ESCOLA DE MEDICINA

PUCRS

New Perspectives in the Treatment of Advanced Urothelial Carcinoma

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March 03rd, 2018

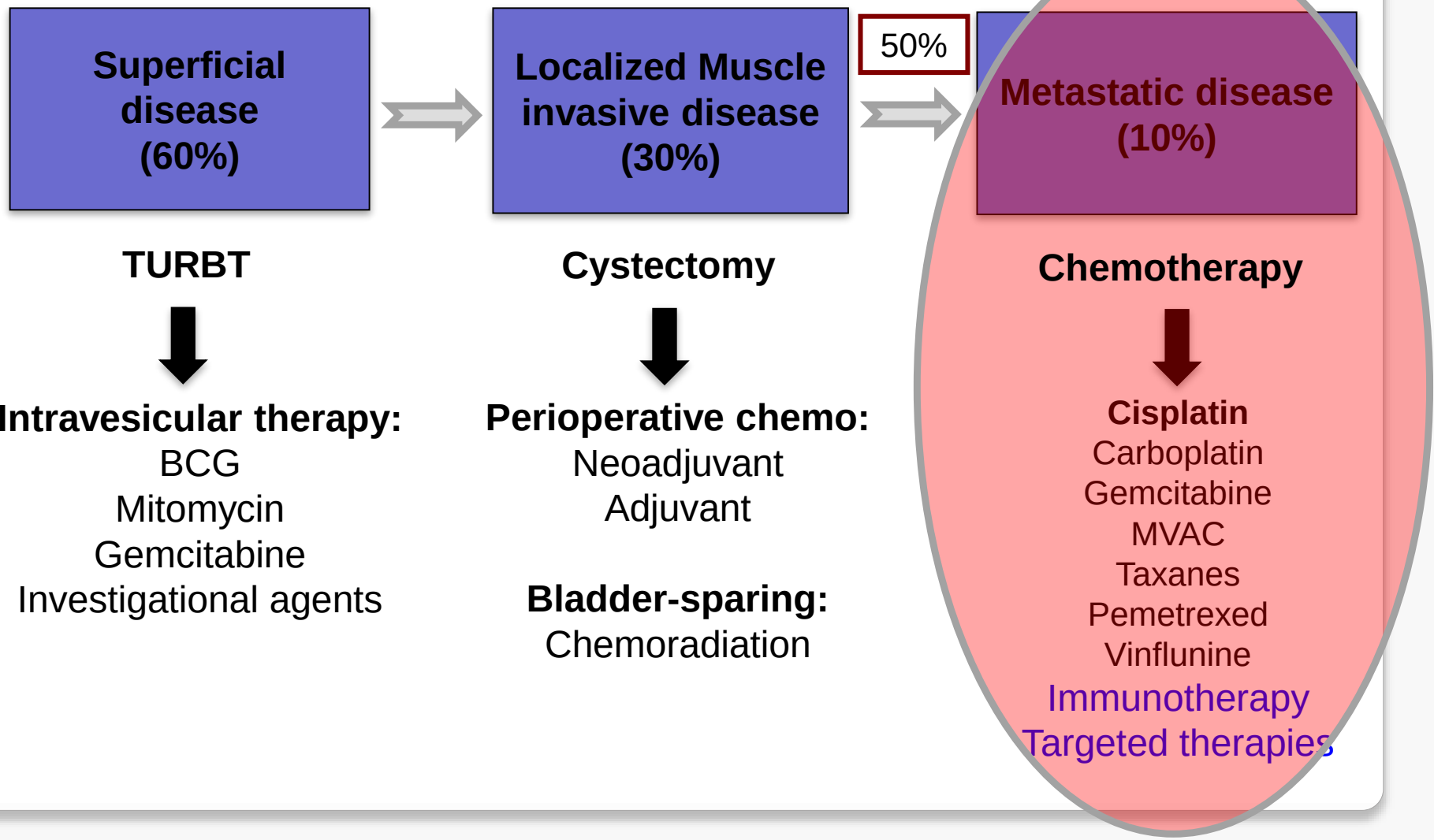
Disclosure

- Honoraria: Pfizer, Astellas, BMS, Novartis, Roche, Astra-Zeneca, MSD
- Scientific Advisory Board: Janssen, Novartis, Roche, Pfizer
- Research Grant: CAPES – CNPq, BMS, Roche, Astra-Zeneca, Pfizer, MSD

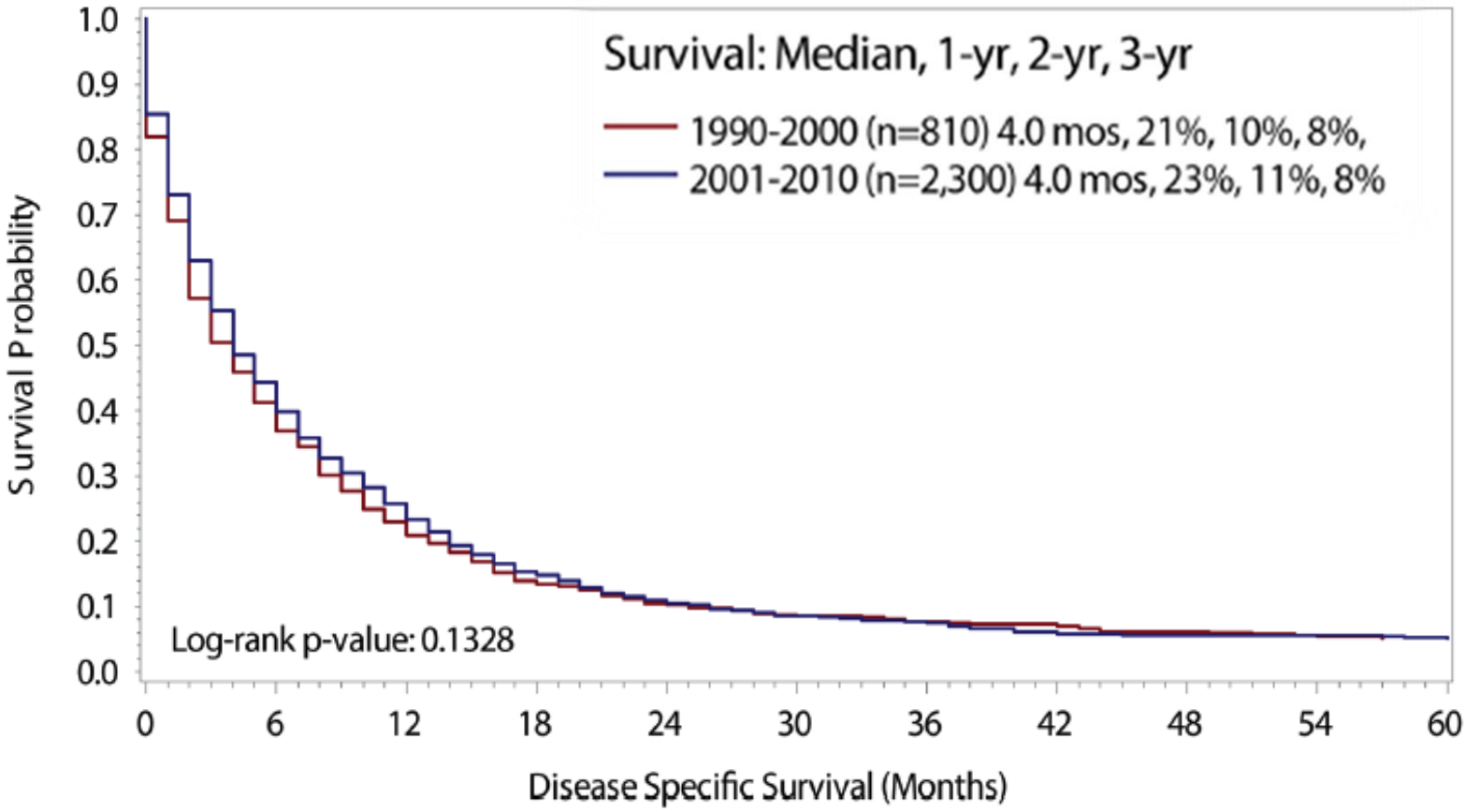
Outline

- Current State of UC Management
- Targeted Therapies
- The new era of immunotherapies
  - The Biology behind checkpoint inhibitors
  - Single agents and combinations with PD-1/PD-L1 inhibition in UC
  - Biomarkers
  - Toxicity

Management of Bladder Cancer by Stage



Metastatic Urothelial Carcinoma: an Unmet Need in the Clinic



Pal et al. PLoS One 2015

FDA Approved Drugs in Genitourinary Tumors in the last 10 years…

Year of FDA approval	Renal Cell Carcinoma	Prostate Cancer	Bladder Cancer
2006	sunitinib		
2007	temsirolimus		
	sorafenib		
2008		degarelix	
2009	everolimus		
	bevacizumab		
	pazopanib		
2010		sipuleucel-T	
		cabazitaxel	
2011		abiraterone	
		denosumab	
2012	axitinib	enzalutamide	
2013		alpharadin	
2014			
2015	nivolumab		
2016			*atezolizumab*

Presented by Andrea Apolo

Randomized Phase III Study in First Line: GC vs MVAC

MVAC

Methotrexate 30 mg/m^2 day 1, 15 and 22

Vinblastine 3 mg/m^2 day 2, 15 and 22

Adriamycin 30 mg/m^2 day 2

Cisplatin 70 mg/m^2 day 2

GC

Gemzar 1000 mg/m^2 day 1, 8 and 15

Cisplatin 70 mg/m^2 day 2

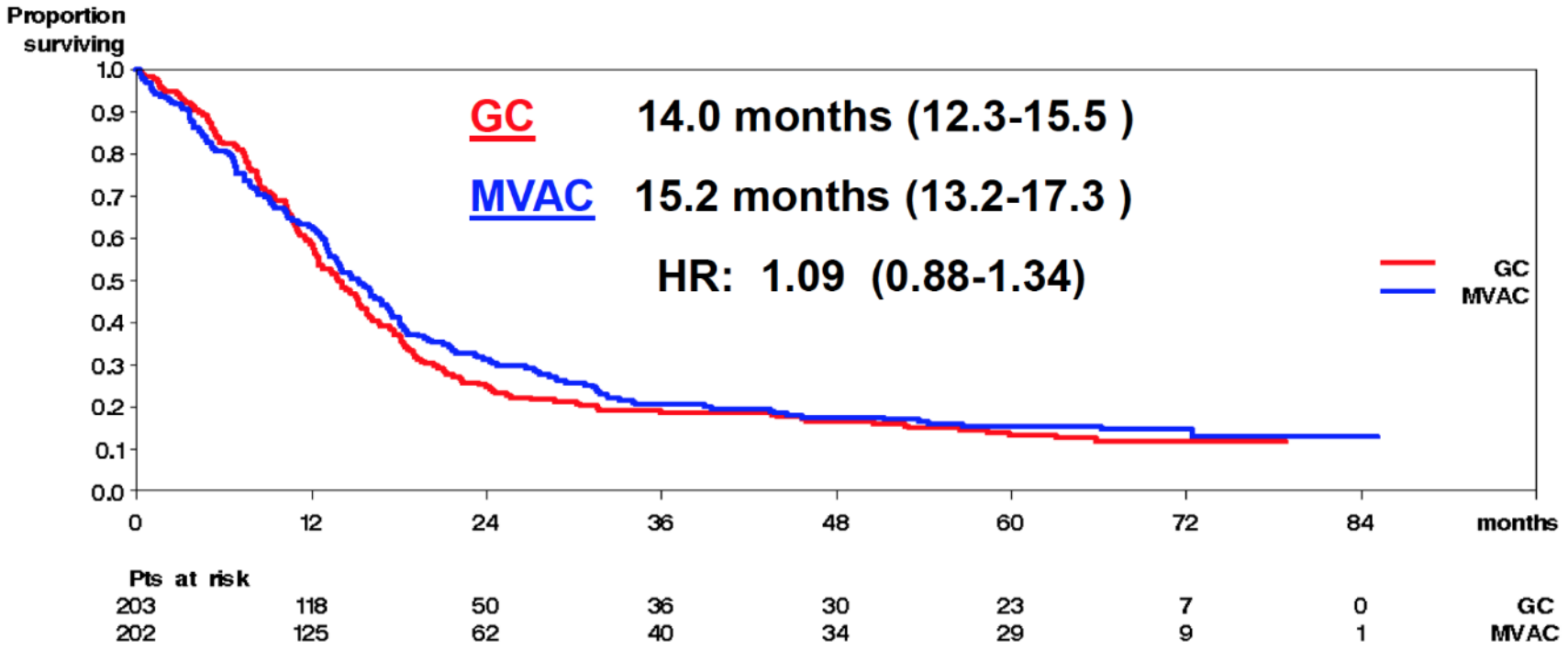
Von der Maase H, et al, JCO 2000;17:3068-77

Randomized Phase III Study in First Line: GC vs MVAC

	GC	MVAC
OVERALL SURVIVAL	13.8 mos	14.8 mos
RESPONSE RATE	49.4%	45.7%
CR	12.2%	11.9%
PR	37.2%	33.8%
SD	33.5%	32.5%
MEDIAN TTP	7.4 mos	7.4 mos

Von der Maase H, et al, JCO 2000;17:3068-77

Overall Survival: 5-year update



Von der Maase H, et al, JCO 2005;23:4602-8

Toxicity

Toxicity	GC	MVAC
Infections (grade 3-4)	3%	15%
Mucositis (grade 3-4)	1%	22%
Diarrhea (grade 3-4)	3%	8%
Alopecia (grade 3)	11%	55%
Anemia (grade 3-4)	27%	18%
Thrombocytopenia (grade 4)	29%	13%
Neutropenia (grade 4)	30%	65%
Neutropenic fever	2%	14%
Neutropenic sepsis	1%	12%
Toxic deaths	1%	3%

Von der Maase H, et al, JCO 2000;17:3068-77

Single Agents (Cytotoxic Chemotherapy) after a platinum-based therapy

Author	Study	n	RR %	OS, Months
Witte 1997	Ifosfamide	56	20	NR
Witte 1997	Topotecan	44	9	6.3
McGaffrey 1997	Docetaxel	30	13	9
Lorusso 1998	Gemcitabine	35	23	5
Paz-Ares 1998	Pemetrexed	31	29	9.5
Roth 2002	Piritrexim	35	7	7
Vaughn 2002	Paclitaxel	31	10	7.2
Albers 2002	Gemcitabine	30	11	8.7
Moore 2003	Oxaliplatin	18	6	NR
Sweeney 2006	Pemetrexed	47	28	9.6
Galsky 2006	Pemetrexed	13	8	NR
Culine 2006	Vinflunine	51	18	6.6
Dreicer 2007	Ixabepilone	45	12	8
Bellmunt 2008	Vinflunine	370	8.6	6.9
Beer 2008	Irinotecan	40	5	5.4
Joly 2009	Paclitaxel	45	9	7
Sridhar 2011	Nab-paclitaxel	48	33	NR

Systemic Therapy for Bladder Cancer Pre 2016

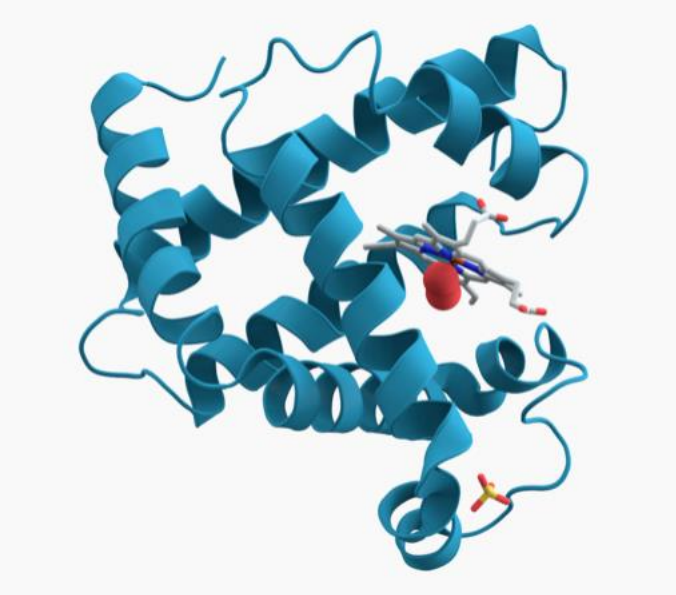
Non-Muscle Invasive	Neoadjuvant Adjuvant	1st Line Metastatic	Next Line Metastatic
No systemic therapy			
	Gem + Cisplatin or DD-MVAC		
		Gem + Cisplatin or DD-MVAC	
			• • el

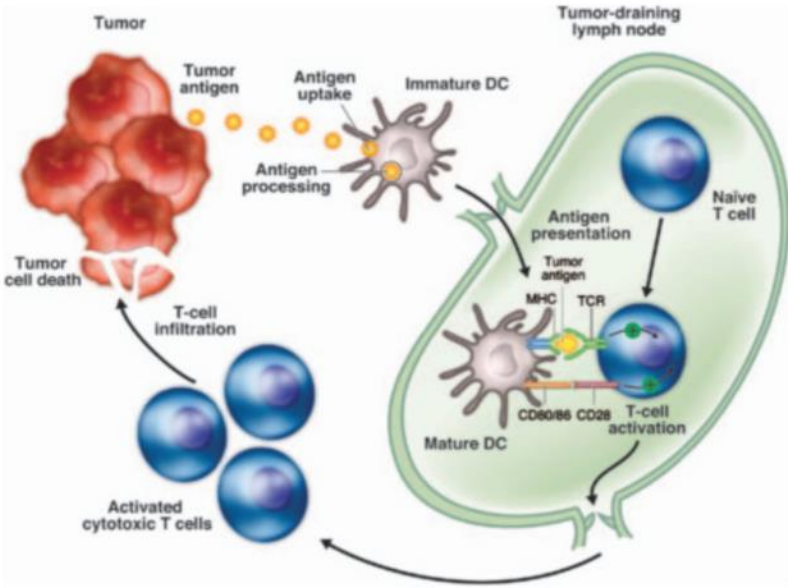
Cisplatin:
ORR 50-60%
median OS 15 mo.
1 year OS 60%
Carboplatin
ORR 36%
median OS 9 mo.
1 year OS 37%

ORR: 12%
Median OS 7 mo.
1 year OS 26%*

NCCN Guidelines. Bladder Cancer. Version 1.2016.

The Paradox of Urothelial Carcinoma

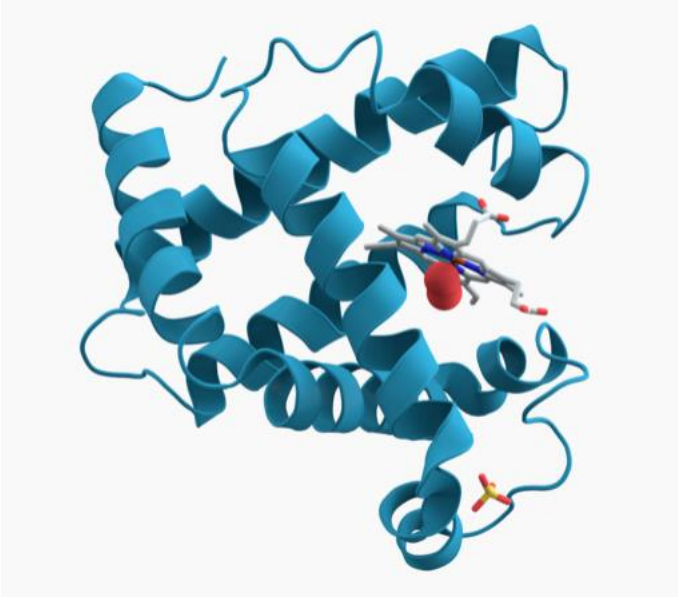




Molecular Biology

Immune System

The Paradox of Urothelial Carcinoma

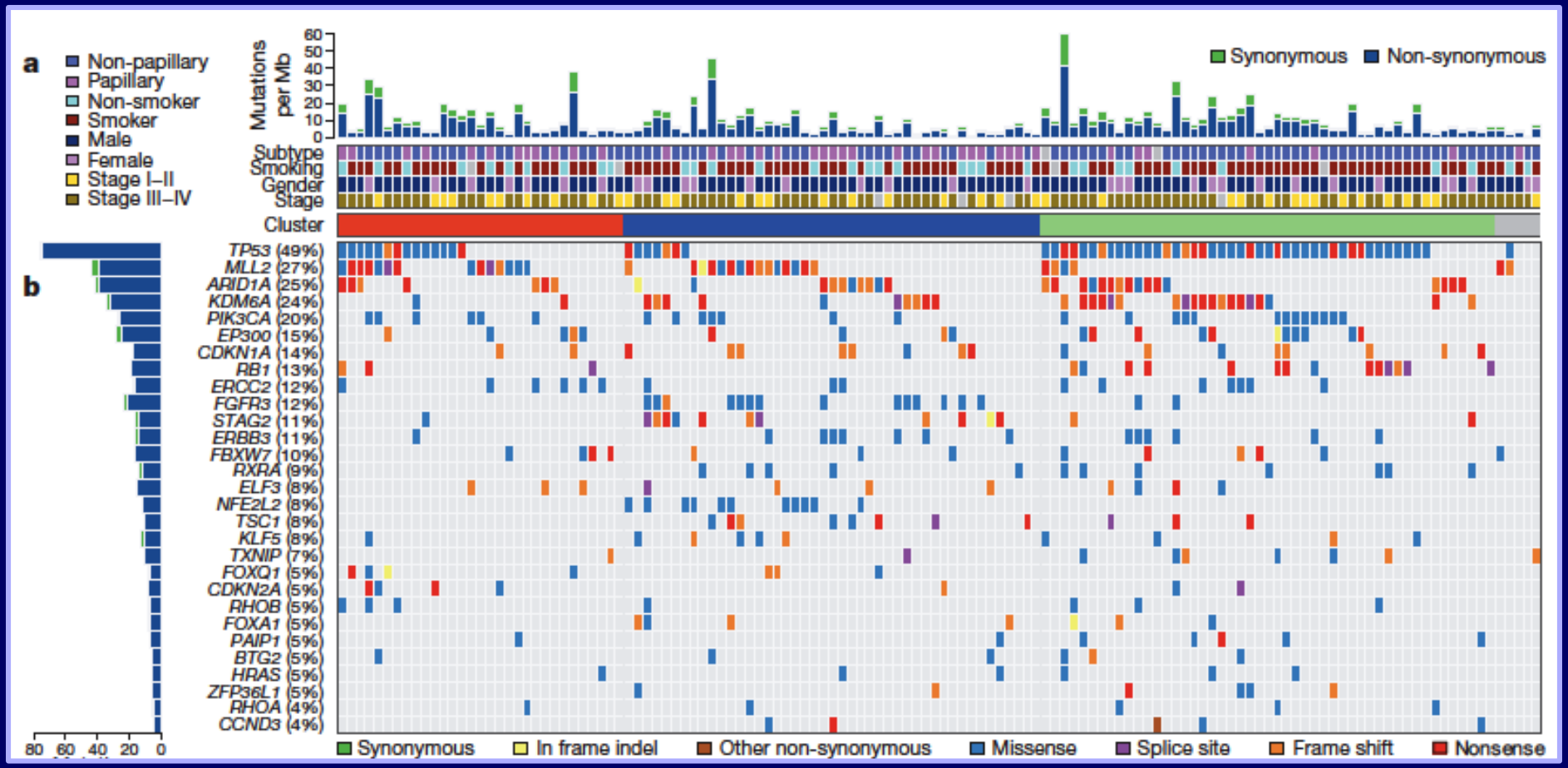


Molecular Biology

Genomics in Urothelial Carcinoma

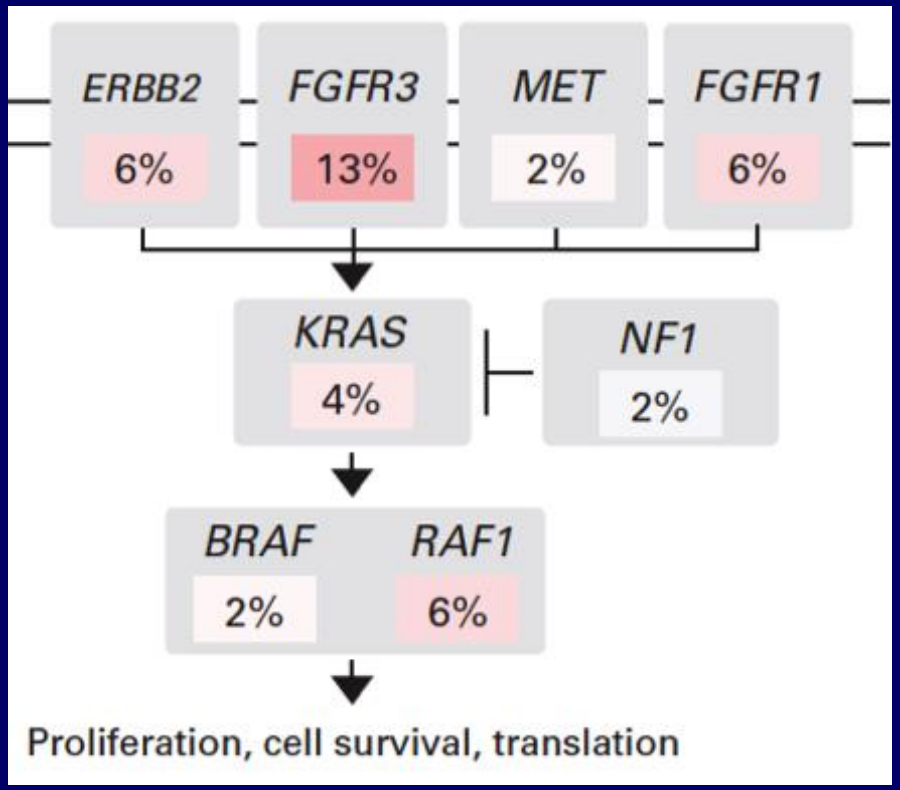
- Cancers emerge from genomic errors
- Sequencing technology is now at the bedside
- Clinical computational biology:
  - Computational algorithms to analyze and interpret genomic data from patient samples

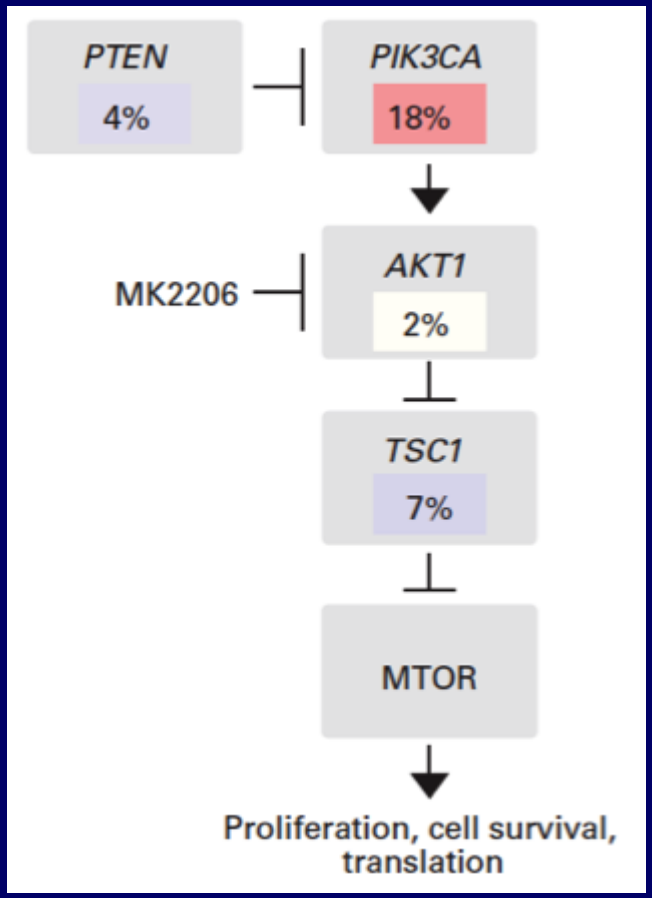
Comprehensive molecular characterization of urothelial bladder carcinoma



The Cancer Genome Atlas Research Network. Nature 2014

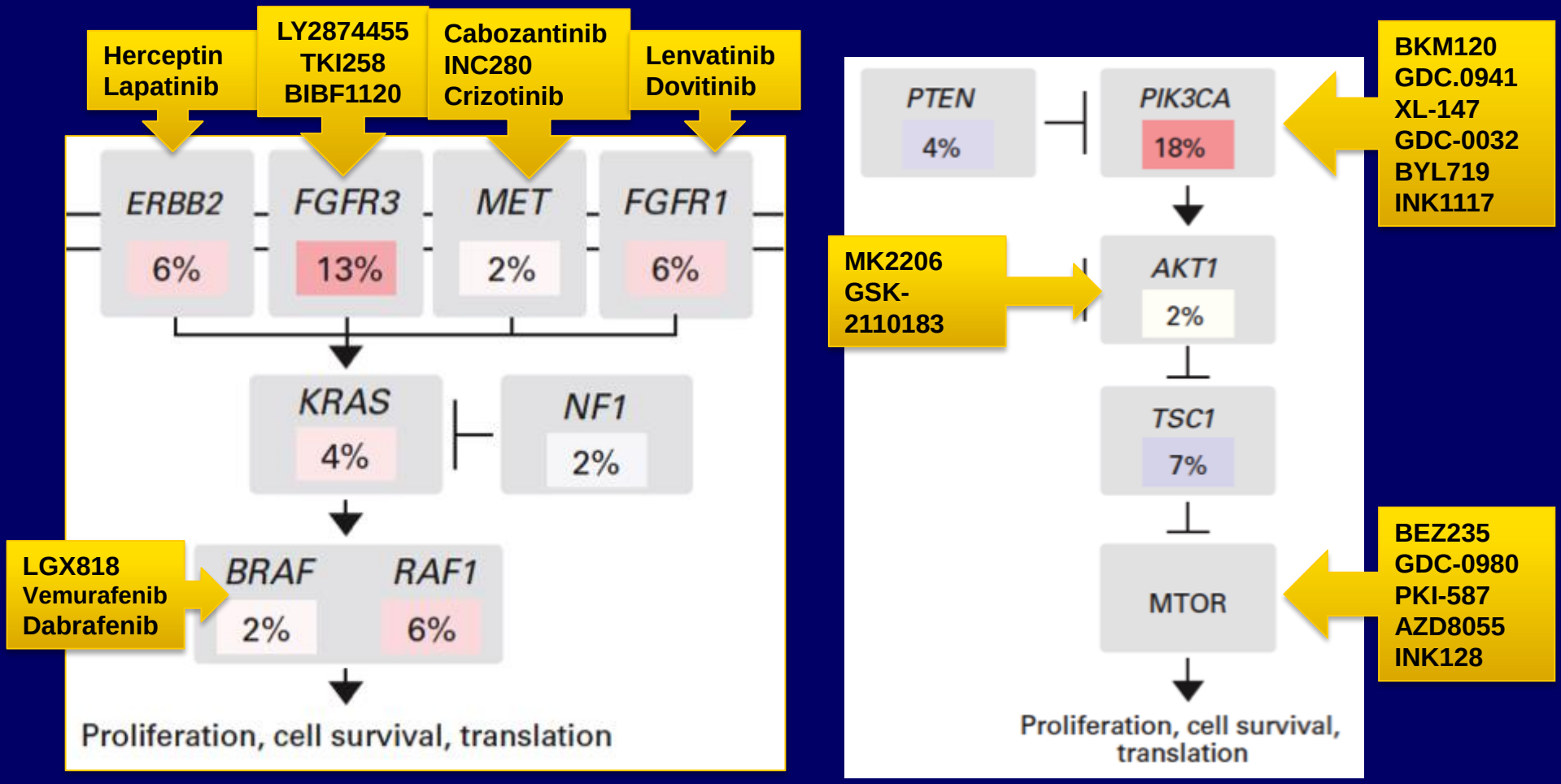
Emerging molecular pathways in Advanced Urothelial Tumors





Iyer G, et al. J Clin Oncol 2013;31(25):3133-40

Emerging molecular pathways in Advanced Urothelial Tumors

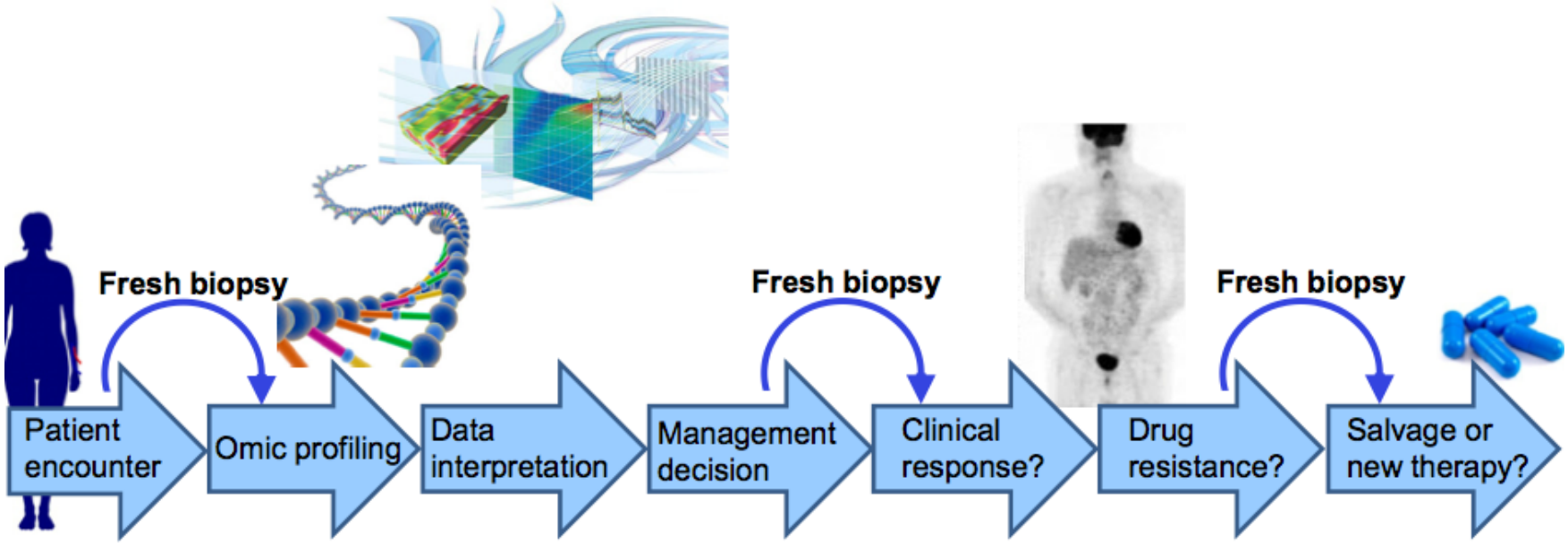


Iyer G, et al. J Clin Oncol 2013;31(25):3133-40

Single Targeted Agents in urothelial Carcinoma

Author	Line	Agent	Target	n	RR %	OS Months
Gomez-Abuin 2007	Second	Bortezomib	Proteasome inhibitor	20	0	NR
Wulfing 2009	Second	Lapatinib	HER1 and HER2	59	3	4.5
Petrylak 2009	Second	Gefitinib	EGFR	31	3	3
Dreicer 2009	Second	Sorafenib	B-Raf,c-Raf, VEGFR-2/3, PDGFR-b	27	0	6.8
Gallagher 2010	Second	Sunitinib	EGFR, VERFR-1/2, C-KIT, PDGFR a/b,FLT3 and RET	45	7	6.9
Milowsky 2011	Second	Everlolimus	PI3K/Akt/mTOR	45	5	10.5

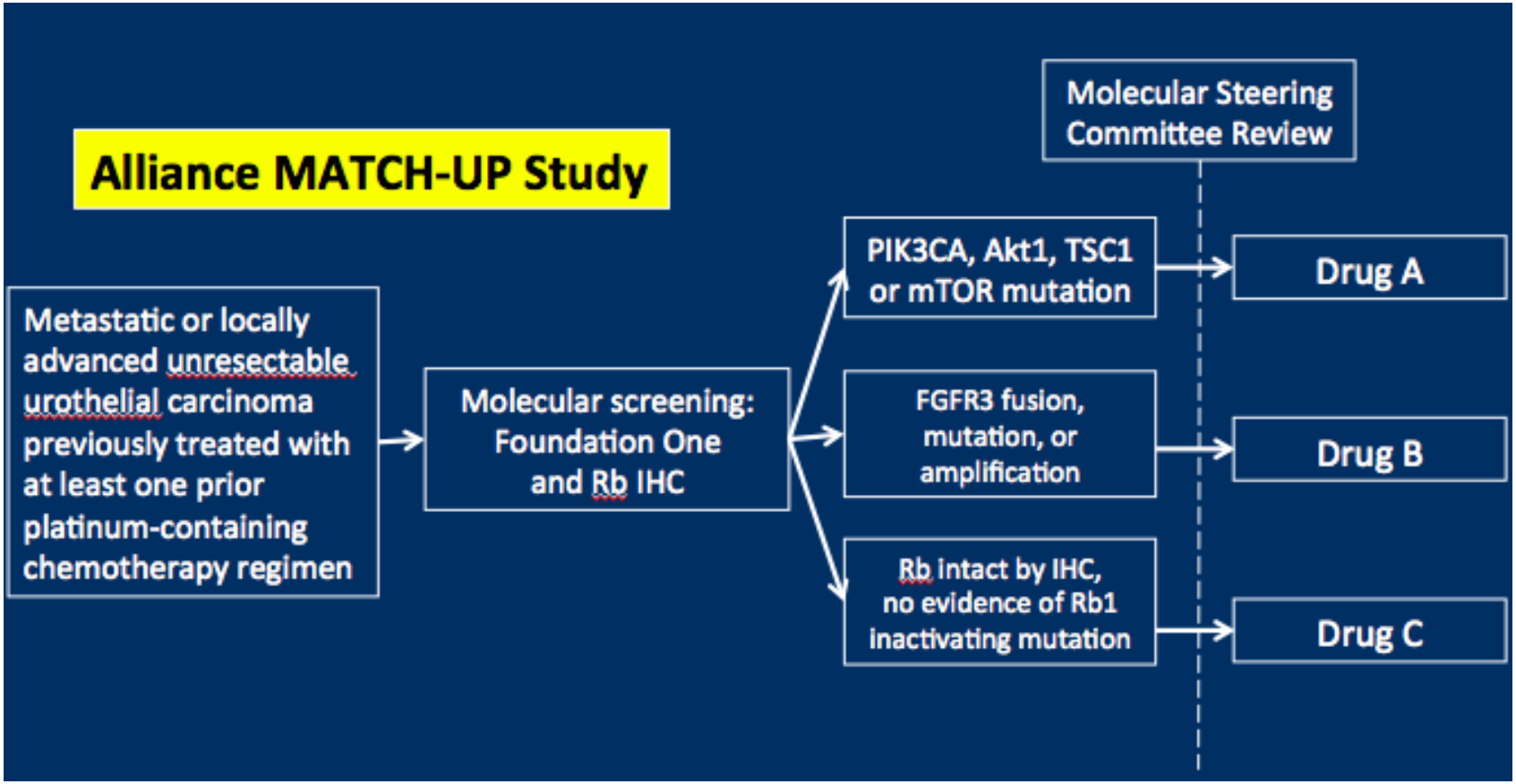
The Engine of Precision Cancer Medicine



- Does genetic/molecular stratification identify patient subgroups that benefit from novel agents?
- Does the drug inhibit the relevant oncogenic pathway?
- What are the mechanisms of resistance to existing or emerging agents?
- What combinations hold promise to achieve more durable control?

Levi Garraway, Journal of Clinical Oncology, 2013

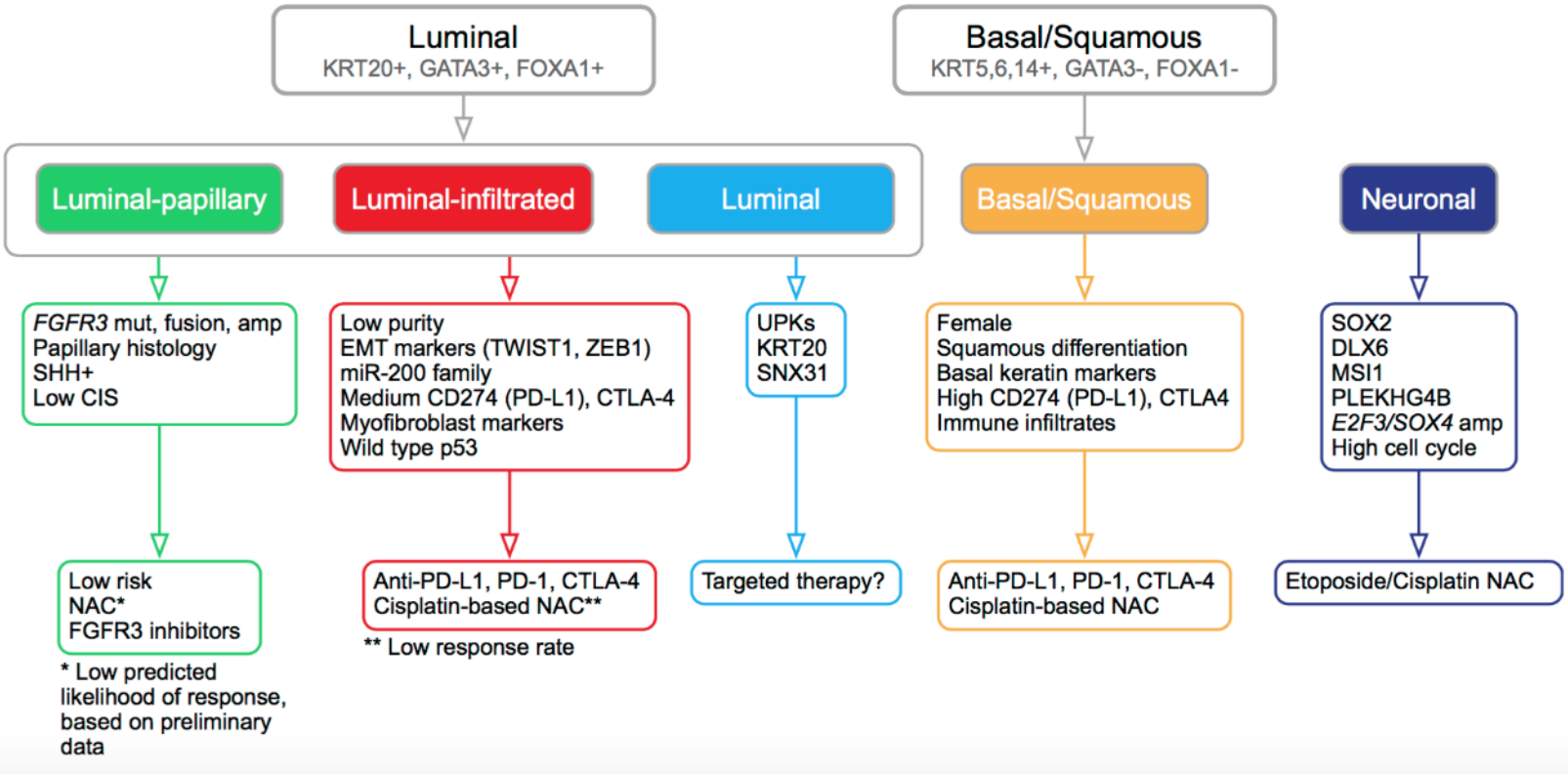
“Umbrella” versus “Basket” studies to accelerate clinical drug development in urothelial cancer?



Alliance for Clinical Trials in Oncology

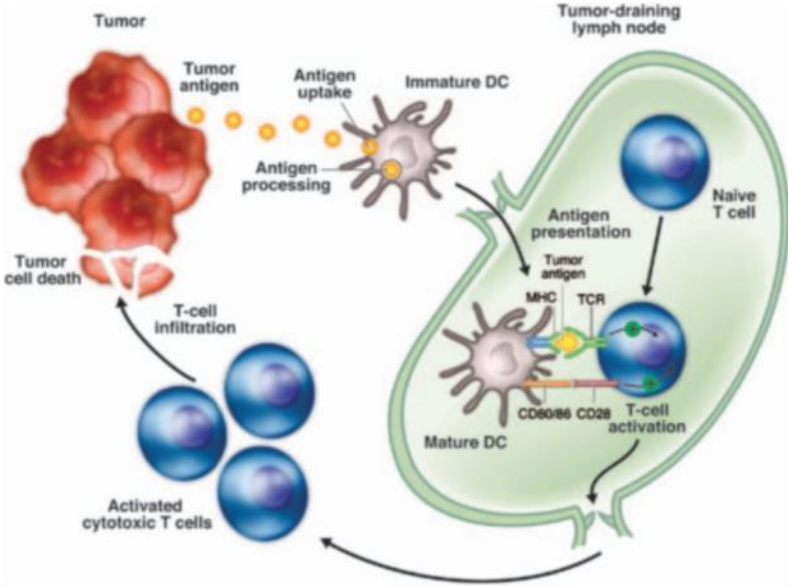
PI: J. Rosenberg

Molecular Classification → Therapeutic Strategies



Robertson G et al. Cell 2017

The Paradox of Urothelial Carcinoma



Immune System

1265 DC

Saint Peregrine, O.S.M. – the patron saint of cancer patients

Some time in the latter part of his life a disease "... which caused this decaying and so strange swelling of his shin, which they call cancer, came most harshly; from it such a horrible stench was given off that it could be endured by no one sitting by him."[1] He was visited by a physician called

Infection and Cancer

his shin was normal. He gave thanks and returned to his room. When the physician came in the morning to perform the operation, Peregrine told of the cure. The physician thought that Peregrine was out of his mind because of the severity of the disease. " 'Show me your shin,' Paulus Salatius said, 'so that I may protect you from the infective destruction of your whole body.' Peregrine replied, 'O doctor, cure yourself; that skill of yours is not necessary for me. The

Jackson,R. Canadian Med Assoc.Journal, 1974,111,827

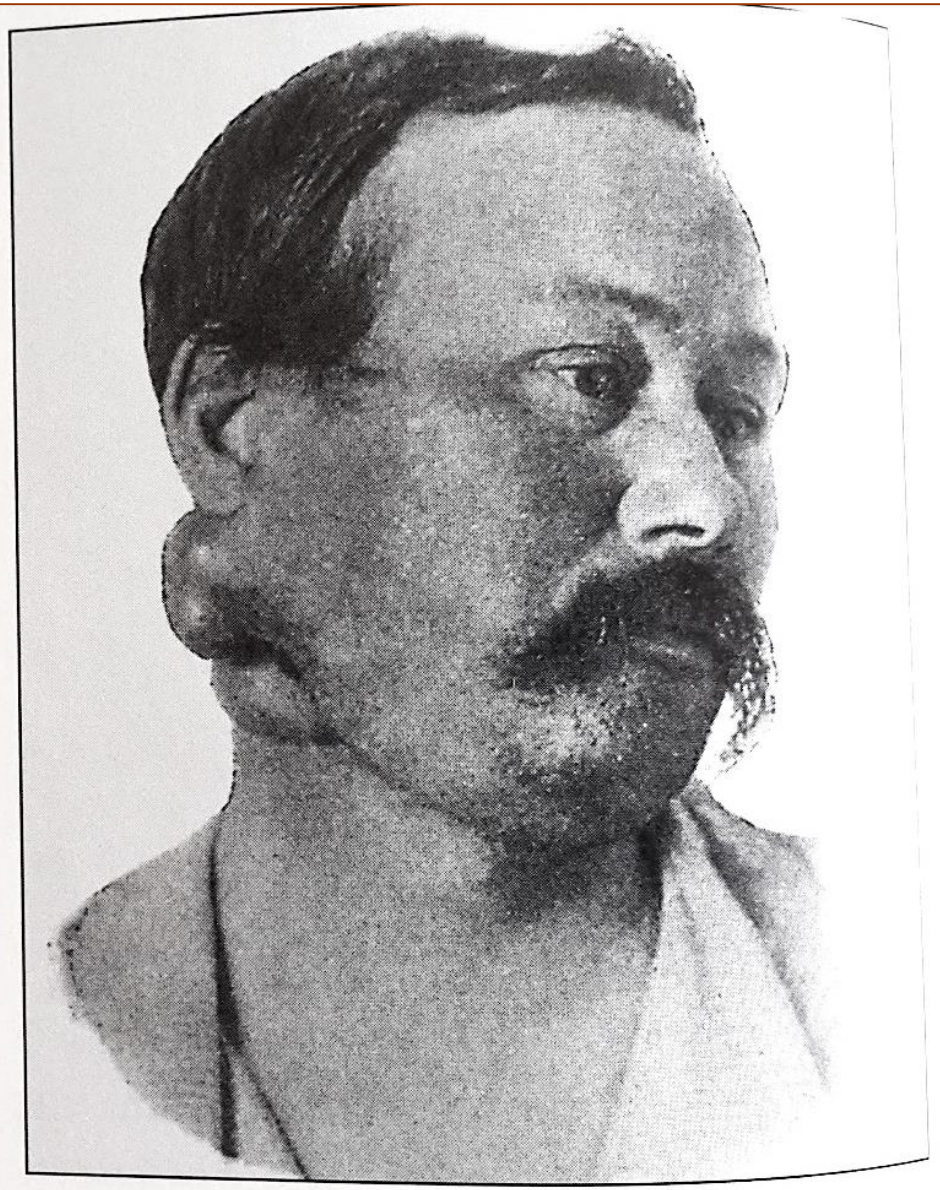
William B Coley, MD (1862-1936)

Mr. Fred Stein

Round-celled sarcoma of neck, cured by erysipelas. Photograph taken seven years after. (Bull's case.)

Coley,WB Am.J.Med.Sciences, May 1893

"Apparently he had only a few weeks to live.": Signor Zola, who was treated by Coley in May 1891 and survived another eight years
(Archives, Cancer Research Institute)



THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES.

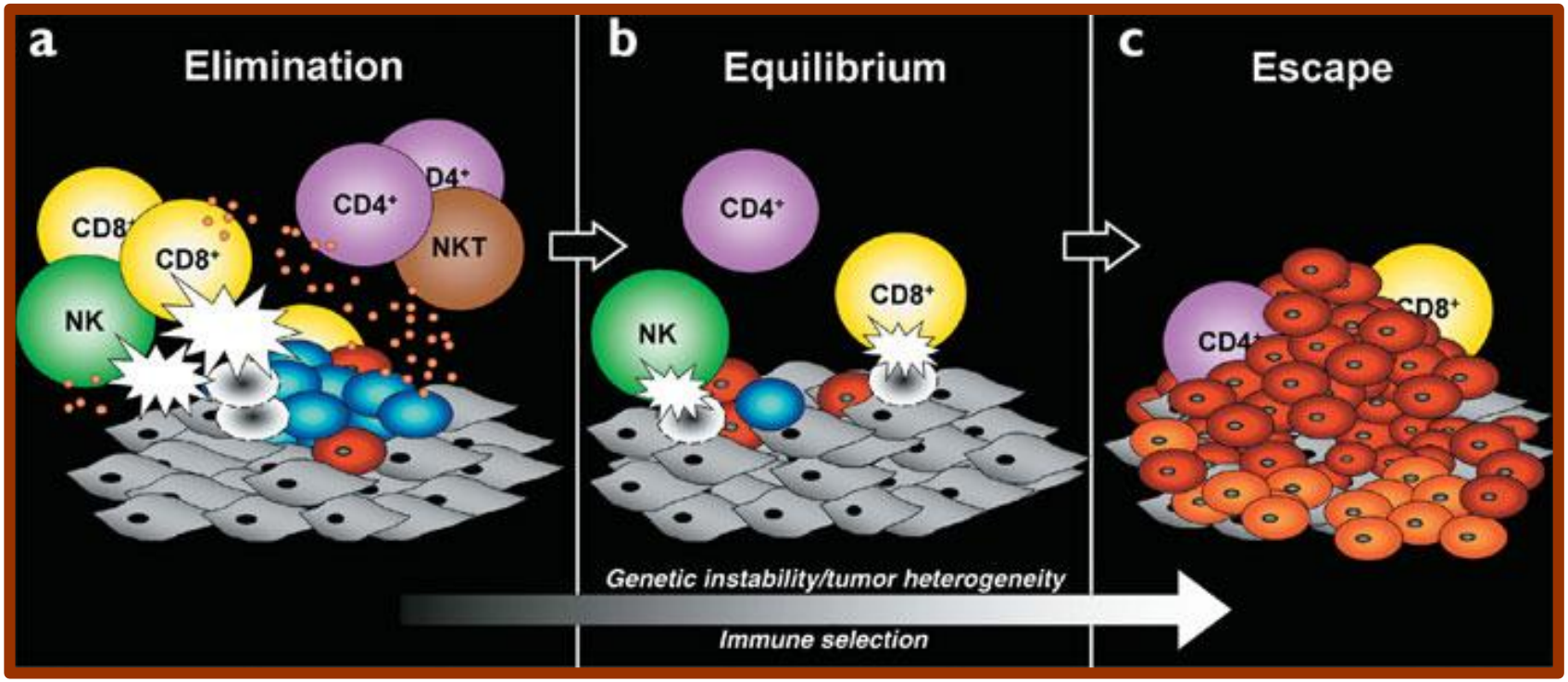
MAY, 1893.

THE TREATMENT OF MALIGNANT TUMORS BY REPEATED INOCULATIONS OF ERYSIPELAS: WITH A REPORT OF TEN ORIGINAL CASES.[1]

By William B. Coley, M.D.,

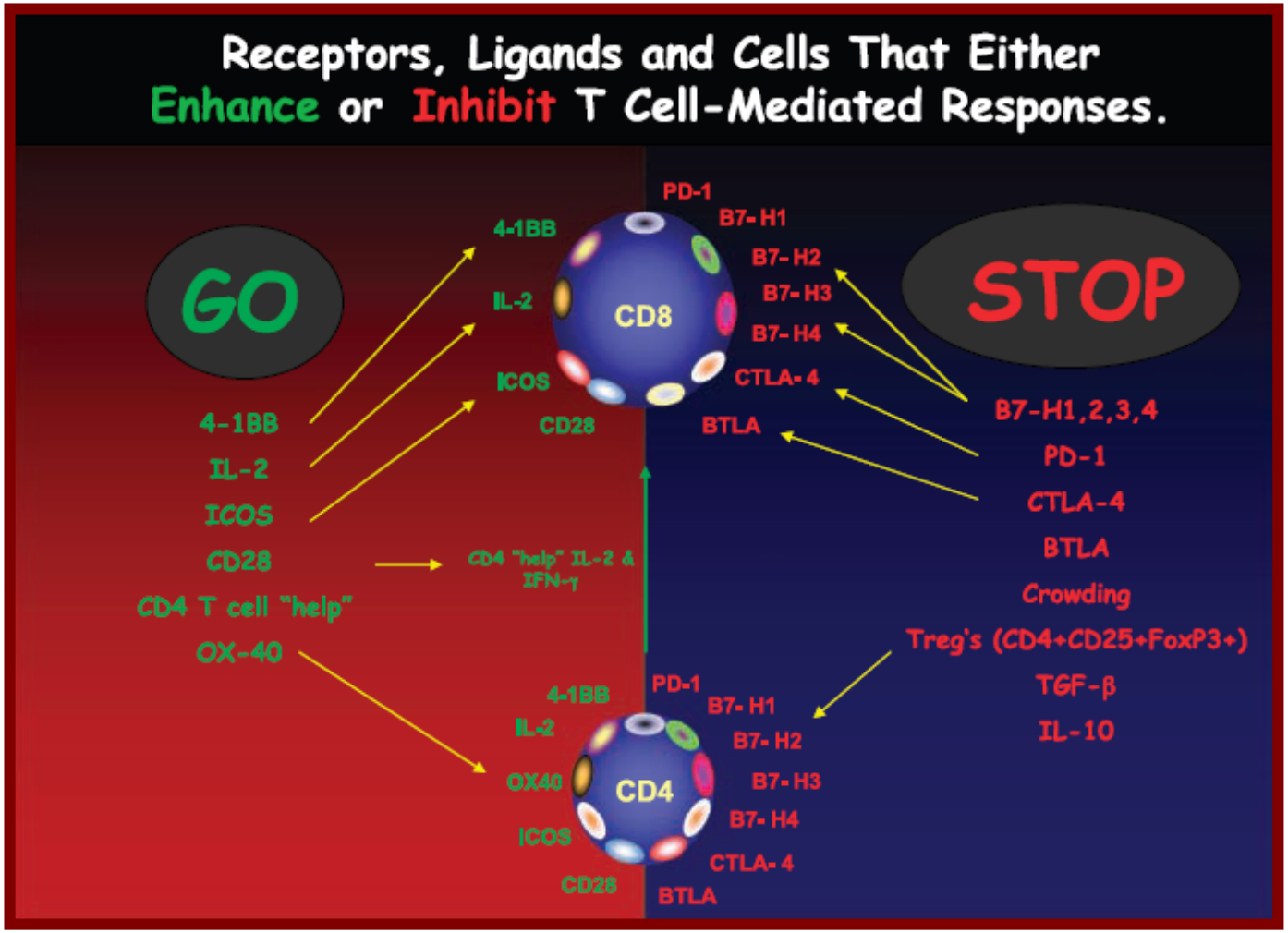
ASSISTANT SURGEON TO THE HOSPITAL FOR RUPTURED AND CRIPPLED; INSTRUCTOR IN SURGERY IN THE POST-GRADUATE MEDICAL SCHOOL, NEW YORK.

The Immunoediting Hypothesis (3E's)

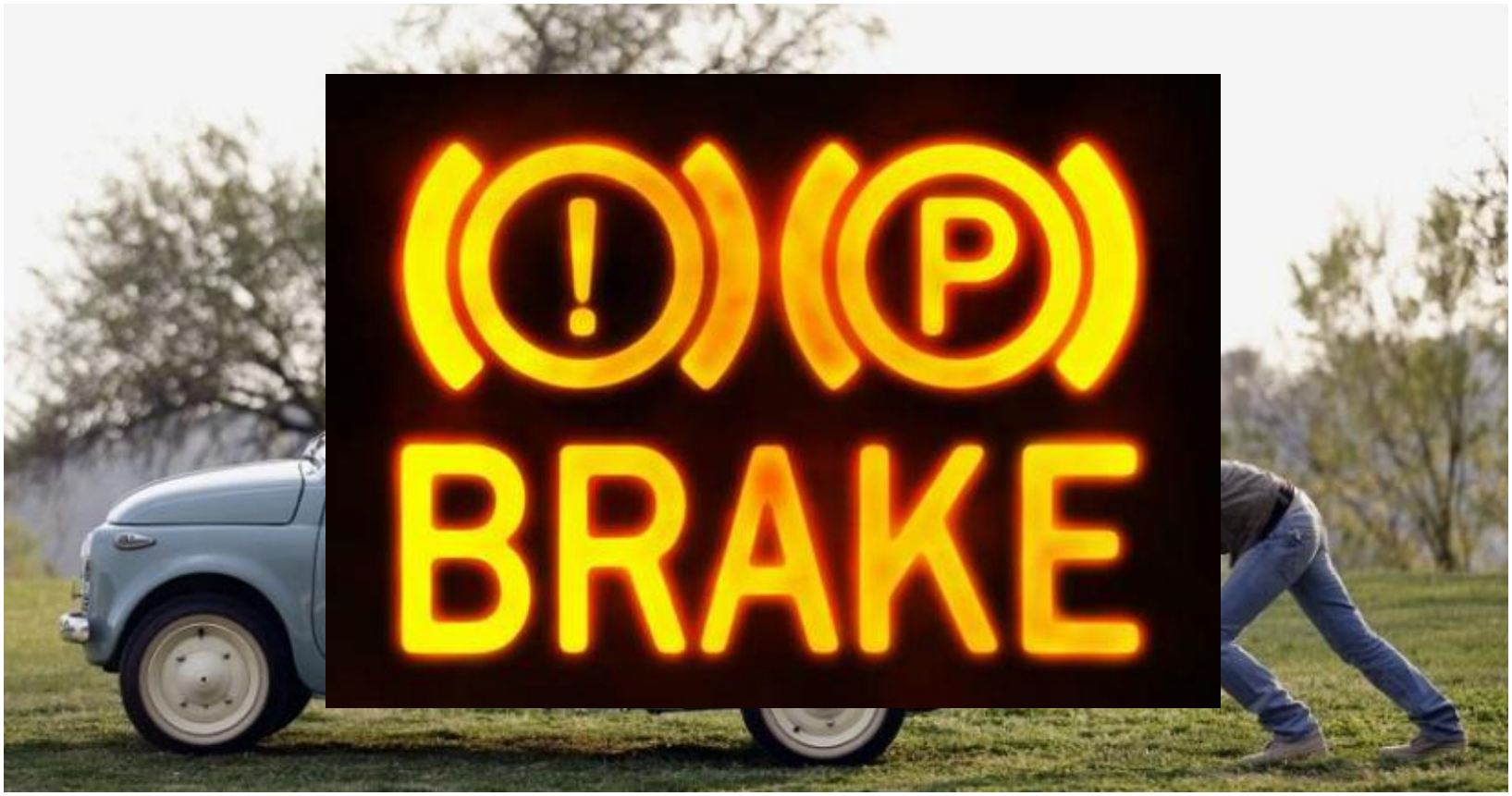


Koebel et al. Nature, 2007
Schreiber et al. Science, 2011
Mittal et al. Curr Immunol Opin, 2014

Regulators of Immunity = Immune Checkpoints



Thompson ,Clin Cancer Res 2007;13:709s-715s

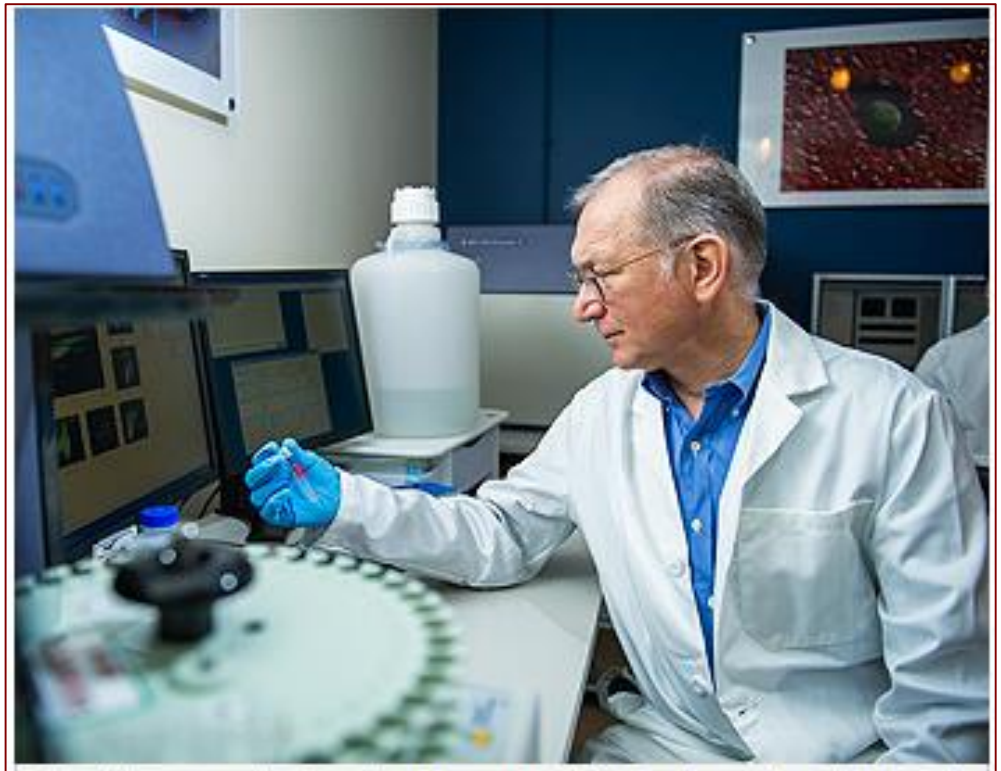

(!) (P)
BRAKE

DANA-FARBER CANCER INSTITUTE

HARVARD MEDICAL SCHOOL

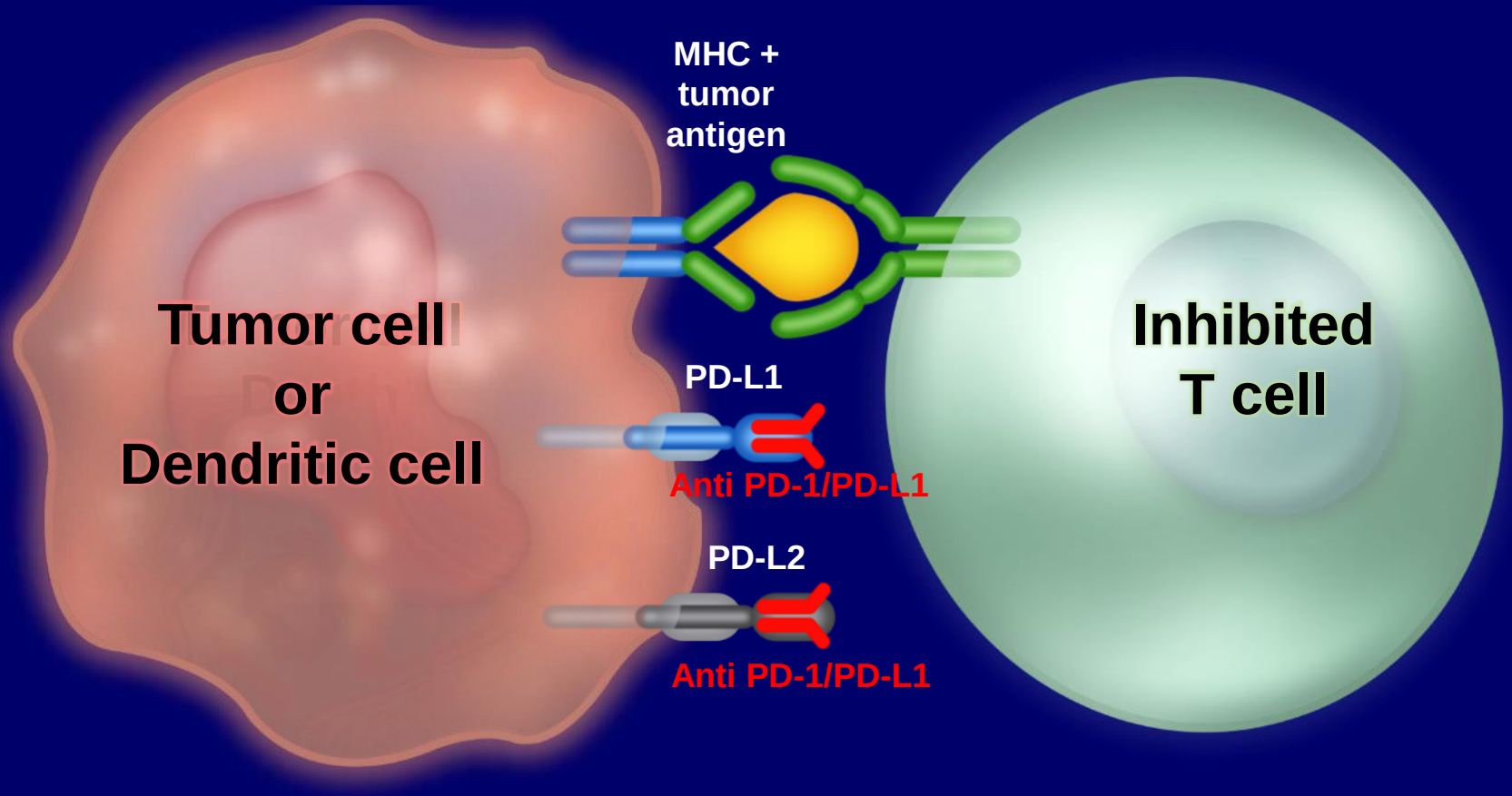
On the news: “Freeman honored for PD-1 immunotherapy discovery”

The discovery of the PD-1 protein, by a team led by Gordon Freeman, PhD, holds promise for therapies that make the body's immune system attack cancer cells.



The discovery by Gordon Freeman, PhD, of proteins that fend off an immune system attack on cancer cells has opened a new avenue of cancer therapy.

Immunosuppressive tumor microenvironment



PD-L1 expression provides immune escape mechanism

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D. , F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D., Wen-Jen Hwu, M.D., Ph.D., Suzanne L. Topalian, M.D., Patrick Hwu, M.D., Charles G. Drake, M.D., Ph.D., Luis H. Camacho, M.D., M.P.H., John Kauh, M.D., Kunle Odunsi, M.D., Ph.D., Henry C. Pitot, M.D., Omid Hamid, M.D., Shailender Bhatia, M.D., Renato Martins, M.D., M.P.H., Keith Eaton, M.D., Ph.D., Shuming Chen, Ph.D., Theresa M. Salay, M.S., Suresh Alaparthy, Ph.D., Joseph F. Grosso, Ph.D., Alan J. Korman, Ph.D., Susan M. Parker, Ph.D., Shruti Agrawal, Ph.D., Stacie M. Goldberg, M.D., Drew M. Pardoll, M.D., Ph.D., Ashok Gupta, M.D., Ph.D., and Jon M. Wigginton, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma

Omid Hamid, M.D., Caroline Robert, M.D., Ph.D., Adil Daud, M.D., F. Stephen Hodi, M.D., Wen-Jen Hwu, M.D., Ph.D., Richard Kefford, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., Peter Hersey, M.D., Ph.D., Richard W. Joseph, M.D., Jeffrey S. Weber, M.D., Ph.D., Roxana Dronca, M.D., Tara C. Gangadhar, M.D., Amita Patnaik, M.D., Hassane Zarour, M.D., Anthony M. Joshua, M.B., B.S., Ph.D., Kevin Gergich, M.A., Jeroen Elassaiss-Schaap, Ph.D., Alain Algazi, M.D., Christine Mateus, M.D., Peter Boasberg, M.D., Paul C. Tumeh, M.D., Bartosz Chmielowski, M.D., Ph.D., Scot W. Ebbinghaus, M.D., Xiaoyun Nicole Li, Ph.D., S. Peter Kang, M.D., and Antoni Ribas, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Advanced Melanoma

Jedd D. Wolchok, M.D., Ph.D., Harriet Kluger, M.D., Margaret K. Callahan, M.D., Ph.D., Michael A. Postow, M.D., Naiyer A. Rizvi, M.D., Alexander M. Lesokhin, M.D., Neil H. Segal, M.D., Ph.D., Charlotte E. Ariyan, M.D., Ph.D., Ruth-Ann Gordon, B.S.N., Kathleen Reed, M.S., Matthew M. Burke, M.B.A., M.S.N., Anne Caldwell, B.S.N., Stephanie A. Kronenberg, B.A., Blessing U. Agunwamba, B.A., Xiaoling Zhang, Ph.D., Israel Lowy, M.D., Ph.D., Hector David Inzunza, M.D., William Feely, M.S., Christine E. Horak, Ph.D., Quan Hong, Ph.D., Alan J. Korman, Ph.D., Jon M. Wigginton, M.D., Ashok Gupta, M.D., Ph.D., and Mario Sznol, M.D.

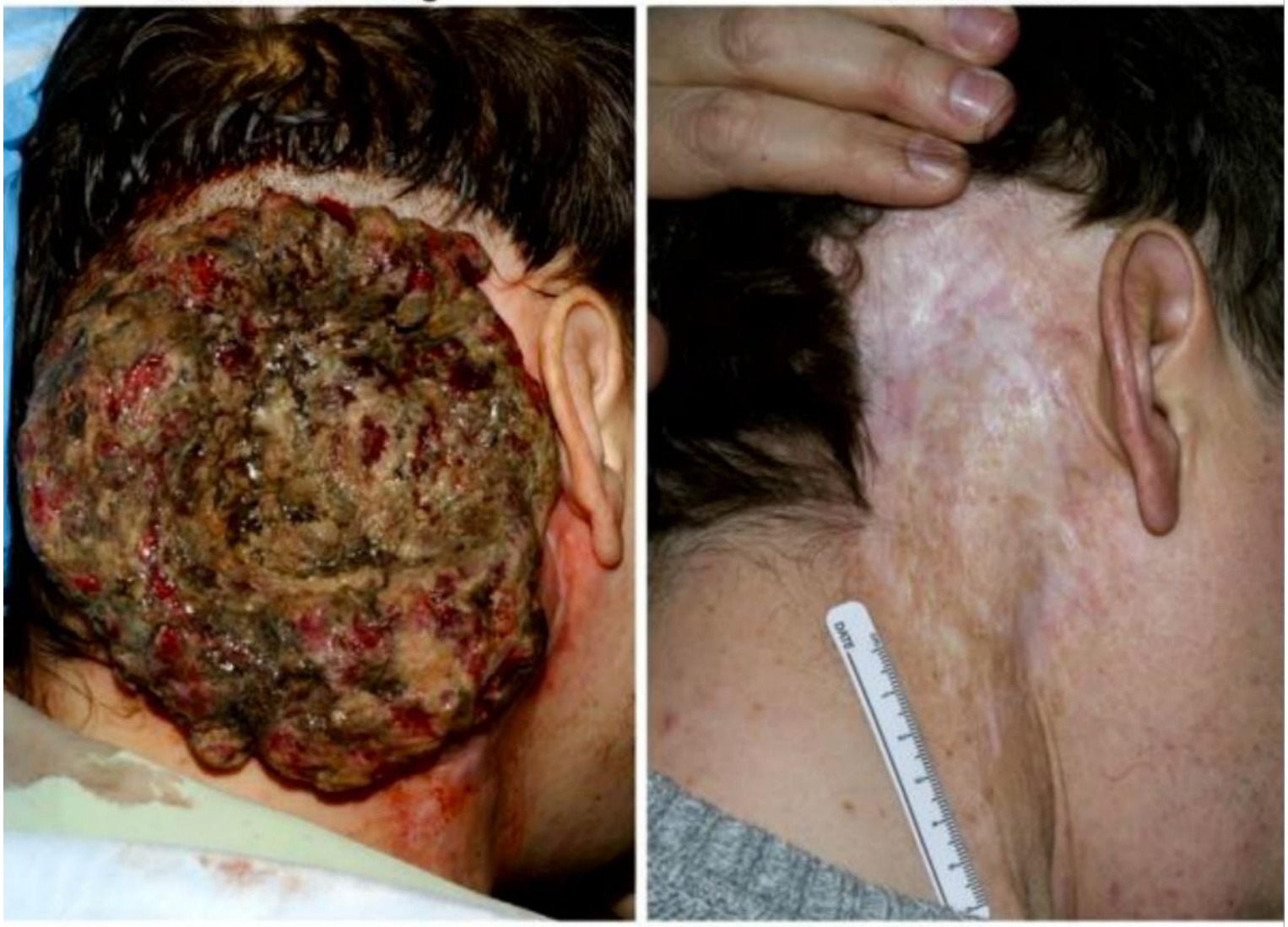
N Engl J Med. June 28, 2012
N Engl J Med. July 11, 2013

2013 **2014**

Indirect targeting of the tumor using the immune system

Other Sites: Lung

CR 59+ mo.



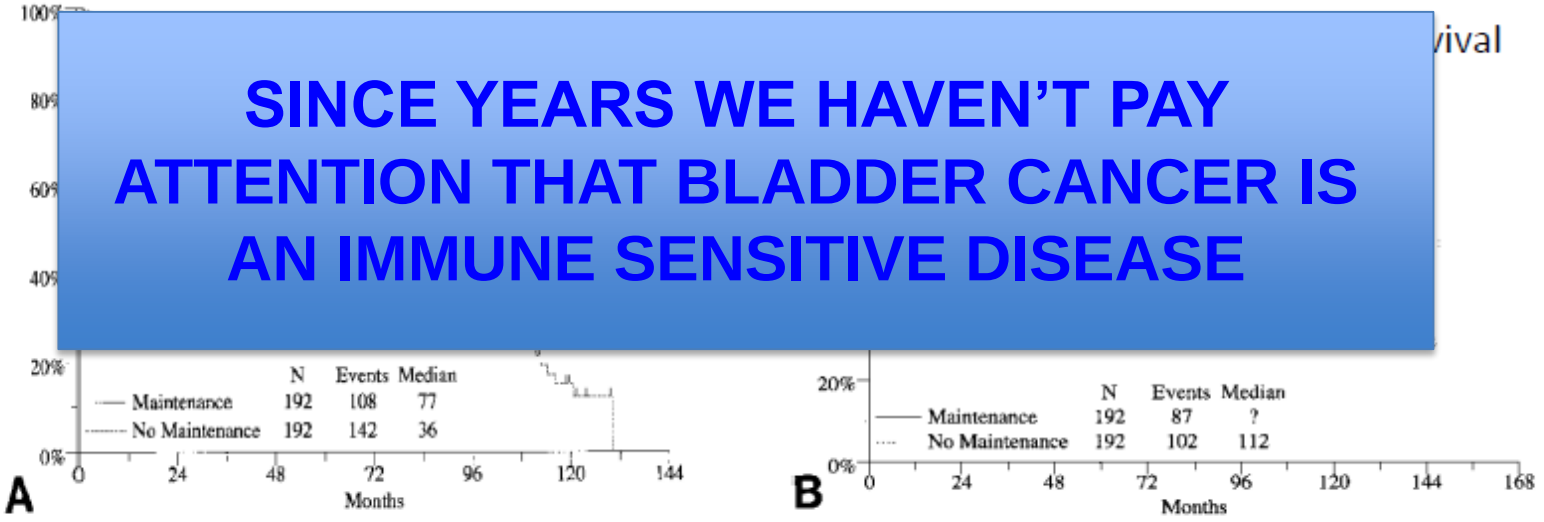
March 21, 2005

Feb 23, 2010

MAINTENANCE BACILLUS CALMETTE-GUERIN IMMUNOTHERAPY FOR RECURRENT TA, T1 AND CARCINOMA IN SITU TRANSITIONAL CELL CARCINOMA OF THE BLADDER: A RANDOMIZED SOUTHWEST ONCOLOGY GROUP STUDY

DONALD L. LAMM,*† BRENT A. BLUMENSTEIN, JOHN D. CRISSMAN, JAMES E. MONTIE, JAMES E. GOTTESMAN, BRUCE A. LOWE, MICHAEL F. SAROSDY,‡ ROBERT D. BOHL, H. BARTON GROSSMAN,§ THOMAS M. BECK, JOSEPH T. LEIMERT AND E. DAVID CRAWFORD‖

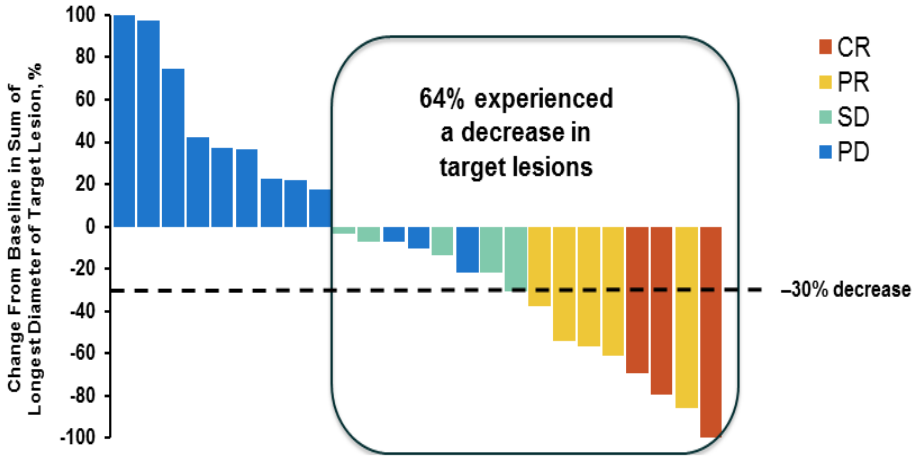
SINCE YEARS WE HAVEN'T PAY ATTENTION THAT BLADDER CANCER IS AN IMMUNE SENSITIVE DISEASE



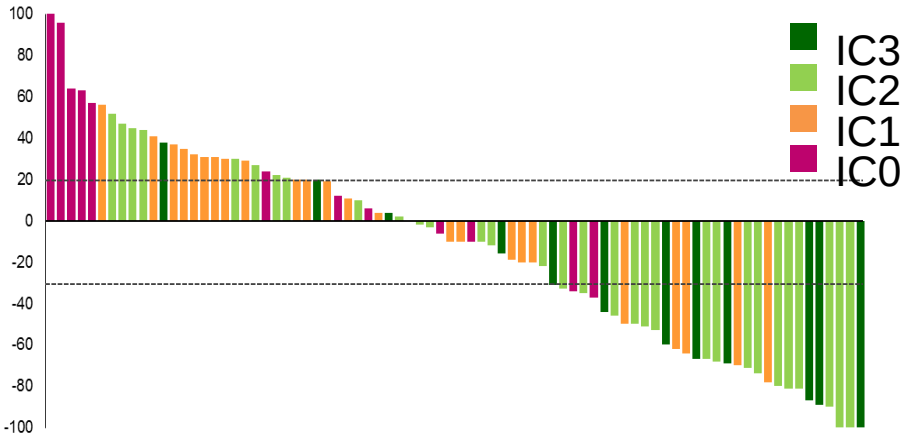
- 5-year recurrence-free survival rate was 60% in the maintenance arm compared to 41% in the no-maintenance arm *(P < .0001)*
- 5-year PFS rate was 76% in the maintenance arm compared with 70% in the no-maintenance arm *(P=.04)*

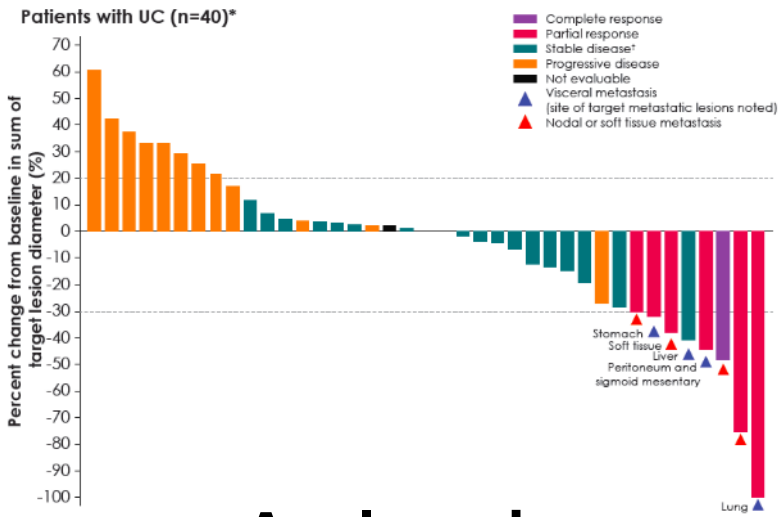
Phase 1 evaluation of pembrolizumab, avelumab, and atezolizumab and durvalumab in advanced UC shows robust activity

Pembrolizumab

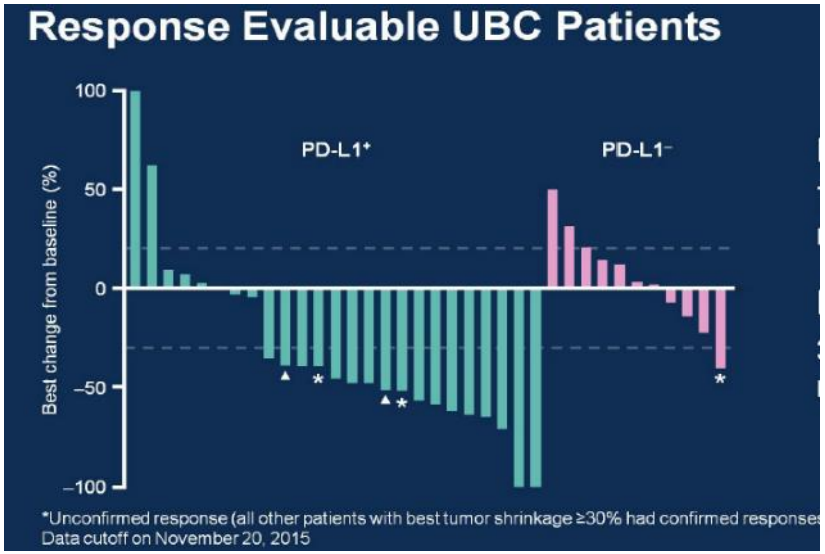


Atezolizumab





Avelumab



Durvalumab

Atezolizumab Phase 2 Trial: Imvigor 210

- Locally advanced or metastatic cancer of the bladder, renal pelvis, ureter or urethra
- Predominant transitional cell histology
- Progression during or following platinum (no restriction on prior lines of therapies)
- Creatinine clearance > 30 mL/min
- ECOG 0-1
- Tumor tissue evaluable for PD-L1 exression

Atezolizumab 1.200mg q3w Until loss of clinical benefit

Response assesment q9 weeks

N = 311

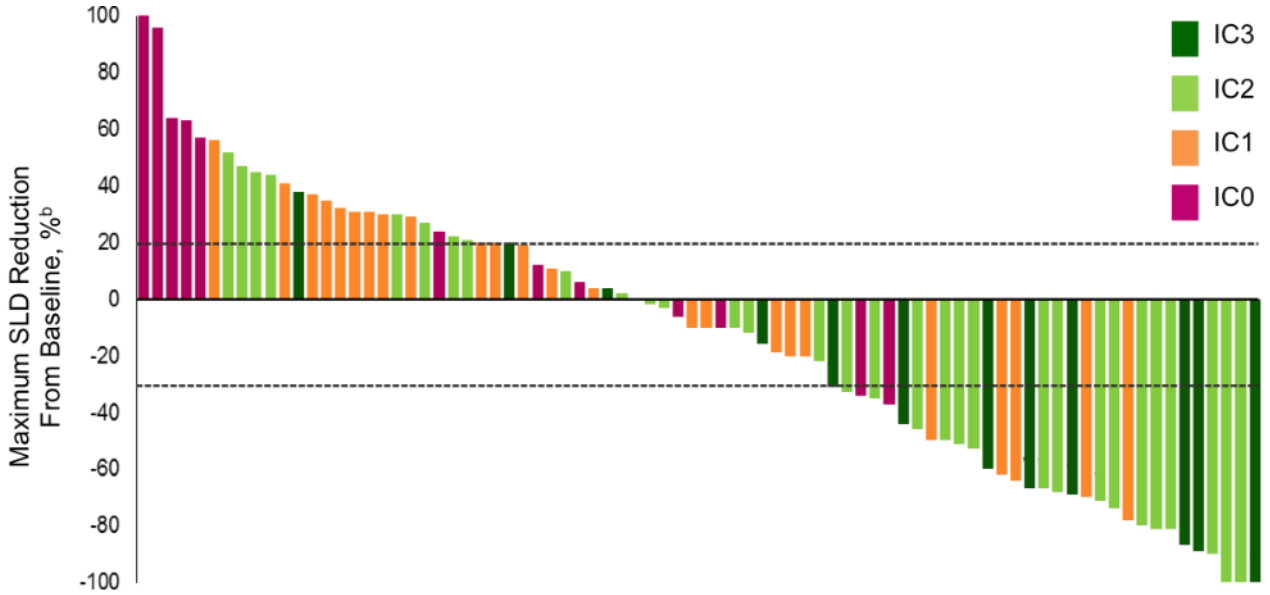
Co-Primary endpoints:

- ORR (confirmed) per RECIST v. 1.1. (CIR)
- Investigator-assessed ORR per modified RECIST

Rosemberg JE, et al. Oral presentation at the ECCO 2015 Congress

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



- Forty-four of 80 patients (55%) with post-baseline tumor assessments experienced a reduction in tumor burden
- Decreased circulating inflammatory marker (CRP) and tumor markers (CEA, CA-19-9) were also observed in patients responding to atezolizumab

Rosemberg et al. Lancet, 2016

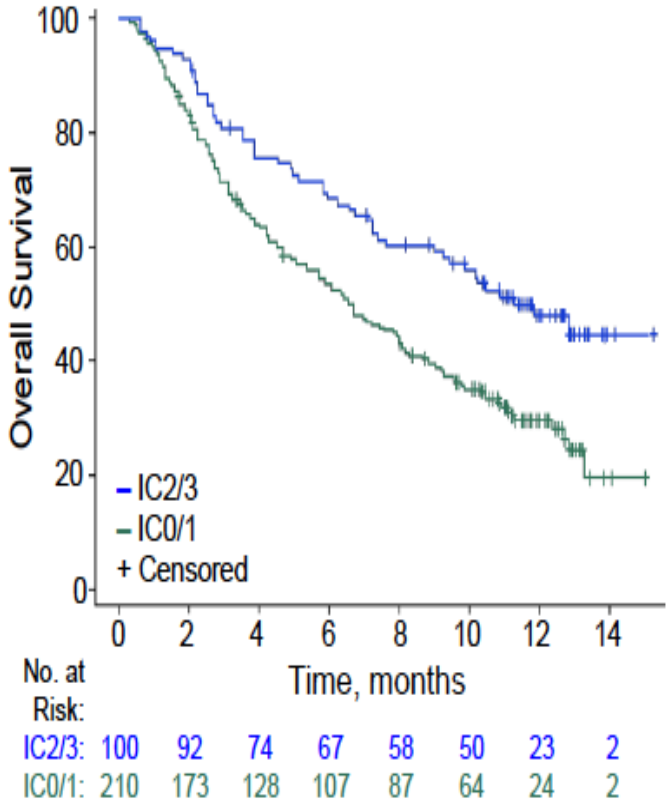
Atezolizumab (MPDL3280A): ORR in UBC by IC Status

PD-L1 IHC n = 87[b]	ORR (95% CI), %[a]		CR, n (%)		PR, n (%)	
IC3 (n = 12)	**67%** (35%-90%)	**50%** (35, 65)	4 (33%)	9 (20%)	4 (33%)	14 (30%)
IC2 (n = 34)	**44%** (27%-62%)		5 (15%)		10 (29%)	
IC1 (n = 26)	19% (7%-39%)	17% (7, 32)	-	-	5 (19%)	7 (17%)
IC0 (n = 15)	13% (2%-40%)		-		2 (13%)	

- Responses were observed all PD-L1 subgroups, with higher ORRs associated with higher PD-L1 expression in IC
- Responders also included patients with visceral metastases at baseline: 38% ORR (95% CI, 21%-56%) in 32 IC2/3 patients and 14% (95% CI, 5%-30%) ORR in 36 IC0/1 patients

Atezolizumab (MPDL3280A): Overall Survival

IMvigor 210: Overall Survival in mUC



	IC2/3 n = 100	IC0/1 n = 210	All N = 310
Median OS (95% CI)	11.4 mo (9.0, NE)	6.7 mo (5.4, 8.0)	7.9 mo (6.6, 9.3)
12-mo OS (95% CI)	48% (38, 58) At risk: 23	30% (23, 36) At risk: 24	36% (30, 41) At risk: 47

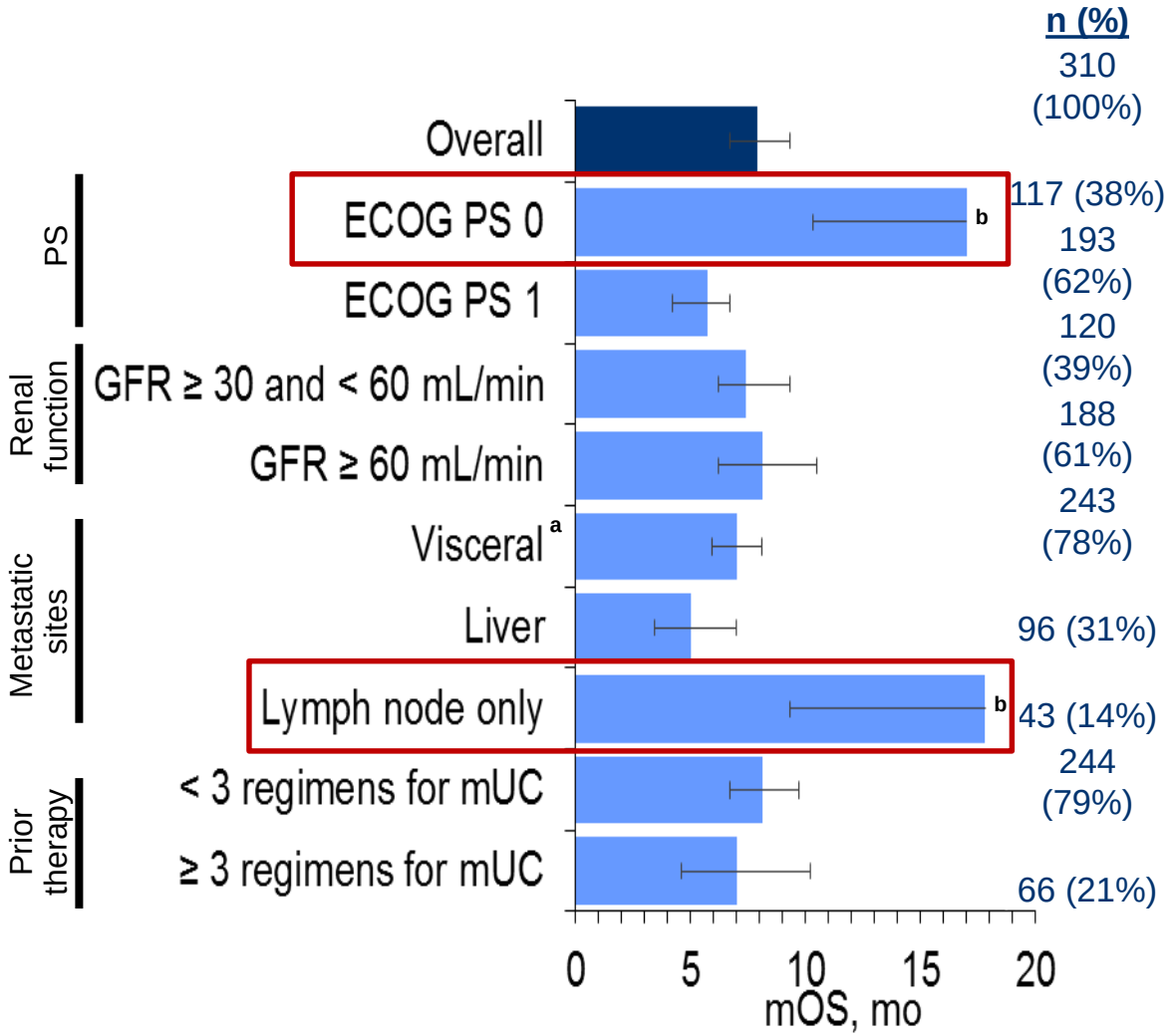
Median follow-up: 11.7 mo (range, 0.2+ to 15.2 mo)

- mOS appears longer in pts with higher PD-L1 IC status
- 12-mo OS compares favorably with estimates of ≈ 20% in a 2L-only setting[1]
  - In 124 pts who had only 1 prior line of therapy for mUC and no prior (neo)adjuvant therapy:
    - mOS (IC2/3): NE (95% CI: 9.3, NE)
    - mOS (entire 2L population): 9.0 months (95% CI: 7.1, 10.9)

NE, not estimable. Data cutoff: September 14, 2015. **Reference: 1.** Agarwal N, et al. *Clin Genitourin Cancer*. 2014; 12(2):130-137.

Rosemberg et al. Lancet, 2016

Baseline Clinical Predictors of Survival With Atezolizumab



PS 0 and LN only remain good prognostic indicators

Median follow-up: 17.5 months
(range, 0.2 to 21.1+ mo)

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

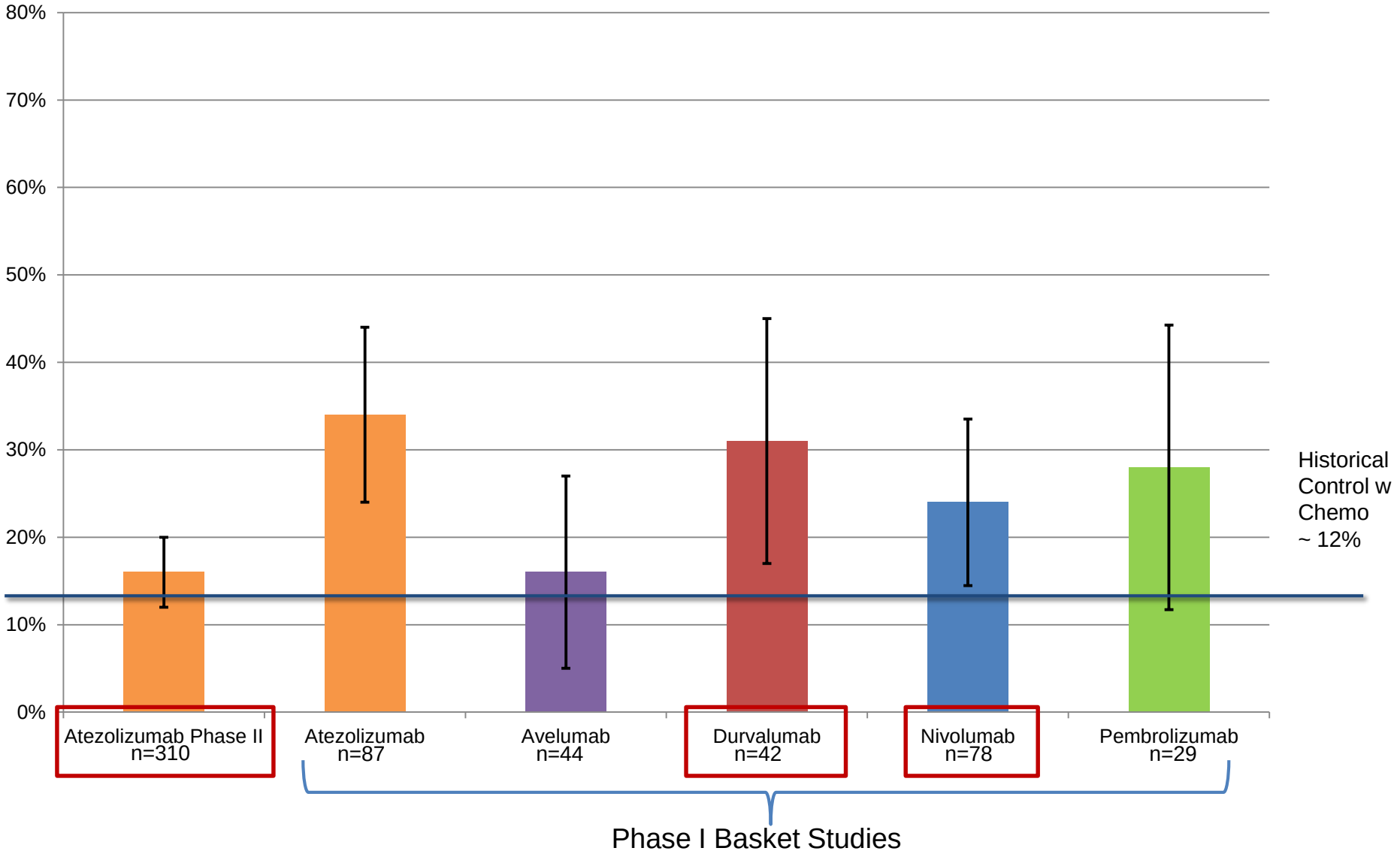
Dreicer R, et al. IMvigor210: Atezolizumab in platinum-treated mUC. ASCO 2016

Updates from ASCO 2016

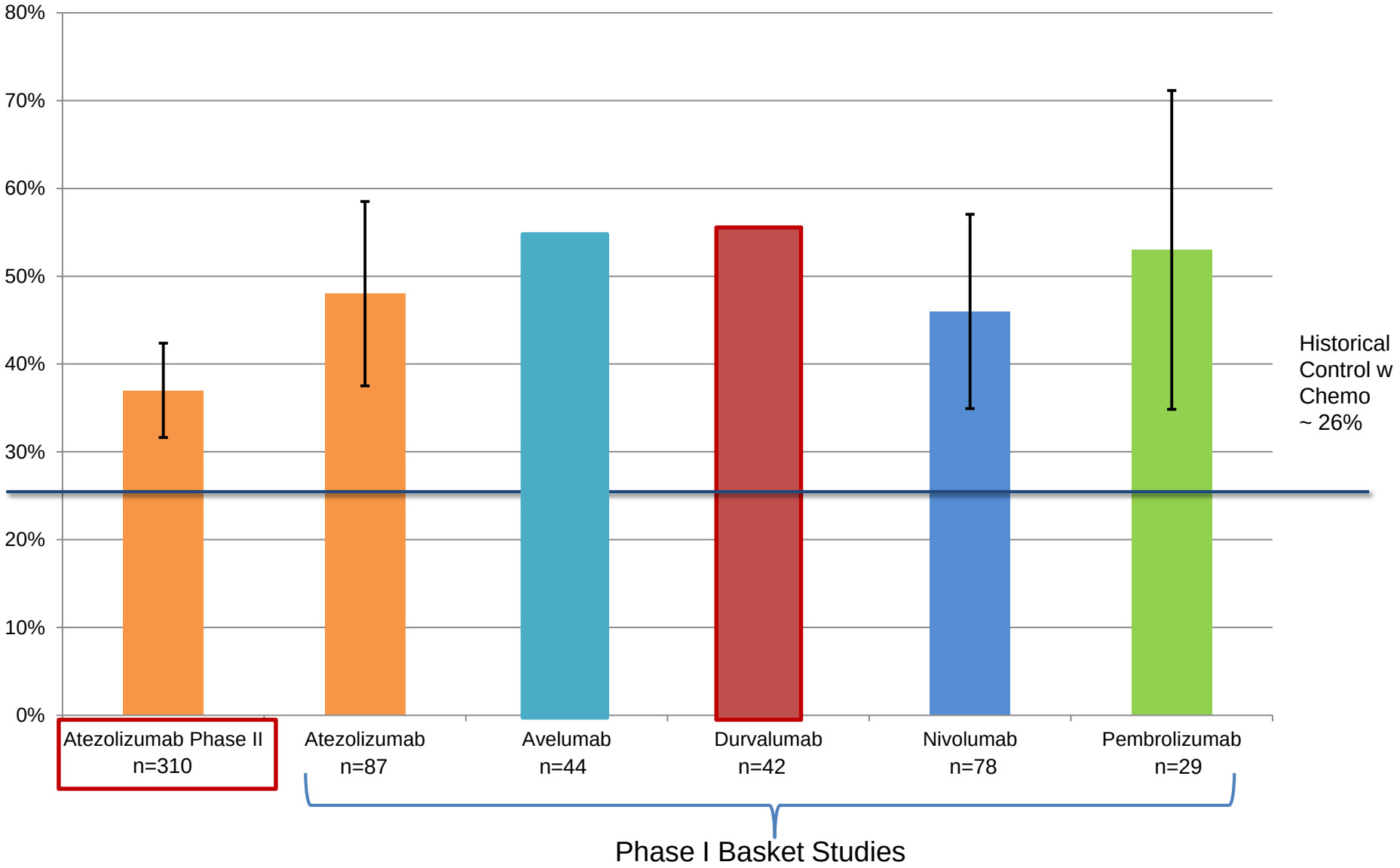
Single arm, single agent PD1 pathway inhibitors

	Drug	Antibody	Target	Setting	Phase	Total n
Balar 4500	Atezolizumab	humanized IgG1	PDL-1	First line cis-ineligible	Phase II	119
Dreicer 4515	Atezolizumab	humanized IgG1	PDL-1	Post platinum	Phase II	310
Sharma 4501	Nivolumab	human IgG4	PD-1	Post platinum	Phase I basket	78
Massard 4502	Durvalumab	Human IgG1	PDL-1	Post platinum	Phase I basket	42

Overall Response Rates: Post-Platinum



12 month OS: Post Platinum



Frontline Therapy for UC: Cis-Ineligible

Gem Carbo

Randomized Phase II/III Trial Assessing Gemcitabine/Carboplatin and Methotrexate/Carboplatin/ Vinblastine in Patients With Advanced Urothelial Cancer Who Are Unfit for Cisplatin-Based Chemotherapy: EORTC Study 30986

Maria De Santis, Joaquim Bellmunt, Graham Mead, J. Martijn Kerst, Michael Leahy, Pablo Maroto, Thierry Gil, Sandrine Marreaud, Gedske Daugaard, Iwona Skoneczna, Sandra Collette, Julie Lorent, Ronald de Wit, and Richard Sylvester

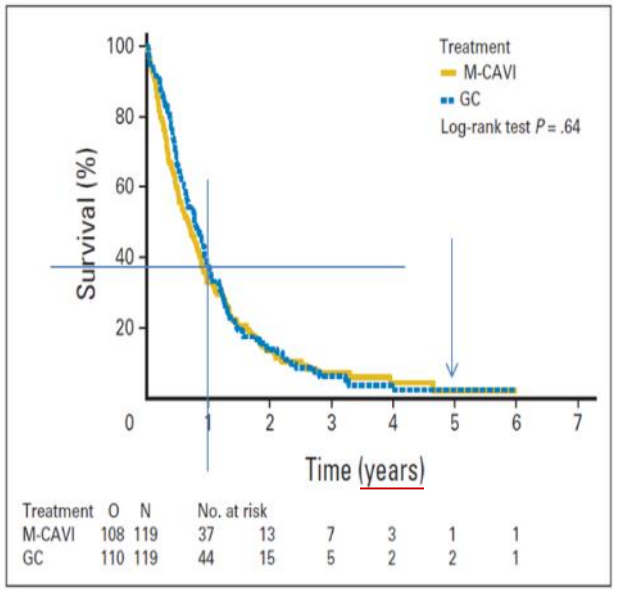
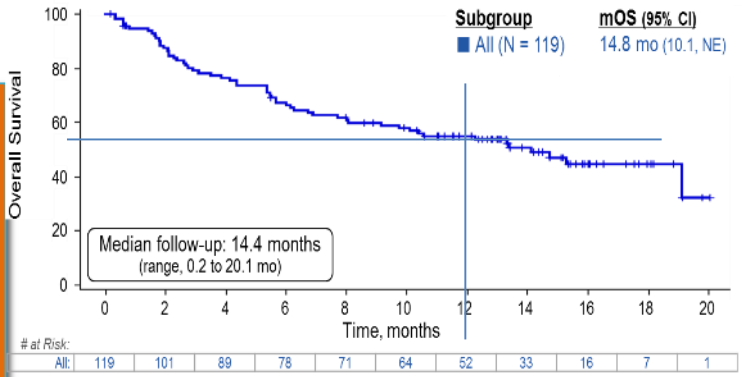


Fig 2. Duration of survival by treatment group. GC, gemcitabine/carboplatin; M-CAVI, methotrexate/carboplatin/vinblastine; O, observed number of deaths.

ORR: 36%	ORR: 24%
mOS: 9.3 mo.	mOS: 14.8 mo.
1-year OS: 37%	1-year OS: 57%
5-year OS: ~ 0	5-year OS: ?

Atezolizumab

Cisplatin ineligibility criteria[1]	N = 119
Renal impairment GFR < 60 mL/min but > 30	70%
Hearing loss, 25 dB[e]	14%
Peripheral neuropathy, ≥ Grade 2	6%
ECOG PS2	20%
Renal impairment **and** ECOG PS2	7%



	All Patients (N = 119)
ORR[a] (95% CI)	24% (16, 32)
CR	7%
PR	17%

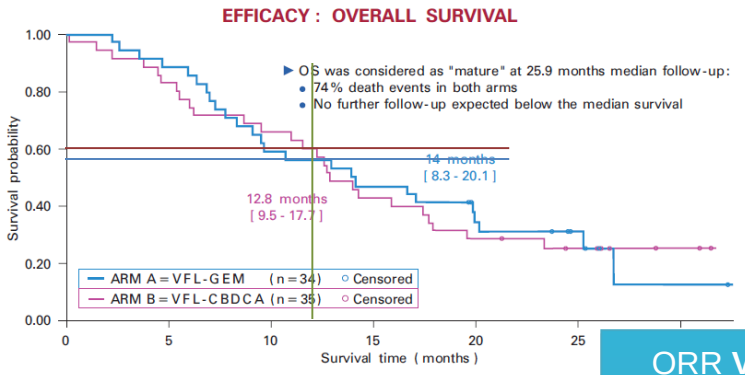
Balar A, et al. IMvigor210: 1L atezolizumab in cisplatin-ineligible mUC. ASCO 2016

Frontline Therapy for UC: Cis-Ineligible

Vinflunine-Gemcitabine (VG) or Carboplatin (VC)

Vinflunine–gemcitabine versus vinflunine–carboplatin as first-line chemotherapy in cisplatin-unfit patients with advanced urothelial carcinoma: results of an international randomized phase II trial (JASINT1)†

M. De Santis[1,2*], P. J. Wiechno[3], J. Bellmunt[4], C. Lucas[5], W.-C. Su[6], L. Albiges[7], C.-C. Lin[8], E. Senkus-Konefka[9], A. Flechon[10], L. Mourey[11], A. Necchi[12], W. C. Loidl[13], M. M. Retz[14], N. Vaissière[5] & S. Culine[15]



- Ineligibility for a cisplatin-based therapy due to at least one of the 2 conditions:
  - CrCl* < 60 mL/min.
  - Congestive heart failure (NYHA stage II-III).

* Creatinine clearance, calculated: Cockroft-Gault formula.

Congestive heart failure, n (%)	Stage I	0 (0%)	4 (11%)
	Stage II	2 (6%)	2 (6%)
Creatinine clearance**, n (%)	Median [range] (mL/min)	47.5 [30.8 - 59.8]	45.0 [30.0 - 59.5]
	≥ 60 mL/min	0	0
	[40 - 60[mL/min	28 (82%)	28 (80%)
	[30 - 40[mL/min	6 (18%)	7 (20%)

ORR **VG** & VC: **53** & 43%

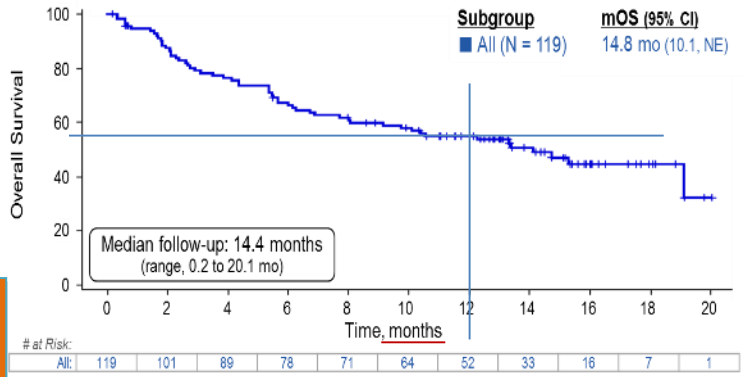
mOS **VG** & VC: **14** & 12.8 mo.

1-year OS **VG** & VC: **56** vs 60%

5-year OS: ...2

Atezolizumab

Cisplatin ineligibility criteria[1]	N = 119
Renal impairment GFR < 60 mL/min but > 30	70%
Hearing loss, 25 dB[e]	14%
Peripheral neuropathy, ≥ Grade 2	6%
ECOG PS2	20%
Renal impairment **and** ECOG PS2	7%



ORR: 24%

mOS: 14.8 mo.

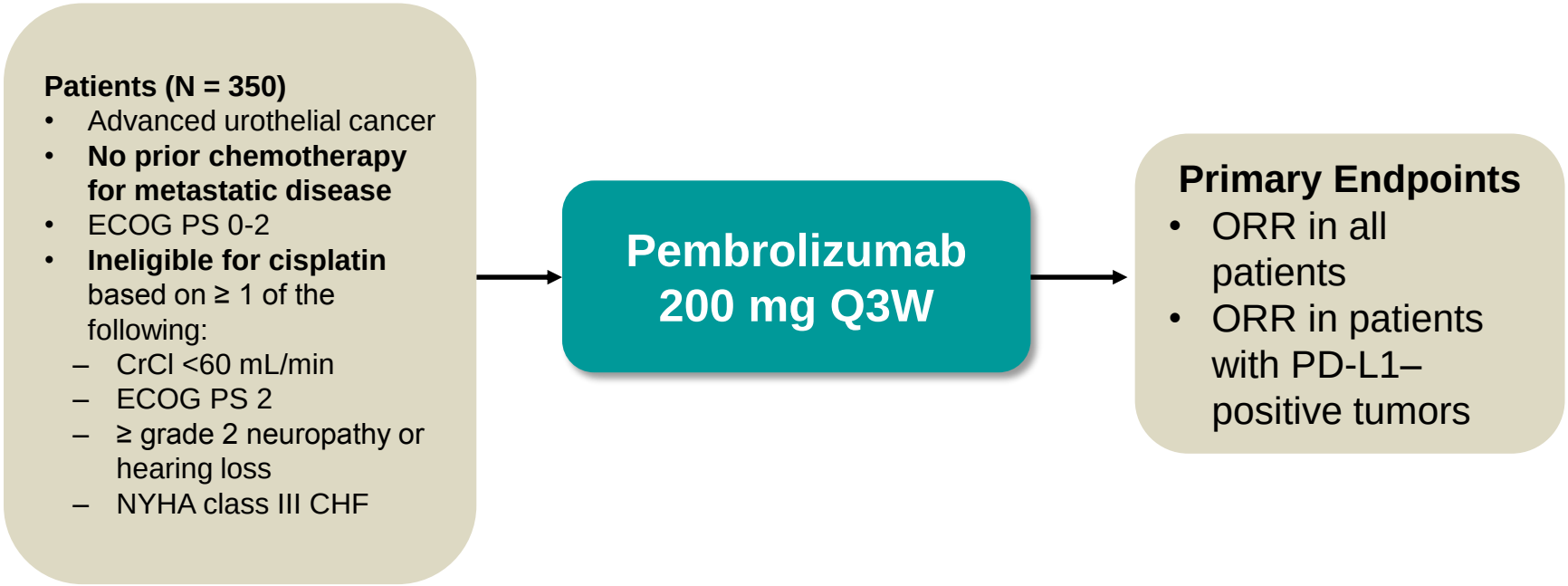
1-year OS: 57%

5-year OS: ...2

	All Patients (N = 119)
ORR ($_{95\%}$CI)	24% (16-32)
CR	7%
PR	17%

Bala A, et al. IMvigor210: 1L atezolizumab in cisplatin-ineligible mUC. ASCO 2016

KEYNOTE-052: Pembrolizumab as 1st-Line Therapy for Cisplatin-Ineligible Advanced Urothelial Cancer



- **Secondary Endpoints:** DOR, PFS, OS, and ORR in all patients, PD-L1 positive and PD-L1–high expressing patients; safety and tolerability; establish an assay cut point for high PD-L1 expression

LBA 32. ESMO 2016

OBJECTIVE RESPONSE RATE BY PD-L1 SUBGROUPS

Per RECIST v1.1, Central Review

*CPS = combined positive score for PD-L1–positive cells (tumor, immune cells)

N = 100	CPS <1%† N = 33		CPS ≥1% to <10% N = 33		CPS ≥10% N = 30	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
ORR (24%)	**6**	**18% (7-36%)**	**5**	**15% (5-32%)**	**11**	**37% (20-56%)**
Complete response	1	3% (0.1-16%)	0	–	4	13% (4-31%)
Partial response	5	15% (5-32%)	5	15% (5-32%)	7	23% (10-42%)
Stable disease	3	9% (2-24%)	5	15% (5-32%)	7	23% (10-42%)

Data cutoff date: June 1, 2016

PEMBROLIZUMAB EFFICACY: SUBGROUPS

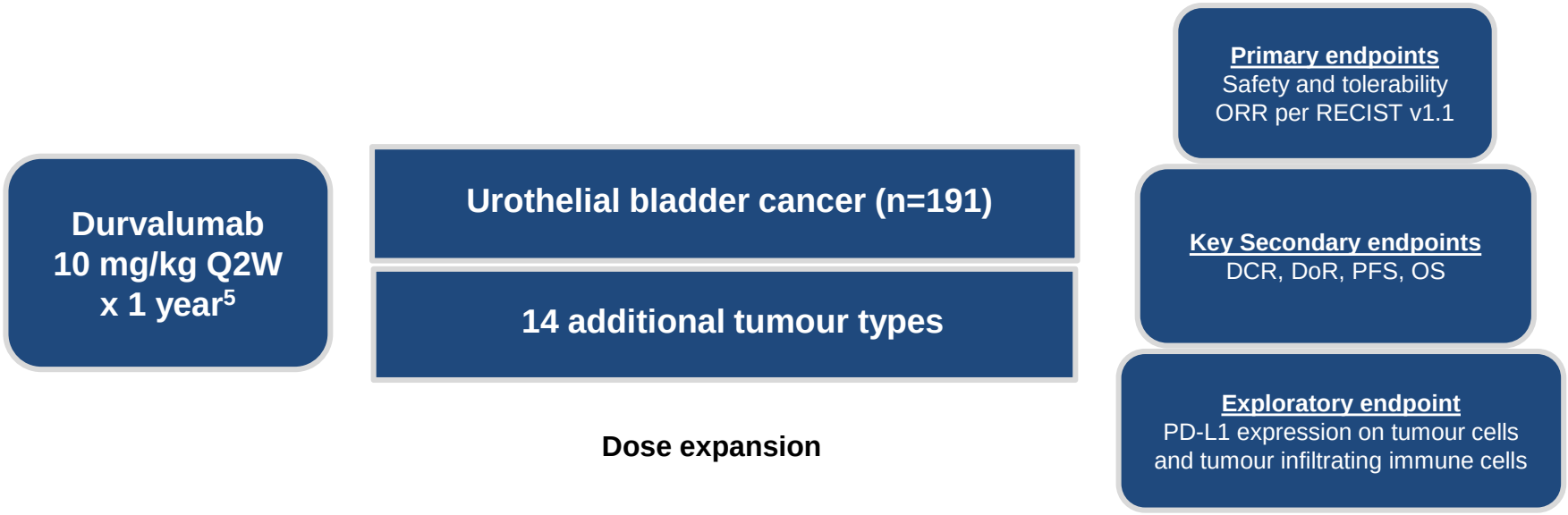
Objective Response Rate Per RECIST v1.1, Central Review

ORR	n/N	% (95% CI)
All patients	**24/100**	**24% (16-34%)**
Prior adjuvant therapy		
Yes	3/13	23 (5-54%)
No	21/87	24 (16-35%)
Metastases location		
Lymph node only	4/10	40% (12-74%)
Visceral disease	18/87	21% (13-31%)
ECOG PS		
0/1	14/54	26% (15-40%)
2	10/46	22% (11-36%)
Primary tumor location		
Upper tract disease	2/20	10% (1-32%)
Lower tract disease	22/88	28% (18-39%)

LBA 32. ESMO 2016

Study 1108: Overview

- Phase I/II study that has shown a consistent safety profile with durvalumab as well as early and durable anti-tumour activity in several tumor types



Adapted from Powles T et al. Online ahead of print. JAMA Onc. 2017.

Estudo 1108 – escalonamento de dose e segurança em tumores sólidos

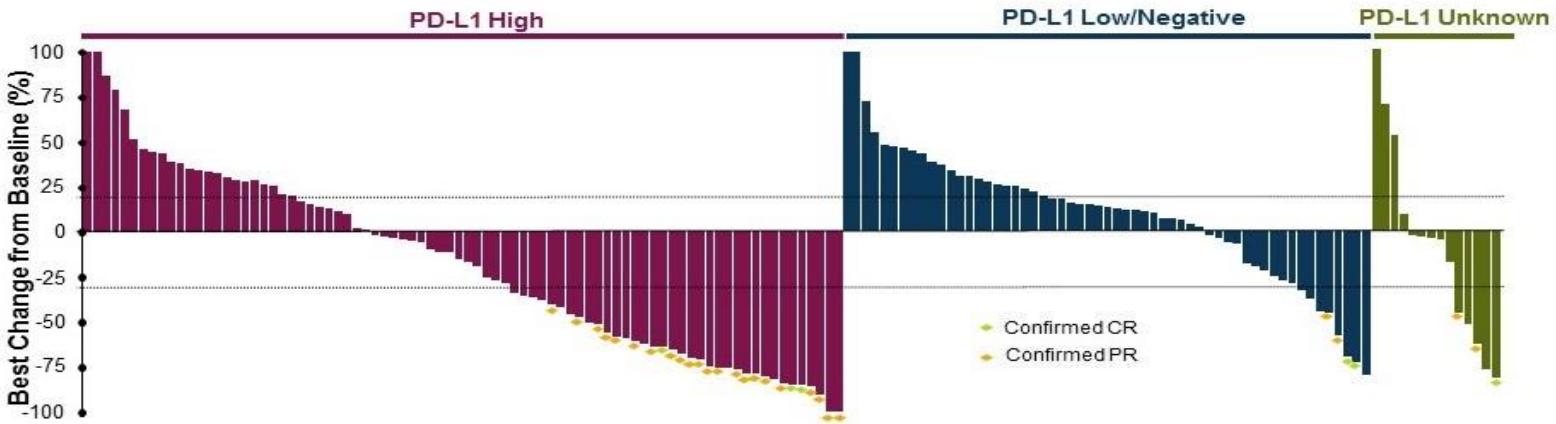
Baseline Demographics and Disease Characteristics

Characteristic	PD-L1+ (n = 40)	PD-L1− (n = 21)	All (N = 61)
Median age, years (range)	67 (34-79)	62 (52-81)	66 (34-81)
Gender, % (n)			
Male	75 (30)	57 (12)	69 (42)
Prior regimens for advanced disease, % (n)			
0	2 (1)	14 (3)	7 (4)
1-2	70 (28)	48 (10)	62 (38)
≥3	28 (11)	38 (8)	31 (19)
ECOG PS, % (n)			
0-1	100 (40)	100 (21)	100 (61)
Liver metastases at baseline, % (n)	32 (13)	24 (5)	29 (18)
Baseline Hb, % (n)			
≥10 g/dL	75 (30)	52 (11)	67 (41)
<10 g/dL	15 (6)	38 (8)	23 (14)

Adapted from Powles T et al. Online ahead of print. JAMA Onc. 2017.

Study 1108: Best Change from Baseline in Target Lesion Size by PD-L1 Status

ORR was 17.8%
7 (3.7%) CRs
PD-L1^{high} → 27.6%
PD-L1$^{low/negative}$ 5. →1%



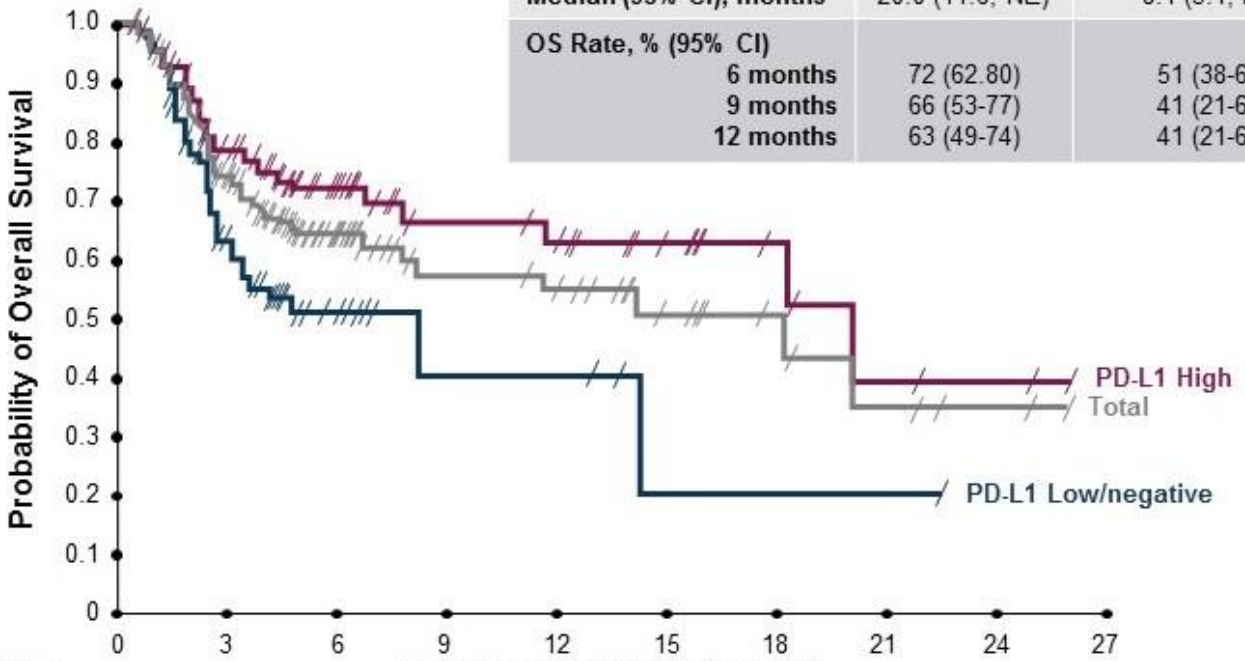
PD-L1^{high} = ≥ 25% of tumour cells exhibit membrane staining;[1] or ICP > 1% and IC+ ≥ 25%; or ICP = 1% and IC+ = 100%[2]

PD-L1$^{low/neg}$ = < 25% of tumour cells exhibit membrane staining[1]

Adapted from Powles T et al. Online ahead of print. JAMA Onc. 2017.

Study 1108: Kaplan-Meier Overall Survival in the UC Cohort - Durvalumab

	PD-LI High	PD-LI Low/negative	Total
# Patients (# Events)	98 (30)	79 (35)	191 (68)
Median (95% CI), months	20.0 (11.6, NE)	8.1 (3.1, NE)	18.2 (8.1, NE)
OS Rate, % (95% CI)			
6 months	72 (62.80)	51 (38-63)	64 (56-71)
9 months	66 (53-77)	41 (21-60)	57 (47-66)
12 months	63 (49-74)	41 (21-60)	55 (44-65)



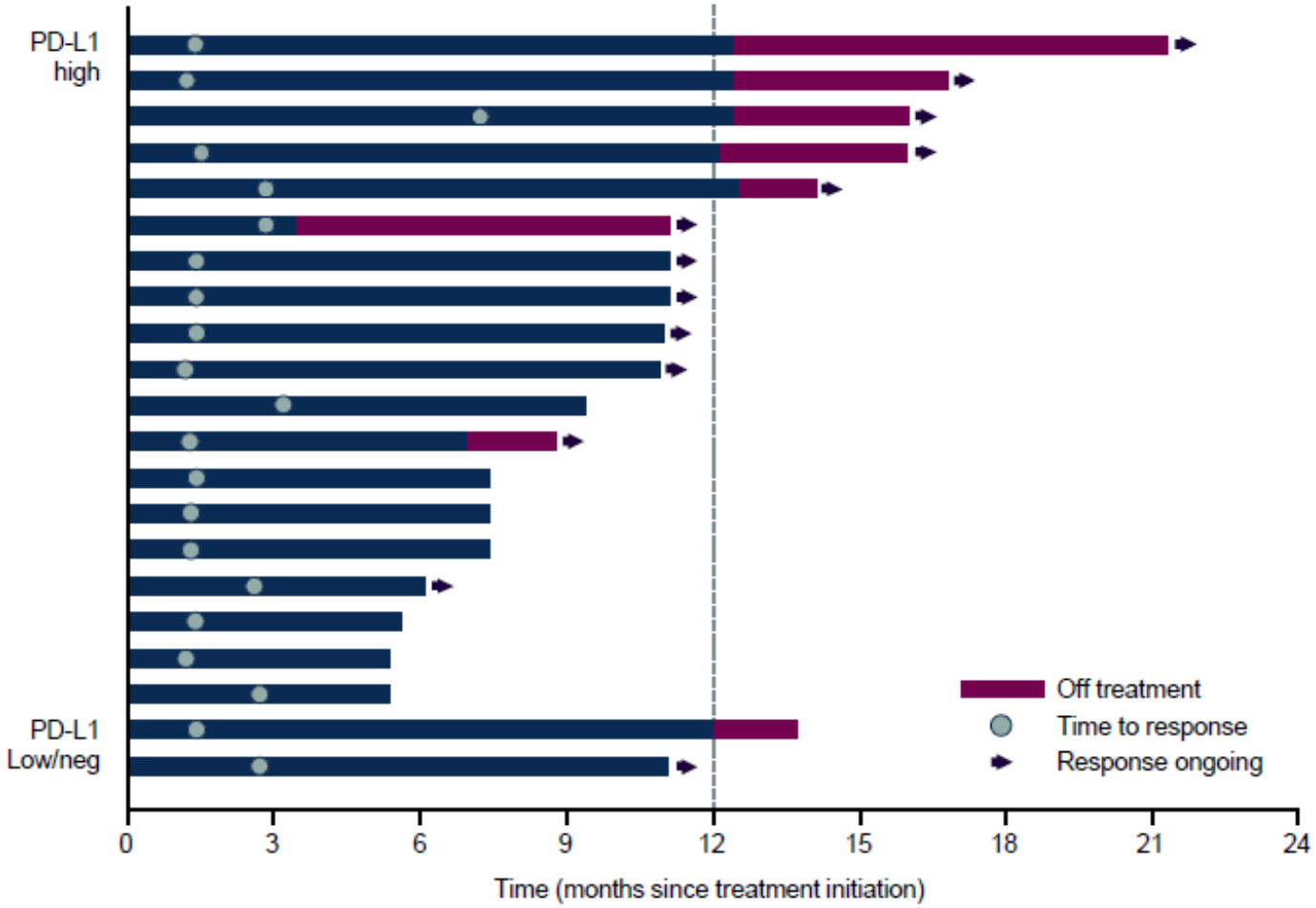
# Patients at Risk:									
PD-L1 High	98	70	35	20	18	11	6	3	2
PD-L1 Low/negative	79	40	10	4	4	1	1	1	
Total	191	124	48	24	22	12	7	4	2

Adapted from Powles T et al. Online ahead of print. JAMA Onc. 2017.

UC Cohort: ORR with Durvalumab

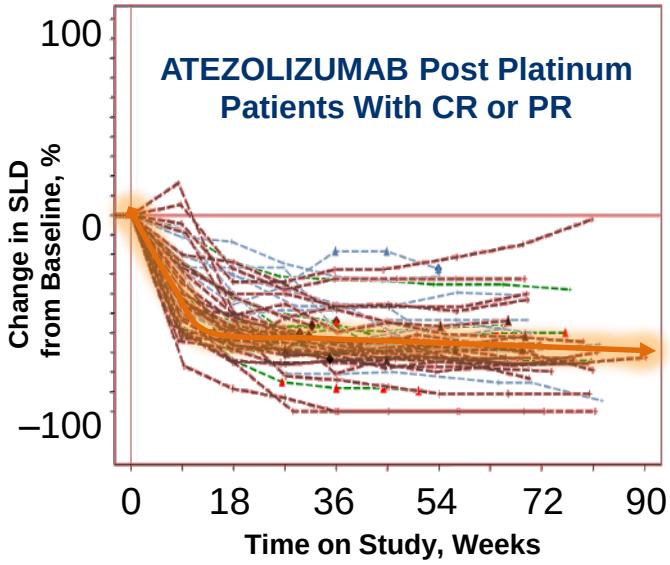
Figure 1. Antitumor Activity in the Primary Efficacy Population of the UC Cohort by PD-L1 Expression Status†

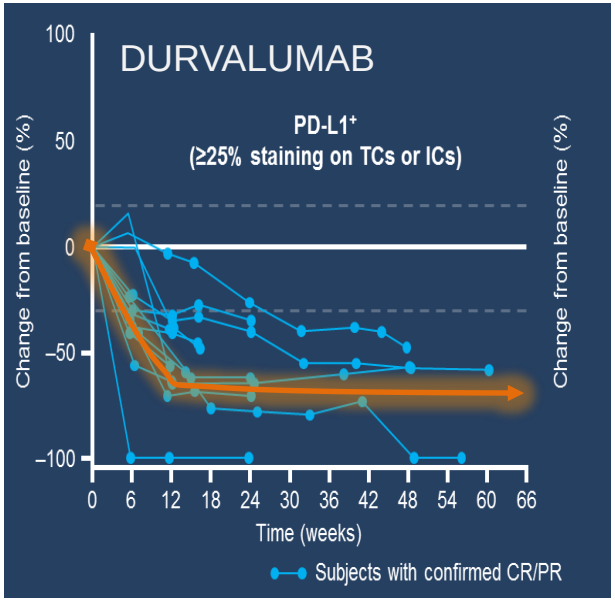
A Time to response and DoR by BICR

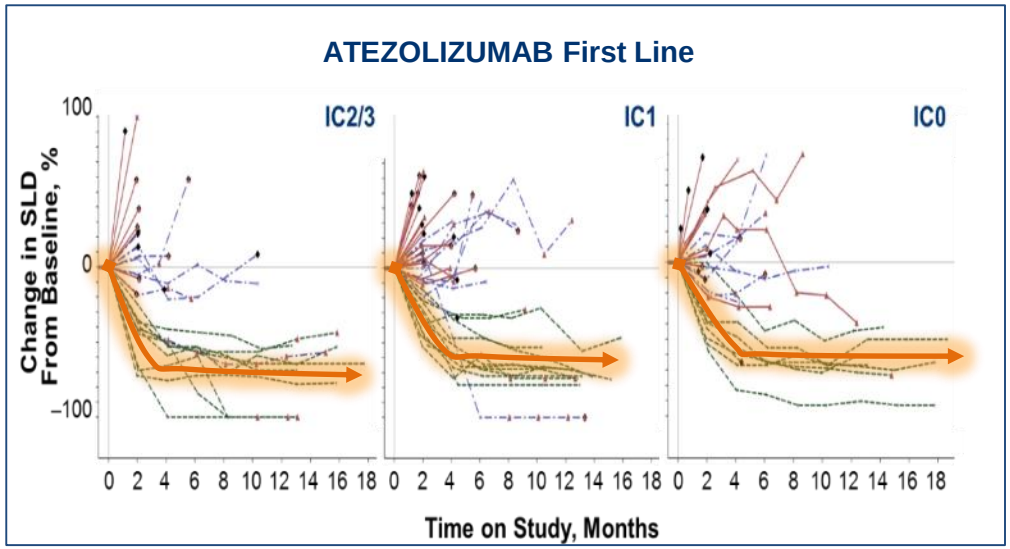


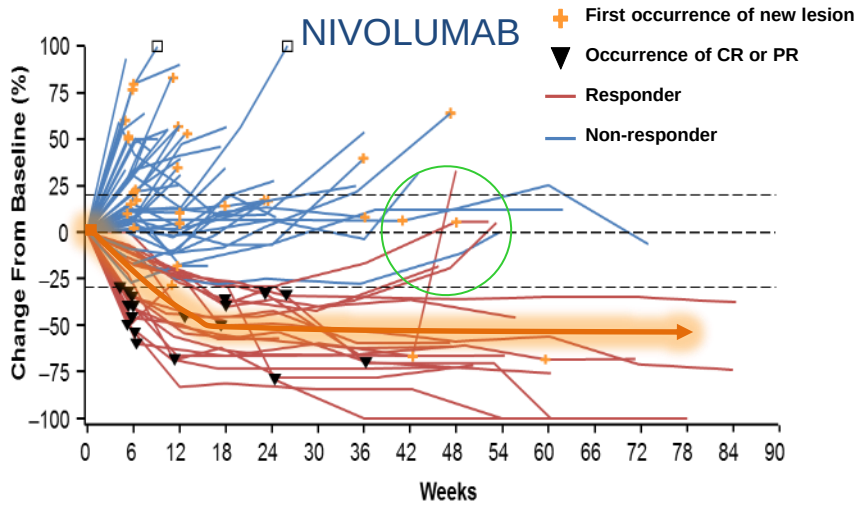
Powles et al. Presented at the 2017 Genitourinary Cancers Symposium (ASCO-GU) February 16-18, 2017 Orlando, Florida

PD-1 Pathway Inhibitors: Progression after Response Seems to Occur Outside of Target Lesions

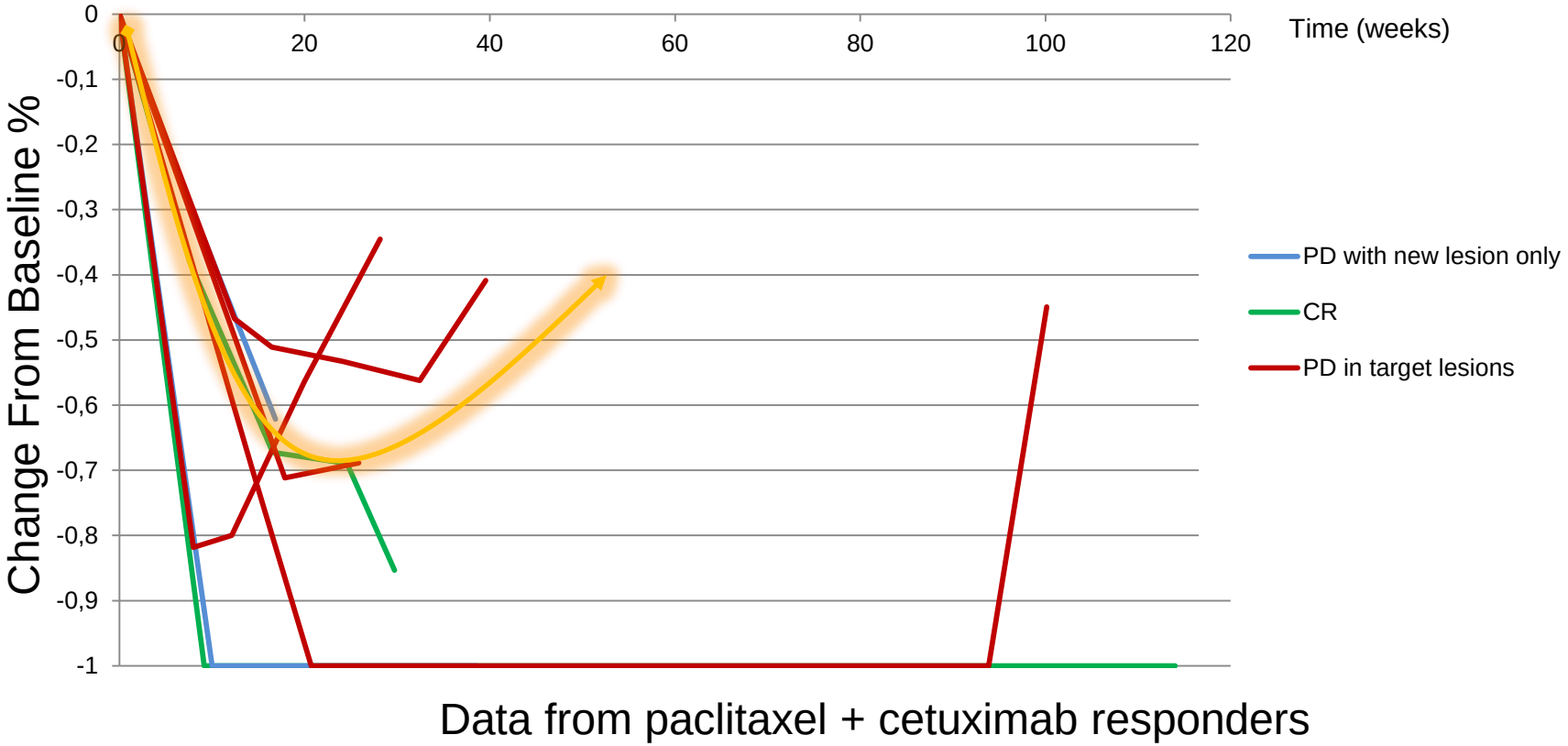






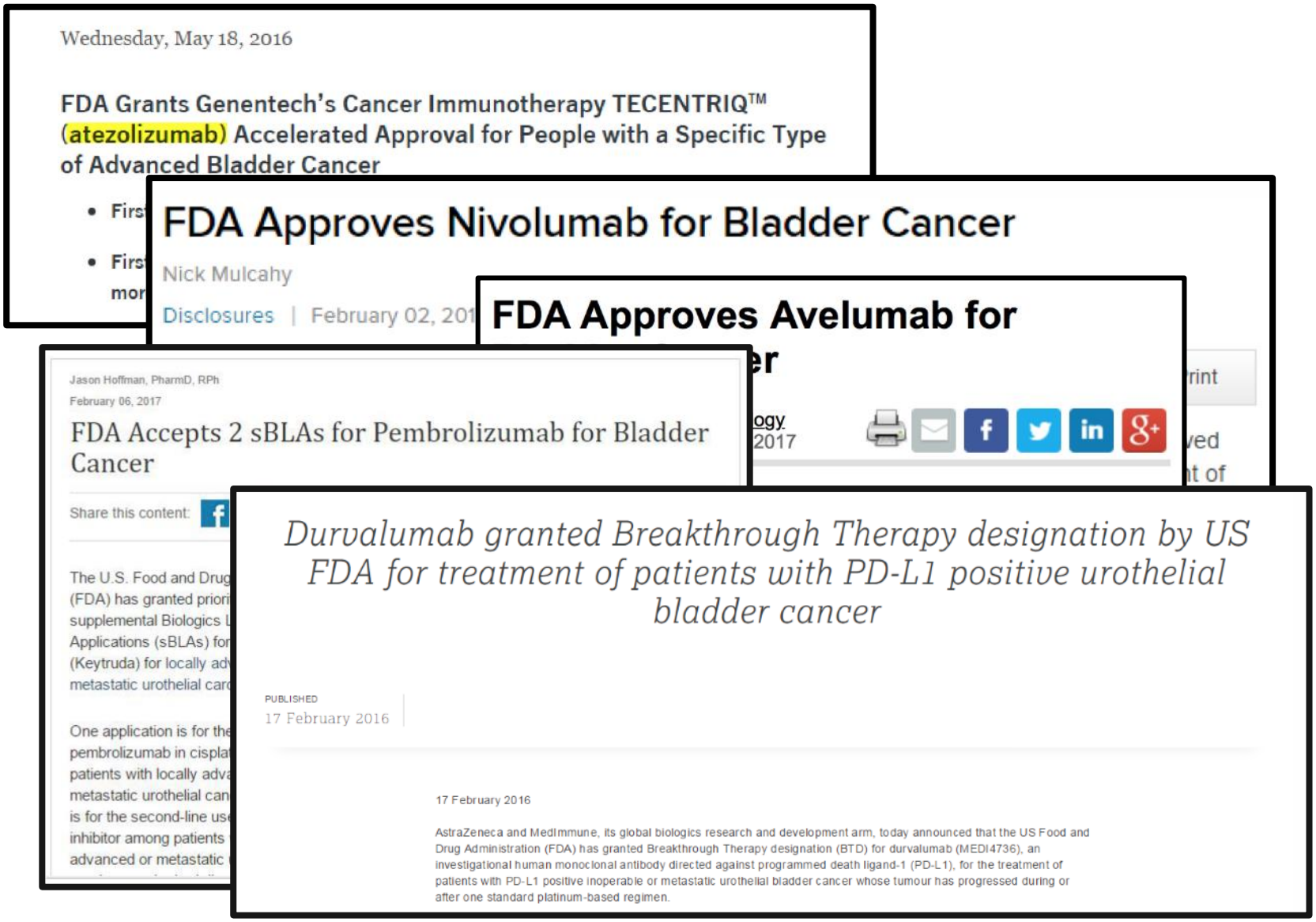


Chemotherapy/Targeted Therapy: Progression After Response Commonly Occurs in Target Lesions



Data from paclitaxel + cetuximab responders

(Wong et al. Phase II trial of cetuximab with or without paclitaxel in patients with advanced urothelial tract carcinoma. JCO 2012)


Wednesday, May 18, 2016
FDA Grants Genentech's Cancer Immunotherapy TECENTRIQ™ (atezolizumab) Accelerated Approval for People with a Specific Type of Advanced Bladder Cancer
FDA Approves Nivolumab for Bladder Cancer
Nick Mulcahy
Disclosures | February 02, 201
FDA Approves Avelumab for
Jason Hoffman, PharmD, RPh
February 06, 2017
FDA Accepts 2 sBLAs for Pembrolizumab for Bladder Cancer
Share this content:
Durvalumab granted Breakthrough Therapy designation by US FDA for treatment of patients with PD-L1 positive urothelial bladder cancer
PUBLISHED
17 February 2016
17 February 2016
AstraZeneca and MedImmune, its global biologics research and development arm, today announced that the US Food and Drug Administration (FDA) has granted Breakthrough Therapy designation (BTD) for durvalumab (MEDI4736), an investigational human monoclonal antibody directed against programmed death ligand-1 (PD-L1), for the treatment of patients with PD-L1 positive inoperable or metastatic urothelial bladder cancer whose tumour has progressed during or after one standard platinum-based regimen.

Systemic Therapy for Bladder Cancer Now

Non-Muscle Invasive	Neoadjuvant Adjuvant	1st Line Metastatic	2nd Line Metastatic	Next Line Metastatic
No systemic therapy				
	Gem + Cisplatin or A-MVAC (Cisplatin)			
		Gem + Cisplatin		
			Pembrolizumab **Atezolizumab** **Durvalumab** **Nivolumabe** **Avelumab**	

Cisplatin:
ORR 50-60%
median OS 15 mo.
1 year OS 60%

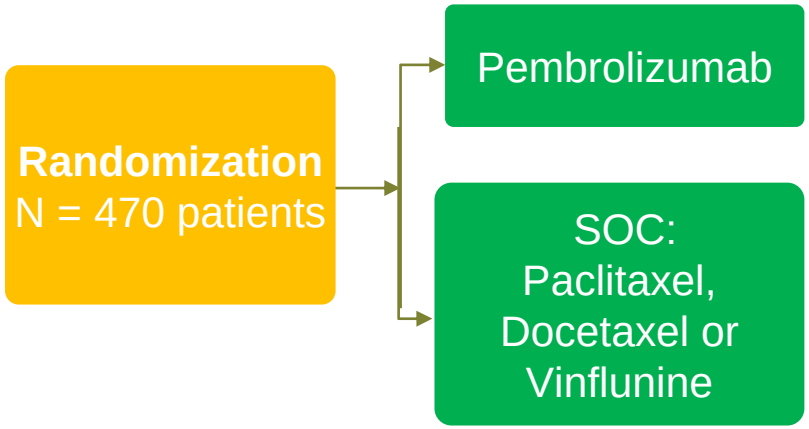
Carboplatin
ORR 36%
median OS 9 mo.
1 year OS 37%

ORR: 12% ?
Median OS 7 mo. ?
1 year OS 26%* ?

SECOND LINE PHASE III

KEYNOTE-045 Study Design (NCT02256436)

- Urothelial cancer
- Progression or recurrence of urothelial cancer following a first-line platinum-containing regimen.
- No more than 2 prior lines of systemic chemotherapy.



Primary end points

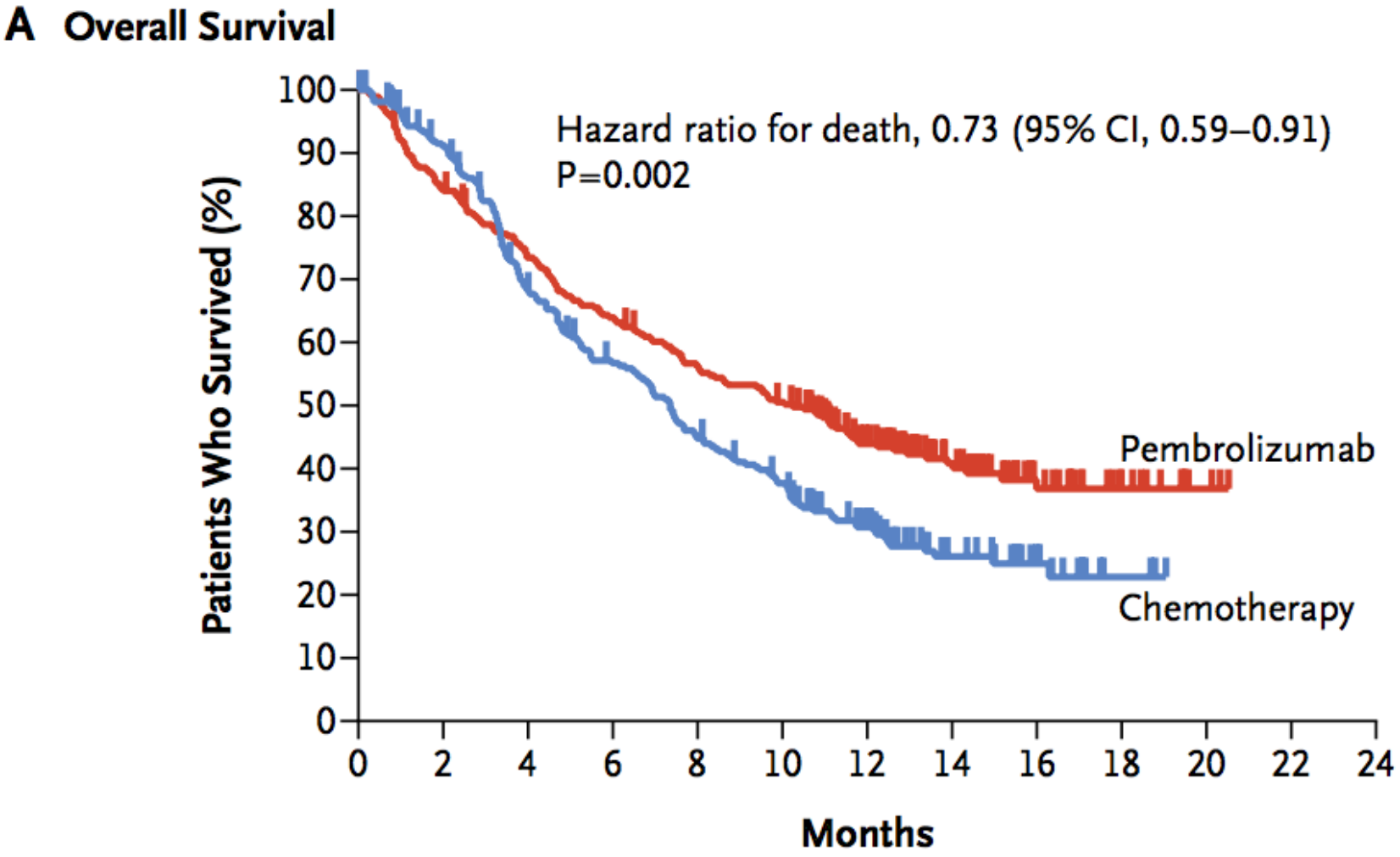
OS & PFS

Secondary end points

- ORR
- Safety

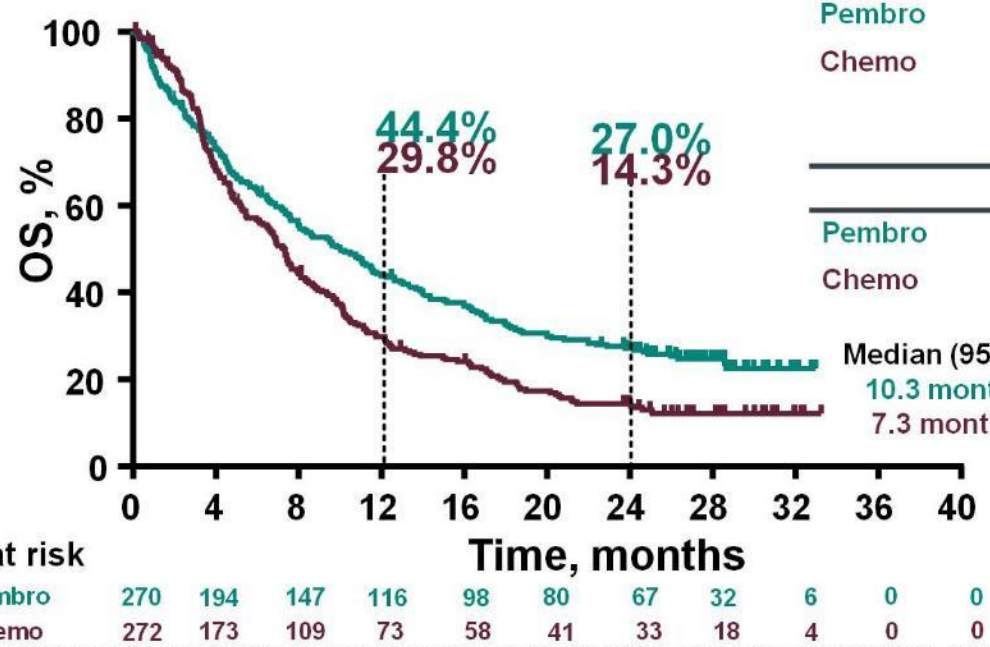
STOPPED EARLY!!!

KEYNOTE-045



Bellmunt J, et al. N Engl J Med 2017; Epub ahead print.

Overall Survival: Total



No. at risk											
Pembro	270	194	147	116	98	80	67	32	6	0	0
Chemo	272	173	109	73	58	41	33	18	4	0	0

14.1 months of follow-up[1]

	Events, n	HR (95% CI)[a]	*P*[b]
Pembro	155	0.73 (0.59-0.91)	0.0022
Chemo	179		

27.7 months of follow-up

	Events, n	HR (95% CI)[a]	*P*[b]
Pembro	199	0.70 (0.57–0.85)	0.00017
Chemo	218		

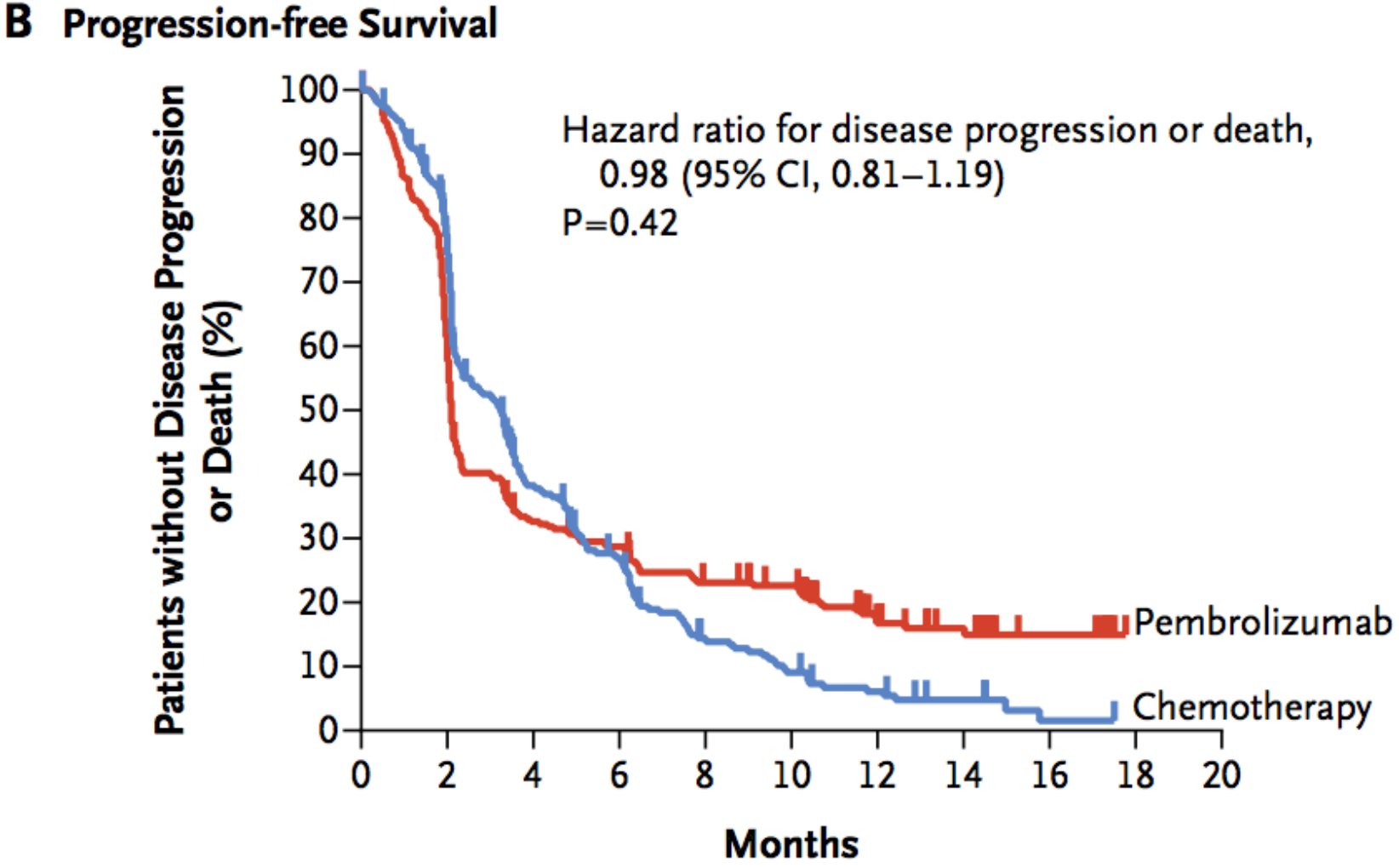
Median (95% CI):
10.3 months (8.0–12.3)
7.3 months (6.1–8.1)

60.6% at 24 months in the chemotherapy arm received an immunotherapeutic agent, including those who received pembrolizumab as part of the cross over.

[a]Based on Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 months). [b]One-sided *P* value based on stratified log-rank test.
Data cutoff date: October 26, 2017.
1. Bellmunt J et al. *N Engl J Med*. 2017;376:1015-1026.

Bellmunt, GU ASCO 2018

KEYNOTE-045



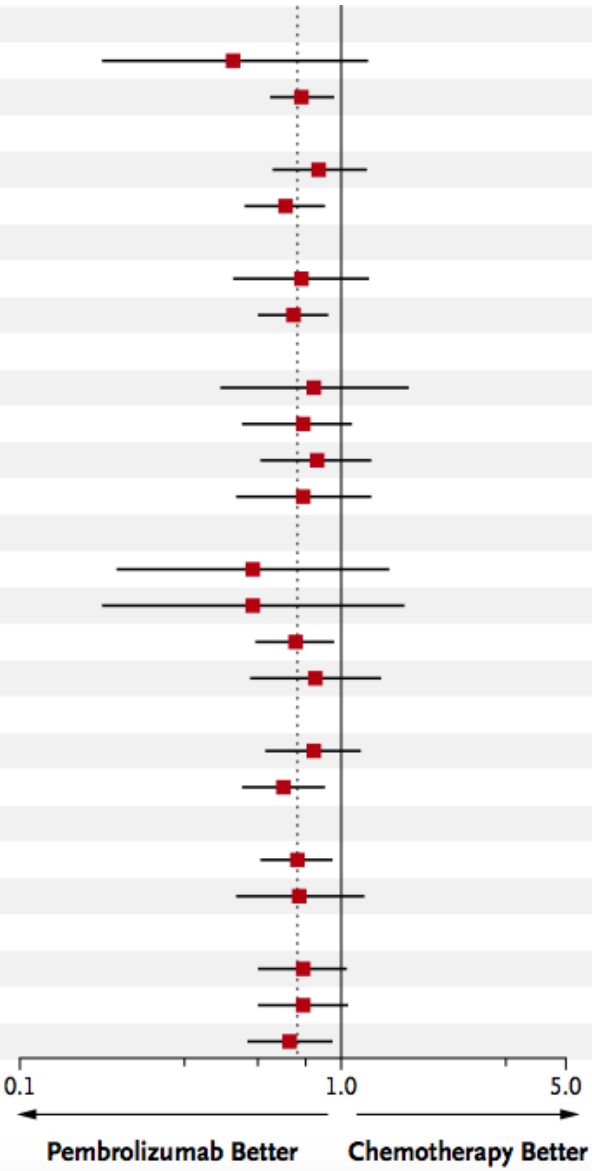
No. at Risk

Pembrolizumab	270	165	85	73	56	51	23	16	7	0	0
Chemotherapy	272	188	85	56	27	17	10	5	1	0	0

Bellmunt J, et al. N Engl J Med 2017; Epub ahead print.

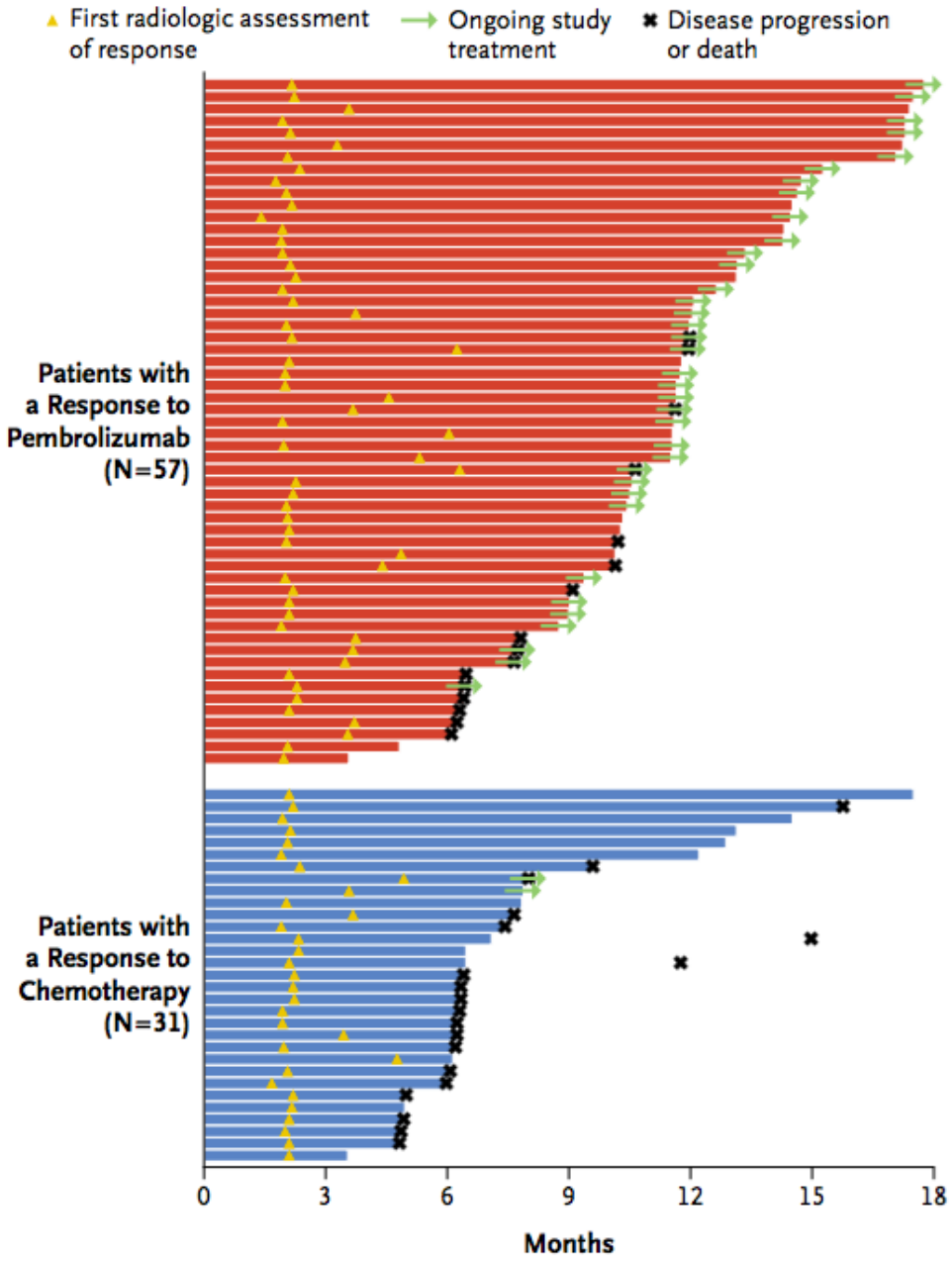
KEYNOTE-045

Subgroup	No. of Deaths/ No. of Patients	Hazard Ratio (95% CI)
Location of metastases		
Lymph node only	22/67	0.46 (0.18–1.21)
Visceral disease	312/473	0.75 (0.60–0.95)
Liver metastases		
Yes	145/186	0.85 (0.61–1.20)
No	189/355	0.67 (0.50–0.89)
Hemoglobin concentration		
<10 g/dl	71/87	0.75 (0.46–1.22)
≥10 g/dl	257/442	0.71 (0.55–0.91)
No. of risk factors		
0	35/98	0.82 (0.42–1.62)
1	104/193	0.73 (0.49–1.08)
2	111/146	0.84 (0.56–1.24)
3 or 4	76/90	0.76 (0.47–1.24)
Context of most recent therapy received		
Neoadjuvant therapy	22/41	0.53 (0.20–1.41)
Adjuvant therapy	27/43	0.53 (0.18–1.57)
First-line therapy for metastatic disease	203/340	0.72 (0.54–0.95)
Second-line therapy for metastatic disease	80/115	0.83 (0.52–1.33)
Time since most recent chemotherapy		
<3 mo	140/207	0.82 (0.58–1.15)
≥3 mo	193/333	0.66 (0.49–0.89)
Previous platinum therapy		
Cisplatin	248/411	0.73 (0.56–0.94)
Carboplatin	82/126	0.74 (0.47–1.18)
Investigator's choice of chemotherapy		
Paclitaxel	208/350	0.76 (0.55–1.04)
Docetaxel	203/350	0.76 (0.55–1.05)
Vinflunine	216/353	0.69 (0.51–0.94)



Bellmunt J, et al. N Engl J Med 2017; Epub ahead print.

KEYNOTE-045



Bellmunt J, et al. N Engl J Med 2017; Epub ahead print.

IMvigor211: A Phase III Randomized Study Examining Atezolizumab vs. Chemotherapy for Platinum-Treated Advanced Urothelial Carcinoma

Powles T, et al. EAS 2017, IMvigor211.

IMvigor211 Study Design

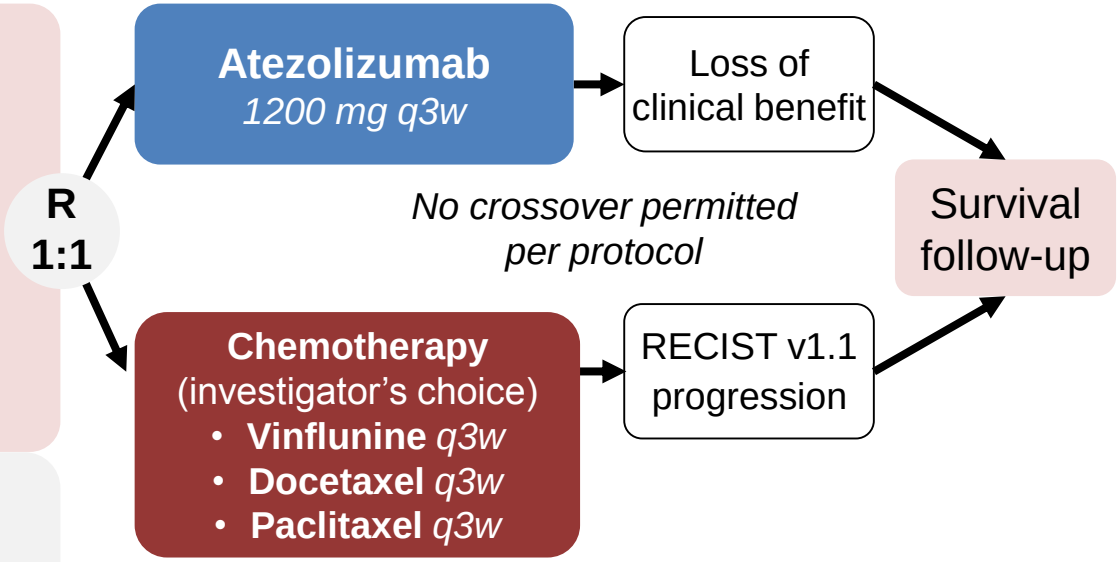
Key Eligibility Criteria[a]

- mUC with progression during or following platinum-based chemotherapy
  - ≤ 2 prior lines of therapy
- Measurable disease per RECIST v1.1
- ECOG PS 0-1
- Evaluable sample for PD-L1 testing
- TCC histology as primary component

(N = 931)

Stratification Factors

- No. of risk factors[b] (0 vs. 1/2/3)
- Liver metastases (yes vs. no)
- PD-L1 status (0/1 vs. 2/3)
- Chemotherapy (vinflunine vs. taxanes)



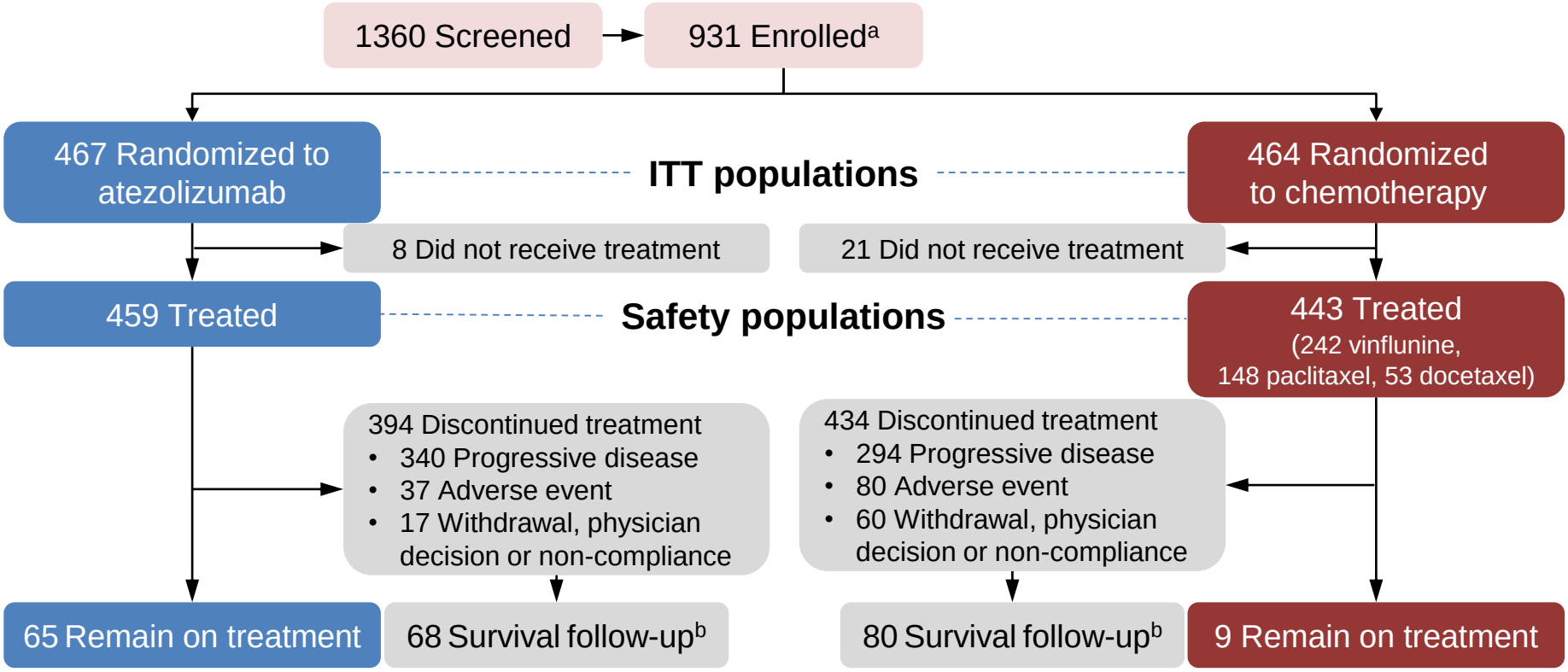
- **Primary endpoint**
  - OS, tested hierarchically in pre-specified populations

- **Additional endpoints**
  - Efficacy: RECIST v1.1 ORR, PFS and DOR[c]
  - Safety
  - PROs: EORTC QLQ-C30

DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; PRO, patient-reported outcome; q3w, every three weeks; RECIST, Response Evaluation Criteria In Solid Tumors; TCC, transitional cell carcinoma. [a] ClinicalTrials.gov, NCT02302807. [b] Defined by time from prior chemotherapy < 3 mo, ECOG performance status > 0 and hemoglobin < 10 g/dL. [c] Confirmed response was not required for secondary efficacy endpoints. This analysis reports exploratory confirmed responses.

Powles T, et al. EAS 2017, IMvigor211.

Patient Flowchart



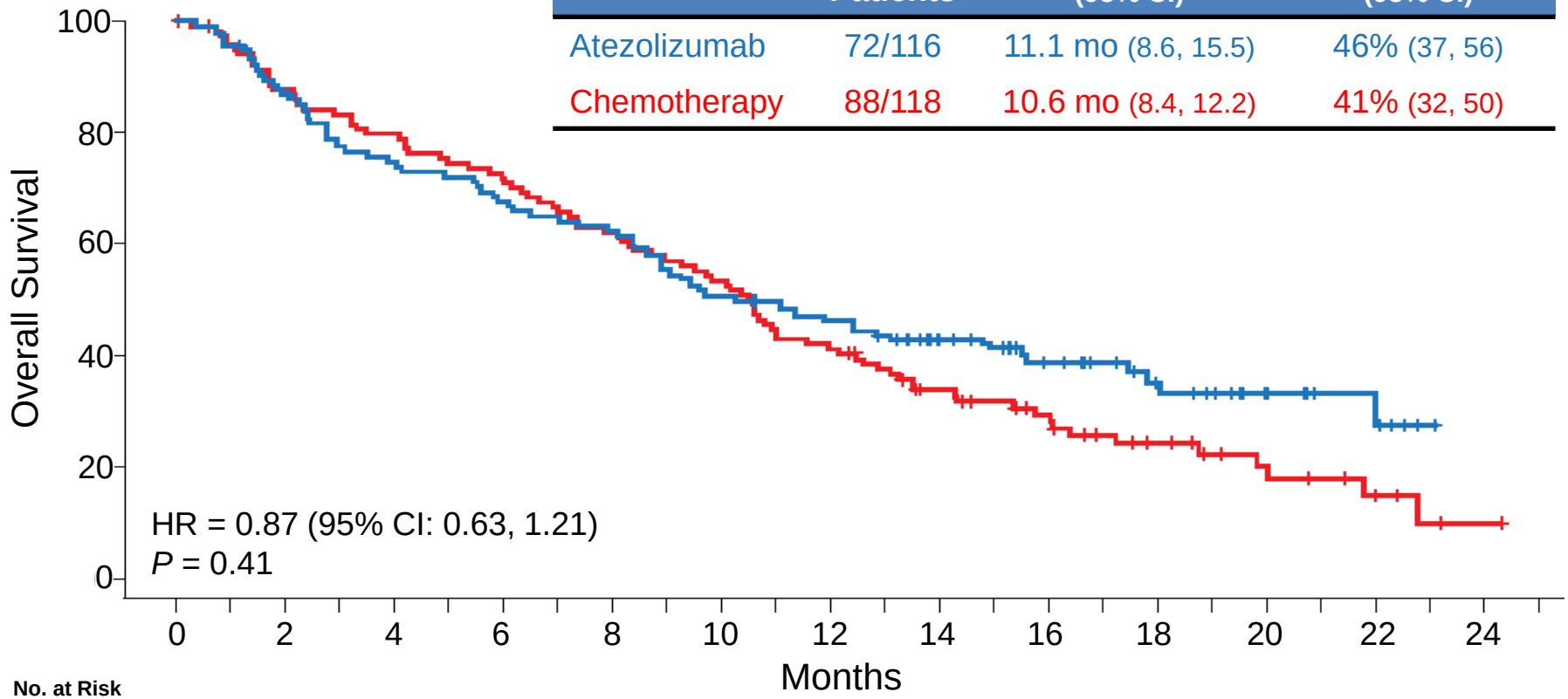
- Enrollment took place at 198 study sites: 712 patients (77%) from Europe, 71 (8%) from North America, 132 (14%) from Asia Pacific, 16 (2%) from other regions
  - Median follow-up duration in ITT population: 17.3 mo (range, 0 to 24.5 mo)

[a] 1 patient was randomized to chemotherapy twice due to a randomization error but counted only once in this analysis.
[b] An additional 5 deaths (4 in the chemotherapy arm; 1 in the atezolizumab arm) were collected from public records and included as uncensored deaths in the efficacy analyses.

Powles T, et al. EAS 2017, IMvigor211.

OS Analysis: IC2/3 Population

	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	72/116	11.1 mo (8.6, 15.5)	46% (37, 56)
Chemotherapy	88/118	10.6 mo (8.4, 12.2)	41% (32, 50)



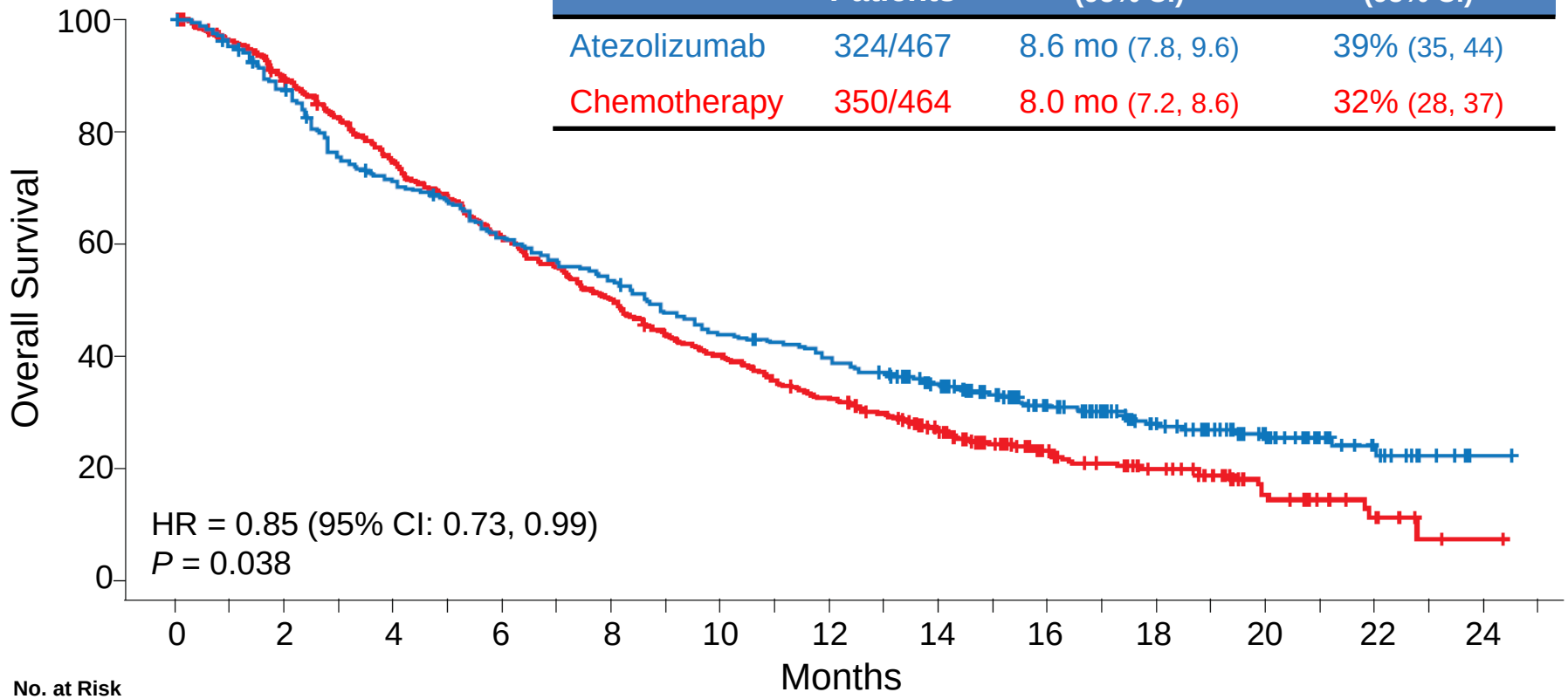
No. at Risk													
Atezolizumab	116	100	85	77	71	58	51	39	27	19	11	6	0
Chemotherapy	118	100	91	82	71	61	47	32	24	15	9	5	1

HR, hazard ratio.

Powles T, et al. EAS 2017, IMvigor211.

OS Analysis: ITT Population

	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	324/467	8.6 mo (7.8, 9.6)	39% (35, 44)
Chemotherapy	350/464	8.0 mo (7.2, 8.6)	32% (28, 37)

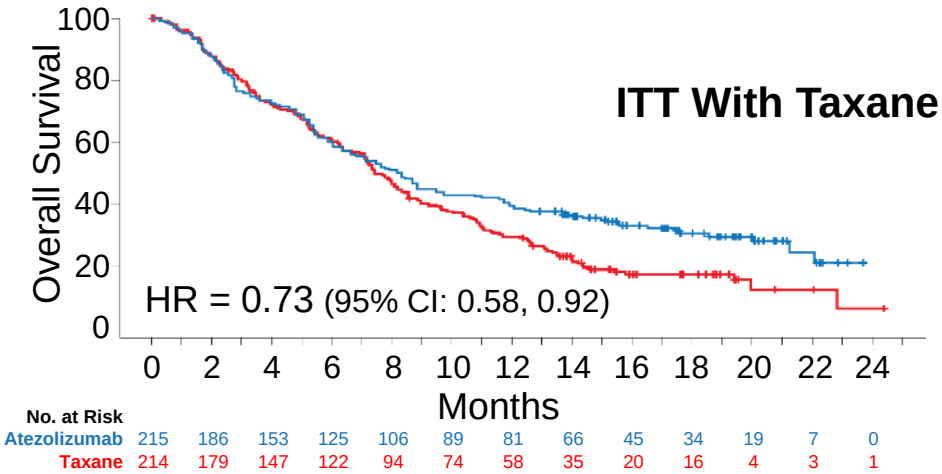


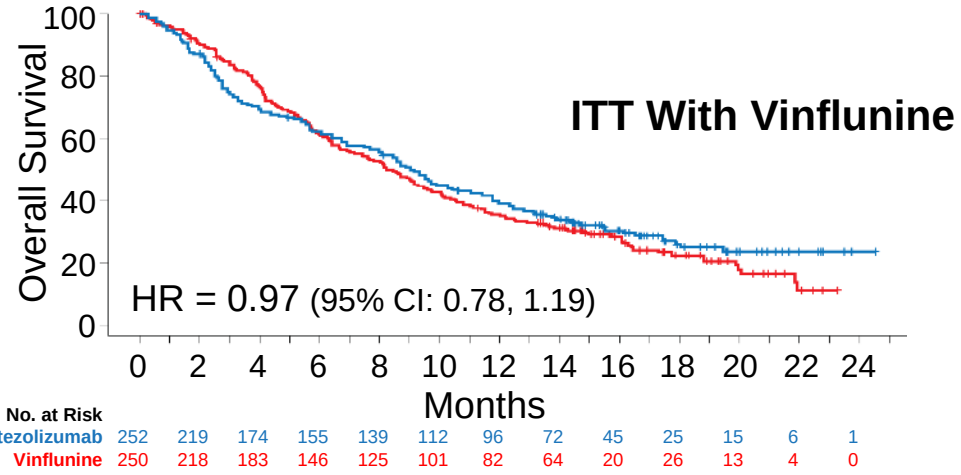
No. at Risk													
Atezolizumab	467	405	327	280	245	201	177	138	90	59	34	13	1
Chemotherapy	464	397	330	268	219	175	140	99	60	42	17	7	1

- Median follow-up duration in ITT population: 17.3 mo (range, 0 to 24.5 mo)

Powles T, et al. EAS 2017, IMvigor211.

OS by Chemotherapy Type





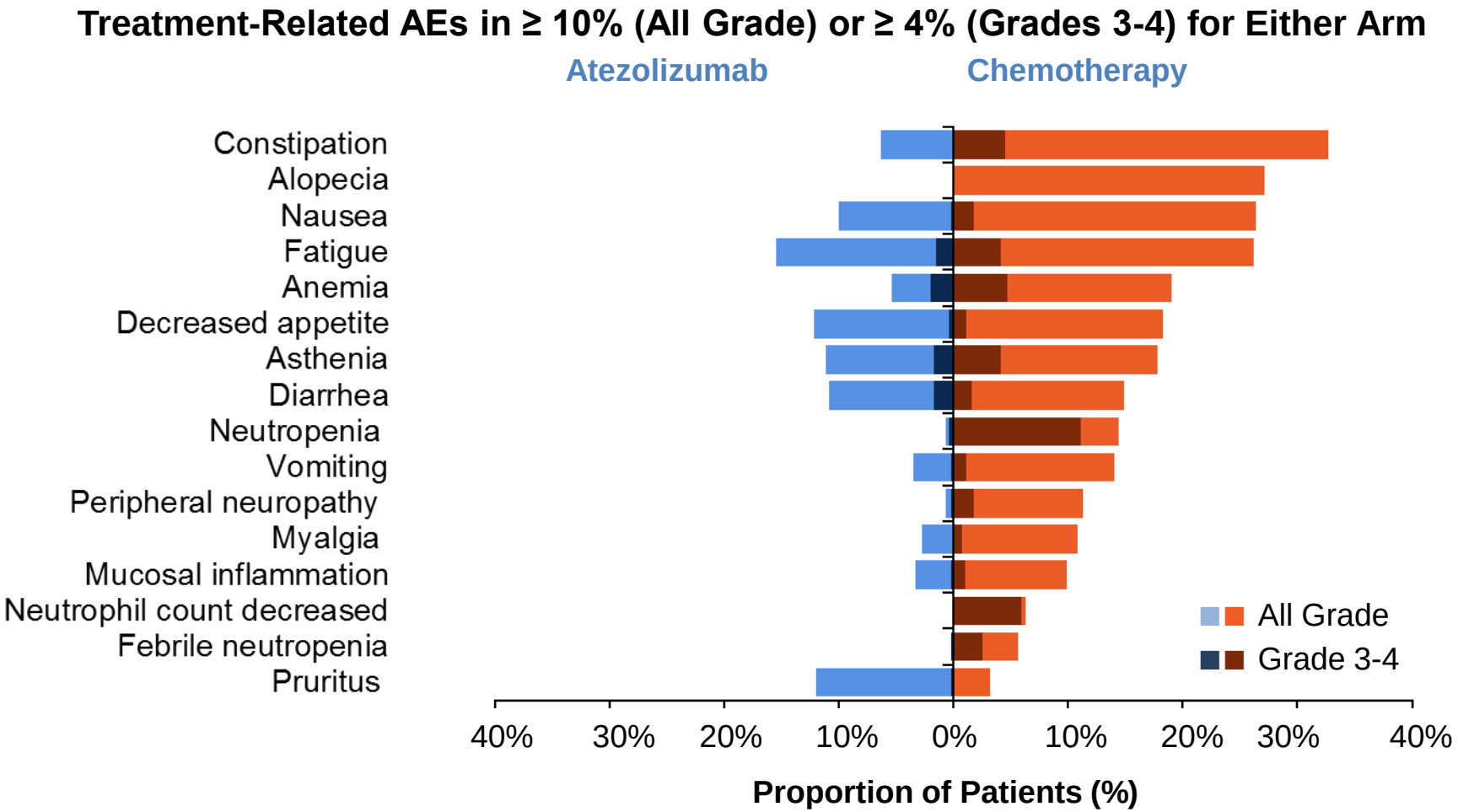
- OS was also examined in subgroups based on chemotherapy type at randomization
  - Improved OS was observed with atezolizumab vs. taxanes

Subgroup	Median OS (95% CI)
Atezolizumab	8.3 mo (6.6, 9.8)
Taxane	7.5 mo (6.7, 8.6)

Subgroup	Median OS (95% CI)
Atezolizumab	9.2 mo (7.9, 10.4)
Vinflunine	8.3 mo (6.9, 9.6)

Powles T, et al. EAS 2017, IMvigor211.

Treatment-Related AEs

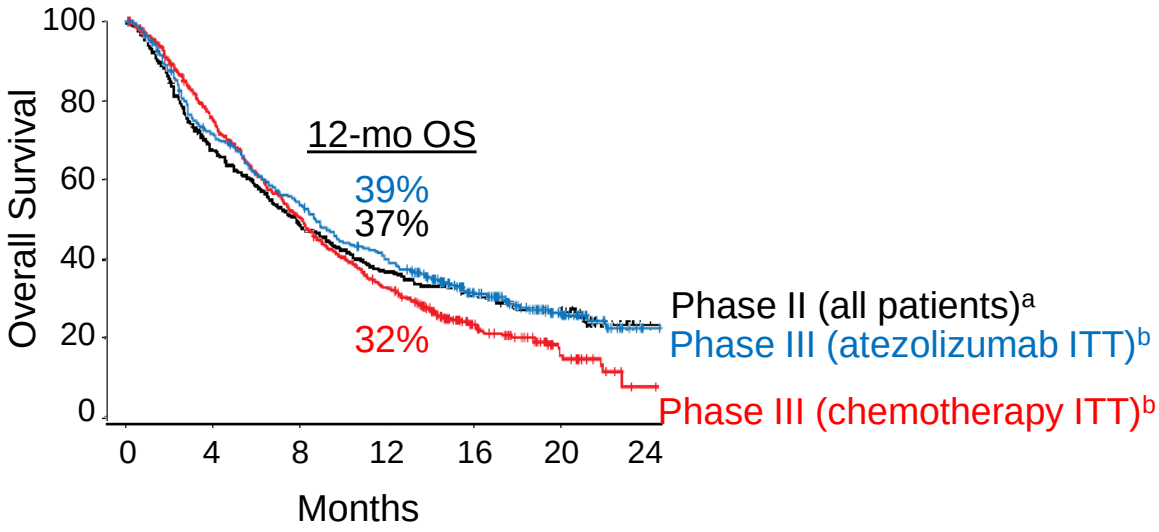


- The safety profile for atezolizumab was consistent with Phase I-II data[1,2]

1. Powles *Nature* 2014. 2. Rosenberg *Lancet* 2016.

Conclusions

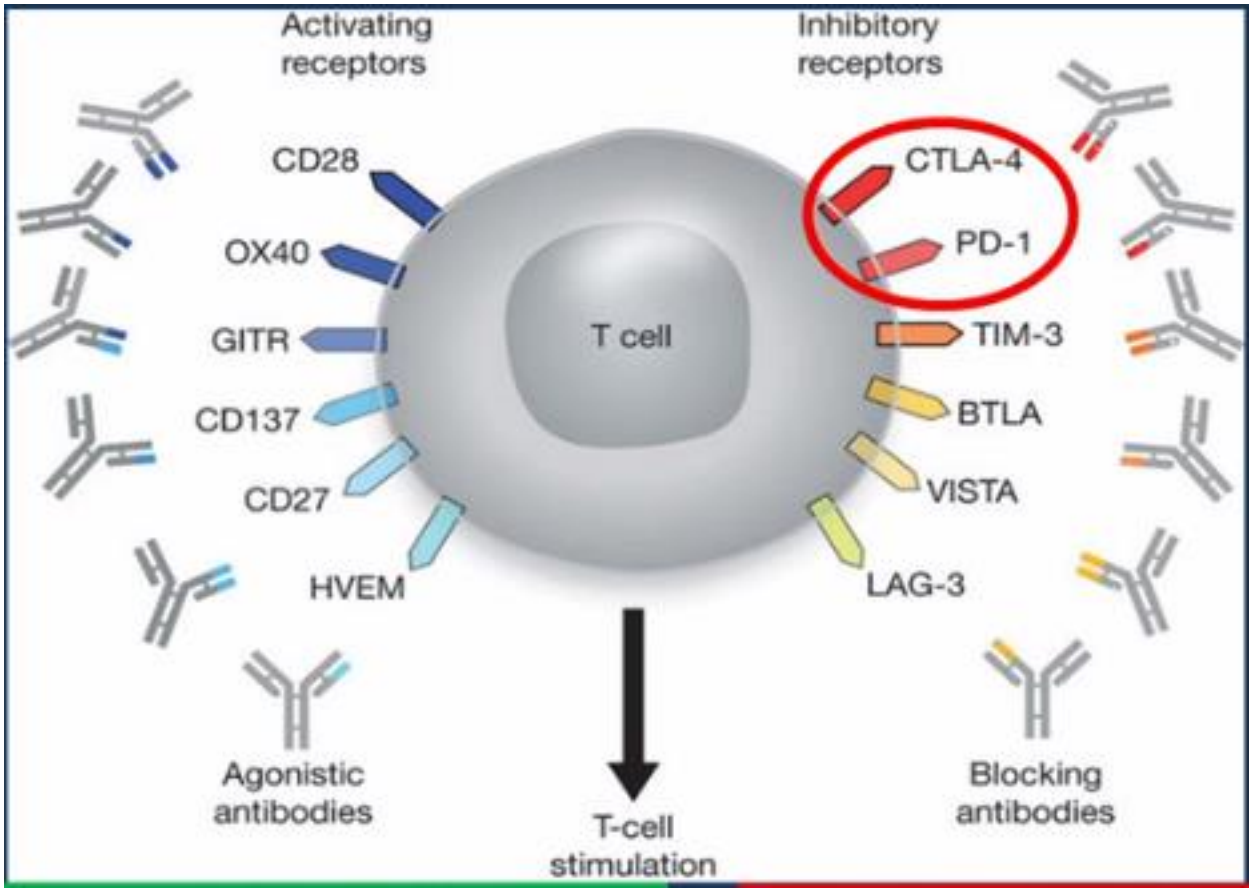
- Atezolizumab OS, ORR and DOR were consistent with the results from IMvigor210 (cohort 2; platinum-treated), confirming the durability of benefit from atezolizumab
  - Atezolizumab 12-mo OS data from IMvigor211 were consistent with Phase I and II data[1,2]



- The positive prognostic (and not predictive) nature of high PD-L1 expression on IC impacted statistical outcomes
- Atezolizumab remains an important treatment option for patients with platinum-treated mUC

1. Petrylak ASCO-GU 2017. 2. Loriot ESMO 2016. Based on median follow-up of [a] 21.0 mo in reference 2 and [b]17.3 mo in IMvigor211.

Ways to keeping the T-Cells “Active”



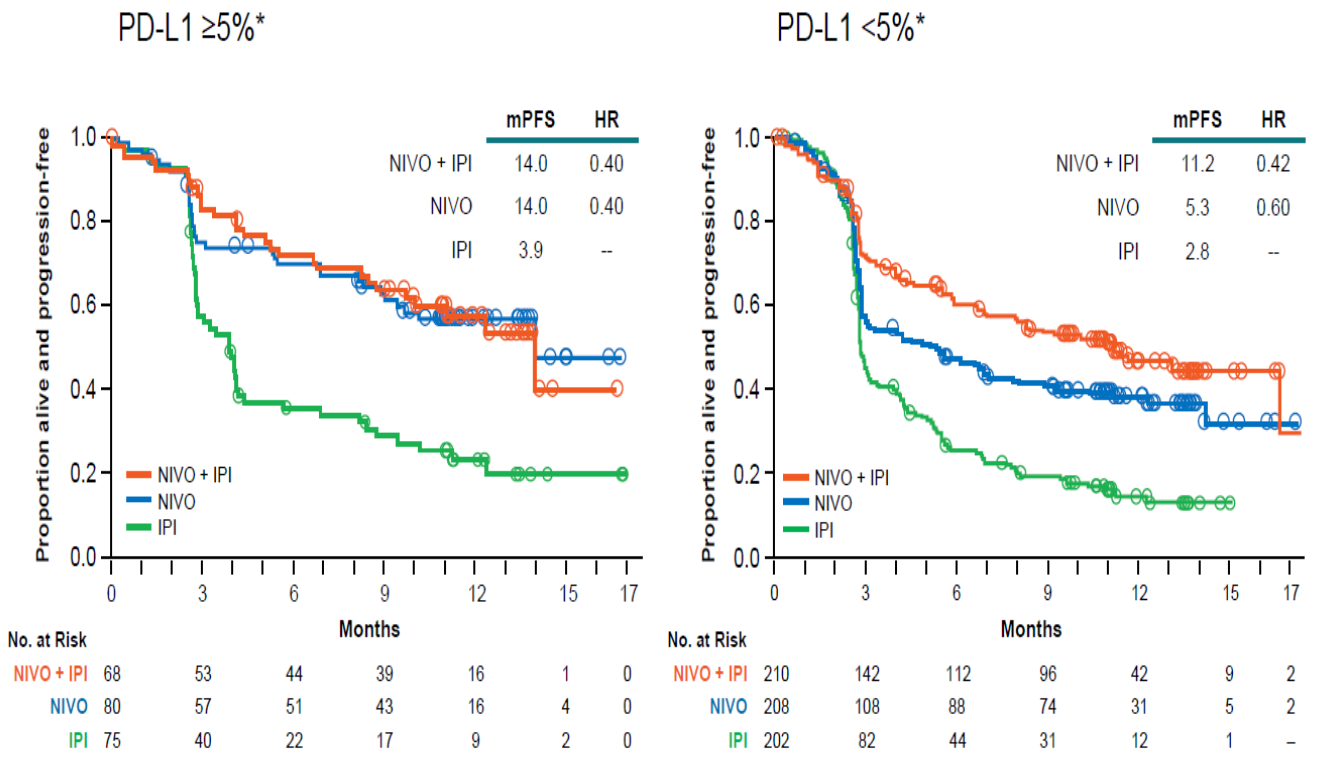
Turning up The Activating

Blocking the Inhibiting

Mellmann et al. Nature, 2011

Phase III trial in Melanoma: IPI + NIVO

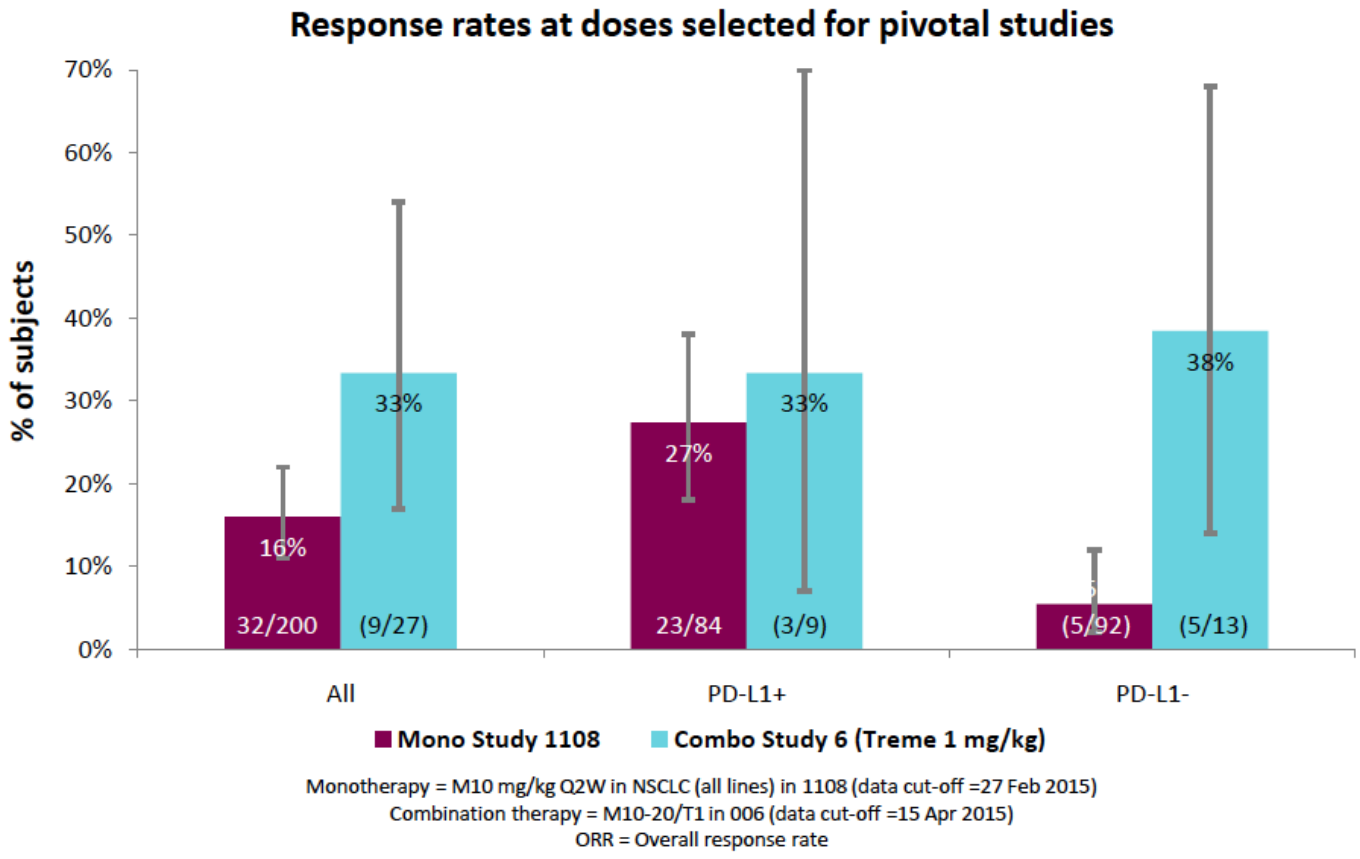
PFS by PD-L1 Expression Level (5%)



*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

MEDI4736 + treme increases ORR over monotherapy

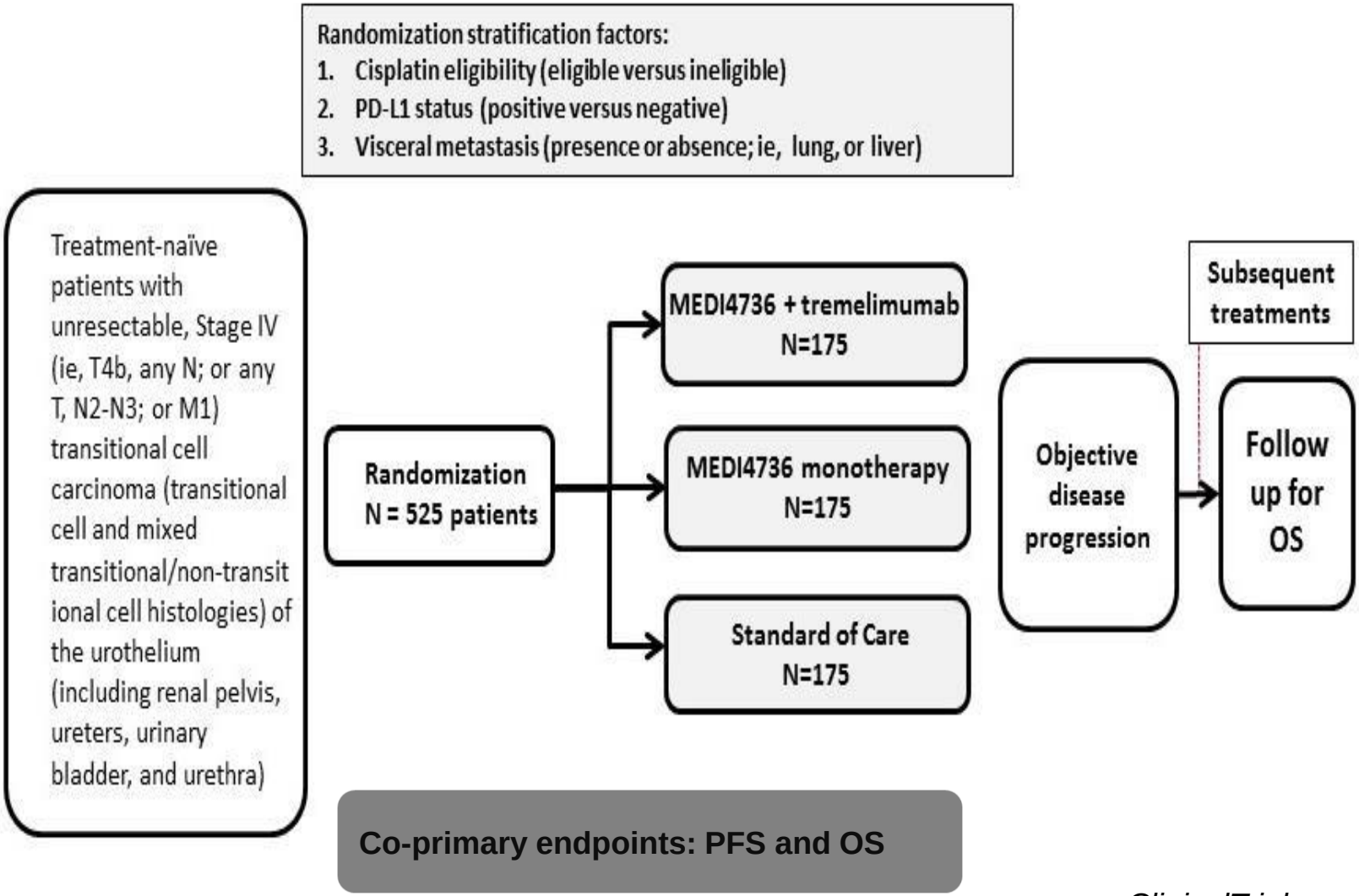
Important improvement in PD-L1 negative patients



Monotherapy = M10 mg/kg Q2W in NSCLC (all lines) in 1108 (data cut-off =27 Feb 2015)
Combination therapy = M10-20/T1 in 006 (data cut-off =15 Apr 2015)
ORR = Overall response rate

DANUBE study design

- **Phase 3, randomized, open-label, controlled, multicentre study**



ClinicalTrials.gov. Available at: http://clinicaltrials.gov/ct2/show/NCT02516241

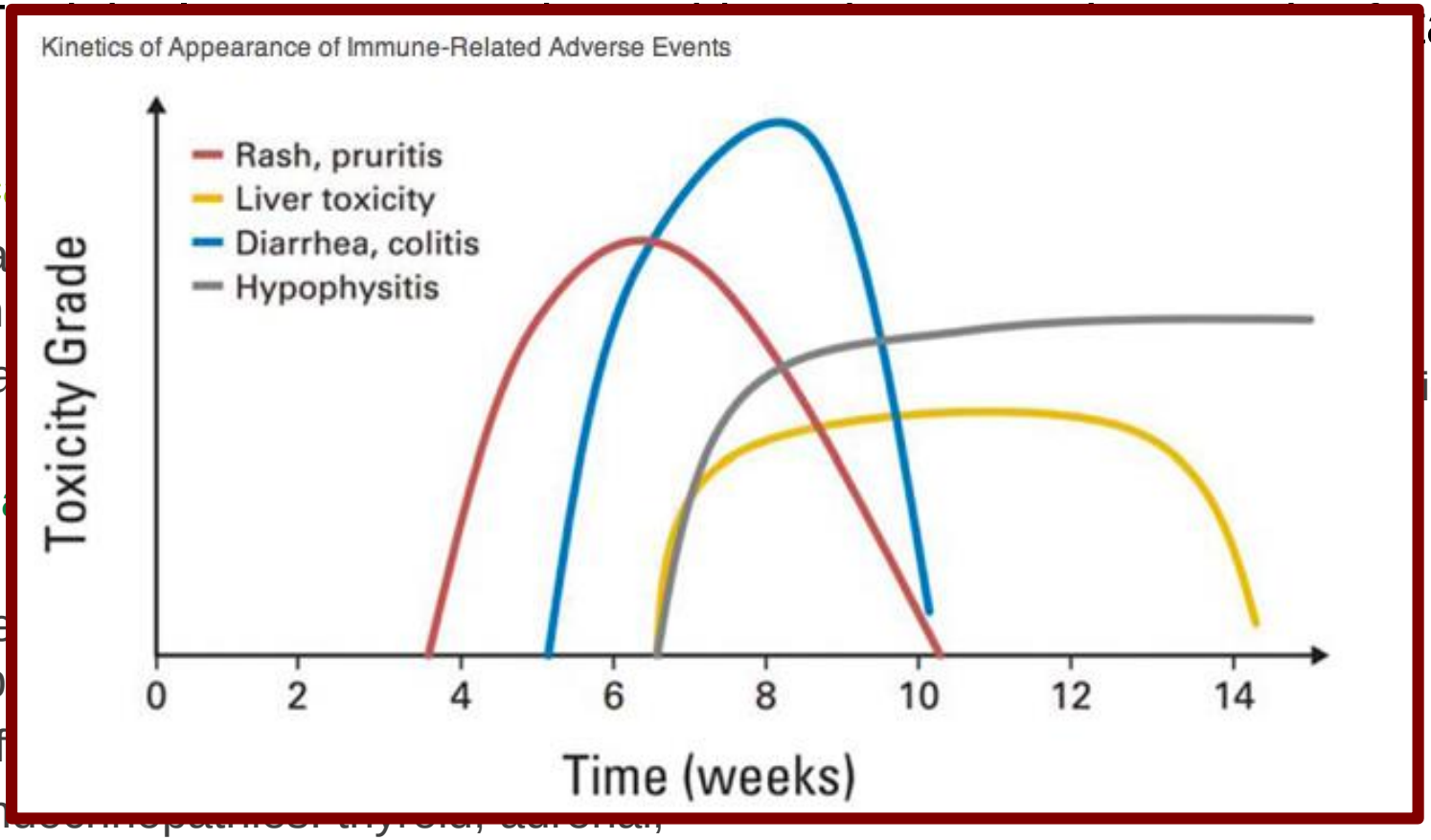
Toxicities from PD-1/PDL1 or CTLA-4 inhibitors

Summary of PD-1/PD-L1 Blockade Immune-Mediated Toxicities

- T…al

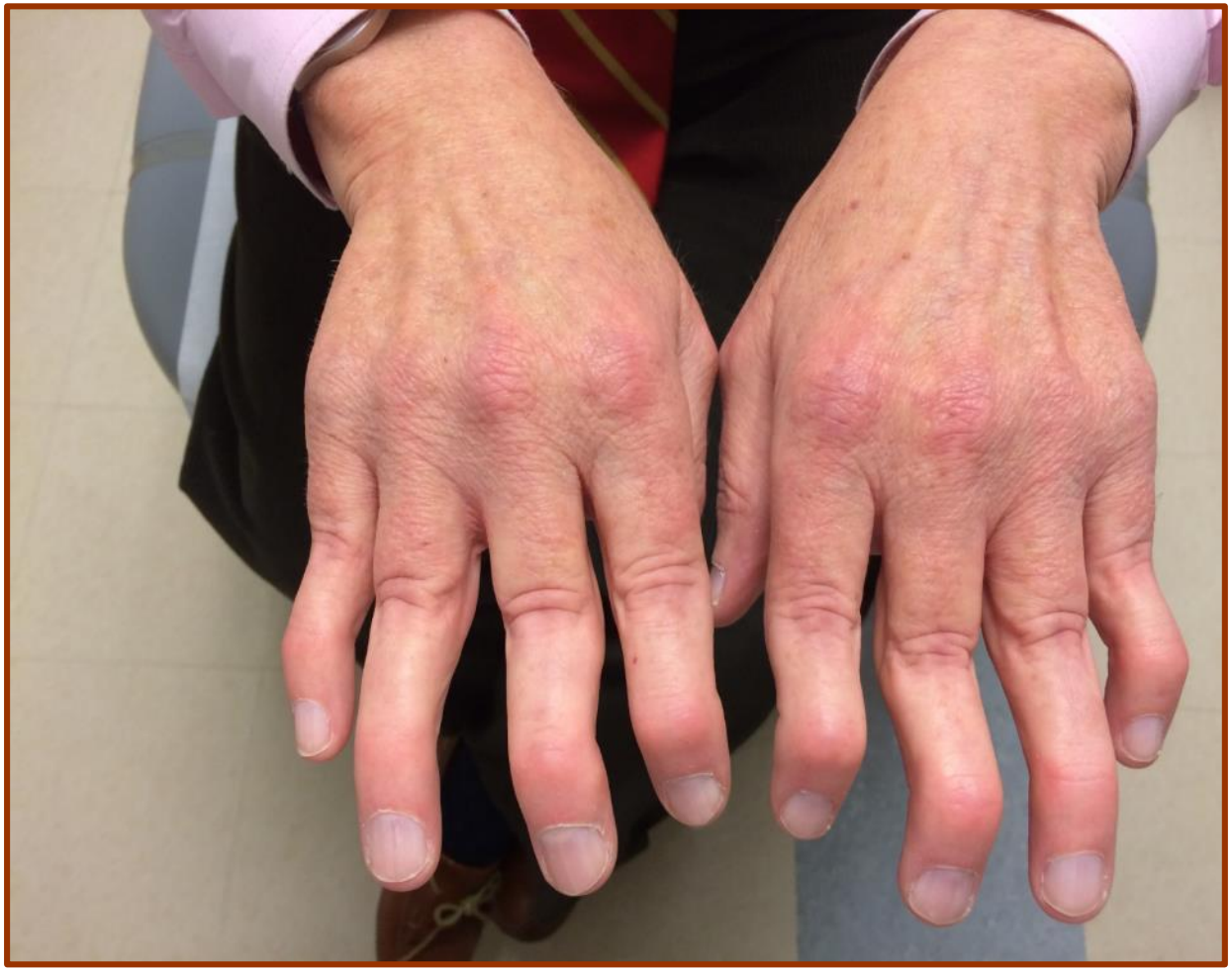
Occ…

- Fa… ch…
- Ra… …ids and – …
- **Di…** – …
- He… ab…
- Inf…
- En… hypophysitis



Weber JS, et al. J Clin Oncol. 2012;30:2691-2697. Weber JS, et al. J Clin Oncol. 2015

Jacoud's arthropathy- very insidious development as gradual stiffness, on PD1 inhibitors



Fulminant type 1 diabetes caused by dual immune checkpoint blockade in metastatic renal cell carcinoma FREE

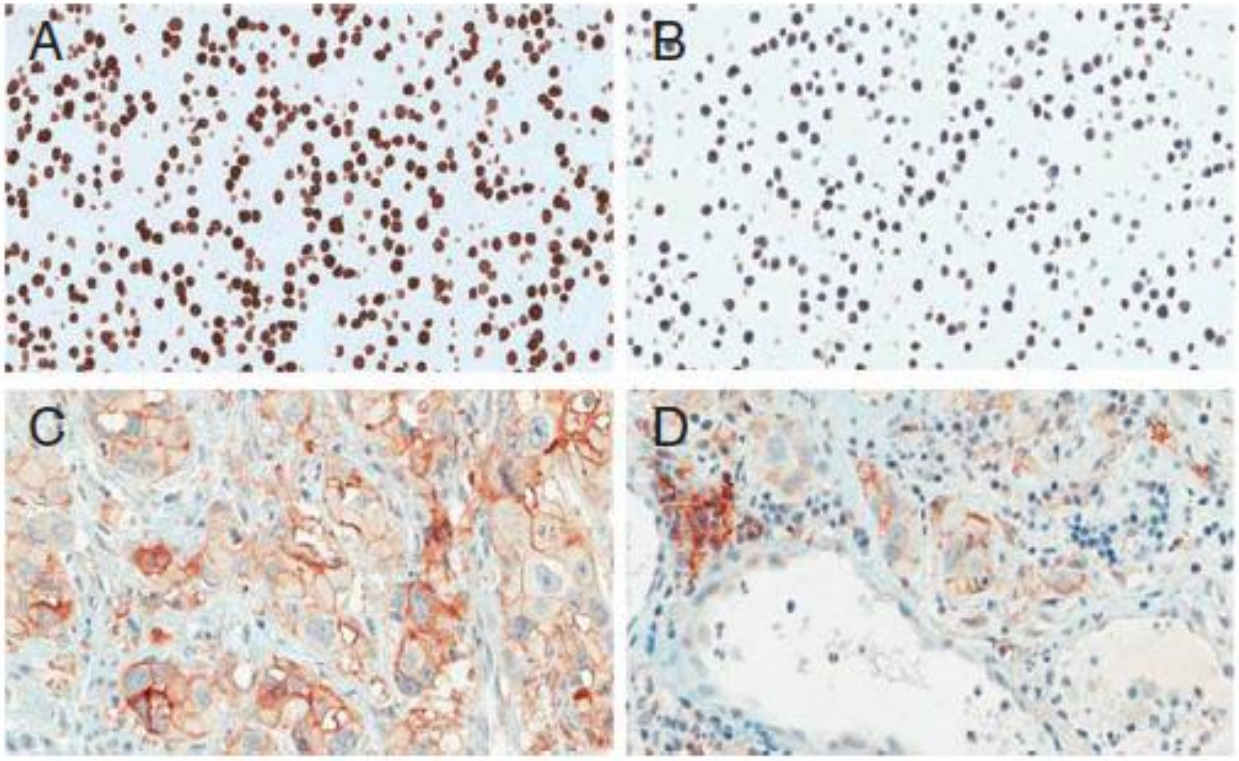
G. H. Teló, G. F. Carvalhal, C. G. S. Cauduro, V. S. Webber, C. H. Barrios, A. P. Fay ✉

Annals of Oncology, Volume 28, Issue 1, 1 January 2017, Pages 191–192,
https://doi.org/10.1093/annonc/mdw447
Published: 18 October 2016

Biomarkers of Response

Association of PD-L1 expression on tumor-infiltrating mononuclear cells and overall survival in patients with urothelial carcinoma

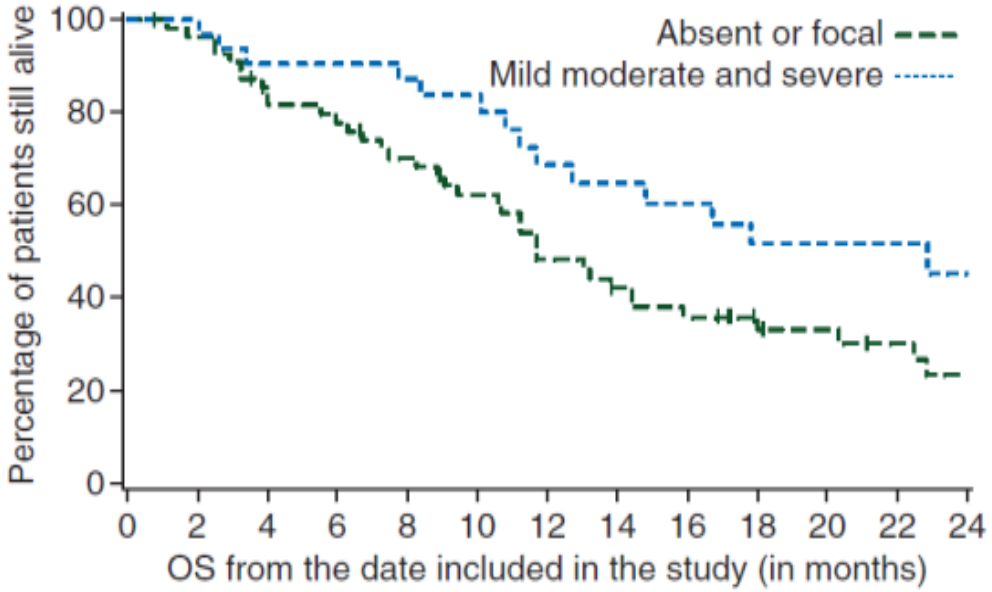
J. Bellmunt[1,2,3,4], S. A. Mullane[1,4,†], L. Werner[1,†], A. P. Fay[1,4], M. Callea[5], J. J. Leow[1], M. E. Taplin[1,2,3,4], T. K. Choueiri[1,2,3,4], F. S. Hodi[3,4,6], G. J. Freeman[3,4] & S. Signoretti[1,3,5]



Annals of Oncology, 2015

Association of PD-L1 expression on tumor-infiltrating mononuclear cells and overall survival in patients with urothelial carcinoma

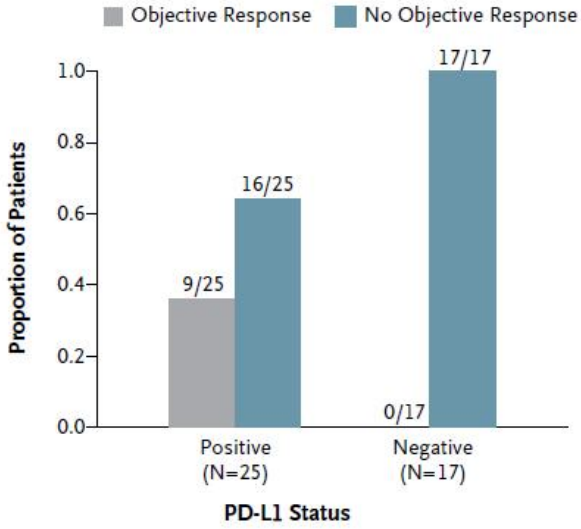
J. Bellmunt[1,2,3,4], S. A. Mullane[1,4,†], L. Werner[1,†], A. P. Fay[1,4], M. Callea[5], J. J. Leow[1], M. E. Taplin[1,2,3,4], T. K. Choueiri[1,2,3,4], F. S. Hodi[3,4,6], G. J. Freeman[3,4] & S. Signoretti[1,3,5]



- Positive PD-L1 expression (score of 2–4) in TIMCs was significantly associated with longer OS (12 versus 23 months) in both univariate (P = 0.04) and multivariable analysis (P = 0.0007) (adjusting for ECOG status and visceral disease)
- PD-L1 expression in tumor cell membrane was not associated with survival (P = 0.45)

Annals of Oncology, 2015

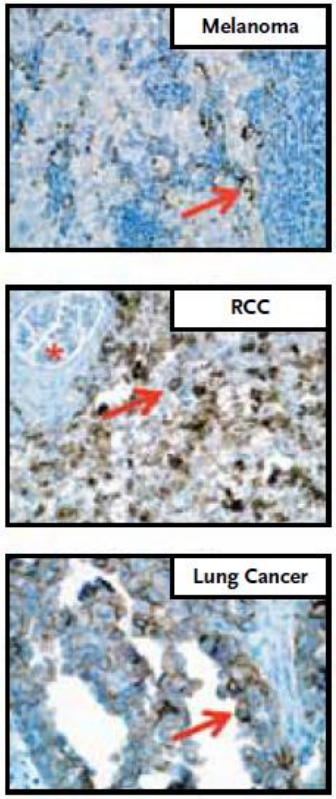
PD-L1 Expression by IHC



Association between Pretreatment Tumor PD-L1 Expression and Clinical Response

Response Status	PD-L1–Positive	PD-L1–Negative	Total
		number (percent)	
Objective response	9 (36)	0	9 (21)
No objective response	16 (64)	17 (100)	33 (79)
All	25	17	42

P=0.006 for association by Fisher's exact test



**Optional biopsies; Non-random subset of the population*

Topalian et al. N Engl J Med 2012;366:2443-54

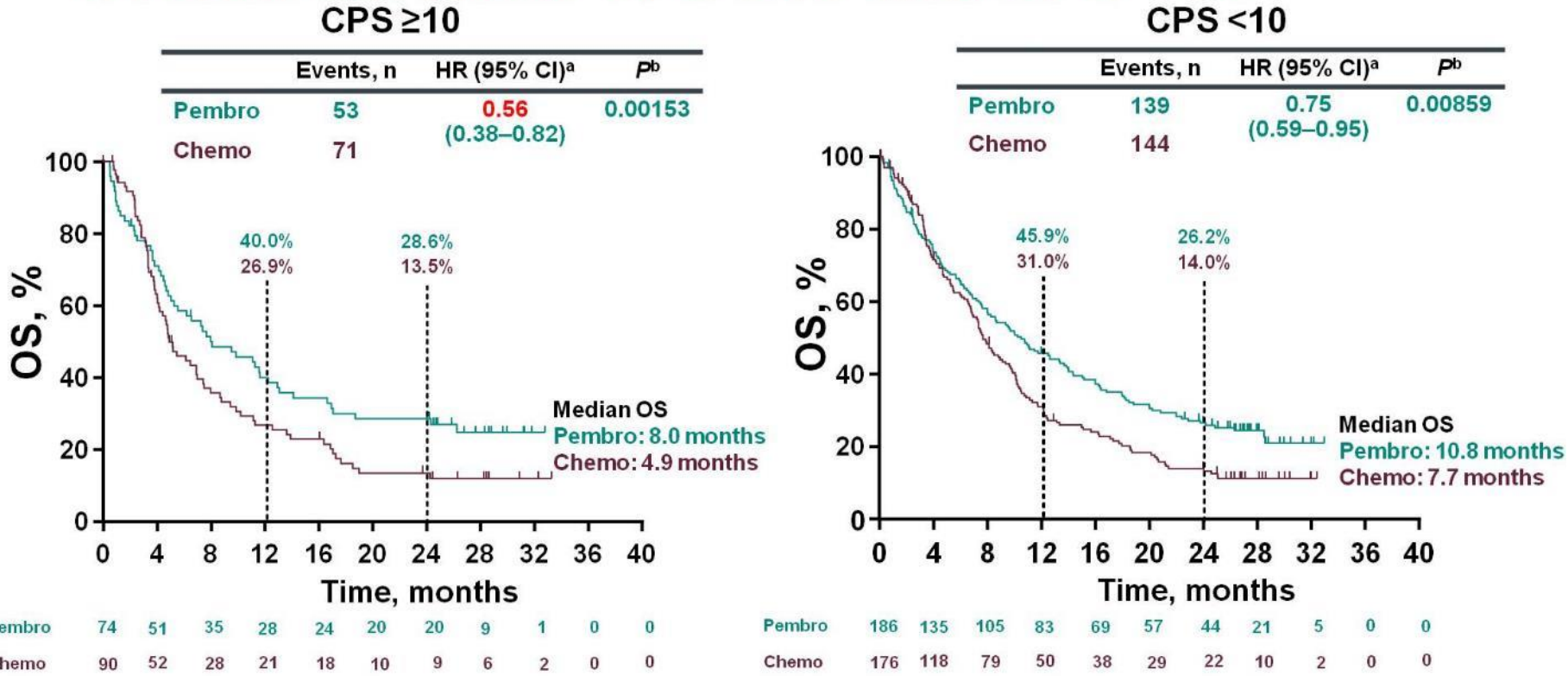
Positive intra-tumoral PD-L1 expression is associated with better response to PD-1/PD-L1blockade

Response rates	Nivolumab – Solid tumors Topalian NEJM 2012	Nivolumab – Melanoma Weber ASCO 2013	Nivolumab – Melanoma Grosso ASCO 2013	MPDL3280 – Solid tumors Herbst ASCO 2013	MPDL3280 – Melanoma Hamid ASCO 2013	MPDL3280 – NSCLC Soria ECC 2013	Pembrolizumab – Melanoma Daud AACR 2014	Pembrolizumab – NSCLC Gandhi AACR 2014	MPDL3280 – Bladder Powels ASCO 2014	Pembrolizumab – Head+Neck Selwert ASCO 2014	Pembrolizumab – Melanoma Ribas ASCO 2014	Nivolumab – NSCLC Spigel ASCO 2015
N=	42	44	34	94	30	53	113	129	65	55	411	117
unselected	21%	32%	29%	22%	23%	23%	40%	19%	26%	18%	40%	30%
PD-L1 +	36%	67%	44%	39%	27%	46%	49%	37%	43%	46%	49%	21%
PD-L1 -	0%	19%	17%	13%	20%	15%	13%	11%	11%	11%	13%	15%

Adapted from slide presented by Margaret Callahan at 2014 ASCO Annual Meeting and updated with 2015 ASCO meeting by TK Choueiri

KEYNOTE 045

Overall Survival: CPS ≥10 and CPS <10

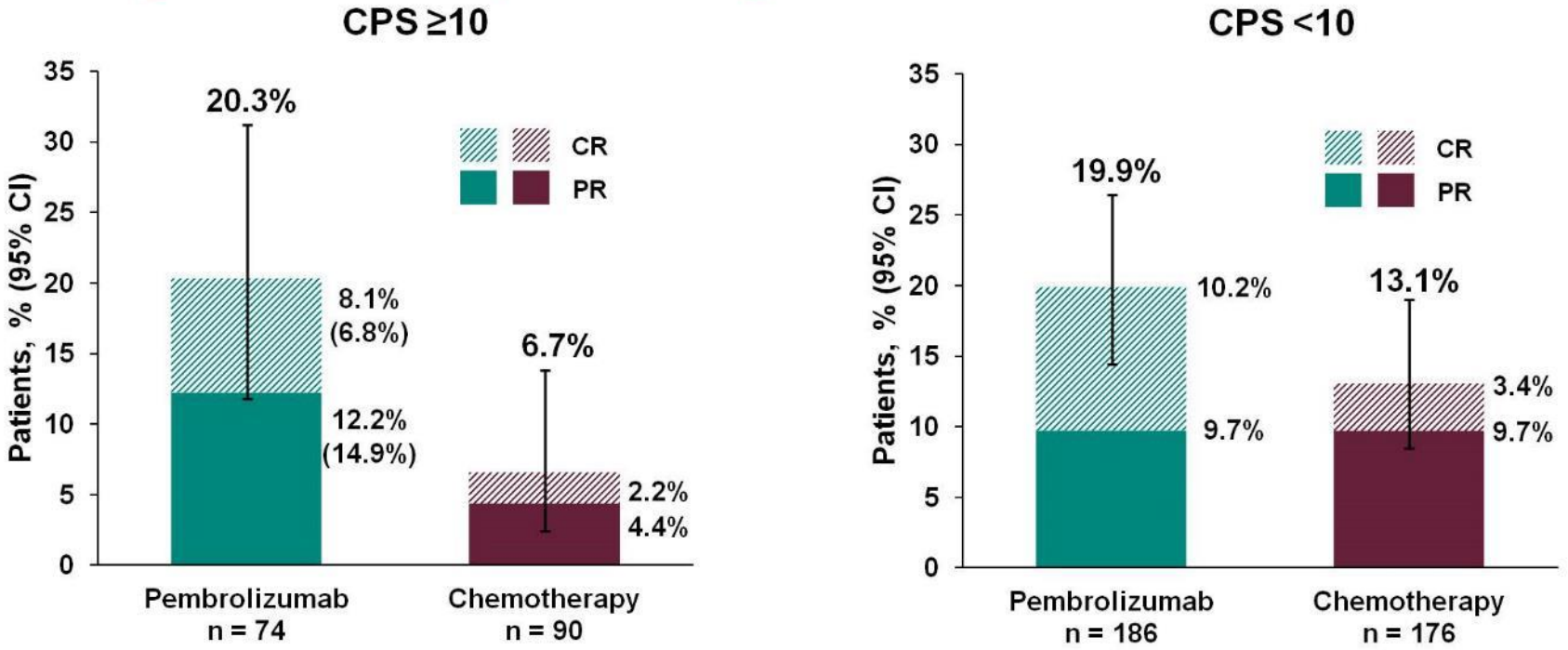


[a]Based on Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 months). [b]One-sided *P* value based on stratified log-rank test.
Data cutoff date: October 26, 2017.

Bellmunt, ASCO GU 2018

KEYNOTE 045

Objective Response by PD-L1 Status

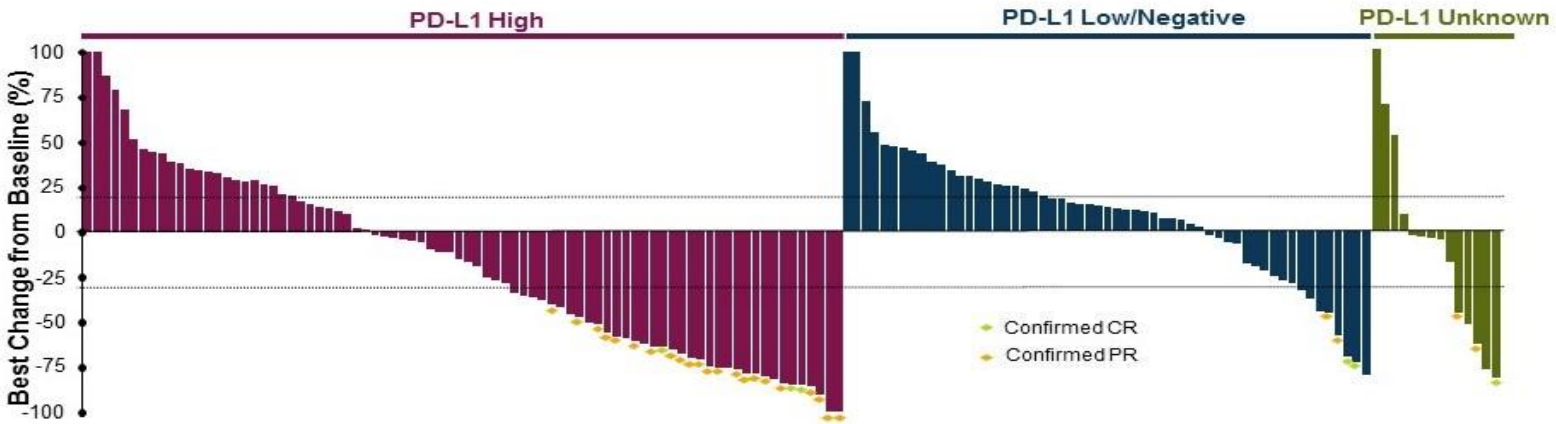


Data cutoff date: October 26, 2017.

Bellmunt, ASCO GU 2018

Study 1108: Best Change from Baseline in Target Lesion Size by PD-L1 Status

ORR was 17.8%
7 (3.7%) CRs
PD-L1^{high} → 27.6%
PD-L1$^{low/negative}$ 5. →1%



PD-L1^{high} = ≥ 25% of tumour cells exhibit membrane staining;[1] or ICP > 1% and IC+ ≥ 25%; or ICP = 1% and IC+ = 100%[2]

PD-L1$^{low/neg}$ = < 25% of tumour cells exhibit membrane staining[1]

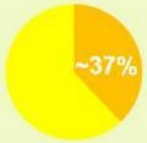
Adapted from Powles T et al. Online ahead of print. JAMA Onc. 2017.

PDL1 Status as Biomarker

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	119	IC 2/3	27%	28%	24%
Dreicer ASCO 16								6%
Sharma ASCO 16	basket	Nivolumab	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%

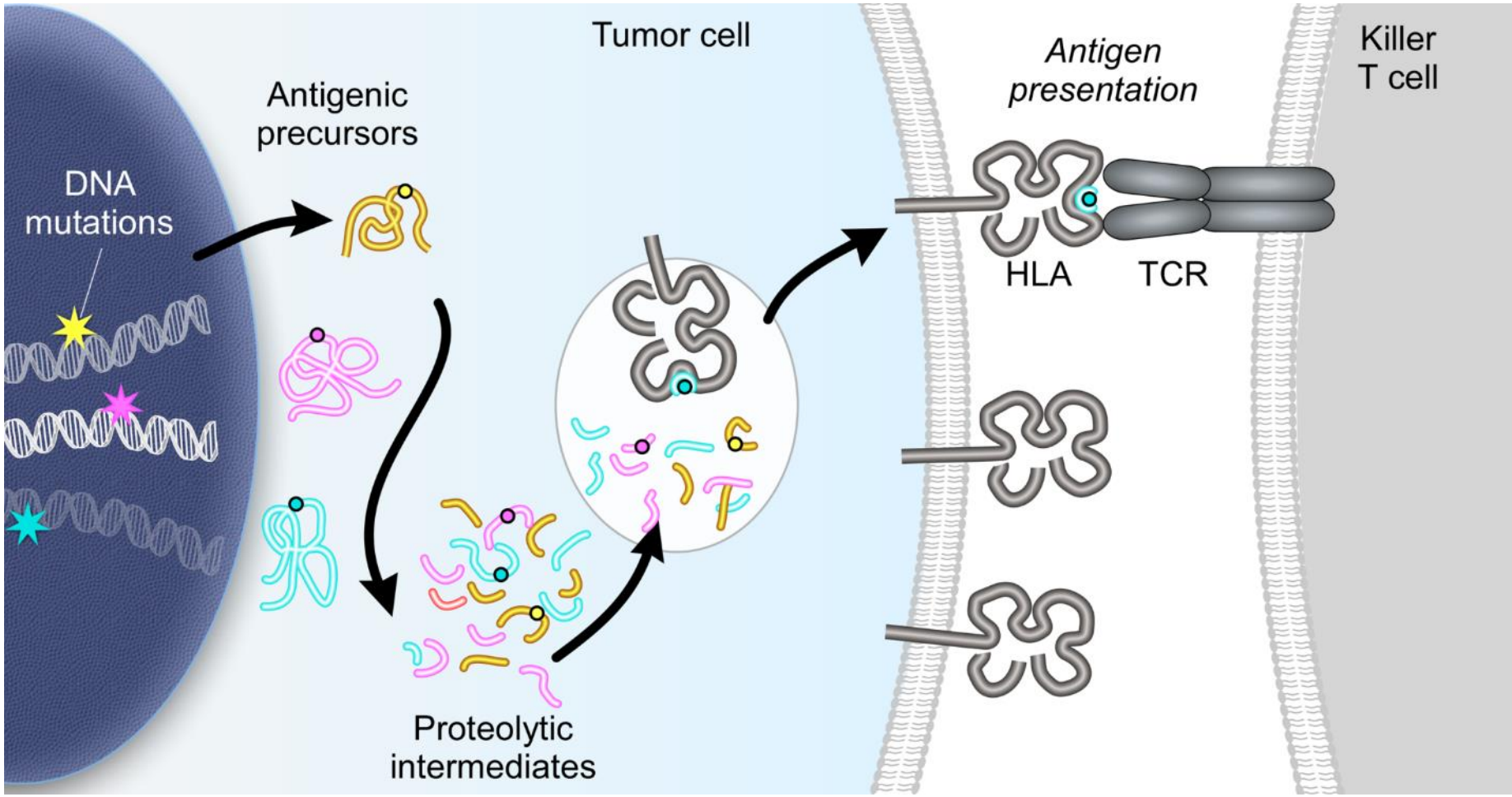
Standardization of PD-L1 IHC assay is URGENTLY needed!

Immune checkpoint inhibitors licensed in metastatic urothelial cancer.

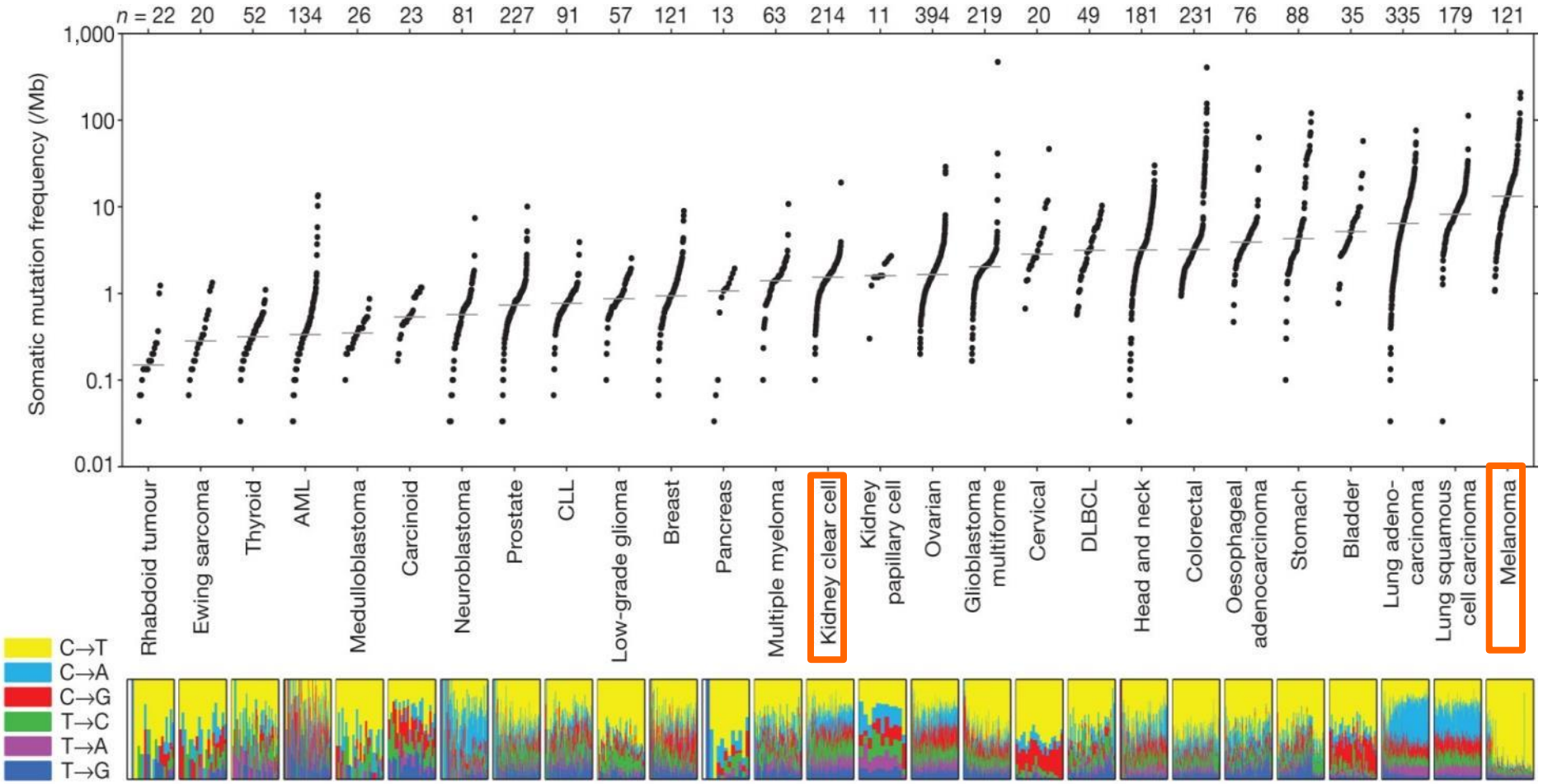
Immunotherapy (IO)	Atezolizumab[1,2]	Nivolumab[3]	Pembrolizumab	Durvalumab[5]	Avelumab[6]
Target for inhibition	PD-L1	PD-1	PD-1	PD-L1	PD-L1
Studies performed	Phase 1-3	Phase 1 and 2	Phase 1 and 3	Phase 1b	Phase 1b
Cell types scored for PD-L1 status	IC	TC	TC + IC	IC + TC	IC + TC
FDA + EMA Licence	Platinum refractory and platinum ineligible.	Platinum refractory	Platinum refractory and platinum ineligible	Platinum refractory	Platinum refractory
Estimated PD-L1 prevalence in urothelial cancer trials					

- IC, immune cells; IHC, immunohistochemistry; IO, immuno-oncology; PD-L1, programmed death ligand-1; TC, tumour cells.
- 1. Rosenberg JE et al. *Lancet* 2016;387:1909–1920; 2. Hoffman-Censits JH et al. *J Clin Oncol* 2016;34(Suppl. 2S):Abstract 355; 3. Sharma P et al. *J Clin Oncol* 2016;34(Suppl.):Abstract 4501; 4. Bellmunt J et al. *N Engl J Med* 2017;376:1015–1026; 5. Powles C et al. *J Clin Oncol* 2016;34:3119–3125; 6. Apolo AB et al. *J Clin Oncol* 2016;34(Suppl.):Abstract 4514.

Somatic mutations have the potential to generate neoantigens



Somatic mutations by tumor type



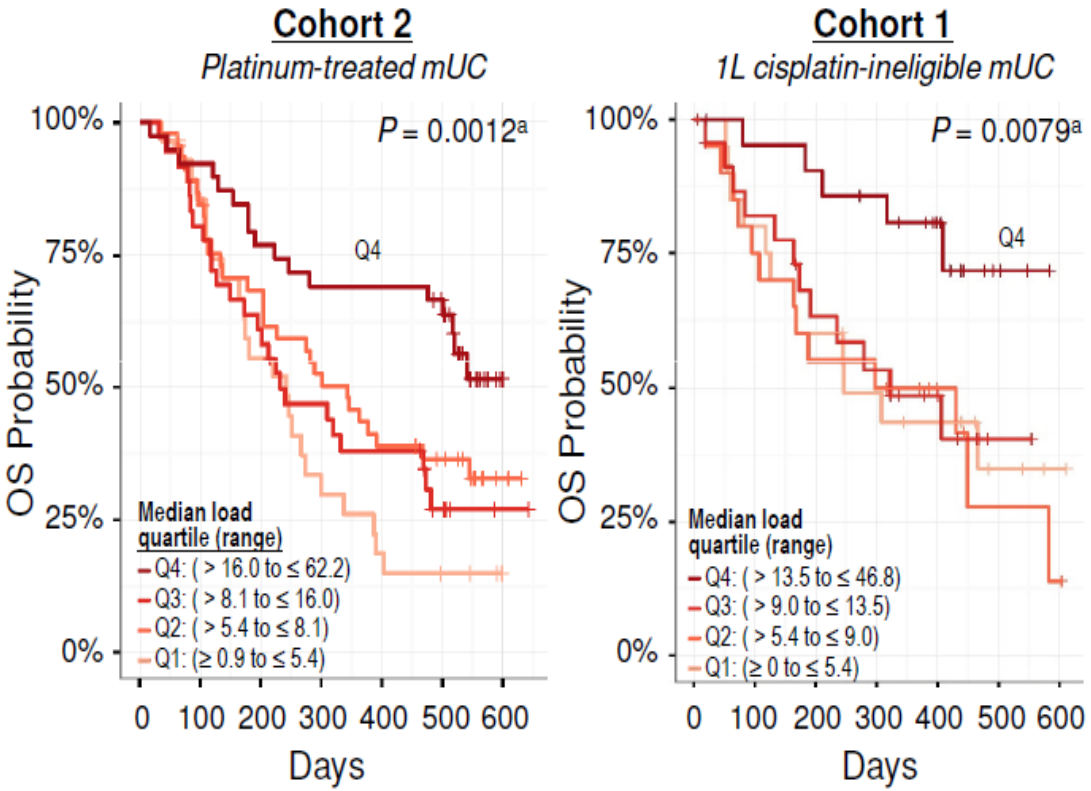
Mutational Burden:

Mutation frequencies vary more than 1000-fold between lowest and highest mutation rates across cancer and also within several tumor types.

Lawrence et al. *Nature* 2013

Mutational status and load

Mutation Load by FoundationOne and Survival



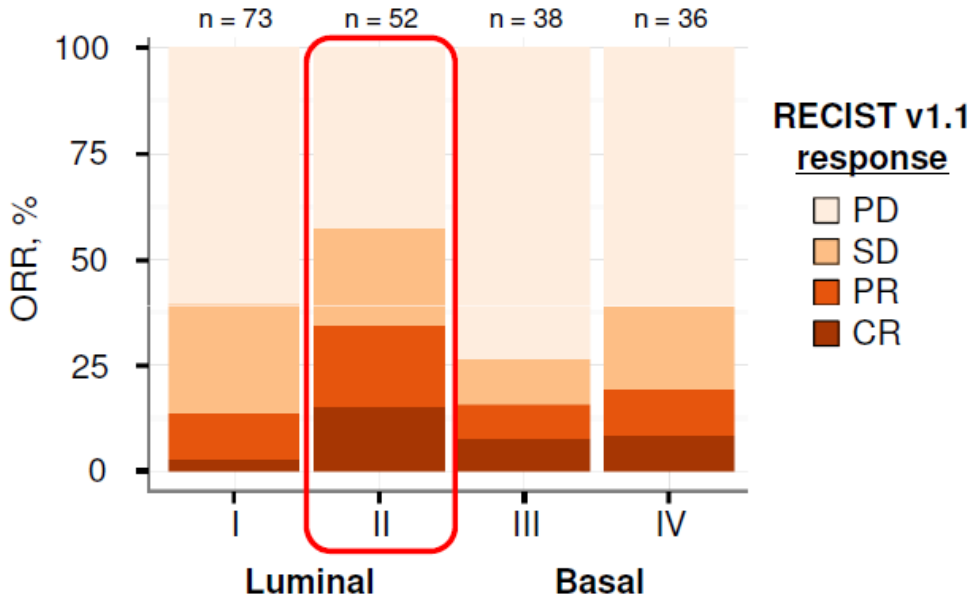
a *P* value for Q4 vs Q1, Q2, Q3. Data cutoff: March 14, 2016.

- 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-Q3a

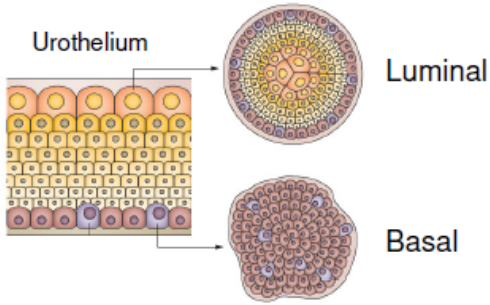
Presented by Rosemberg ASCO 2016

Gene signatures in the tumor immune environment

TCGA Subtype II Is Associated With Higher ORR



- Gene expression data used to classify IMvigor210 tumor samples recapitulated TCGA subtypes[1,2]
- Responses occurred in all subtypes, but ORR was significantly higher in luminal II vs other subtypes ($P = 0.0072$)



TCGA, The Cancer Genome Atlas. Data cutoff: March 14, 2016.
1. Cancer Genome Atlas Research Network *Nature* 2014. 2. Rosenberg *Lancet* 2016.

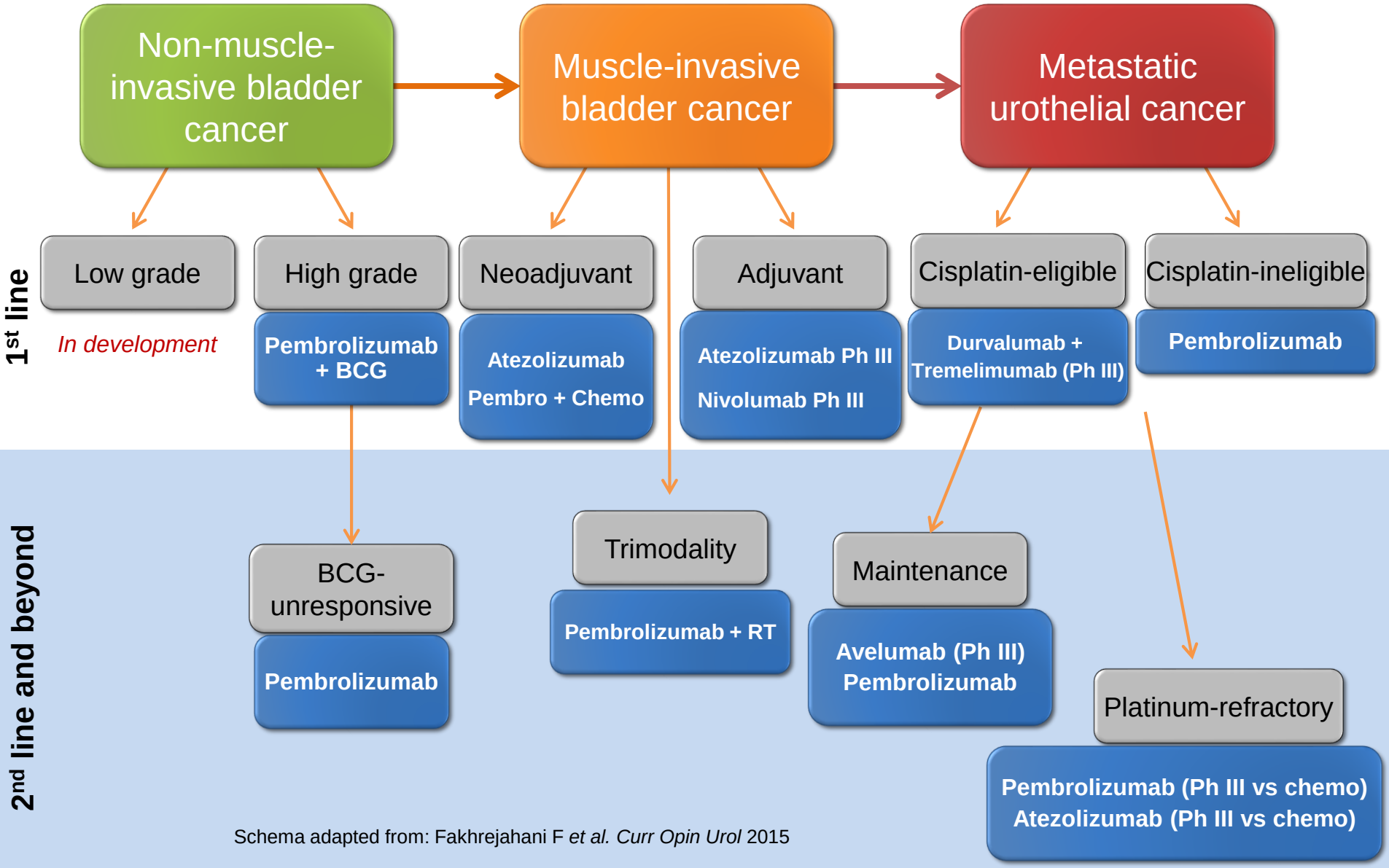
Presented by Rosemberg ASCO 2016

Novel Biomarkers: Beyond PD-1/PD-L1

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

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

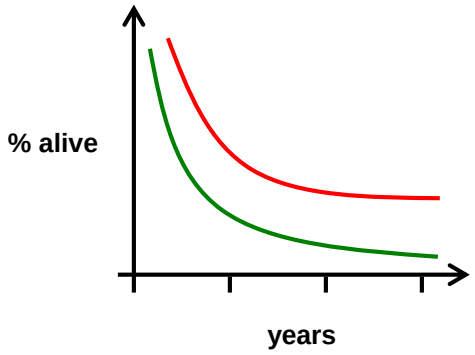
Future development of PD1 inhibitors in UC



Schema adapted from: Fakhrejahani F *et al. Curr Opin Urol* 2015

Future: Combination of therapies

Immunotherapy



Moderate Responses
Long-term duration

Targeted Therapy

High Responses
Short-term duration

Combination

High Responses
Long-term duration

?

The first chapter has been good but the next chapters need to be better.

- Identify the best setting to use the drugs
- Identify the best combination of agents
- identify predictive biomarkers

Conclusion

- Immune-checkpoint blockers (ICB) are redefining the field of oncology:
  - Cytotoxic chemo→targeted agents→Immuno-Oncology
  - The 3rd wave…
- Combination therapies are more active but may be more toxic
- Toxicities are different and auto-immune in nature:
  - Prompt evaluation/Closer follow up/Steroids early
  - Multidisciplinary management
- “Precision ImmunoOncology” is an open field:
  - Patient selection is crucial to optimize benefit of therapy!

Conclusion

- PD-1 pathway inhibition represents a significant advance in the treatment of metastatic UC:
  - Favorable rates of response, survival and toxicity profile
- Current data supports PD-1 pathway inhibition post-platinum as the standard of care and in frontline in cisplatin-ineligible patients

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New Perspectives in the Treatment of Advanced Urothelial Carcinoma

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