THE CURRENT STANDARD OF TREATMENT OF GENITOURINARY MALIGNANCIES WITH IMMUNOTHERAPEUTIC AGENTS

Timothy M. Kuzel MD
Chief, Division of Hematology/Oncology
Rush University Medical Center
Chicago IL

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Potential Conflict(s) of Interest

Any Industry funding for:

Leadership (e.g. officer, director, president):

-None

Ownership/Equity (e.g. stock, options, partnership interest):

-None

Intellectual Property income

-None

Consulting or Other Income (Advisory Brds, Speaking honoraria, Data Safety Monitoring Boards)

-Amgen	-Bayer	-Celgene
-Genentech	-Medivation/Astellas	
-Seattle Genetics	-Merck	-Argos
-Eisai	-Exelexis	-BMS

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

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Topics to be Covered

- **Immunotherapy for RCC**
  - **-Historic rationale**
  - **-Phase II experience with Nivolumab**
  - **-Phase III experience with Nivolumab**
  - **-New agents/combinations**
- **Bladder cancer Immunotherapy**
  - **-Historic rationale**
  - **-Anti PD-1/PDL-1 approaches**
  - **-Future combinations/strategies**

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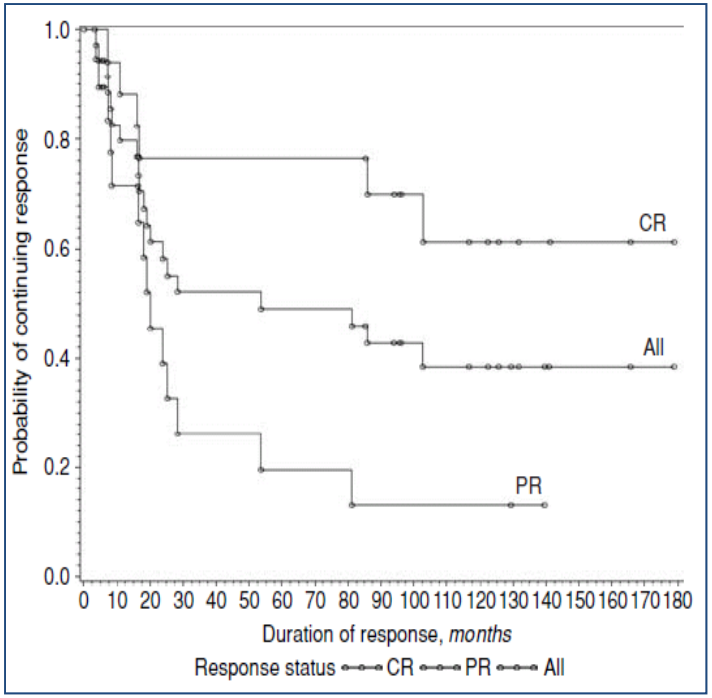
Response in metastatic RCC to High Dose Interleukin-2

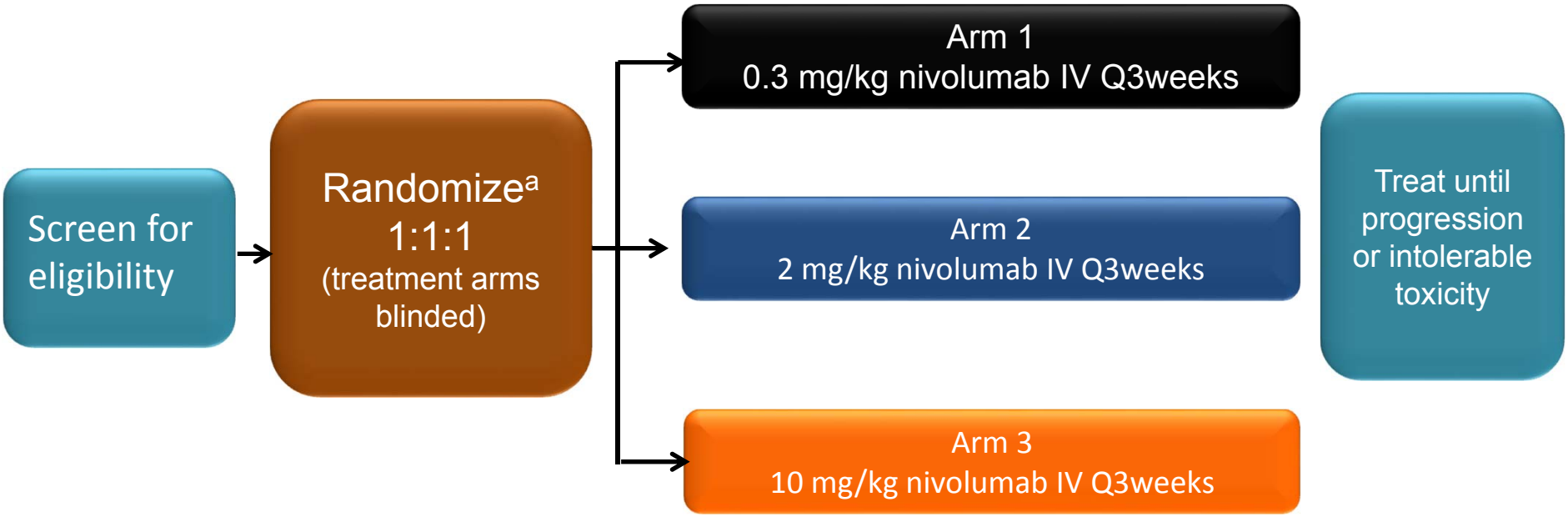
- **15% response rate (7% CR, 8% PR).[1]**
- **Median duration of response was 54 months for all responders, 20 months for partial responders, and has not yet been reached for complete responders.[1]**
- **38% of responders began therapy with tumor burdens > 50 cm^2 on pretreatment scans.**
- **60% of partial responders had > 90% regression of all measurable disease.[1]**
- **60% of complete responders remain in remission after 30 months.**
- **Residual disease from some partial responders could be resected.**
  - **Patients remain alive and disease-free at a minimum of 65+ months**



Response Duration for Patients receiving HD IL-2[2]

1. McDermott, *Med Oncol* 2009; 26:S13-S17; 2. Atkins *Kidney Int* 2005; 67:2069-2083

Nivolumab in RCC
Phase II study design



[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 R, et al. JCO Dec 2014

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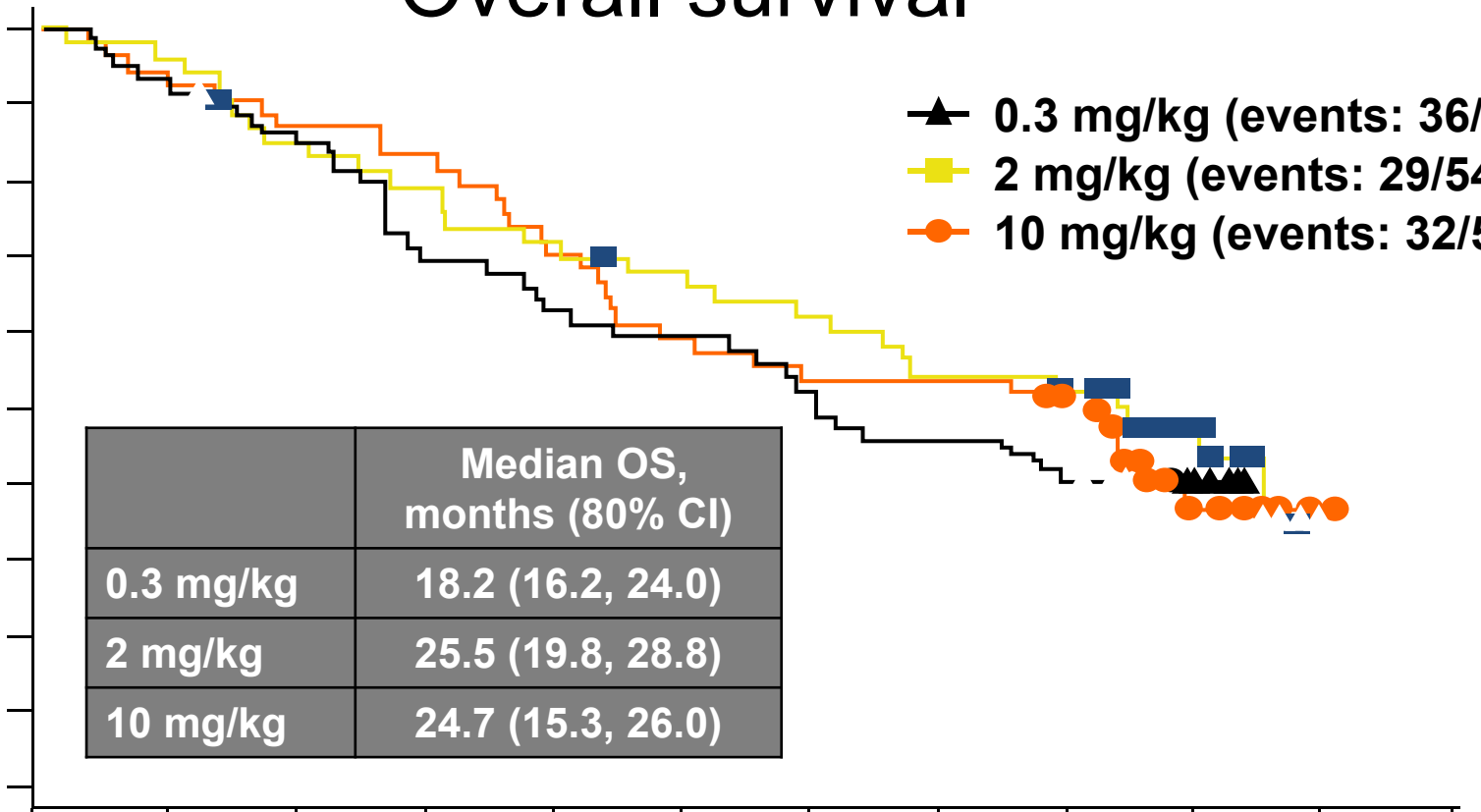
Nivolumab in RCC
Overall survival



	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.

Overall survival in phase III trials and nivolumab phase II study

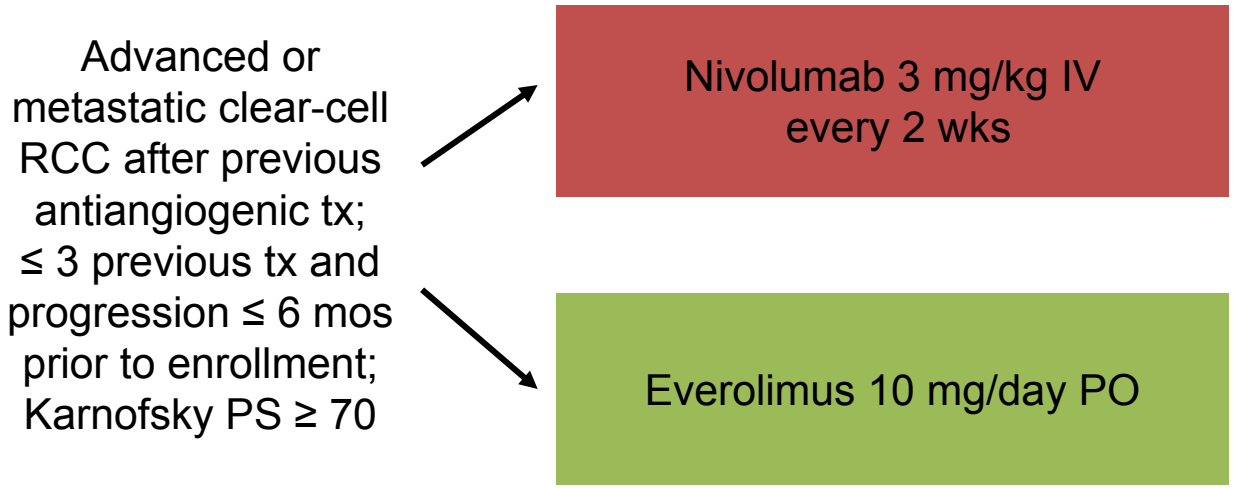
	AXIS[1,a]	INTORSECT[2]	RECORD-1[3]	GOLD[4]	Nivolumab study
Drug	Axitinib; sorafenib	Temsirolimus; sorafenib	Everolimus; placebo	Dovitinib; sorafenib	**Nivolumab; 0.3; 2; 10 mg/kg**
Patients, n	389	512	416	570	168
Risk group, %[b]					
Favorable	Not stated	19	29	20	33
Intermediate		69	56	58	42
Poor		12	14	22	25
Prior therapy	Sunitinib	Sunitinib	VEGF	VEGF + mTOR	VEGF ± mTOR
Line of therapy	2nd	2nd	2nd or higher	3rd or higher	2nd to 4th
Median OS, months	15.2; 16.5	12.3; 16.6	14.8; 14.4	11.1; 11.0	**18.2; 25.5; 24.7**
CI	12.8, 18.3[c] 13.7, 19.2[c]	10.1,14.8[c] 13.6, 18.7[c]	Not stated	9.5, 13.4[c] 8.6, 13.5[c]	16.2, 24.0[d] 19.8, 28.8[d] 15.3, 26.0[d]

[a]Post TKI subset; [c]95% CI; [d]80% CI.

1. Motzer R, et al. *Lancet Oncol.* 2013;14:552-62; 2. Hutson TE, et al. *J Clin Oncol.* 2014;32:760-7; 3. Motzer R, et al. *Cancer.* 2010;116:4256-65; 4. Motzer R, et al. *Lancet Oncol.* 2014;15:286-96.

CheckMate 025-Phase III Study of Nivolumab vs Everolimus in Pts With mRCC

- A randomized, open-label phase III trial



Treat until:

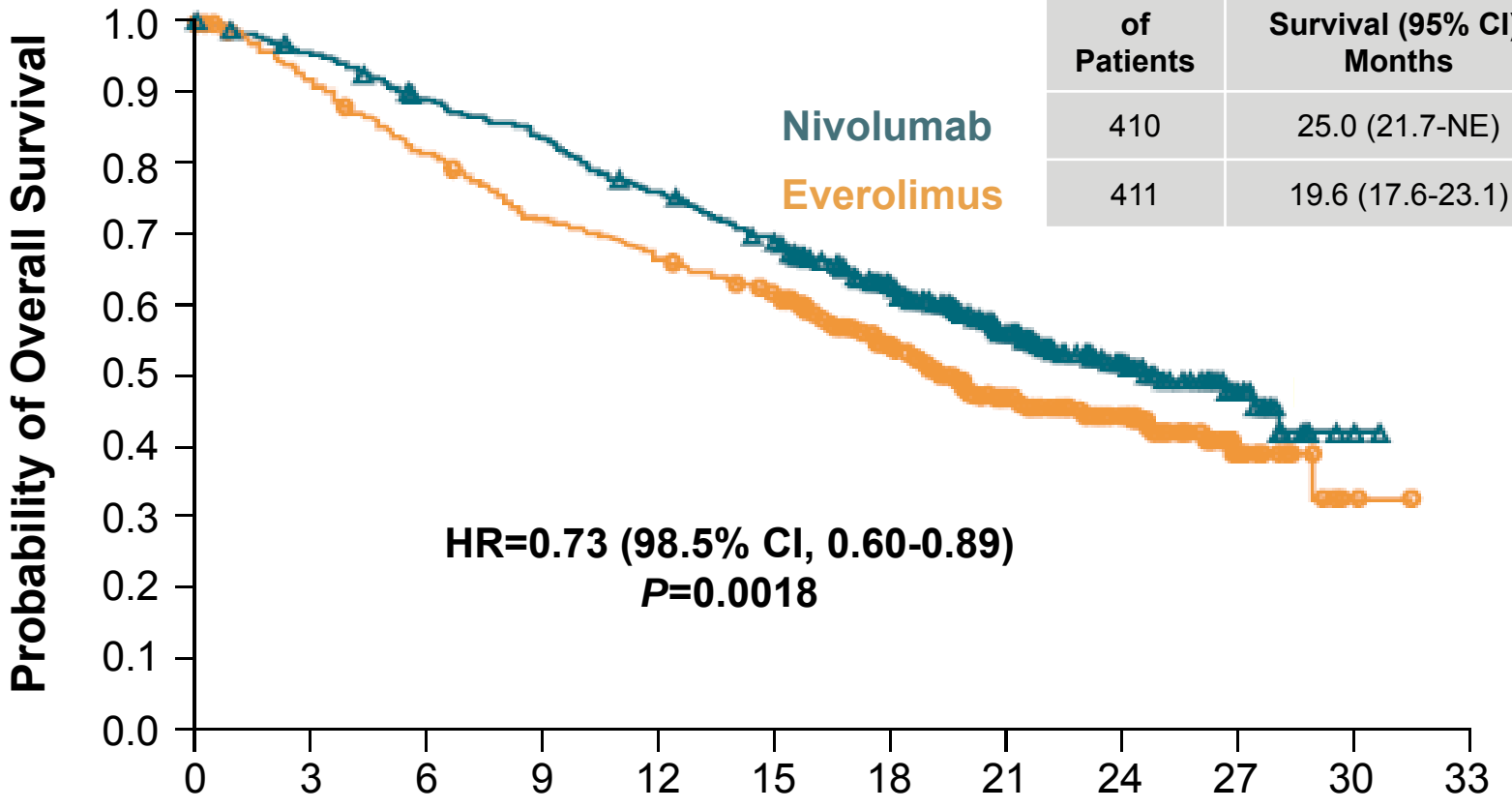
- Progression
- Unacceptable toxicity
- Withdrawal of consent

- **Primary endpoint: OS**
- **Secondary endpoints: PFS, ORR, DoR, OS in PD-L1 subgroup, safety**

ClinicalTrials.gov NCT01668784

CheckMate 025: OS Kaplan-Meier Curve

	Number of Patients	Median Overall Survival (95% CI), Months	Number of Deaths
Nivolumab	410	25.0 (21.7-NE)	183
Everolimus	411	19.6 (17.6-23.1)	215



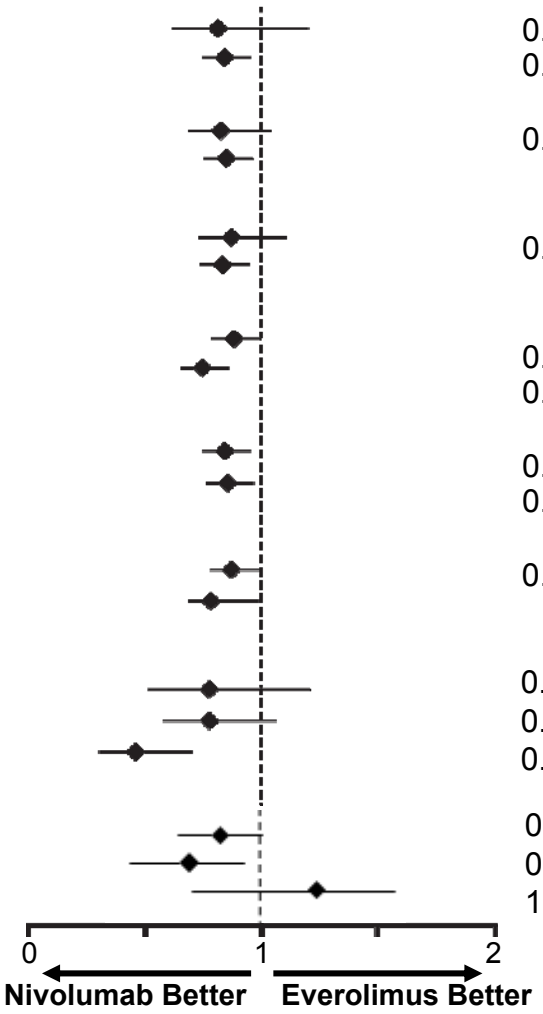
Number at risk

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

(Nivolumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 2015.

CheckMate 025: OS Subgroup Analysis

Subgroup	Events (Patients) Nivolumab	Everolimus	HR (95% CI)
Number of sites of metastases			
1	14 (68)	21 (71)	0.68 (0.34-1.35)
≥2	168 (341)	194 (338)	0.74 (0.60-0.91)
Bone metastases			
Yes	42 (76)	45 (70)	0.72 (0.47-1.09)
No	141 (334)	170 (341)	-
Liver metastases			
Yes	54 (100)	52 (87)	0.81 (0.55-1.18)
No	129 (310)	163 (324)	-
Prior therapy			
Sunitinib	123 (257)	138 (261)	0.81 (0.64-1.04)
Pazopanib	53 (126)	79 (136)	0.60 (0.42-0.84)
Months on first-line therapy			
<6	61 (110)	81 (130)	0.76 (0.55-1.06)
≥6	122 (300)	134 (281)	0.78 (0.61-0.99)
Prior anti-angiogenic therapies			
1	144 (317)	162 (312)	0.79 (0.63-0.99)
2	37 (90)	53 (99)	-
MSKCC risk score			
Favorable	38 (137)	50 (145)	0.80 (0.52-1.21)
Intermediate	95 (193)	104 (192)	0.81 (0.61-1.06)
Poor	50 (79)	61 (74)	0.48 (0.32-0.70)
Age			
<65 years	111/257	118/240	0.78 (0.60-1.01)
≥65 to <75 years	53/119	77/131	0.64 (0.45-0.91)
≥75 years	19/34	20/40	1.23 (0.66-2.31)



Motzer RJ, et al. Poster. ASCO GU. 2016 (abstr 3657).
Motzer, et al. *N Engl J Med.* 2015;373:1803-1813.

CheckMate 025: Tumor Response

	Nivolumab (n=410)	Everolimus (n=411)
Confirmed objective response rate (95% CI), %	21.5 (17.6-25.8)	3.9 (2.2-6.2)
Median duration of response (95% CI), months	23.0 (12.0-NE)	13.7 (8.3-21.9)
Median time to onset of confirmed response (min, max), months	3.0 (1.4-13.0)	3.7 (1.5-11.2)

OPDIVO® (nivolumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 2015.

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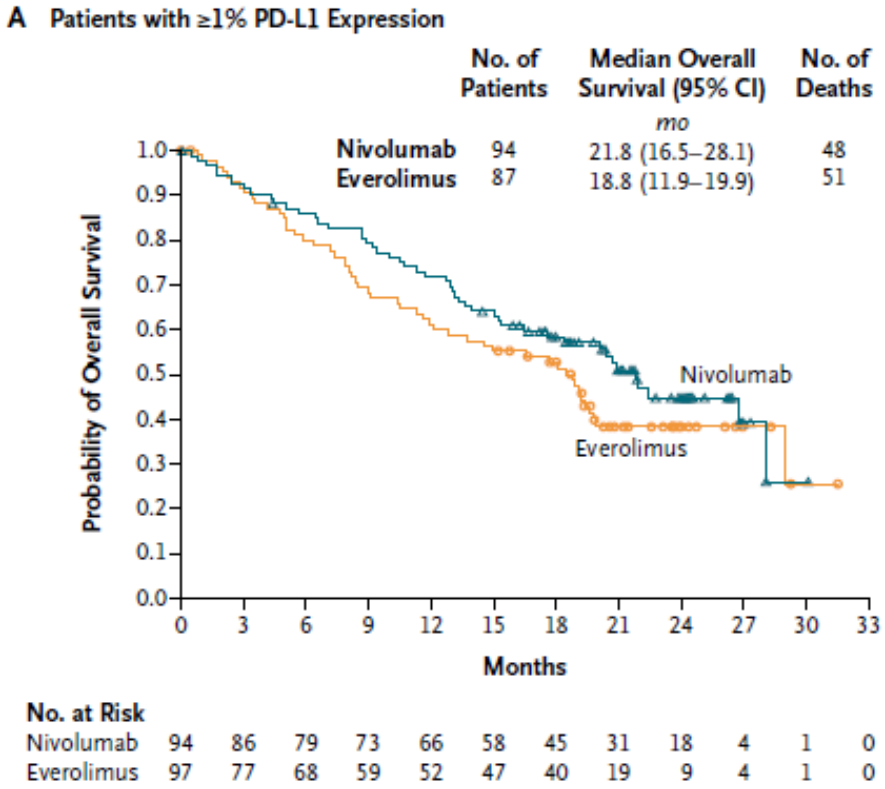
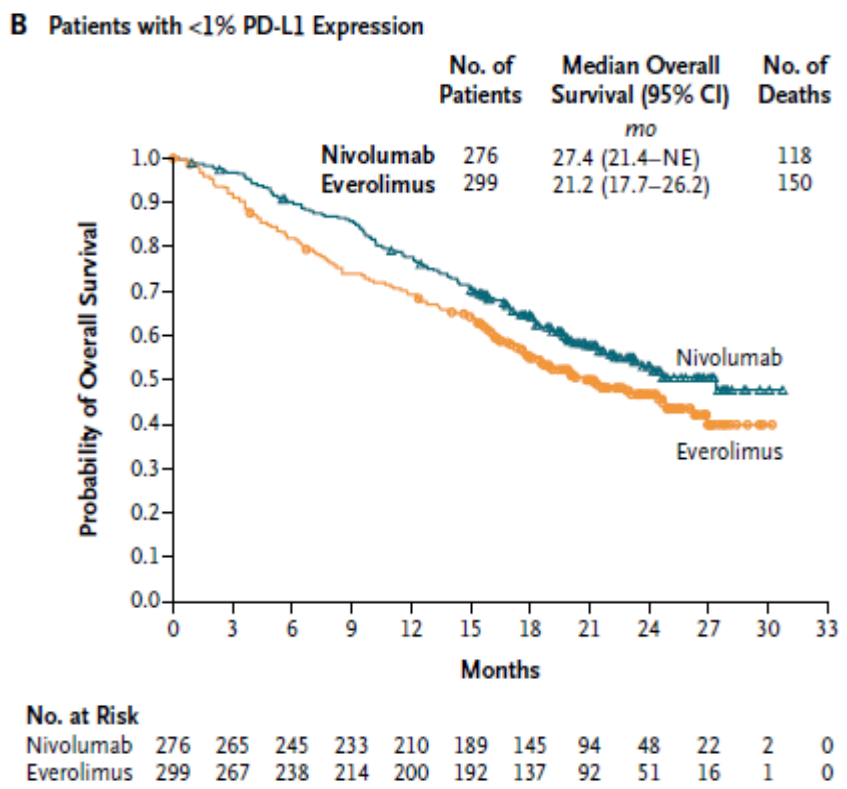
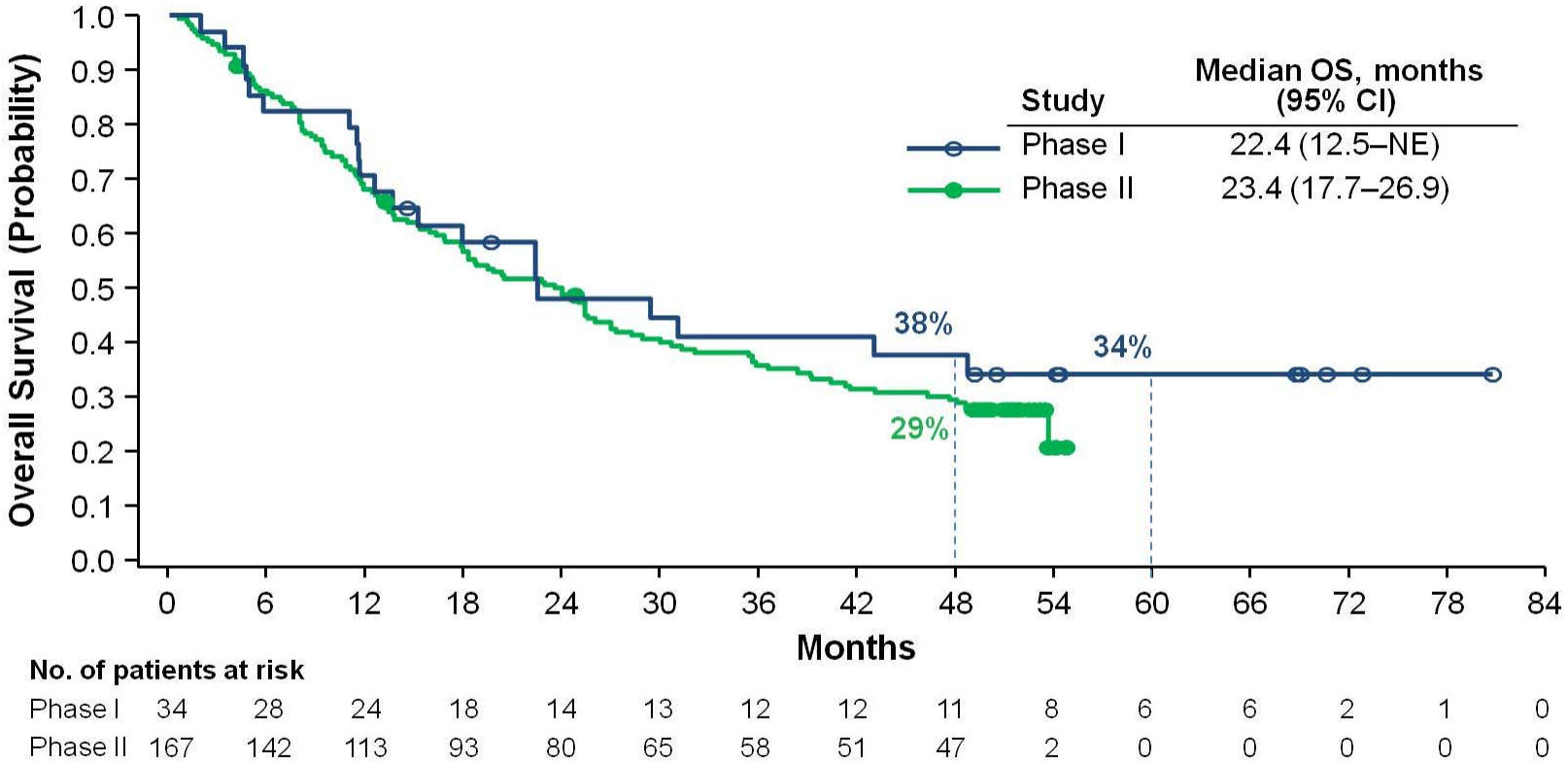
CheckMate 025: OS by PD-L1 Expression





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

Overall survival in phase I and II studies



No. of patients at risk

Phase I	34	28	24	18	14	13	12	12	11	8	6	6	2	1	0
Phase II	167	142	113	93	80	65	58	51	47	2	0	0	0	0	0

- In phase I and II studies, minimum follow-up was 50.5 months and 49.2 months, respectively

NE, not estimable.

David McDermott et al: 2016 ASCO Annual Meeting

Anti PD-directed RCC Immunotherapy Trials
Treatment Naive

Elements	Atezolizumab (MPDL3280A)[1]	Nivolumab + Ipilimumab[2,3]	Axitinib + Avelumab[4]
Phase/size	IMmotion151 (Ph 3/550 pts)	CheckMate 214 (Ph 3/1070 pts)	(Ph 1b/55)
Dosing	Atezolizumab 1,200 mg day 1 and 22 of each 42-day cycle + bevacizumab 15 mg/kg day 1 and 22 of each 42-day cycle	Nivolumab 3 mg/kg + ipilimumab 1 mg/kg q 3 wk	Avelumab 10 mg/kg IV q 2 wk + axitinib 5 or 3 mg BID
Comparator	Sunitinib 50 mg days 1 through 28 of each 42-day cycles	Sunitinib 50 mg (4 wk on/2 wk off)	Avelumab 5 mg/kg IV q 2 wk + axitinib 5 or 3 mg BID
Eligibility	Untreated advanced RCC	Previously untreated advanced or metastatic RCC	Previously untreated advanced RCC with clear-cell component
Endpoints	Primary endpoint: PFS by investigator RECIST	• Primary endpoints: PFS, OS • Secondary endpoints: ORR, adverse event rate	Primary endpoint: DLT Secondary endpoints: OR, DR, safety, pharmacokinetics, PFS, TTR, immunogenicity, biomarkers, ADA
Timing	Completion date: February 2019	• Primary completion (final data collection for primary endpoint): Jan 2018 • Completion date: Sept 2019	• Completion date: Feb 2018

ADA, anti-drug antibody; BID, twice a day; DLT, dose-limiting toxicities; DR, duration of response; OR, objective response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pts, patients; q, every; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.

1. NCT02420821. 2. NCT02231749. 3. Hammers et al, *J Clin Oncol*. 2015;33(suppl): abstract TPS4578. 4. NCT02493751.

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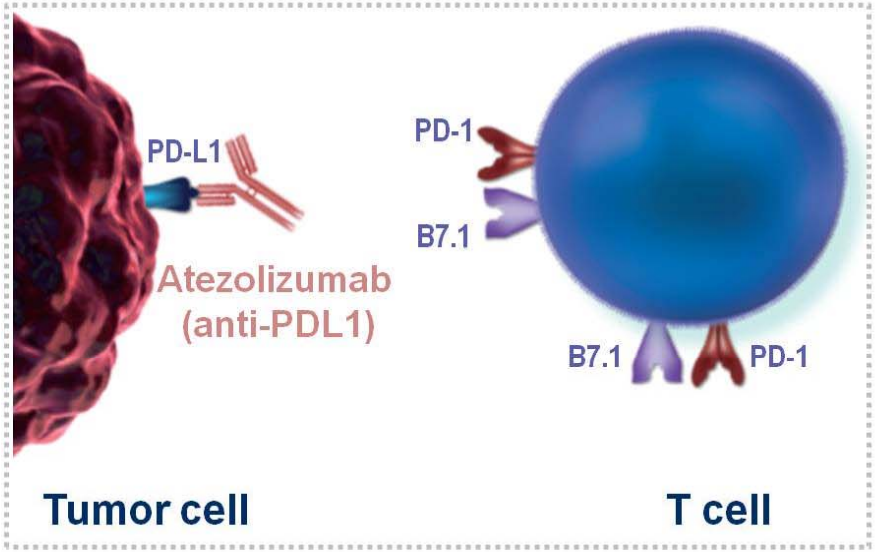
Immunotherapy approaches in Urothelial Cancer

Checkpoint Inhibitors show great promise in urothelial CA

PD-L1 Biology and Atezolizumab (MPDL3280A)

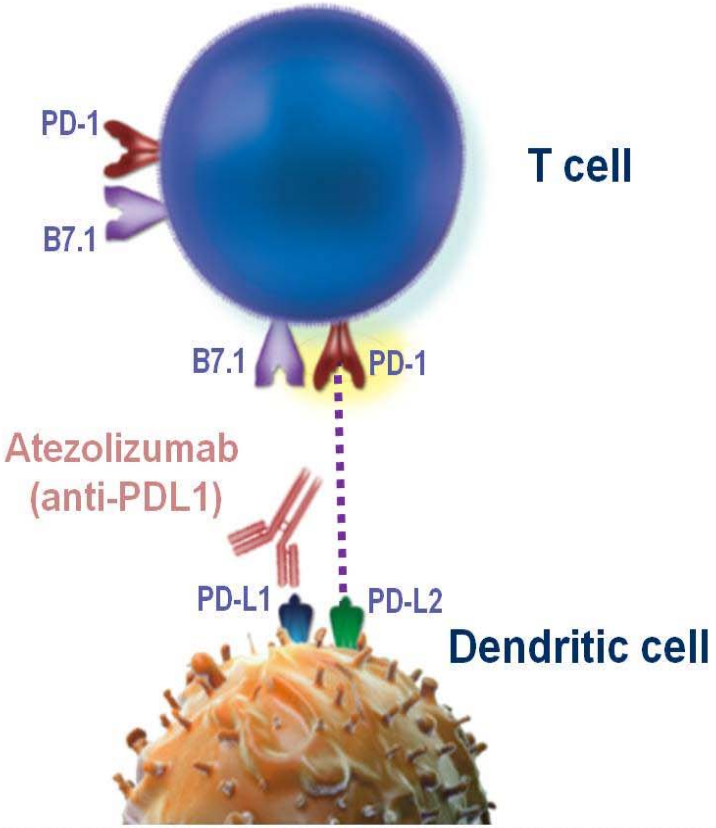


- Signaling mediated by PD-L1, expressed in many cancers including mUC, can inhibit antitumor immune responses[1-5]
- By inhibiting binding of PD-L1 to PD-1 and B7.1, atezolizumab can:
  - Enhance T-cell priming
  - Reinvigorate suppressed immune cells

PD-L1, programmed death-ligand 1.

References: 1. Brown JA, et al. *J Immunol.* 2003;170(3):1257-1266. **2.** Latchman Y, et al. *Nat Immunol.* 2001; 2(3):261-268. **3.** Powles T, et al. *Nature.* 2014; 515(7528):558-556. **4.** Zou et al. *Nat Rev Immunol.* 2008;8(6):467-477. **5.** Chen and Mellman. *Immunity.* 2013;39(1):1-10.

PD-L1 Biology and Atezolizumab (MPDL3280A)



PD-L1, programmed death-ligand 1.

- Signaling mediated by PD-L1, expressed in many cancers including mUC, can inhibit antitumor immune responses[1-5]
- By inhibiting binding of PD-L1 to PD-1 and B7.1, atezolizumab can:
  - Enhance T-cell priming
  - Reinvigorate suppressed immune cells
- By leaving the PD-L2/PD-1 interaction intact, atezolizumab may preserve peripheral immune homeostasis[6,7]

References: 1. Brown JA, et al. *J Immunol.* 2003;170(3):1257-1266. **2.** Latchman Y, et al. *Nat Immunol.* 2001; 2(3):261-268. **3.** Powles T, et al. *Nature.* 2014;515(7528): 558-556. **4.** Zou et al. *Nat Rev Immunol.* 2008;8(6):467-477. **5.** Chen and Mellman. *Immunity.* 2013;39(1):1-10. **6.** Akbari et al. *Mucosal Immunol.* 2010;3(1):81-91. **7.** Matsumoto et al. *Biochem Biophys Res Commun.* 2008;365:170-175.

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IMvigor210 Cohort 2: Study Design

Basis for Accelerated Approval

- Locally advanced or metastatic urothelial carcinoma
- Predominantly TCC histology
- Tumor tissue for PD-L1 testing[a]

Cohort 1 (N = 119)
1L cisplatin ineligible → *Cohort 1 presented earlier this morning*[1]

Cohort 2 (N = 310)
Platinum-treated mUC → Atezolizumab 1200 mg IV q3w until loss of benefit

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

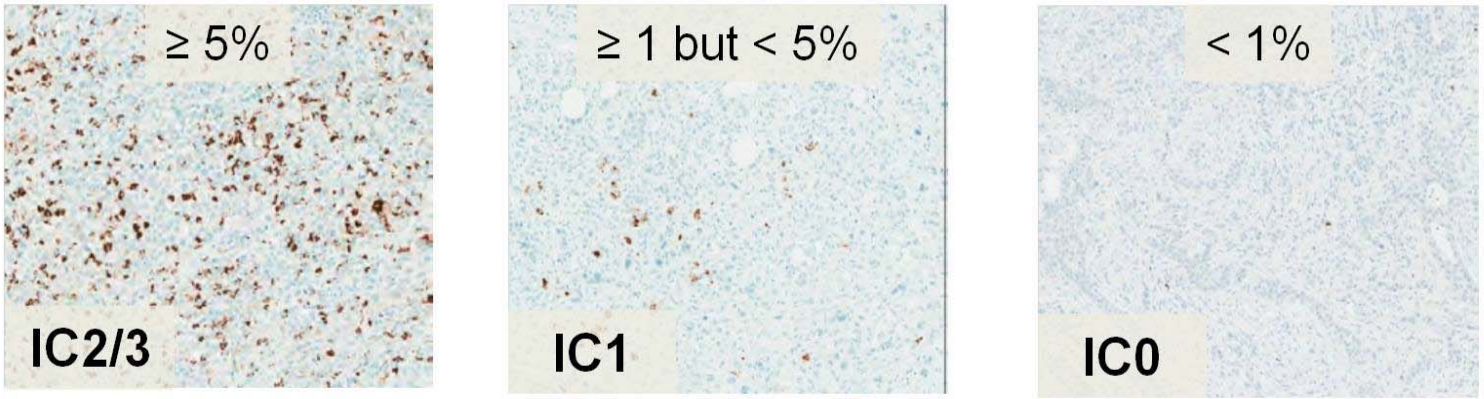
Key exploratory endpoints

- 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)

IMvigor 210: PD-L1 Immune Cell Expression (IHC)

- PD-L1 expression on IC was evaluated with the VENTANA SP142 IHC assay based on 3 scoring levels: IC2/3 (≥ 5%), IC1 (≥ 1 but < 5%), IC0 (< 1%)[1]



Images at 10x magnification.

Reference: 1. Rosenberg JE, et al. ECC 2015 [abstract 21LBA].

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Efficacy

Responses to Atezolizumab by PD-L1 IC Subgroup

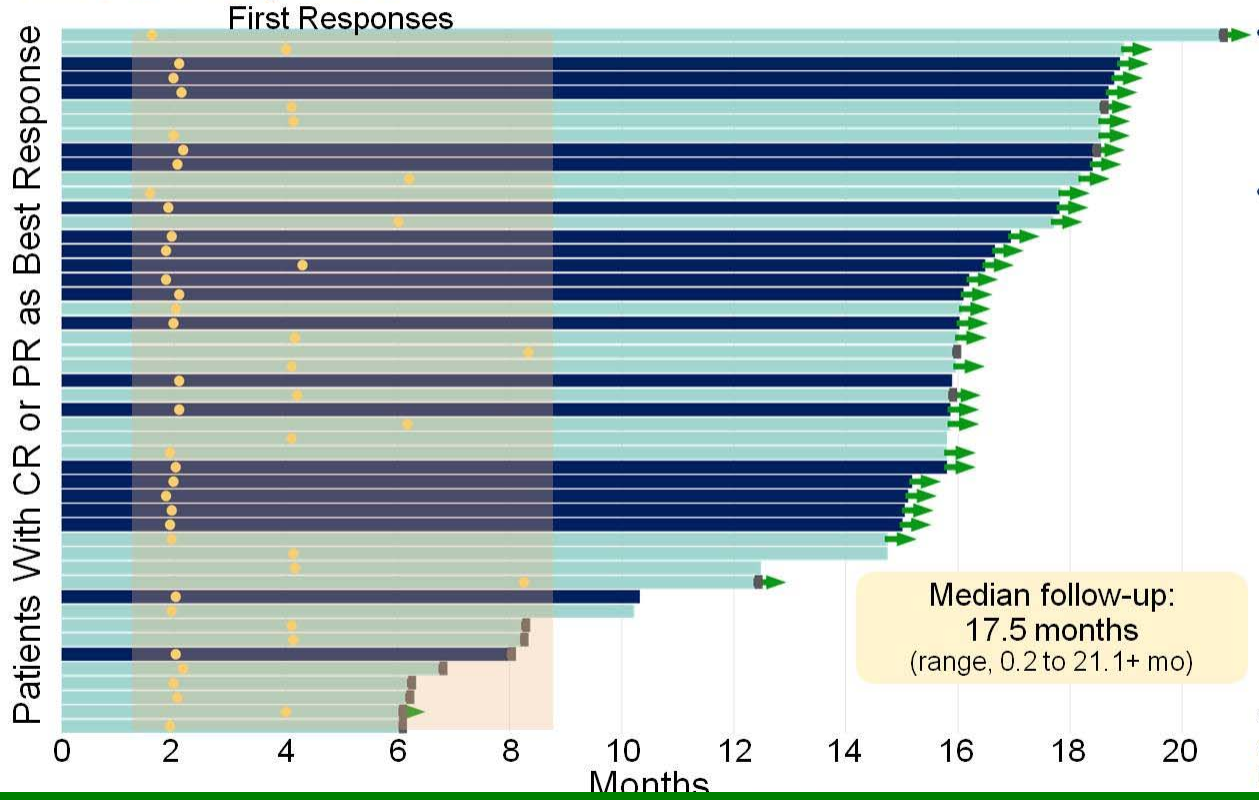
	IC2/3 n = 100	IC1/2/3 n = 207	All[a] N = 310	IC1 n = 107	IC0 n = 103
ORR: confirmed IRF RECIST v1.1 (95% CI)	28% (19, 38)	19% (14, 25)	16% (12, 20)	11% (6, 19)	9% (4, 16)
CR rate: confirmed IRF RECIST v1.1 (95% CI)	**15% (9, 24)**	**9% (6, 14)**	**7% (4, 10)**	**4% (1, 9)**	**2% (0, 7)**

- 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
- 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

Time to Response



- Median time to first response[a] was 2.1 mo
  - Range, 1.6 to 8.3 mo
- Additional CRs and PRs were observed with longer follow-up
  - 5 PR-to-CR and 2 SD-to-PR conversions

CR as Best Response
PR as Best Response
First CR/PR
Treatment Discontinuation[b]
Ongoing Response[c]

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

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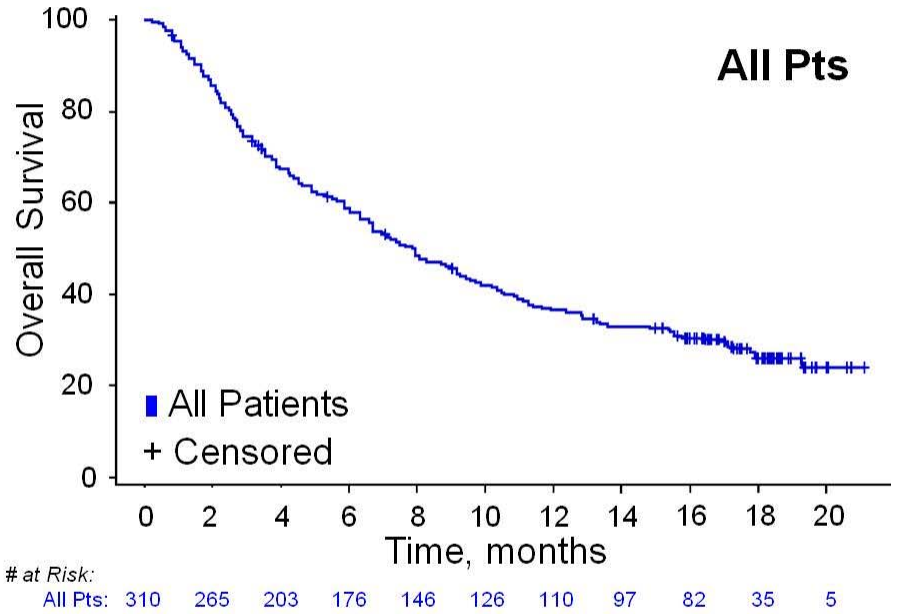
Dreicer et al: 2016 ASCO Annual Meeting

Efficacy

Overall Survival



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)

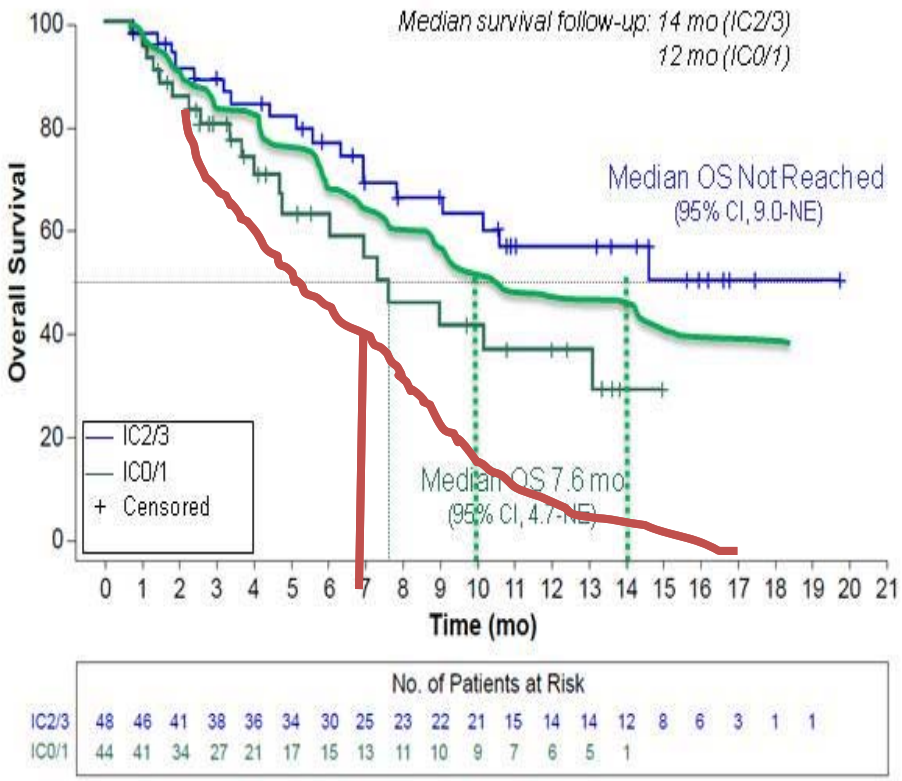
Subgroup	12-mo OS (95% CI)		
	IC2/3	IC0/1	All
All pts (N = 310)	50% (40, 60)	31% (24, 37)	37% (31, 42)
2L only (n = 120)	61% (44, 77)	29% (19, 39)	38% (29, 47)

- Longer OS observed in patients with higher PD-L1 IC status
- 12-mo OS compares favorably with historic estimates of ≈ 20%[1]

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

Atezolizumab (MPDL3280A): Survival in UBC



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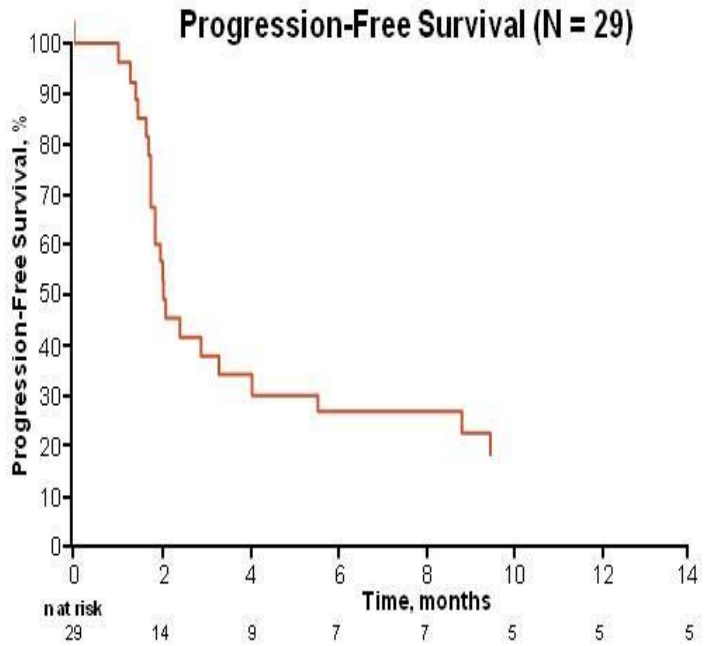
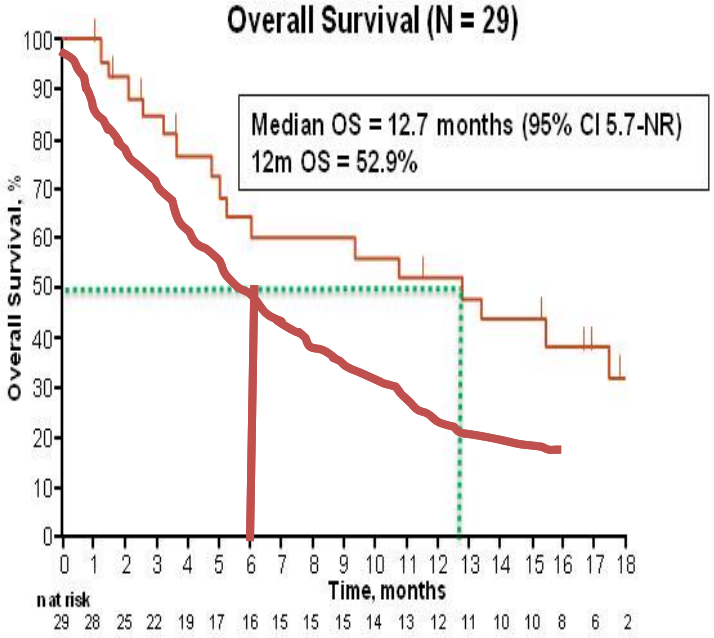
Plimack ASCO 2015

KEYNOTE-012 (NCT01848834)

Phase Ib Multi-Cohort Study of Pembrolizumab in Patients With PD-L1 Positive Advanced Solid Tumors





- Median PFS: 2 months (95% CI, 1.7–4.0)
- PFS rate at 12 months: 19.1%

- Median OS:12.7 months (95% CI, 5.0–NR)
- OS rate at 12 months: 52.9%

Analysis cutoff date: March 23, 2015.

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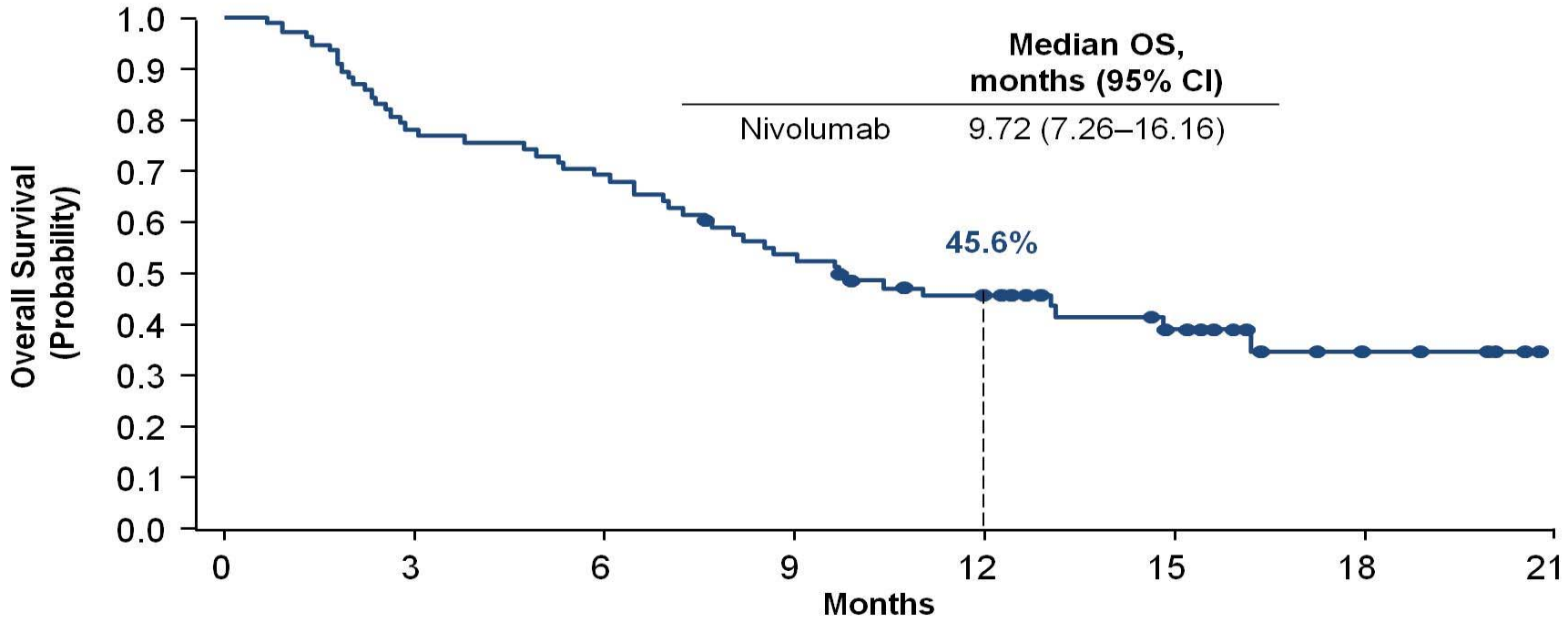
Elizabeth Plimack et al: 2015 ASCO Annual Meeting

Nivolumab in relapsed (2nd and later) UroCA (n=78)

Overall survival



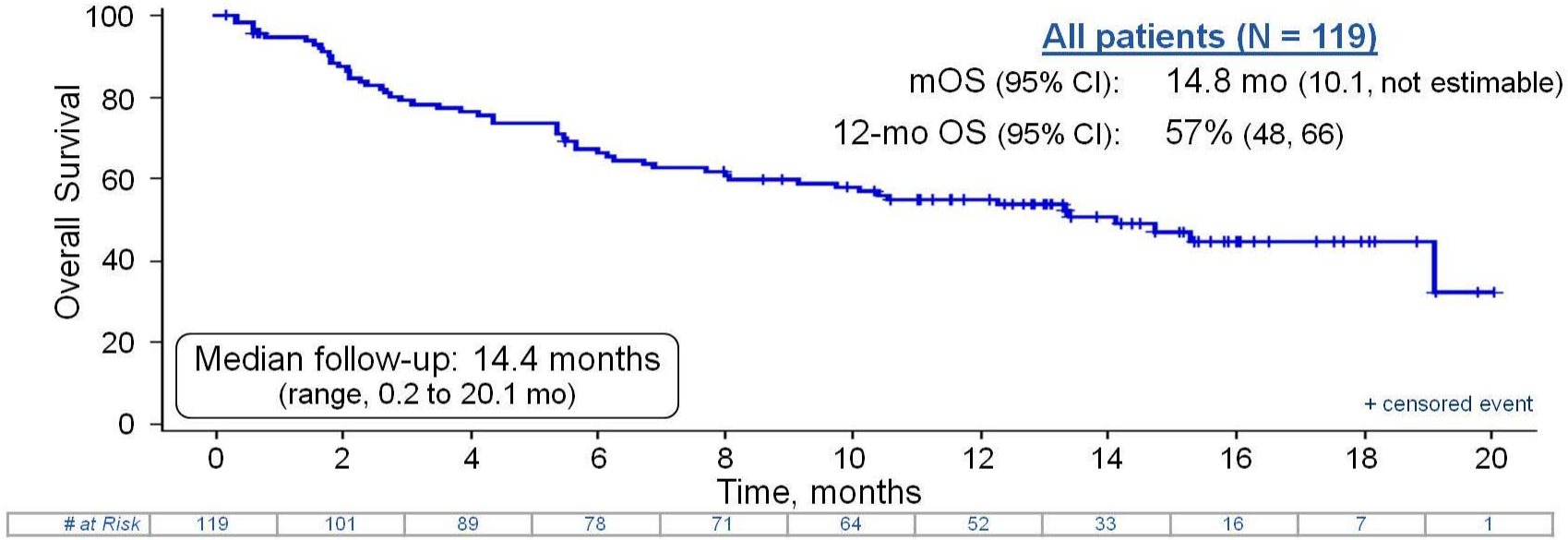
All treated patients.

Padmanee Sharma et al: 2016 ASCO Annual Meeting

Atezolizumab 1st line CDDP ineligible (Cohort-1)

Efficacy

Overall Survival (Median and Landmark 12-Month OS)



- Only 47% of patients experienced an event
- Kaplan-Meier OS curves were similar in pre-defined PD-L1 subgroups
- Atezolizumab compares favorably with historic data from cisplatin-ineligible patients, both from clinical trials and real-world studies[1,2]

Median follow-up: 14.4 months (range, 0.2 to 20.1 mo). Data cutoff: March 14, 2016. 1. De Santis *J Clin Oncol* 2012. 2. Galsky ECC 2015 [poster 115].

IMvigor 210: Safety Summary

AE (N = 310)	All Cause	Treatment Related
Any Grade	97%	69%
Serious AEs	48%	11%
Grade 3-4	55%	16%
Grade 5[a]	1%	0%
Immune-mediated AEs	7%	—
AEs leading to withdrawal from atezolizumab	4%	N/A
AEs leading to dose modification/interruption	30%	N/A

- Median treatment duration 12 wks (range, 0 to 66 wks)
  - Median of 5 doses (range, 1 to 23 doses)
- Atezolizumab was well tolerated with no treatment-related deaths
  - AE profile was consistent across IC populations

[a] 3 all-cause Grade 5 AEs were seen (n = 1 each): cerebral hemorrhage, pulmonary sepsis, subileus (intestinal occlusion). Data cutoff: September 14, 2015

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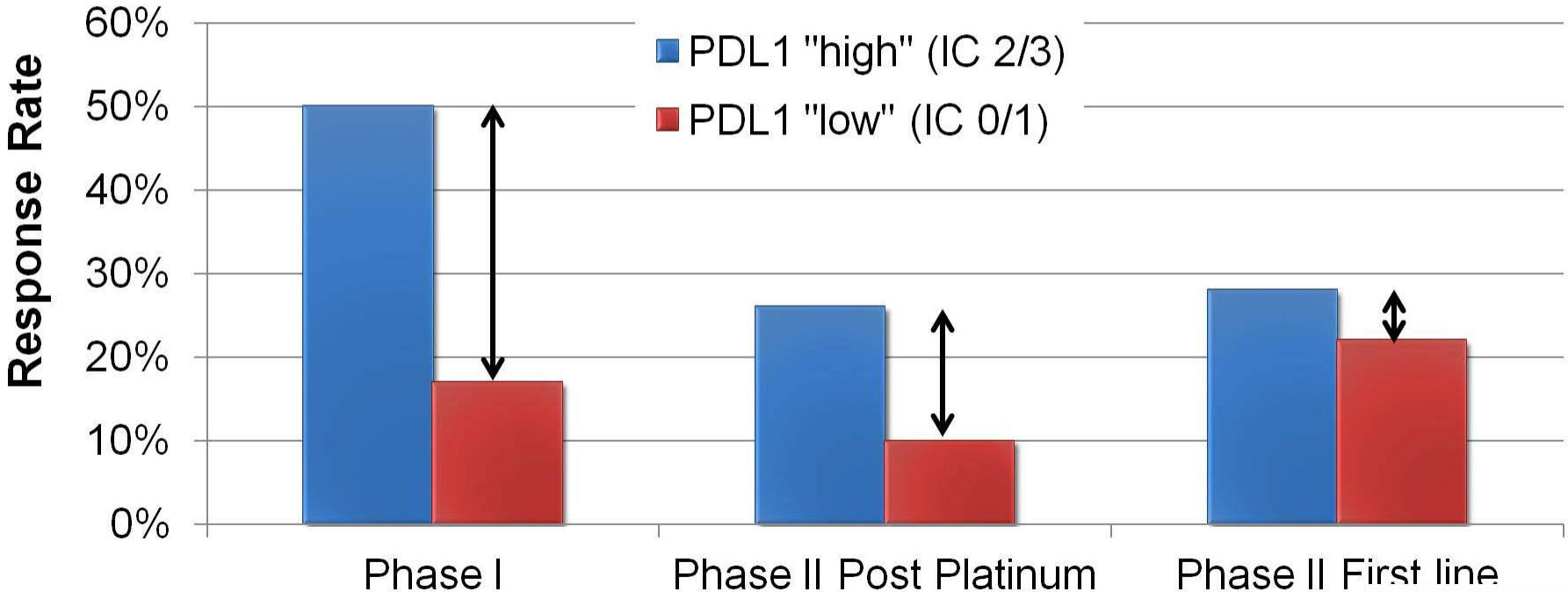
PDL1 Testing (IC 2/3 vs. 1/2) Loses Ability to Enrich for Response Across Atezolizumab Studies



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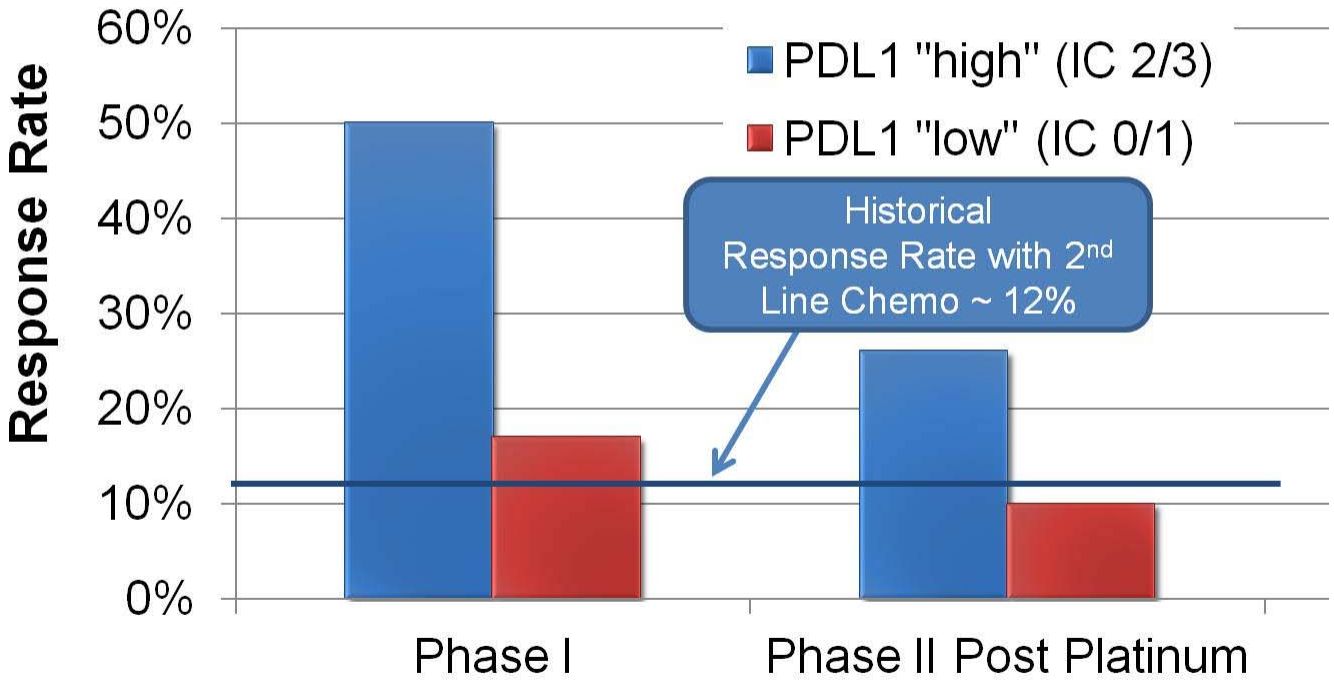
PDL1 Low (IC 0/1) Patients Still Respond to Atezolizumab



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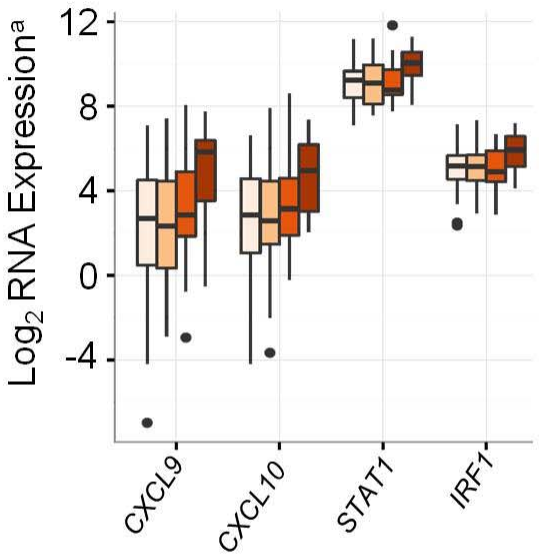
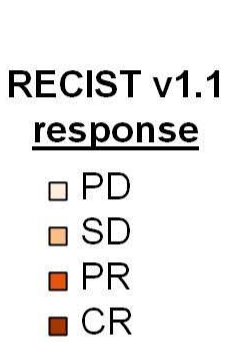
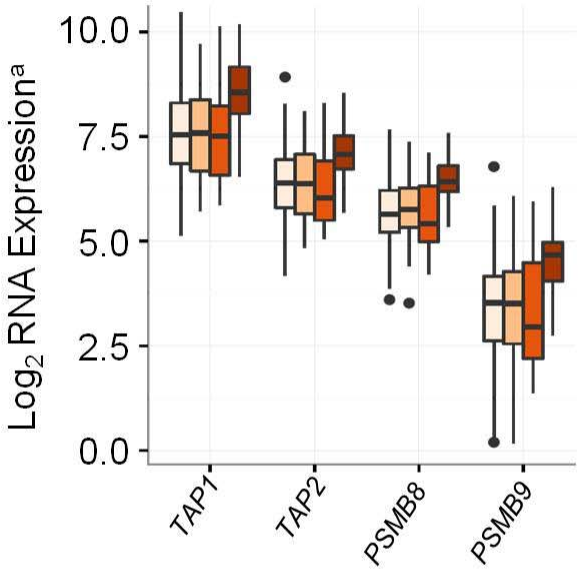
T_{eff} IFNγ-Induced Gene Expression is Associated With Response





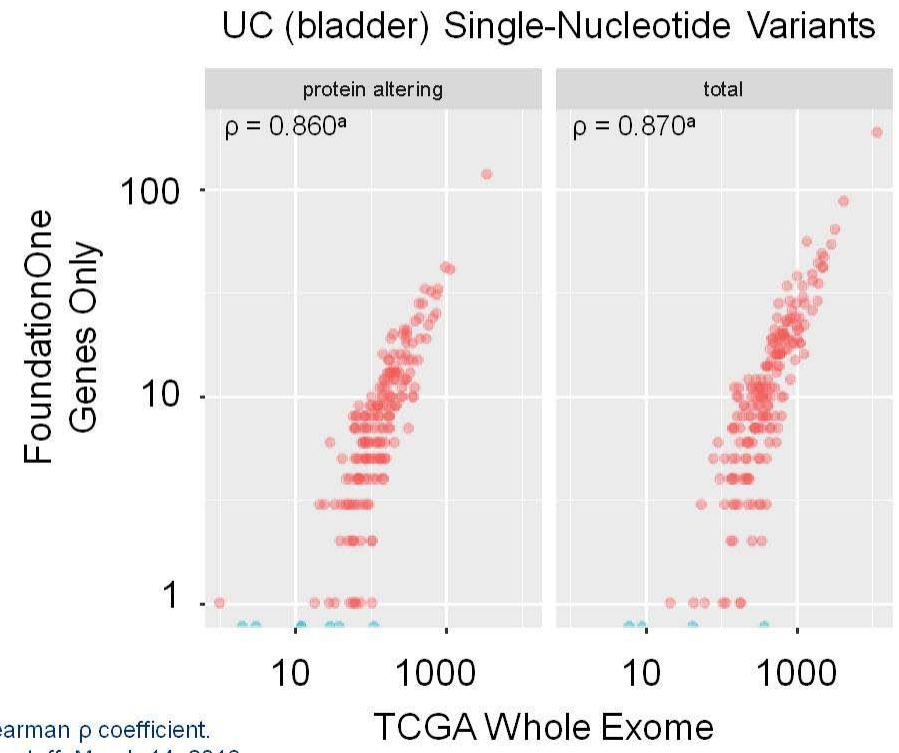


- Higher baseline IFNγ response genes were observed in atezolizumab responders
- These data are consistent with Th1 and CTL immune responses

- IFNγ-inducible MHC-I antigen processing and transport genes were also associated with response

CTL, cytotoxic T lymphocyte; IRF1, interferon regulatory factor 1; MHC-I, major histocompatibility complex I; PSMB, proteasome subunit β; STAT1, signal transducer and activator of transcription 1; TAP, transporter. [a] RNAseq data. Data cutoff: March 14, 2016.

Mutation Load Represented by FoundationOne Genes Correlates With Mutation Load in TCGA Whole-Exome Sequencing



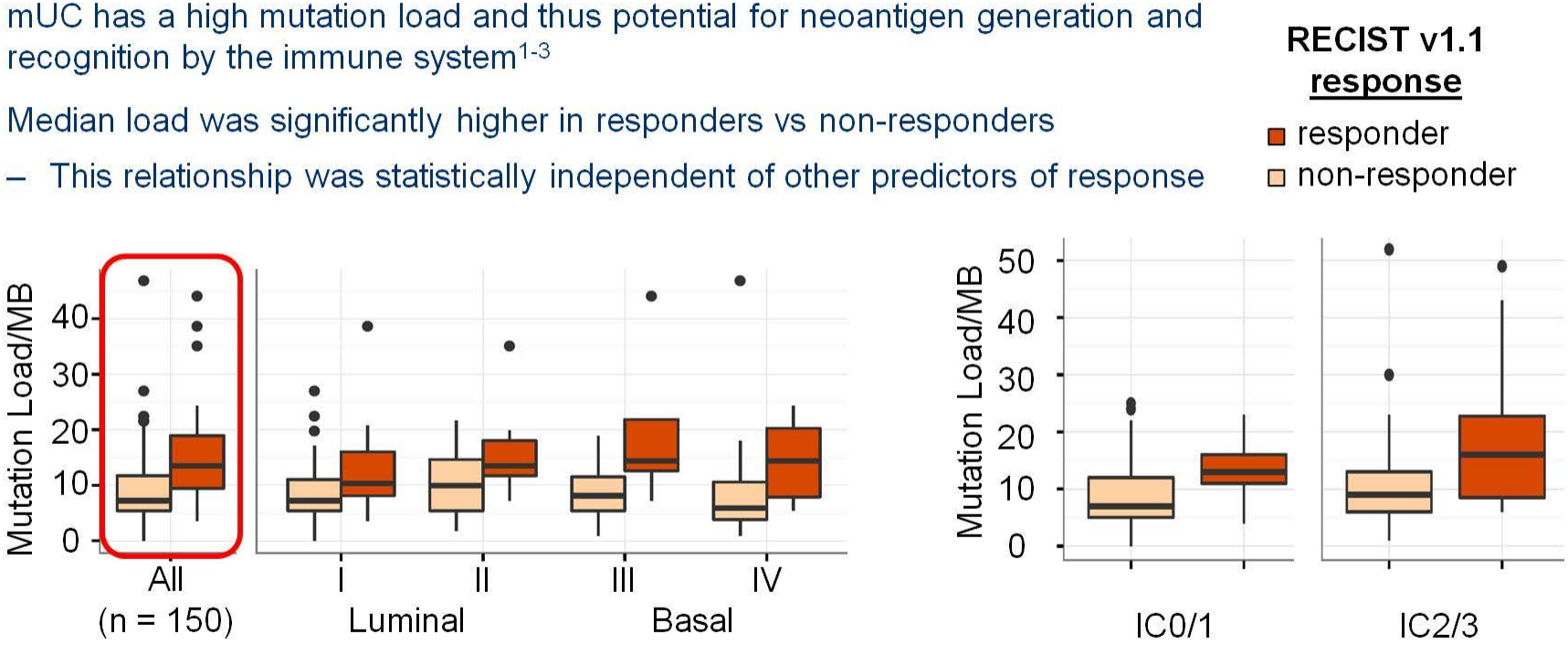
- To estimate mutation load, we used a 315-gene FoundationOne panel that covers ≈ 3% of the exome[1]
- Whole-exome results correlated with the FoundationOne regions, indicating that the restricted target region was sufficient to rank patients based on mutation load

[a] Spearman ρ coefficient.
Data cutoff: March 14, 2016.

1. Rosenberg *Lancet* 2016.

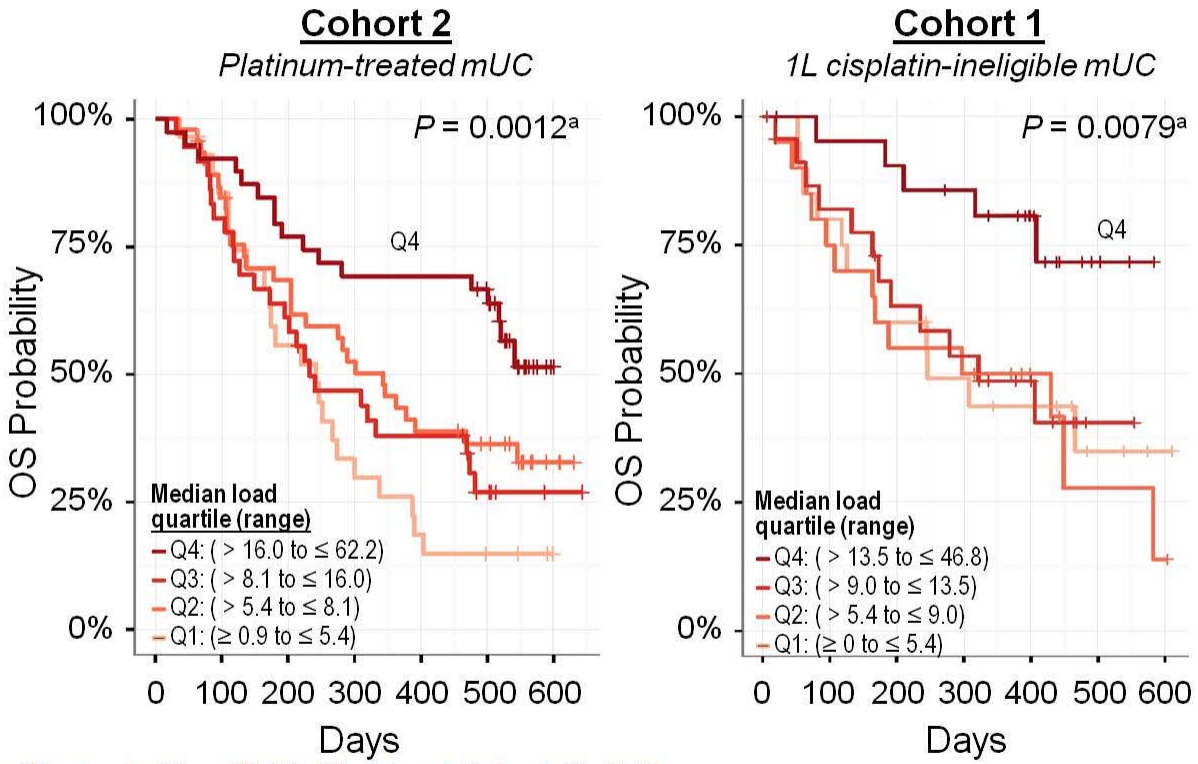
Mutation Load by FoundationOne and Response

- mUC has a high mutation load and thus potential for neoantigen generation and recognition by the immune system[1-3]
- Median load was significantly higher in responders vs non-responders
  - This relationship was statistically independent of other predictors of response



1. Lawrence *Nature* 2013. 2. Cancer Genome Atlas Research Network *Nature* 2014. 3. Kandoth *Nature* 2013. Data cutoff: March 14, 2016.

Mutation Load by FoundationOne and Survival



[a] *P* value for Q4 vs Q1, Q2, Q3. Data cutoff: March 14, 2016.

- Quartile-split mutation load was associated with OS in platinum-treated patients (cohort 2)
- Similar results were seen for 1L cisplatin-ineligible patients (cohort 1)
  - In both cohorts, patients with the highest median mutation load (Q4) had significantly longer OS vs those in Q1-Q3[a]

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Neurologic Toxicities associated with Checkpoint Inhibitors

- Non-reversible paralysis/myasthenia gravis
- Polyradiculitis
- Meningoradiculitis
- Guillian-Barré syndrome
- Seizure
- Neuritis, paresthesia, parkinsonoid symptoms

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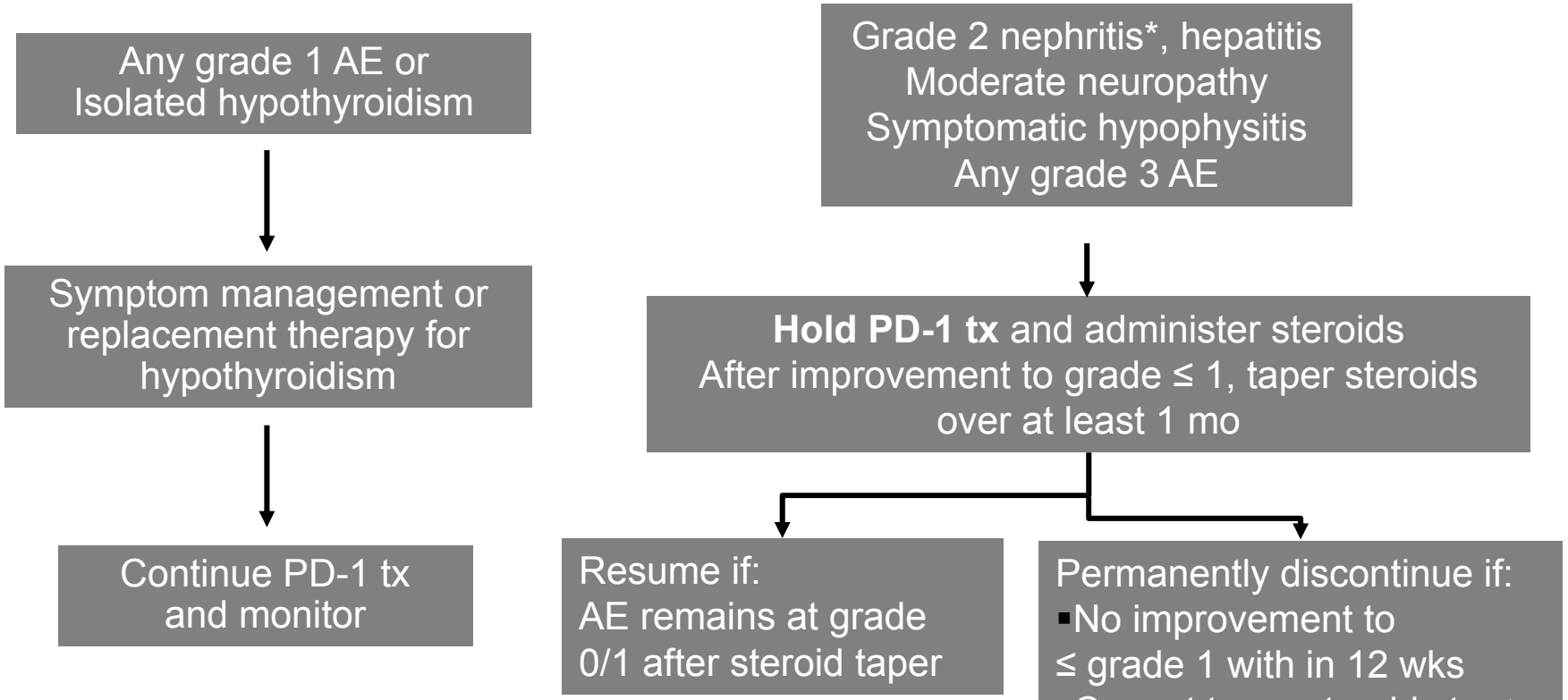
Checkpoint Inhibition: Managing Treatment-Related Adverse Events



*Consider renal biopsy to confirm immune infiltrate

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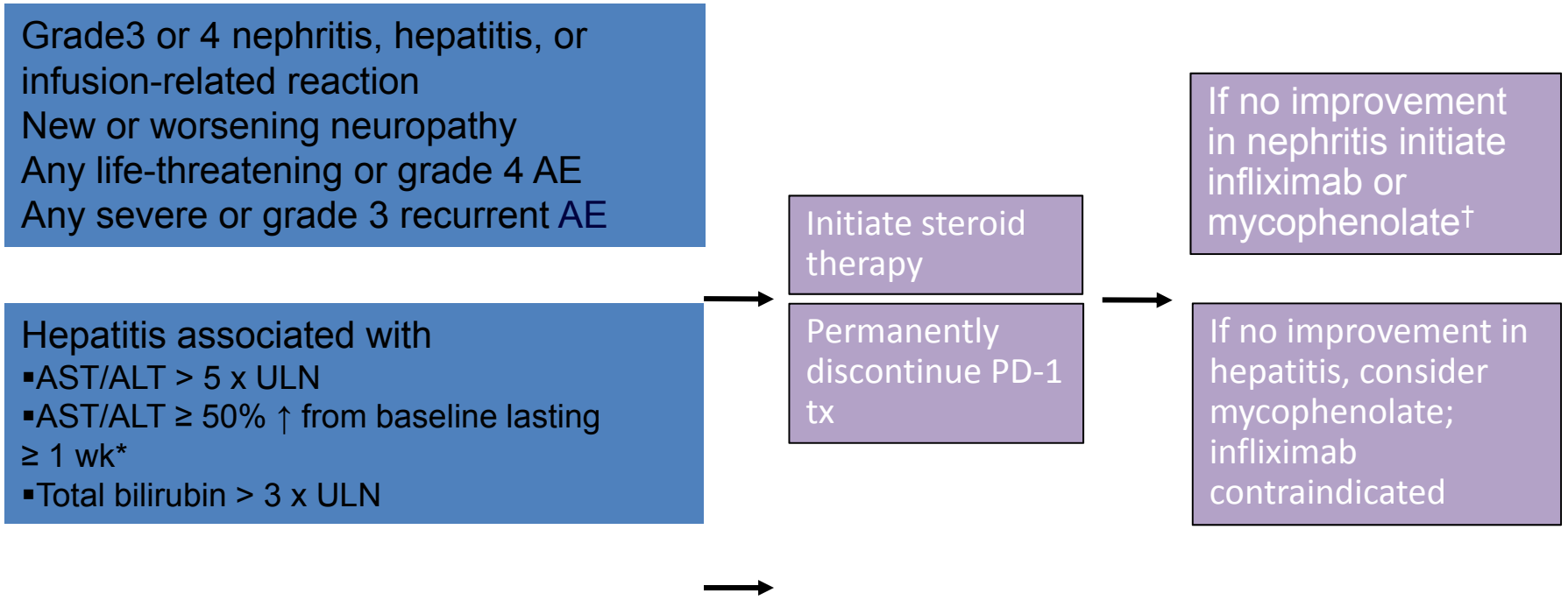
Checkpoint Inhibition: Managing Select Grade 3/4 Treatment-Related Adverse Events



*In pts with liver metastasis who begin treatment with grade 2 elevation of AST/ALT.
†Pts receiving ipilimumab may tolerate treatment with PD-1/PD-L1 inhibitor alone.
‡Steroids do not appear to accelerate the rate of improvement.

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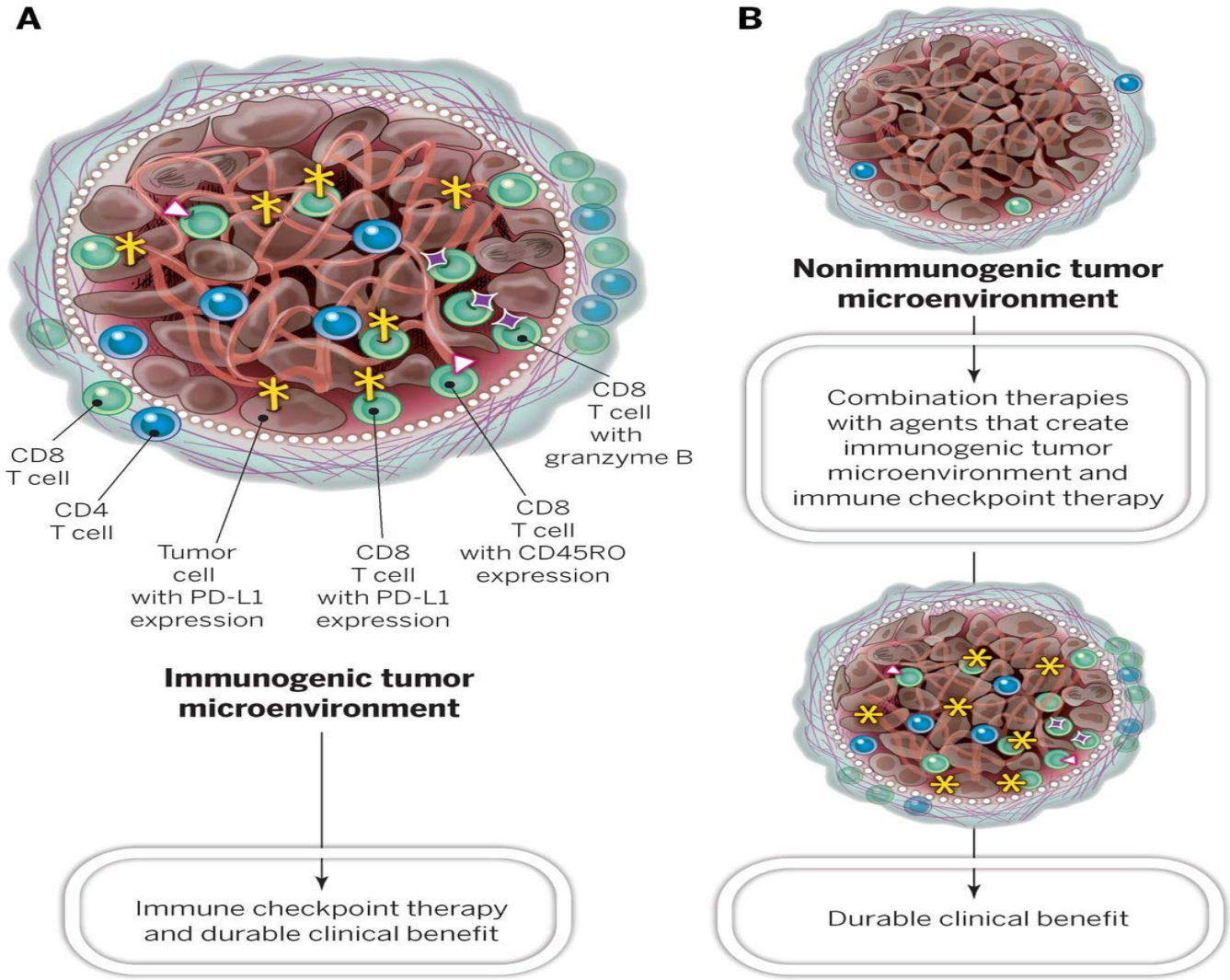
Fig. 3 Potential characteristics of immunogenic and nonimmunogenic tumors.



Padmanee Sharma, and James P. Allison Science 2015;348:56-61