Immunotherapy for Genitourinary Cancers

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Disclosures

- Consulting: Pfizer, Novartis, Genentech, GSK, Astellas, Medivation
- Honoraria: Genentech

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Nurses: The Center of Every Great Oncology Program

- Rowena, Kaddie, Sulma and Mary (Left to right)

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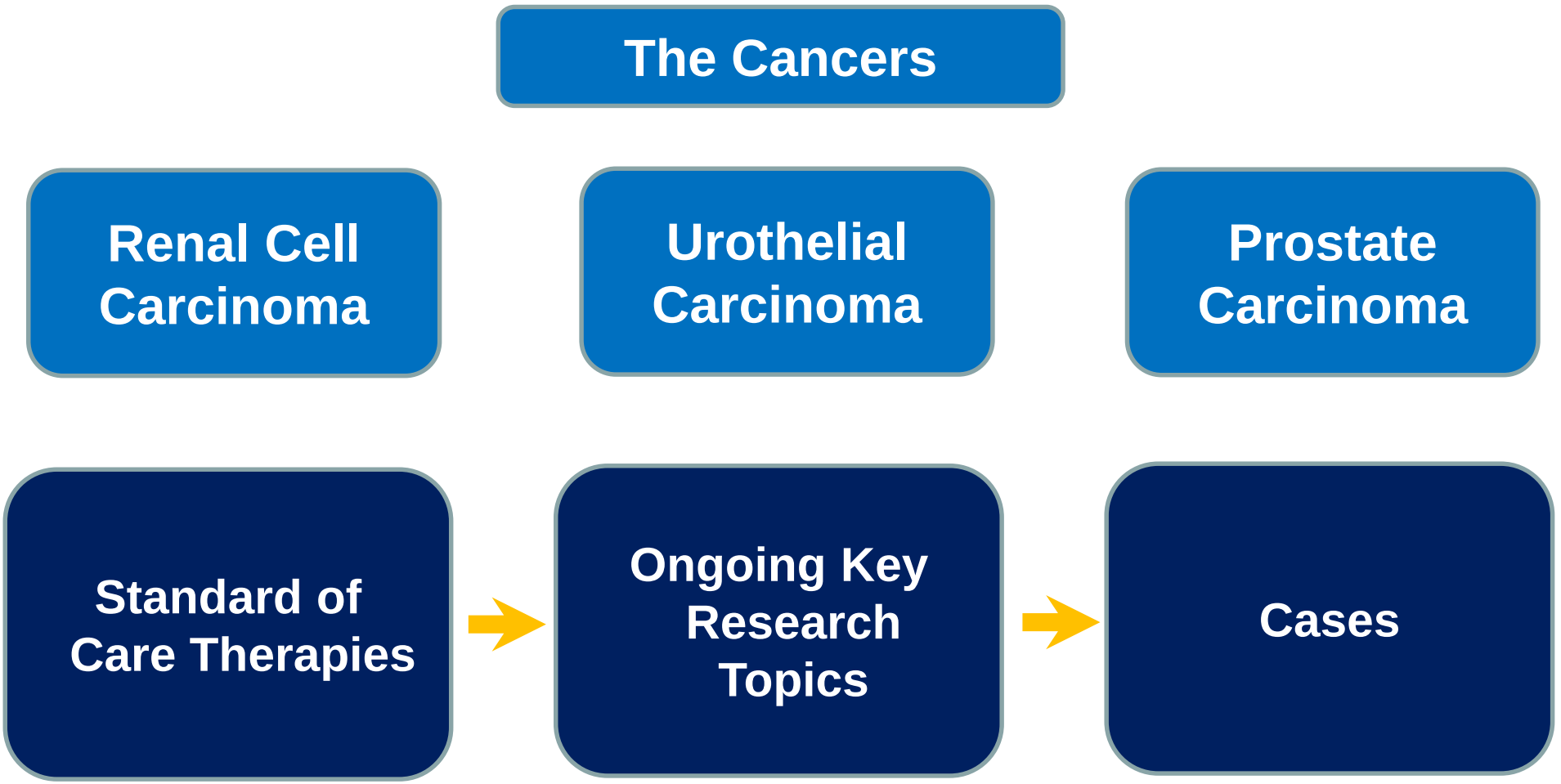
Discussion Topics



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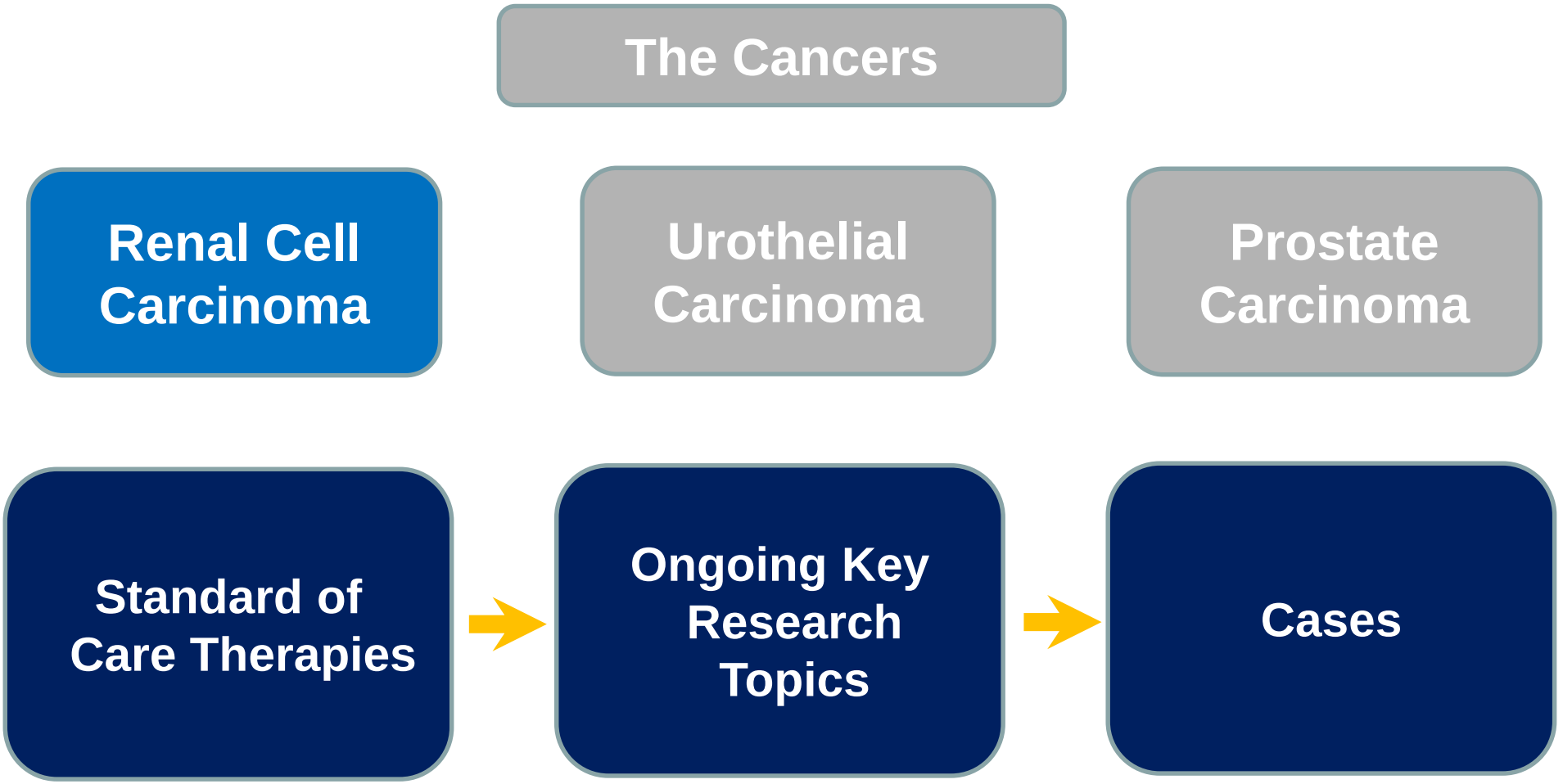
Discussion Topics



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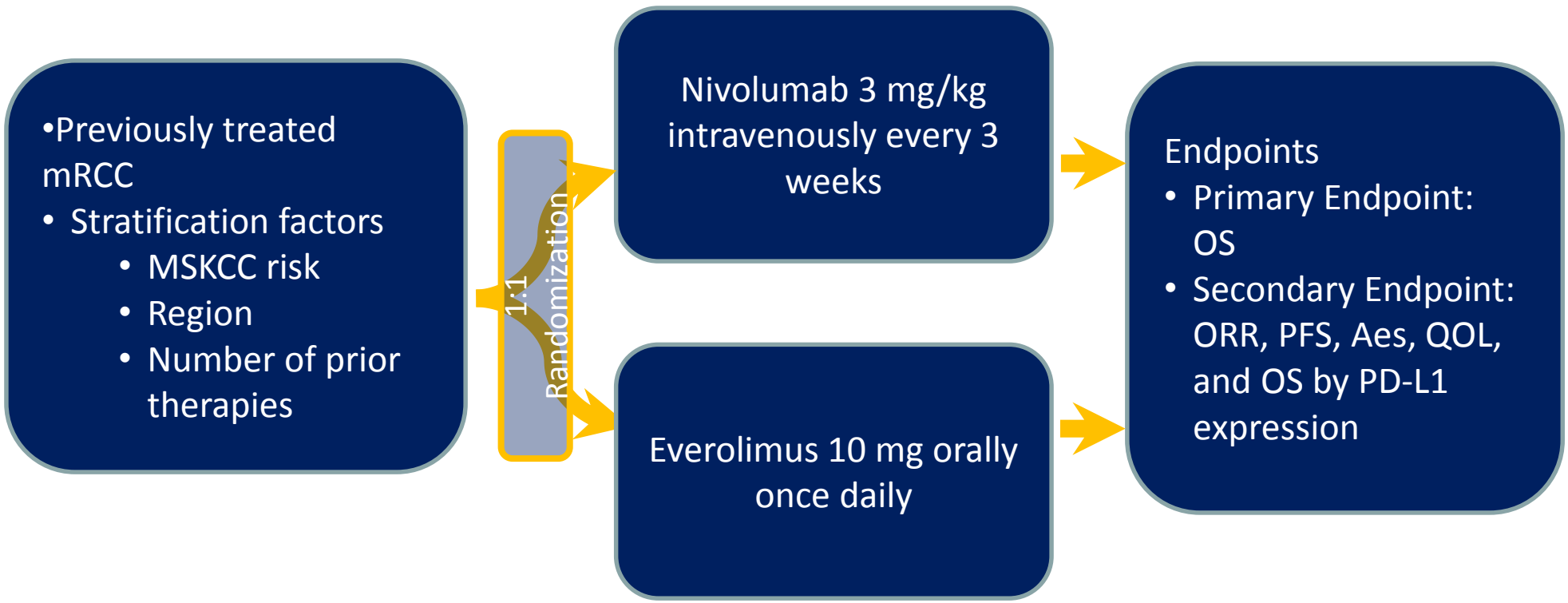
Second and Third Line for RCC



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

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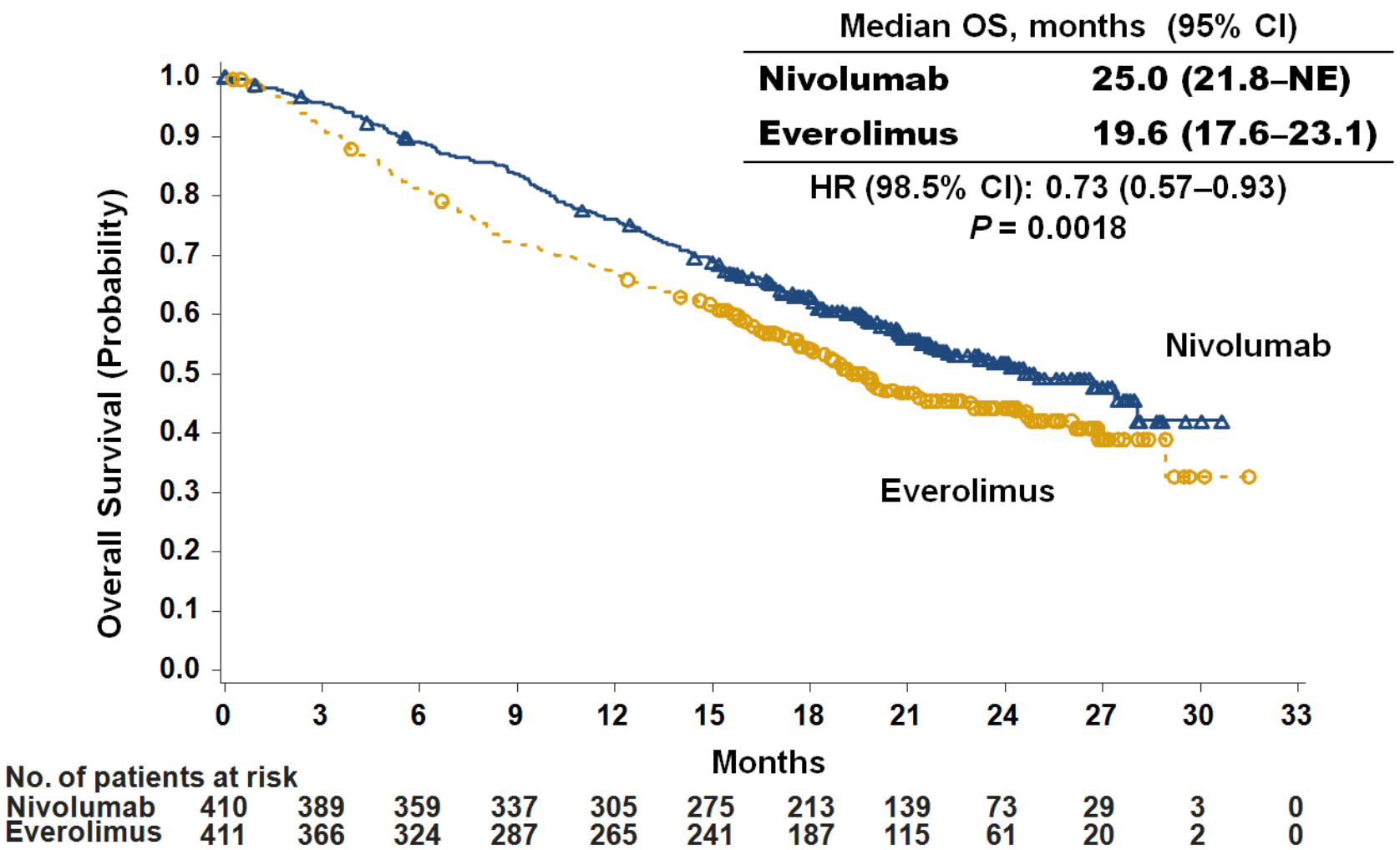
Nivolumab is Superior for OS



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

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Response Rate

	Nivolumab N = 410	Everolimus N = 411
Objective response rate, %	25	5
Odds ratio (95% CI) *P* value	5.98 (3.68–9.72) <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.

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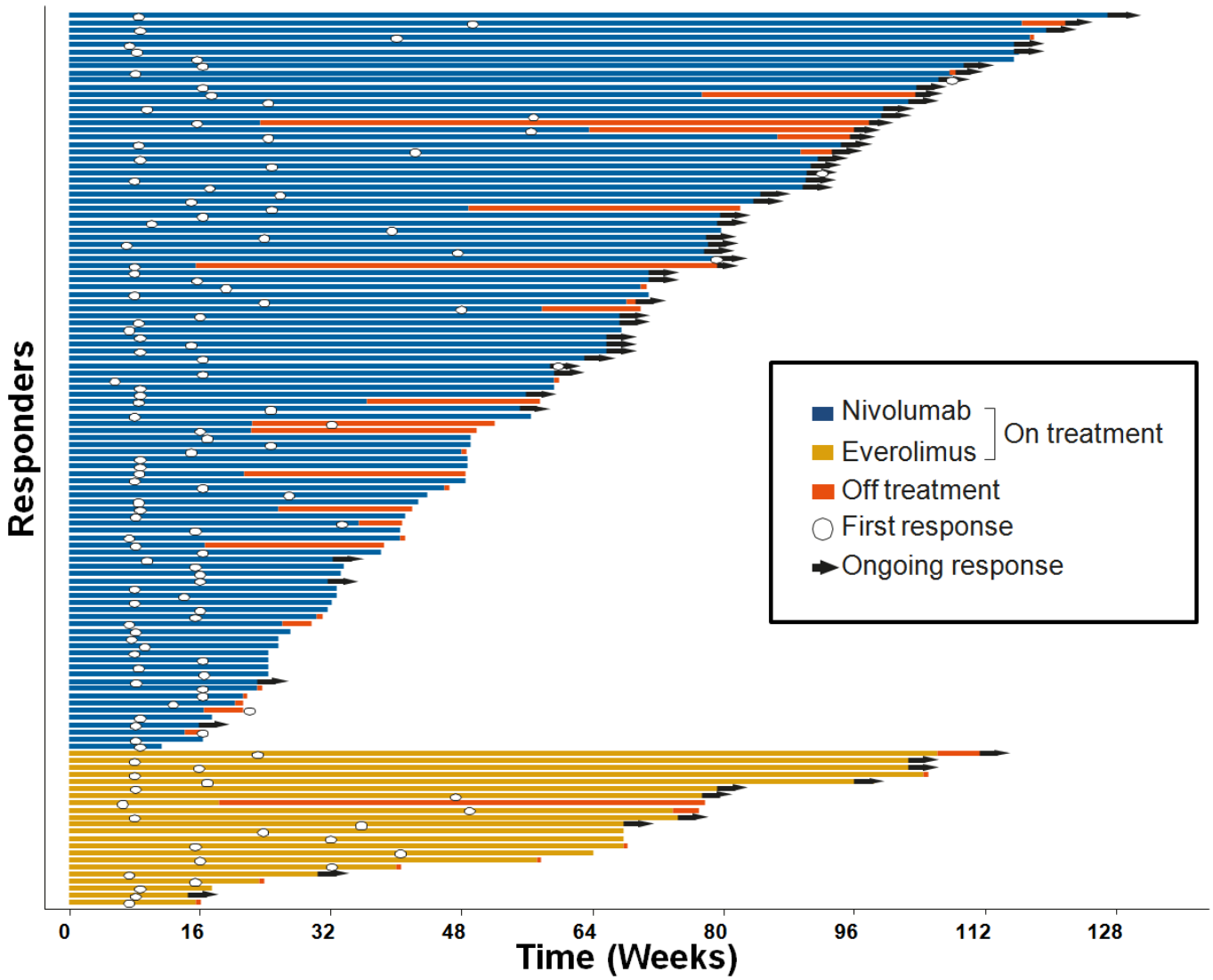
Durability of Response



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

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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.

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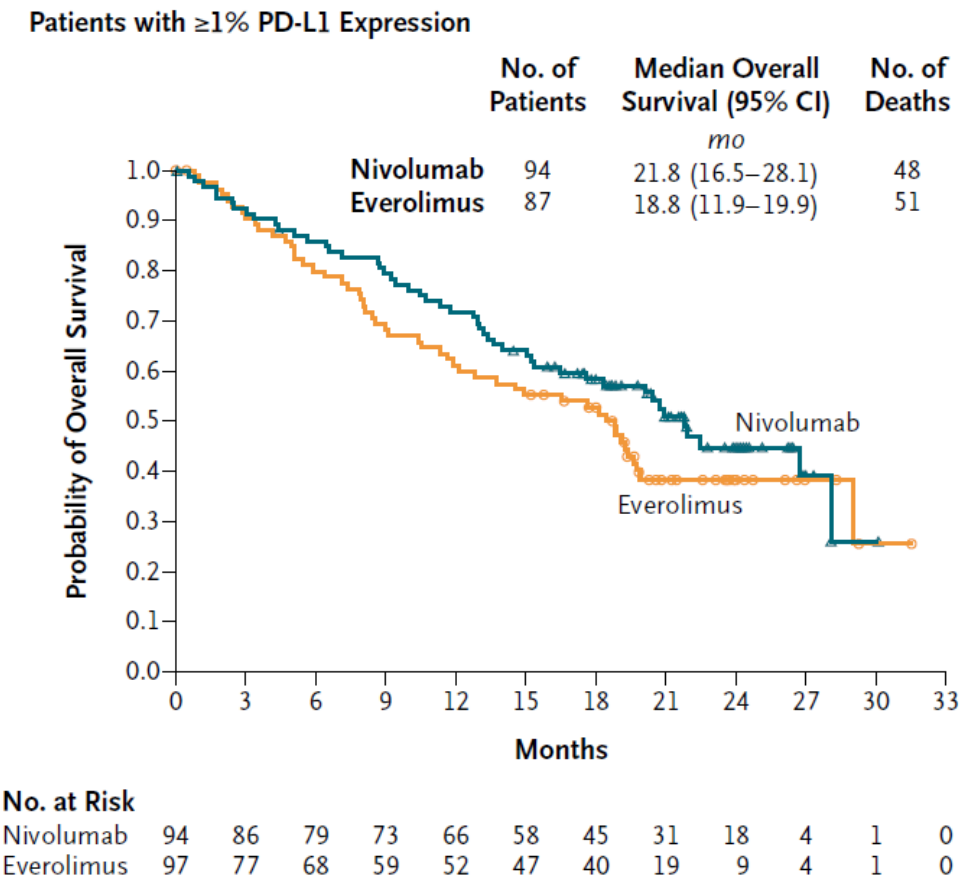
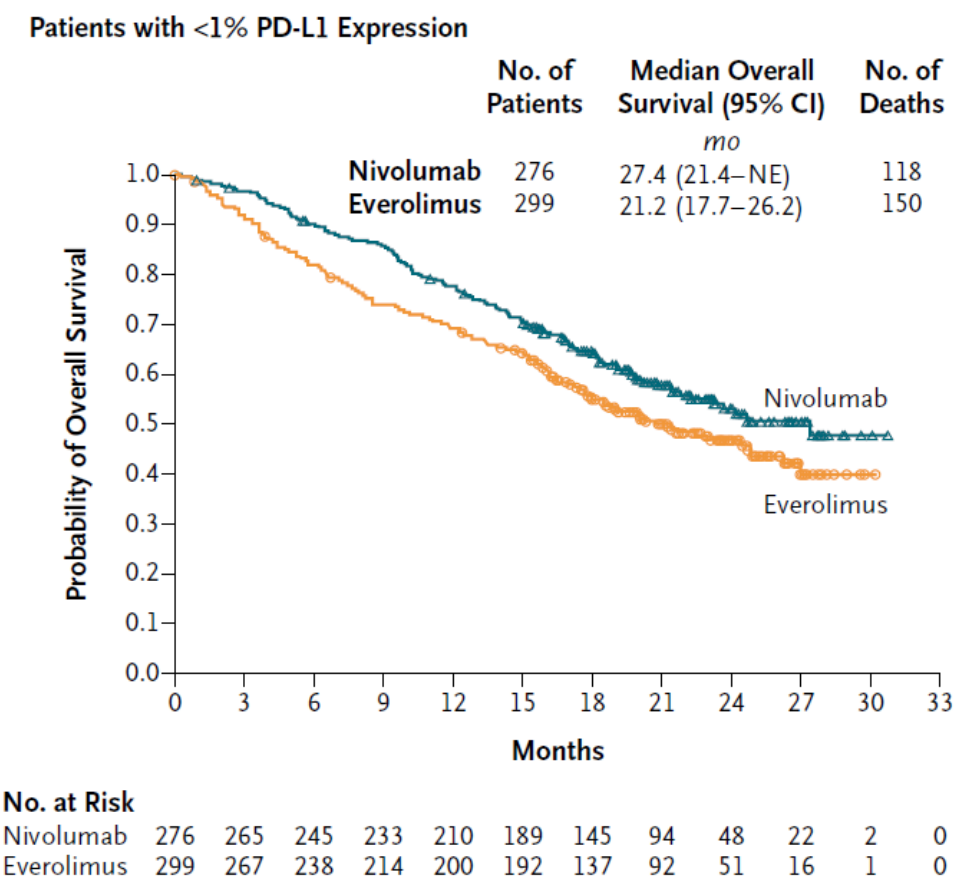
PD-L1 Staining for RCC – Unclear Importance





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

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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.

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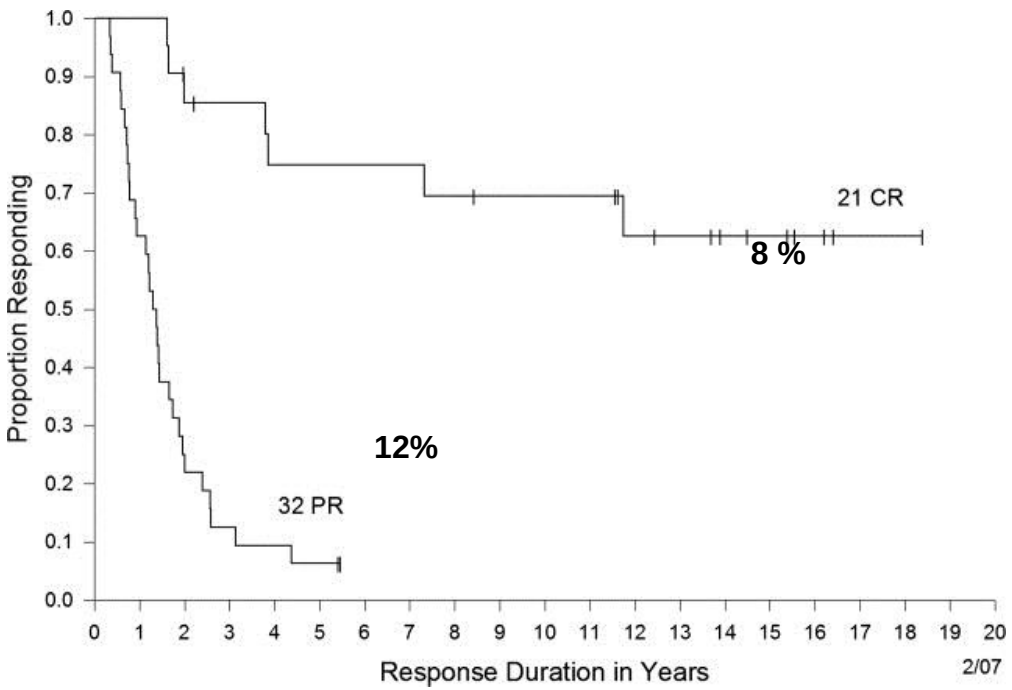
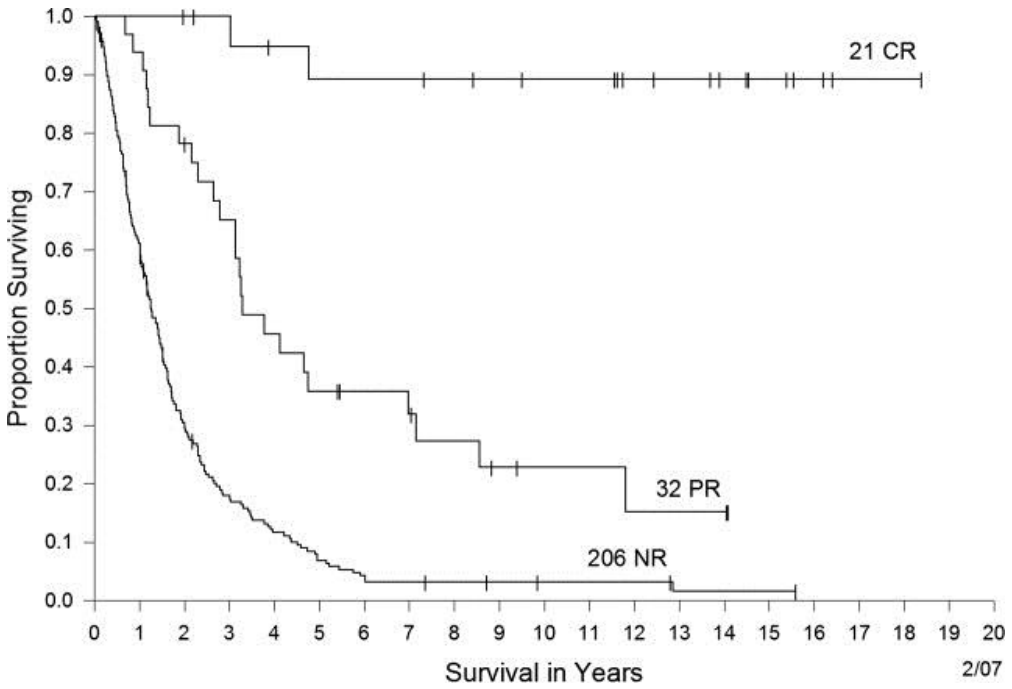
High Dose IL-2 Outcomes

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.

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High dose IL-2 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

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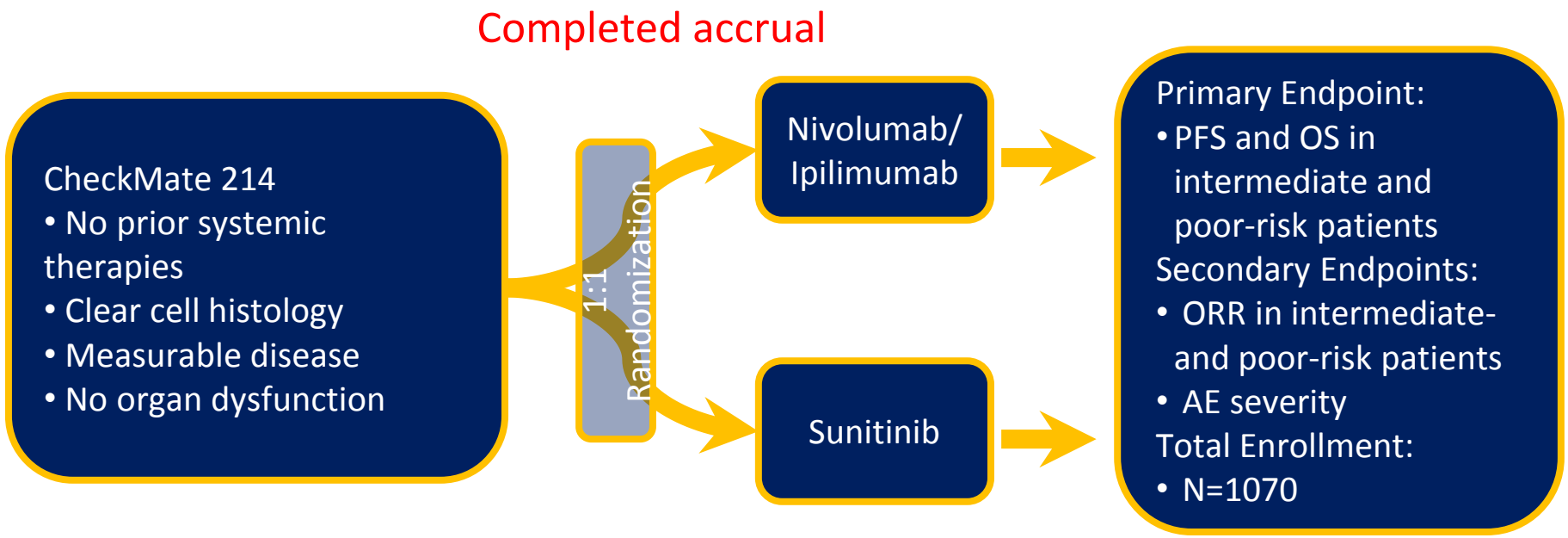
A Reasonable First-line Trial: Combining Anti-PD1 (Nivolumab) with Anti-CTLA4 (Ipilumumab)



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)

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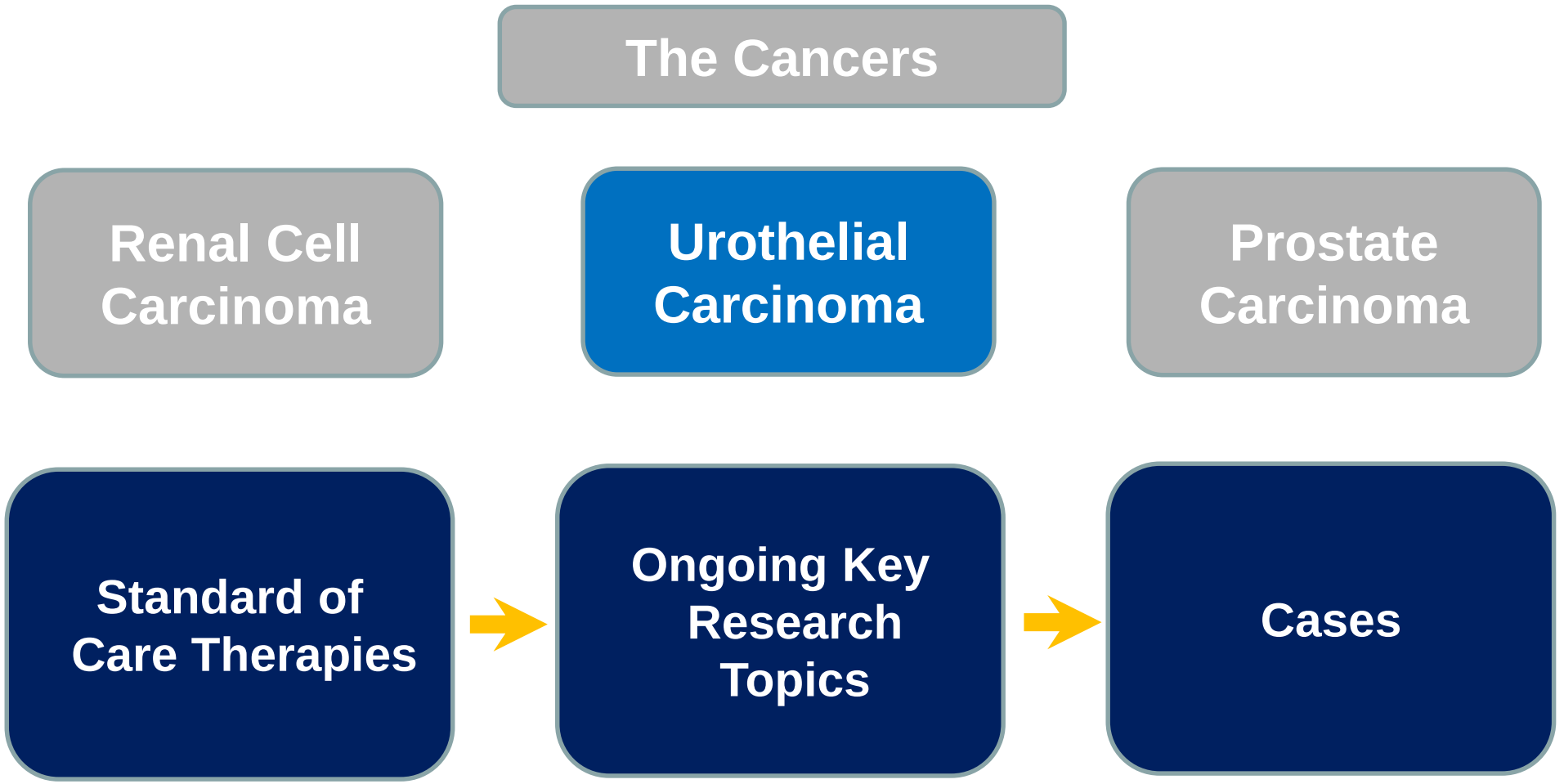
Discussion Topics



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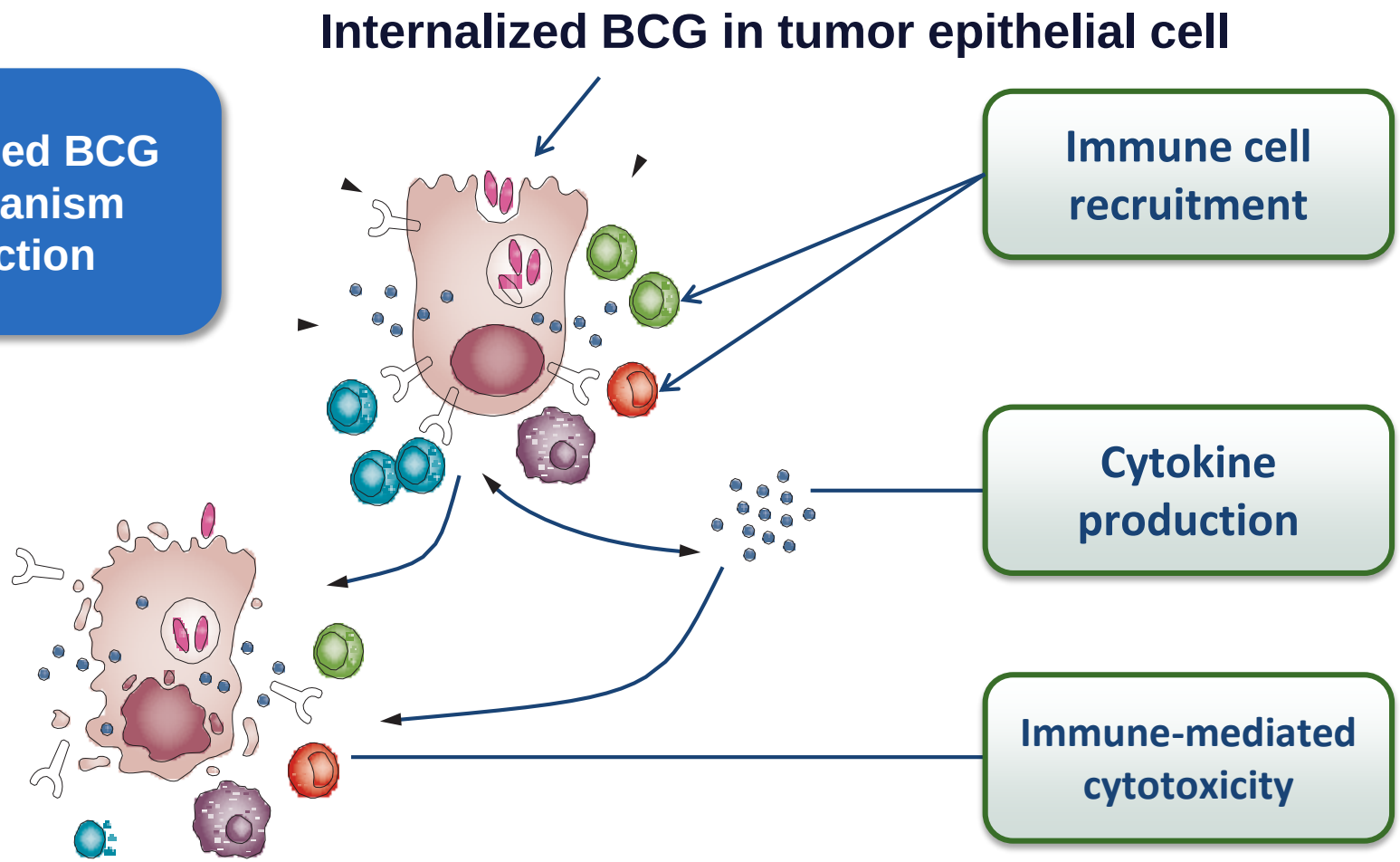
BCG was FDA Approved in 1990

Proposed BCG mechanism of action



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

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FDA approved the use of atezolizumab

LETTER

doi:10.1038/nature13904

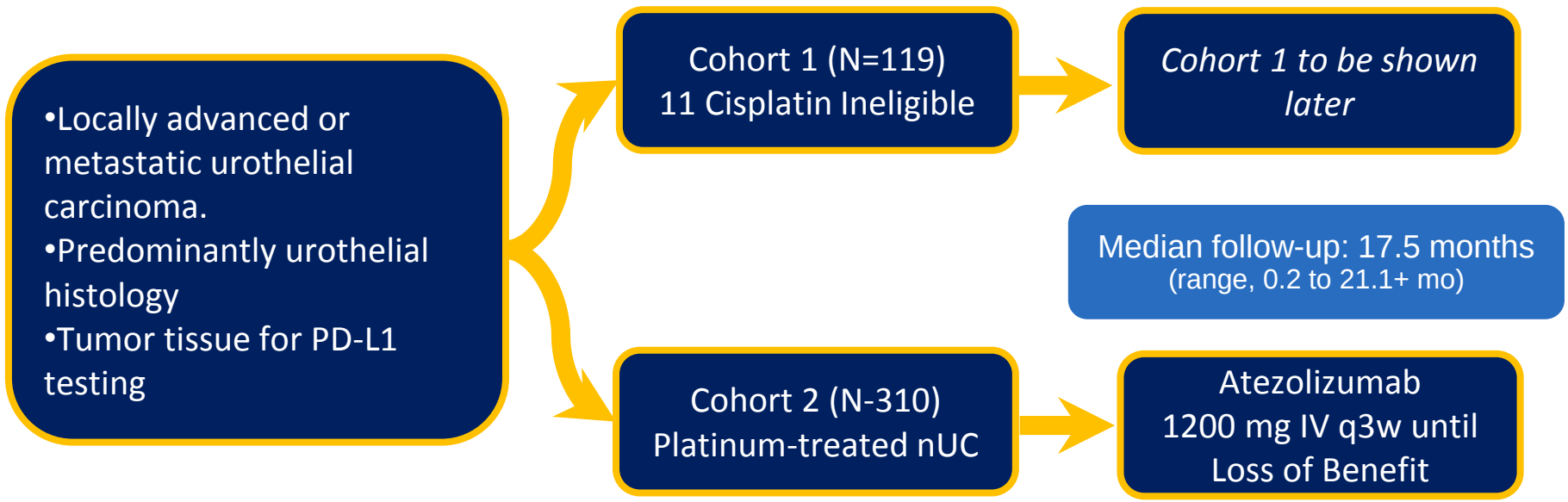
MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer

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

Imvigor210 Study Design



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

Cohort 2-Specific Inclusion Criteria

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

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

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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.

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

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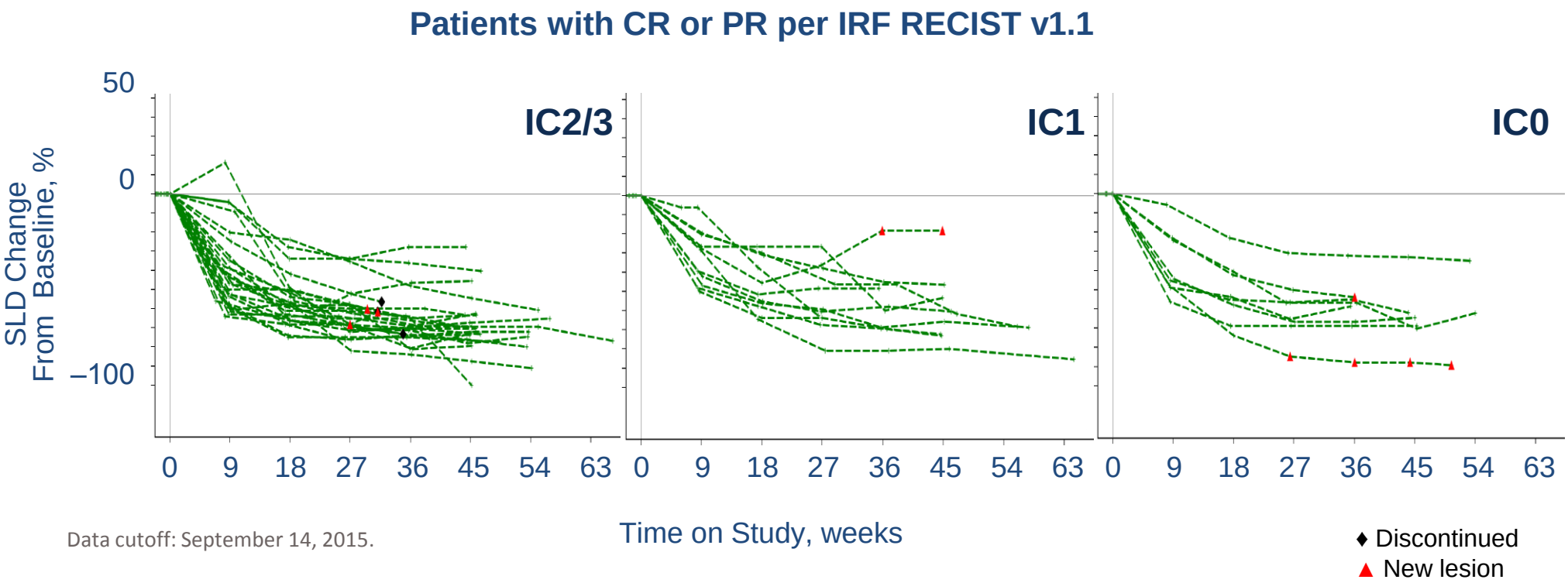
Duration of Response to Atezolizumab



- 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)

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

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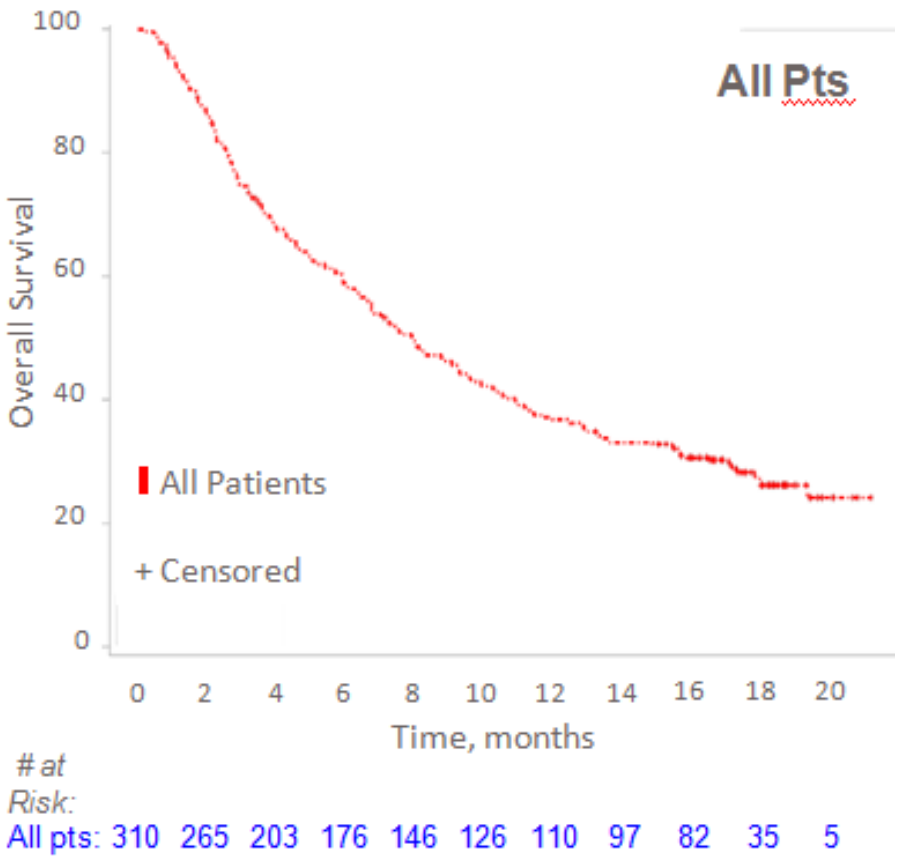
Overall Survival with Atezolizumab



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)

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

- 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

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

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

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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.

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

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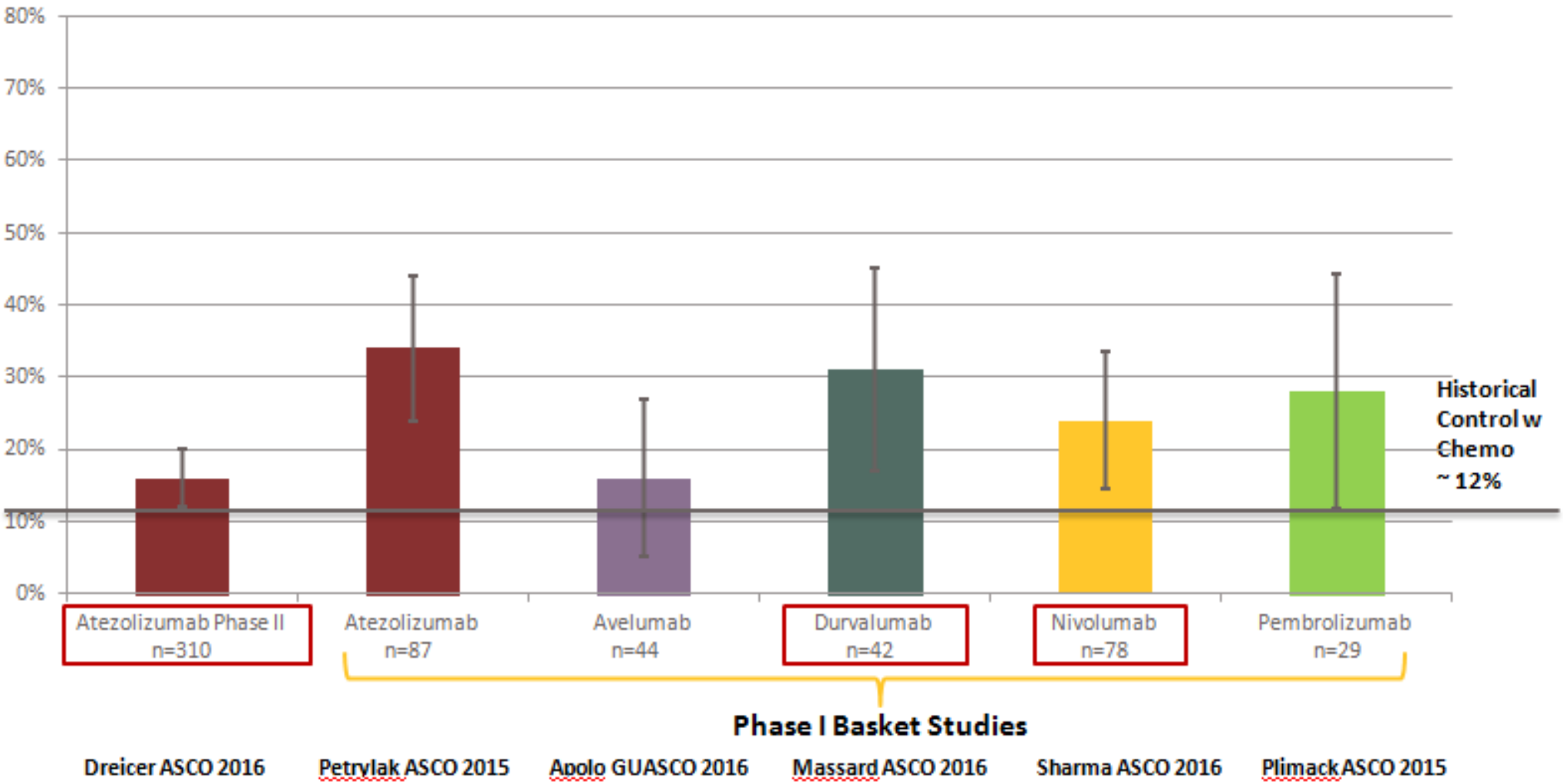
Overall Response Rates of PD-1/PD-L1 Antibodies in Post-Platinum Setting



Slide courtesy of Betsy Plimack from ASCO 2016 Discussion

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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

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Next Steps and Key Data on the Horizon

- 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, neoadjuvant, adjuvant, and combinations
- Will it emerge as a standard in our cisplatin-ineligible patients?

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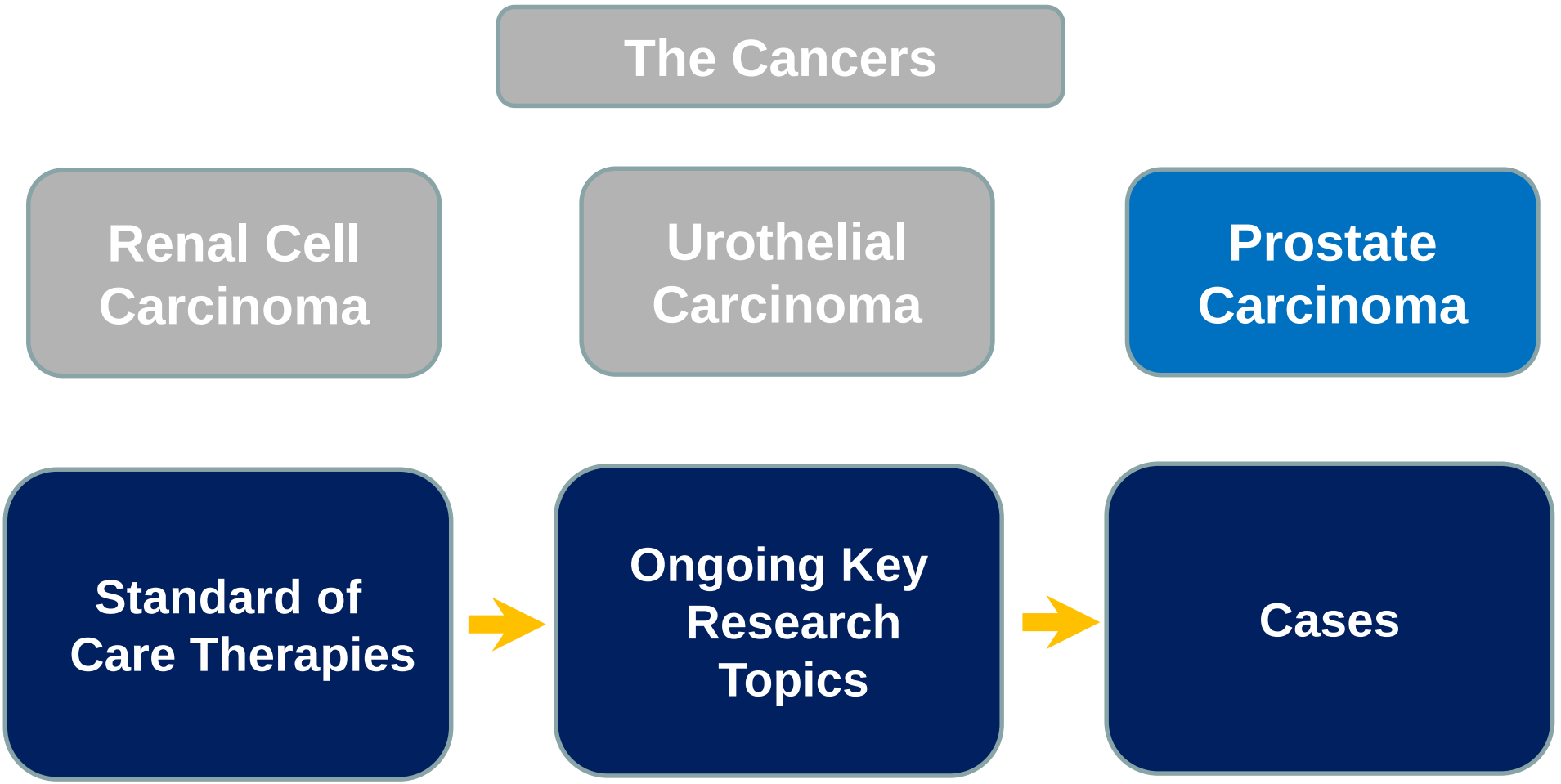
Discussion Topics



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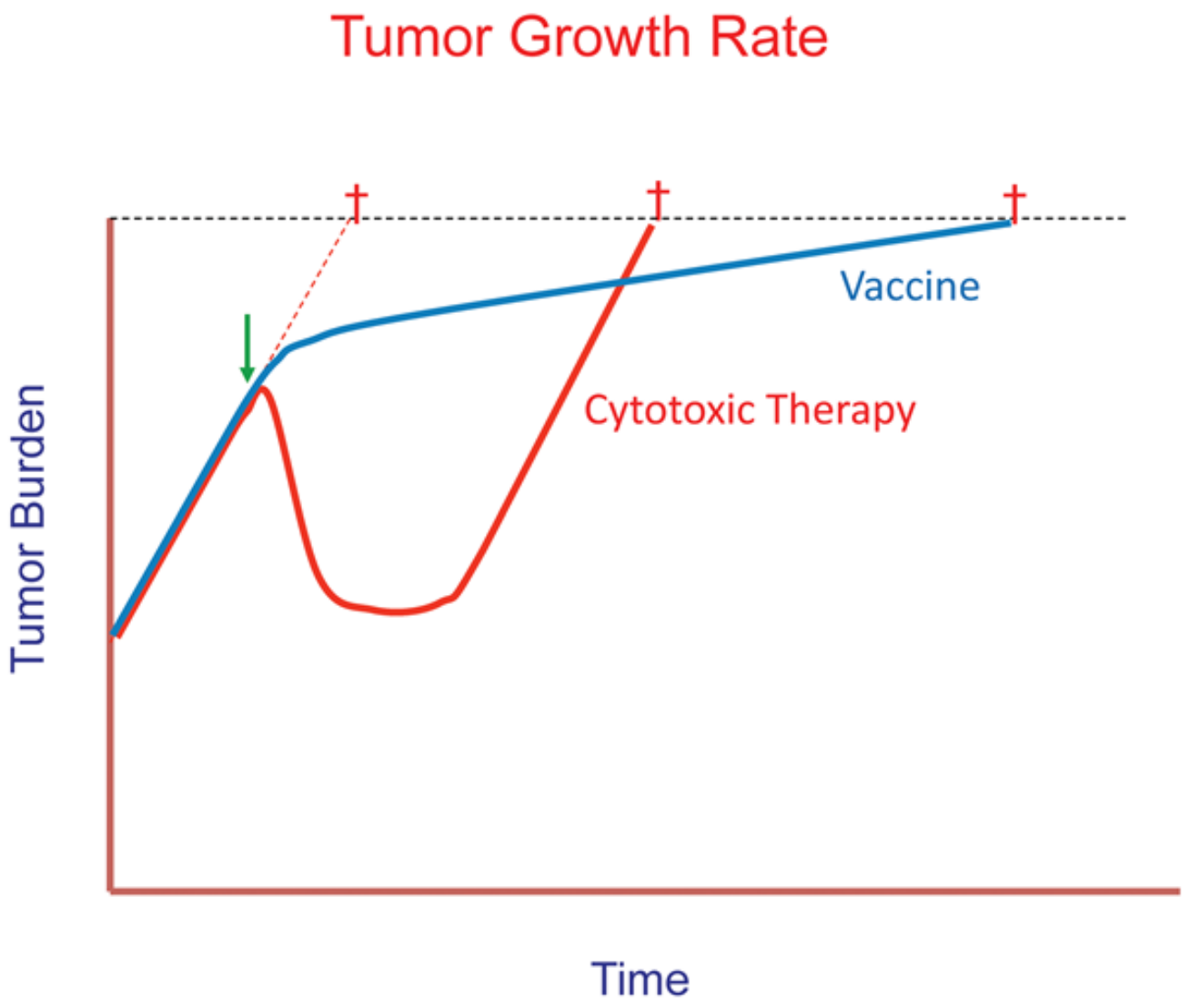
Therapeutic Vaccines



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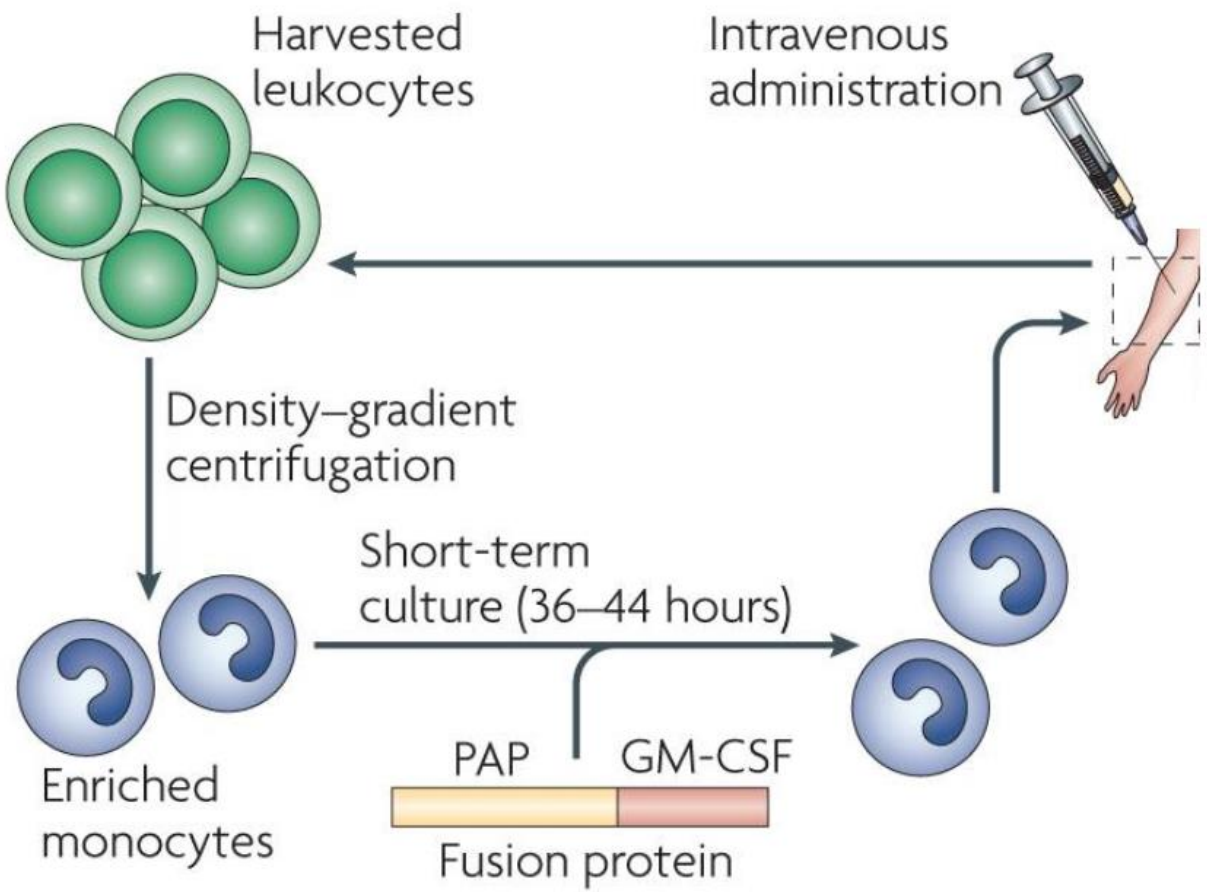
Sipuleucel-T



Drake CG: Nat Rev Immunol 10:580-593, 2010.

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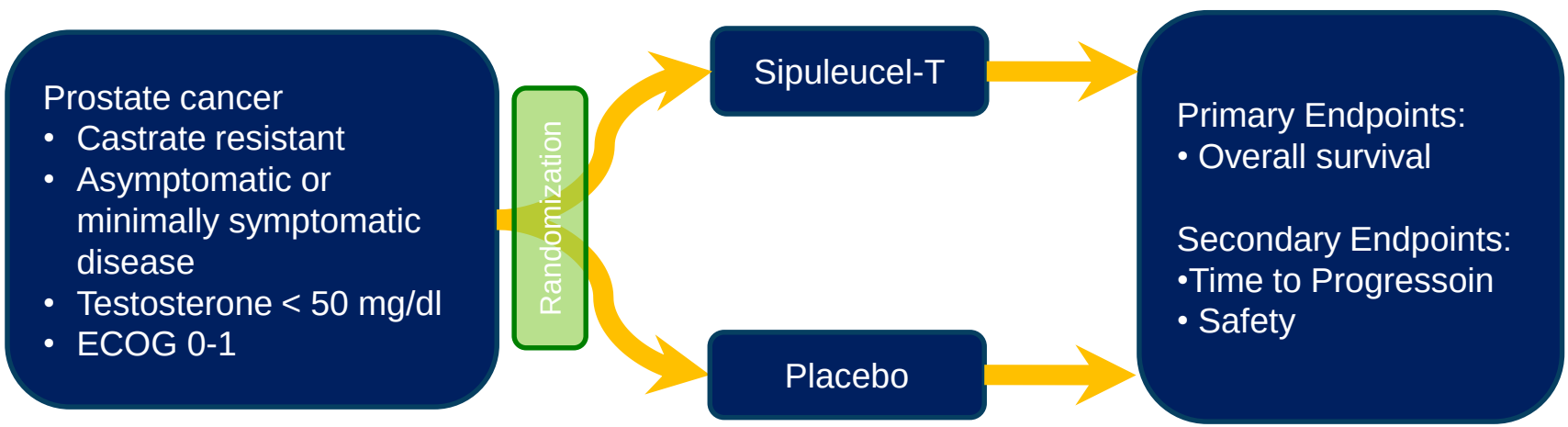
Sipuleucel-T

Phase III IMPACT Study

- Much larger cohort enrolled (N=512)
- 1º endpoint changed to OS



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

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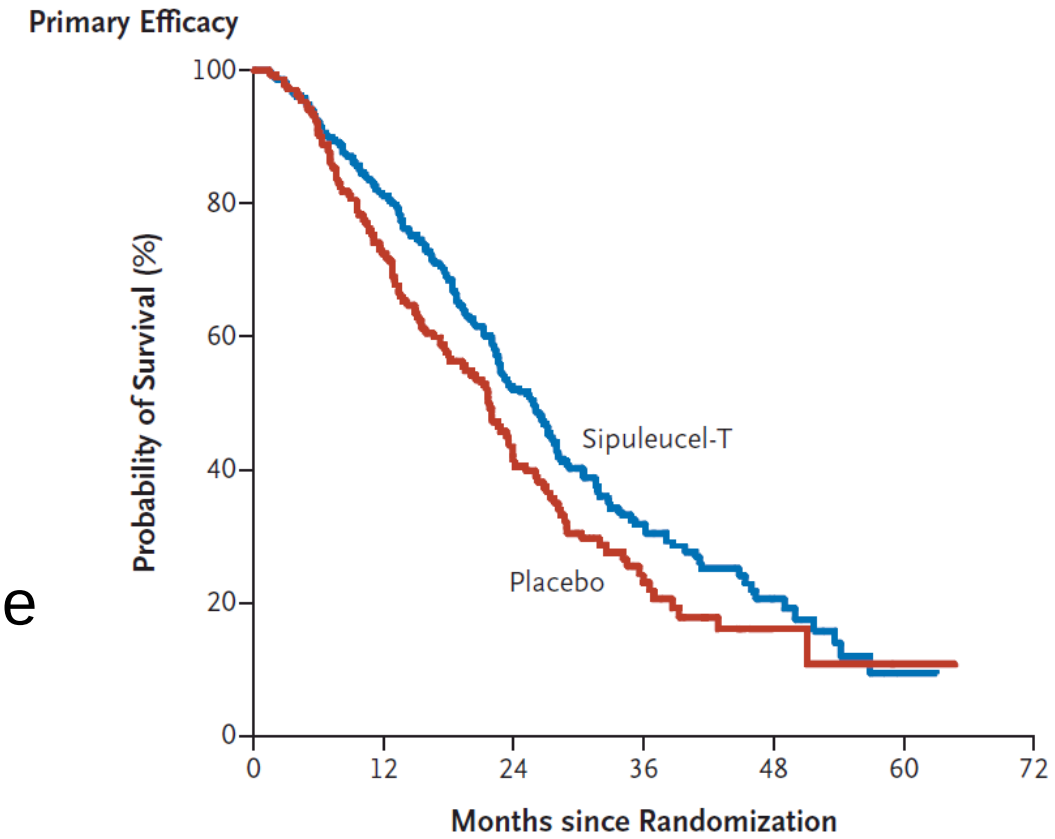
Sipuleucel-T

Primary Outcome

- Survival was improved
- 25.8 *v* 21.7 months (P=0.03)
- No difference in objective disease progression
- No difference in PSA response



No. at Risk						
Sipuleucel-T	341	274	129	49	14	1
Placebo	171	123	55	19	4	1

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411-22

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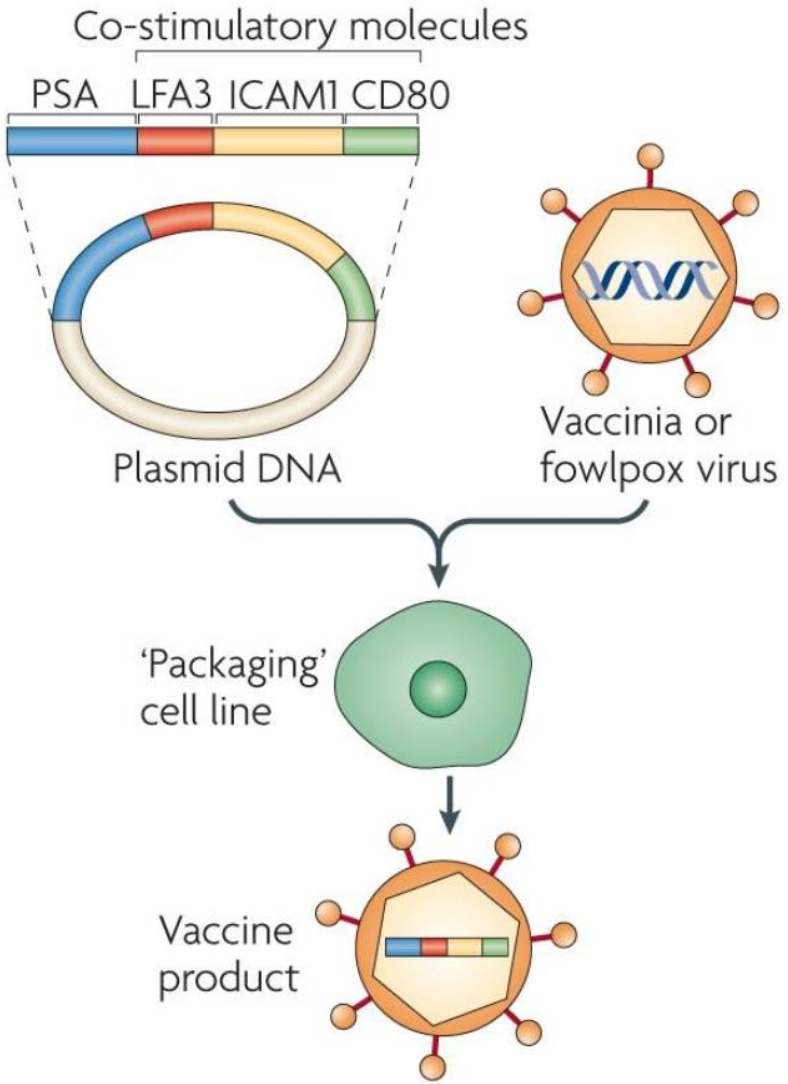
PROSTVAC



Drake CG: Nat Rev Immunol 10:580-593, 2010.

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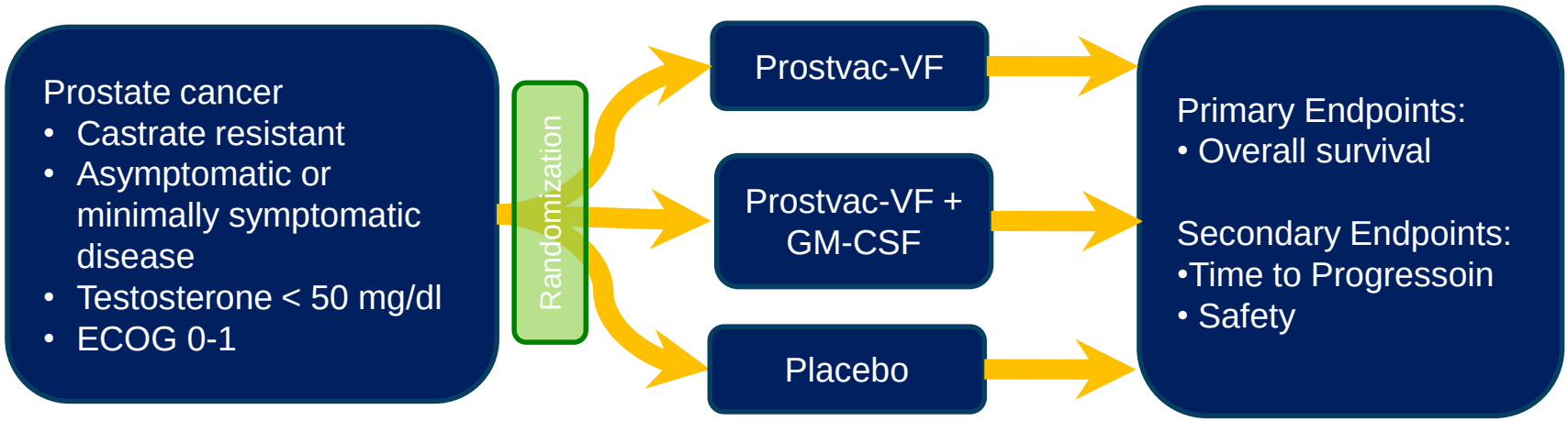
PROSTVAC

PROSPECT

- Completed enrollment of 1200 patients
- Study excludes patients with (1) visceral mets or (2) rapidly progressing disease
- Targeting OS HR of 0.82



Kantoff P *et al* J Clin Oncol. 2010 Mar 1;28(7):1099-105.

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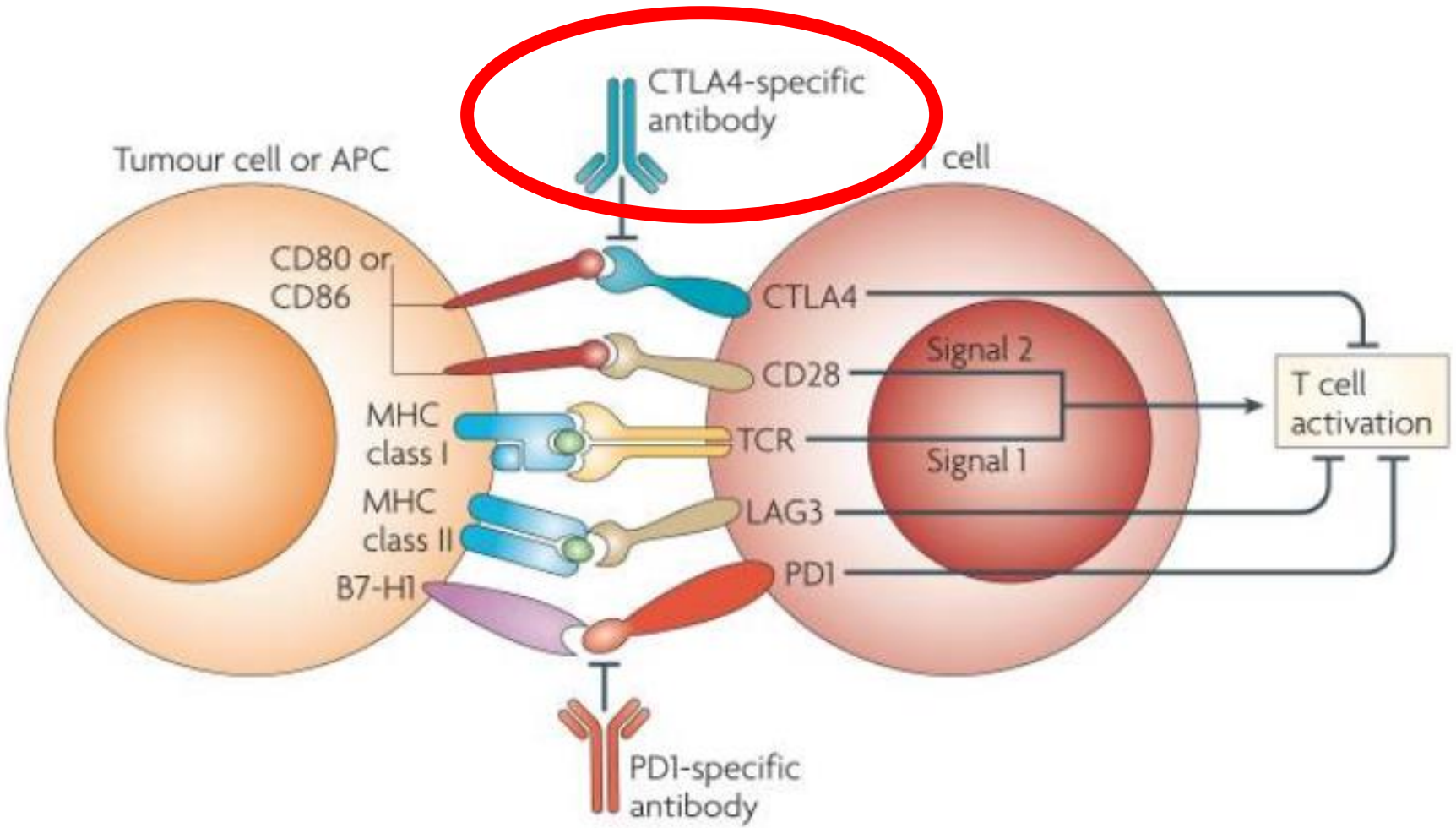
Ipilimumab



Drake CG: Nat Rev Immunol 10:580-593, 2010.

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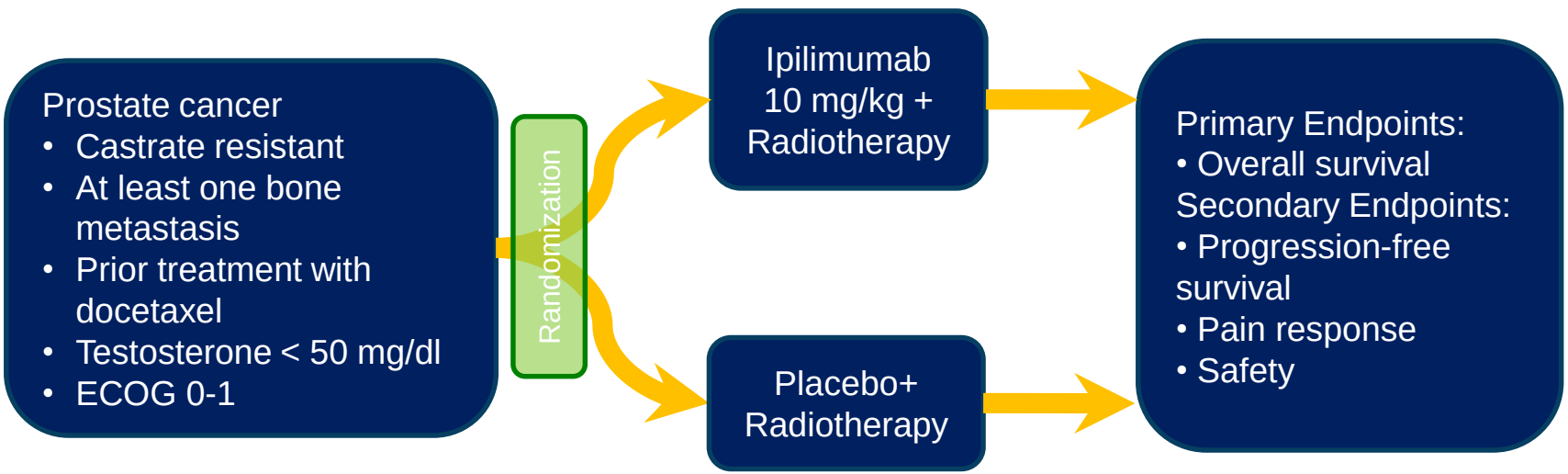
Ipilimumab

CA184-043 (NCT00861614)

- Phase III, multi-institutional, randomized trial



Kwon ED et al. Lancet Onc 15(7):700-712, 2014.

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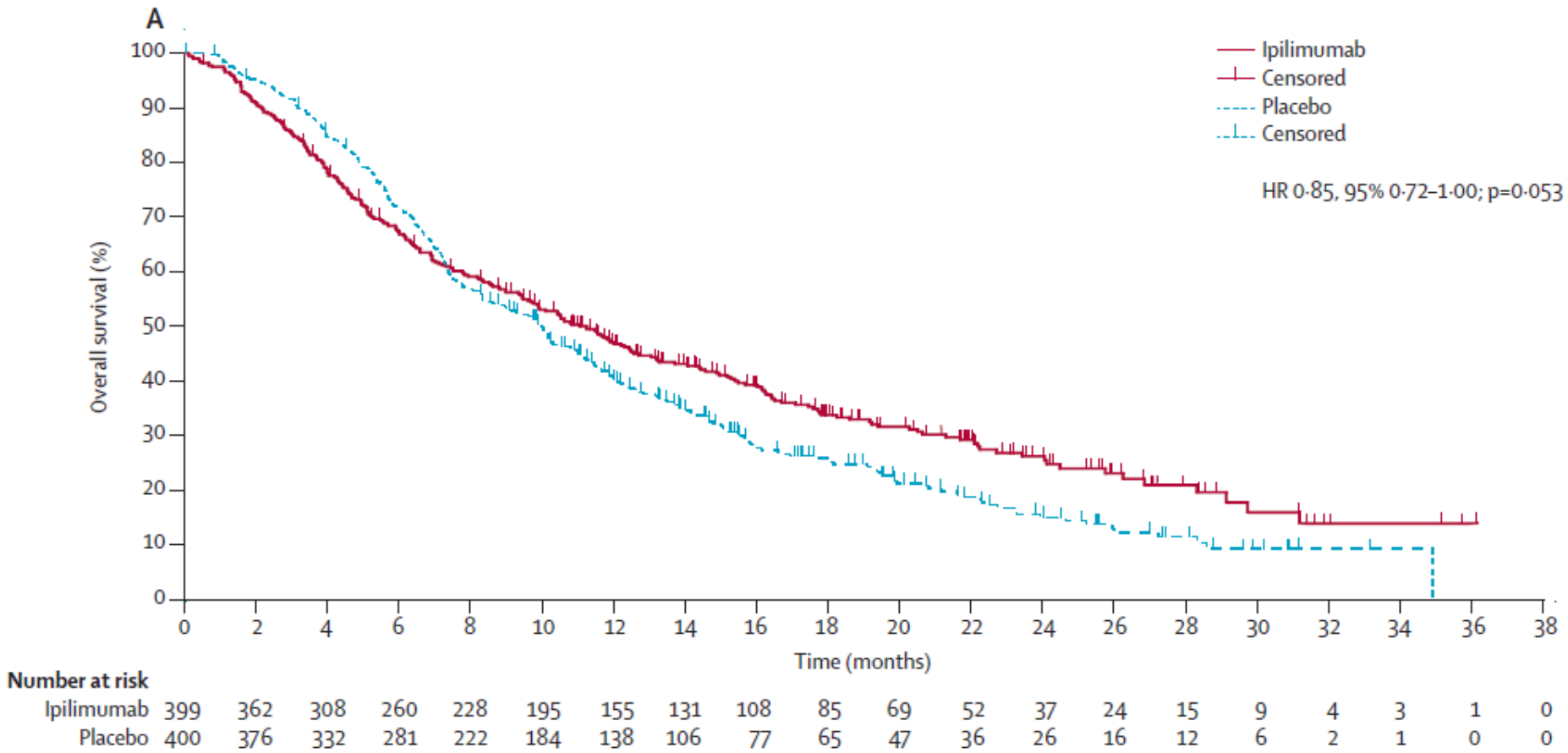

Kwon ED et al. Lancet Onc 15(7):700-712, 2014.

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Ipilimumab

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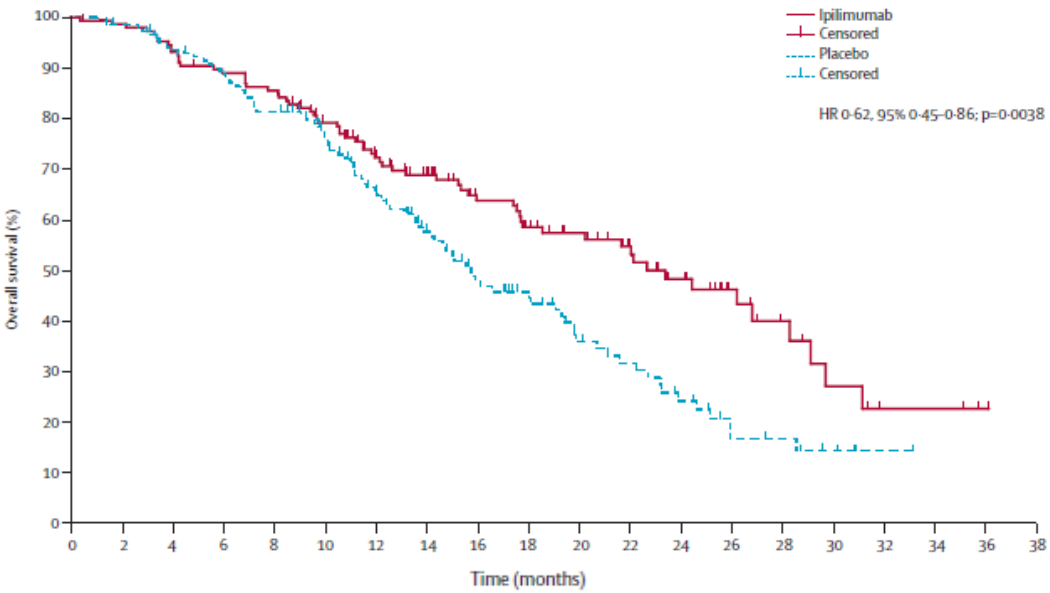
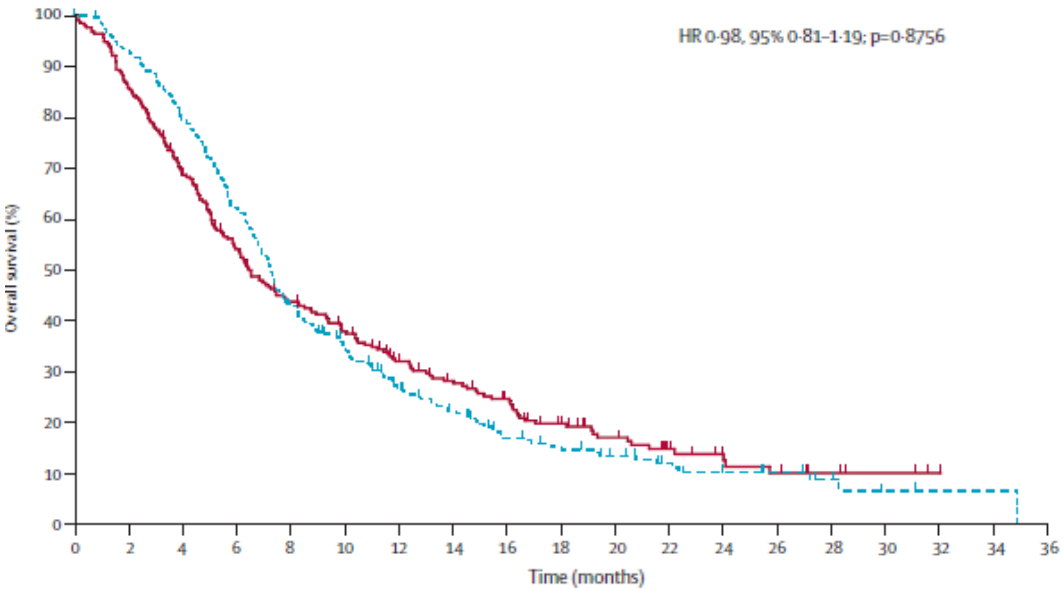
- Phase III, multi-institutional, randomized trial

Good prognosis



Bad prognosis



Kwon ED et al. Lancet Onc 15(7):700-712, 2014.

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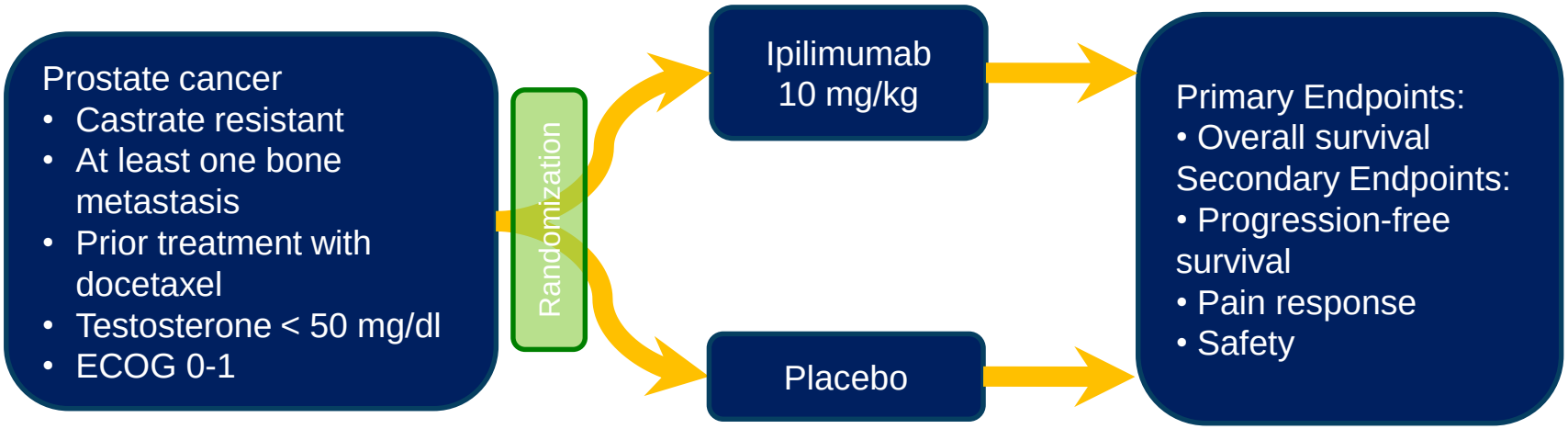
Ipilimumab

CA184-095 (NCT01057810)

- Chemotherapy-naïve (N=602)
- Negative result cited in press release



Press release: Bristol-Myers Squibb Company, New York, July 23, 2015

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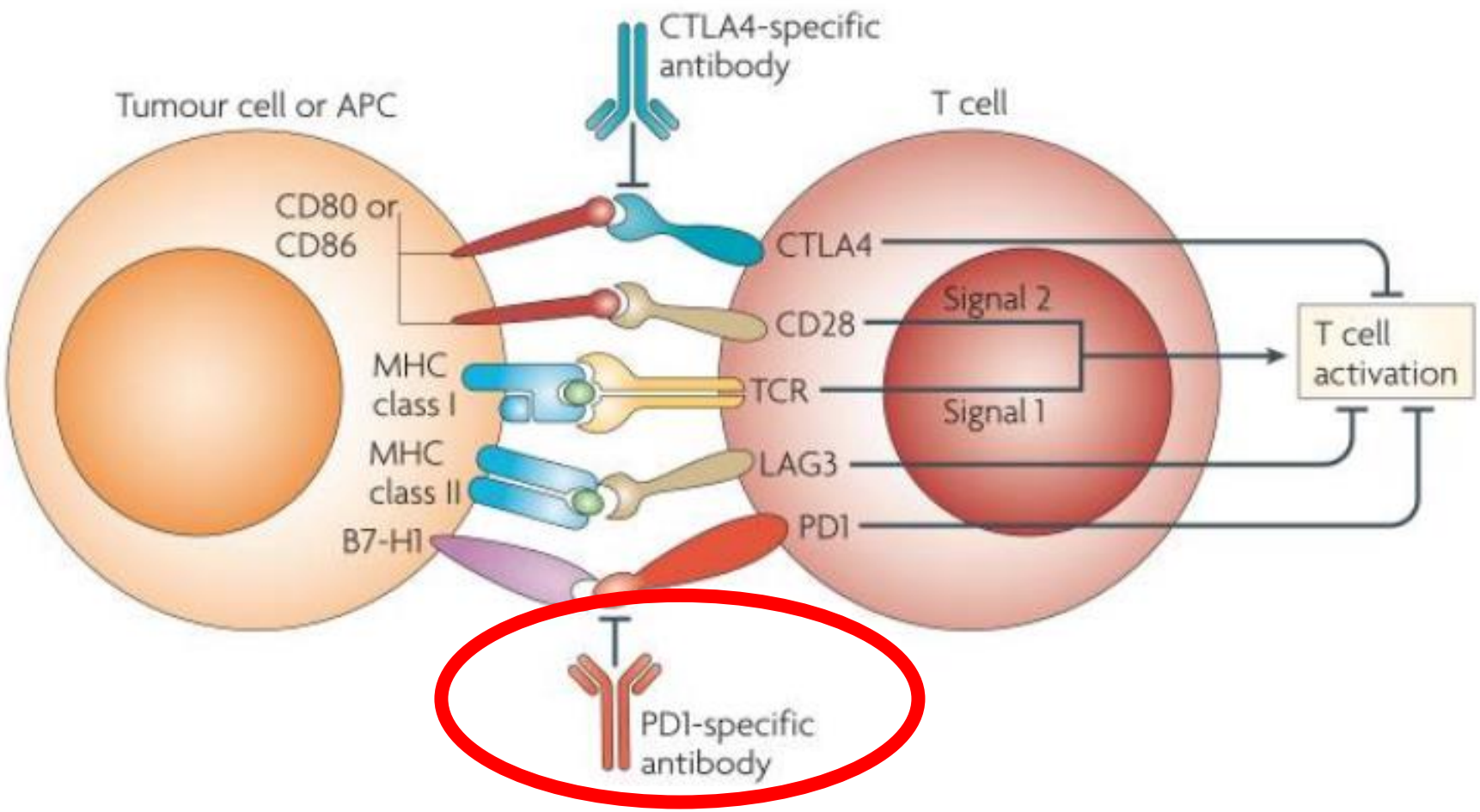
PD-1 Inhibition



Drake CG: Nat Rev Immunol 10:580-593, 2010.

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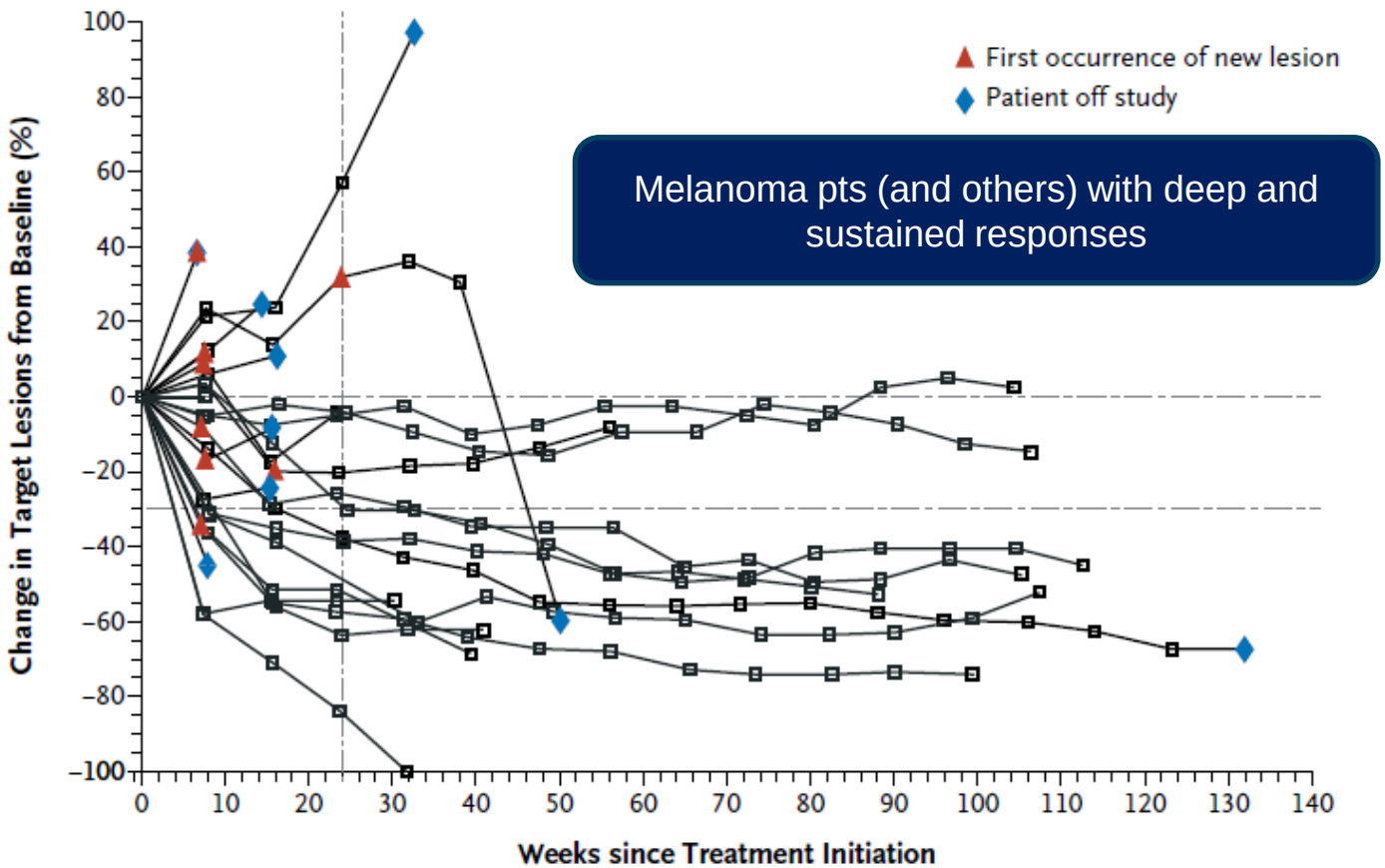
PD-1 Inhibition

Nivolumab

- 17 pts with mCRPC enrolled out of 296
- No responses observed!



Topalian SL: N Engl J Med 366(26):2443-2454, 2012.

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PD-1 Inhibition

Pembrolizumab

- 10 patients
- 3 dramatic responses; 2 with radiographic responses

	Pre-PSA	Post-PSA
Patient 1	70.65	0.08
Patient 2	46.89	0.02
Patient 3	2502	< 0.01

Graff et al Oncotarget 2016

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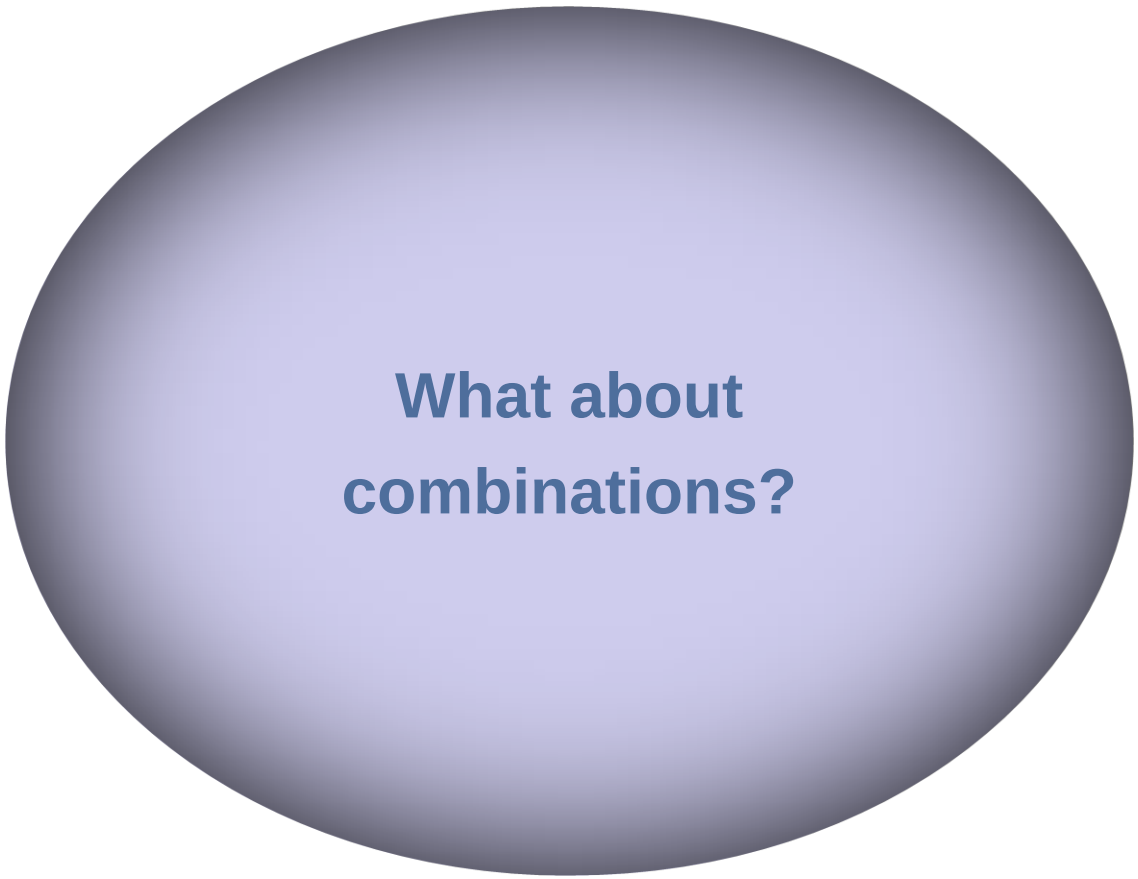
Overview



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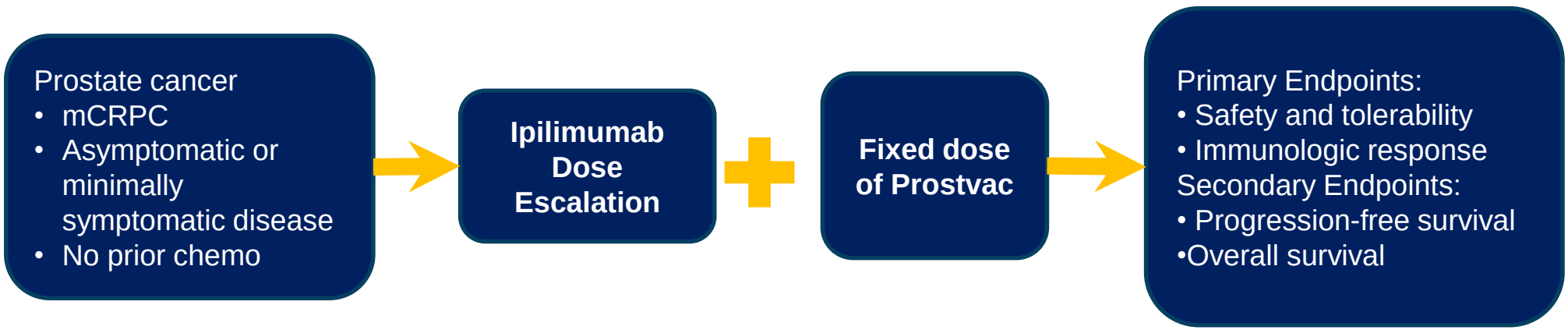
Combining CTLA4 blockade with vaccines

Ipilimumab + Prostvac-VF

- Phase II study conducted at NCI
- Target enrollment of 30 patients



https://clinicaltrials.gov/ct2/show/NCT02601014

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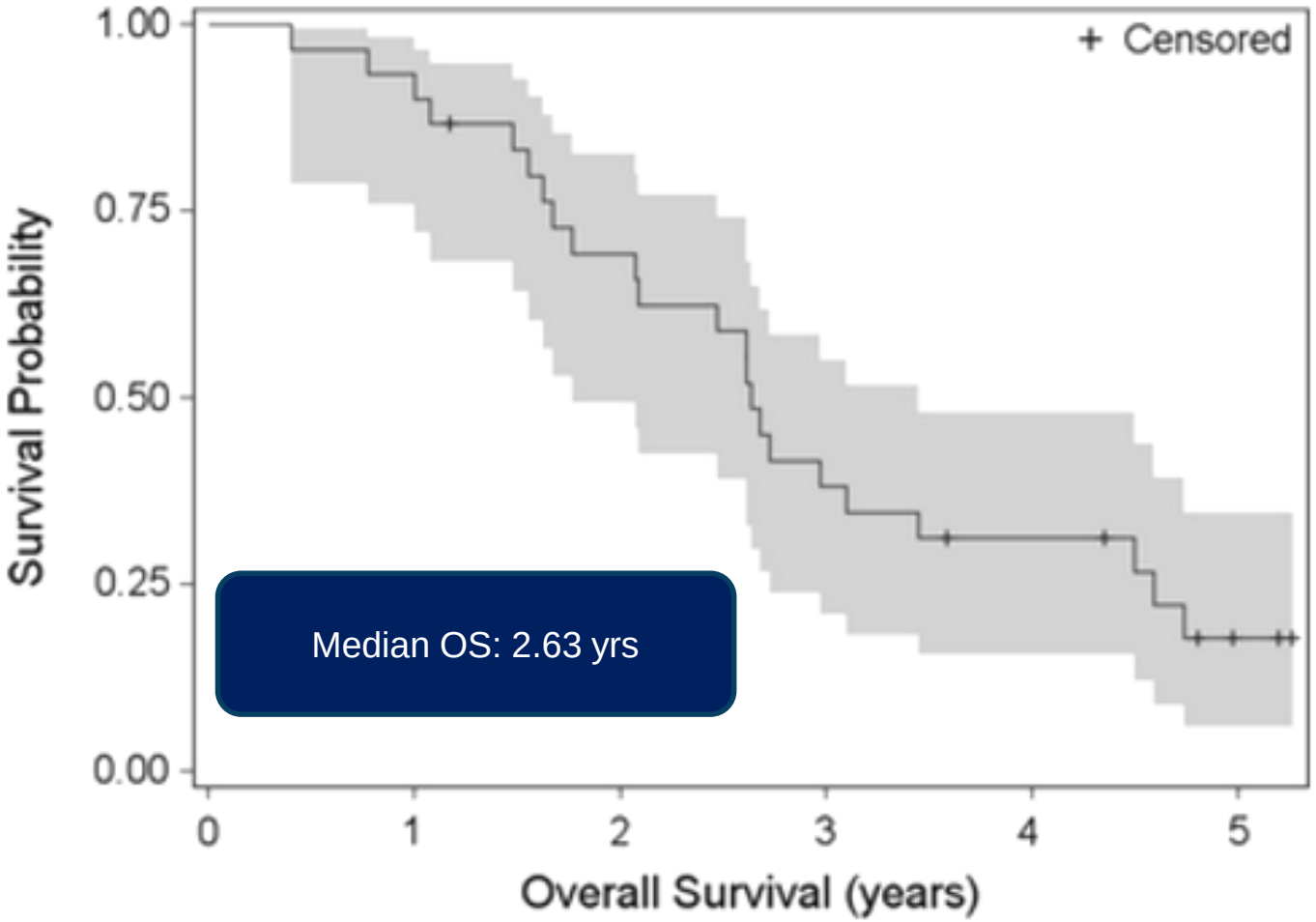
Combining CTLA4 blockade with vaccines



Jochems C: Cancer Immunol Immunother 64(4):407-418, 2014.

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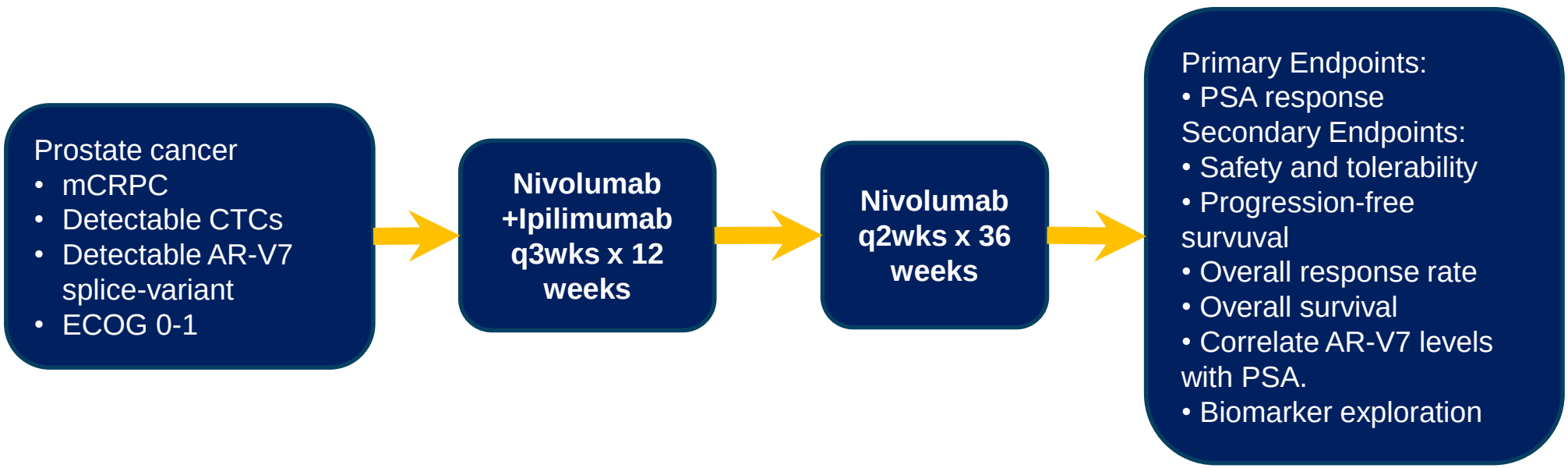
Combining checkpoint inhibitors

STARVE-PC (NCT02601014)

- Phase II
- Biomarker-driven therapy with nivolumab and ipilimumab in patients expressing AR-V7



https://clinicaltrials.gov/ct2/show/NCT02601014

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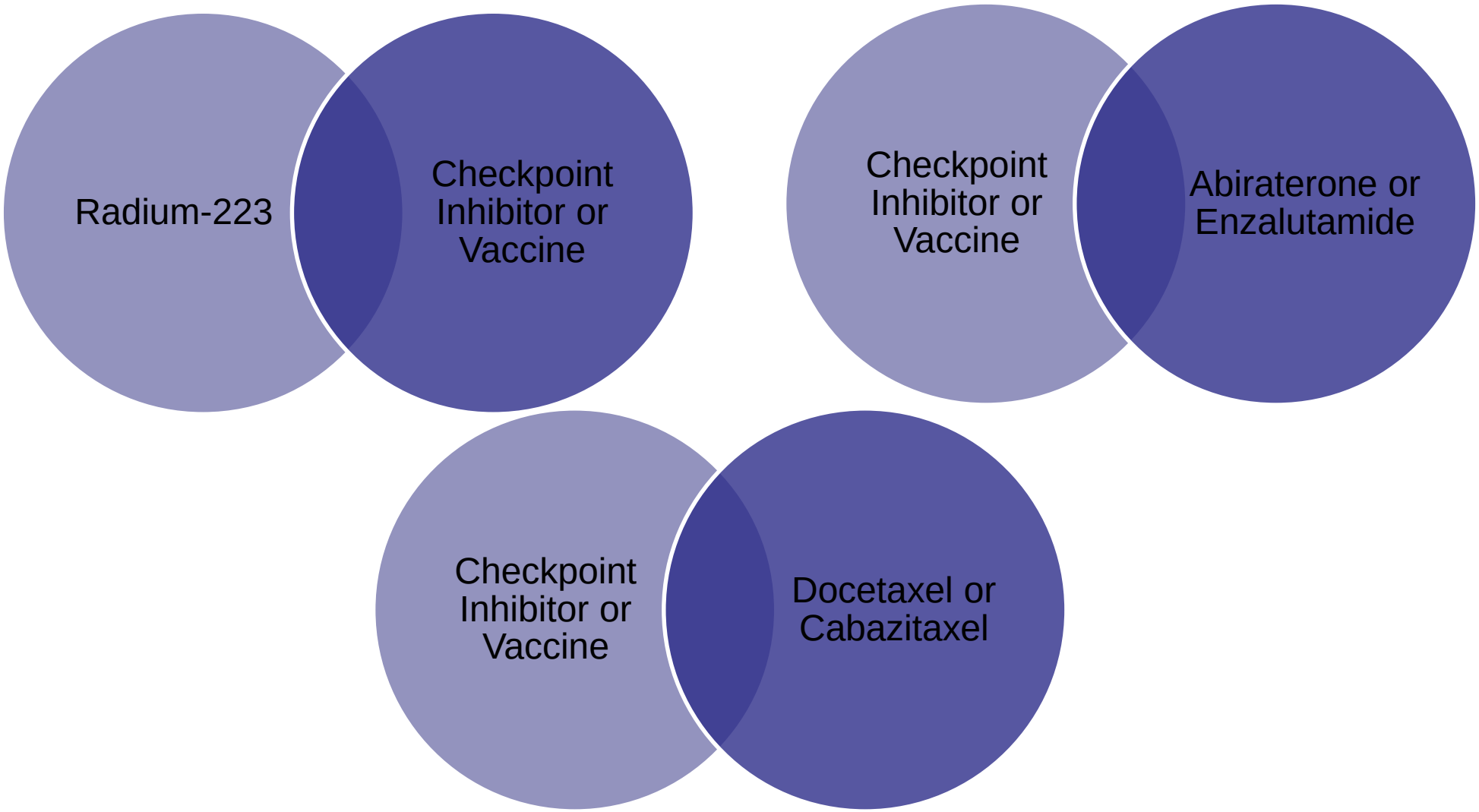
Other potential combinations



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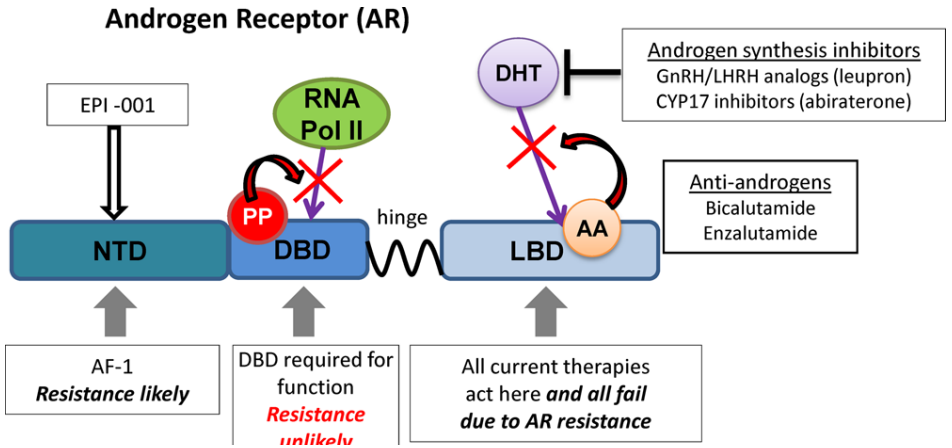
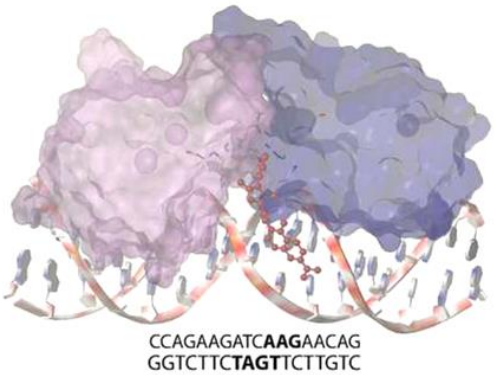
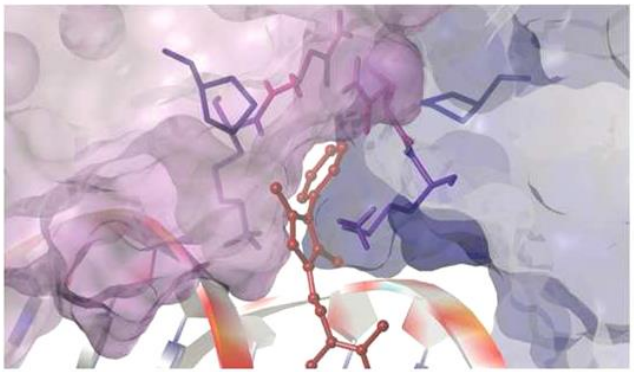
Pipeline Agents

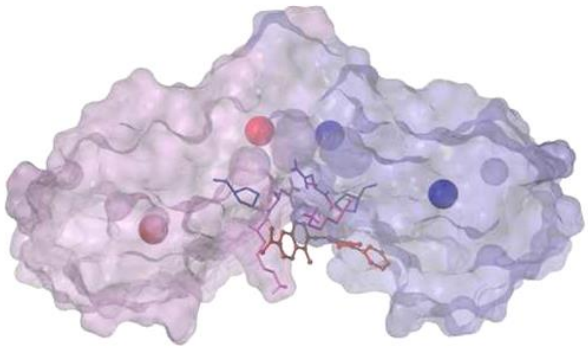
Mechanisms of resistance to current pathway inhibitors

- Circumventing splice variants (Jeremy Jones, PhD)









Lim M *et al* ACS Chem Biol 2013

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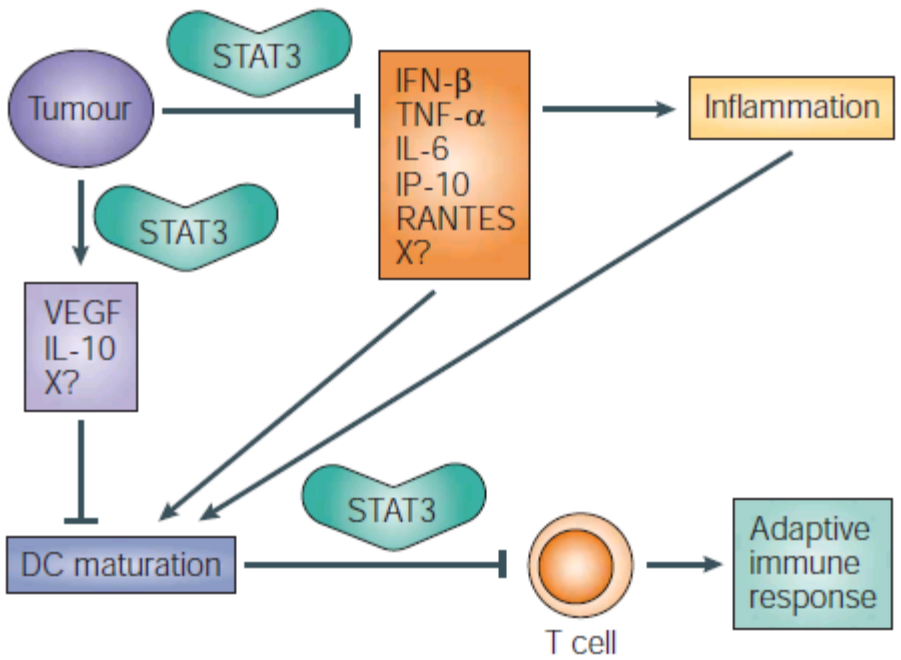
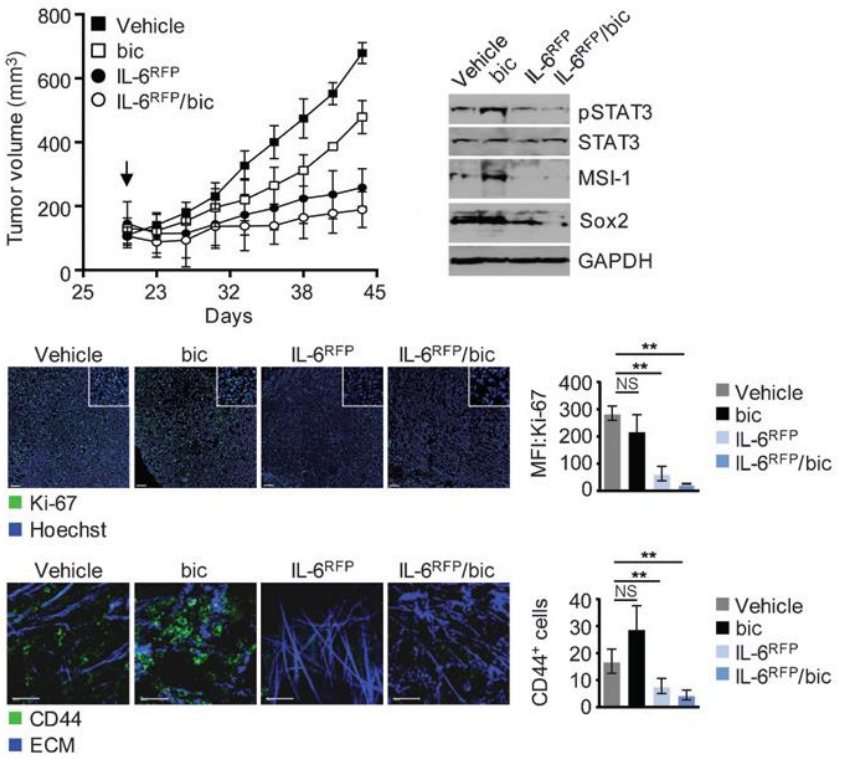
Pipeline Agents

Mechanisms of resistance to current pathway inhibitors

- Possible synergy between antiandrogen and STAT3-directed treatment





Yu *et al* Nat Rev Cancer 2009; Schroeder *et al* Cancer Res 2014

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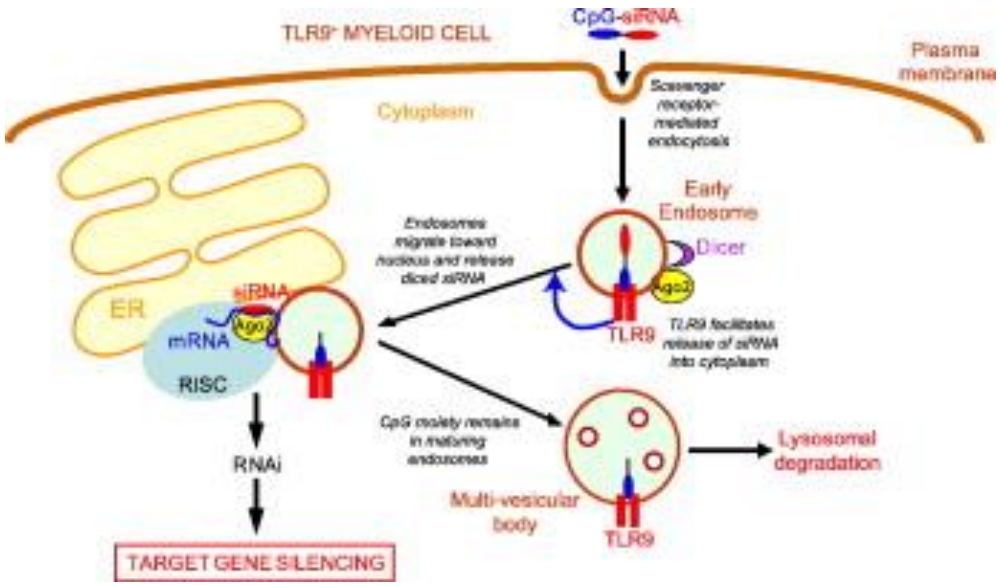
Mechanisms of resistance to current pathway inhibitors

- Possible synergy between antiandrogen and STAT3-directed treatment



mCRPC
- Histologically confirmed PC
- ≥ 2 sites of bone metatastasis
- Prior docetaxel
- Sites of metastases amenable to CT-guided biopsy

Site directed administration of CpG-STAT3-siRNA
(Phase I 6+6 design evaluating 2 dose levels)

Movember-PCF Challenge Grant (PI: Forman, Co-I: Pal)

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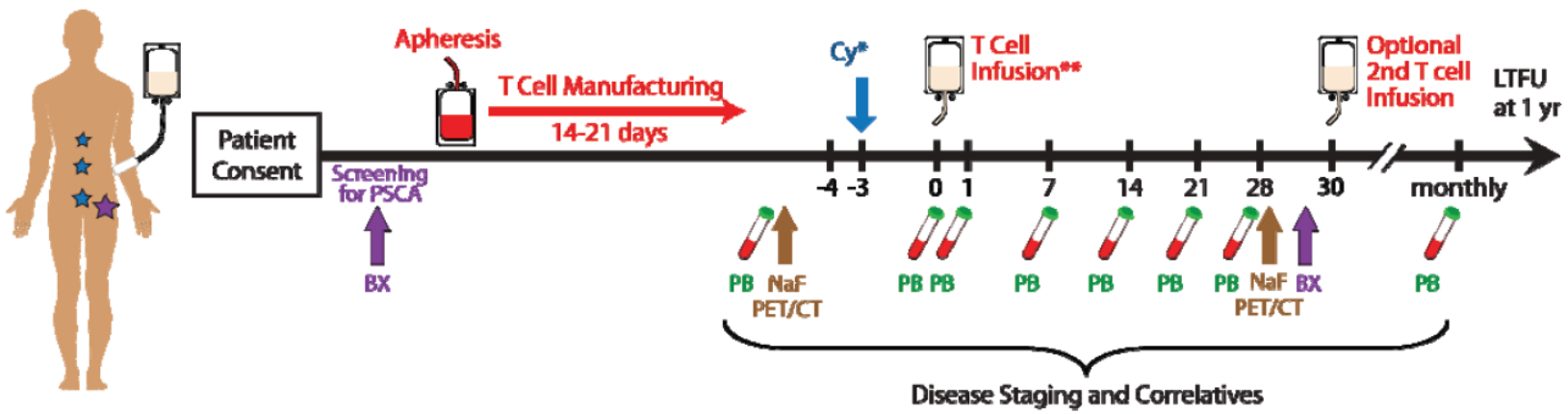
Pipeline Agents

CAR-T directed at PSCA

- Preclinical data shows substantial efficacy
- Early phase clinical trials currently being planned



Movember-PCF Challenge Grant (PI: Forman, Co-I: Pal)

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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?

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Thank you!

- Please e-mail me with questions!
- Sumanta K. Pal, MD – spal@coh.org

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