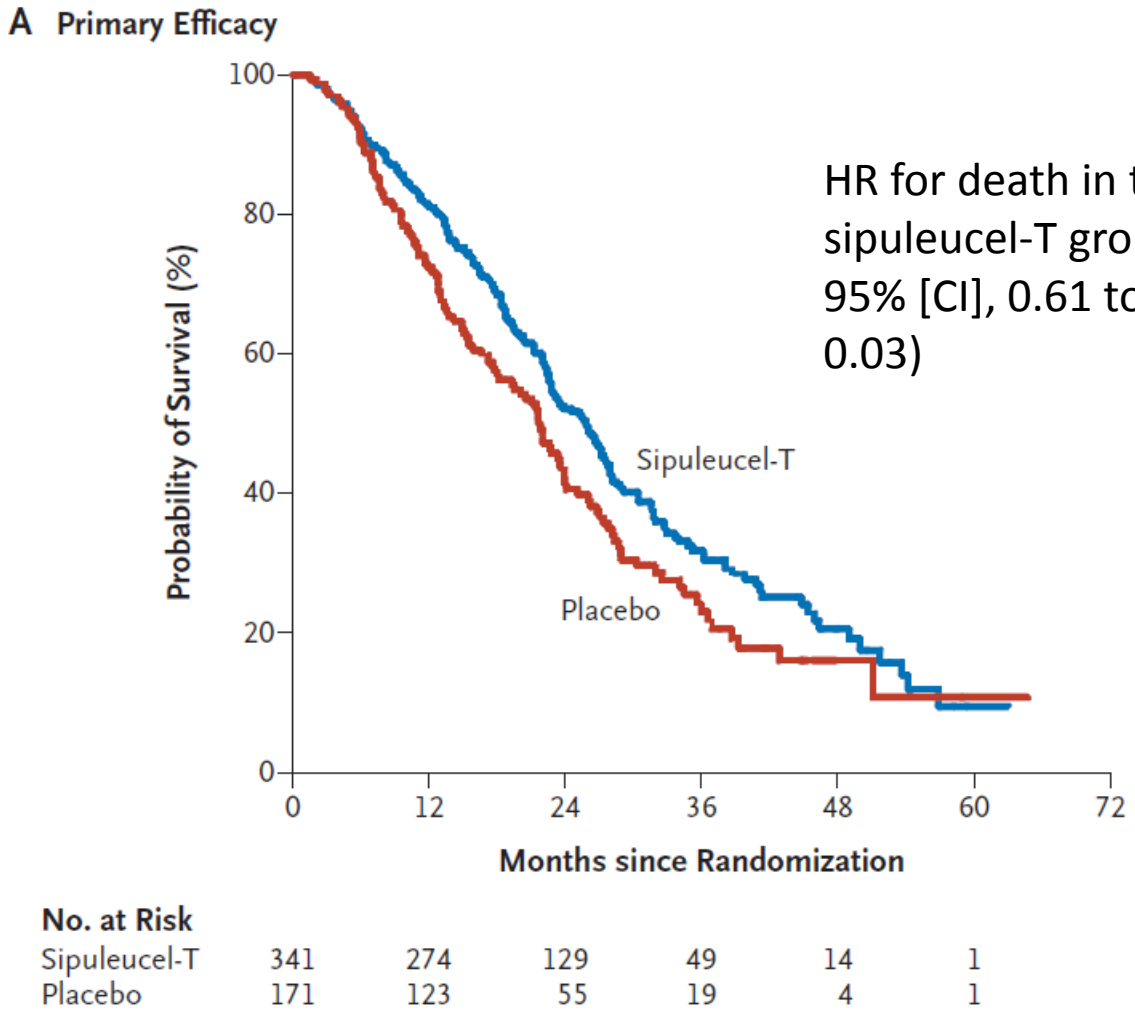
(IMmunotherapy Prostate AdenoCarcinoma Treatment)



Primary endpoint: Overall Survival

Secondary endpoint: Time to Objective Disease Progression

Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer



HR for death in the sipuleucel-T group, 0.78; 95% [CI], 0.61 to 0.98; P = 0.03)

Kantoff, P et al. N Engl J Med 363;5 2010

IMPACT: Lower Baseline PSA is Associated with a Greater Overall Survival Benefit

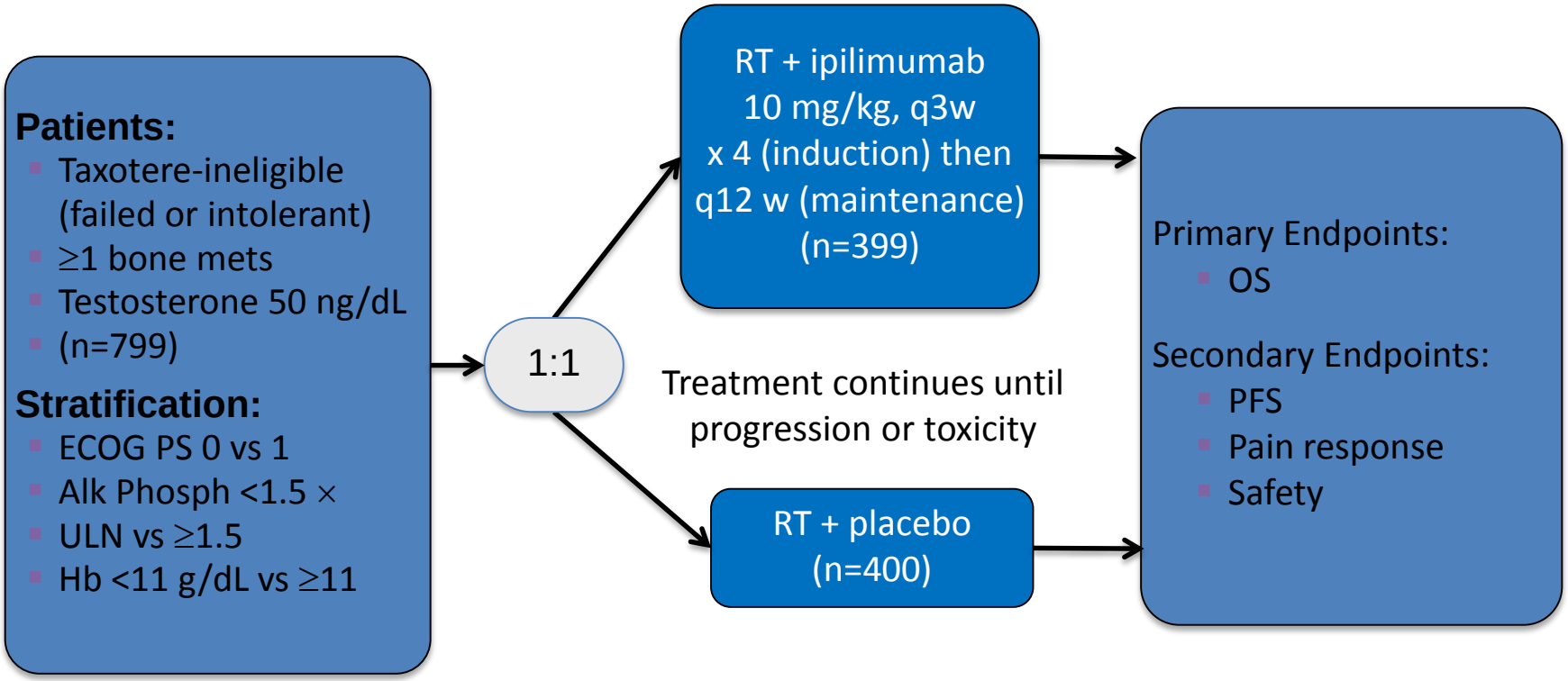
	Baseline PSA, ng/mL			
	≤ 22.1 (n = 128)	**22.1 – 50.1** (n = 128)	**50.1 – 134.1** (n = 128)	**134.1** (n = 128)
Median OS, months				
Sipuleucel-T	**41.2**	27.1	20.4	18.4
Control	**28.3**	20.1	15.0	15.6
HR (95% CI)	0.51 (0.31-0.85)	0.74 (0.47-1.17)	0.81 (0.52 -1.24)	0.84 (0.55-1.29)

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

The Sipuleucel-T Conundrum

- What sipuleucel-T appears to provide patients
  - A potential improvement in survival
- What sipuleucel-T DOES NOT DO
  - It is not a therapeutic replacement for therapy in patients in need of an objective anti tumor response in real time
- Unprecedented development and integration of a novel therapy
  - No improvement in OR/PFS
  - Limited access dampens learning curve
  - Cost (less of an outlier in current environment)
- Metaphysical issues: Men make therapy choices differently than women

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



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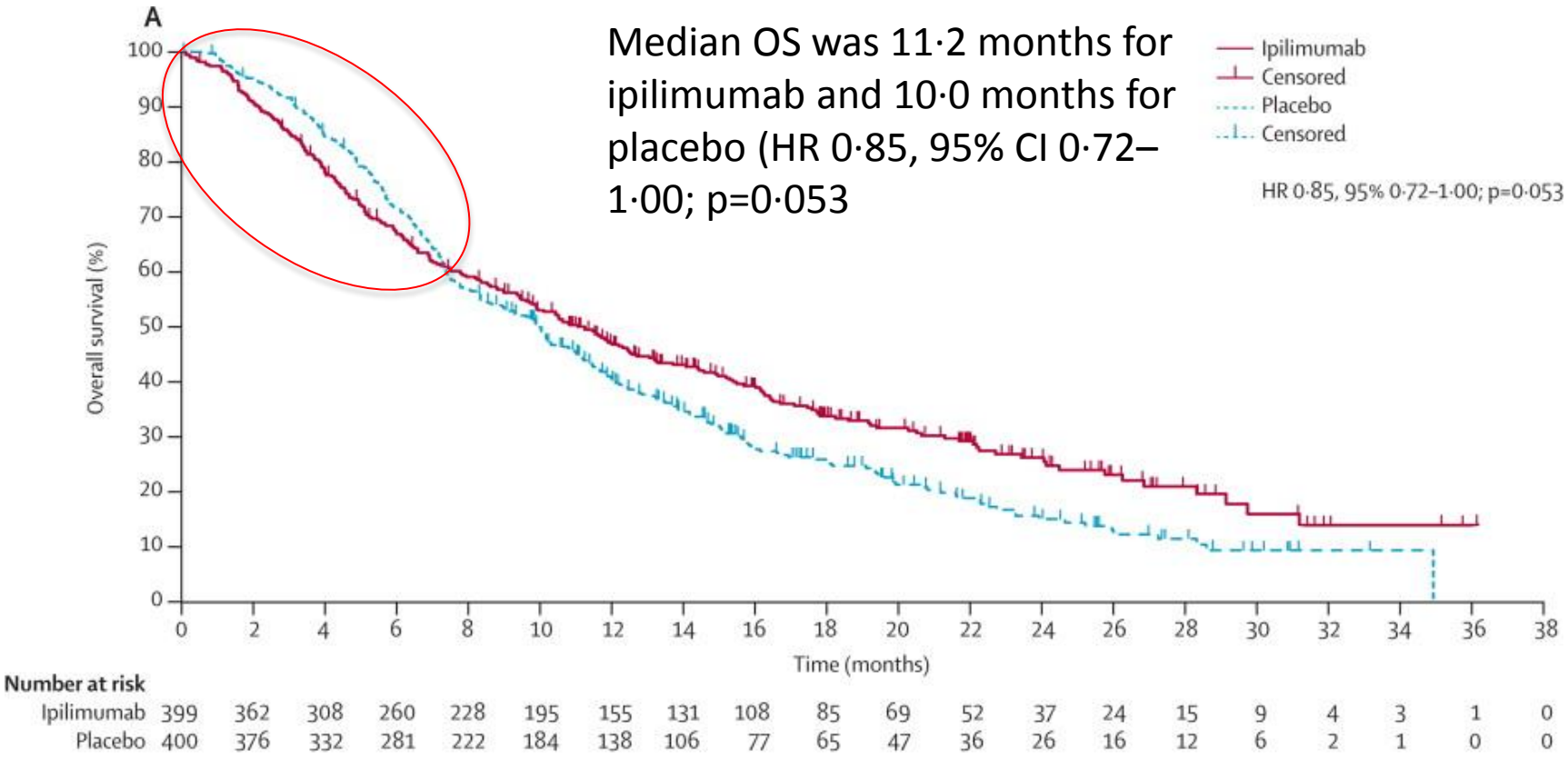
Kwon E, et al, Lancet Oncol 15:700 – 712, 2014

Overall Survival: ITT

Median OS was 11·2 months for ipilimumab and 10·0 months for placebo (HR 0·85, 95% CI 0·72–1·00; p=0·053



THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

Kwon E, et al, Lancet Oncol 15:700 – 712, 2014

Anti PD1/PDL1 Immunotherapy

- Primary prostate cancers are infiltrated with programmed death-1 (PD-1) expressing CD8+ T-cells
- In early clinical trials, men with metastatic castrate-resistant prostate cancer did not respond to PD-1 blockade as a monotherapy
- **The primary reason for this is likely that prostate cancer patients have little or no PD-L1 expression in their tumors**
- The paucity of PD-L1 expression in patients may be because of a locally immunosuppressive environment that very effectively dampens CD8+ T-cell production of IFN-γ, as has been clearly demonstrated in several animal models

Martin AM, et al. *Prostate Cancer and Prostatic Disease* (2015) **18,** 325–332; doi:10.1038/pcan.2015.39; published online 11 August 2015

Renal Cell Carcinoma Therapeutics

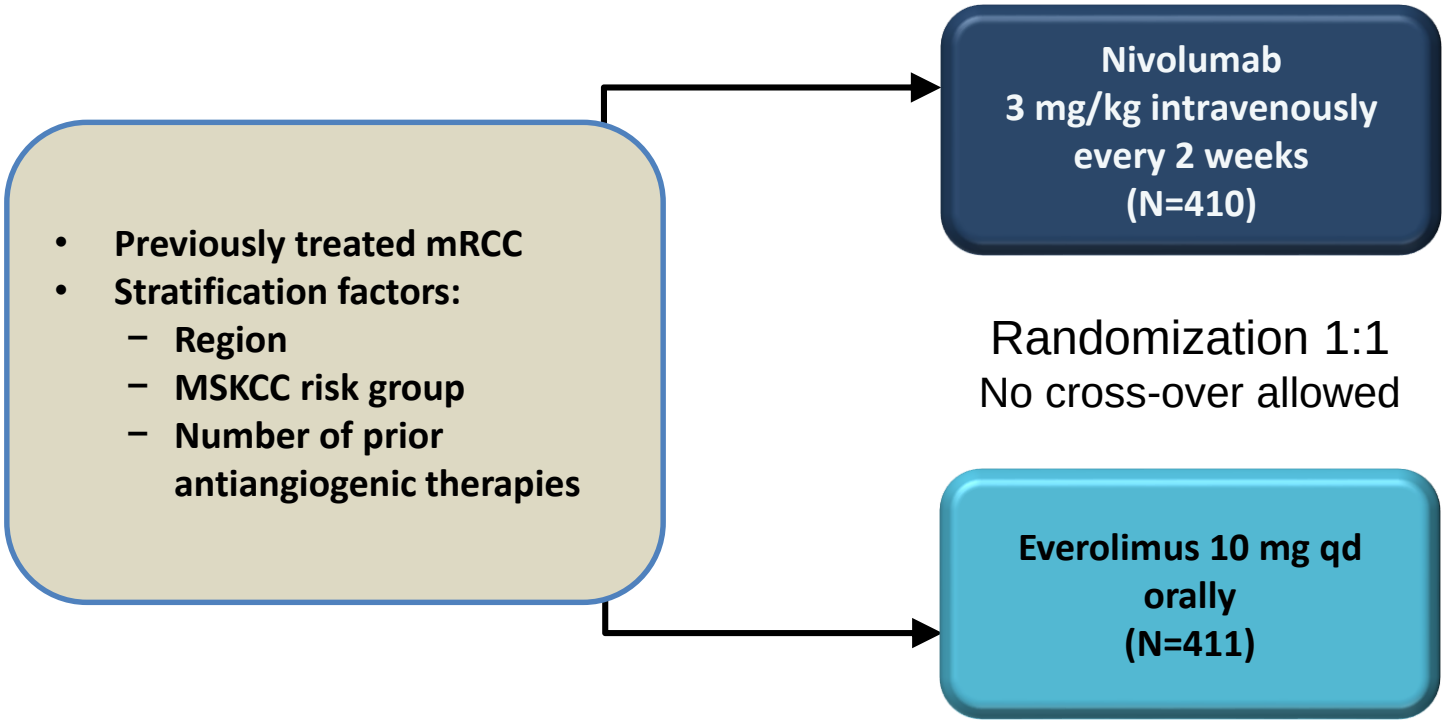
- Interferon/IL2 era
- “Targeted” agents (sorafenib approved 2004)
- Check point inhibitors (2016)

RCC (Clear Cell) Treatment Algorithm: 2016

Setting	Patients	Therapy (level 1evidence)	Other Options (≥ level 2)
Untreated	Good/ Intermediate risk	Pazopanib Sunitinib Bevacizumab + IFN HD IL-2	Sorafenib axitinib Clinical trial Observation
	Poor risk	Temsirolimus	Sunitinib Clinical trial
Second-Line		Nivolimab Cabozantinib Everolimus Axitinib Lenvatinib + everolimus Clinical trial	Sunitinib Sorafenib Pazopanib

*Adapted from M Atkins, ASCO 2006 & R Bukowski ASCO 2007

CheckMate 025: Study Design



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

Primary endpoint:

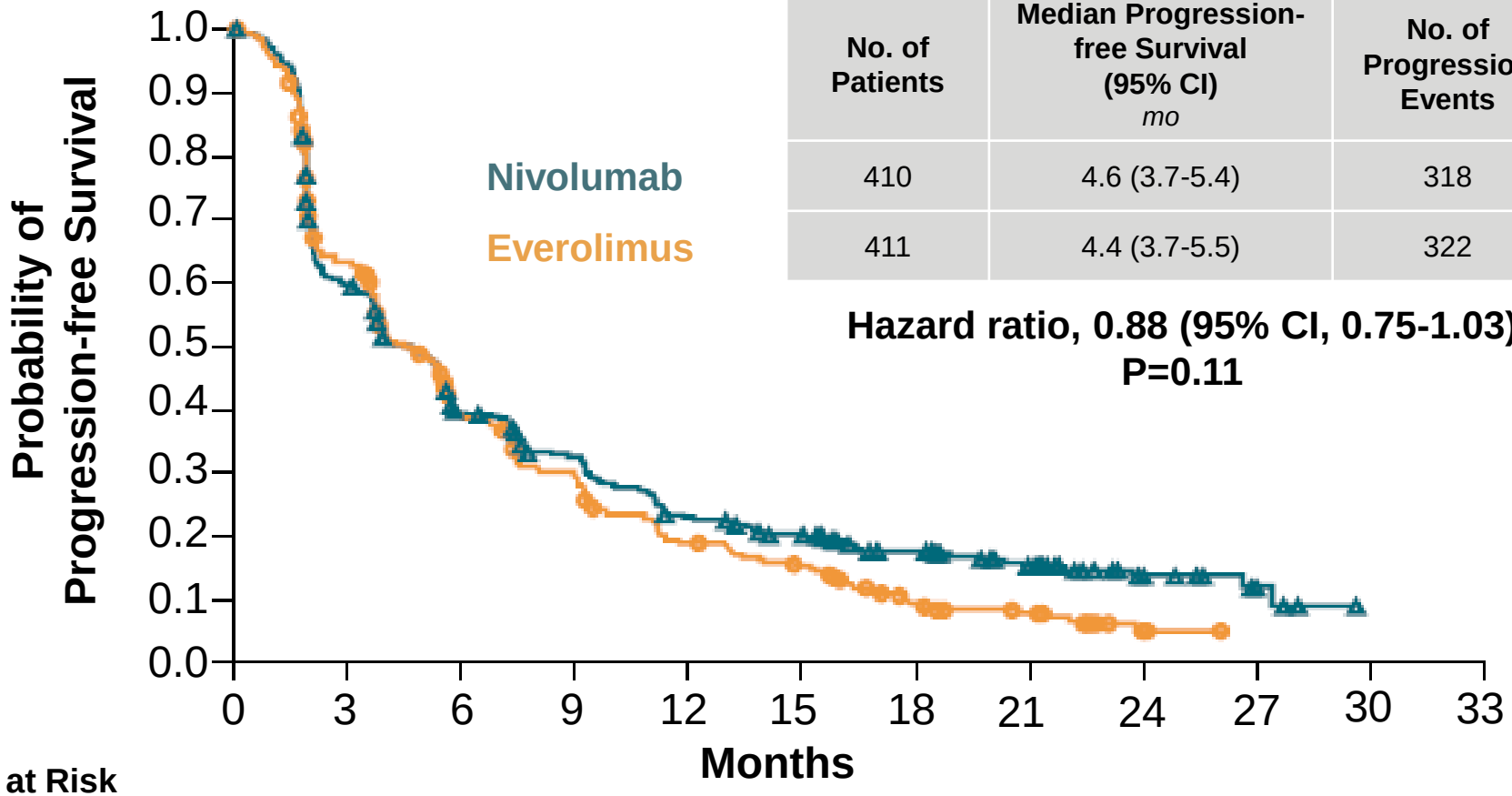
- OS

Secondary endpoints:

- ORR, PFS, AEs, QOL, OS by PD-L1 expression

Motzer, et al. *N Engl J Med.* 2015;373:1803-1813.

CheckMate 025: Progression Free Survival



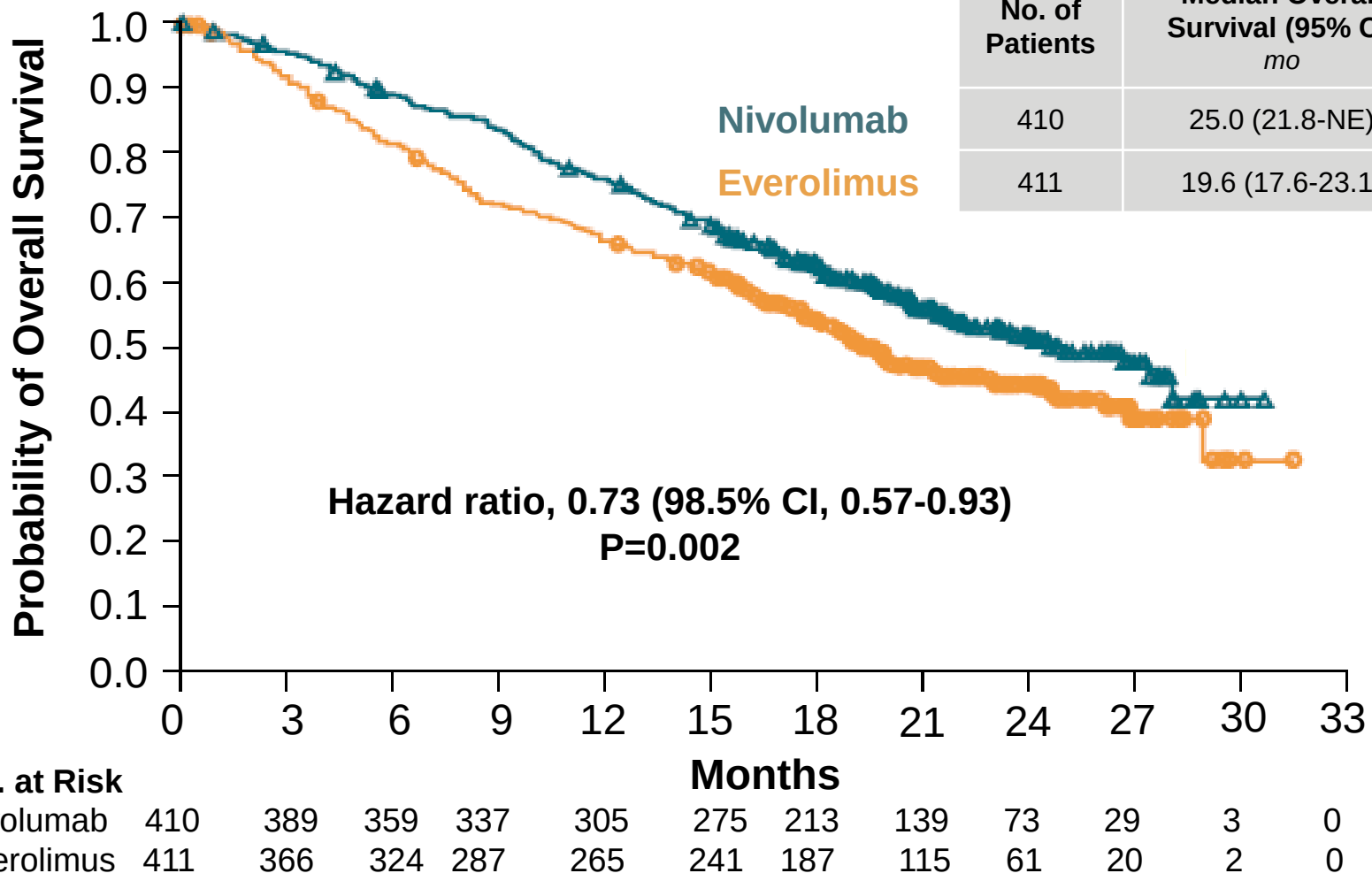
No. of Patients	Median Progression-free Survival (95% CI) *mo*	No. of Progression Events
410	4.6 (3.7-5.4)	318
411	4.4 (3.7-5.5)	322

Hazard ratio, 0.88 (95% CI, 0.75-1.03)
P=0.11

No. at Risk												
Nivolumab	410	230	145	116	81	66	48	29	11	4	0	0
Everolimus	411	227	129	97	61	47	25	16	3	0	0	0

Motzer, et al. *N Engl J Med.* 2015;373:1803-1813.

CheckMate 025: Overall Survival

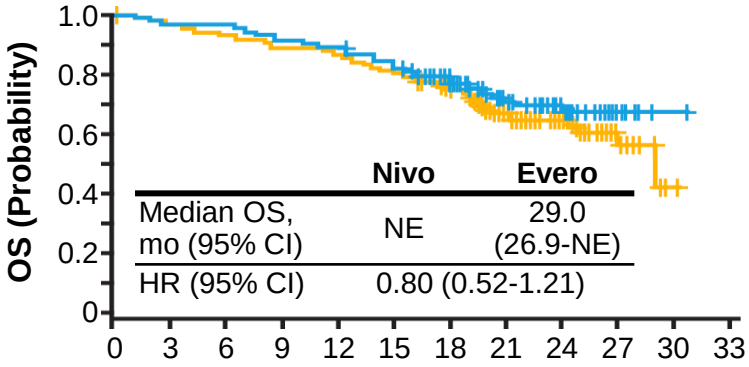


No. of Patients	Median Overall Survival (95% CI) *mo*	No. of Deaths
410	25.0 (21.8-NE)	183
411	19.6 (17.6-23.1)	215

Motzer, R et al. *N Engl J Med.* 2015;373:1803-1813

OS by MSKCC Risk Status

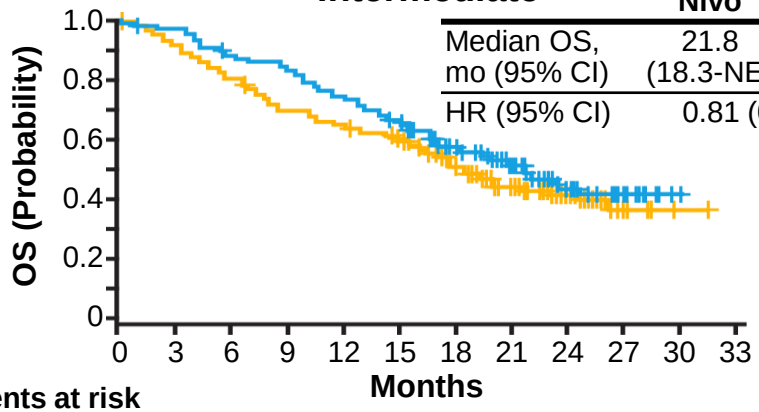
Favorable



	Nivo	Evero
Median OS, mo (95% CI)	NE	29.0 (26.9-NE)
HR (95% CI)	0.80 (0.52-1.21)	

Patients at risk						
Nivo	137	133	122	88	35	1
Evero	145	132	123	98	35	1

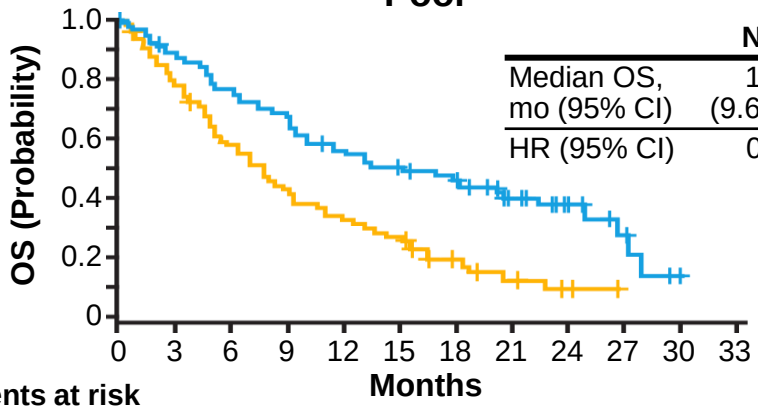
Intermediate



	Nivo	Evero
Median OS, mo (95% CI)	21.8 (18.3-NE)	18.4 (16.1-23.1)
HR (95% CI)	0.81 (0.61-1.06)	

Patients at risk						
Nivo	193	167	141	91	26	1
Evero	192	151	118	80	24	1

Poor



	Nivo	Evero
Median OS, mo (95% CI)	15.3 (9.6-22.4)	7.9 (5.4-9.7)
HR (95% CI)	0.48 (0.32-0.70)	

Patients at risk						
Nivo	79	59	42	34	12	1
Evero	74	41	24	9	2	0

Motzer RJ, et al. ASCO GU 2016 (poster 3657).

CheckMate-025: Safety Overview

	Nivolumab (n=406)	Everolimus (n=397)
Grade 3-4 adverse events, n (%)	76 (19)	145 (37)
Treatment related AEs leading to treatment discontinuation, n (%)	31 (8)	52 (13)
Drug-related deaths, n	0	2*
Treatment beyond progression^, n (%)	179 (44)	183 (46)

- The most common treatment-related adverse events with nivolumab:
  - Fatigue (33%)
  - Nausea (14%)
  - Pruritus (14%)
- The most common treatment-related adverse events with everolimus:
  - Fatigue (34%)
  - Stomatitis (29%)
  - Anemia (24%)
- The most common grade 3-4 adverse events:
  - For nivolumab: fatigue (10 patients, 2%)
  - For everolimus: anemia (31 patients, 8%)

Motzer, R et al. N Engl J Med. 2015;373:1803-1813

Advanced Renal Cell Cancer Optimal 2nd Line Therapy?

- Survival improvement for both nivolumab and cabozantinib
- ORR similar between these agents, but PFS benefit favors cabozantinib
- No impact of PDL1 expression

Management of Metastatic Urothelial Cancer: Summary of Current Evidence

- Cisplatin-based combination chemotherapy provides the potential to cure in the range of 5-15%, primarily in good PS pts with low volume nodal disease
- Non-cisplatin based chemotherapy appears to be primarily palliative, may impact slightly on PFS
- A small group of highly selected patients may benefit from an integrated chemotherapy/surgical approach

Second Line Chemotherapy for Advanced Urothelial Cancer

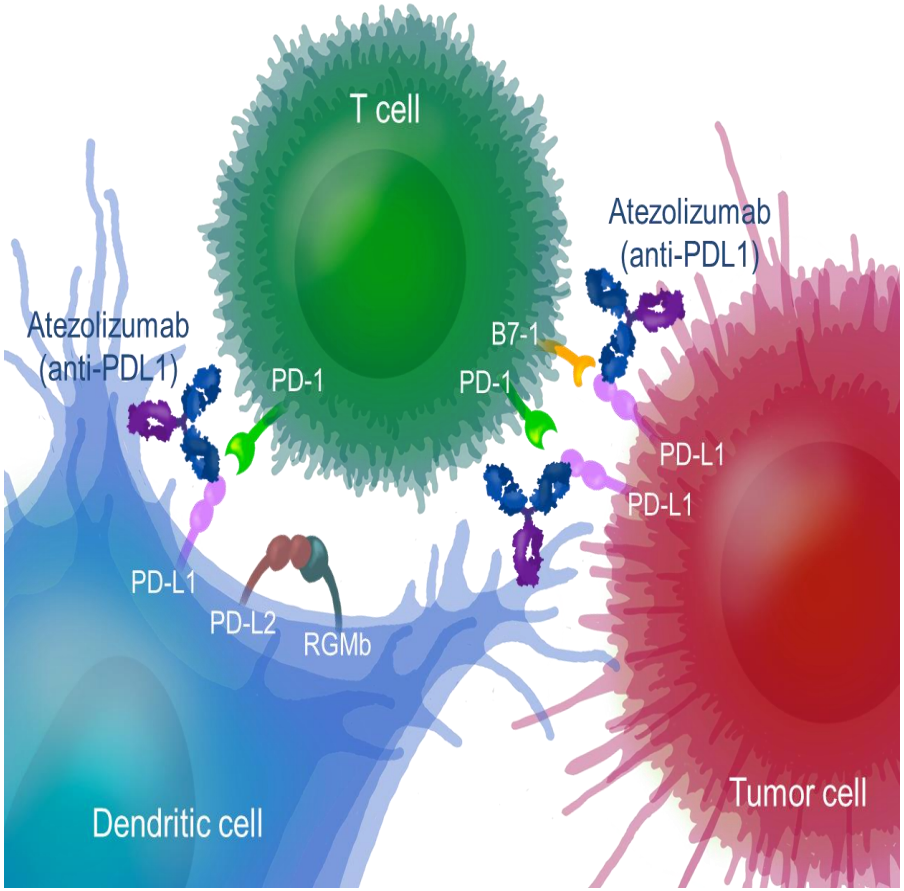
- To date no level 1 evidence supporting improvement in survival
- There is no current evidence for the superiority of salvage combination chemotherapy compared to monotherapy, or precise delineation of non-cross resistant regimens

Updated Efficacy From IMvigor210: Atezolizumab in Platinum-Treated Locally Advanced/Metastatic Urothelial Carcinoma (mUC)

Robert Dreicer,[1] Jean Hoffman-Censits,[2] Thomas Flaig,[3] Enrique Grande,[4] Ani Balmanoukian,[5] Gunhild von Amsberg,[6] Christine Theodore,[7] Simon Chowdhury,[8] Sergio Bracarda,[9] Jessica M. Clement,[10] Evan Y. Yu,[11] Arash Rezazadeh Kalebasty,[12] Günter Niegisch,[13] Stephane Culine,[14] Michael S. Gordon,[15] Beiying Ding,[16] Sanjeev Mariathasan,[16] Fatema Legrand,[16] Oyewale O. Abidoye[16] and Daniel P. Petrylak[17]

[1]Division of Hematology/Oncology, University of Virginia, Charlottesville, VA; [2]Sidney Kimmel Cancer Center, Thomas Jefferson University Hospital, Philadelphia, PA; [3]University of Colorado Cancer Center, Aurora, CO; [4]Hospital Universitario Ramón y Cajal, Madrid, Spain; [5]The Angeles Clinic and Research Institute, Los Angeles, CA; [6]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [7]Hôpital Foch, Suresnes, France; [8]Sarah Cannon Research Institute, London, UK; [9]USL8 Ospedale San Donato, Arezzo, Italy; [10]Neag Comprehensive Cancer Center, UConn Health, Farmington, CT; [11]University of Washington and Seattle Cancer Care Alliance, Seattle, WA; [12]Norton Cancer Institute, Louisville, KY; [13]Heinrich Heine University Düsseldorf, Düsseldorf, Germany; [14]Hôpital Saint-Louis, Paris, France; [15]Pinnacle Oncology Hematology, Scottsdale, AZ; [16]Genentech, Inc., South San Francisco, CA; [17]Yale Cancer Center, New Haven, CT, USA.

PD-L1 and Atezolizumab

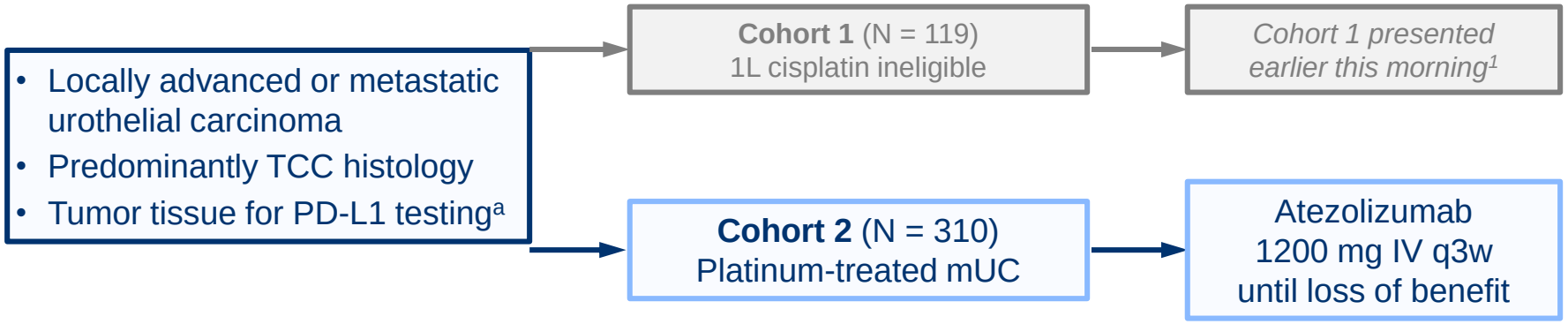


- Atezolizumab is a humanized engineered mAb that selectively targets PD-L1
  - By inhibiting interactions with receptors PD-1 and B7.1, anti-cancer immunity can be reinvigorated and enhanced[1,2]
- Atezolizumab has demonstrated efficacy and safety in a broad range of cancer types, including mUC, NSCLC and RCC[1,3,4]
- PD-L1 expression on immune cells (IC) was evaluated (VENTANA SP142 IHC assay) based on 3 scoring levels: IC2/3 (≥ 5%), IC1 (≥ 1% but < 5%), IC0 (< 1%)

1. Herbst *Nature* 2014. 2 Chen *Immunity* 2013. 3. Powles *Nature* 2014. 4. Rosenberg *Lancet* 2016.

IMvigor210 Cohort 2: Study Design

Basis for Accelerated Approval



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)

IMvigor210 Cohort 2: Baseline Characteristics

Representative of the Greater mUC Population

Characteristic (Safety and Efficacy-Evaluable Patients)	N = 310
Age, median (range)	66 y (32-91 y)
Male	78%
PD-L1 status on immune cells (IC)[a]: IC2/3 | IC1 | IC0	32% | 35% | 33%
Bladder primary tumor site	75%
Metastatic sites: visceral[b] | liver | lymph node only	78% | 31% | 14%
Creatinine clearance 30-60 mL/min	35%
ECOG PS 1	62%
Prior cystectomy or nephroureterectomy	66%
Prior regimens (metastatic setting): 1 | 2 | ≥ 3	39% | 21% | 21%

[b] Defined as liver, lung, bone, or any non-lymph node or soft tissue metastasis.

Efficacy

Responses to Atezolizumab by PD-L1 IC Subgroup

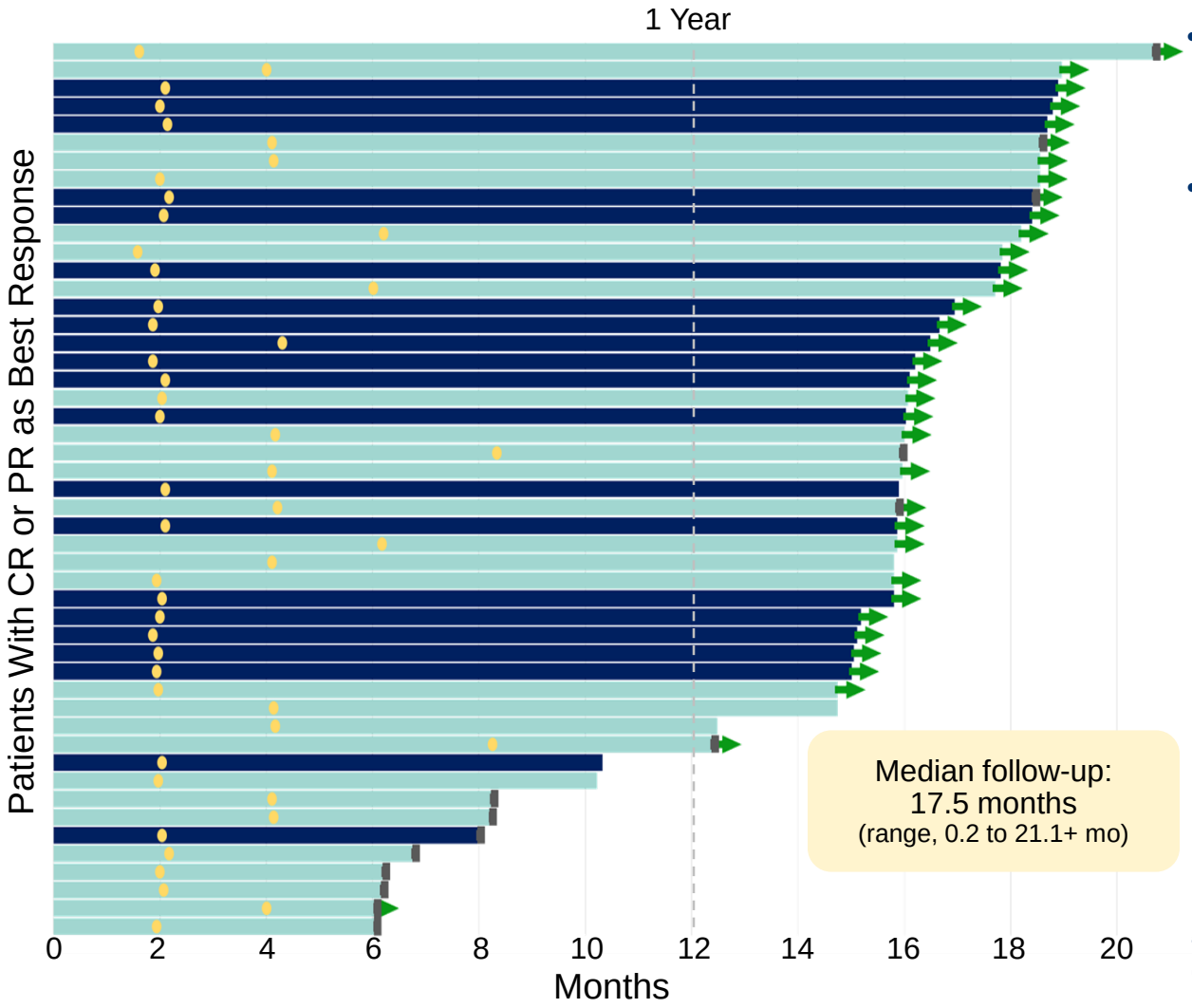
	IC2/3 n = 100	IC1/2/3 n = 207	All[a] N = 310	IC1 n = 107	IC0 n = 103
ORR: confirmed IRF RECIST v1.1 (95% CI)	28% (19, 38)	19% (14, 25)	16% (12, 20)	11% (6, 19)	9% (4, 16)
CR rate: confirmed IRF RECIST v1.1 (95% CI)	**15% (9, 24)**	**9% (6, 14)**	**7% (4, 10)**	**4% (1, 9)**	**2% (0, 7)**

- …th higher PD-L1 status
  - …nses
  - CRs were observed in all PD-L1 subgroups, with the highest rate in IC2/3 patients
- ORRs per immune-modified RECIST were concordant

IRF, independent review facility. [a] Includes 46 patients with missing/unevaluable responses. Treated patients had measurable disease at baseline per investigator-assessed RECIST v1.1. Data cutoff: March 14, 2016.

Efficacy

Duration of Treatment and Response

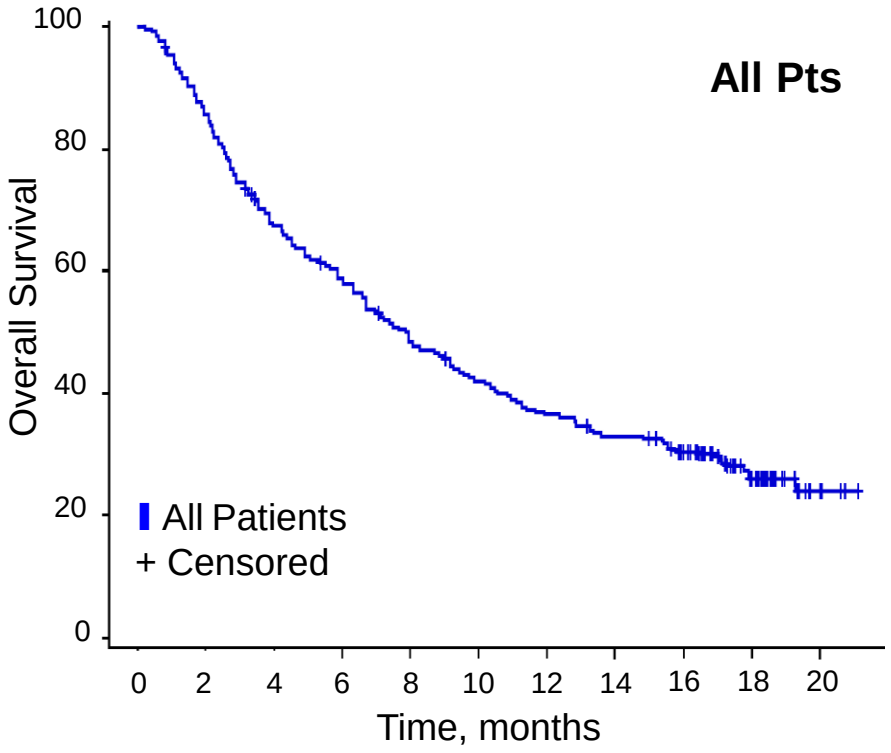


- 71% of responses (35/49) were ongoing
  - 86% of CRs ongoing
- mDOR was not yet reached in any PD-L1 IC subgroup (range, 2.1+ to 19.2+ mo)[a]

[a] Per IRF RECIST v1.1. [b] Discontinuation symbol does not indicate timing. [c] No PD or death only. Data cutoff: March 14, 2016.

Efficacy

Overall Survival



 # 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)
2L only (n = 120)	NE (10.9, NE)	7.1 mo (5.0, 9.2)	9.0 mo (7.2, 11.3)

Subgroup	(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 sta
- 12-mo OS compares favorably with historic estimates of ~ 20 %

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.

Safety: Adverse Event Profile

Treatment-Related AEs

AE (N = 310)[a]	All Grade	Grade 3-4
Fatigue	31%	2%
Nausea	14%	0%
Decreased appetite	11%	1%
Pruritus	11%	< 1%
Pyrexia	9%	< 1%
Diarrhea	8%	< 1%
Rash	7%	< 1%
Vomiting	7%	< 1%
Arthralgia	7%	1%
AST increased	4%	1%
ALT increased	3%	1%
Hypertension	1%	1%

[a] Frequency ≥ 7% (all Grade) or ≥ 3 patients (Grade 3-4). Data cutoff: March 14, 2016.

- Most treatment related AEs were Grade 1-2
- No decline in renal function was observed in patients with pre-existing renal impairment

Other PD1/PDL1 targeted agents in development

- Nivolumab similar clinical activity/toxicity
- Durvalumab (anti PDL1)
  - Small experience, no activity in non PDL1 expressing cells
- PDL1 expression issues
  - Tumor cells/Immune cells
  - Timing of assessment
  - Assays

Massard C, et al. J Clin Oncol 34, 2016 (suppl; abstr 4502) and Sharma P, et al. J Clin Oncol 34, 2016 (suppl; abstr 4501)

Immunotherapy in GU Cancers

- Renal cancer: major impact on management, upfront studies reporting soon
- Prostate cancer: circling back re: Checkpoint inhibitors, novel vaccine strategies
- Urothelial cancer: potential for paradigm shift
  - Atezolizumab FDA approved 5/16
  - upfront, cisplatin ineligible, adjuvant studies ongoing
- Combinatorial immunotherapeutic strategies key

“ A doctor can bury his mistakes, but an architect can only advise his clients to plant vines”

Frank Lloyd Wright (1868-1959)