Society for Immunotherapy of Cancer (SITC)

Immunotherapy for the Treatment of GU Malignancies

Igor Puzanov, MD, MSCI, FACP
Associate Professor of Medicine
Director, Melanoma Clinical Research
Clinical Director, Renal Cancer
Associate Director, Phase I Drug Development Program
Vanderbilt University Medical Center
Nashville, Tennessee

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Disclosures: Igor Puzanov, M.D.

I have the following financial relationships to disclose relevant to the content of this presentation:

- Paid Consultant
  - Amgen, Genentech, Roche

- There will be discussion about the use of products for non-FDA approved indications in this presentation.

Overview

- General Principles
- Renal Cancer
- Urothelial Cancer
- Prostate Cancer

Cancer Immunotherapy

- **Association between febrile illness and cancer regression known for centuries**

- **19th century - William Coley demonstrated regression of soft tissue sarcomas in subset of patients who received intratumoral injections of heat-killed S. pyogens and S. marcescens**

- **Modern immunotherapy currently divided into three broad categories:**

  - A ctive immunization (peptides, whole tumor cells, recombinant viruses encoding tumor associated antigens, dendritic cells loaded with tumor antigen)

  - Nonspecific/semi-specific Immune Stimulation (IL-2, GM-CSF, ipilimumab, nivolumab, pembrolizumab, atezolizumab)

  - Adoptive Cell Transfer

Recent results in immunotherapy (2015)

The NEW ENGLAND JOURNAL of MEDICINE

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

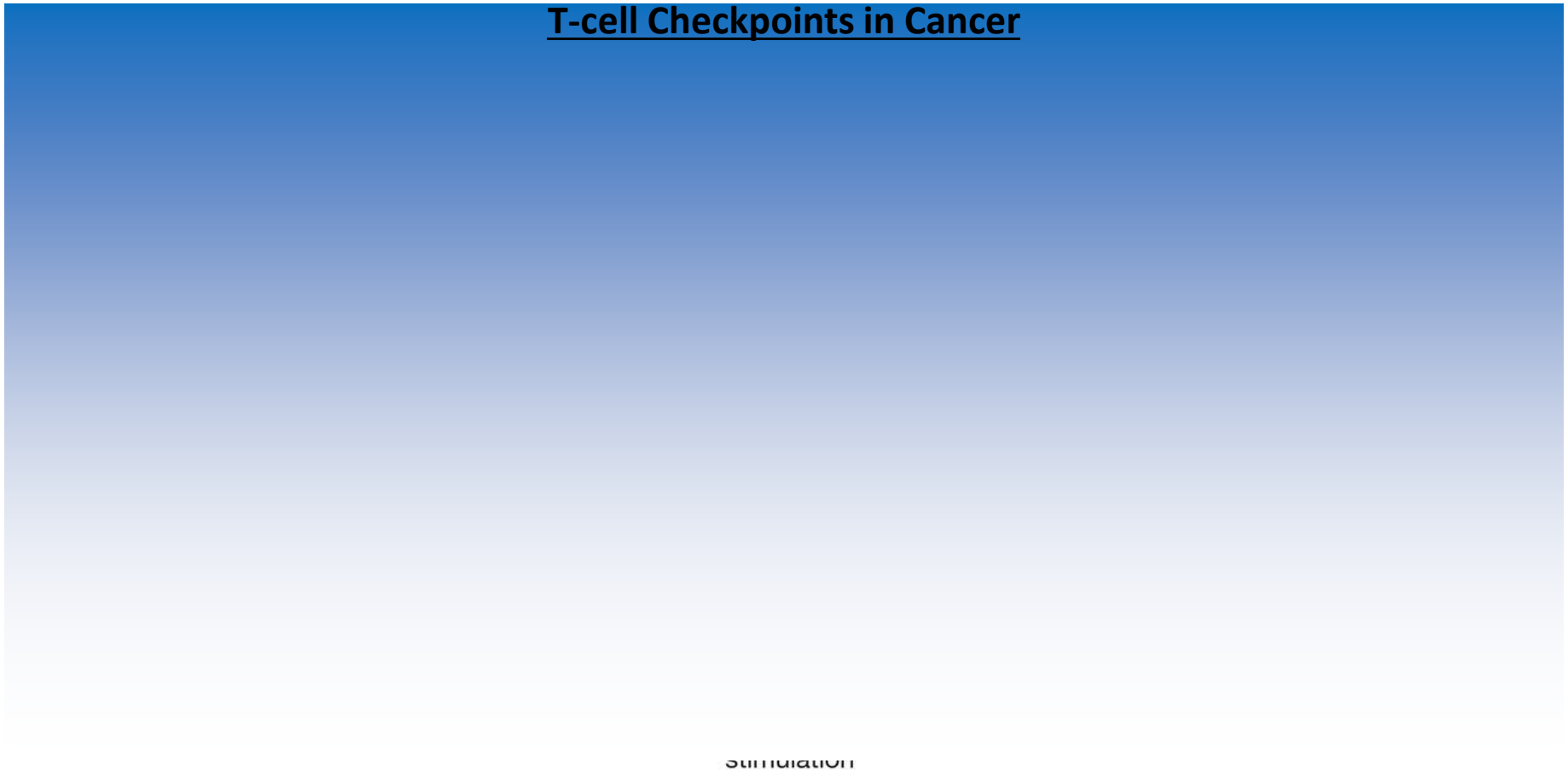
- **PFS 11.5 months (both) vs 2.9 months (ipi) vs 6.9 (nivolumab)**
- **There was, however, significant increase in treatment related adverse events in combination group**

Anti-programmed Cell Death Protein 1 (PD-1) Antibody Nivolumab Leads to a Dramatic and Rapid Response in Papillary Renal Cell Carcinoma with Sarcomatoid and Rhabdoid Features

- **After 3 doses of nivolumab, patient showed significant radiographic improvement of pulmonary, subcutaneous, and bony lesions**

Larkin et al. N Engl J Med 2015
Geynisman Eur Urol 2015

Multiple activating and inhibitory T cell receptors



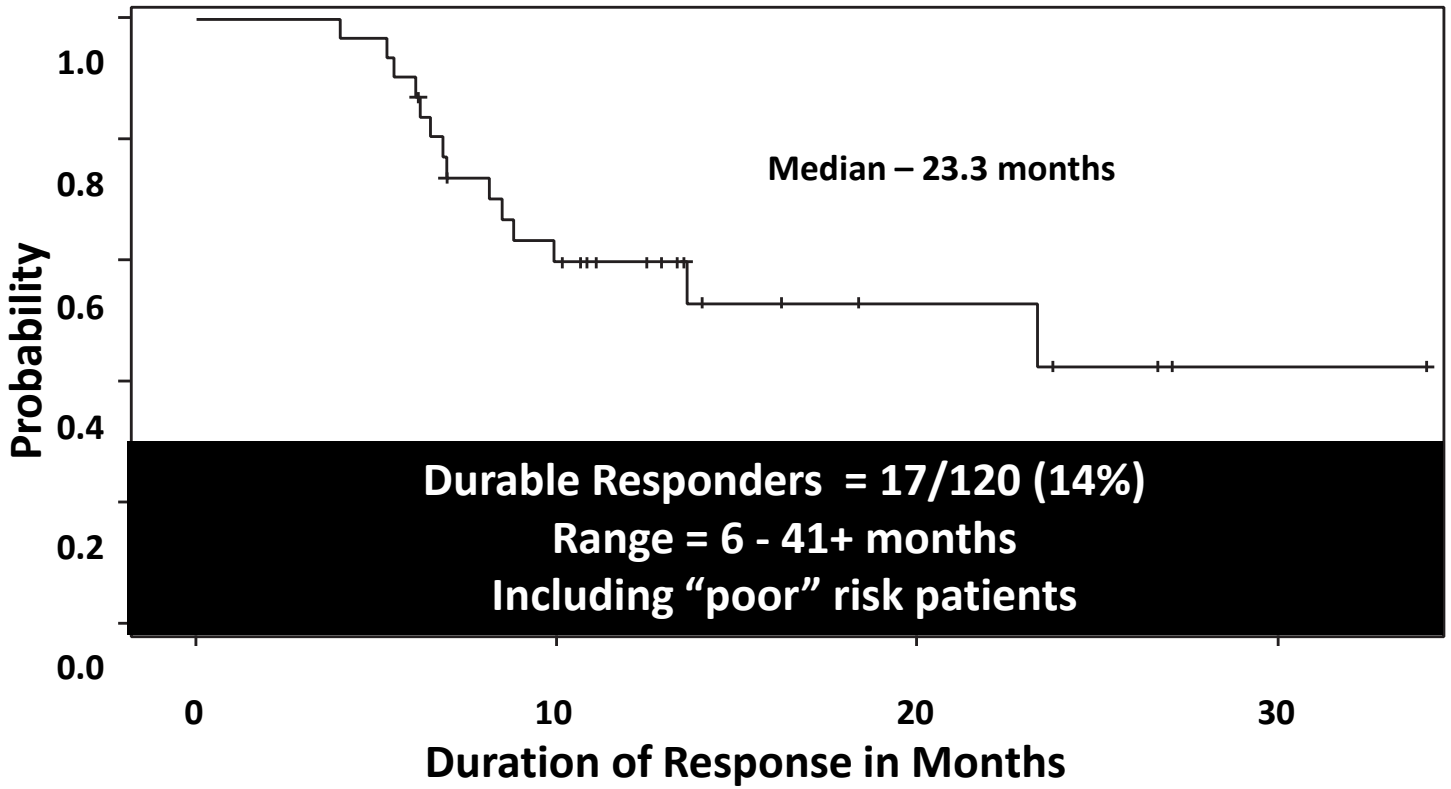
- **Drugs modulating multiple receptors beyond CTLA-4 and PD-1 are in development**
- **Genetic analysis of the pathways downstream of these receptors will shed light on patient response**
- **Combinatorial potential with independent receptors/ ligands may lead to enhanced immune responses**

Source: Nature, 2013; 2. Curr Opin Immunol. 2015

Overview

- General Principles
- Renal Cancer
- Urothelial Cancer
- Prostate Cancer

High dose Interleukin-2 (IL-2) can induce durable responses



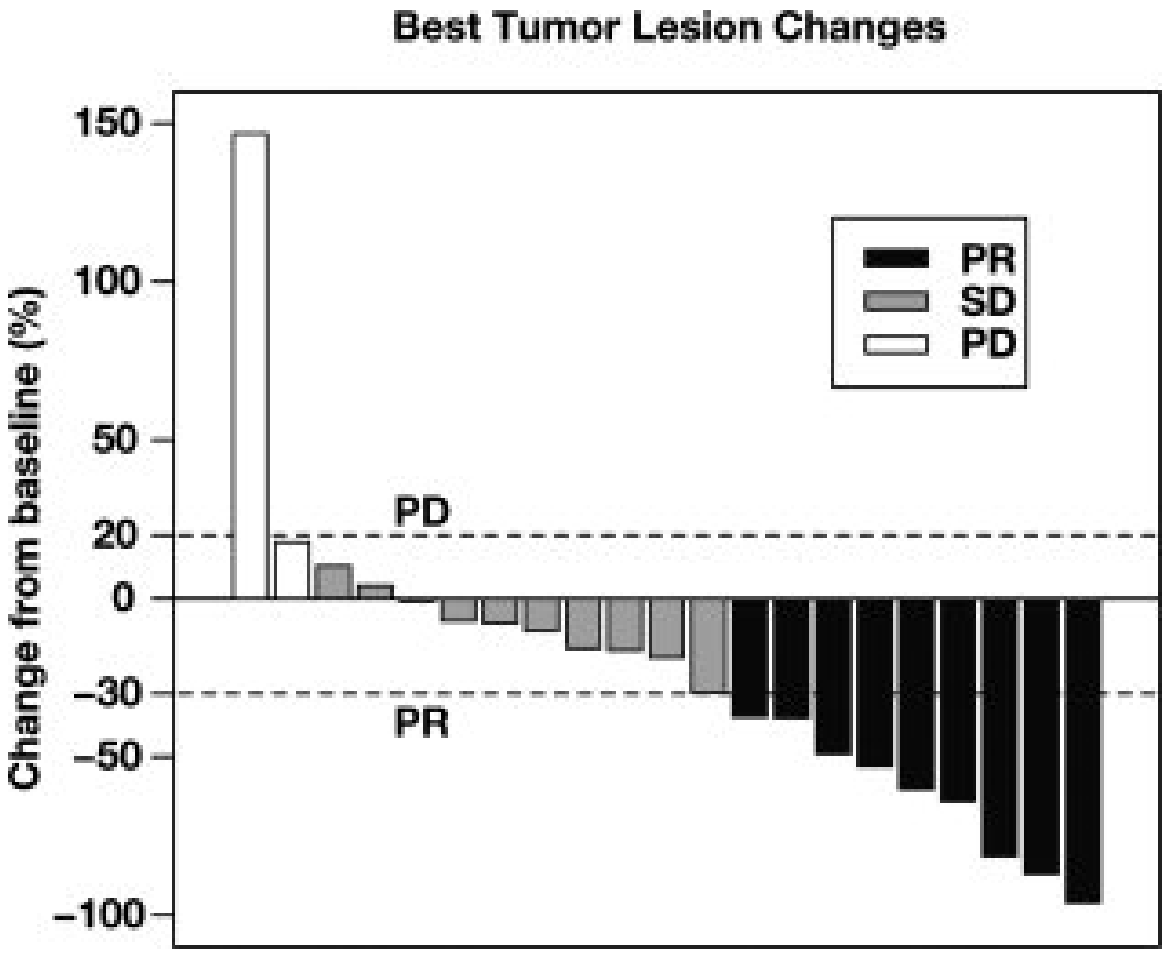
- 15-20% Objective response rate, **5-7% durable CRs**
- Significant toxicity: better selection criteria imperative

Objective Tumor Regressions With Ipilimumab Monotherapy in Metastatic RCC

	No. Patients	Doses of Ipilimumab	Response Duration
Cohort A loading dose of 3 mg/kg, then1 mg/kg	21		
PR	**1 (5%)**	**5**	**18 months**
Cohort B: all doses at 3 mg/kg			
Previous IL2	26		
PR	**2 (8%)**	**4, 4**	**7, 8 months**
No previous IL2	14		
PR	**3 (21%)**	**3, 6, 4**	**12, 17, 21 months**

Yang et al. *J Immunother.* 2007

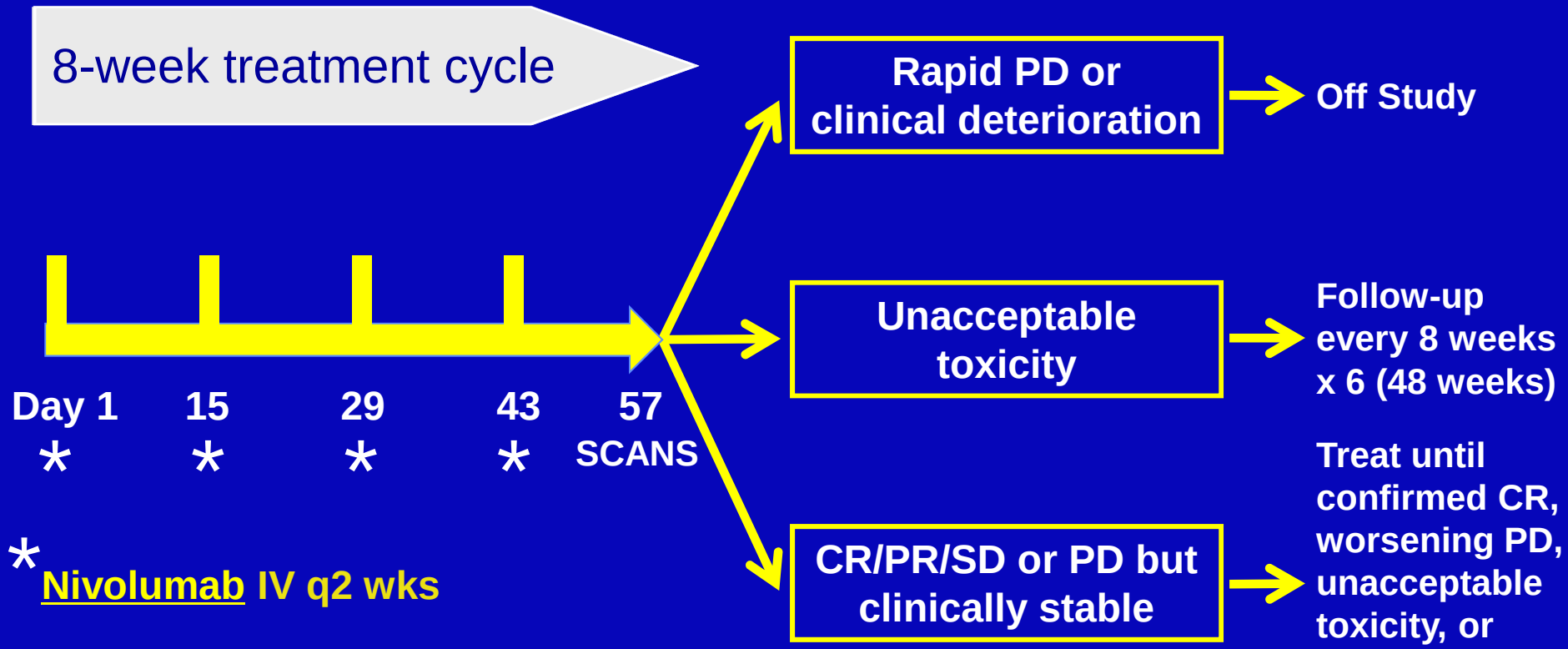
Phase 1 dose-escalation trial of tremelimumab plus sunitinib in patients with metastatic renal cell carcinoma



* Study terminated early due to renal toxicity

Rini et al. *Cancer* 2010

Phase I Nivolumab (anti-PD-1 ab) Study



Eligibility: Advanced MEL, mRCC, NSCLC, CRC, or CRPC with PD after 1-5 systemic therapies

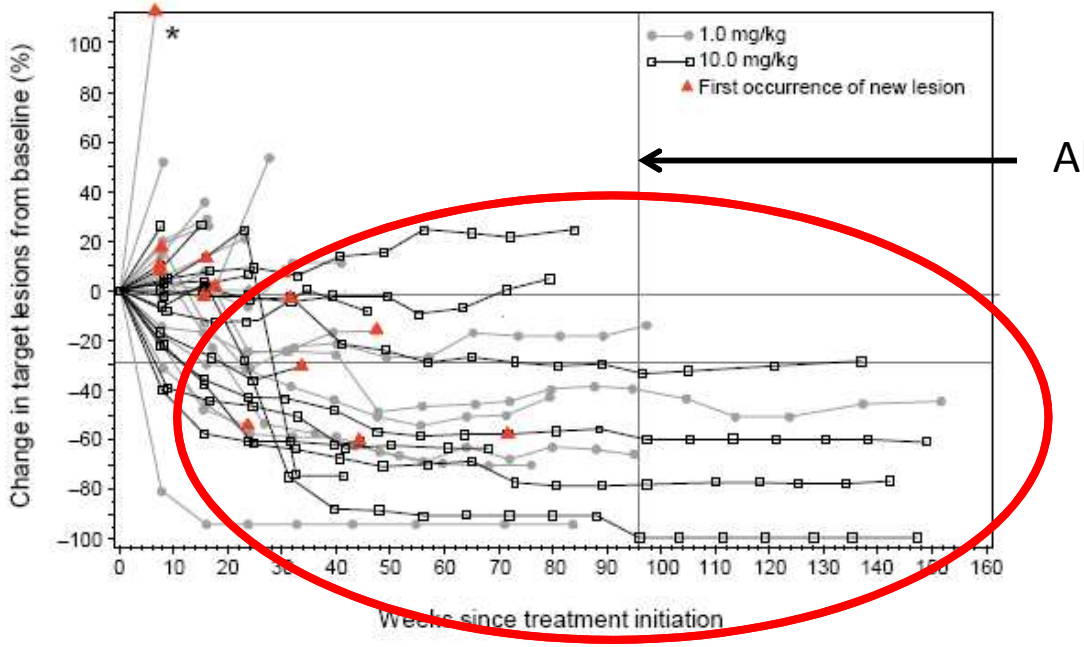
CR = complete response; CRC = colorectal cancer; CRPC = castrate-resistant prostate cancer; MEL = melanoma; mRCC = metastatic renal cell carcinoma; NSCLC = non-small cell lung cancer; PD = progressive disease; PR = partial response; SD = stable disease

Brahmer et al. NEJM

Phase I Nivolumab: RCC cohort (n=34)

- Generally tolerable: fatigue, rash, pruritus, diarrhea
  - 3 deaths: pneumonitis (non-RCC)

- Preliminary efficacy in heavily pre-treated patients:
  - 29% objective responses
  - Median PFS 7.3 months

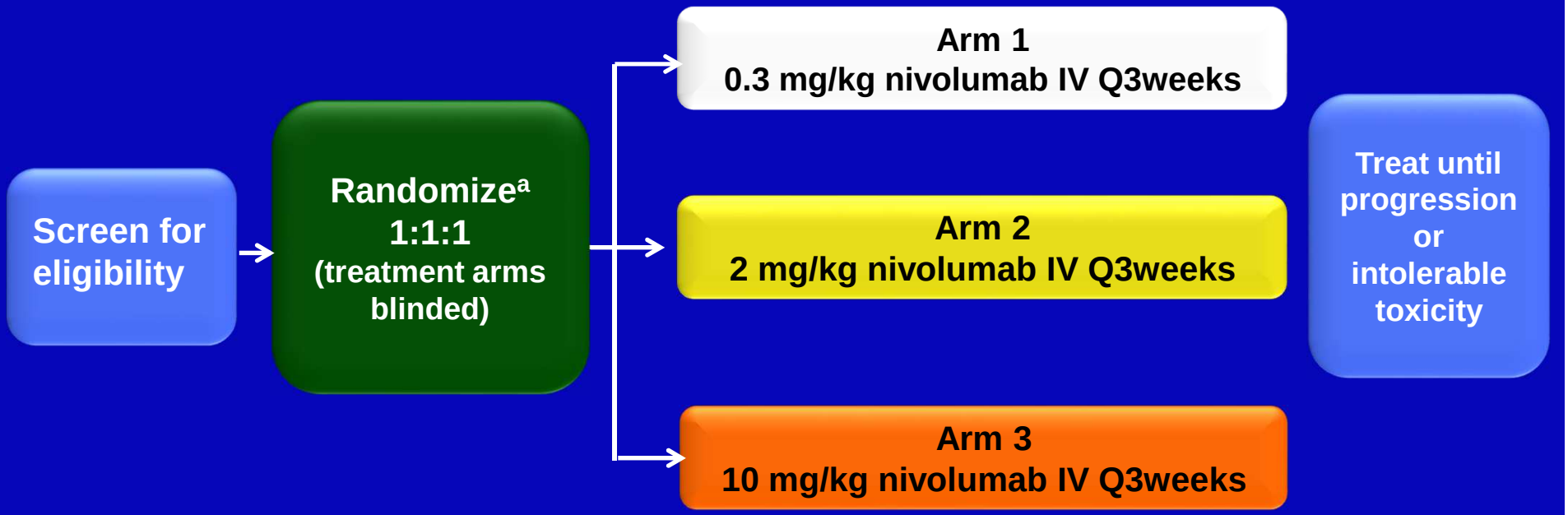


All stopped therapy

Durability of Response Even Off Drug

Drake ASCO 2013

Nivolumab rII study design

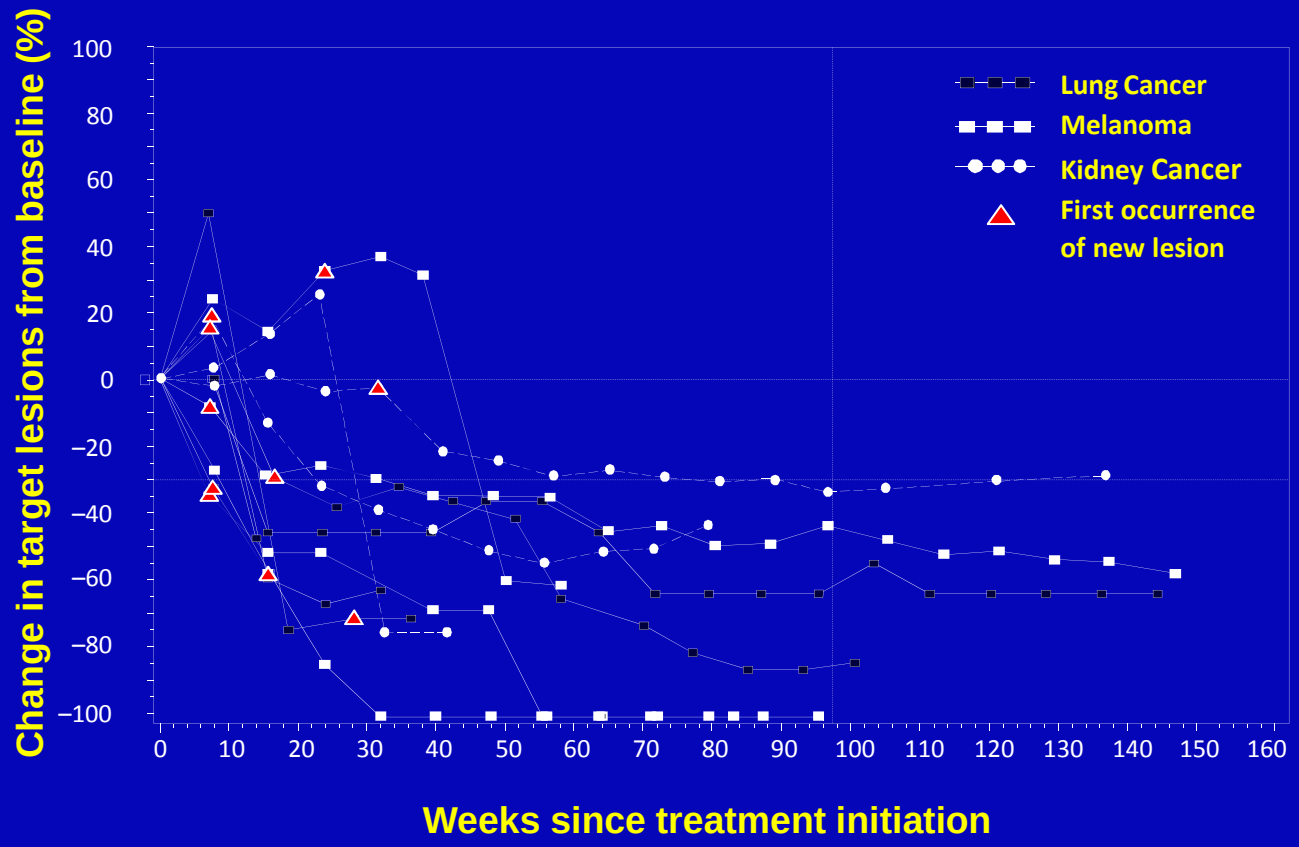


ClinTrials.gov NCT01354431

[a]Stratified by MSKCC prognostic score (0 vs 1 vs 2/3) and number of prior lines of therapy in the metastatic setting (1 vs >1).

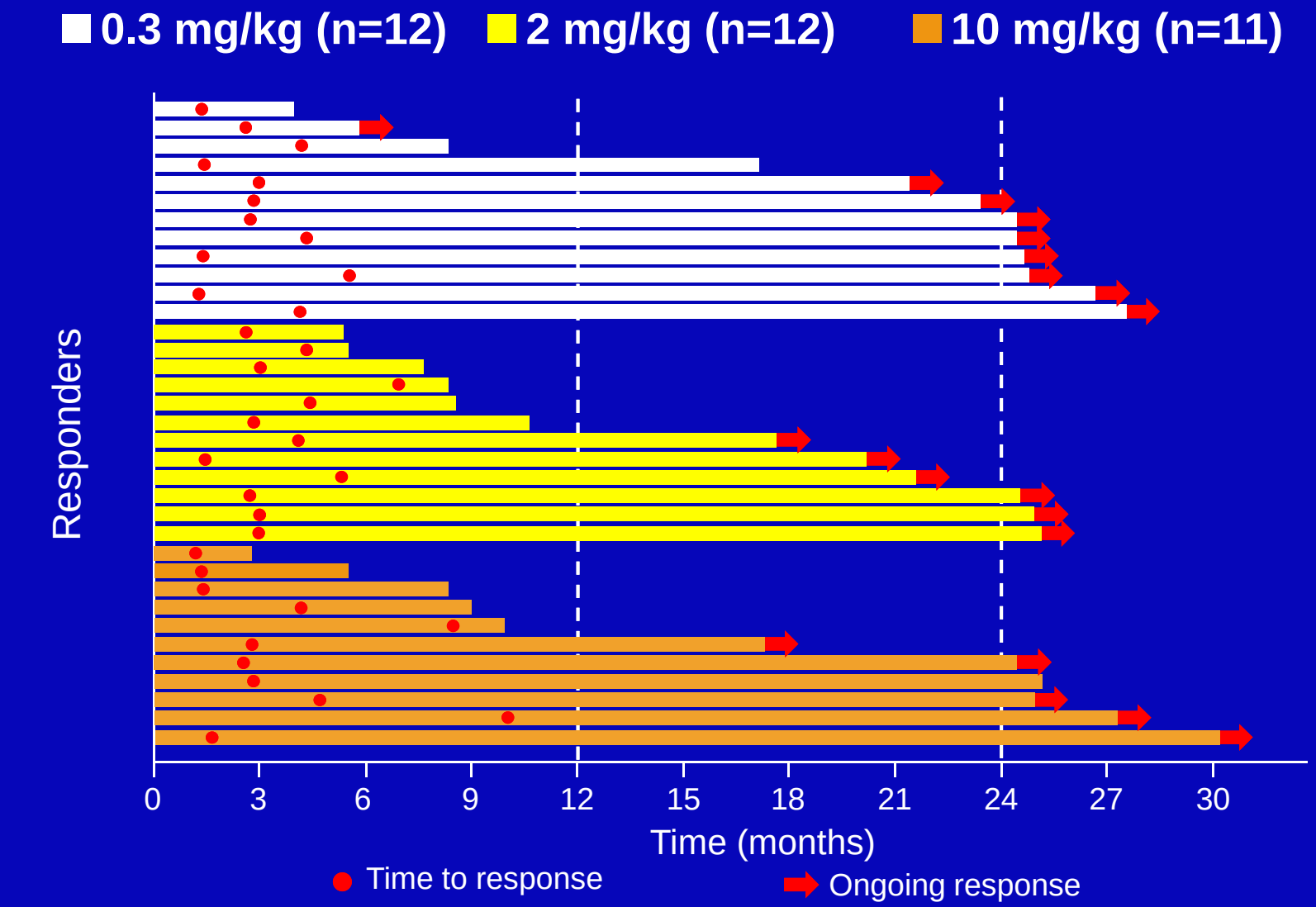
Motzer et al. JCO 2015

Unconventional “immune-related” responses in 13 patients with NSCLC, MEL and RCC



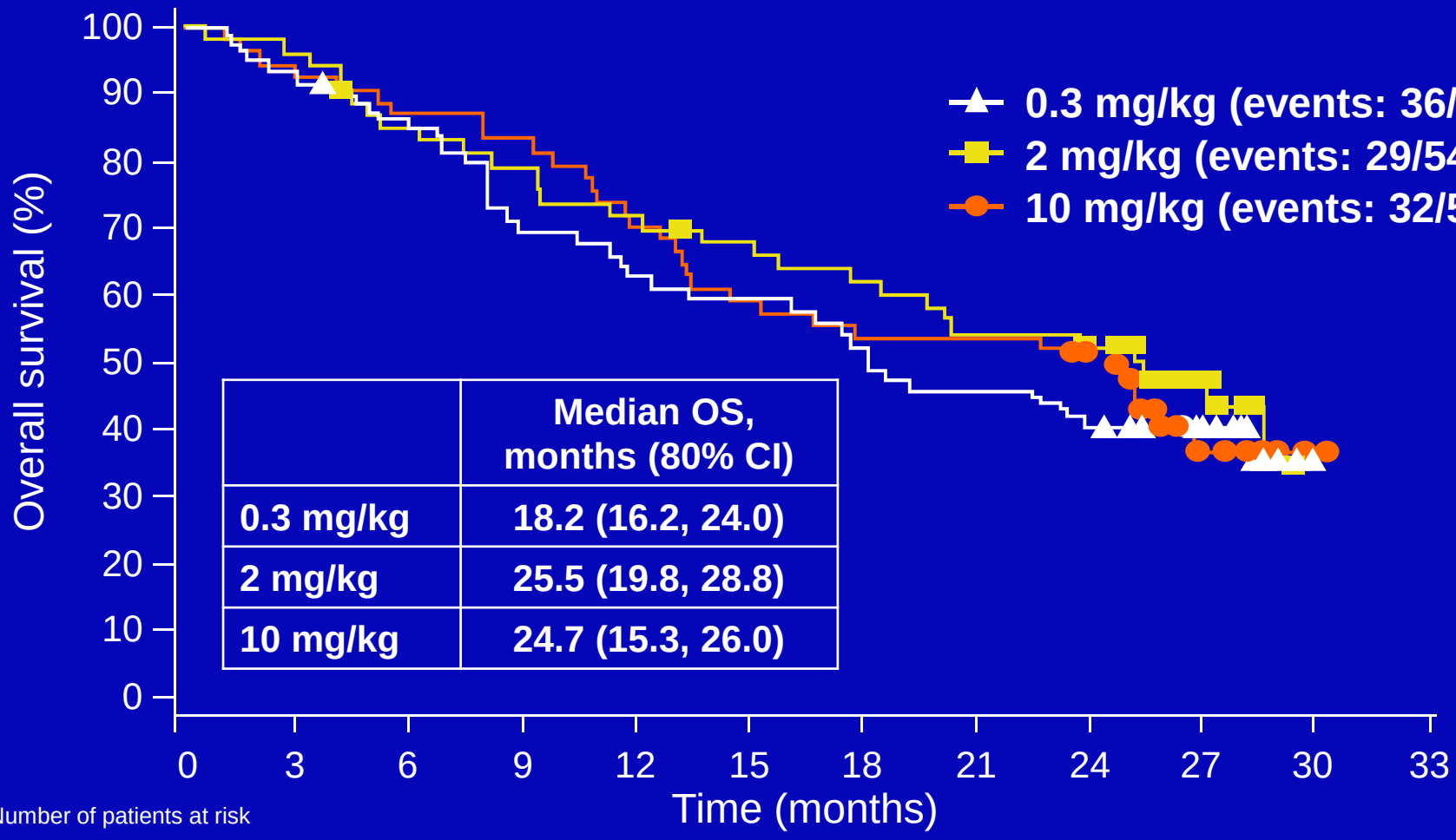
- 13 of 270 pts (**5%**) with NSCLC/MEL /RCC had unconventional responses
- irResponse durability and persistence off-drug were similar to conventional RECIST responses

Duration of response



Based on data cutoff of March 5, 2014.

Overall survival



	Median OS, months (80% CI)
0.3 mg/kg	18.2 (16.2, 24.0)
2 mg/kg	25.5 (19.8, 28.8)
10 mg/kg	24.7 (15.3, 26.0)

Number of patients at risk

0.3 mg/kg	60	56	50	41	37	35	31	27	24	13	0	0
2 mg/kg	54	52	45	42	38	35	32	28	26	12	0	0
10 mg/kg	54	50	47	45	38	32	29	29	26	8	1	0

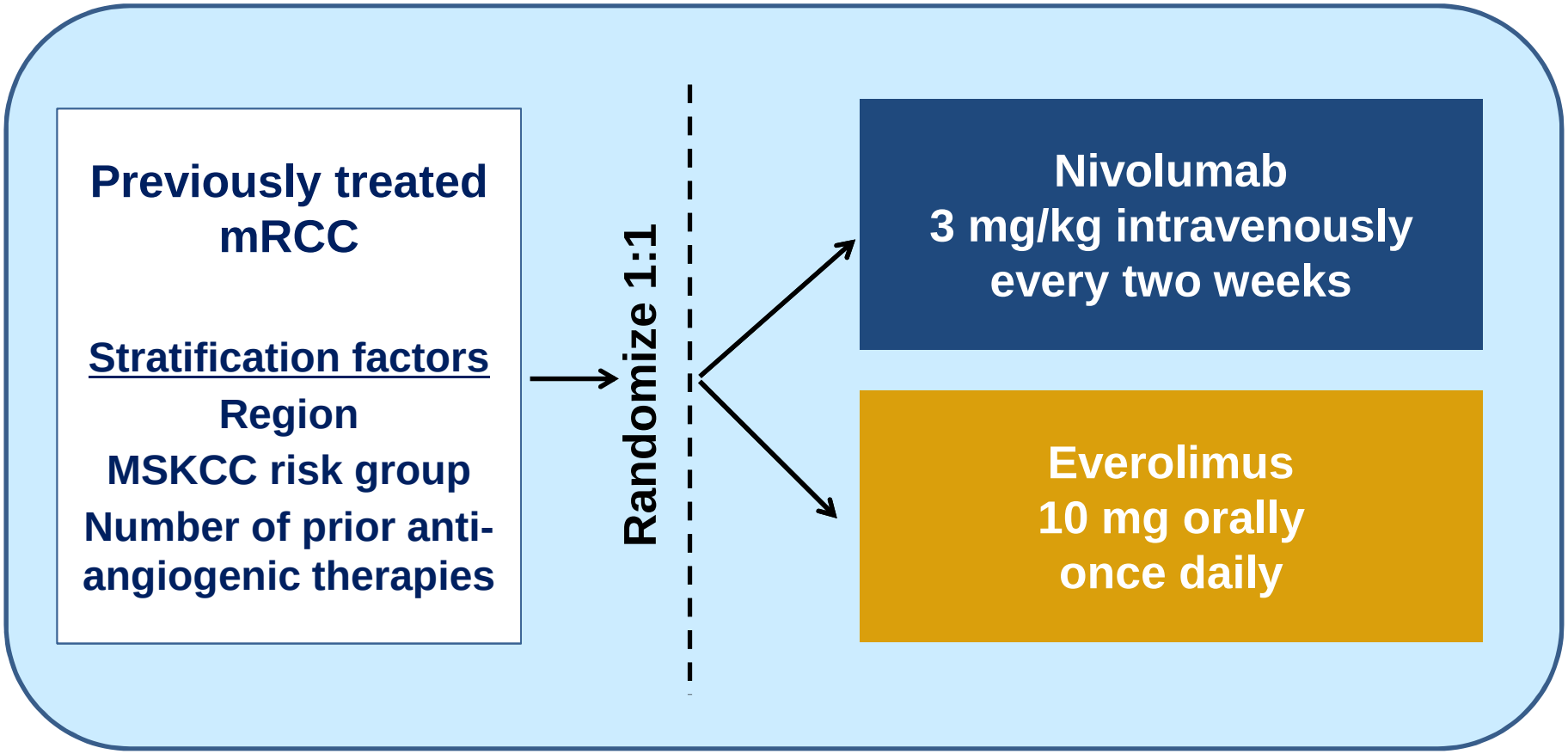
Based on data cutoff of March 5, 2014; Symbols represent censored observations.

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

Padmanee Sharma, Bernard Escudier, David F. McDermott, Saby George, Hans J. Hammers, Sandhya Srinivas, Scott S. Tykodi, Jeffrey A. Sosman, Giuseppe Procopio, Elizabeth R. Plimack, Daniel Castellano, Howard Gurney, Frede Donskov, Petri Bono, John Wagstaff, Thomas C. Gauler, Takeshi Ueda, Li-An Xu, Ian M. Waxman, Robert J. Motzer,
on behalf of the CheckMate 025 investigators

WWW.ECCO-ORG.EU

Study design



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

MSKCC, Memorial Sloan-Kettering Cancer Center.

Key eligibility criteria

- Advanced or metastatic clear-cell RCC
- One or two prior anti-angiogenic therapies
- Measurable disease (RECIST v1.1)
- Karnofsky performance status (KPS) ≥70%
- Progression on or after most recent therapy and within 6 months of enrollment

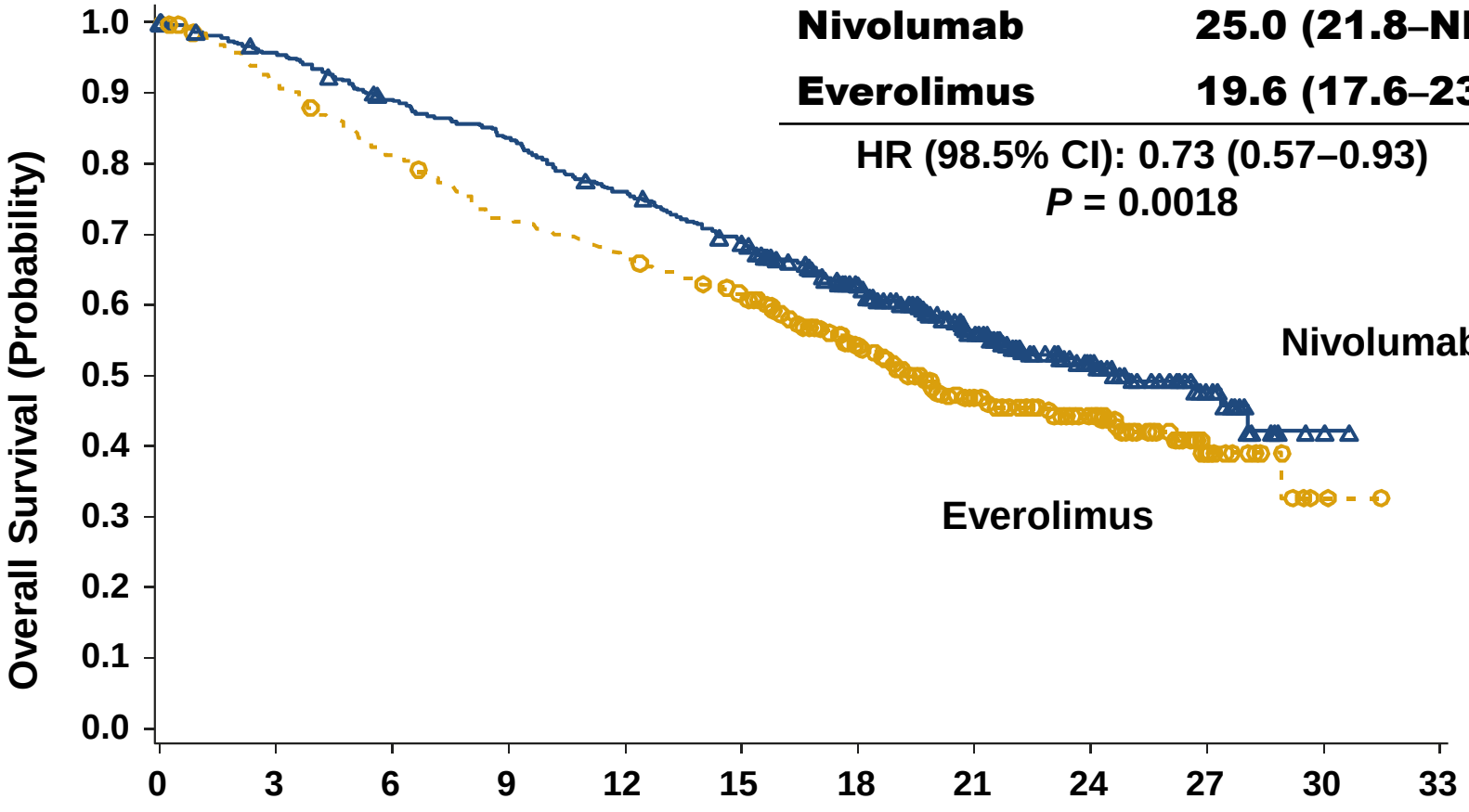
Demographics and baseline characteristics

Characteristic	Nivolumab N = 410	Everolimus N = 411
Median age (range), years	62 (23–88)	62 (18–86)
Sex, %		
Female	23	26
Male	77	74
MSKCC risk group, %		
Favorable	35	36
Intermediate	49	49
Poor	16	15
Number of prior anti-angiogenic regimens in advanced setting, %		
1	72	72
2	28	28
Region, %		
US/Canada	42	42
Western Europe	34	34
Rest of the world	23	24

Overall survival

Median OS, months (95% CI)	
Nivolumab	**25.0 (21.8–NE)**
Everolimus	**19.6 (17.6–23.1)**

HR (98.5% CI): 0.73 (0.57–0.93)
***P* = 0.0018**



No. of patients at risk

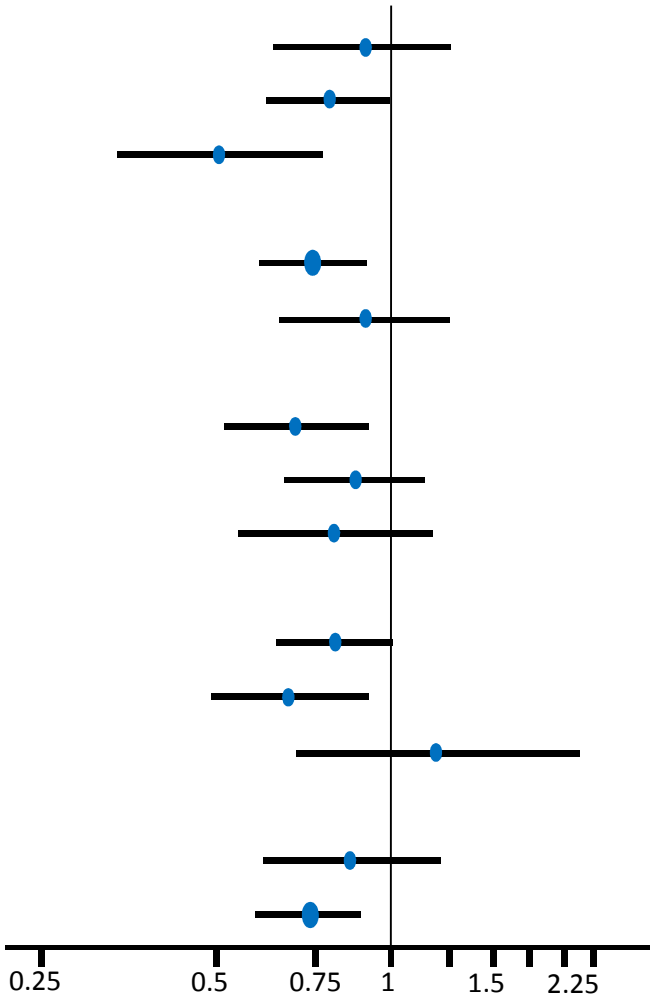
Nivolumab	410	389	359	337	305	275	213	139	73	29	3	0
Everolimus	411	366	324	287	265	241	187	115	61	20	2	0

Minimum follow-up was 14 months.

NE, not estimable.

Overall survival by subgroup analyses

Subgroup	Nivolumab n/N	Everolimus n/N
MSKCC risk group		
Favorable	45/145	52/148
Intermediate	101/201	116/203
Poor	37/64	47/60
Prior anti-angiogenic regimens		
1	128/294	158/297
2	55/116	57/114
Region		
US/Canada	66/174	87/172
Western Europe	78/140	84/141
Rest of the world	39/96	44/98
Age, years		
<65	111/257	118/240
≥65 to <75	53/119	77/131
≥75	19/34	20/40
Sex		
Female	48/95	56/107
Male	135/315	159/304



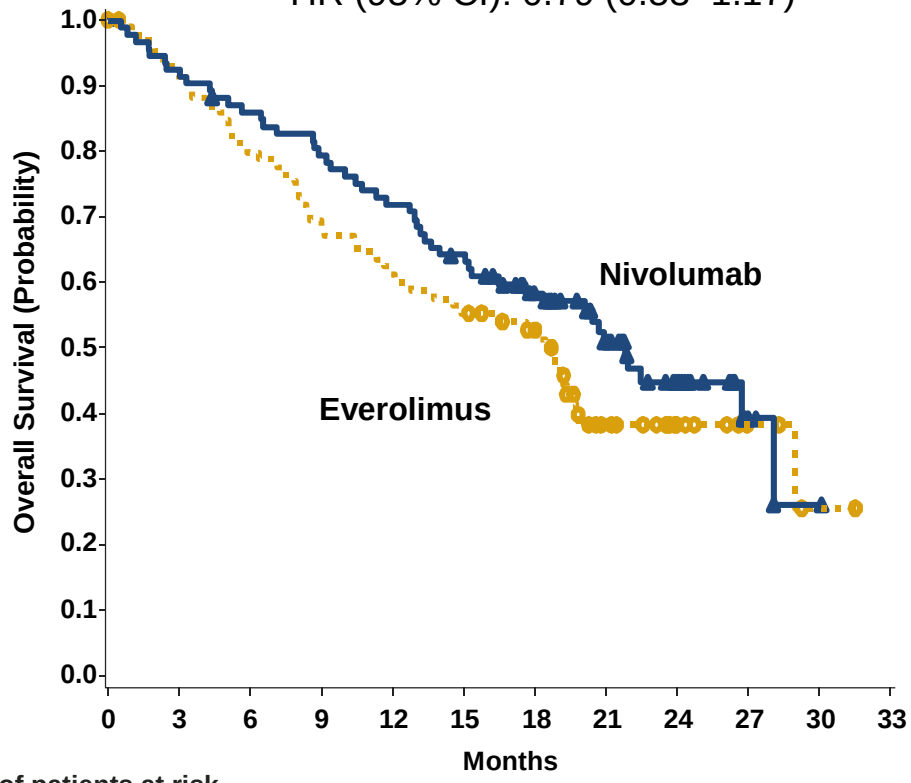
Analyses based on interactive voice response system data.

Overall survival by PD-L1 expression

PD-L1 ≥1% (n = 24%)

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

HR (95% CI): 0.79 (0.53–1.17)



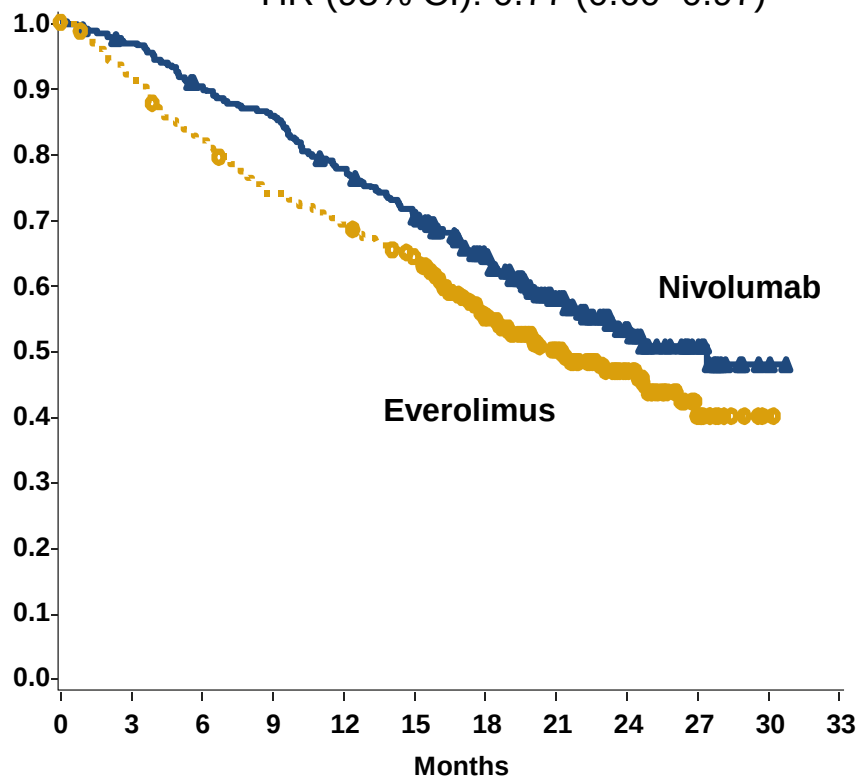
No. of patients at risk

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

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

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

HR (95% CI): 0.77 (0.60–0.97)



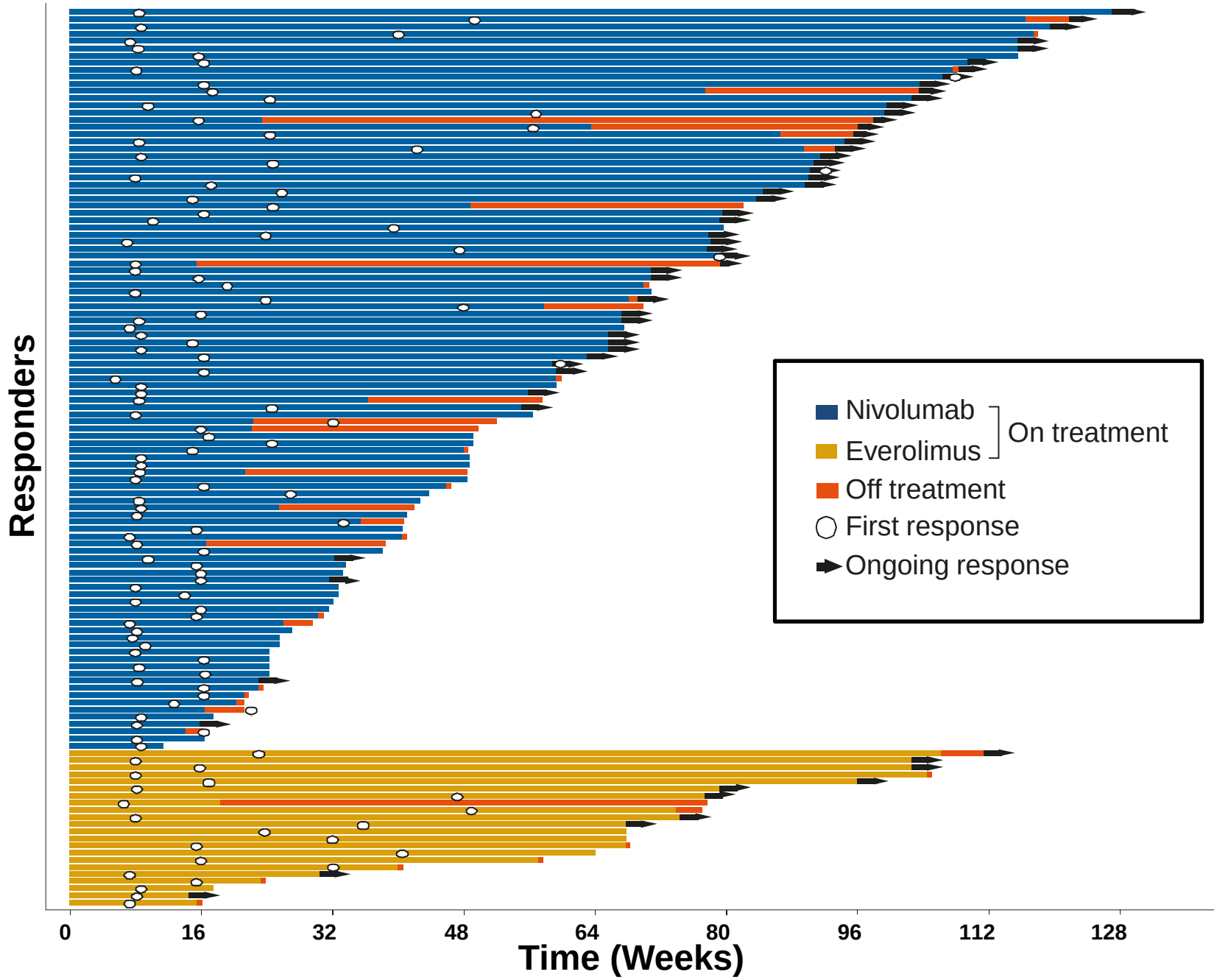
Nivolumab	276	265	245	233	210	189	145	94	48	22	2	0
Everolimus	299	267	238	214	200	182	137	92	51	16	1	0

Antitumor activity

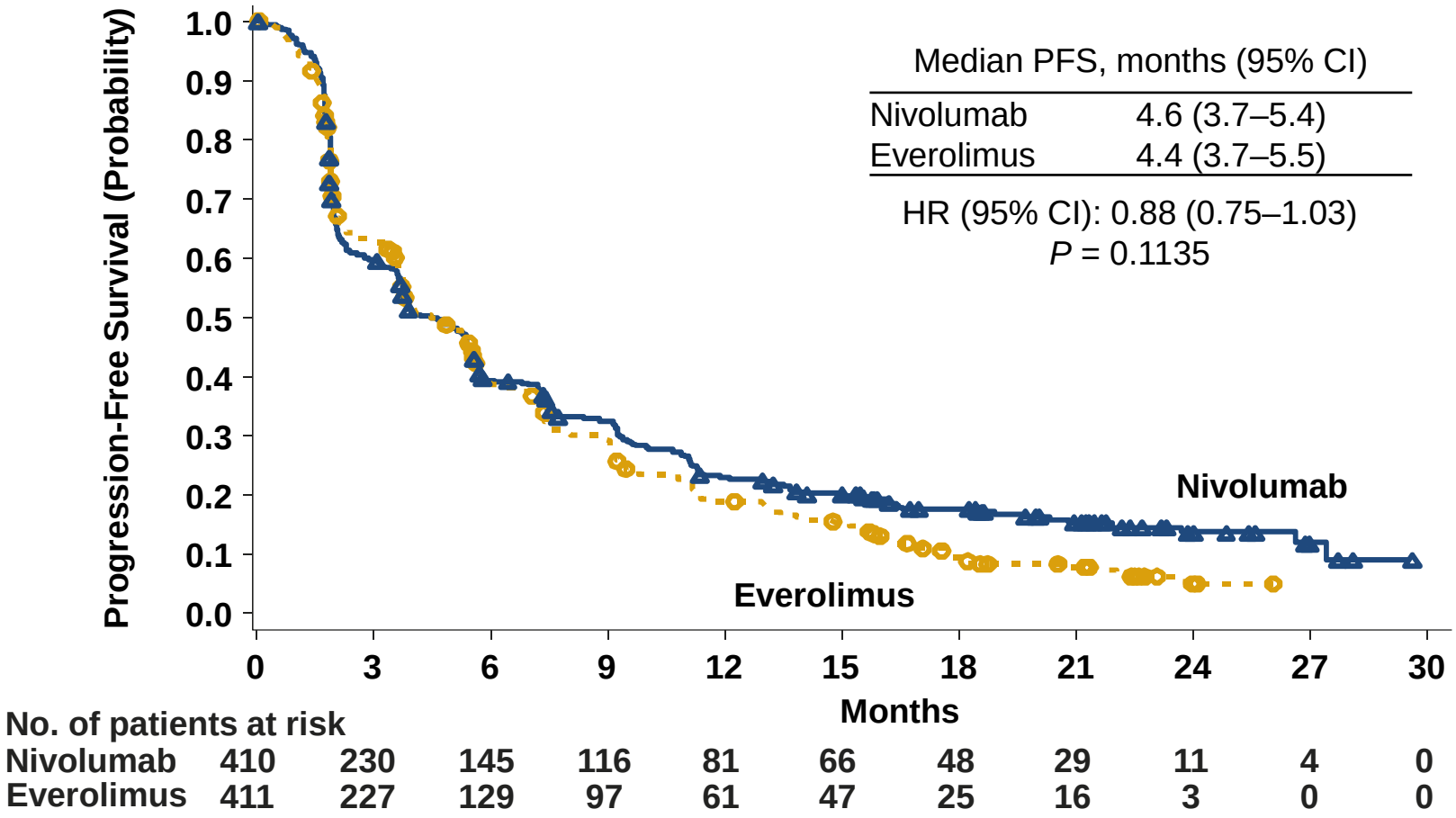
	Nivolumab N = 410	Everolimus N = 411
Objective response rate, %	25	5
Odds ratio (95% CI)	5.98 (3.68–9.72)	
P value	<0.0001	
Best overall response, %		
Complete response	1	1
Partial response	24	5
Stable disease	34	55
Progressive disease	35	28
Not evaluated	6	12
Median time to response, months (range)	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)

*For patients without progression or death, duration of response is defined as the time from the first response (CR/PR) date to the date of censoring.

Response characteristics



Progression-free survival



- In a post-hoc analysis of patients who had not progressed or died at 6 months, median PFS was 15.6 months for nivolumab vs 11.7 months for everolimus (HR (95% CI): 0.64 (0.47–0.88))

Safety Summary

	Nivolumab N = 406		Everolimus N = 397	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Treatment-related AEs, %	79	19	88	37
Treatment-related AEs leading to discontinuation, %	8	5	13	7
Treatment-related deaths, n	0		2[a]	

- 44% of patients in the nivolumab arm and 46% of patients in the everolimus arm were treated beyond progression

[a] Septic shock (1), bowel ischemia (1).

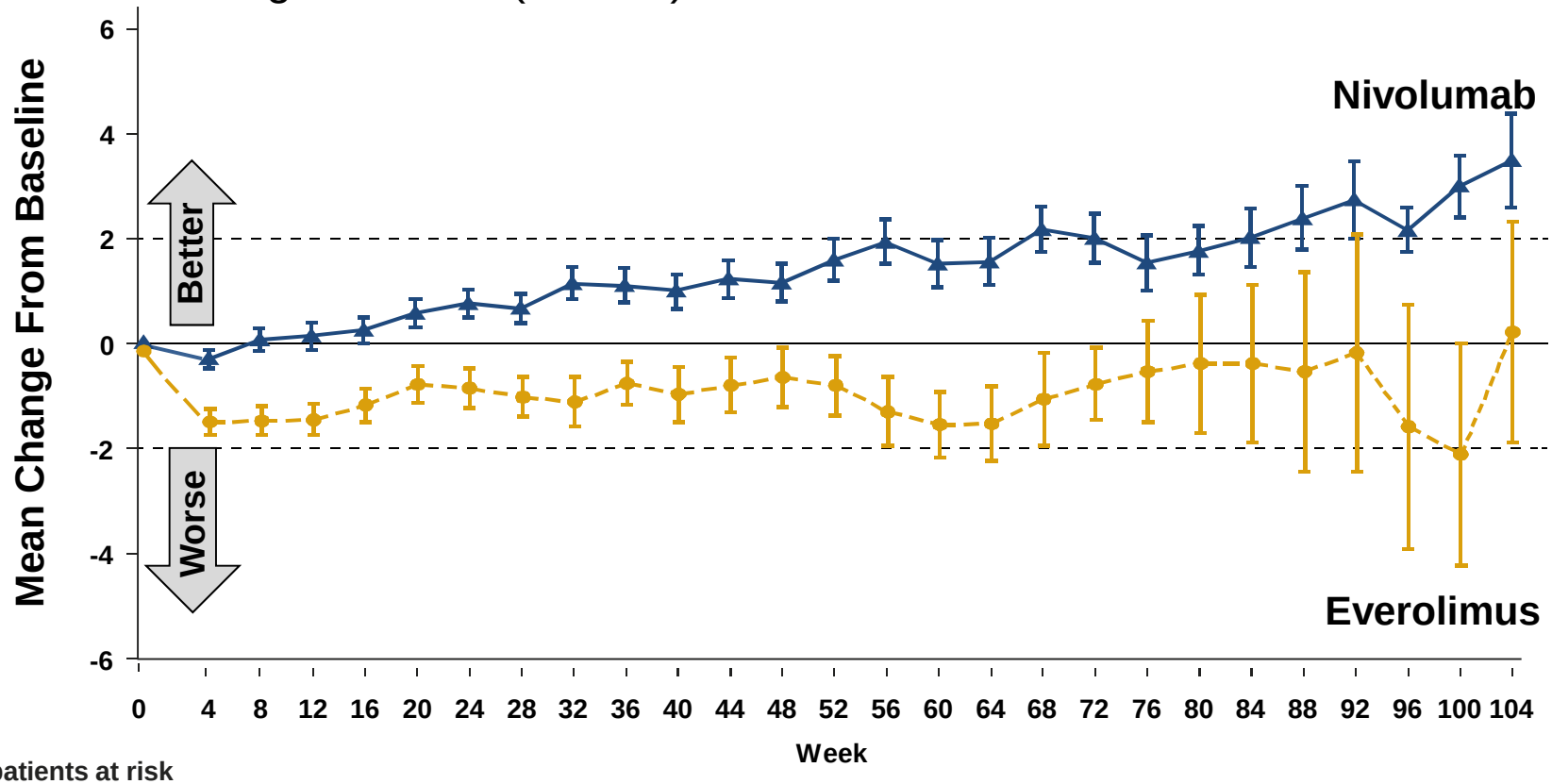
Treatment-related AEs in ≥10% of patients

	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

[a] Grade 4 AEs not listed in table: increased blood creatinine (1), acute kidney injury (1), anaphylactic reaction (1).
[b] Grade 4 AEs not listed in table: increased blood triglycerides (2), acute kidney injury (1), sepsis (1), chronic obstructive pulmonary disorder (1), increased blood cholesterol (1), neutropenia (1), pneumonia (1).

Change from baseline in quality of life scores on FKSI-DRS

- Mean change from baseline in the nivolumab group increased over time and differed significantly from the everolimus group at each assessment through week 76 ($P<0.05$)



No. of patients at risk

Nivolumab	362	334	302	267	236	208	186	164	159	144	132	119	112	97	90	89	81	72	63	59	53	44	43	31	30	26	20
Everolimus	344	316	270	219	191	157	143	122	102	97	87	74	73	63	58	49	44	35	30	28	24	21	15	12	12	9	9

Questionnaire completion rate: ≥80% during the first year of follow-up.

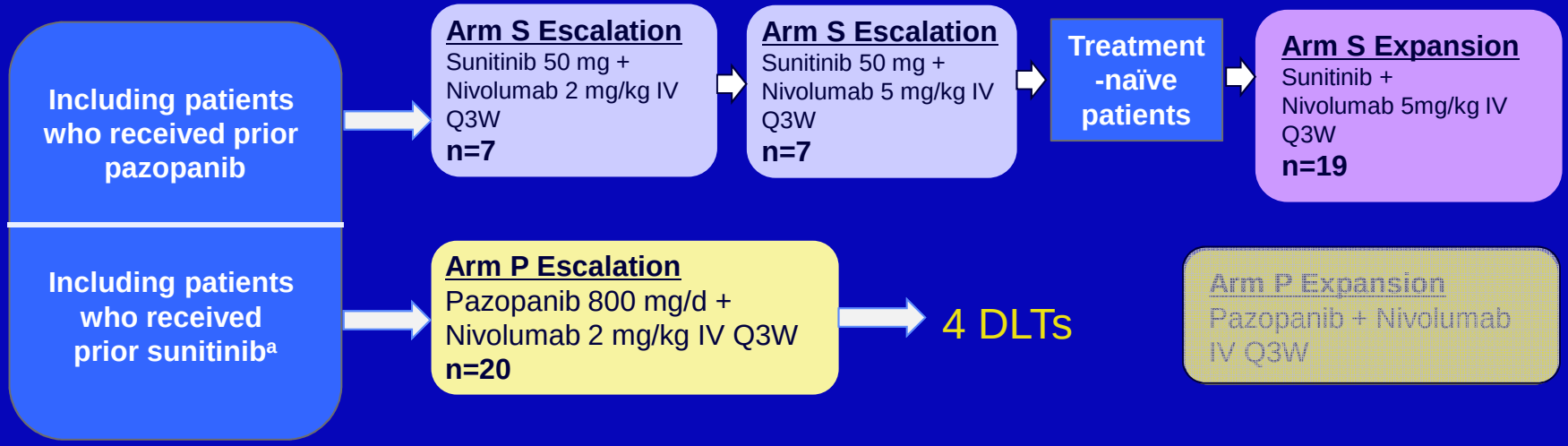
Conclusions (1)

- CheckMate 025 met its primary endpoint, demonstrating superior OS with nivolumab versus everolimus
- This is the only phase III trial to demonstrate a survival advantage in previously-treated patients with mRCC versus standard therapy
- Survival benefit with nivolumab was consistent across subgroups and irrespective of PD-L1 expression
- Nivolumab was associated with a greater number of objective responses

Conclusions (2)

- Nivolumab was associated with fewer grade 3 and 4 treatment-related AEs and fewer treatment-related AEs leading to discontinuation than everolimus
- FKSI-DRS results demonstrate a consistent improvement in QoL with nivolumab versus everolimus
- The superior survival and favorable safety profile in this phase III trial provide evidence for nivolumab as a potential new treatment option for previously treated patients with mRCC

Nivolumab + sunitinib or pazopanib in patients with mRCC



S + N arm

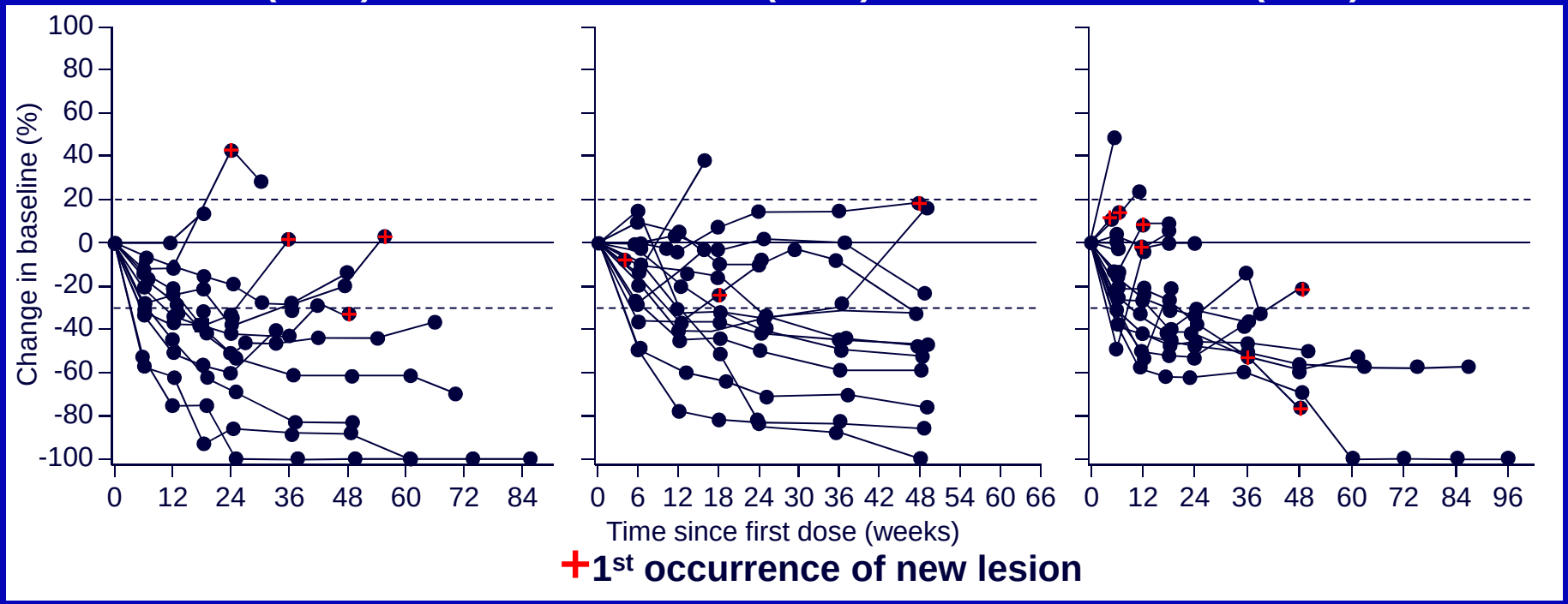
- S + N2: n=7 pretreated patients
- S + N5: n=7 pretreated patients
- S + N5 expansion: n=19 treatment-naïve patients

P + N arm

- P + N2: n=20 pretreated patients

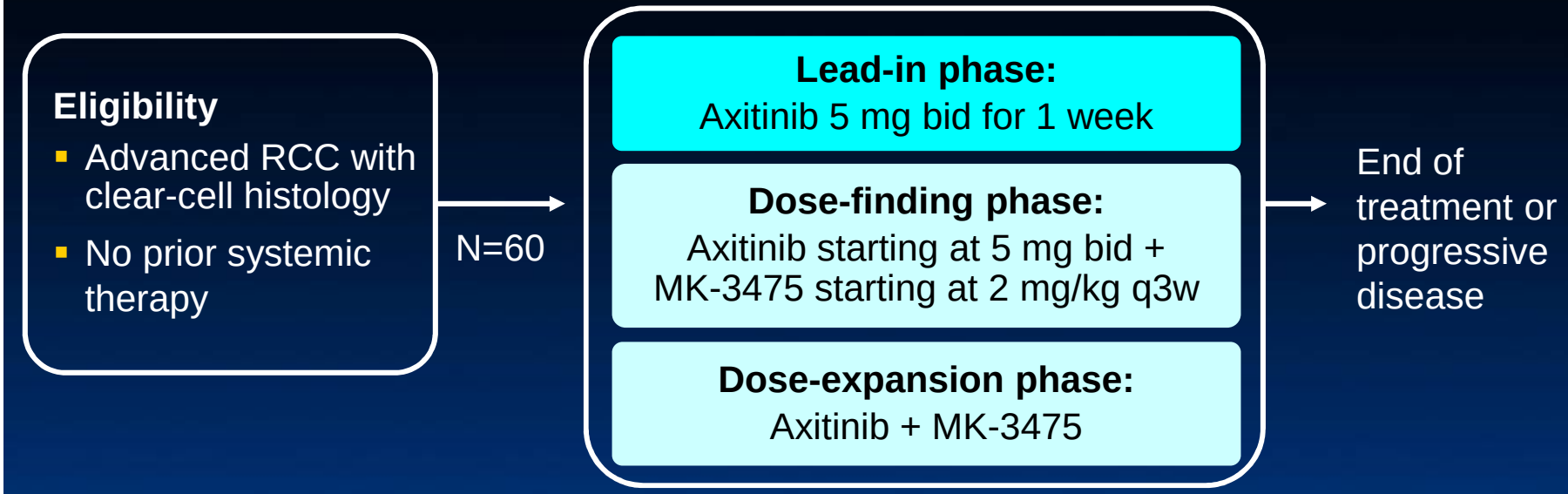
Change from baseline in target tumor burden by prior treatment status

ORR 52% sunitinib arm; 45% pazo arm



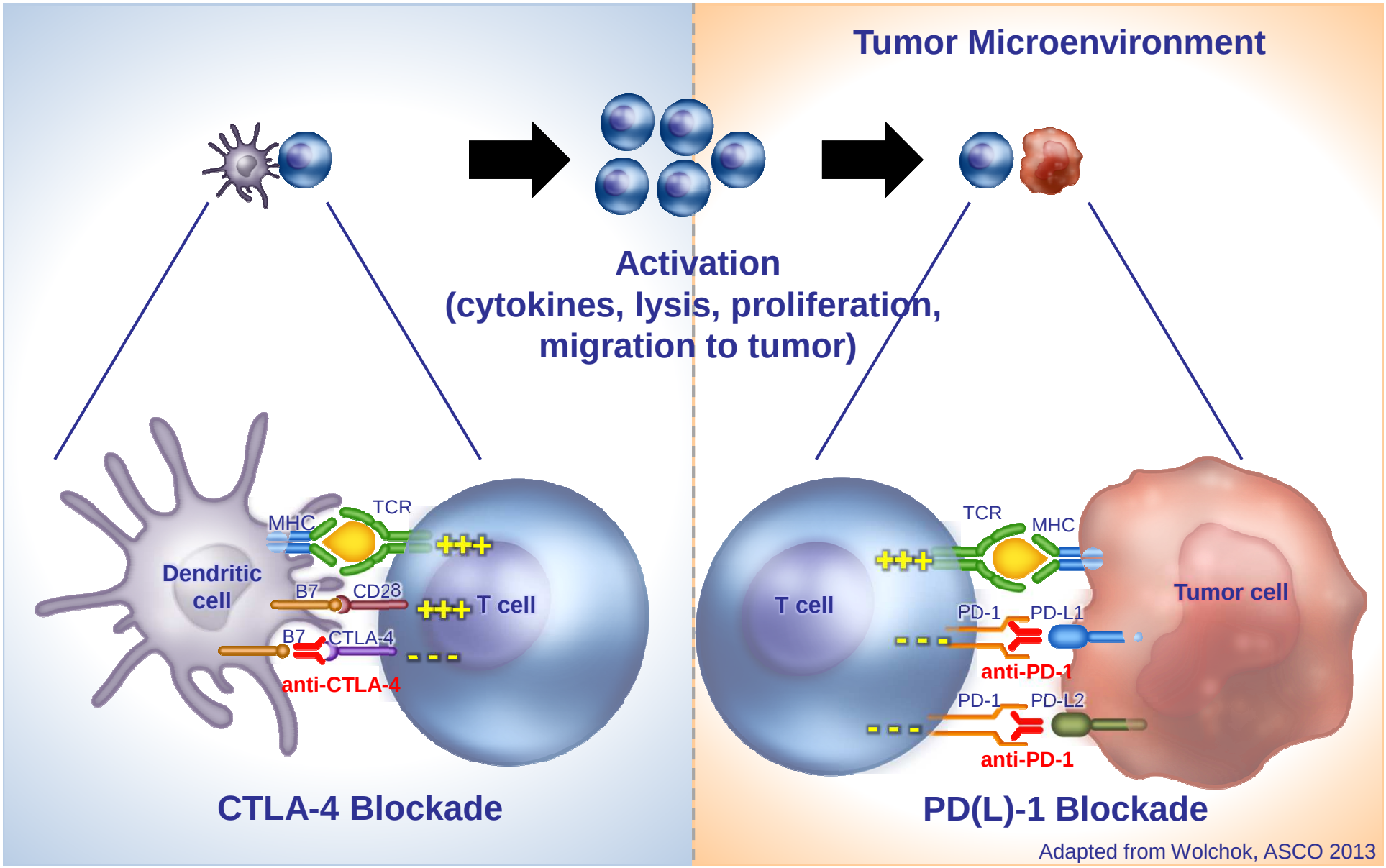
Positive change in tumor burden indicates tumor growth; negative change indicates tumor reduction.

Axitinib Plus Pembrolizumab (MK-3475)



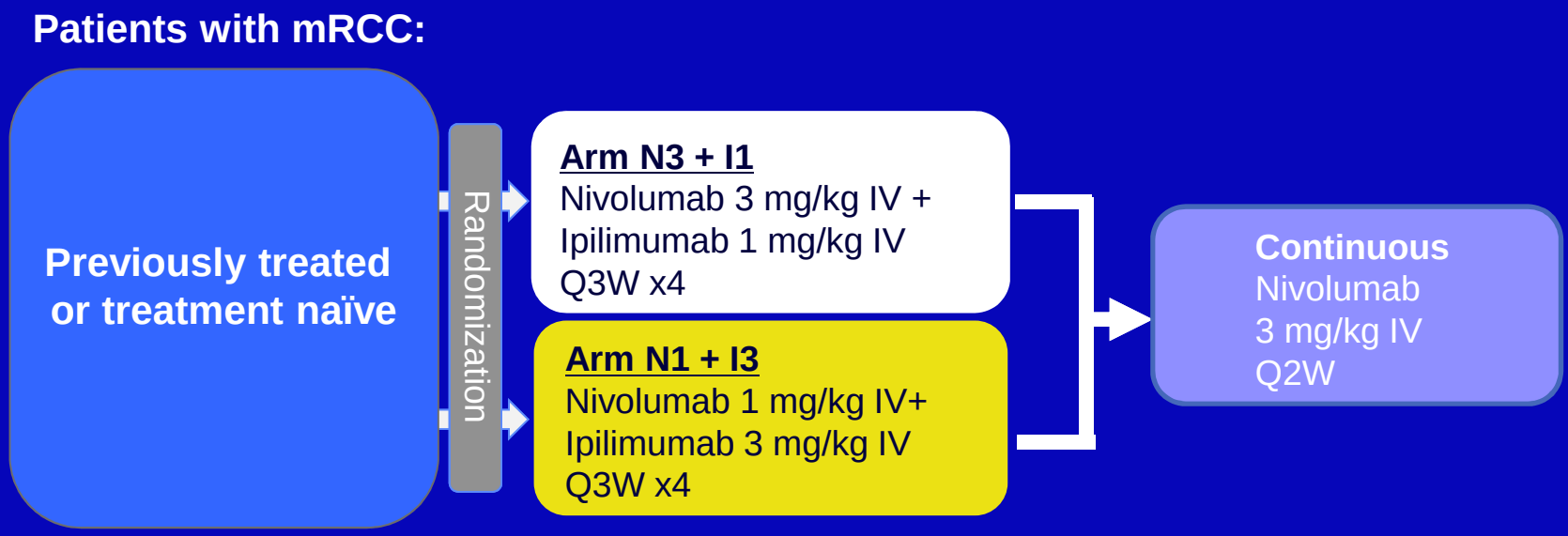
- Primary endpoint: Safety, maximum tolerated dose (dose-limiting toxicities through Week 6 of dose-finding phase, 2 cycles)
- Select secondary endpoints: ORR, TTP, PFS (median, 1 year, 18 months), OS, biomarkers including PD-L1
- Sponsor: Pfizer (collaborator: Merck)
- Estimated primary/study completion date: April 2016

Blocking CTLA-4 and/or PD-1



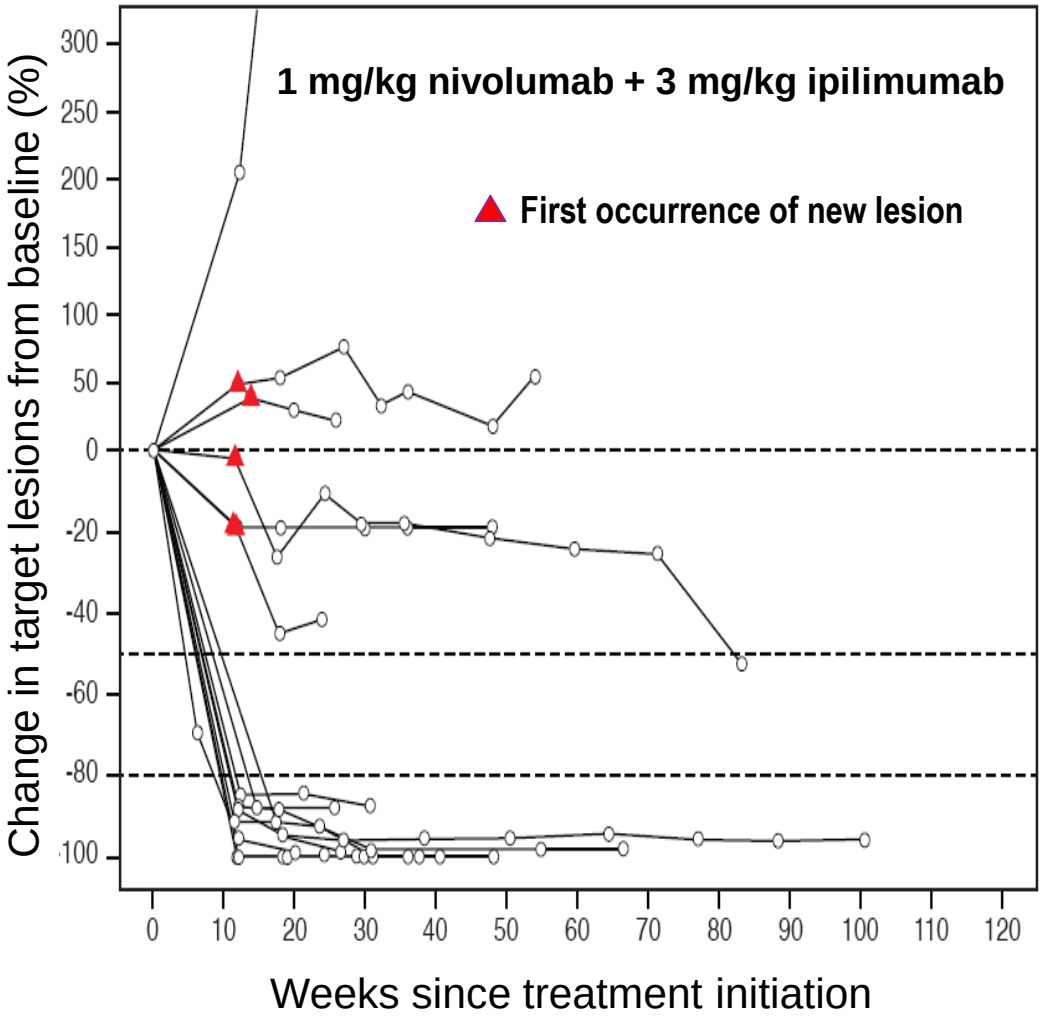
Adapted from Wolchok, ASCO 2013

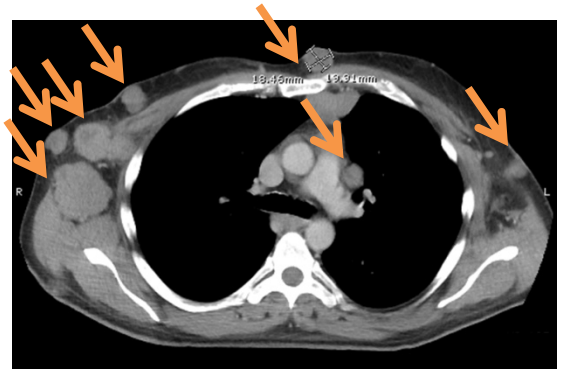
Nivolumab + Ipilumimab study design



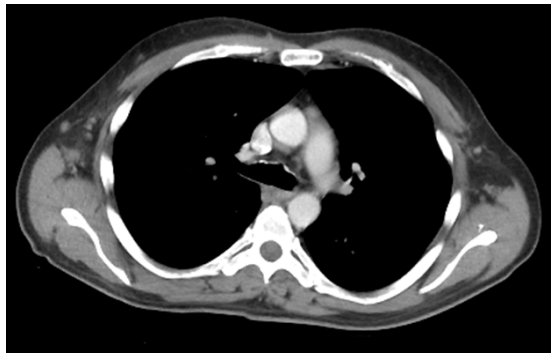
- Primary endpoint: Safety (AEs, laboratory tests)
- Secondary endpoint: Efficacy (ORR, duration of response, PFS)
- Exploratory endpoint: Response by tumor PD-L1 status
- Study assessments: Tumor response (RECIST v1.1) evaluated at screening, every 6 weeks (first 4 assessments), then every 12 weeks until disease progression

Rapid and Durable Changes in Target Lesions





Pre-treatment

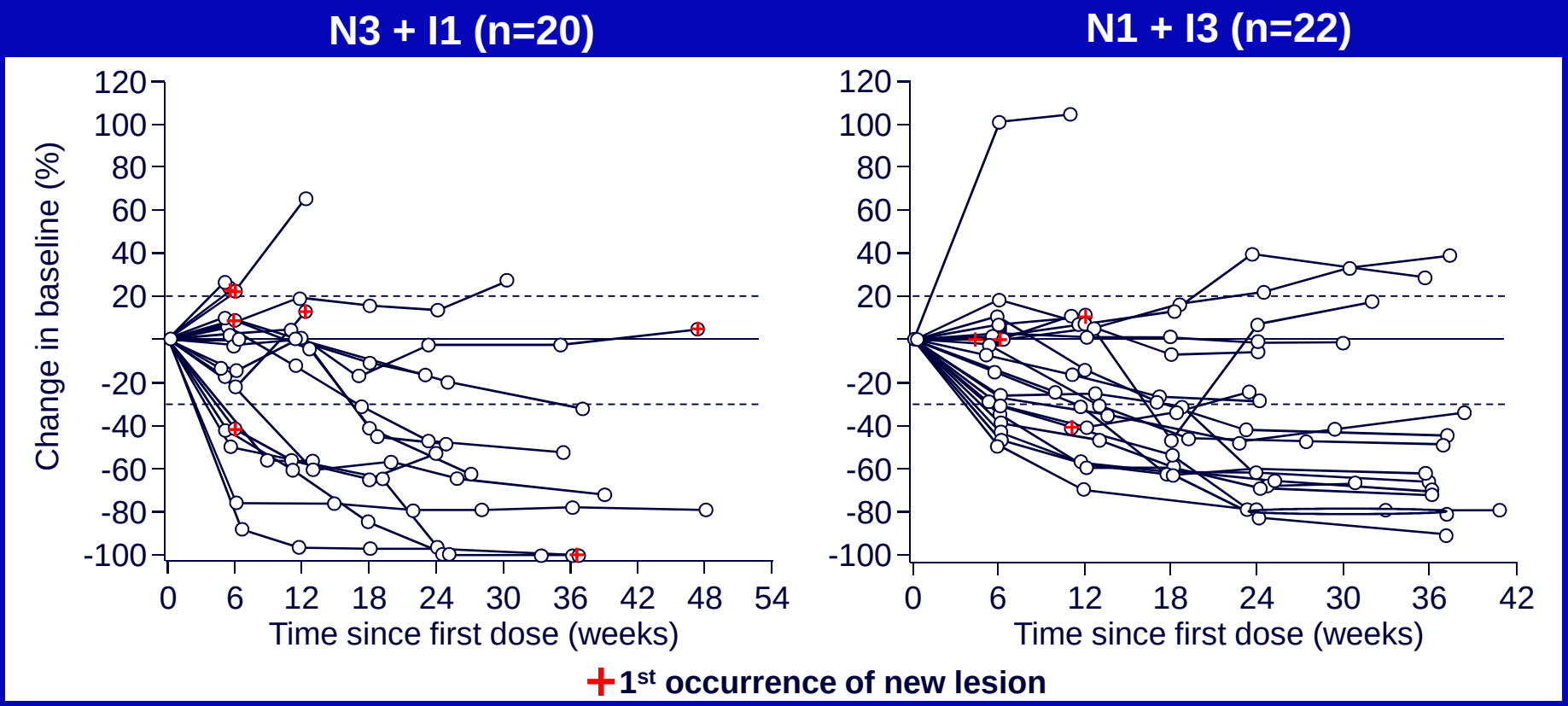


12 weeks

- A 52-year-old patient presented with extensive nodal and visceral disease
- Baseline LDH was elevated (2.3 x ULN); symptoms included nausea and vomiting
- Within 4 wk, LDH normalized and symptoms resolved
- At 12 wk, there was marked reduction in all areas of disease as shown

Change from baseline in target tumor burden

ORR about 45% in both arms

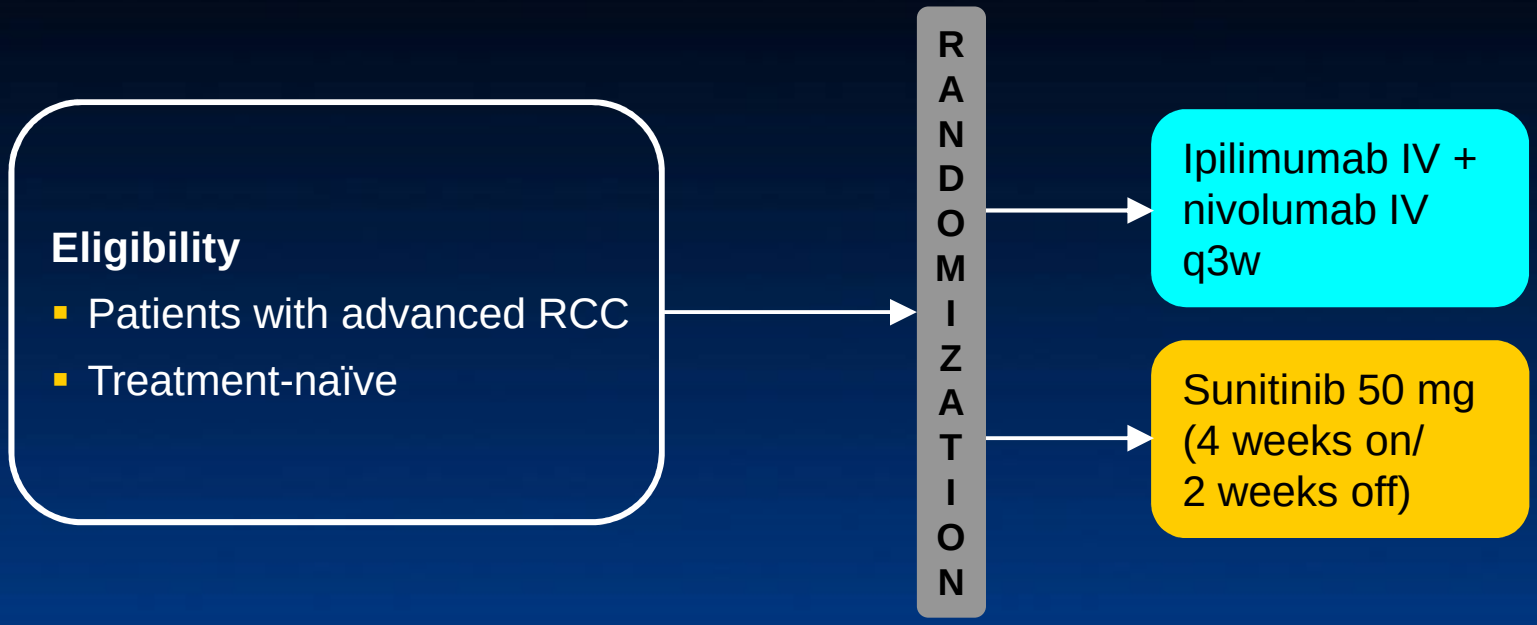


Treatment-related AEs (≥10% of patients)

	N3 + I1 (n=21)		N1 + I3 (n=23)	
	All	Grade 3-4	All	Grade 3-4
Total patients with an event, n (%)	16 (76.2)	6 (28.6)	23 (100)	14 (60.9)
Fatigue	11 (52.4)	0	16 (69.6)	2 (8.7)
Rash	8 (38.1)	0	4 (17.4)	0
Pruritus	6 (28.6)	0	5 (21.7)	0
Diarrhea	6 (28.6)	1 (4.8)	8 (34.8)	3 (13.0)
Dry skin	4 (19.0)	0	3 (13.0)	0
Nausea	4 (19.0)	0	9 (39.1)	0
Pyrexia	4 (19.0)	0	4 (17.4)	0
Chills	3 (14.3)	0	2 (8.7)	0
Constipation	3 (14.3)	0	2 (8.7)	0
Hypothyroidism	3 (14.3)	0	6 (26.1)	0
Lipase increased	3 (14.3)	3 (14.3)	6 (26.1)	6 (26.1)
Amylase increased	1 (4.8)	1 (4.8)	3 (13.0)	1 (4.3)
ALT increased	1 (4.8)	0	9 (39.1)	6 (26.1)
AST increased	0	0	9 (39.1)	3 (13.0)

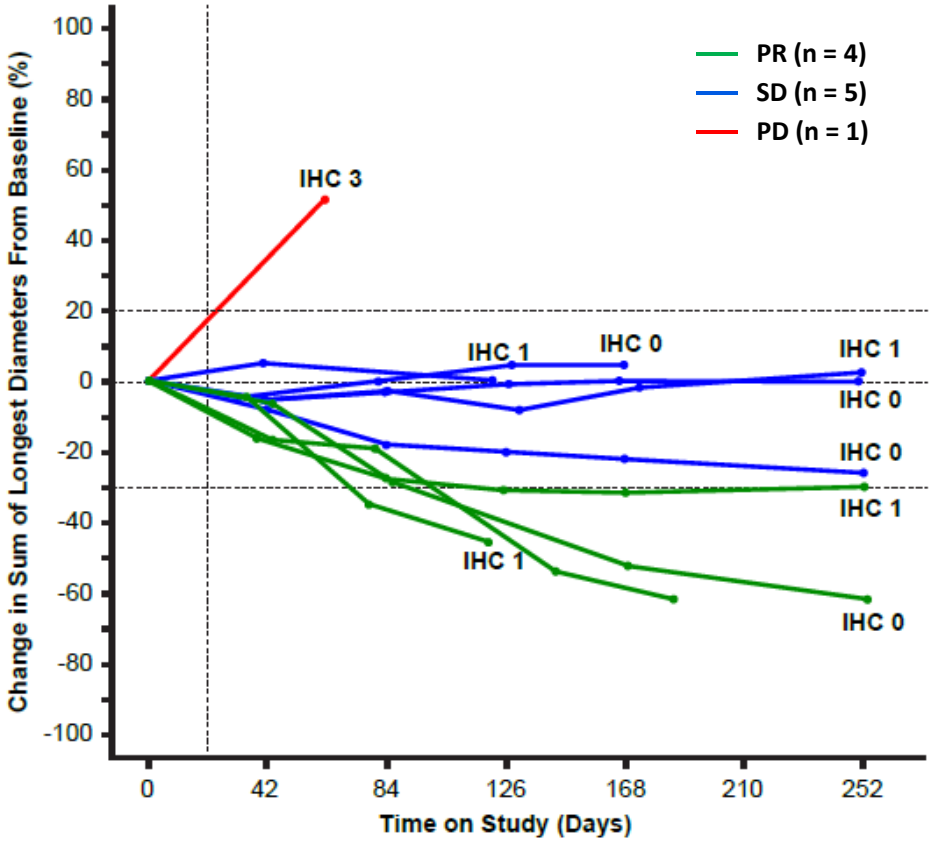
- **No grade 5 treatment-related AEs were reported.**

A Phase III Study of Nivolumab in Combination with Ipilimumab in 1st Line mRCC



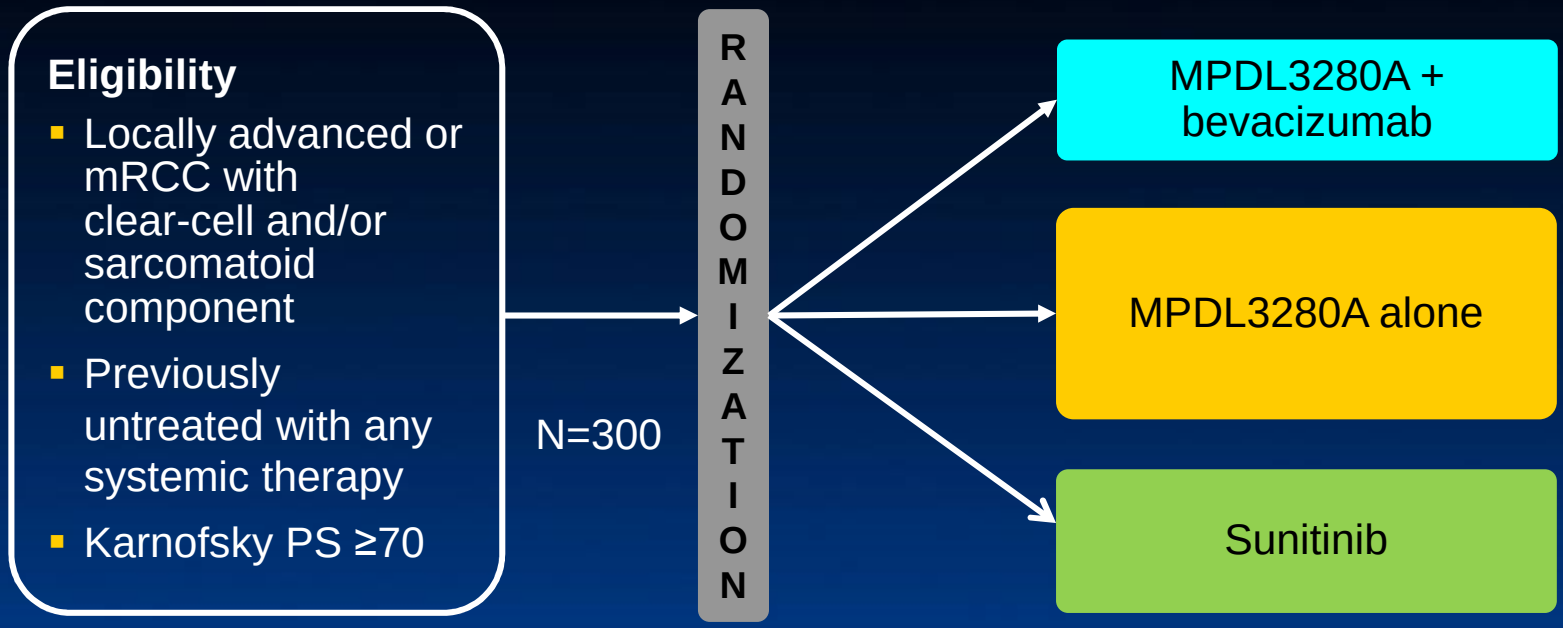
MPDL3280A + Bevacizumab: Summary of Phase Ib Results

- Safety
  - All patients in Arm A (n = 35) experienced an AE, with 49% experiencing a G3-4 AE, regardless of attribution
  - 1 MPDL3280A-related Grade 3 AE occurred (1 case of neutropenia in Arm A)
  - No Grade 4 AEs or deaths were attributed to MPDL3280A
- Efficacy in patients with 1L clear cell RCC
  - 4 of 10 patients demonstrated an objective response
  - 5 of 10 patients experienced stable disease
  - Responding patients included 2 with IHC (IC) 1, 1 with IHC (IC) 0 and 1 with IHC (IC) unknown



[a] Lieu et al., abstract 1049O, presented Saturday.
Patients dosed by Apr 7, 2014; data cutoff Jul 7, 2014; Unconfirmed best responses by RECIST v1.1.
IHC 3: ≥ 10% of ICs are PD-L1+; IHC 2: ≥ 5% and < 10% of ICs are PD-L1+. IHC 1: ≥ 1% and < 5% of ICs are PD-L1+; IHC 0: < 1% ICs are PD-L1+.

MPDL3280A as Monotherapy or in Combination with Bevacizumab vs Sunitinib: Phase II Study in Untreated Advanced RCC



- Primary endpoints: PFS per RECIST v.1.1 via central ICR assessment
- Secondary endpoints: PFS using investigator assessment per immune-related criteria, ORR, duration of response, OS, duration of response and PFS in patients progressing on sunitinib and MPDL alone arms who subsequently cross over to combination, safety, PK of MPDL3280A alone and in combination with bevacizumab

www.clinicaltrials.gov (NCT01984242)

Checkpoint Inhibitors in Metastatic RCC

Study	Population	Design	ORR	PFS
Nivolumab Dose-finding	Treatment-refractory	Randomized Phase II	~20%	~4 months
Nivolumab + TKI (sunitinib or pazopanib)	Treatment-naïve and refractory	Single-arm phase II	~50%	~10 months
Nivolumab + ipilumimab	Treatment-naïve and refractory	Single-arm phase II	~45%	~9 months

Motzer et al. ASCO 2013, Amin et al. ASCO 2013, Hammers et al. ASCO 2013

PD-L1 Expression and Response

Agent(s)	Tumor Type	n	RR (%) PD-L1 pos	RR(%) PD-L1 neg
Nivolumab[1]	Multiple Solid Tumors	42	36%	0%
MPDL3280A[2]	Kidney Cancer	47	20%	10%
Nivolumab[3]	Melanoma	34	44%	17%
Nivo/Ipi[4]	Melanoma	27	40%	47%

[1]Topalian et al, NEJM, 2012, [2]Cho et al ASCO 2013, [3]Grosso et al ASCO 2013, [4]Wolchok et al, NEJM 2013

Overview

- General Principles
- Renal Cancer
- Urothelial Cancer
- Prostate Cancer

Immunotherapy in bladder cancer began with BCG

- **Febrile response following intravesicular instillation of BCG has been shown to be good prognostic factor and correlates with longer recurrence free survival**

- **Effective BCG response is dependent on CD4 and CD8 T-cell mediated inflammatory monocyte recruitment**

- **PPD positivity prior to intravesicular instillation of BCG correlated with improved recurrence free survival and that pre-existing BCG-specific T-cells improved intravesicular therapy**

Biot et al. Sci Transl Med 2012

Current immunotherapeutic approaches in bladder cancer

- **Equivocal results with IFN-α-2b**
  - **No advantage when used with BCG for BCG naïve patients (Neppel et al. J Urol 2010)**
  - **May have some benefit in BCG failure patients (O'Donnell et al. J Urol 2004)**

- **Carthon et al. *Clin Cancer Res 2010* in a dose escalation trial for ipilimumab in localized bladder cancer showed limited toxicity and increased frequency of $CD4^{+}$ $ICOS^{high}$ (activated T-cells) in systemic circulation**

- **Powles et al. *Nature* 2014 demonstrated efficacy for PD-L1 blockade in advanced urothelial tumors**

- **2015 ASCO - Petrylak et al. A phase Ia study of MPDL3280A. Updated response and survival data in urothelial bladder cancer**

  -Atezolizumab (formerly known as MPDL3280A) was well tolerated and had durable activity in UBC pts. Response, PFS and OS data are promising for IHC 2/3 and IHC 0/1 UBC pts vs historic controls. Response also correlated with in-tumor and blood-based biomarkers

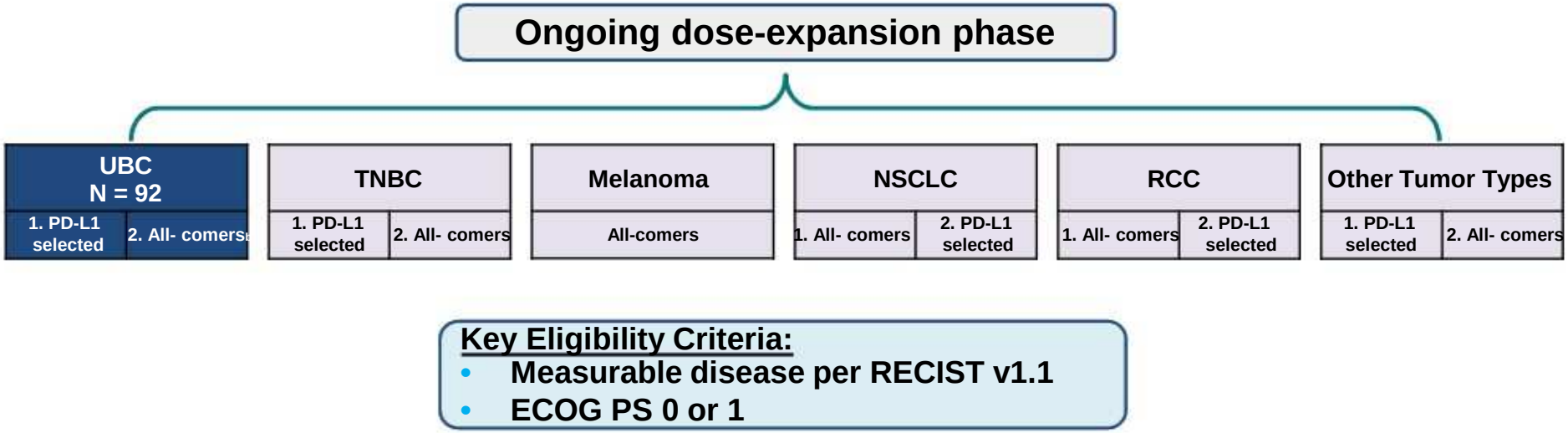
A Phase Ia Study of Atezolizumab (MPDL3280A/Anti-PDL1): Updated Response and Survival Data in Urothelial Bladder Cancer (UBC)

Daniel P. Petrylak,[1] Thomas Powles,[2] Joaquim Bellmunt,[3] Fadi Braiteh,[4] Yohann Loriot,[5] Cristina Cruz,[6] Howard A. Burris III,[7] Joseph W. Kim,[1] Howard M. Mackey,[8] Zachary S. Boyd,[8] Priti S. Hegde,[8] Oyewale Abidoye,[8] Nicholas J. Vogelzang[9]

[1]Yale Cancer Center, New Haven, CT; [2]Barts Cancer Institute, Queen Mary University of London, London, UK; [3]Bladder Cancer Center, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA; [4]Comprehensive Cancer Centers of Nevada, Las Vegas, NV; [5]Gustave Roussy, Villejuif, France; [6]Vall d'Hebron University Hospital, Barcelona, Spain; [7]Sarah Cannon Research Institute, Nashville, TN; [8]Genentech, Inc., South San Francisco, CA; [9]University of Nevada School of Medicine, Las Vegas, NV, and US Oncology/Comprehensive Cancer Centers of Nevada, Las Vegas, NV

Petrylak, D.P., ***et al. ASCO Meeting Abstracts*** 33, 4501 (2015).

Atezolizumab (MPDL3280A): UC Cohort

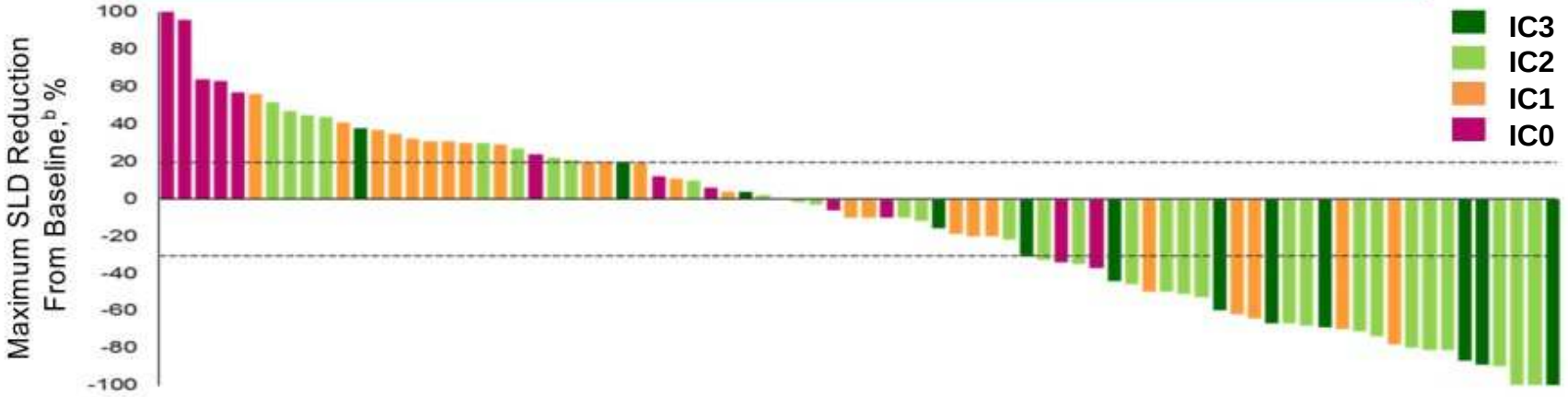


- **Atezolizumab (MPDL3280A) administered IV Q3W 15 mg/kg or 1200 mg flat dose**

Petrylak, D.P., ***et al. ASCO Meeting Abstracts*** 33, 4501 (2015)

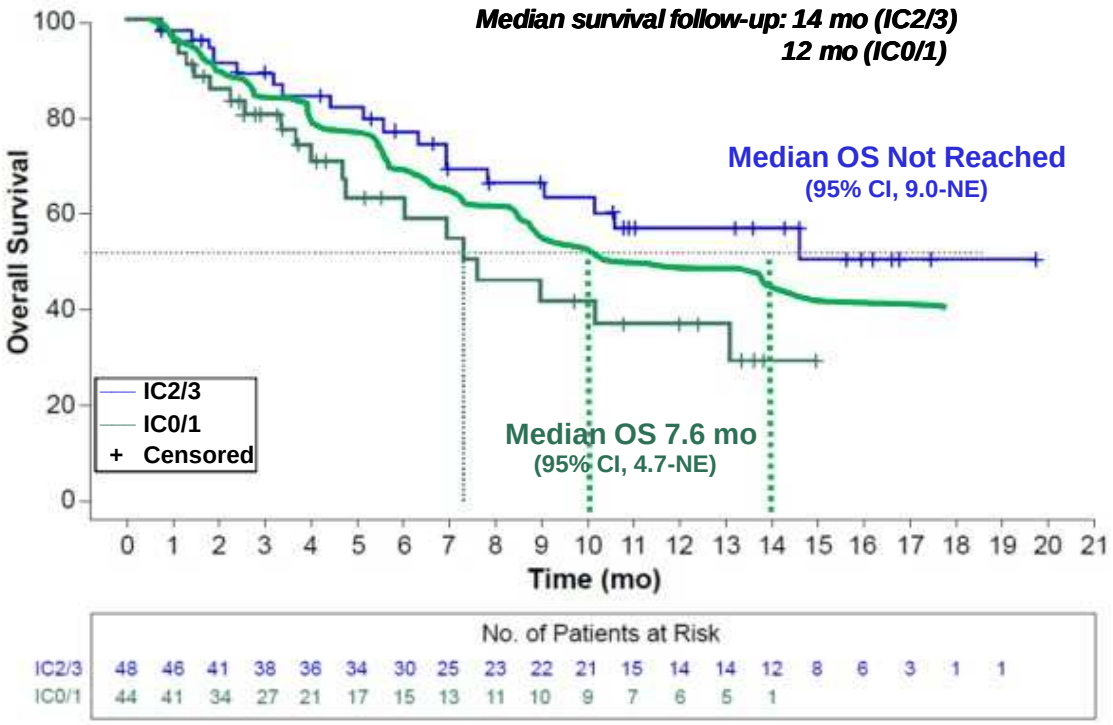
Atezolizumab (MPDL3280A): Response

Overall Response Rate = 34% (30/87)



Petrylak, D.P., ***et al. ASCO Meeting Abstracts*** 33, 4501 (2015).

Atezolizumab (MPDL3280A): Survival



Survival[a] N = 92	IC2/3 n = 48	IC0/1 n = 44
OS		
Median OS (range)	Not reached (1 to 20+ mo)	8 mo (1 to 15+ mo)
1-y survival (95% CI)	57% (41-73)	38% (19-56)

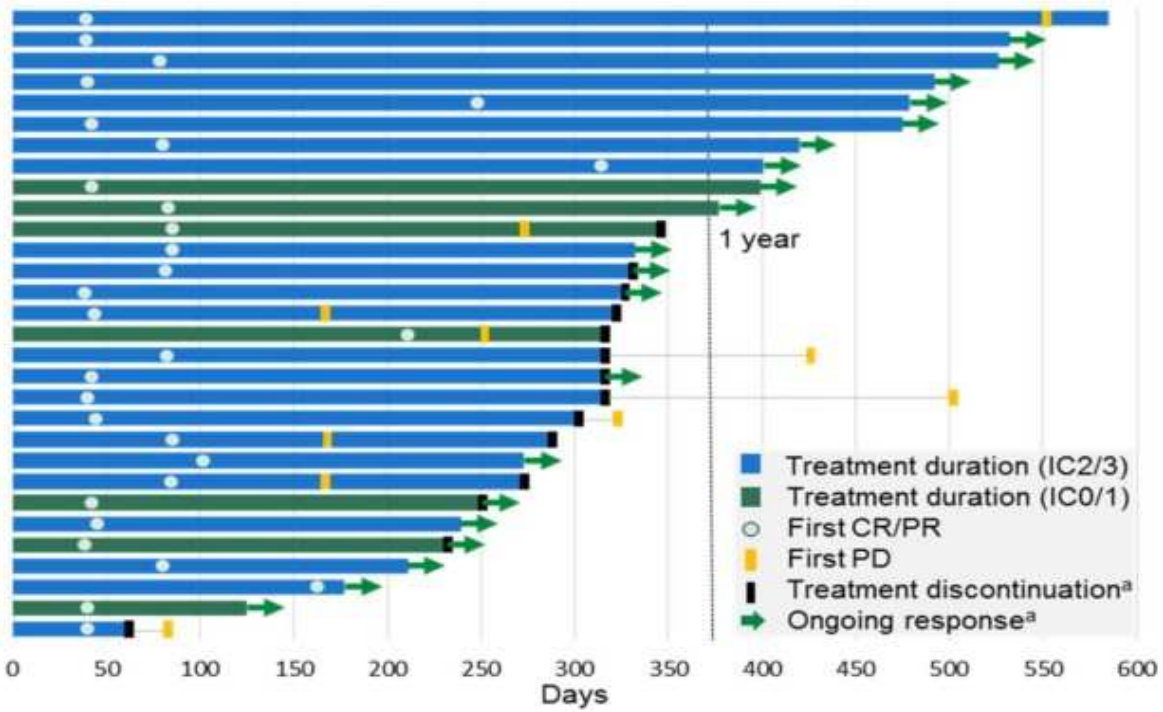
Estimated overall results

- **Median OS 10-14 mo**
- **48% alive at 12 months**

Data cutoff, Dec 2, 2014. Reference: 1. Genentech, unpublished data.

Slide adapted, courtesy Noah Hahn, ASCO 2015

Atezolizumab (MPDL3280A): Duration of Treatment and Response in UC



- **Median duration of response not yet reached in either IC group (range, 0+ to 43 mo)**
- **Median time to response was 62 days**
- **20 of 30 responding patients had ongoing responses at the time of data cutoff**

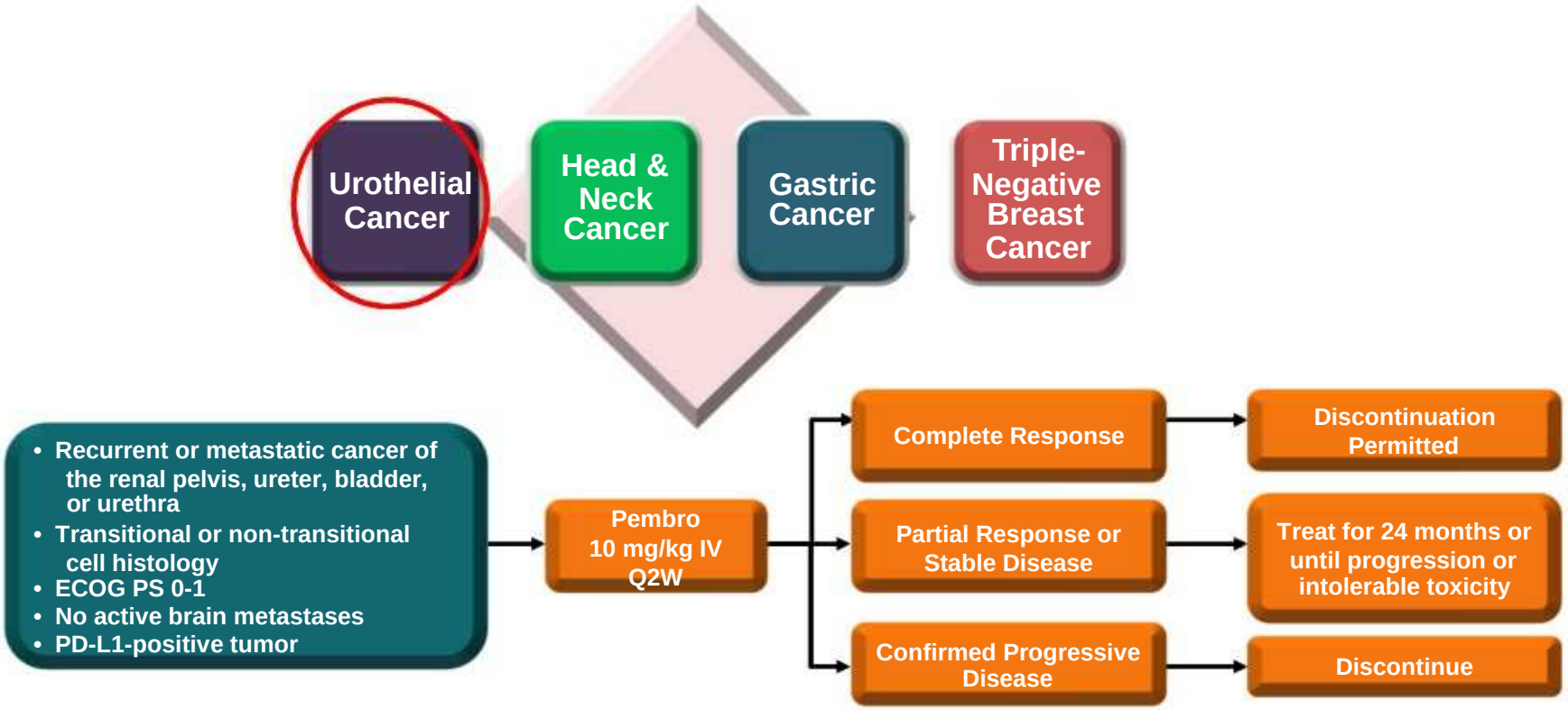
Petrylak, D.P., ***et al. ASCO Meeting Abstracts*** 33, 4501 (2015)

Pembrolizumab (MK-3475) for Advanced Urothelial Cancer: Updated Results and Biomarker Analysis from KEYNOTE-012

Elizabeth R. Plimack,[1] Joaquim Bellmunt,[2] Shilpa Gupta,[3] Raanan Berger,[4] Bruce Montgomery,[5] Karl Heath,[6] Jonathan Juco,[6] Kenneth Emancipator,[6] Kumudu Pathiraja,[6] Jared Lunceford,[6] Rodolfo Perini,[6] Peter H. O'Donnell[7]

[1]Fox Chase Cancer Center, Philadelphia, PA, USA,
[2]Dana-Farber Cancer Institute, Boston, MA, USA,
[3]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA,
[4]Sheba Medical Center, Tel Hashomer, Israel, [5]University of Washington, Seattle, WA, USA, [6]Merck & Co., Inc., Kenilworth, NJ, USA, [7]University of Chicago, Chicago, IL, USA

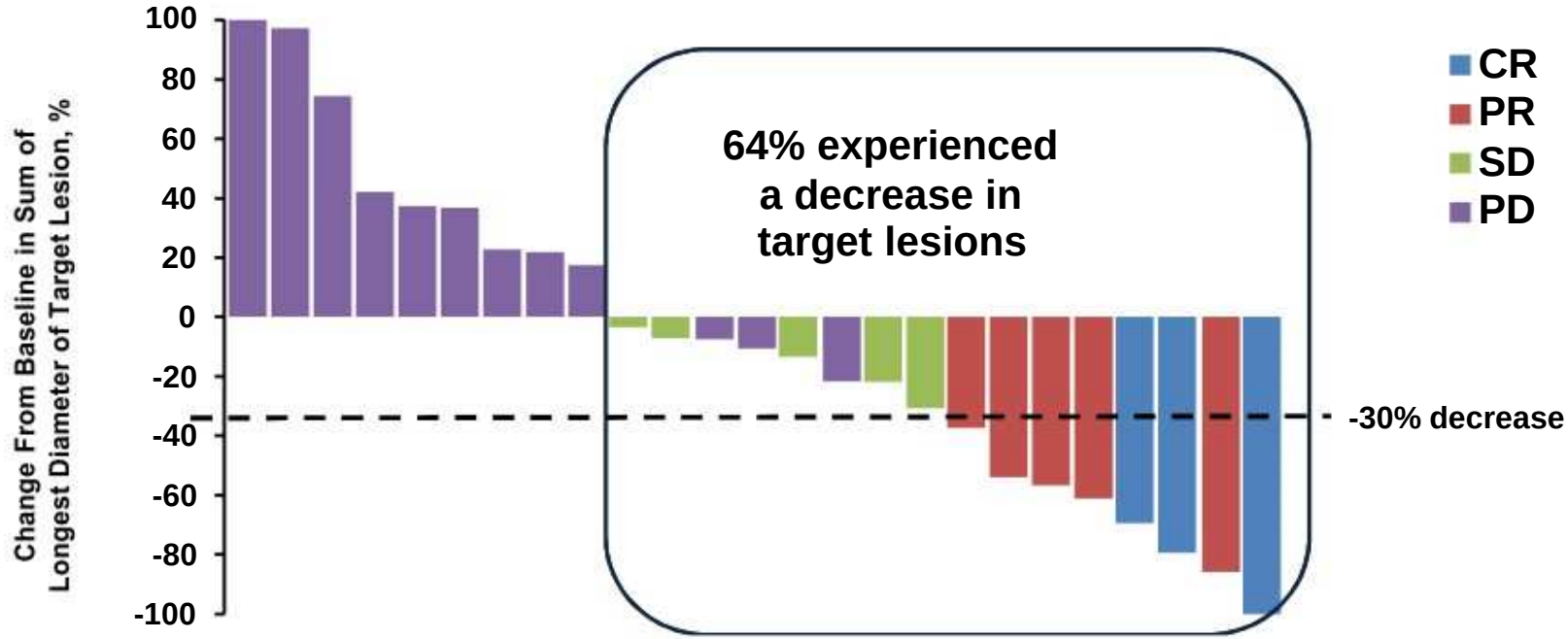
Pembrolizumab KEYNOTE-012 : UC Cohort



Plimack, E.R., ***et al. ASCO Meeting Abstracts*** 33, 4502 (2015).

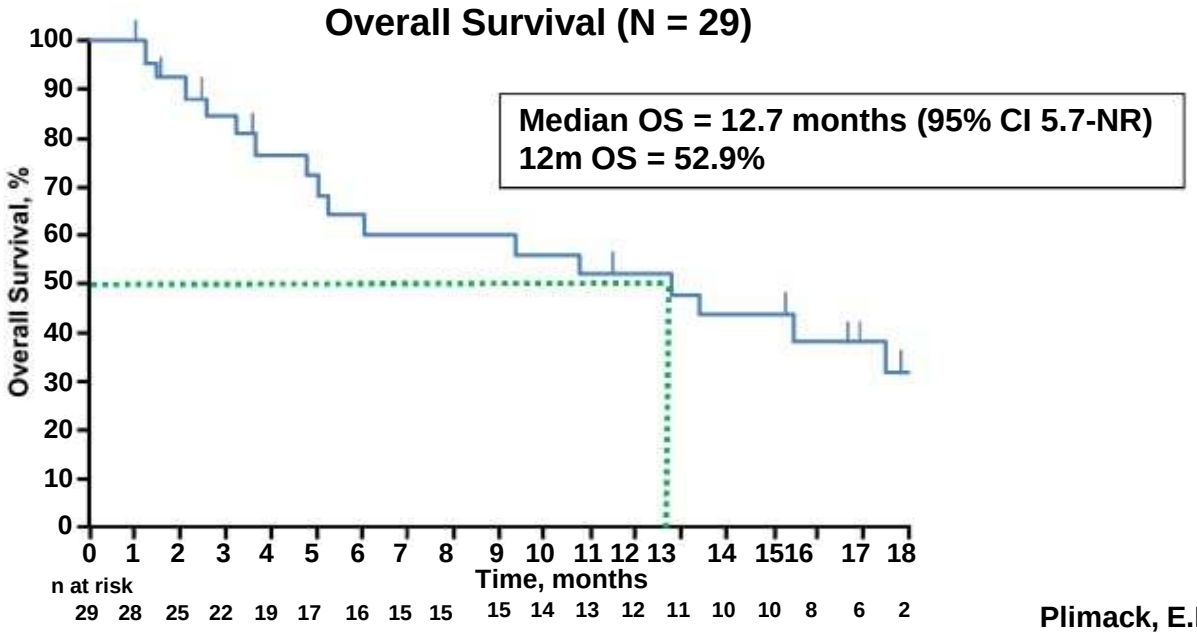
Pembrolizumab: Response

Overall Response Rate = 28% (8/33)



Plimack, E.R., ***et al. ASCO Meeting Abstracts*** 33, 4502 (2015).

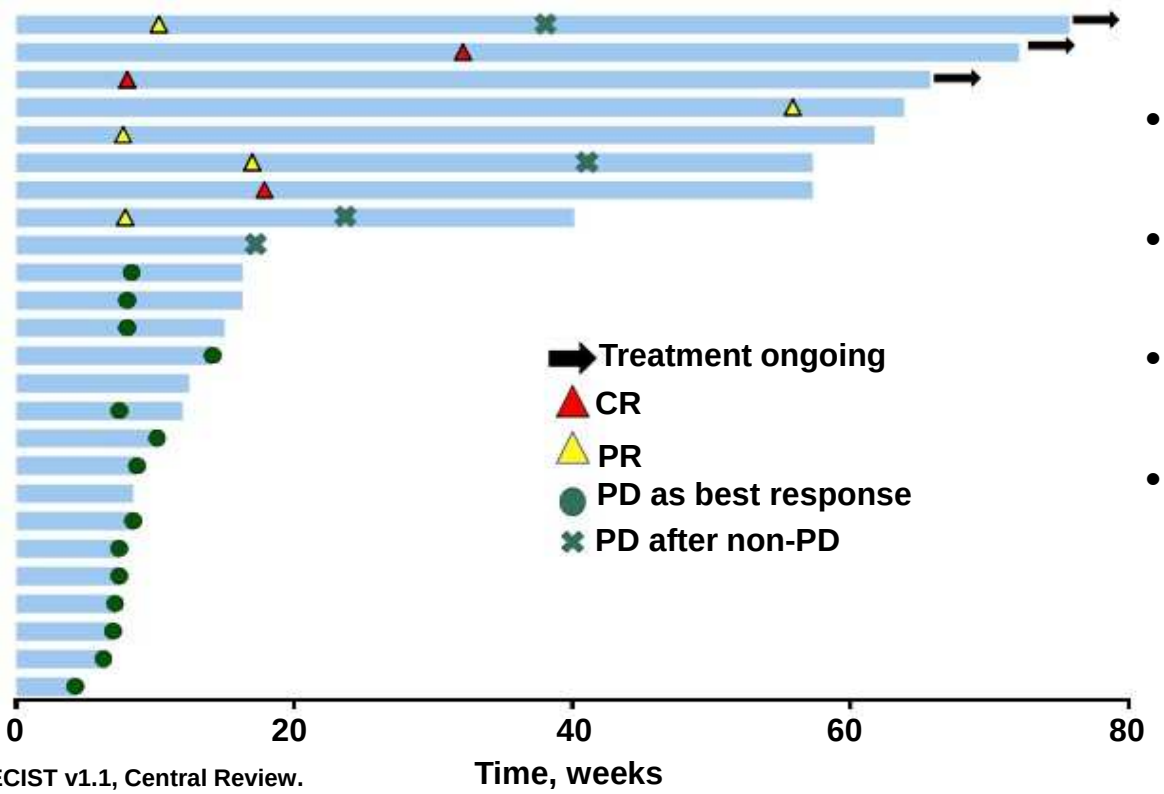
Pembrolizumab: Overall Survival



Analysis cutoff date: March 23, 2015.

Plimack, E.R., ***et al.***
ASCO Meeting Abstracts
33, 4502 (2015).
Slide: Noah Hahn

Pembrolizumab: Duration of Response



RECIST v1.1, Central Review.
Analysis cutoff date: March 23, 2015.

- Median follow-up duration:
  - 15 (0.6-20) months
- Median time to response:
  - 9 (7.7−55.9) weeks
- Response duration:
  - 8.1 to 64.1+ weeks
- 3 patients remain on therapy

Plimack, E.R., *et al. ASCO Meeting Abstracts* 33, 4502 (2015).

Atezo and Pembro Fast Facts

	[1]Atezo-lizumab	[2]Pembro-lizumab	History
Target	PD-L1	PD-1	Cytotoxics and TKIs
Schedule	q3wk	q2wk	Variable
Grade 3-4 Toxicity	8%	15%	~40-50%
ORR	35%	28%	12%
Median OS	10-14 months	13 months	7 months

[1]ASCO 2015;abst 4501 / [2]ASCO2015;abst 4502.

Slide courtesy Noah Hahn, ASCO 2015

Effect of PD-L1 status on mUC Response

[1]Atezolizumab (Petrylak et al)

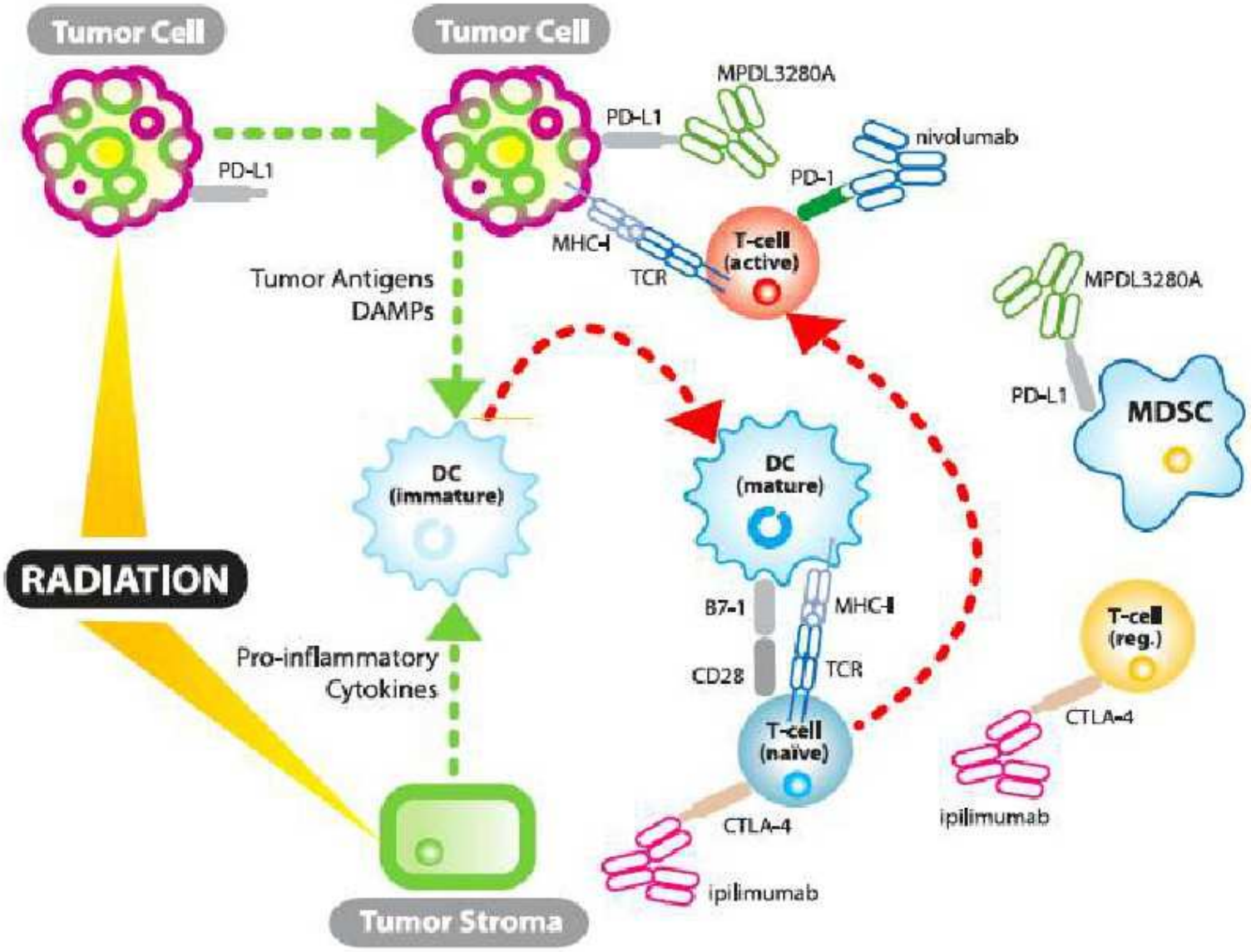
PD-L1 IHC n = 87	ORR % (95% CI)	
IC3 (n = 12)	67% (35, 90)	50% (35, 65)
IC2 (n = 34)	44% (27, 62)	
IC1 (n = 26)	19% (7, 39)	17% (7, 32)
IC0 (n = 15)	13% (2, 40)	

[2]Pembrolizumab (Plimack et al)

Tumor and TILS (N = 28 evaluable)		Tumor Only (N = 29 evaluable)	
	ORR (95%CI)		ORR (95%CI)
Positive (N = 24)	29% (13%-51%)	Positive (N = 18)	33% (13%-59%)
Negative (N = 4)	0% (0%-60%)	Negative (N = 11)	9% (0%-41%)

[1]ASCO 2015;abst 4501 / [2]ASCO2015;abst 4502.

Slide courtesy Noah Hahn, ASCO 2015



Bladder Cancer 2015

Recent data for RT + immunotherapy

Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial

Encouse B Golden, Arpit Chhabra, Abraham Chachoua, Sylvia Adams, Martin Donach, Maria Fenton-Kerimian, Kent Friedman, Fabio Ponzo, James S Babb, Judith Goldberg, Sandra Demaria, Silvia C Formenti

Lancet Oncol 2015

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

Eugene D Kwon, Charles G Drake, Howard I Scher, Karim Fizazi, Alberto Bossi, Alfons J M van den Eertwegh, Michael Krainer, Nadine Houede, Ricardo Santos, Hakim Mahammedi, Siobhan Ng, Michele Maio, Fabio A Franke, Santhanam Sundar, Neeraj Agarwal, Andries M Bergman, Tudor E Ciuleanu, Ernesto Korbenfeld, Lisa Sengelov, Steinbjorn Hansen, Christopher Logothetis, Tomasz M Beer, M Brent McHenry, Paul Gagnier, David Liu, Winald R Gerritsen, and for the CA184-043 Investigators*

Lancet Oncol 2014

Combining Radiation and Immunotherapy

- **Some potential relevant therapeutics:**

  - atezolizumab (anti-PD-L1)
  – ipilimumab (anti-CTLA-4)
  – nivolumab (anti-PD-1)
  - pembrolizumab (anti-PD-1)
  - Interferon-α2b
  - GM-CSF

- **Timing and Dose of Radiation**

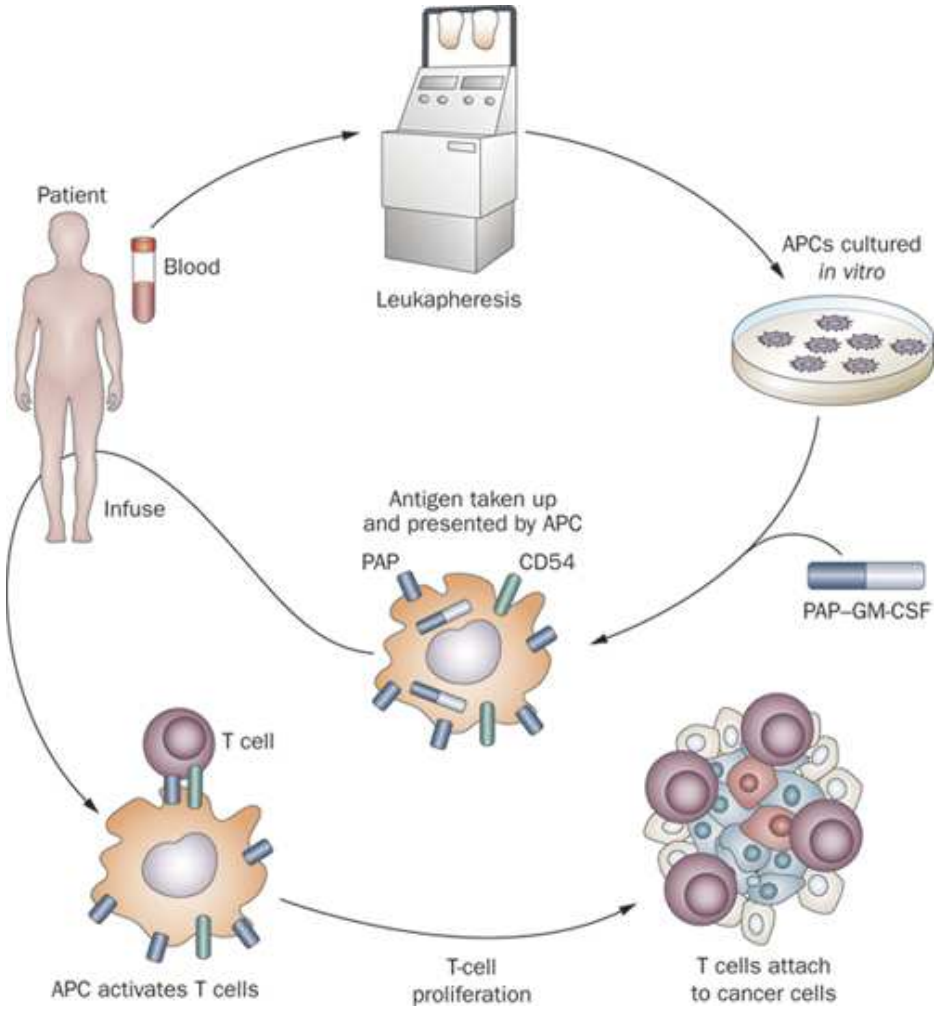
  - Current data from pre-clinical model supports concurrent administration of RT + immunotherapy

  - Data also demonstrates fractionated regimen is generally superior to single dose (8 Gy x 3 > 6 Gy x 5 > 20 Gy x 1) for the induction of an abscopal effect. However, absocopal effect also observed with 8 Gy x 1

Overview

- General Principles
- Renal Cancer
- Urothelial Cancer
- Prostate Cancer

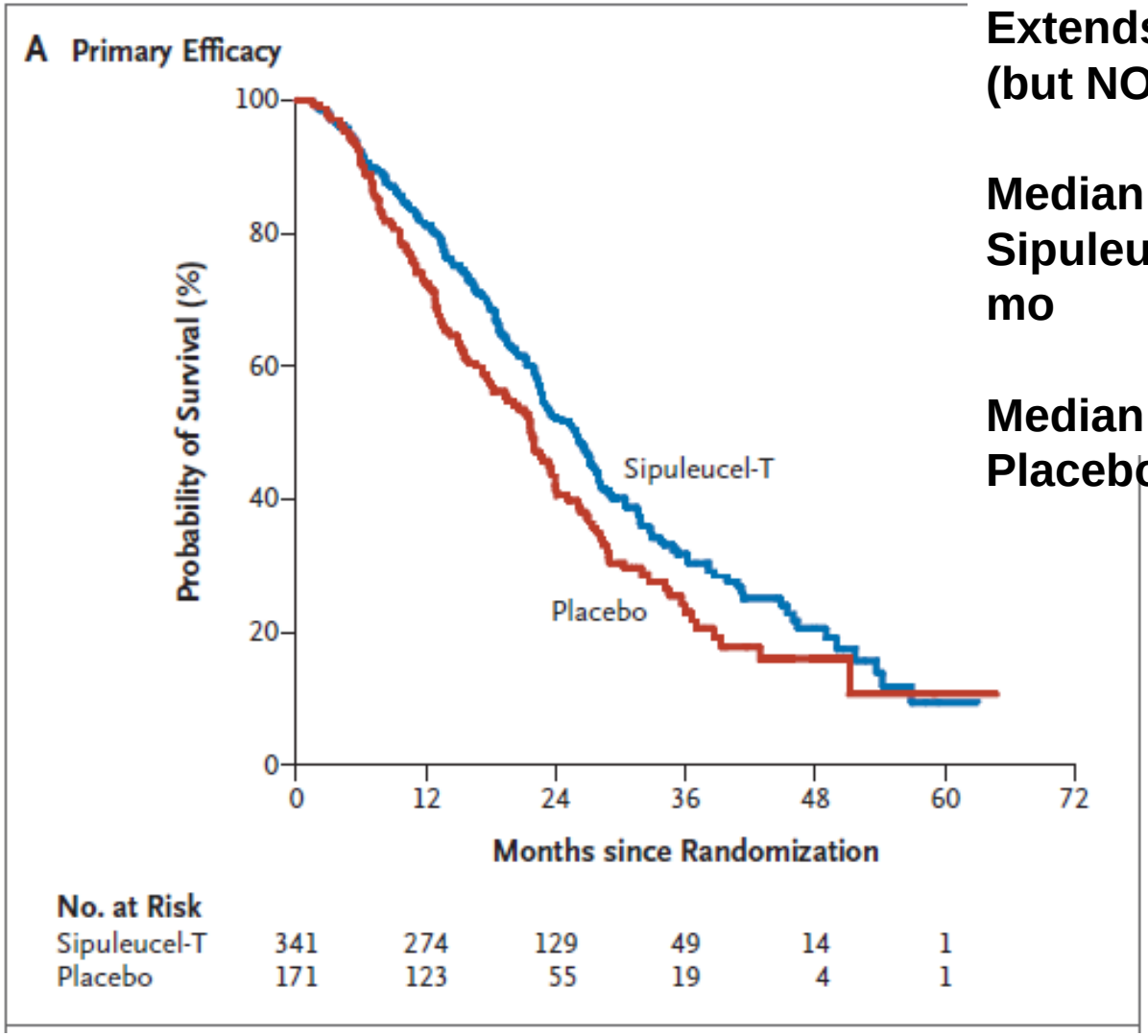
Sipuleucel-T



Di Lorenzo, G. et al. Nat Rev Clin Onc. 2011

Sipuleucel-T

- Which patients?
  - FDA approved for men with **asymptomatic** metastatic CRPC **with life expectancy > 6 months**
- Side Effects
  - fever/chills, nausea, back pain, infusion reactions, hypertension, rare stroke/thrombotic complications
- Which patients are poor candidates?
  - Patients with symptomatic disease, rapidly progressive disease (short PSA doubling time), limited life-expectancy, visceral metastases (?)



Extends survival (but NOT PFS)

Median OS Sipuleucel-T = 25.8 mo

Median OS Placebo = 21.7 mo

Hazard Ratio = 0.78, p=0.03

Kantoff P, et al. NEJM. 2010; 411-22.

Conclusions

- Inhibiting various elements of the PD-1 / PD-L1 pathway has clinical activity in GU cancers-RCC, TCC
  - Durable responses (?off therapy) are possible
  - Issues of dose and schedule are not completely understood
  - Sequencing and the need for ongoing therapy are open questions
- Combination checkpoint inhibition holds particular promise balanced against toxicity
- Novel regulatory pathway(s) for approval may exist

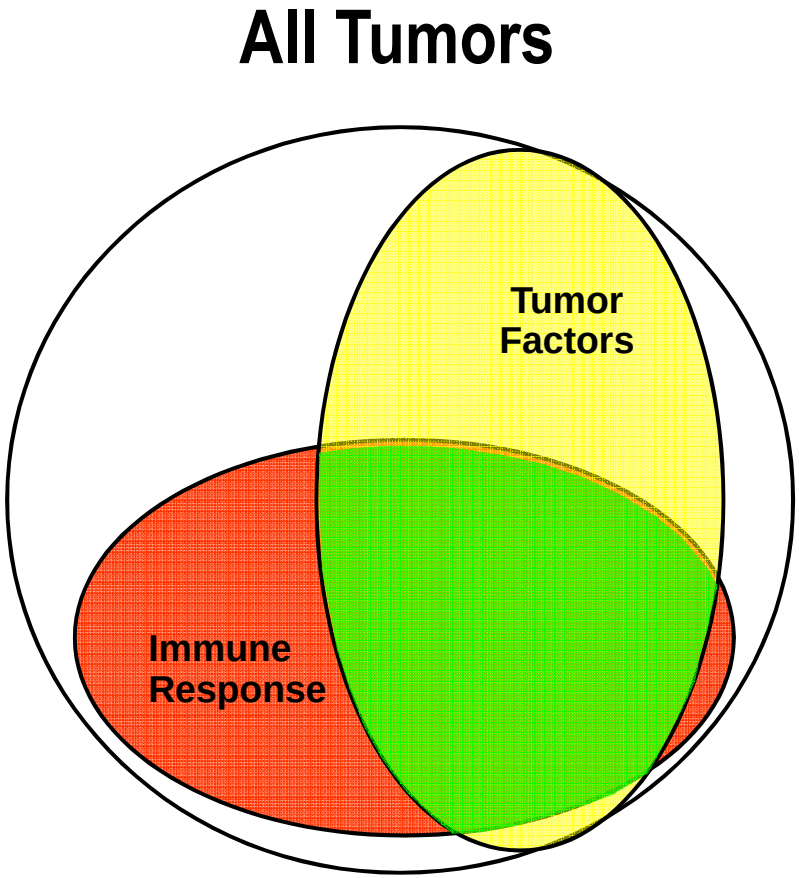
Unanswered Clinical Questions

- Is the clinical benefit a reflection of patient selection?
  - Or will SD pts = improved OS?
- How many responses will be durable off therapy?
    - Similar to IL-2 and ipilimumab?
- Will uncommon toxicities prove vexing?
    - (e.g. nephritis, hepatitis, pneumonitis)

Unanswered Translational Questions

- Predictive Biomarkers
  - Does PD-L1 expression alone reliably predict responders?
  - Will tumor heterogeneity complicate biomarker development?
  - Can biomarkers guide front-line/combination trials?

Immunotherapy Improvement Model



Inflamed Tumors (PD-L1+,Sensitive):
Single agents PD-1/PD-L1 Ab

Inflamed Tumors (PD-L1+/-, Resistant):
Combination Therapy

1) Elimination of Tregs: CTLA4 Ab, anti-GTR
2) Inhibition of MDSC (VEGF TKI, HDM2 Antagonists)
3) Support effector T cells: IL-2,CD137 Ab, IL-15, IL-21
4) Support DCs: GM-CSF
5) Other checkpoint inhibitors (PDL2, LAG3, TIM3 etc)

Non-Inflamed Tumors (PD-L1 neg)
Induce Antitumor Immunity
1) Enhance Antigen Expression:
   - Demethylating Agents
   - SBRT, IT IFN, T-VEC, PV-10
2) Focus Immune Response:
   - Listeria Based Vaccines
   - DC Vaccines

THANK YOU