Immunotherapy for the treatment of genitourinary cancers

SITC, Tampa 12/2016

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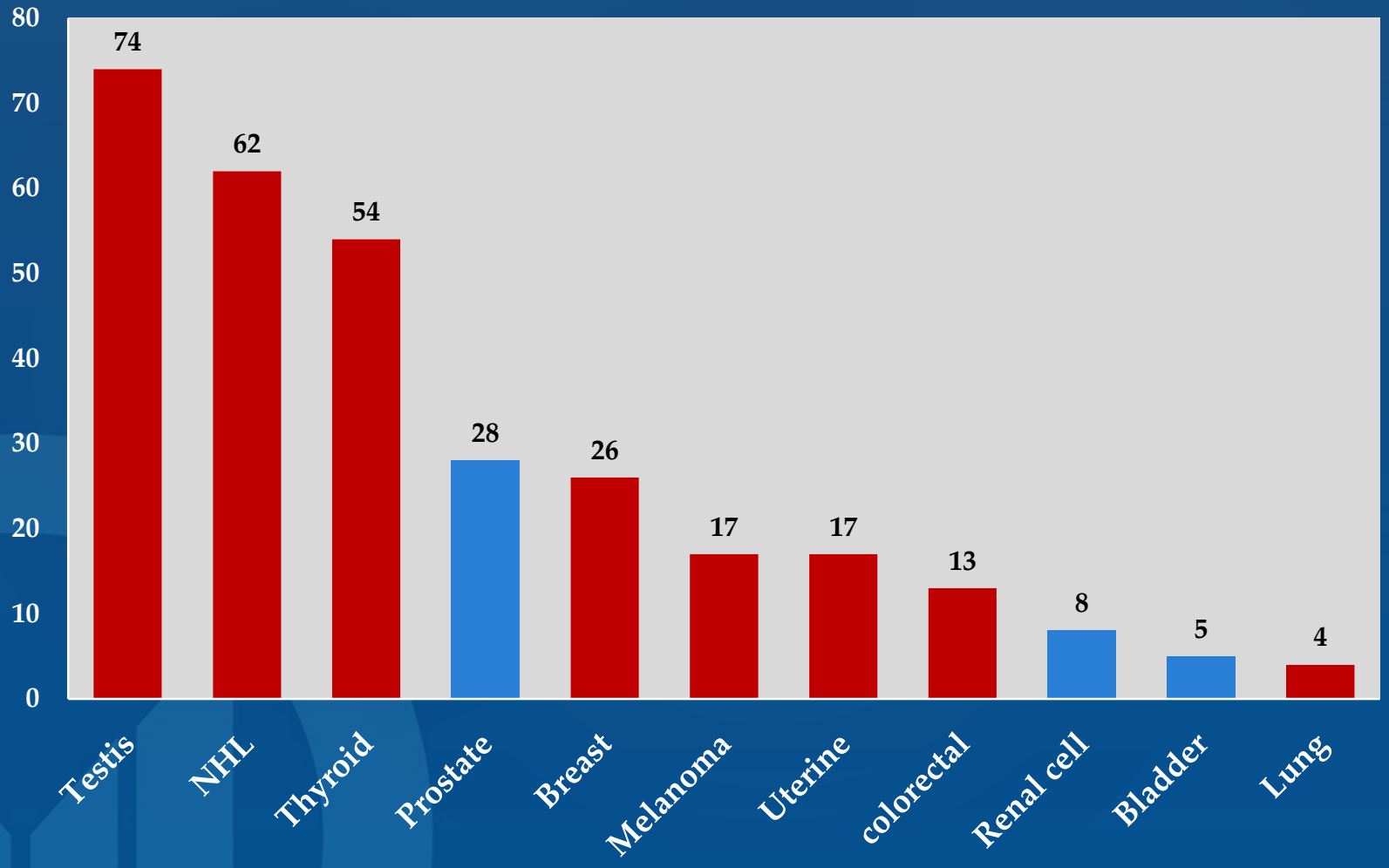
Disclosures:

- Research funding from AstraZeneca, Astellas, Bayer, and Medivation
- Consulting fees: Bayer & Sanofi
- I will *not* be discussing non-FDA approved treatments during my presentation.

5-year Relative Survival Rates (%) by Metastatic Cancer Type



http://www.cancer.org/acs/groups/cid/documents

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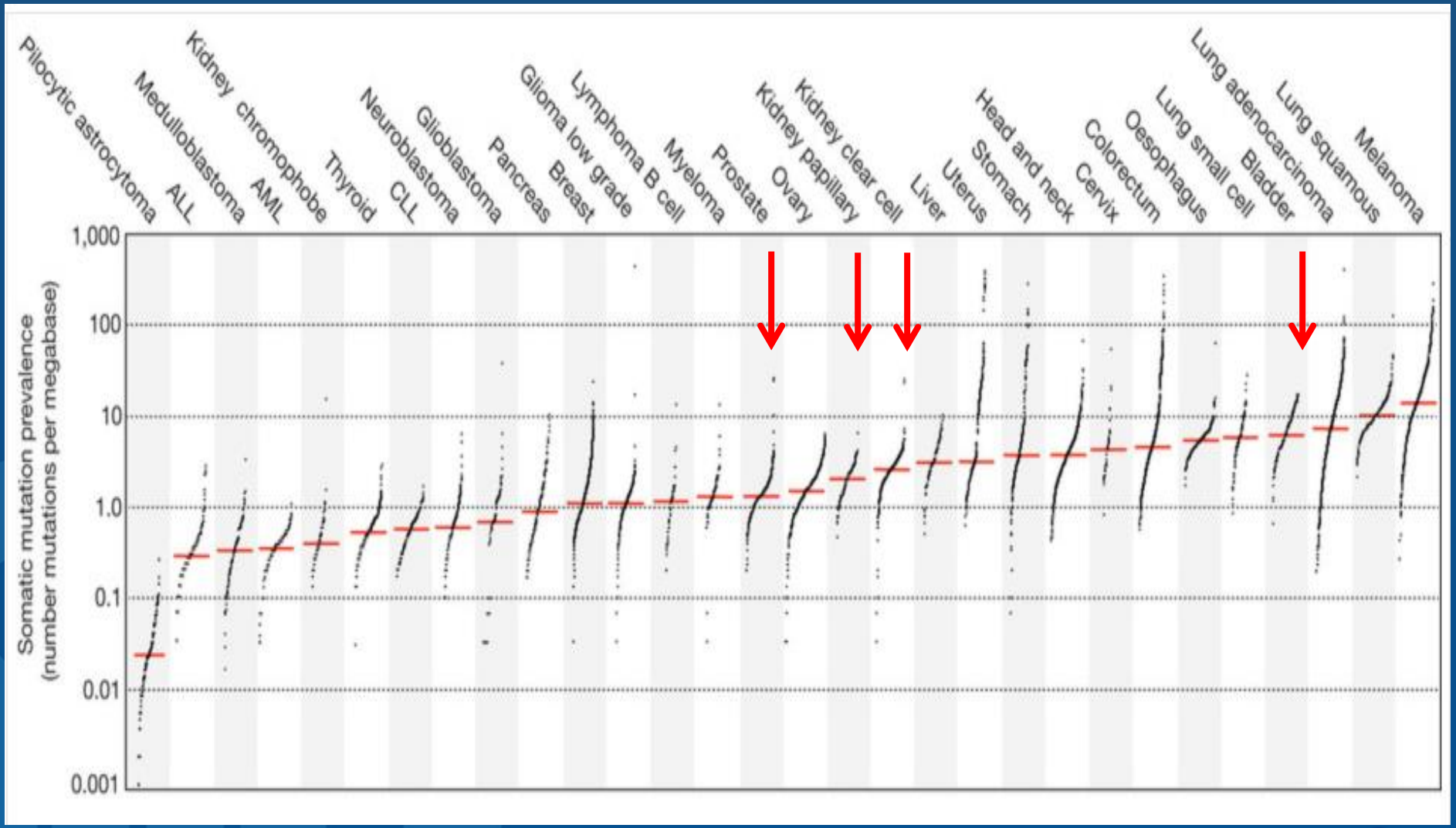
Somatic Mutation Prevalence in GU malignancy



Alexandrov LB et al. *Nature* 2013, 500, 415-21

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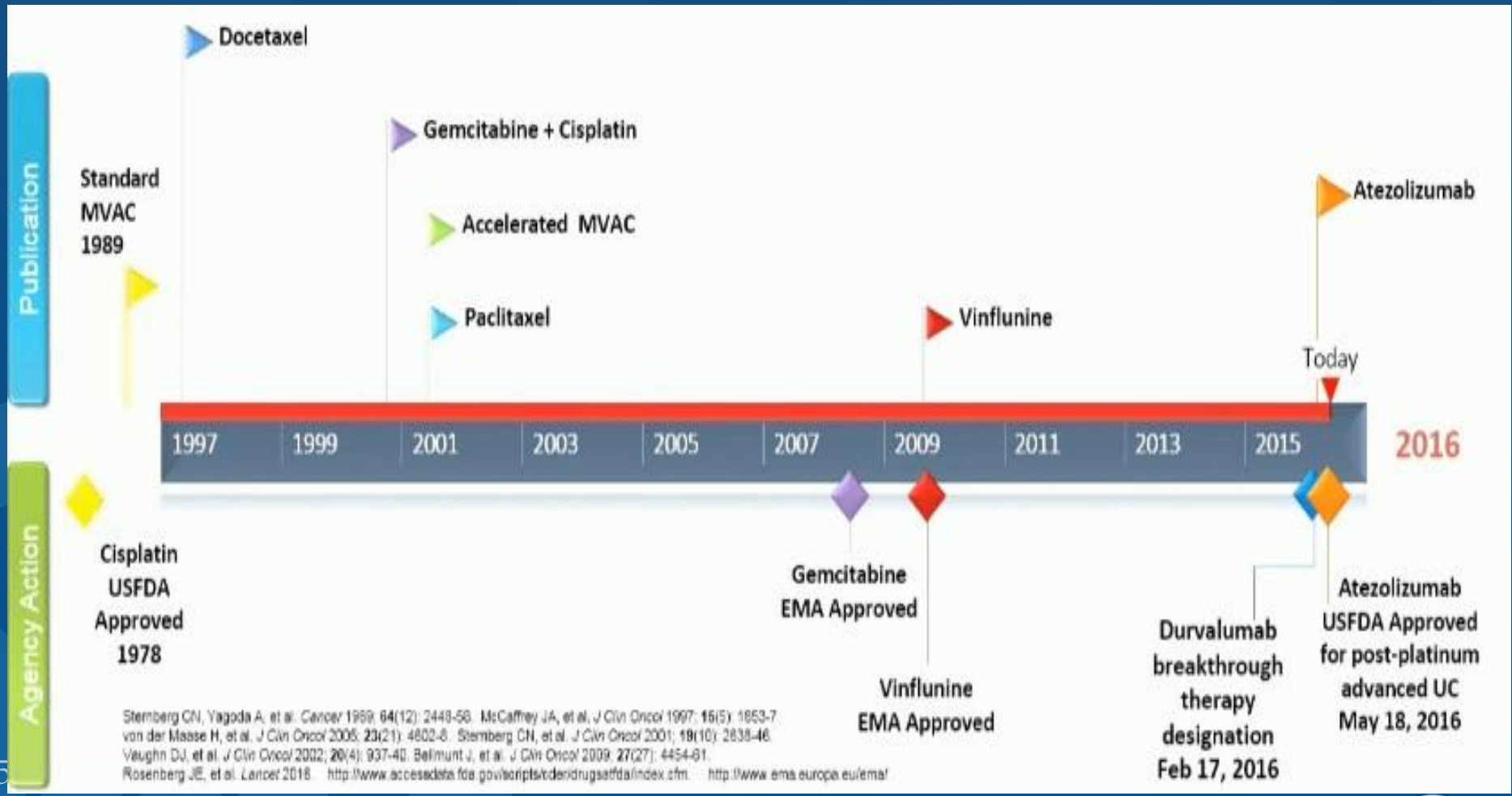
Evolution of Systemic Therapy for Metastatic Urothelial Carcinoma (mUC)



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Bacillus Calmette-Guerin (BCG): First Immune therapy for bladder cancer

STEPS	MEDIATED BY
Infection of Urothelial and Bladder Cancer Cell	Fibronectin
Induction of Immune Reaction	Cells: T-Helper, Dendritic, Macrophages Immune Mediaters, CD4+, IL2,6,8,10,12,17
Induction of Anti-tumor Activity	TH1 cells: CD4+ T, CD8+ T -* INF Gamma NK cells

Morles et al *J Urol* 1976

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Intravesicle BCG vs Epirubicin Chemotherapy: EORTC 30911

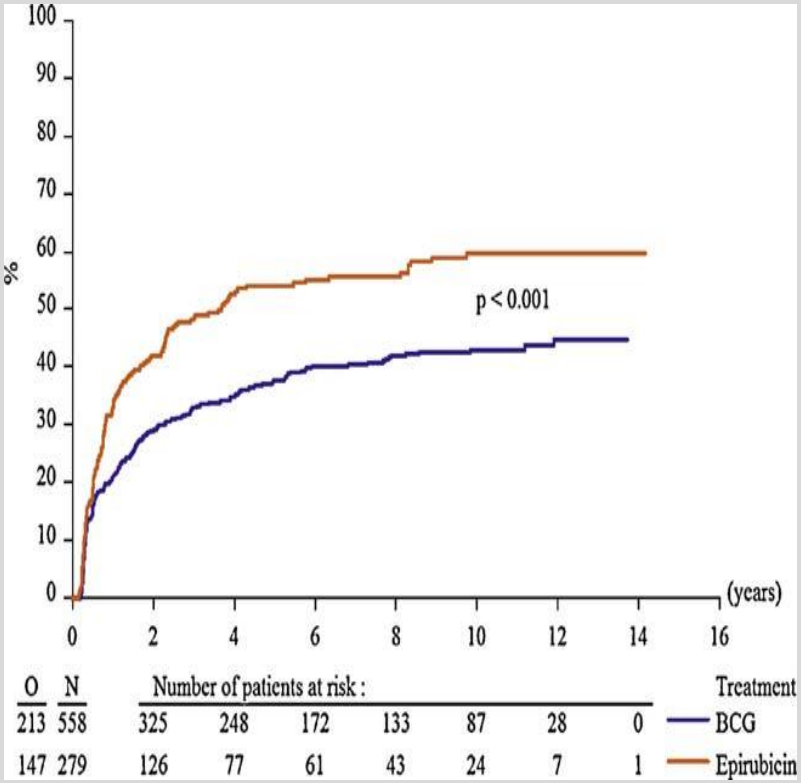

Fig. 2 – Cumulative incidence of first recurrence. BCG = bacillus Calmette-Guérin. O = observed number of events; N = number of patients.

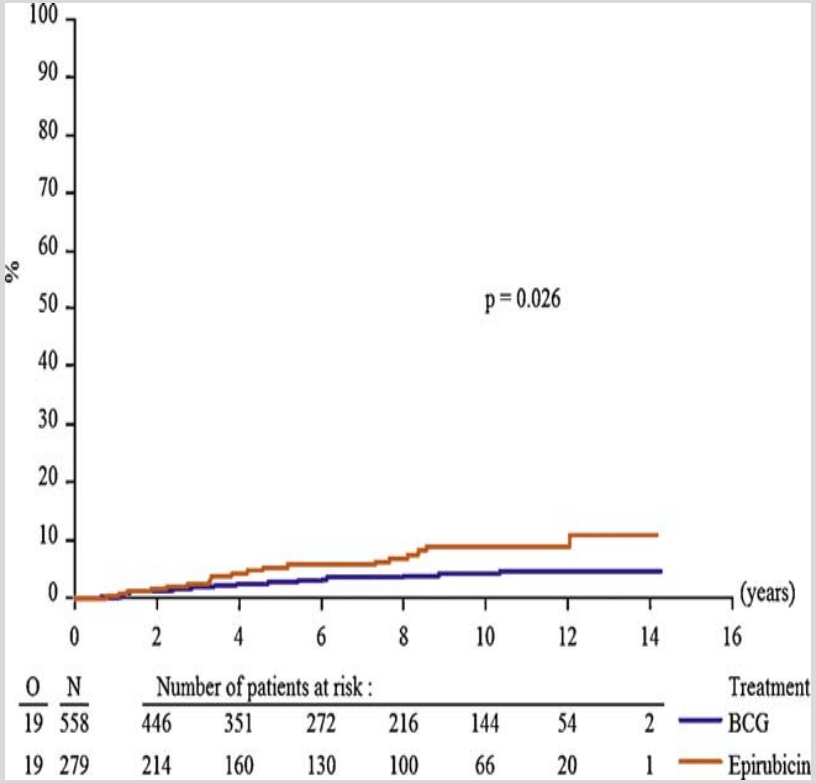

Fig. 6 – Cumulative incidence of death due to bladder cancer. BCG = bacillus Calmette-Guérin. O = observed number of events; N = number of patients.

Sylvester et al Eur Urol 2010

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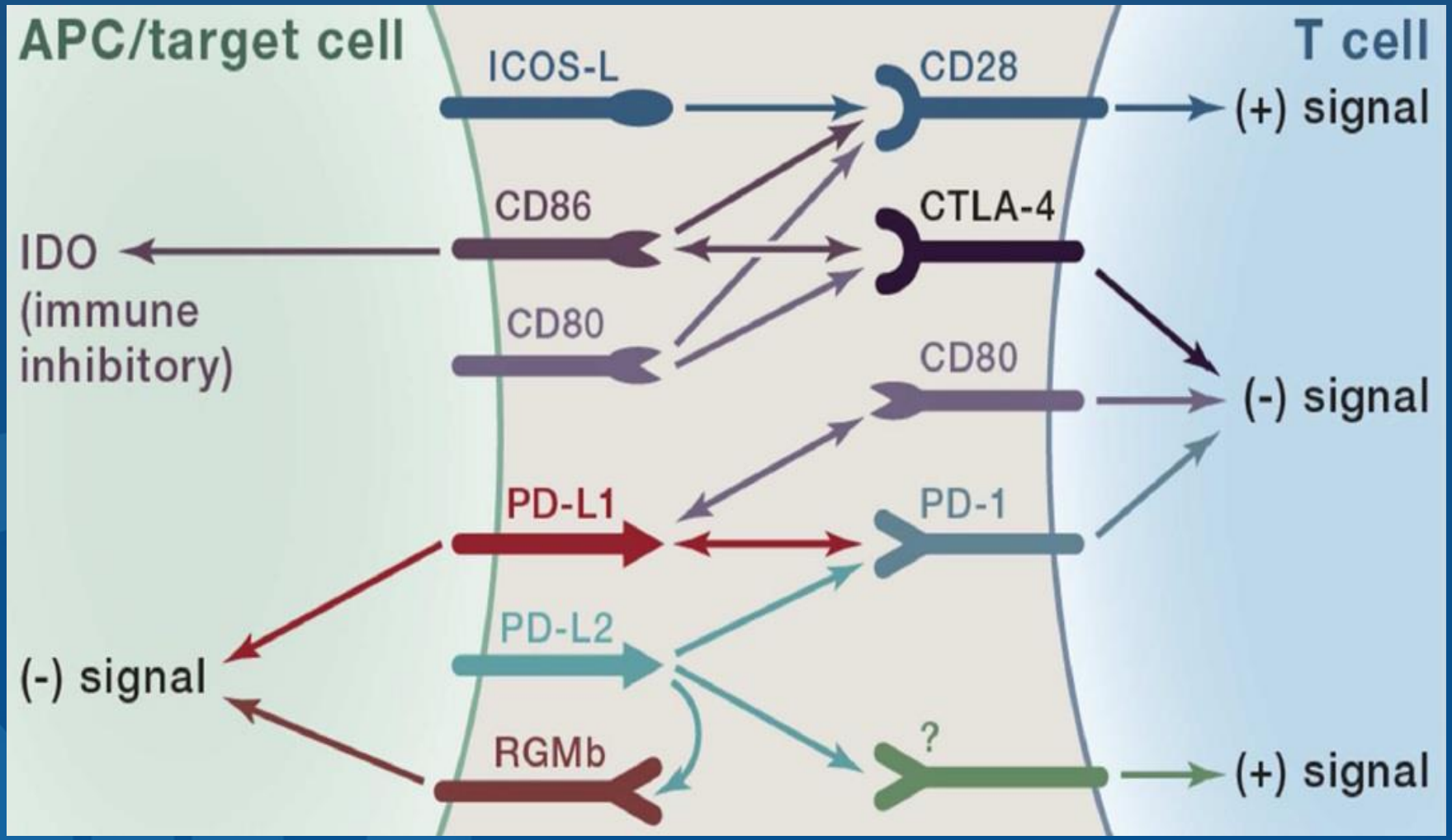
Complex interactions between the CTLA-4/CD28 and PD-1 families of receptors and ligands



Topalian SL et al. *Cancer Cell* 2015, 450-61

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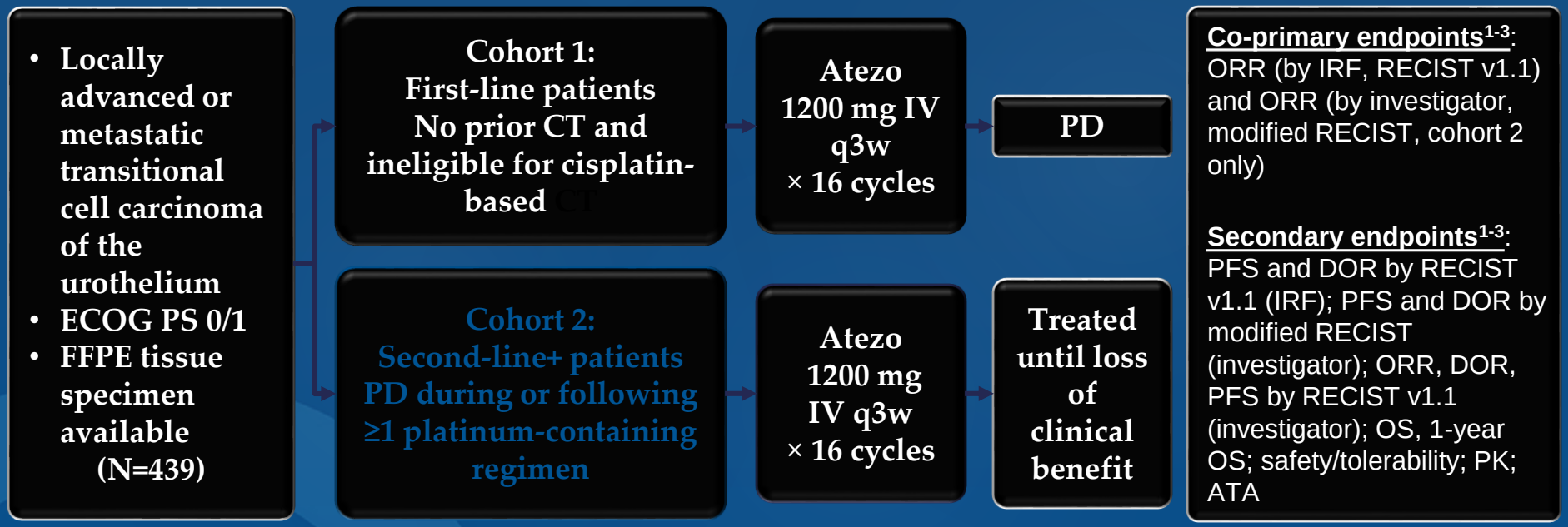
IMvigor 210 (GO29293)* Single-Arm Phase II in Metastatic Urothelial Carcinoma: **Study Design**[1-3]



Study locations[1]: United States, Canada, France, Germany, Italy, Netherlands, Spain, United Kingdom

ATA=anti-therapeutic antibodies; Atezo=atezolizumab; CT=chemotherapy; FFPE=formalin-fixed, paraffin-embedded; IRF=independent review facility; RECIST=Response Evaluation Criteria in Solid Tumors

1. https://www.clinicaltrials.gov/ct2/show/study/NCT02108652. Accessed 04/08/16. 2. Protocol GO29293. Version 7. September 2015. 3. Rosenberg JE, et al. Lancet 2016;387:1909-1920.

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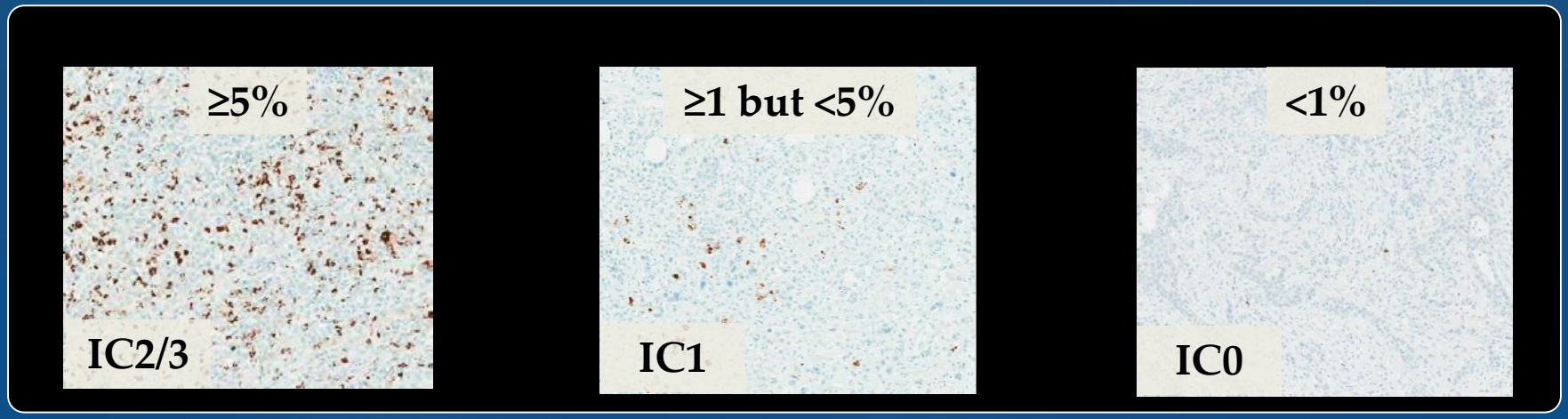
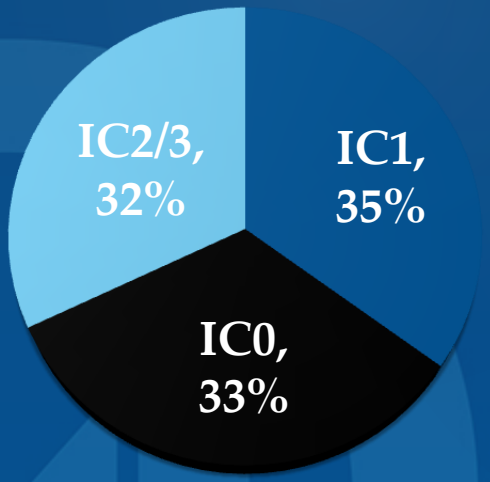
IMvigor 210 (GO29293)* Single-Arm Phase II in Metastatic Urothelial Carcinoma: PD-L1 IC Expression and Prevalence (Cohort 2)[1,2]





- IMvigor 210 enrolled an all-comer population
- VENTANA PD-L1 (SP142) CDx Assay was used to prospectively measure tumor-infiltrating IC PD-L1 expression based on 3 IHC scoring levels
- Patients were evenly distributed between the PD-L1 IC groups[2]

Images at 10x magnification
IC=immune cells

1. Rosenberg JE, et al. Presented at: ESMO. 2015 (abstr 21LBA). 2. Rosenberg JE, et al. Lancet 2016;387:1909-1920.

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	IC2/3 (n=100)	IC1/2/3 (n=207)	All patients (n=310)*
Age, years	66 (41–84)	67 (32–91)	66 (32–91)
Male sex	78 (78%)	160 (77%)	241 (78%)
White race	87 (87%)	184 (89%)	282 (91%)
Site of primary tumour			
Bladder	79 (79%)	159 (77%)	230 (74%)
Renal pelvis	11 (11%)	27 (13%)	42 (14%)
Ureter	5 (5%)	12 (6%)	23 (7%)
Urethra	3 (3%)	5 (2%)	5 (2%)
Other	2 (2%)	4 (2%)	10 (3%)
Baseline creatinine clearance <60 mL/min	40 (40%)	69 (33%)	110 (36%)
ECOG performance status			
0	42 (42%)	83 (40%)	117 (38%)
1	58 (58%)	124 (60%)	193 (62%)
Haemoglobin concentration <100 g/L	24 (24%)	50 (24%)	69 (22%)
Tobacco use			
Current	6 (6%)	19 (9%)	35 (11%)
Never	34 (34%)	72 (35%)	107 (35%)
Previous	60 (60%)	116 (56%)	168 (54%)
Number of Bellmunt risk factors			
0	31 (31%)	61 (30%)	83 (27%)
1	35 (35%)	72 (35%)	117 (38%)
2	28 (28%)	59 (29%)	89 (29%)
3	6 (6%)	15 (7%)	21 (7%)
Metastatic sites at baseline			
Visceral†	66 (66%)	152 (73%)	243 (78%)
Liver	27 (27%)	61 (30%)	96 (31%)
Lymph node only	24 (24%)	39 (19%)	43 (14%)
Previous cystectomy	44 (44%)	83 (40%)	115 (37%)
Time since previous chemotherapy ≤3 months	43 (43%)	87 (42%)	121 (39%)

IMvigor 210: Patient Characteristics

78% (66% for IC2/3) had cisplatin-based chemo

26% (17% for IC2/3) had carboplatin based chemo

Rosenberg JE, et al. *Lancet* 2016;387:1909-1920

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Imvigor 210 : Objective response rate by PD-L1 immune cell score

	Patients, n	Objective response rate, n (% [95% CI])	Complete response	Partial response	Stable disease	Progressive disease
RECIST version 1.1 criteria by independent review						
IC2/3	100	26 (26% [18–36])	11 (11%)	15 (15%)	16 (16%)	44 (44%)
IC1/2/3	207	37 (18% [13–24])	13 (6%)	24 (12%)	34 (16%)	107 (52%)
All patients	310	45 (15% [11–19])	15 (5%)	30 (10%)	59 (19%)	159 (51%)
IC1*	107	11 (10% [5–18])	2 (2%)	9 (8%)	18 (17%)	63 (59%)
IC0*	103	8 (8% [3–15])	2 (2%)	6 (6%)	25 (24%)	52 (50%)

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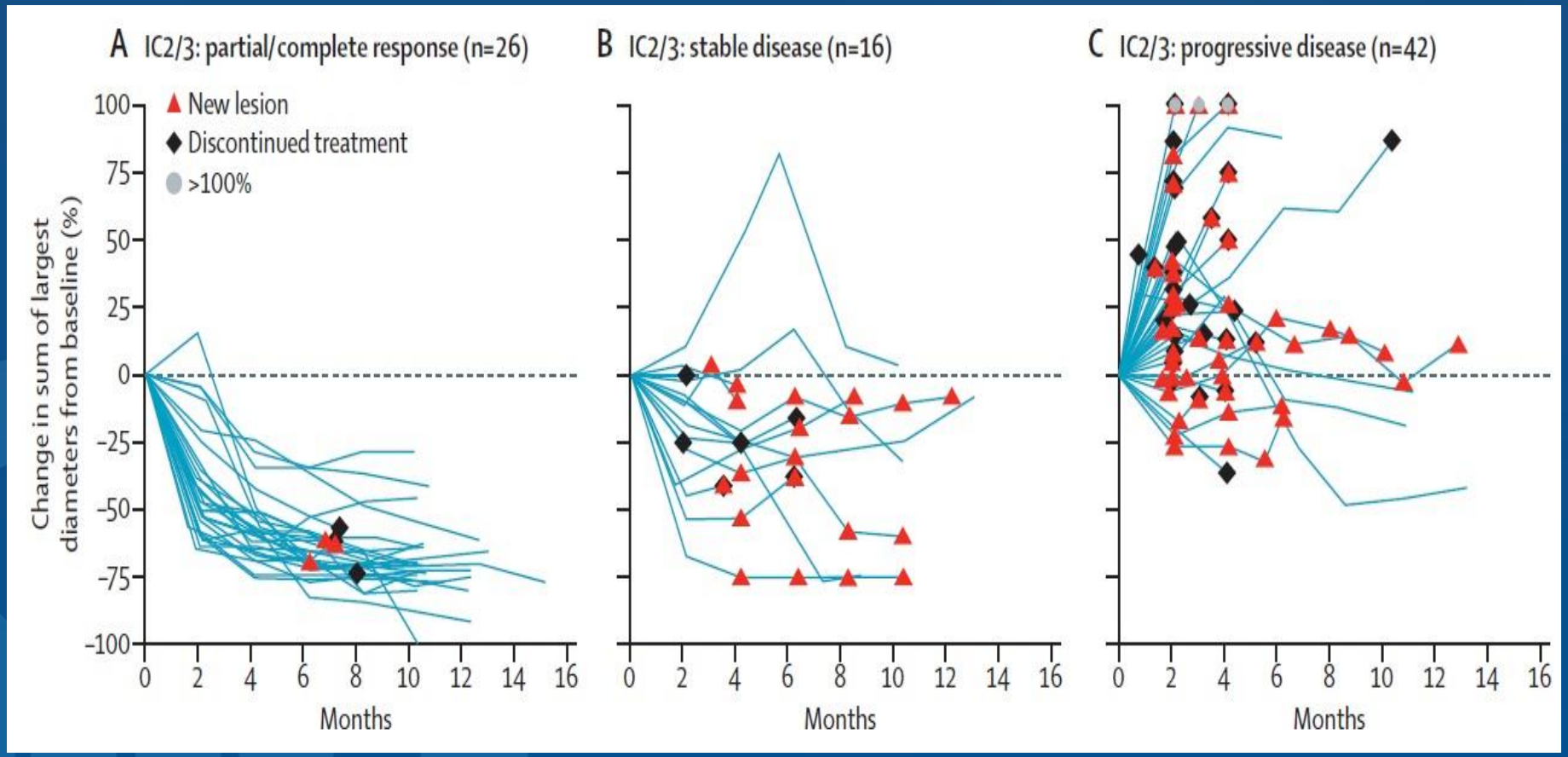
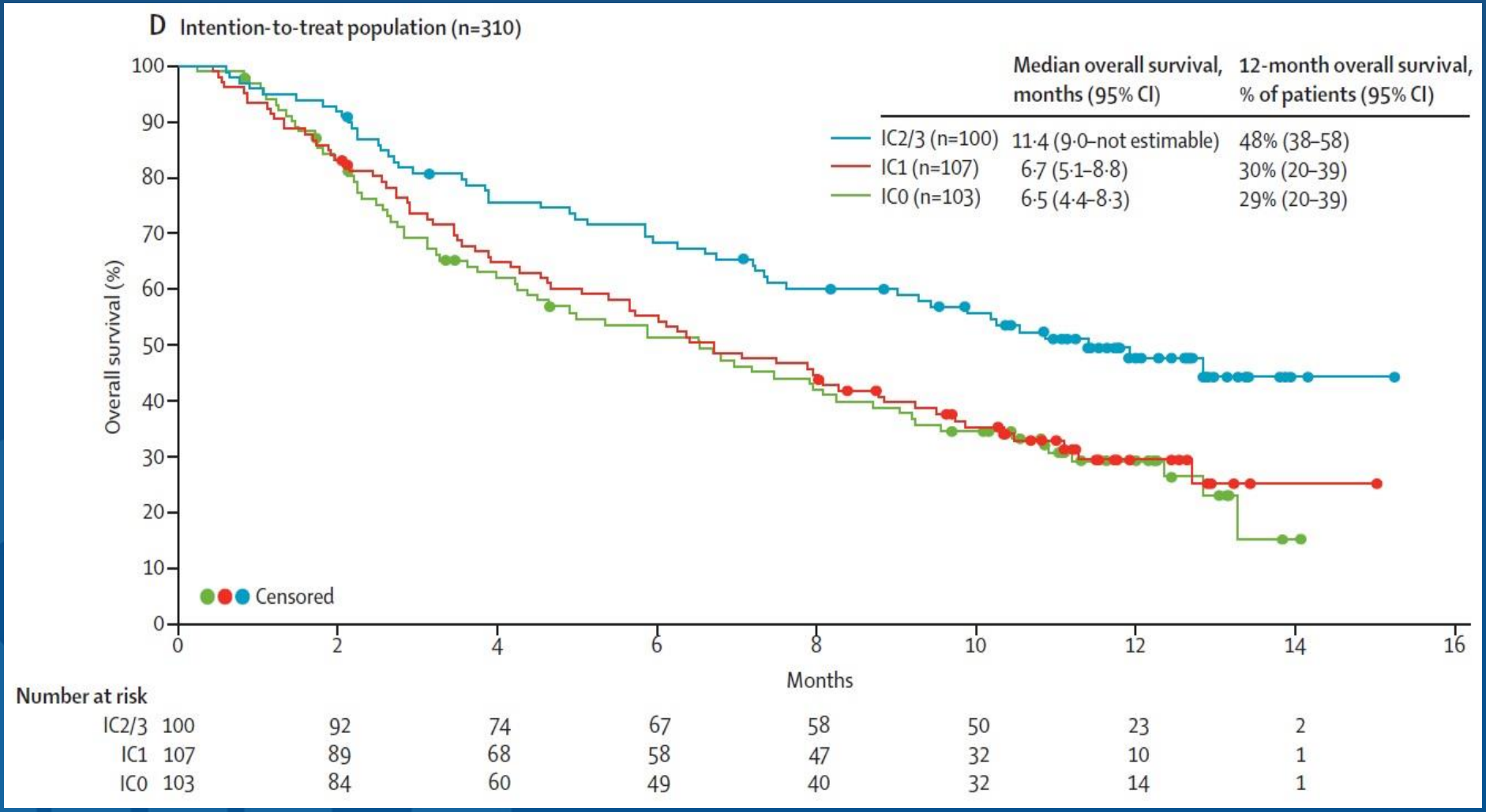
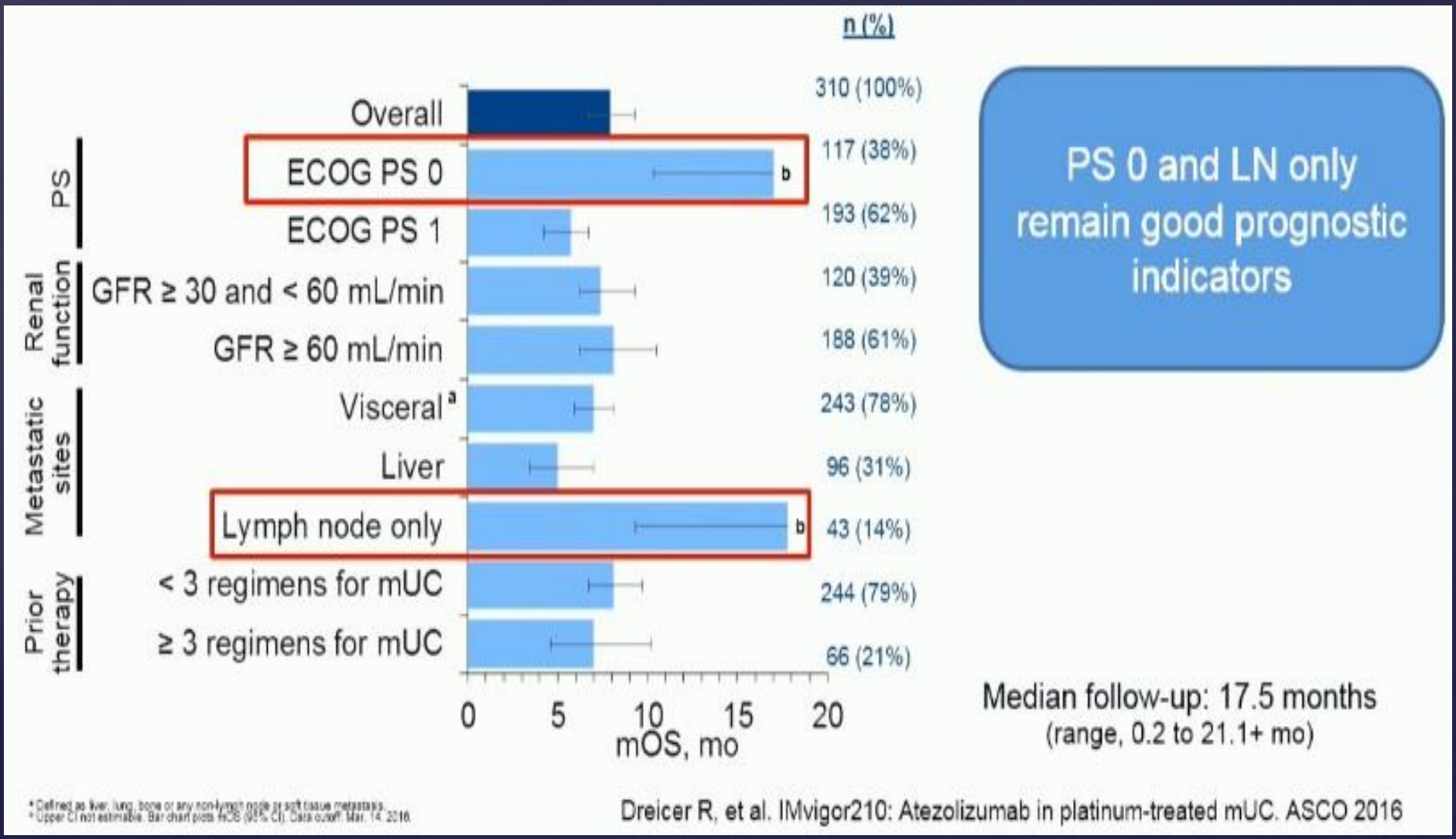
Imvigor 210: Change in sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) over time by best response in the PD-L1 IC2/3 group



Imvigor 210:Kaplan-Meier overall survival curves for the IC0, IC1, and IC2/3 groups. IC=immune cell



Baseline clinical features and their associations with overall survival after Atezolizumab



a Defined as liver, lung, bone or any non-lymph node or soft tissue metastasis.
b Upper CI not estimable. Bar chart plots mOS (95% CI). Data cutoff: Mar. 14, 2016.

Dreicer R, et al. IMvigor210: Atezolizumab in platinum-treated mUC. ASCO 2016

IMvigor 210 Adverse Events

	Any grade	Grade 3–4
Any adverse event	215 (69%)	50 (16%)
Fatigue	93 (30%)	5 (2%)
Nausea	42 (14%)	0
Decreased appetite	36 (12%)	2 (1%)
Pruritis	31 (10%)	1 (<1%)
Pyrexia	28 (9%)	1 (<1%)
Diarrhoea	24 (8%)	1 (<1%)
Rash	23 (7%)	1 (<1%)
Arthralgia	21 (7%)	2 (1%)
Vomiting	18 (6%)	1 (<1%)
Dyspnoea	10 (3%)	2 (1%)
Anaemia	9 (3%)	3 (1%)
Aspartate aminotransferase increased	10 (3%)	2 (1%)
Pneumonitis	7 (2%)	2 (1%)
Hypotension	5 (2%)	2 (1%)
Hypertension	3 (1%)	3 (1%)
Colitis	3 (1%)	2 (1%)

Adverse events reported up until data cutoff on Sept 14, 2015.

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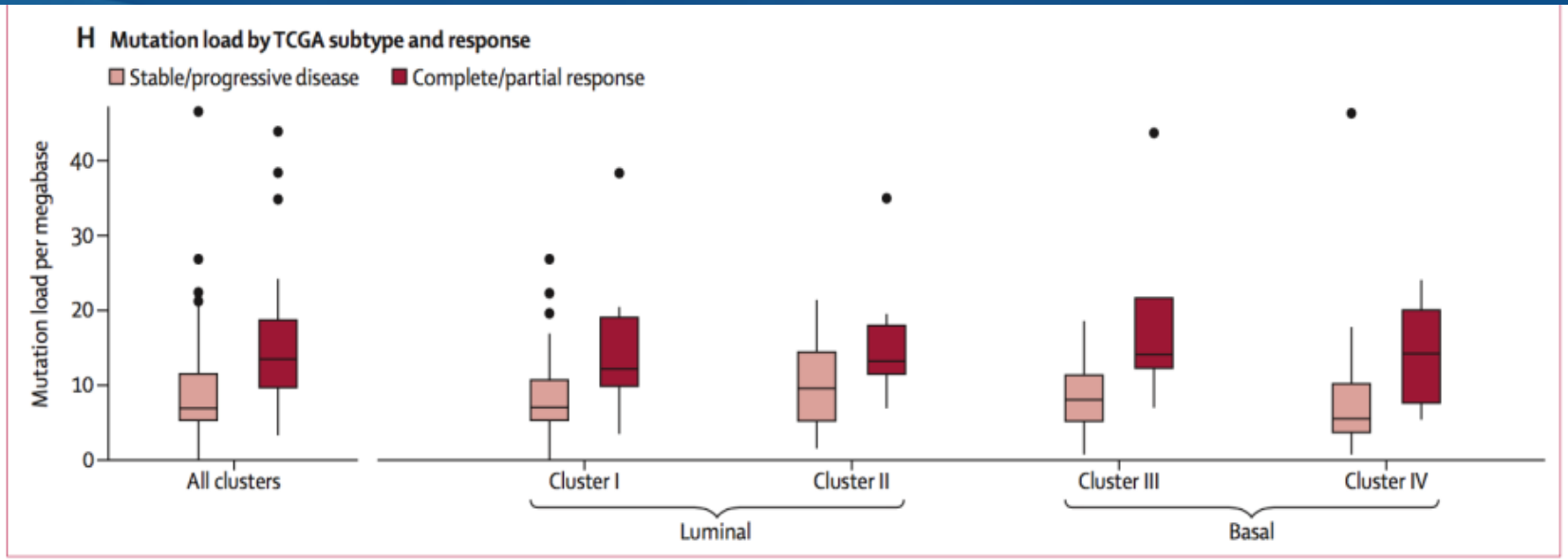
PD-L1 expression as a potential predicative biomarker for anti-PDL1 or anti-PD1 therapy in mUC

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%

Other potential predicative biomarkers

Early data suggests the following may enrich for response to PD1 pathway inhibition:

- Higher mutational load
- TCGA Subtype (Luminal II)
- CD8 infiltration
- Immune related gene expression signatures (Nanostring)
- Peripheral expansion of certain TCR clones



Ongoing clinical trials for Check point inhibitors in urothelial carcinoma

NMIBC (non-muscle invasive bladder cancer)

Phase II Pembrolizumab for BCG refractory NMIBC

Phase III trials in MIBC (muscle invasive bladder cancer)

- Adjuvant setting: Atezolizuma vs observation; Nivolumab vs observation

- Phase III trials for frontline metastatic BC :

❖ Imvigor 310: Atezolizumab (Anti PD-L1 Antibody) in Combination With Gemcitabine/Carboplatin Versus Gemcitabine/Carboplatin Alone in Patients With Untreated Locally Advanced or Metastatic Urothelial Carcinoma Who Are Ineligible For Cisplatin-Based Therapy

❖ Danube: Durvalumab/MEDI4736 Monotherapy and MEDI4736 in Combination With Tremelimumab Versus Standard of Care Chemotherapy

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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*

- Randomized (1:1) , open-label, phase 3 study of 821 patients with advanced clear-cell renal-cell carcinoma for which they had received previous treatment with one or two regimens of antiangiogenic therapy
- Nivolumab 3mg/kg IV Q2 weeks vs 10-mg everolimus tablet orally once daily
- The primary end point was overall survival
- The secondary end points included the objective response rate and safety.

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Table 1. Baseline Demographic and Clinical Characteristics of the Patients Who Underwent Randomization.

Characteristic	Nivolumab Group (N=410)	Everolimus Group (N=411)	Total (N=821)
Median age (range) — yr	62 (23–88)	62 (18–86)	62 (18–88)
Sex — no. (%)			
Male	315 (77)	304 (74)	619 (75)
Female	95 (23)	107 (26)	202 (25)
Race — no. (%)*			
White	353 (86)	367 (89)	720 (88)
Asian	42 (10)	32 (8)	74 (9)
Black	1 (<1)	4 (1)	5 (1)
Other	14 (3)	8 (2)	22 (3)
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)
Disease sites that could be evaluated — no. (%)			
1	68 (17)	71 (17)	139 (17)
≥2	341 (83)	338 (82)	679 (83)

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)
Site of metastasis — no. (%)			
Lung	278 (68)	273 (66)	551 (67)
Liver	100 (24)	87 (21)	187 (23)
Bone	76 (19)	70 (17)	146 (18)
Previous nephrectomy — no. (%)			
Yes	364 (89)	359 (87)	723 (88)
No	46 (11)	52 (13)	98 (12)
Median time from initial diagnosis to randomization (range) — mo	31 (1–392)	31 (2–372)	31 (1–392)
Previous antiangiogenic regimens for treatment of advanced renal-cell carcinoma — no. (%)			
1	294 (72)	297 (72)	591 (72)
2	116 (28)	114 (28)	230 (28)

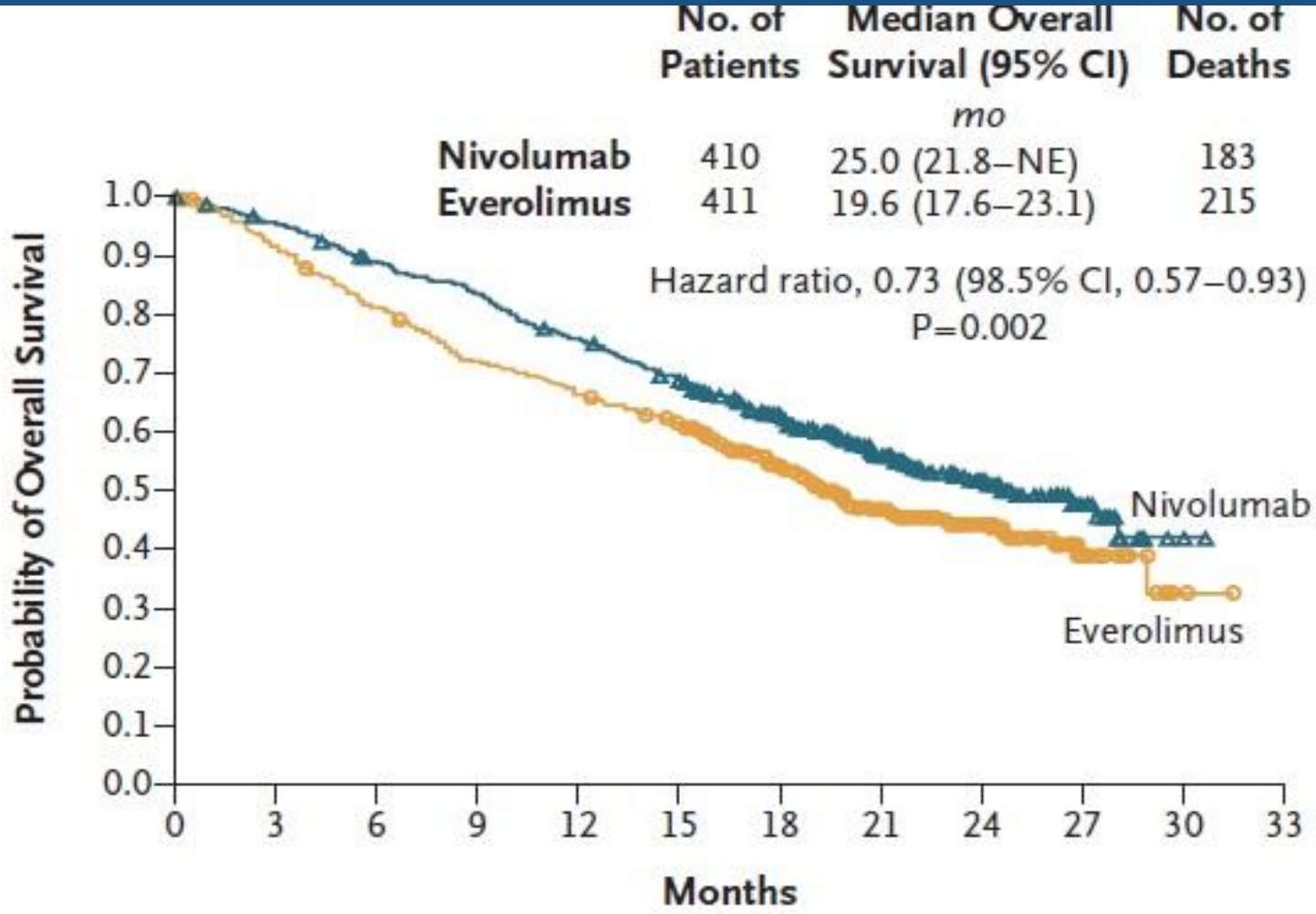
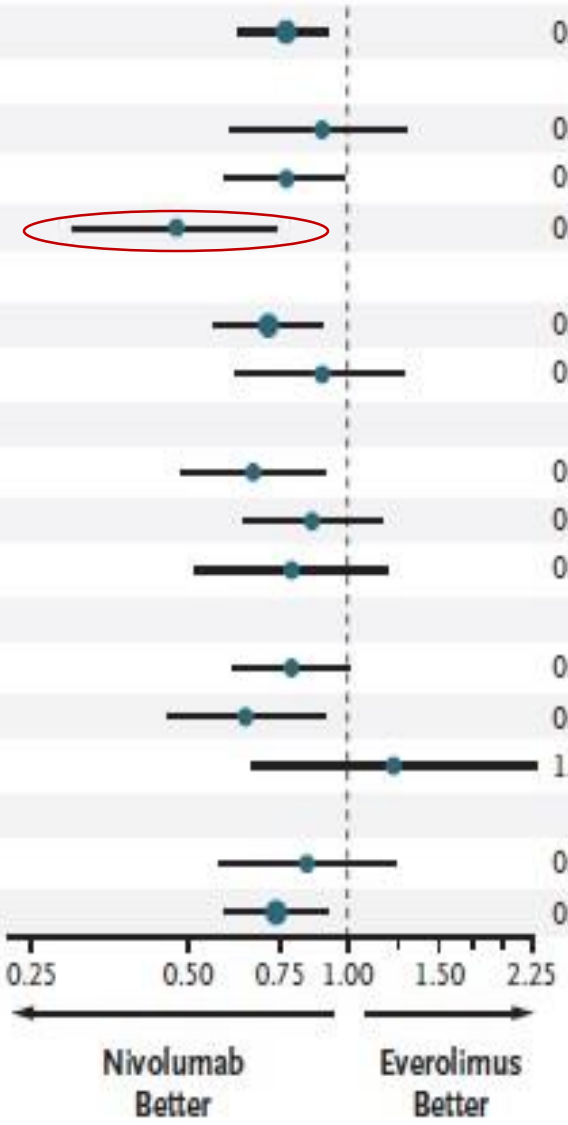


Figure 1. Kaplan–Meier Curve for Overall Survival.

CI denotes confidence interval, and NE not estimable.

A Subgroup Analyses of Overall Survival

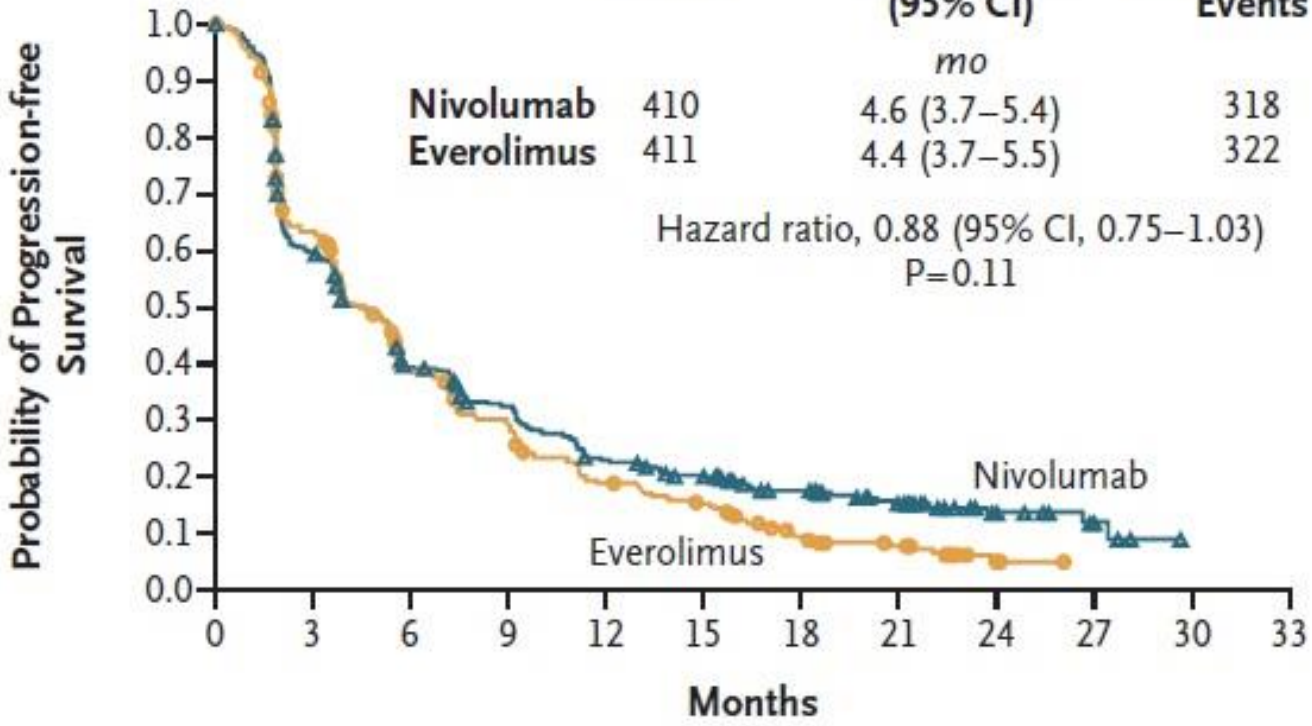
Subgroup	Nivolumab	Everolimus	Unstratified Hazard Ratio for Death (95% CI)
	no. of events/total no.		
Overall	183/410	215/411	0.76 (0.62–0.92)
MSKCC prognostic score			
Favorable	45/145	52/148	0.89 (0.59–1.32)
Intermediate	101/201	116/203	0.76 (0.58–0.99)
Poor	37/64	47/60	0.47 (0.30–0.73)
Previous antiangiogenic regimens			
1	128/294	158/297	0.71 (0.56–0.90)
2	55/116	57/114	0.89 (0.61–1.29)
Region			
United States or Canada	66/174	87/172	0.66 (0.48–0.91)
Western Europe	78/140	84/141	0.86 (0.63–1.16)
Rest of the world	39/96	44/98	0.78 (0.51–1.20)
Age			
<65 yr	111/257	118/240	0.78 (0.60–1.01)
≥65 to <75 yr	53/119	77/131	0.64 (0.45–0.91)
≥75 yr	19/34	20/40	1.23 (0.66–2.31)
Sex			
Female	48/95	56/107	0.84 (0.57–1.24)
Male	135/315	159/304	0.73 (0.58–0.92)



B Kaplan–Meier Curve for Progression-free Survival

	No. of Patients	Median Progression-free Survival (95% CI)	No. of Progression Events
		mo	
Nivolumab	410	4.6 (3.7–5.4)	318
Everolimus	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

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Kaplan–Meier Curve for Overall Survival, According to Programmed Death 1 Ligand (PD-L1) Expression Level

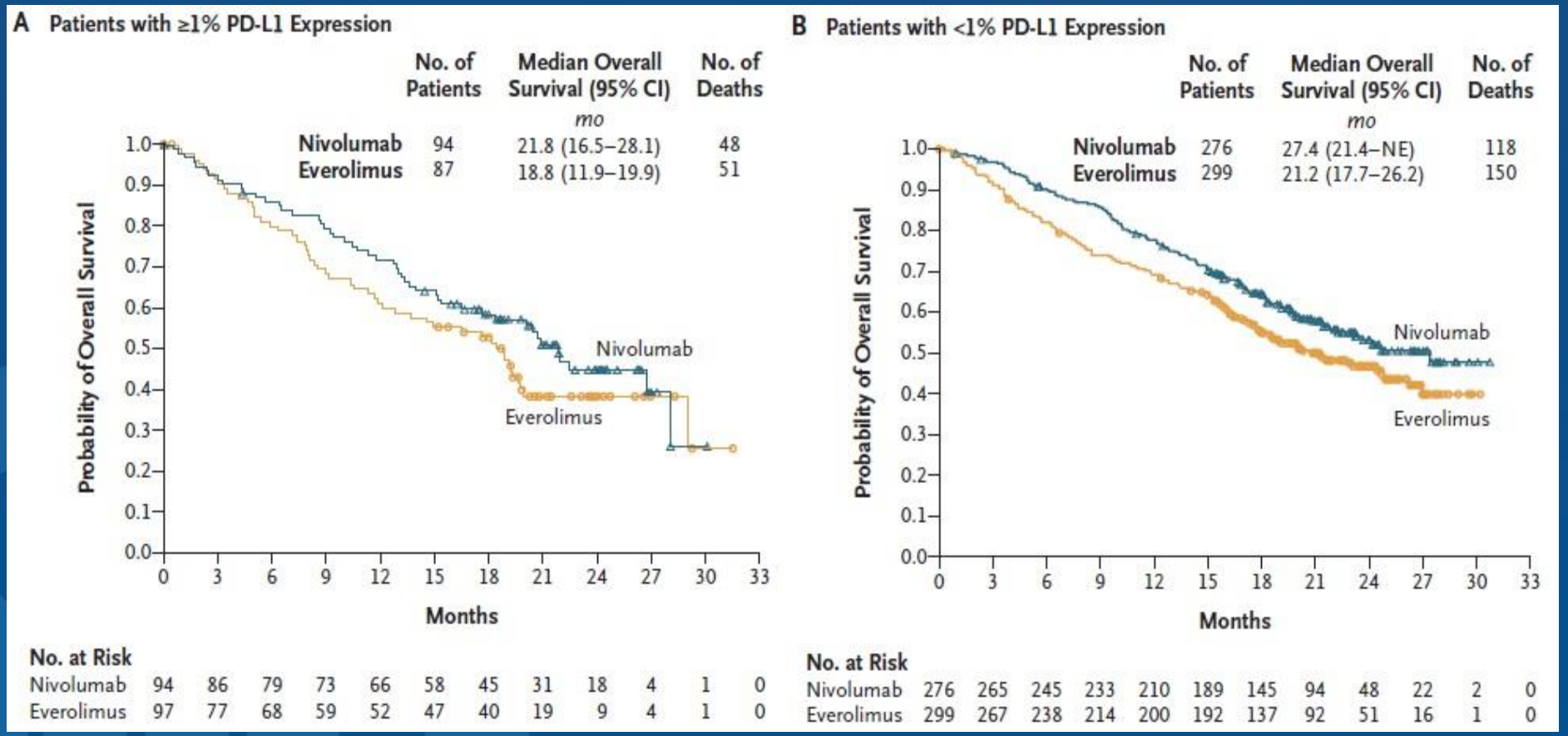

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Table 2. Treatment-Related Adverse Events Reported in 10% or More of Treated Patients in Either Group.

Event	Nivolumab Group (N=406)		Everolimus Group (N=397)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
All events	319 (79)	76 (19)	349 (88)	145 (37)
Fatigue	134 (33)	10 (2)	134 (34)	11 (3)
Nausea	57 (14)	1 (<1)	66 (17)	3 (1)
Pruritus	57 (14)	0	39 (10)	0
Diarrhea	50 (12)	5 (1)	84 (21)	5 (1)
Decreased appetite	48 (12)	2 (<1)	82 (21)	4 (1)
Rash	41 (10)	2 (<1)	79 (20)	3 (1)
Cough	36 (9)	0	77 (19)	0
Anemia	32 (8)	7 (2)	94 (24)	31 (8)
Dyspnea	30 (7)	3 (1)	51 (13)	2 (1)
Peripheral edema	17 (4)	0	56 (14)	2 (1)
Pneumonitis	16 (4)	6 (1)	58 (15)	11 (3)
Mucosal inflammation	11 (3)	0	75 (19)	12 (3)
Dysgeusia	11 (3)	0	51 (13)	0
Hyperglycemia	9 (2)	5 (1)	46 (12)	15 (4)
Stomatitis	8 (2)	0	117 (29)	17 (4)
Hypertriglyceridemia	5 (1)	0	64 (16)	20 (5)
Epistaxis	3 (1)	0	41 (10)	0

Ongoing frontline checkpoint inhibitor phase III trials for metastatic renal cell carcinoma (RCC)

- Lenvatinib/Everolimus or Lenvatinib/Pembrolizumab Versus Sunitinib Alone (NCT02811861)
  - PFS
- A Study of Atezolizumab in Combination With Bevacizumab Versus Sunitinib (NCT02420821)
  - PFS and OS in in participants with detectable PD-L1
- Pembrolizumab (MK-3475) in Combination With Axitinib Versus Sunitinib Monotherapy (NCT02853331)
  - PFS and OS
- Avelumab (anti-PDL1) In Combination With Axitinib Versus Sunitinib (Sutent) Monotherapy (NCT02684006)
  - PFS

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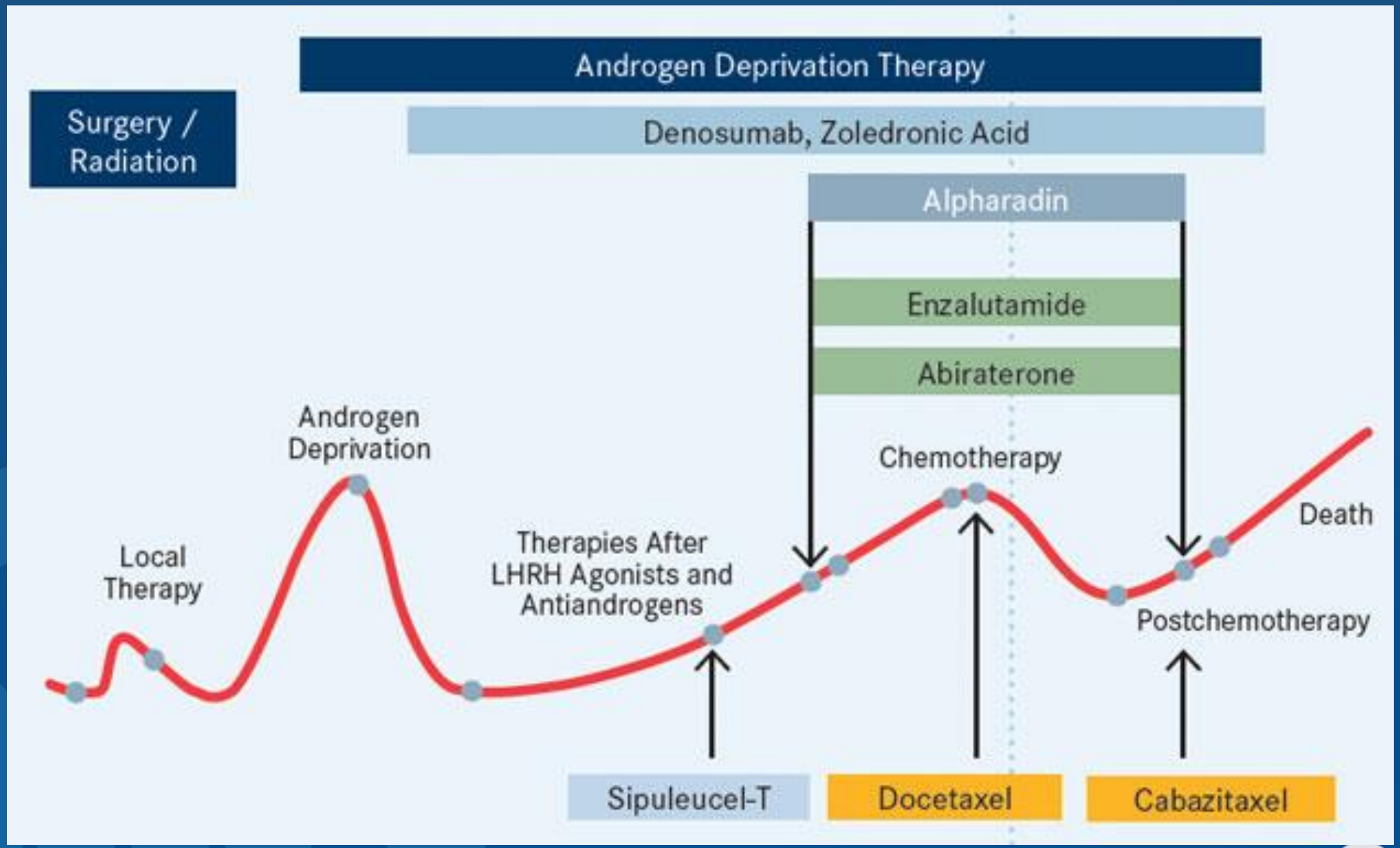
Treatment Paradigms for Prostate Cancer



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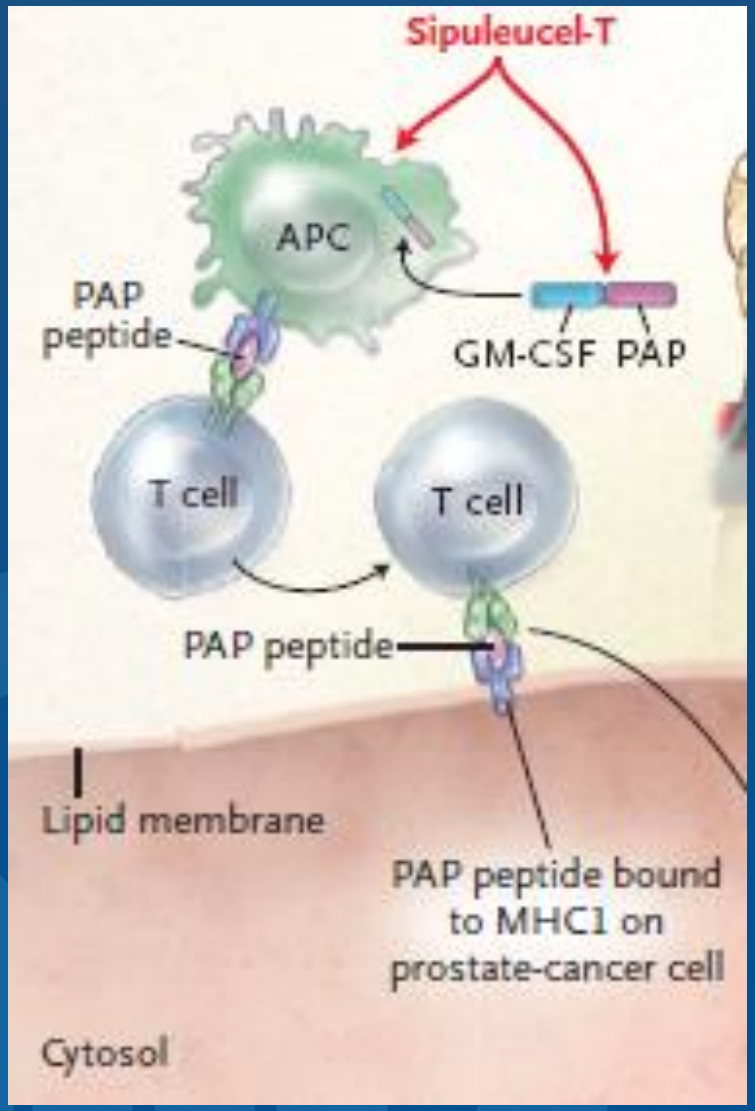
Immunotherapies for mCRPC: Sipuleucel-T



Sipuleucel-T is approved by FDA for patients who are asymptomatic or minimally symptomatic from their mCRPC.

Harvesting the pt's PBMCs (including APCs)

↓

Culturing PBMC with a chimeric protein PA2024 (GM-CSF + PAP prostatic acid phosphatase) to activate presentation of a tumor-associated antigen

↓

Infusing the antigen-pulsed APCs back into the patient, which in theory will activate T cell to kill PAP positive prostate cancer cells

Lango NEJM 2010

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Summary of 2 phase III data for Sipuleucel-T

	Kantoff NEJM 2010	Small JCO 2006
Patient number, S vs. P	341 vs. 171	82 vs. 45
Median f/u, months	34.1	36
Improvement in median survival, months	25.8 – 21.7 = 4.1	25.9 – 21.4 = 4.5
3-yr survival rate, S vs. P	31.7% vs. 23%	34.1% vs. 11%
Median TTP, S vs P, weeks P value	14.6 vs. 14.4 P=0.63	11.7 vs. 10 p= 0.052

- **In general, Sipuleucel-T was well tolerated, and 335/338 patients received all three scheduled infusions.**
- **Only 1 of 341 pts in the sipuleucel-T group had a PR and 3% had at least 50% reduction in PSA**
- **Survival was improved for patients who had an antibody response to PA2024 but not for those with a T-cell proliferative response.**

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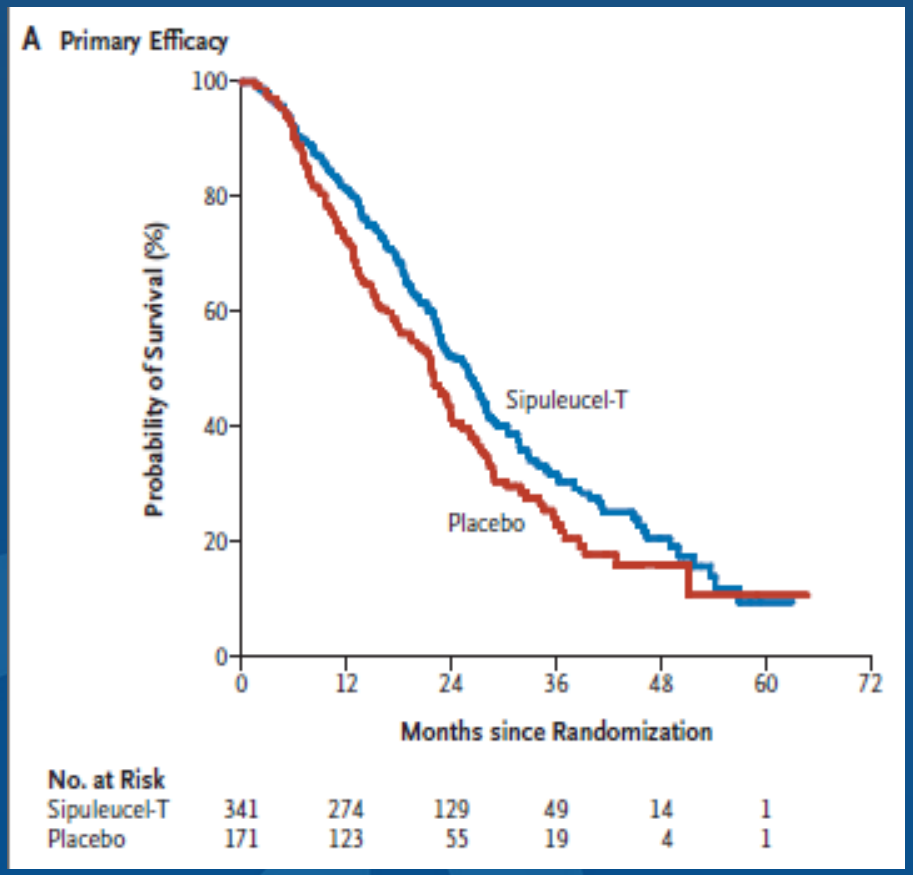
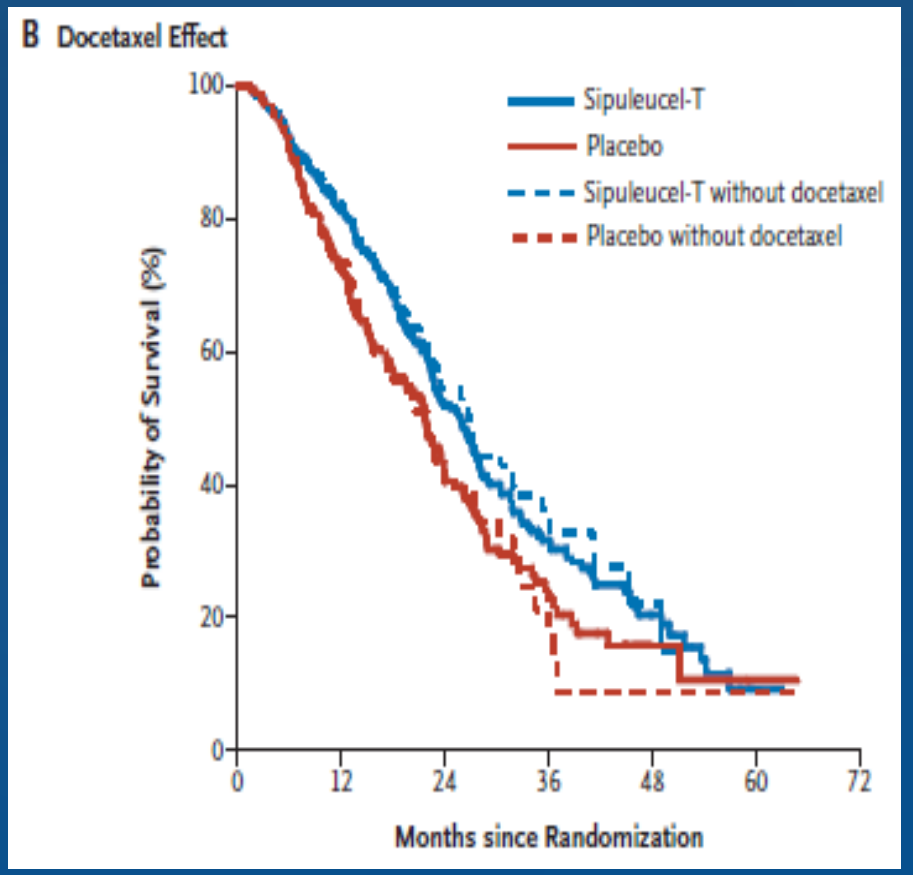
Sipuleucel –T improved survival for mCRPC





Sipuleucel-T HR for death:
w/o censoring at the time of docetaxel initiation: 0.78; 95% CI, 0.61 to 0.98; P = 0.03
censoring at the time of docetaxel initiation: 0.65; 95% CI, 0.47 to 0.90; P = 0.009

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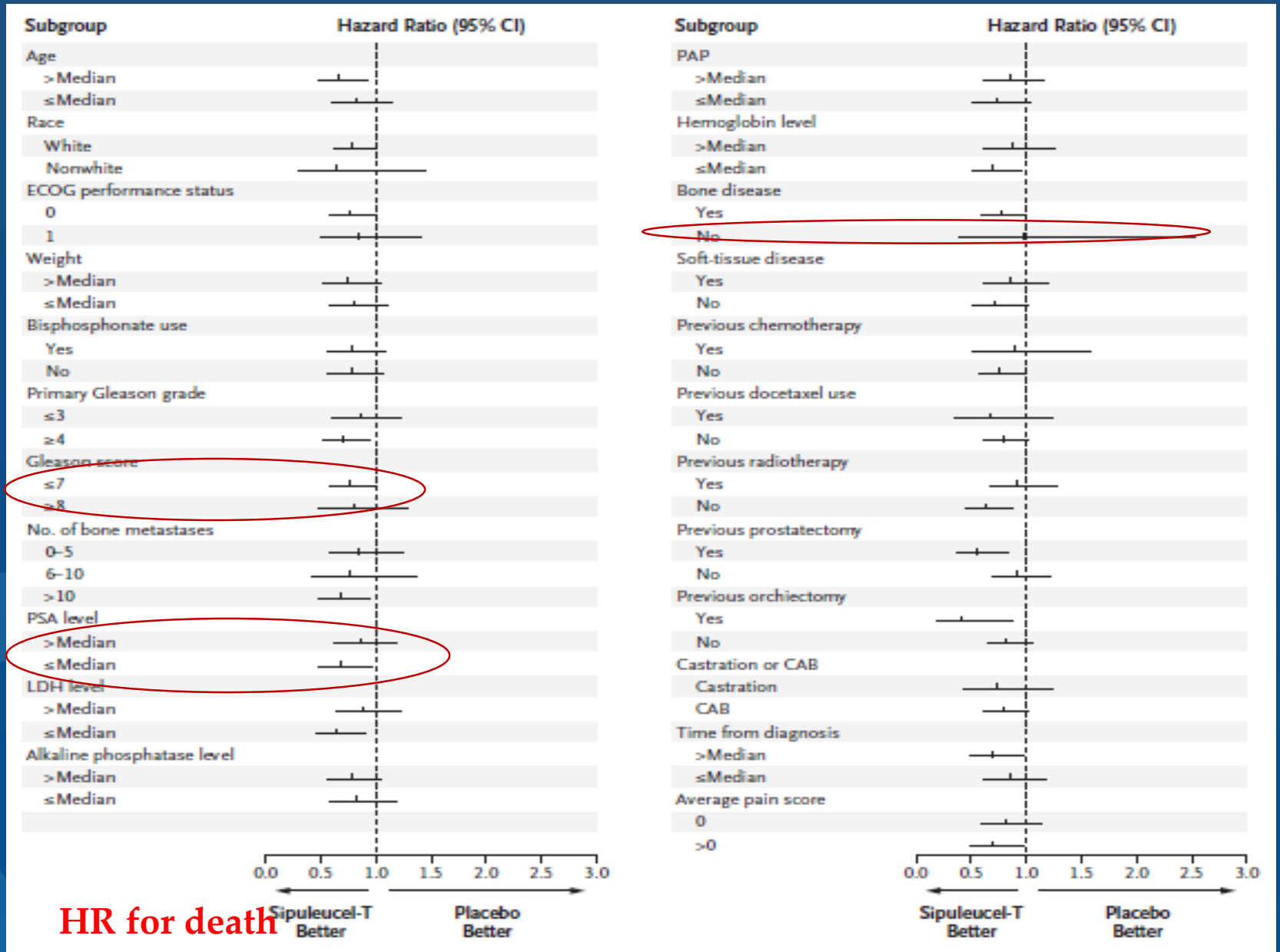
Kantoff PW et al. NEJM 2010 363, 411



Kantoff PW et al. NEJM 2010 363, 411

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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

- A multicentre, randomized, double-blind, phase 3 trial in which 799 men with at least one bone metastasis from castration-resistant prostate cancer that had progressed after docetaxel treatment were randomly assigned in a 1:1 ratio to receive bone-directed radiotherapy (8 Gy in one fraction) followed by either ipilimumab 10 mg/kg or placebo every 3 weeks for up to 4 doses.
- Non-progressing patients could continue to receive ipilimumab at 10 mg/kg or placebo as maintenance therapy every 3 months until disease progression, unacceptable toxic effect, or death.
- The primary endpoint was overall survival

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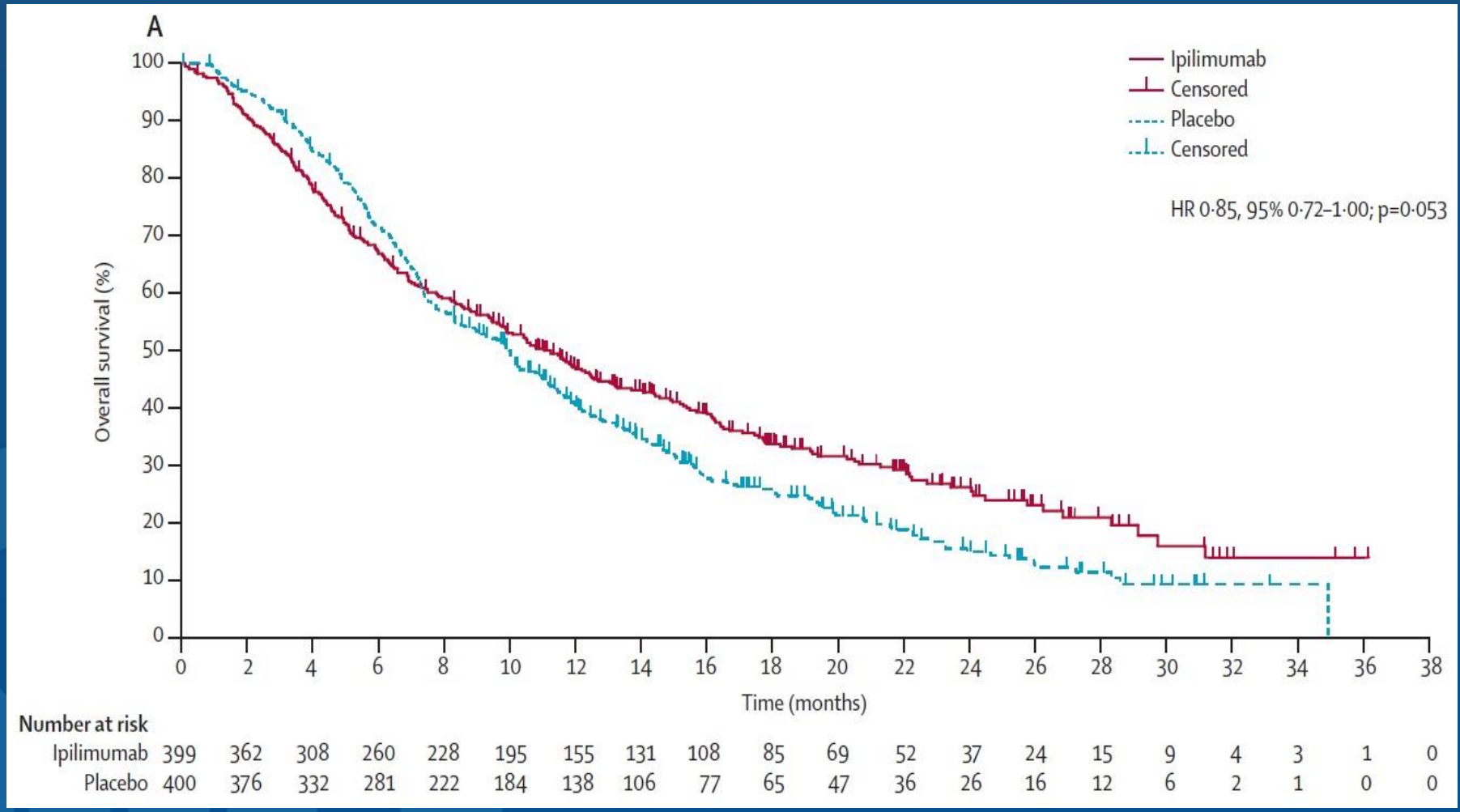
Overall survival in the intention-to-treat population



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

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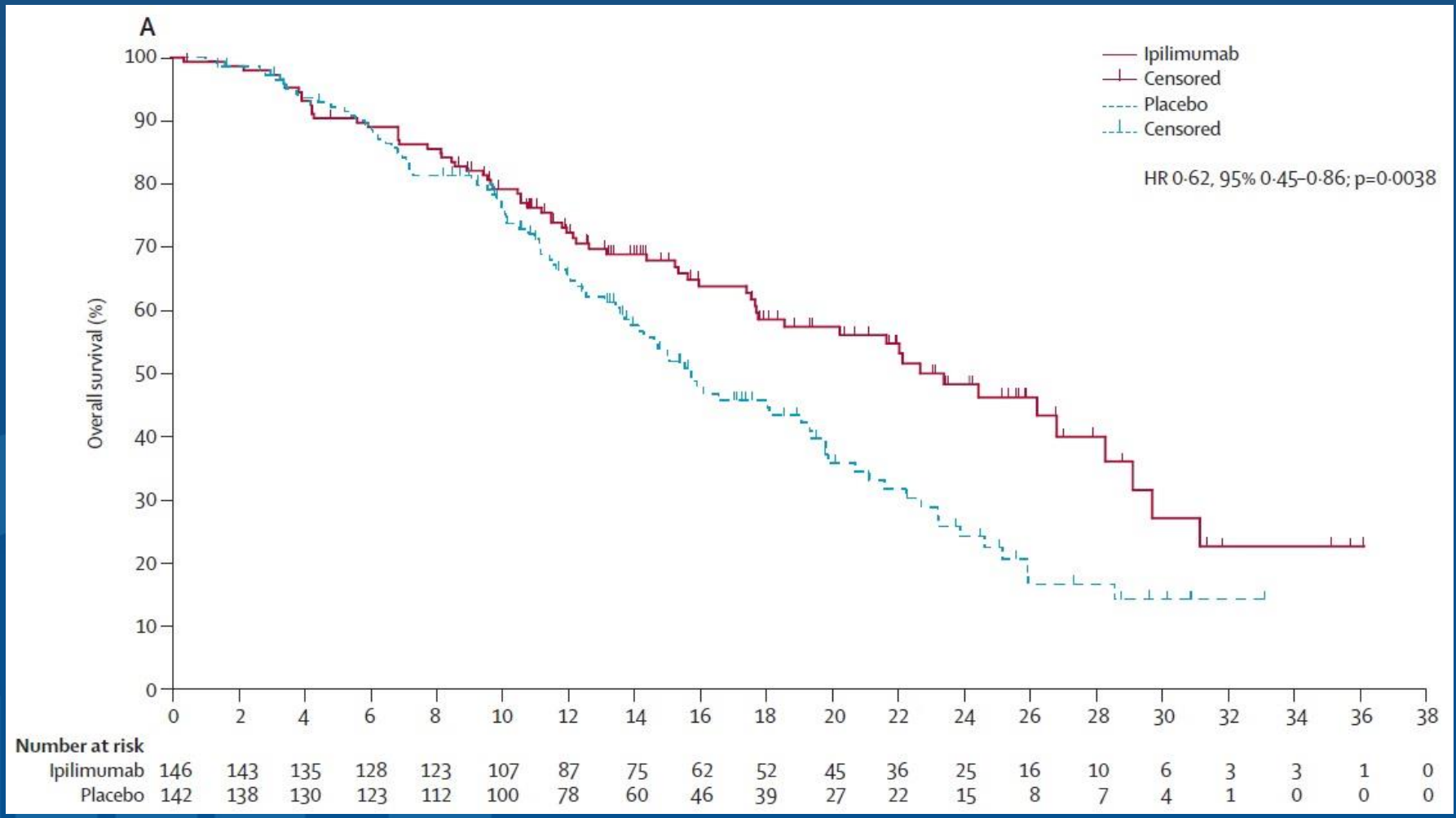
Post-hoc subgroup analyses of overall survival in patients with good prognostic features: alkaline phosphatase < 1·5 x ULN, haemoglobin >110g/L, and no visceral metastases (ipilimumab, n=146; placebo, n=142).



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

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Ongoing checkpoint inhibitor trials for prostate ca

- Phase II Safety and Efficacy Study of Ipilimumab 3 mg/kg Versus Ipilimumab 10 mg/kg in Subjects With mCRPC Who Are Chemotherapy Naïve
- Phase II Biomarker-Driven Therapy With Nivolumab and Ipilimumab in Treating Patients With mCRPC Expressing AR-V7 (STARVE-PC)

  Patients receive nivolumab IV over 60 minutes and ipilimumab IV over 90 minutes every 3 weeks for 12 weeks. Patients then receive nivolumab IV over 60 minutes every 2 weeks for 36 weeks in the absence of disease progression or unacceptable toxicity.
  Primary Objective: PSA response rate (>50%)
- Pilot Trial of pTVG-HP DNA Vaccine and Pembrolizumab in Patients With mCRPC (*Primary Objectives: toxicity, rPFS, PSA RR, 6m progression free survival rate)*

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