

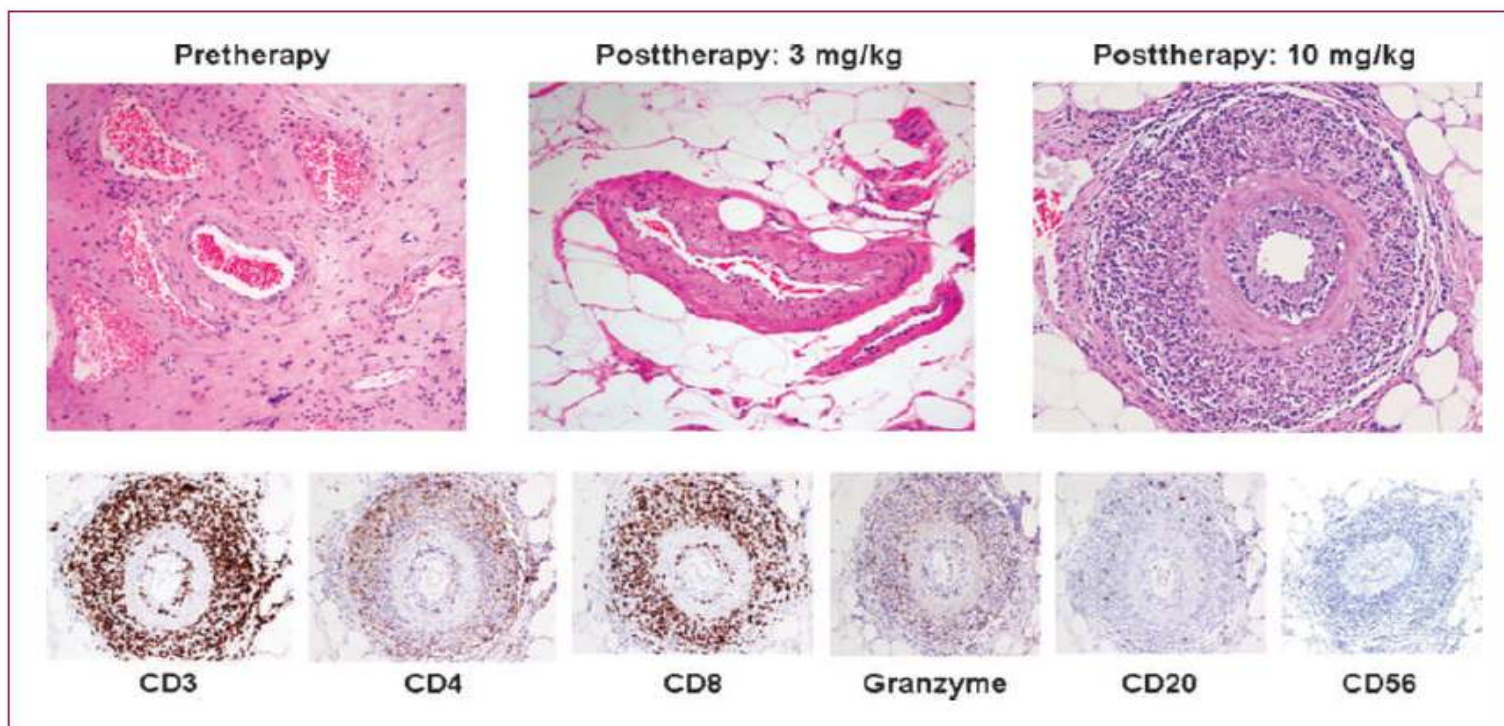
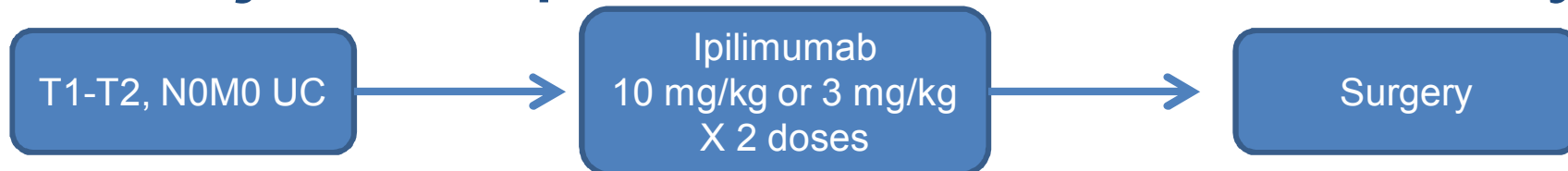
# IMMUNE CHECKPOINT BLOCKADE IN UROTHELIAL CANCER

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Elizabeth R. Plimack MD MS  
Director, Genitourinary Clinical Research  
Associate Professor, Hematology/Oncology  
Fox Chase Cancer Center, Temple Health

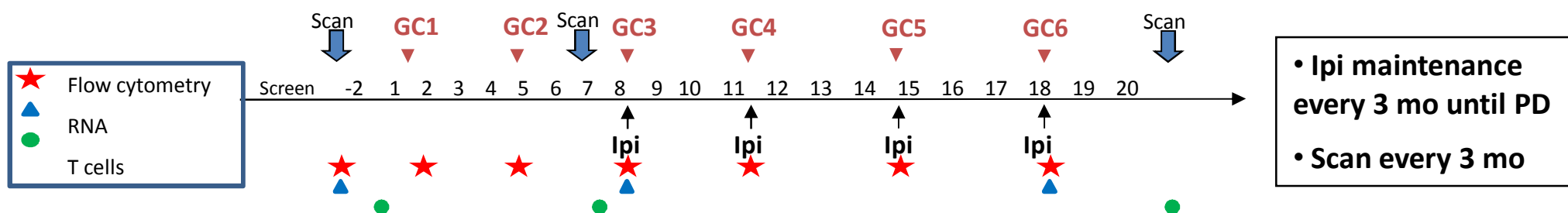


# Neoadjuvant Ipilimumab “window” study



Carthon, B.C., Sharma, P. Clin Cancer Res, 2010. NCT00362713

# Gem Cis + Ipilimumab in Metastatic UC



Trial completed enrollment (n=36), await clinical results

Immune Cell Subset	Baseline (median, IQR)	Post GC (median, IQR)	Post GC + Ipi (median, IQR)	Wilcoxon signed-rank test (p value)		
				Post-GC versus Baseline	Post-GC + Ipi versus Post GC	Post-GC + Ipi versus Baseline
%CD4	8.3 (5.5-13.0)	9.7 (5.1-16.4)	15.8 (9.4-27.0)	0.13	0.008	0.001
%CD8	4.4 (2.6-6.7)	4.8 (3.1-7.6)	7.3 (4.2-13.5)	0.9	0.06	0.01
%Tregs	6.5 (4.1-7.4)	6.2 (5.2-8.8)	6.2 (4.4-8.0)	0.6	0.4	0.8
%Gran MDSC	0.05 (0.01-.1)	0.04 (0.01-0.1)	0.04 (0.01-0.08)	0.7	0.8	0.4
%Mono MDSC	0.01 (0.007-0.03)	0.01 (0.004-0.02)	0.02 (0.007-0.03)	0.3	0.09	0.9

Galsky, M.D., et al. ASCO Meeting Abstracts **33**, 4586 (2015) NCT01524991

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

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

<sup>1</sup>Yale Cancer Center, New Haven, CT; <sup>2</sup>Barts Cancer Institute, Queen Mary University of London, London, UK;

<sup>3</sup>Bladder Cancer Center, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA;

<sup>4</sup>Comprehensive Cancer Centers of Nevada, Las Vegas, NV; <sup>5</sup>Gustave Roussy, Villejuif, France;

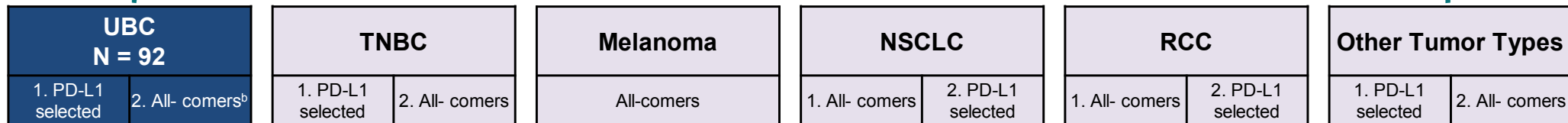
<sup>6</sup>Vall d'Hebron University Hospital, Barcelona, Spain; <sup>7</sup>Sarah Cannon Research Institute, Nashville, TN;

<sup>8</sup>Genentech, Inc., South San Francisco, CA; <sup>9</sup>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

Ongoing dose-expansion phase



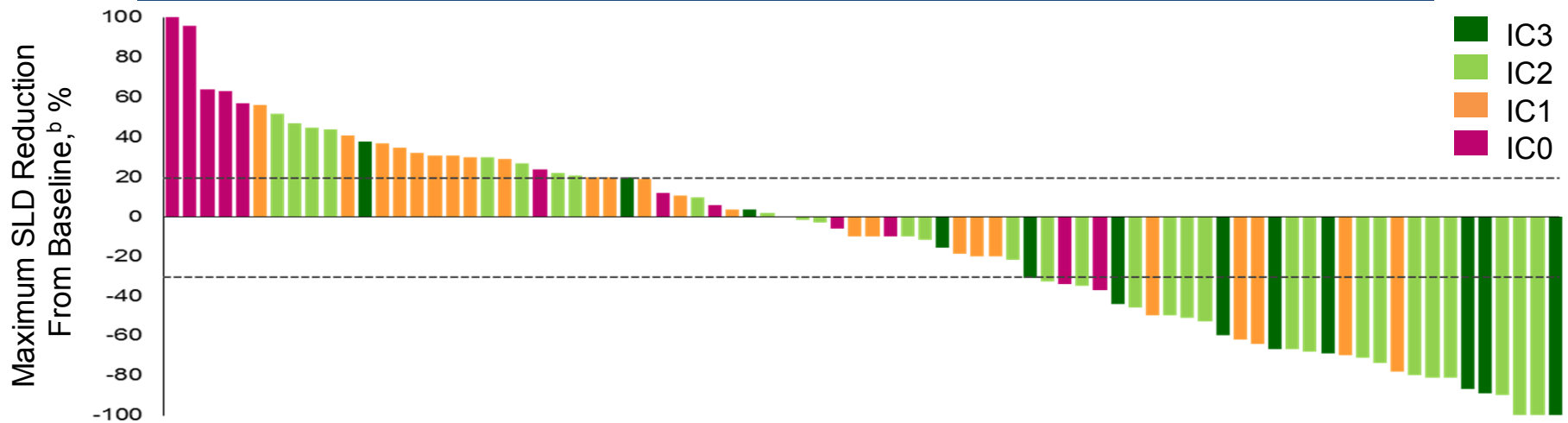
## Key Eligibility Criteria:

- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1

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

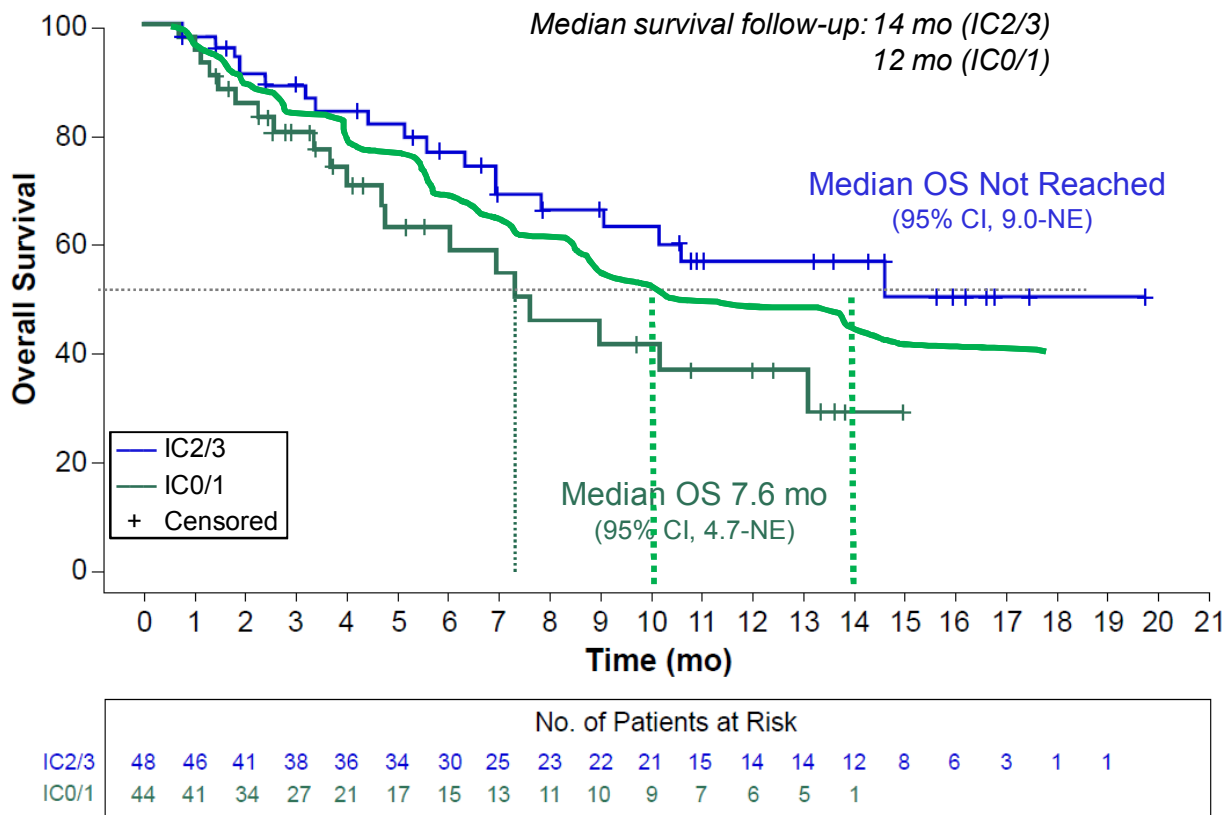
# Atezolizumab (MPDL3280A): Response

Overall Response Rate = 34% (30/87)



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

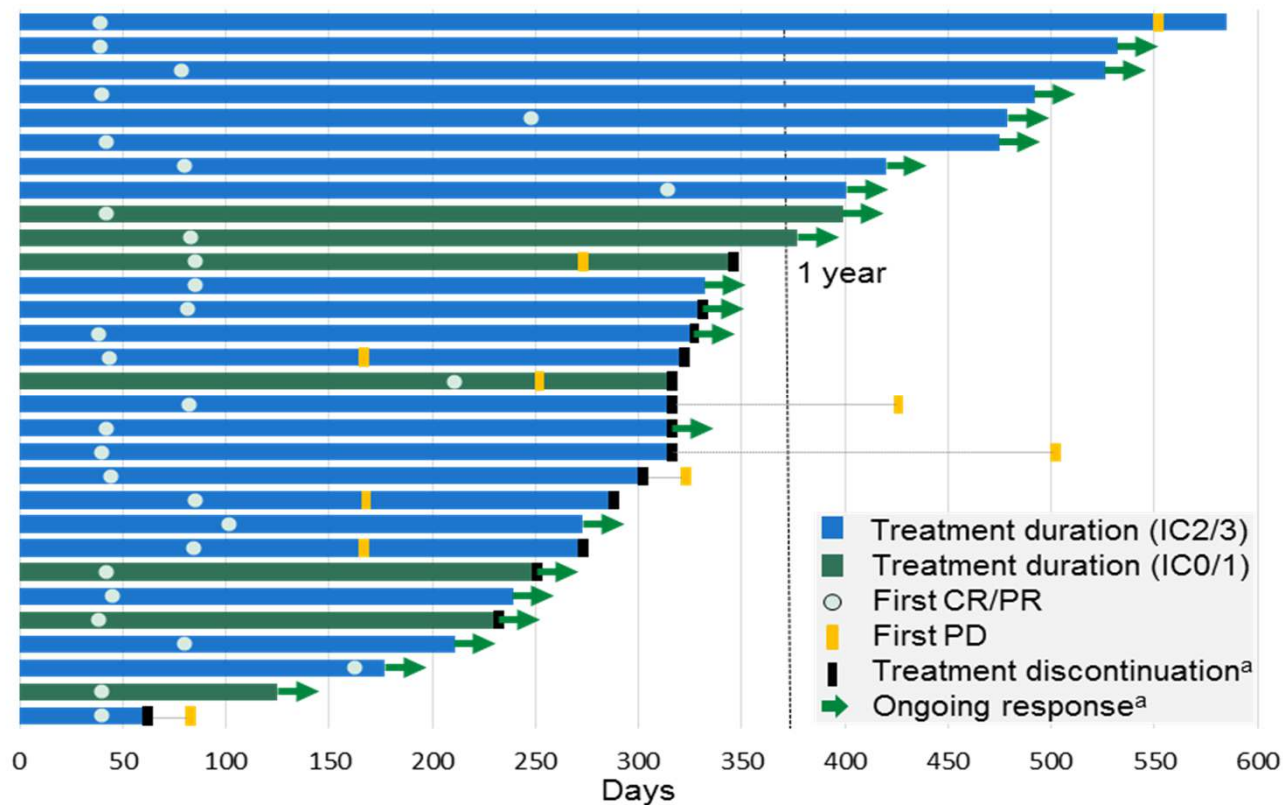
# Atezolizumab (MPDL3280A): Survival



Survival <sup>a</sup>	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

# 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



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

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

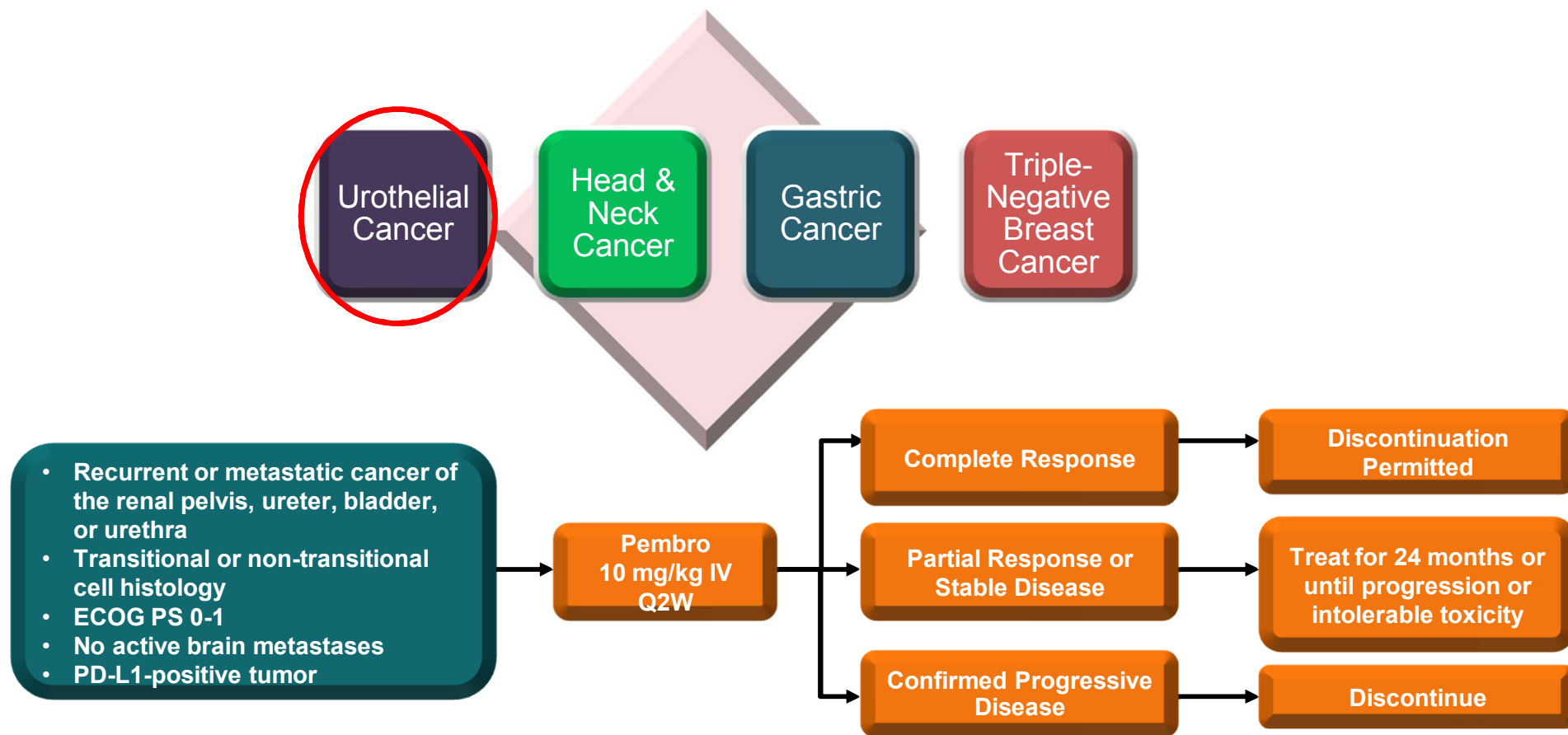
<sup>1</sup>Fox Chase Cancer Center, Philadelphia, PA, USA,

<sup>2</sup>Dana-Farber Cancer Institute, Boston, MA, USA,

<sup>3</sup>H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA,

<sup>4</sup>Sheba Medical Center, Tel Hashomer, Israel, <sup>5</sup>University of Washington, Seattle, WA, USA, <sup>6</sup>Merck & Co., Inc., Kenilworth, NJ, USA, <sup>7</sup>University of Chicago, Chicago, IL, USA

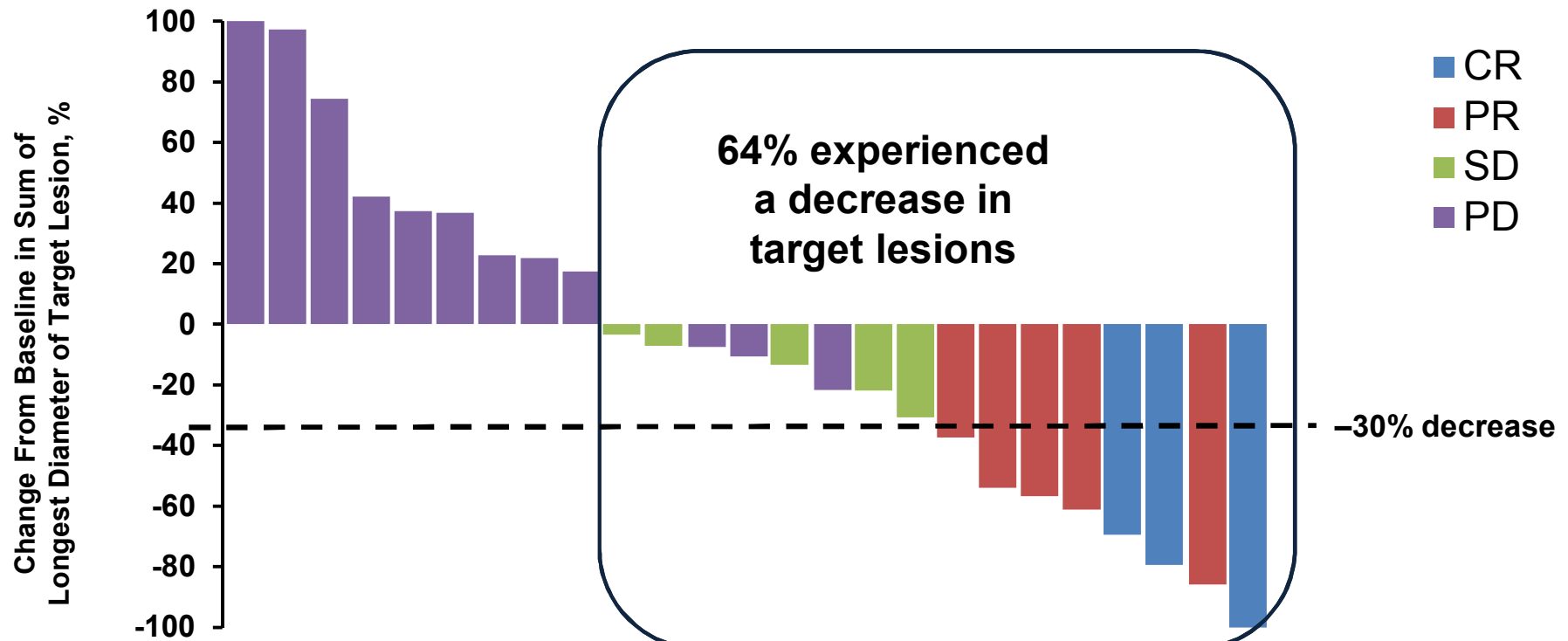
# Pembrolizumab KEYNOTE-012 : UC Cohort



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

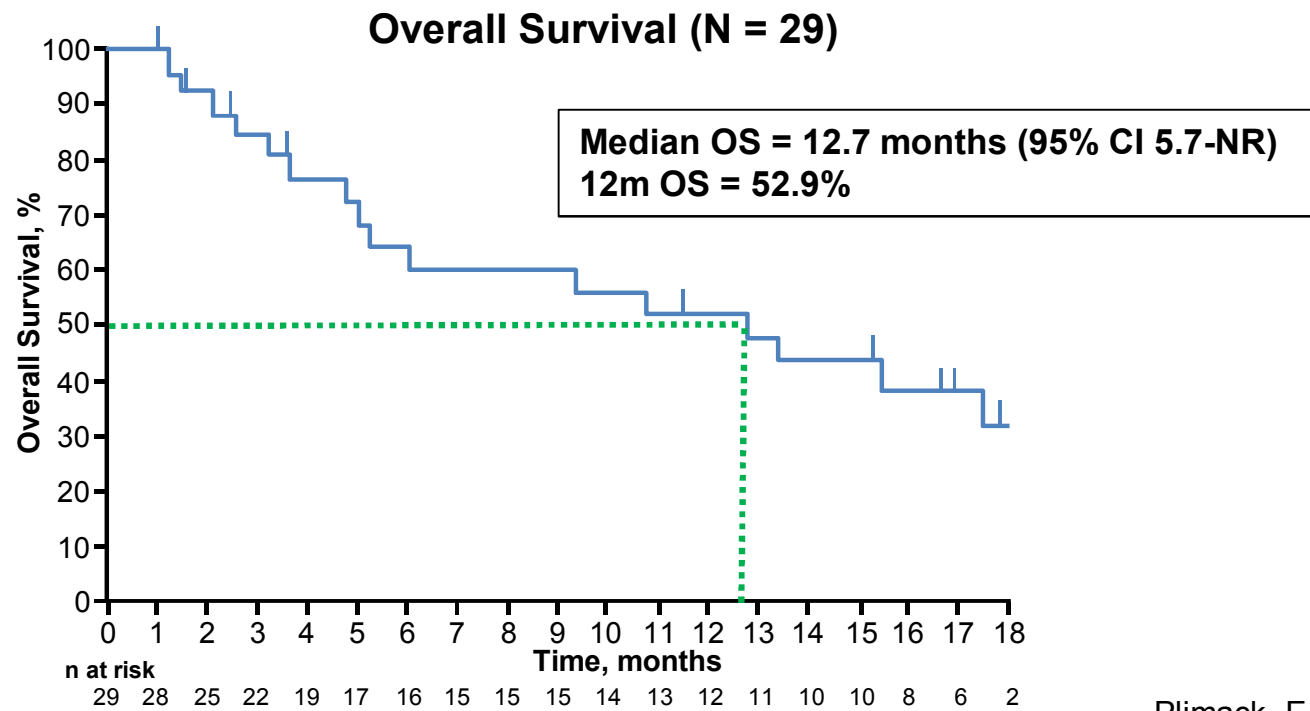
# Pembrolizumab: Response

**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



# Post-Platinum mUC Single Agent Studies

**Response Rate = 12%**

**PFS = 3 months**

**OS = 7 months**

<sup>1</sup>JCO 1997;15(1):589-93 / <sup>2</sup>JCO 1997;15(5):1853-7 / <sup>3</sup>Eur J Can 1998;34(8):1208-12 / <sup>4</sup>JCO 2002;20(4):937-40 / <sup>5</sup>JCO 2006;24(21):3451-7 / <sup>6</sup>Invest New Drugs 2007;25(3):265-70 / <sup>7</sup>The Oncologist 2015;20(5):508-15 / <sup>8</sup>Cancer 2007;110(4):759-63 / <sup>9</sup>JCO 2009;27(27):4454-61 / <sup>10</sup>Cancer 2009;115(18):4090-5 / <sup>11</sup>Cancer 2009;115(13):2881-90 / <sup>12</sup>JCO 2010;28(8):1373-79 / <sup>13</sup>Lancet Oncol 2013;14(8):769-76.

Slide courtesy Noah Hahn, ASCO 2015

# Atezo and Pembro Fast Facts

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

<sup>1</sup>ASCO 2015;abst 4501 / <sup>2</sup>ASCO2015;abst 4502.

Slide courtesy Noah Hahn, ASCO 2015

# Effect of PD-L1 status on mUC Response

<sup>1</sup>Atezolizumab (Petrylak et al)

<sup>2</sup>Pembrolizumab (Plimack 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)	

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%)

<sup>1</sup>ASCO 2015;abst 4501 / <sup>2</sup>ASCO2015;abst 4502.

Slide courtesy Noah Hahn, ASCO 2015



# PD-L1 Status Summary

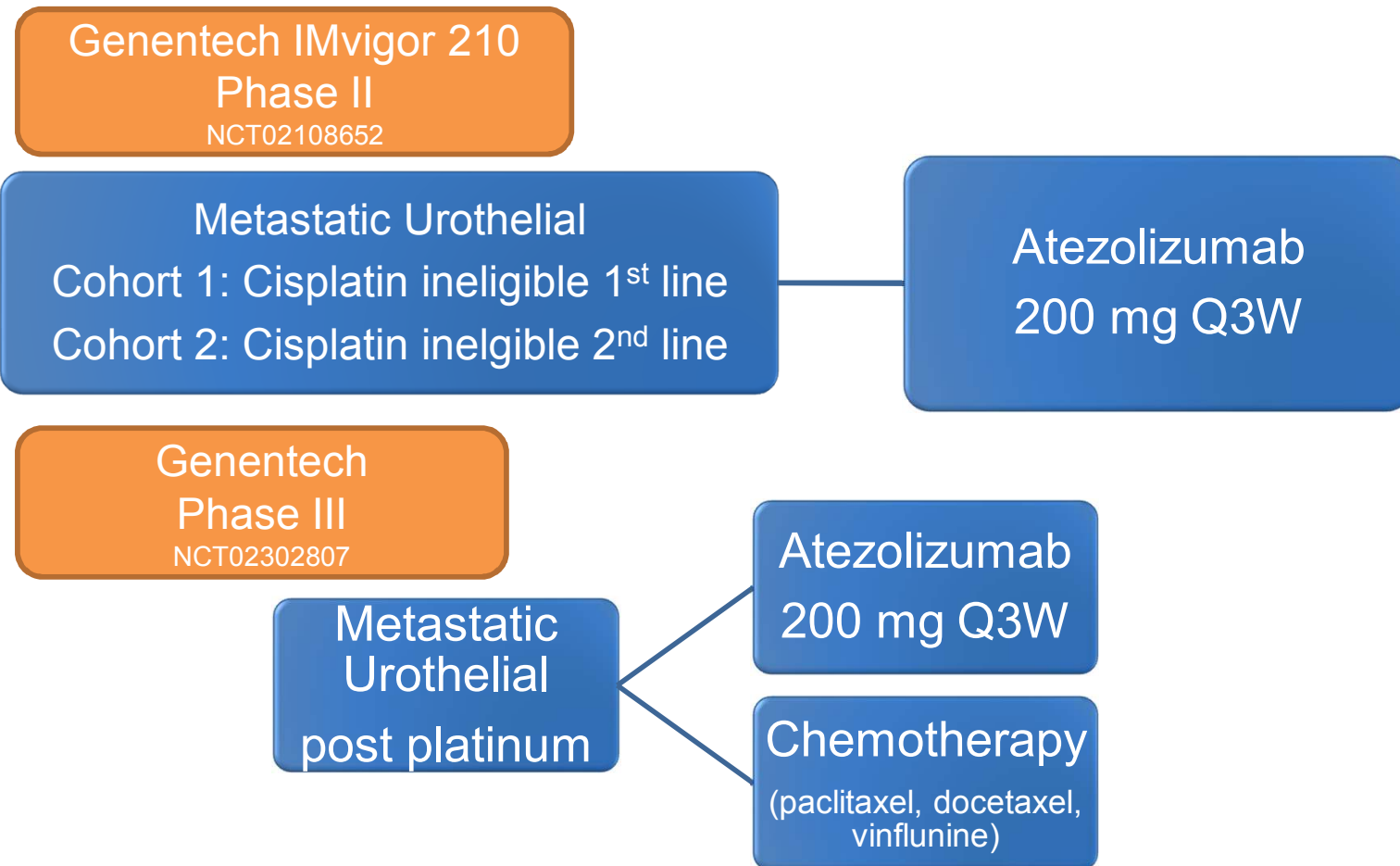
Author	Population	Agent	Target	PD-L1 Ab	Cutoff	PD-L1+ ORR	PD-L1- ORR
<sup>1</sup> Petrylak	mUC	Atezolizumab	PD-L1	SP142	5% IC	50%	17%
<sup>17</sup> Herbst	mSolid Tumors	Atezolizumab	PD-L1	SP142	5% IC	34%	16%
<sup>18</sup> McDermott	mRCC	Atezolizumab	PD-L1	SP142	1% IC	20%	10%
<sup>19</sup> Horn	mNSCLC	Atezolizumab	PD-L1	SP142	10% IC or TC	45%	14%
<sup>2</sup> Plimack	mUC	Pembrolizumab	PD-1	22C3	1% TC	33%	9%
<sup>20</sup> Daud	mMel	Pembrolizumab	PD-1	22C3	1%TC	53%	6%
<sup>21</sup> Garon	mNSCLC	Pembrolizumab	PD-1	22C3	50% TC+IC	45%	17%
<sup>3,22</sup> Choueiri	mRCC	Nivolumab	PD-1	28-8	5% TC	22%	8%
<sup>23</sup> Brahmer	mNSCLC	Nivolumab	PD-1	28-8	5% TC	15%	14%
<sup>24</sup> Callahan	mMel	Nivolumab + Ipilimumab	PD-1/CTLA-4	28-8	5% TC	41%	46%
<sup>25</sup> Hammers	mRCC	Nivolumab + Ipilimumab	PD-1/CTLA-4	28-8	1% TC	50%	55%
<sup>26</sup> Larkin	mMel	Nivolumab + Ipilimumab	PD-1/CTLA-4	28-8	5% TC	72%	58%
<sup>27</sup> Grasso	mMel	Nivolumab	PD-1	28-8	5% TC	44%	17%
<sup>28</sup> Topalian	mSolid Tumors	Nivolumab	PD-1	5H1	5% TC	36%	0%

UC = Urothelial Cancer; RCC = Renal Cell Carcinoma; NSCLC = Non-small cell lung cancer; Mel = Melanoma; IC = Immune Cells, TC = Tumor Cells

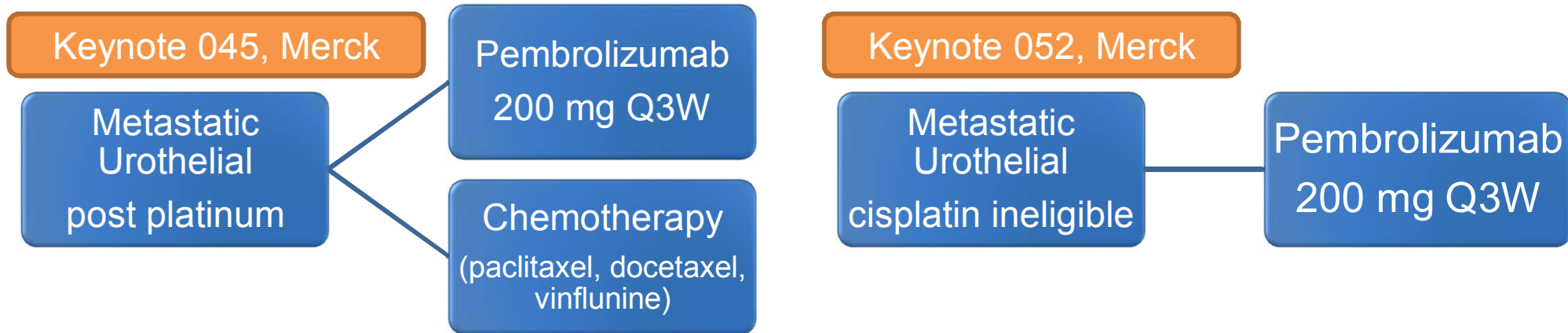
<sup>1</sup>ASCO 2015;abst 4501 / <sup>17</sup>Nature 2014;515(7528):563-67 / <sup>2</sup>ASCO2015;abst 4502 / <sup>3</sup>ASCO 2015;abst 4500 / <sup>18</sup>ESMO 2014;abst 8090 / <sup>19</sup>ASCO2015;abst 8029 / <sup>20</sup>AACR 2014;abst / <sup>21</sup>NEJM 2015;372(21):2018-28 / <sup>22</sup>ASCO 2014;abst 5012 / <sup>23</sup>ASCO 2014;abst 8112 / <sup>24</sup>J Immuno Ther Cancer 2013;1(Suppl 1):O6 / <sup>25</sup>ASCO 2014;abst 4504 / <sup>26</sup>NEJM 2015;515:in-press / <sup>27</sup>ASCO 2013;abst 3016 / <sup>28</sup>NEJM 2012;366(26):2443-54.

Slide courtesy Noah Hahn, ASCO 2015

# mUC Trial Watch: Atezolizumab (PD-L1)



# mUC Trial Watch: Pembrolizumab (PD-1)



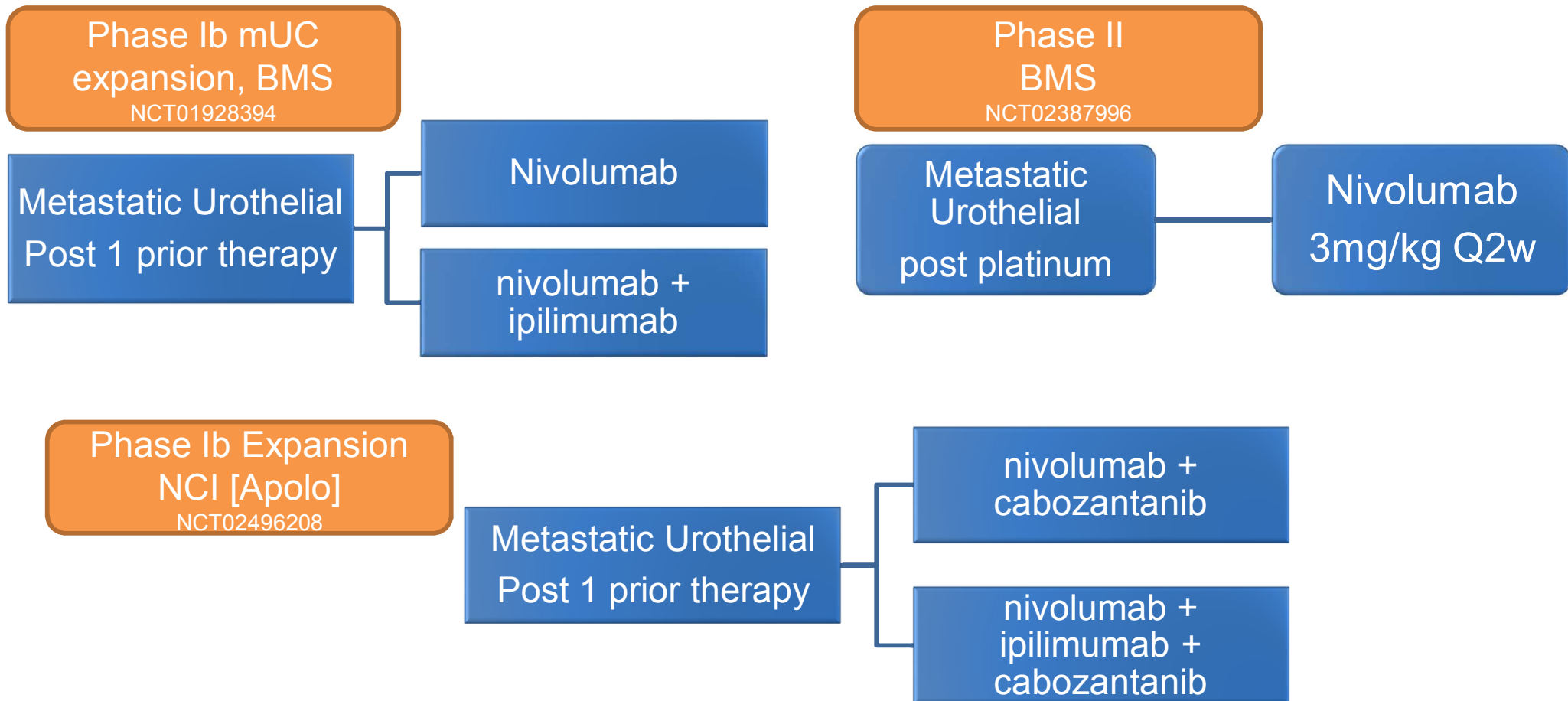
## Bladder Specific Trials

- ACP-196 (BTK inhibitor) + pembro vs. pembro [Acerta/Merck] NCT02351739
- Pembrolizumab after Initial Chemotherapy [Galsky, HOG] NCT02500121

## Basket Trials with Bladder Arm

- Pembrolizumab + Ramacicrumab [Lilly] NCT02443324
- Pembrolizumab + Radiation [Lin, Jefferson] NCT02318771
- Pembrolizumab + Lenvatinib [Eisai] NCT02501096

# mUC Trial Watch: Nivolumab (PD-1)



# Upcoming Non-metastatic Trials

## Neoadjuvant

- Atezolizumab [Fong / UCSF]
- Pembrolizumab + GC [Hoimes / Hoosier Oncology]

## Adjuvant

- Atezolizumab [Imvigor 010 / Genentech]

Others planned, not yet announced

THANK YOU

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