XXV CONGRESSO NAZIONALE
AIRO 2015
PALACONGRESSI - Rimini, 7-10 novembre

Systemic therapy and a new paradigm in Urothelial Bladder Cancer – on the cusp of a sea change?

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EORTC Genito-Urinary Cancers Group
The future of cancer therapy

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Disclosures

- Consultant and advisory role, GlaxoSmithKline (GSK)
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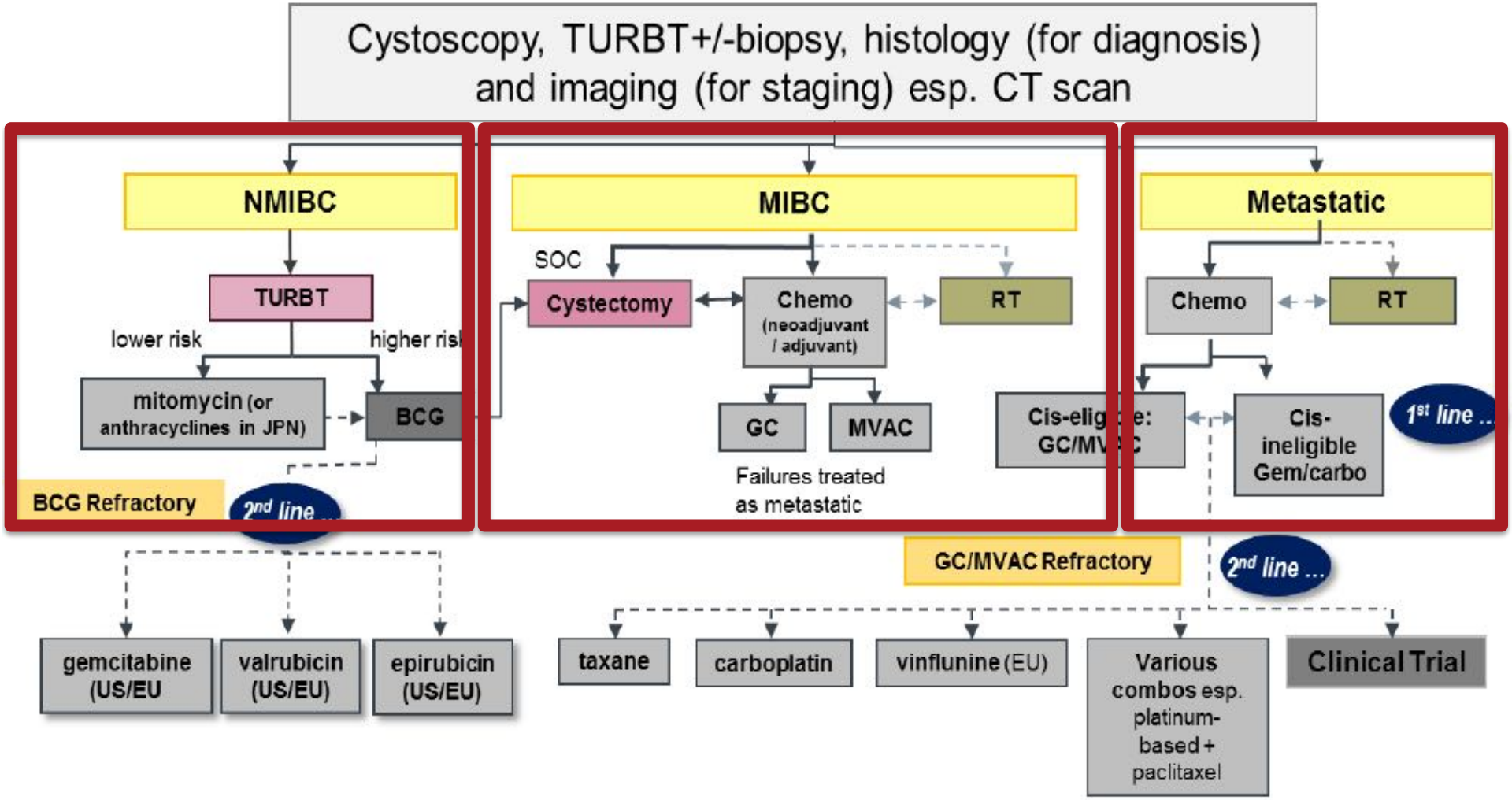
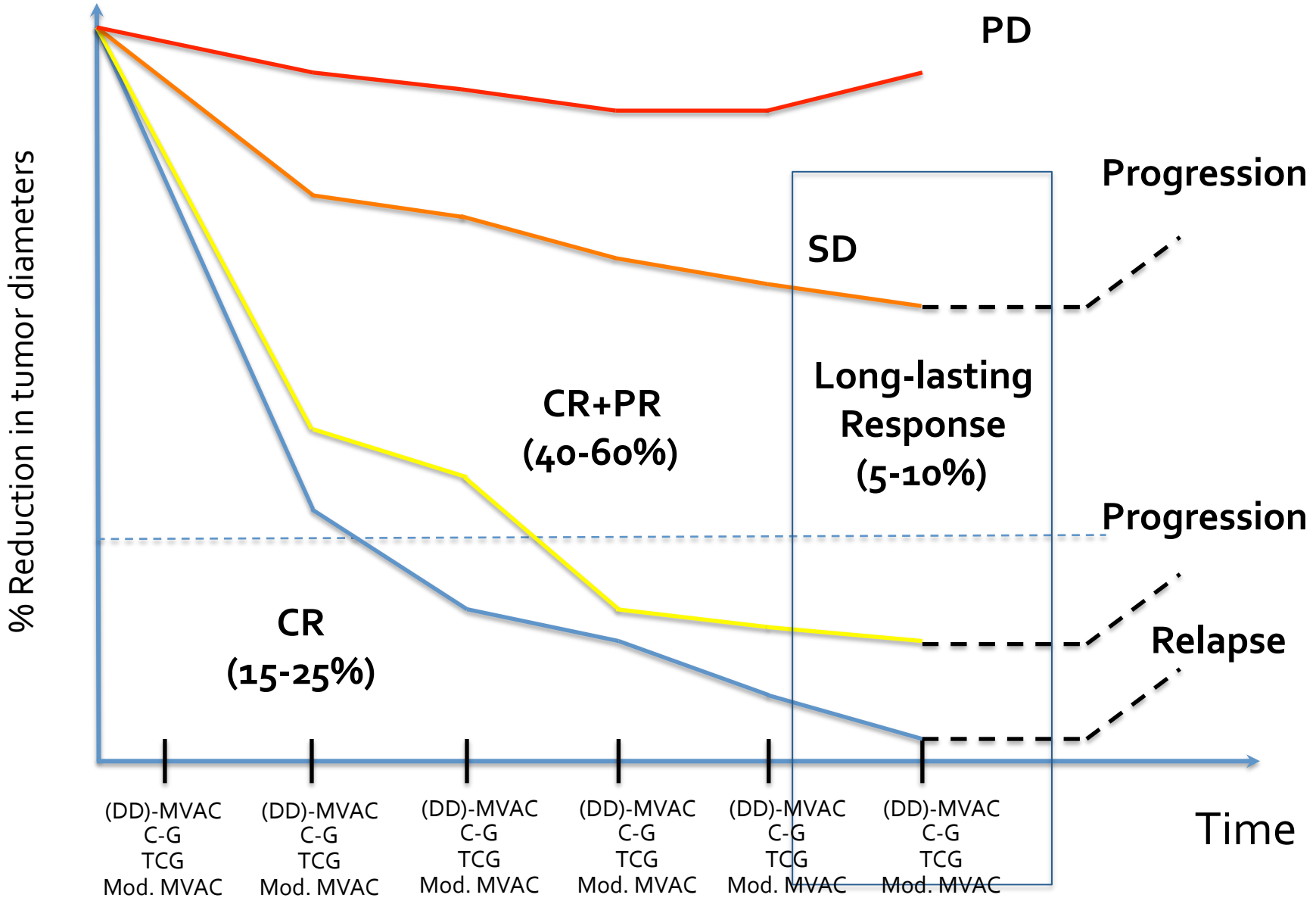
- *Treasurer of the EORTC-GU Cancers Group*
- *Member of the EAU-YAU Bladder Cancer Working Group*
- *Member of the ESMO Faculty – Genitourinary Cancers*

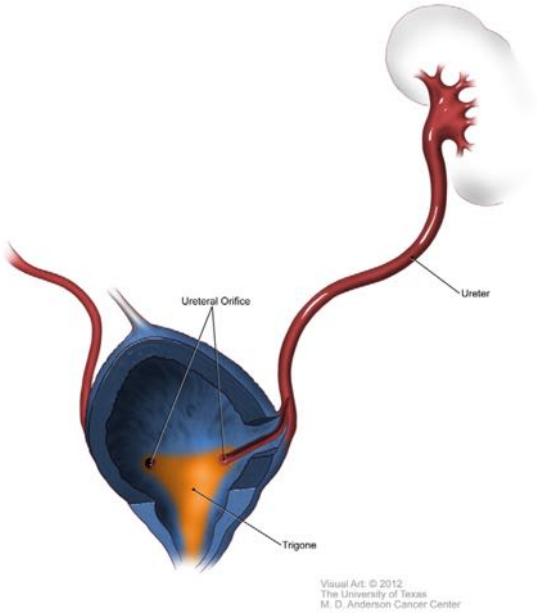
Bladder Cancer Treatment Paradigm (US & EU)



Unresectable to metastatic UC



Logothetis CJ, JCO 1990, Sternberg CN, JCO 2001, Bajorin DF, JCO 2009, von der Maase H, JCO 2000 & 2005, Bellmunt J, JCO 2012, Bamias A, Ann Oncol 2013, Necchi A, Clin Genitourin Cancer 2014



- Rational delivery of conventional chemotherapeutic options
- Molecularly-driven patient selection
- Future directions (immunotherapy revolution beyond the corner)

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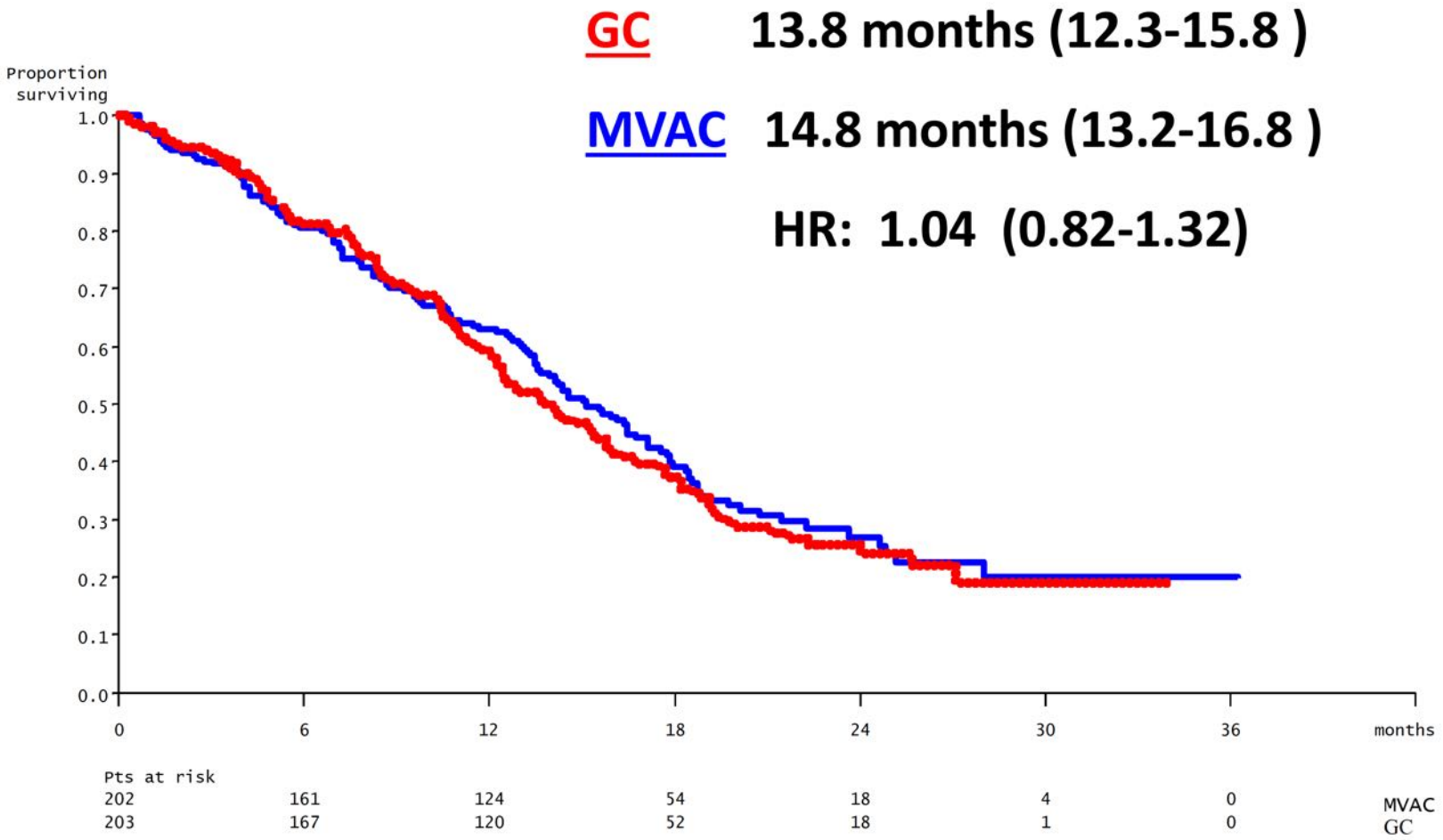
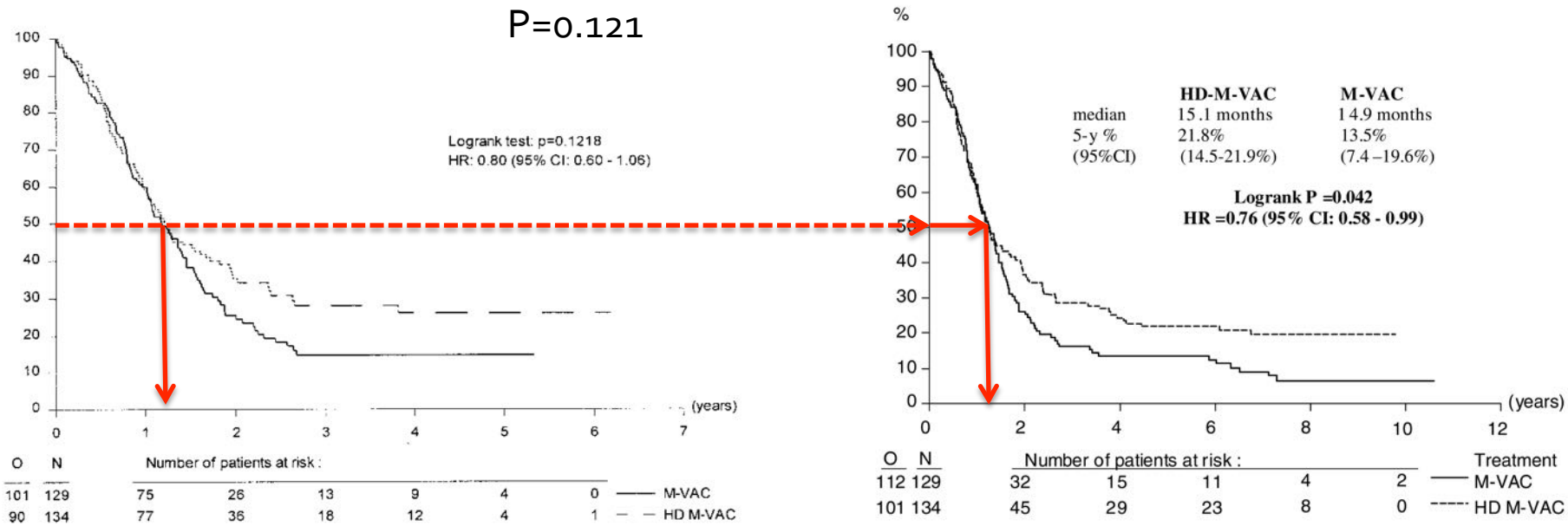
First-line chemotherapy:
Overall Survival for MVAC vs Gem/Cis



von der Maase H et al, J Clin Oncol 2000

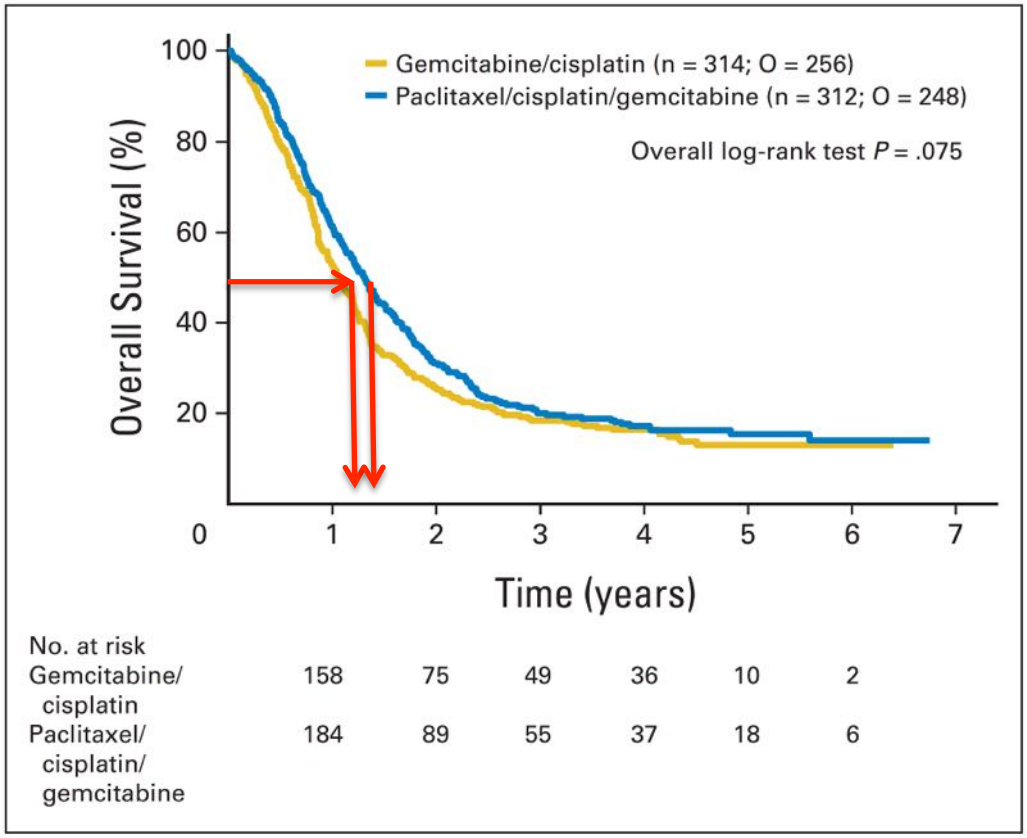
First-line chemotherapy:
Accelerated MVAC vs. standard MVAC

P=0.121



Sternberg CN et al, J Clin Oncol 2001; Eur J Cancer 2006

First-line chemotherapy:
The addition of Paclitaxel to Gem/Cis



ORR: 55.5 *vs* 43.6%
Median PFS (mos): 8.3 (PCG) vs 7.6 (CG)
Median OS (mos): 15.8 (PCG) vs 12.7 (CG)

Bellmunt J et al, J Clin Oncol 2012

Approximating 50%

Sonpavde G et al. Clin Genitourin Cancer 2012

Galsky MD et al. ASCO 2013

Cisplatin ineligibility

Galsky MD, Rosenberg JE, Hahn N, Sonpavde G, Bellmunt J, JCO 2011

Table 4. Proposed Working Group Eligibility Criteria for Clinical Trials Enrolling Patients With Metastatic Urothelial Carcinoma "Unfit" for Cisplatin-Based Chemotherapy

Eligibility Criteria (at least one of the following)
WHO or ECOG PS of 2 or Karnofsky PS of 60%-70%
Creatinine clearance (calculated or measured) $<$ 60 mL/min
CTCAE v4 grade $\geq$ 2 audiometric hearing loss
CTCAE v4 grade $\geq$ 2 peripheral neuropathy
NYHA Class III heart failure

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; NYHA, New York Heart Association; PS, performance status.

Outcome of different populations treated with different chemotherapy

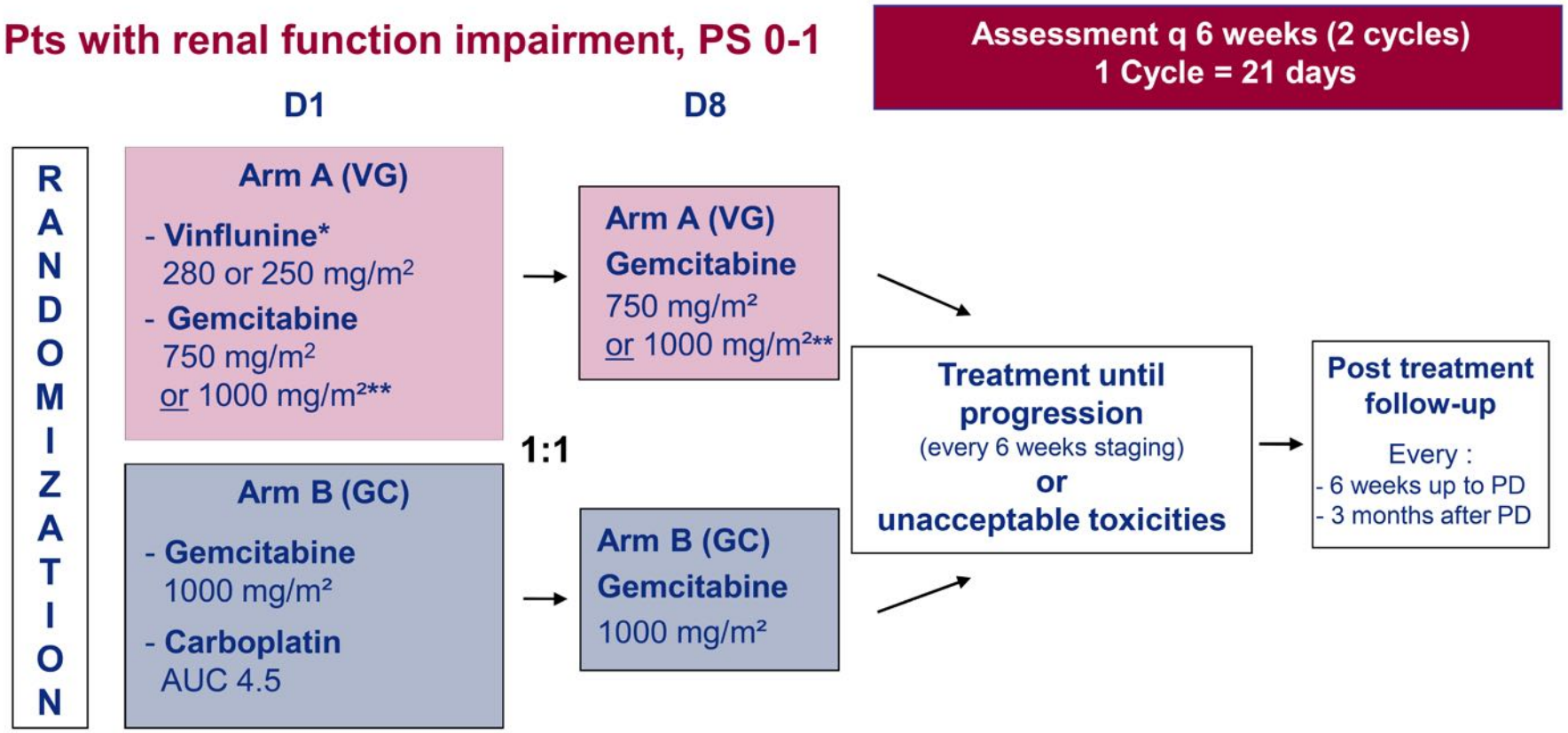
GEM/CIS +/-PAC			VIN + GEM or CARBO			CARBO + GEM or VINBLAST METHOTREX		
PS 0/1 GFR-good			PS 0/1 GFR-poor			PS2 or GFR-poor		
RR %	PFS months	OS months	RR %	PFS months	OS months	RR %	PFS months	OS months
55-43	7.6-8.3	12.7-15.8	54 -43	5.9-6.1	12.8-14	41-30	4.2-5.8	8.3-9.3

Pending publication

J Clin Oncol. 2012 Apr 1;30(10):1107-13.
J Clin Oncol. 2001 May 15;19(10):2638-46
J Clin Oncol. 2000 Sep;18(17):3068-77.
J Clin Oncol. 2012 Jan 10; 30(2): 191–199.

JASINT-2: Randomized phase III study comparing vinflunine-gemcitabine and gemcitabine carboplatin combinations in patients ineligible to cisplatin with advanced or metastatic urothelial carcinoma.

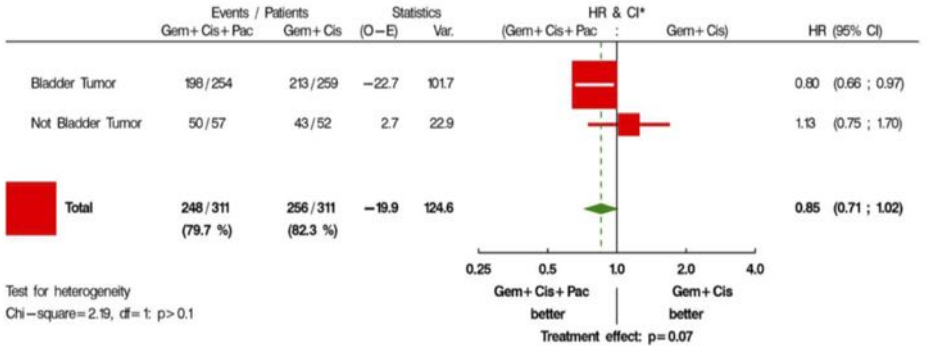
Study Scheme



* Starting dose of drug depending on calculated creatinine clearance (Cockroft-Gault formula) randomization value.
** Beyond cycle 1, if no toxicity of Grade > 2 occurs in cycle 1.

Role of primary tumor location on survival in first-line therapy for advanced UC (EORTC 30987 Study)

Primary Tumor Location	Patients (N)	Observed Events (O)	Hazard Ratio (95% CI)	P-Value (Log-Rank)	Median (95% CI) (Months)	% at 4 Year(s) (95% CI)
Bladder Tumor	513	411	1.00	0.8631	13.60 (12.19, 15.11)	17.01 (13.74, 20.57)
Not Bladder Tumor	109	93	0.98 (0.78, 1.23)		14.98 (13.31, 16.79)	15.65 (9.31, 23.48)



Bellmunt J, Semin Oncol 2012

Gem-Platinum vs Gem-Platinum-Taxane in the first-line setting of UC: A Systematic review and Meta-analysis

Table 3 – Efficacy outcomes according to the combination chemotherapy

Outcome	GEM-CDDP	GEM-CBDCA	GEM-CDDP-taxane	GEM-CBDCA-taxane
RR (%)	13, 47 (38–65.3)	13, 45.1 (24–67)	5, 55.5 (40–81)	2, 55.5 (43–68)
Median PFS (mo)	12, 7.3 (3.5–8.5)	9, 7.5 (4.6–9.4)	5, 8.3 (7.4–10)	1, 7.4 (7.4–7.4)
Median OS (mo)	14, 13 (8.5–18)	13, 10 (3.3–20)	5, 15.8 (14–22)	2, 12.9 (11–14.7)
1-yr OS (%)	6, 53.4 (28–82)	5, 42 (26–58.5)	3, 68 (61.4–73.3)	2, 52.3 (46–58.5)

CBDCA = carboplatin; CDDP = cisplatin; GEM = gemcitabine; OS = overall survival; PFS = progression-free survival; RR = response-rate.

Giannatempo P et al, Eur Urol (2015), http://dx.doi.org/10.1016/j.eururo.2015.09.051

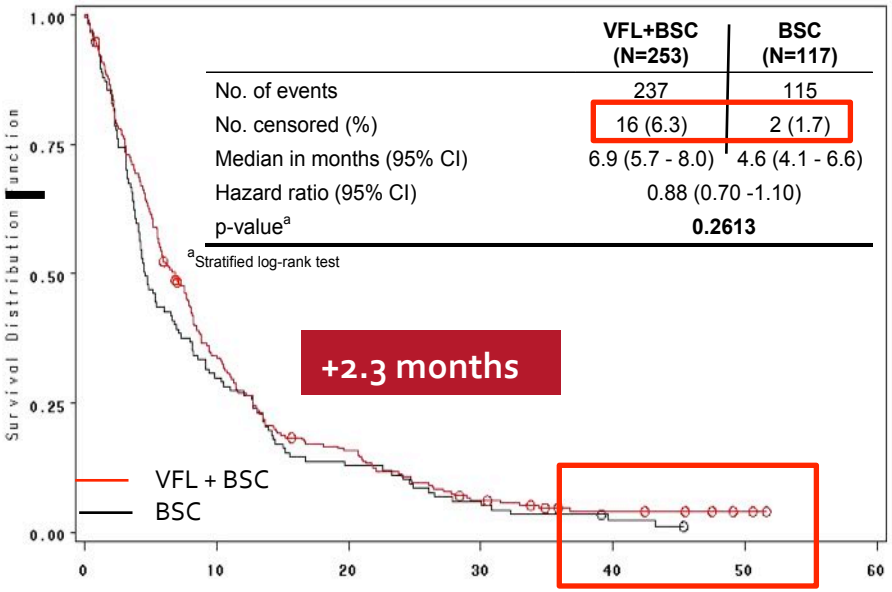
	Previous perioperative therapy counted as first-line therapy	N	RR (%)	PFS (months)	OS (months)
Weekly paclitaxel	No	31	10	2·2	7·2
Paclitaxel q21d	Yes	14	7	-	.
Nab-paclitaxel	Yes	47	27.7	6.0	10.8
Eribulin	Yes	48	27	4.1	10.4
Irinotecan	No	40	5	2·1	5·4
Ixabepilone	Yes	42	11·9	2·7	8·0
Pemetrexed	Yes if <1 year	47	27·7	2·9	9·6
Oxaliplatin	Yes if <6 months	18	6	1·5	7·0
Ifosfamide	NA	56	20	2·4	5·5
Pralatrexate	NA	30	3·3		
Pemetrexed	Yes	12	8		
Docetaxel	Yes	30	13	-	9·0
Gemcitabine	NA	30	11	4·9	8·7
Gemcitabine	Yes	35	22·5	-	5·0
Topotecan	NA	44	9·1	1·5	6·3
Paclitaxel+gemcitabine	Yes	41	60	-	14·4
Ifosfamide+gemcitabine	NA	34	21	4·0	9·0
Carboplatin+paclitaxel	Yes if <1 year	44	16	4·0	6·0
Gemcitabine+Ifosfamide	No	23	22	3.5	4.8

3 mos **6 mos**

Second-line phase III trial: Vinflunine + BSC vs. BSC

Bellmunt J, J Clin Oncol 2009

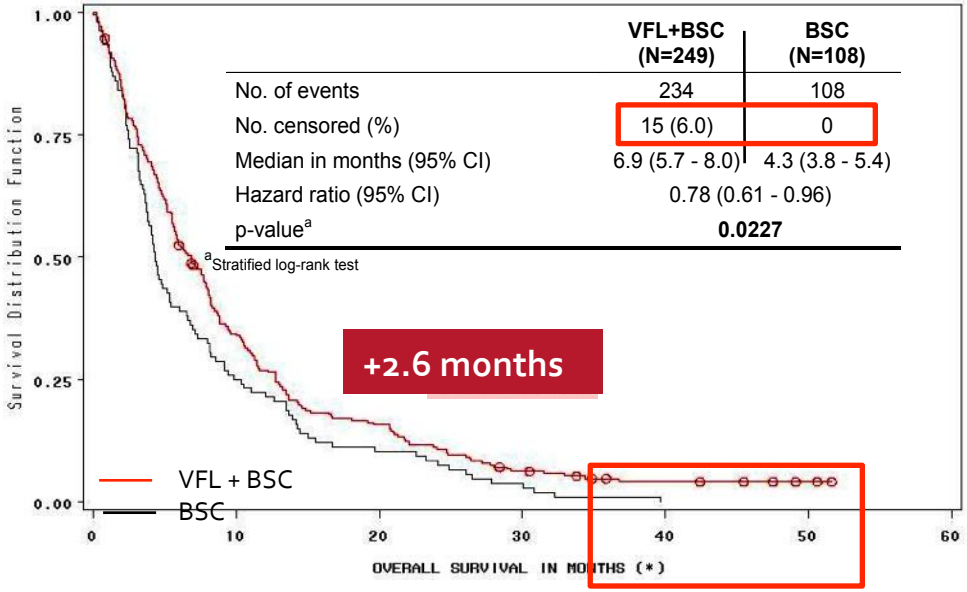
>2 months, maintained at > 3.5 yr FUP



	VFL+BSC (N=253)	BSC (N=117)
No. of events	237	115
No. censored (%)	16 (6.3)	2 (1.7)
Median in months (95% CI)	6.9 (5.7 - 8.0)	4.6 (4.1 - 6.6)
Hazard ratio (95% CI)	0.88 (0.70 -1.10)	
p-value[a]	**0.2613**	

[a]Stratified log-rank test

ITT Population



	VFL+BSC (N=249)	BSC (N=108)
No. of events	234	108
No. censored (%)	15 (6.0)	0
Median in months (95% CI)	6.9 (5.7 - 8.0)	4.3 (3.8 - 5.4)
Hazard ratio (95% CI)	0.78 (0.61 - 0.96)	
p-value[a]	**0.0227**	

[a]Stratified log-rank test

Eligibile population

Culine S.et al. Eur. Urol. Supplements, vol 9;2; April 2010 p. 38

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

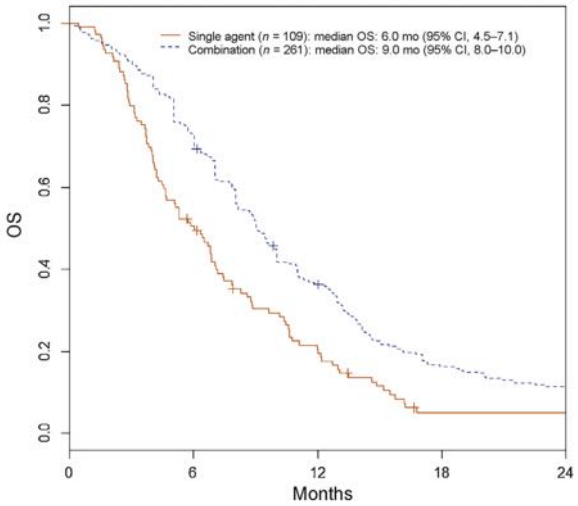
European Association of Urology

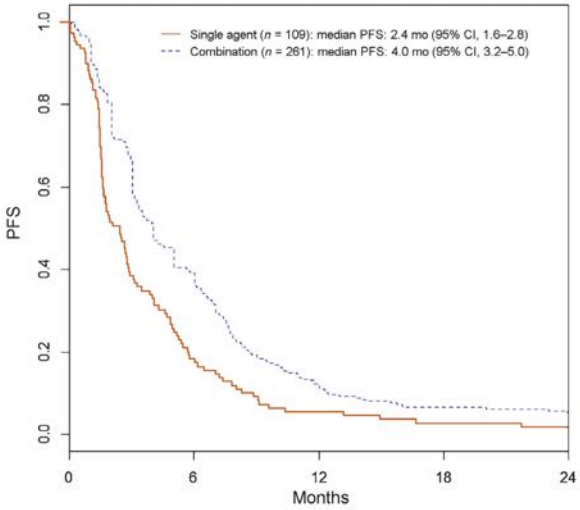
Platinum Priority – Urothelial Cancer
Editorial by XXX on pp. x-y of this issue

Single-agent Taxane Versus Taxane-containing Combination Chemotherapy as Salvage Therapy for Advanced Urothelial Carcinoma

Guru Sonpavde [a,i,], Gregory R. Pond [b,i], Toni K. Choueiri [c], Stephanie Mullane [c], Guenter Niegisch [d], Peter Albers [d], Andrea Necchi [e], Giuseppe Di Lorenzo [f], Carlo Buonerba [g], Antonio Rozzi [h], Kazumasa Matsumoto [i], Jae-Lyun Lee [j], Hiroshi Kitamura [k], Haruki Kume [l], Joaquim Bellmunt [c]*

Sonpavde G et al, Eur Urol 2015



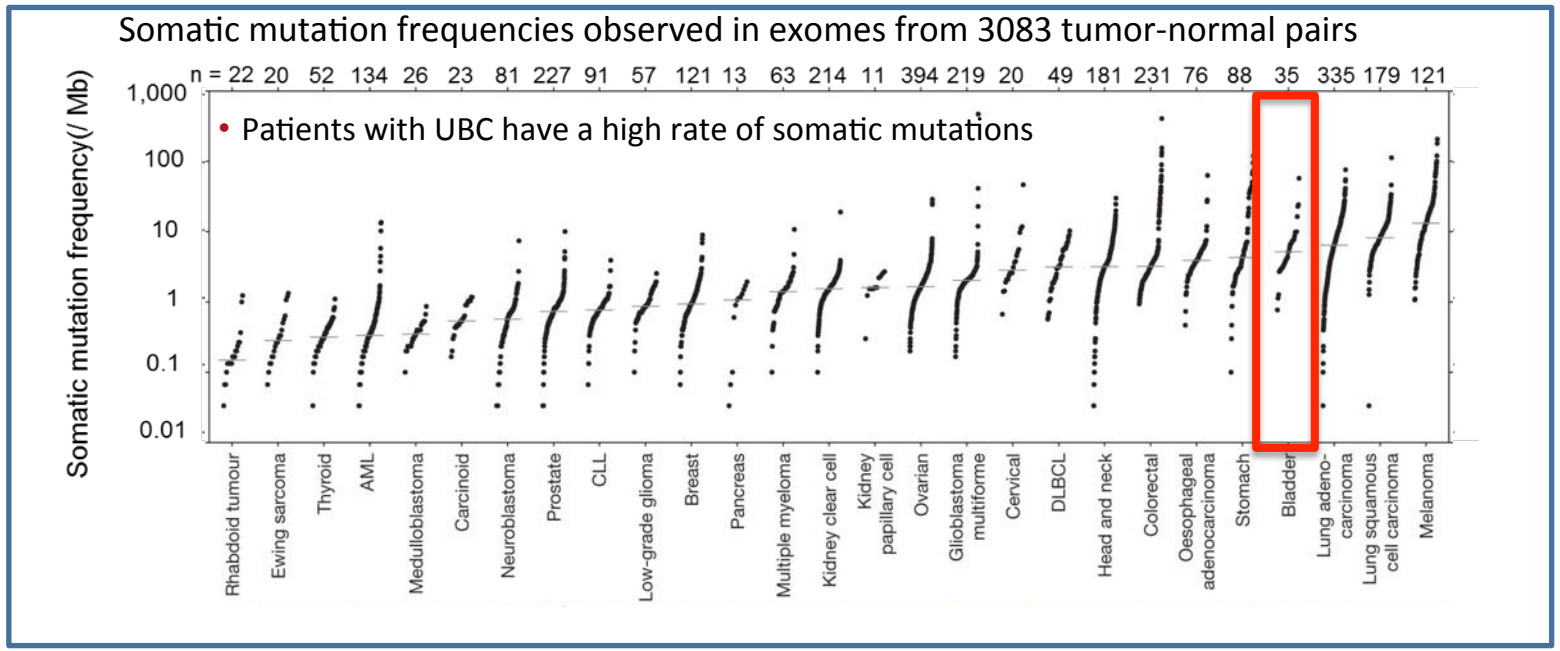


Second-line single-agent versus doublet chemotherapy as salvage therapy for metastatic urothelial cancer: a systematic review and meta-analysis

	ORR		PFS		OS	
Study selection	**No. of evaluable arms of studies**	**Probability % (95%CI)**	**No. of evaluable arms of studies**	**Median PFS (95%CI)**	**No. of evaluable arms of studies**	**Median OS (95%CI)**
Single agent chemotherapy	22	14.2 (11.1-17.9)	18	2.65 (2.22-3.07)	20	6.98 (6.19-7.78)
Vinflunine	3	11.7 (6.2-20.9)	3	2.92 (2.56-3.29)	3	7.20 (6.30-8.10)
Paclitaxel or docetaxel	5	10.5 (6.9-15.8)	3	2.15 (1.36-2.94)	4	7.35 (6.16-8.55)
Doublet chemotherapy	24	31.9 (27.3-36.9)	15	4.76 (3.70-5.82)	23	8.50 (7.35-9.64)
Doublet with cisplatin	2	40.4 (28.5-53.5)	1	6.20 (3.95-8.45)	2	10.39 (7.53-13.26)
Doublet without cisplatin	22	30.9 (26.1-36.3)	14	4.66 (3.55-5.77)	21	8.35 (7.15-9.55)
Doublet with carboplatin	4	25.4 (17.9-34.7)	4	3.88 (3.15-4.62)	4	8.14 (5.76-10.52)

Raggi D et al, Ann Oncol 2015. doi: 10.1093/annonc/mdv509

High rate of mutations detected in bladder cancer



- High mutational complexity rates due to tobacco/environmental carcinogen exposure.
- Potential for many neo-antigens to be seen as foreign by host immune system, leading to increased activity of immunotherapy.
- <u>Mutational load could be a response biomarker.</u>

TCGA. *Nature.* 2014; 3. Lawrence MS et al. *Nature.* 2013; 4. Kandoth C et al. *Nature.* 2013.

A Phase 2, Two-arm Multicenter, Open-Label Study to Determine the Efficacy and the Safety of Two Different Dose Regimens of a pan-FGFR Tyrosine Kinase Inhibitor JNJ-42756493 in Subjects with Metastatic or Surgically Unresectable Urothelial Cancer with FGFR Genomic Alterations

"...Tumors must have at least 1 of the following translocations: FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3, FGFR3-BAIAP2L1; or
One of the following FGFR3 gene mutations: R248C, S249C, G370C, Y373C"

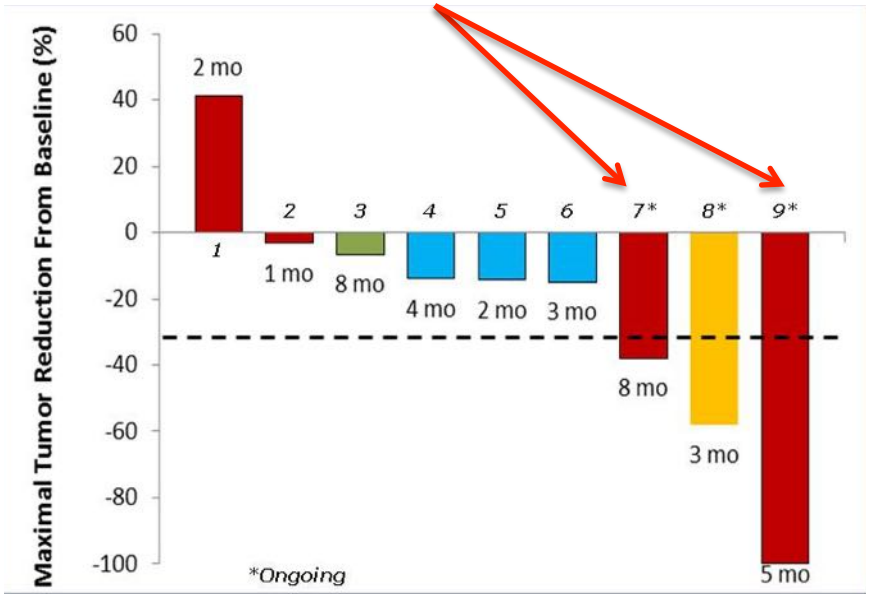
BGJ-398 in FGFR3-mutated UBC

Age/Sex	Tumor	Schedule (125 mg/day)	Best Overall Response (% tumor change)	Duration on Study
86 ♀	*FGFR3*-mutated	Continuous	PR (–48%)	5 cycles
62 ♀	*FGFR3*-mutated	3 weeks on/ 1 week off	PR (–45%)	9+ cycles
53 ♂	*FGFR3*-mutated	3 weeks on/ 1 week off	SD (–28%)	4 cycles
77 ♂	*FGFR3*-mutated	Continuous	SD (–27%)	4 cycles
52 ♂	*FGFR3*-mutated	Continuous	SD (+11.4%)	3 cycles
80 ♀	*FGFR1*-amplified	3 weeks on/ 1 week off	PD	< 2 weeks

In *FGFR3*-mutated urothelial carcinoma: Overall response rate 40% (2/5); Disease control rate 100% (5/5)

Sequist LV, AACR 2014

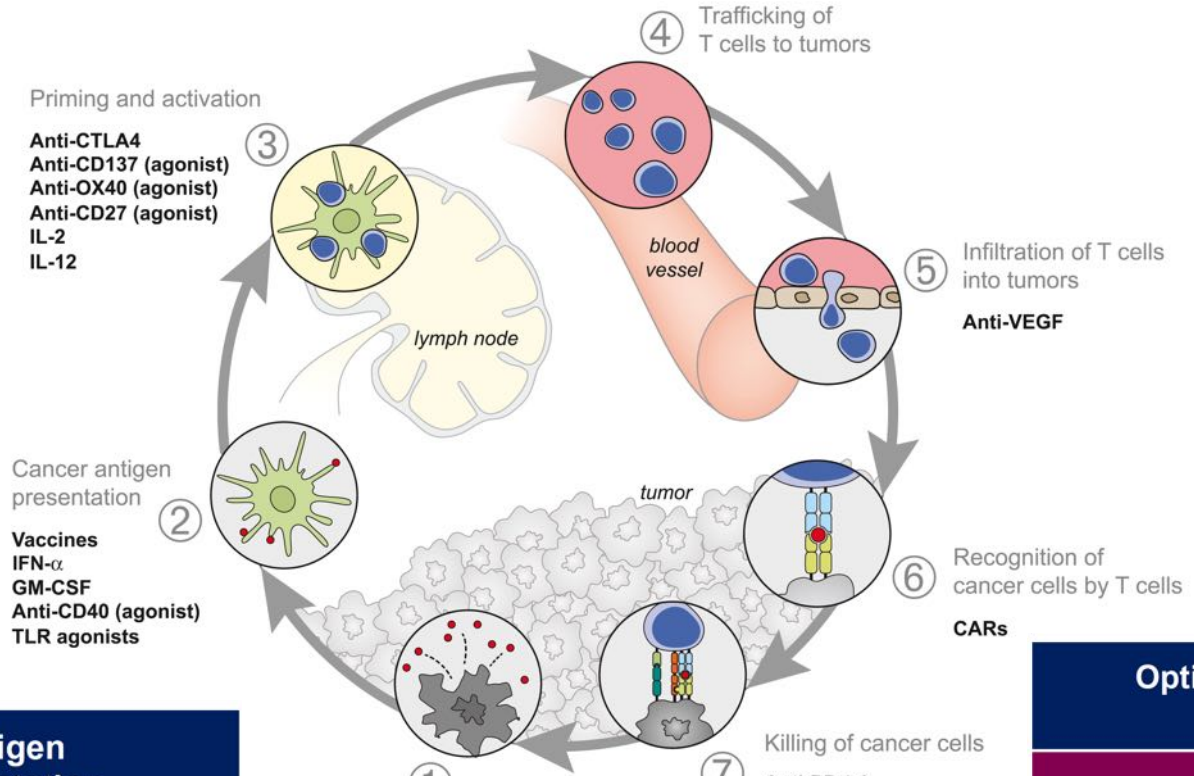
JNJ-42756493 at ≥6mg dose in UBC with FGFR aberrations



Bahleda R, ASCO 2014

Rationale for the development of immunotherapy in early stage urothelial bladder carcinoma

The Cancer Immunity Circle



Antigen presentation

Radiation, Chemotherapy
Small Molecules, ADCs
+ 4 NMEs entering clinic 2014/15

Optimising T-cell function and memory

Brakes Off:
PD-L1, PD-1, CTLA-4
+ 1 NME entering clinic 2015
Gas On:
mOX40 + 2 NMEs entering clinic 2014/15

Chen DS & Mellman I. Immunity 2013

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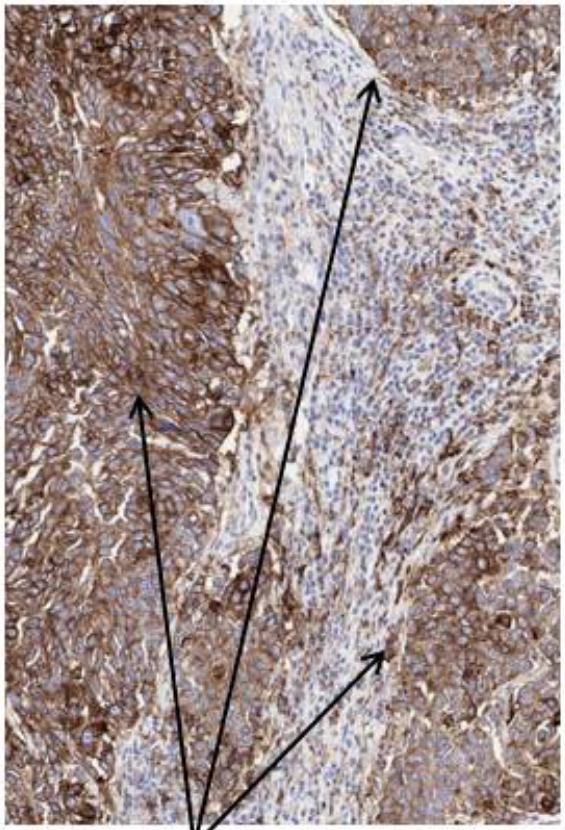
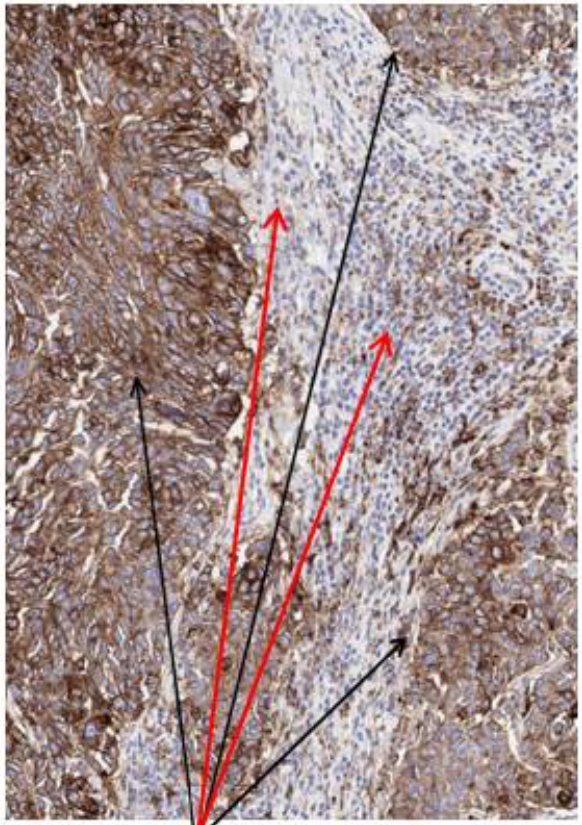
PD-L1 IHC staining in urothelial bladder cancer



Tumor cells

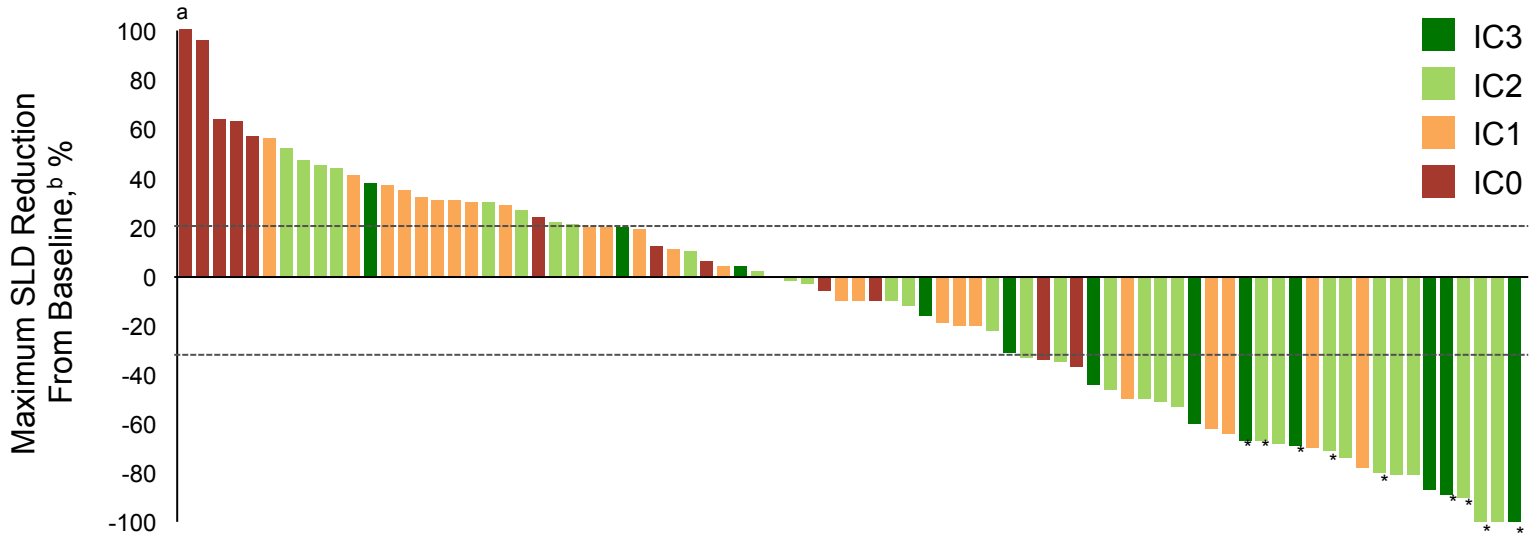


Tumor + inflammatory cells

Phase Ia Study PCD4989g:

Clinical Activity of Atezolizumab in mUC Cohort

Presented by Petrylak et al. ASCO 2015

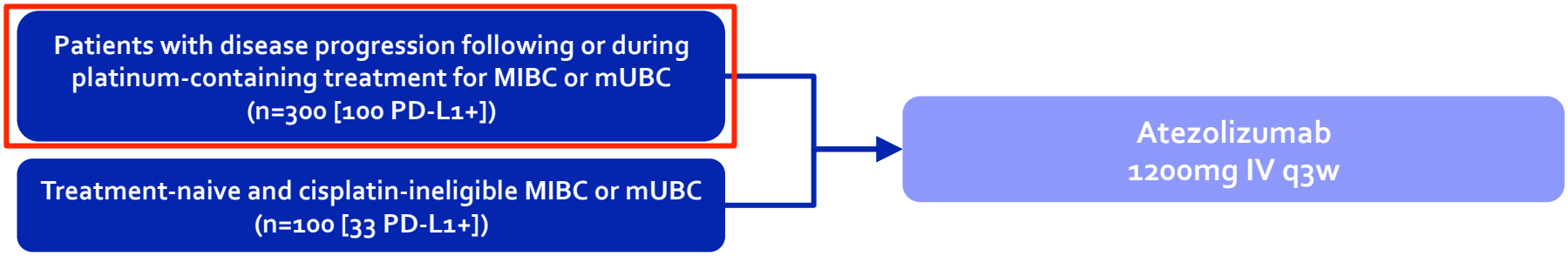


- Median DOR not reached (range, 0+ to 43 mo) in any IHC subgroup
- Median overall survival
  - Not reached in IC2/3 (median survival follow up 14 months)
  - 7.6 months in IC0/1 (median survival follow up 12 months)

SLD, sum of longest diameters. [a]Change in SLD > 100%. [b]Seven patients without post-baseline tumor assessments not included. Asterisks denote 9 CR patients, 6 of whom have been confirmed by data cutoff date (Dec 2, 2014) and 7 of whom had < 100% reduction due to lymph node target lesions. All lymph nodes returned to normal size per RECIST v1.1.

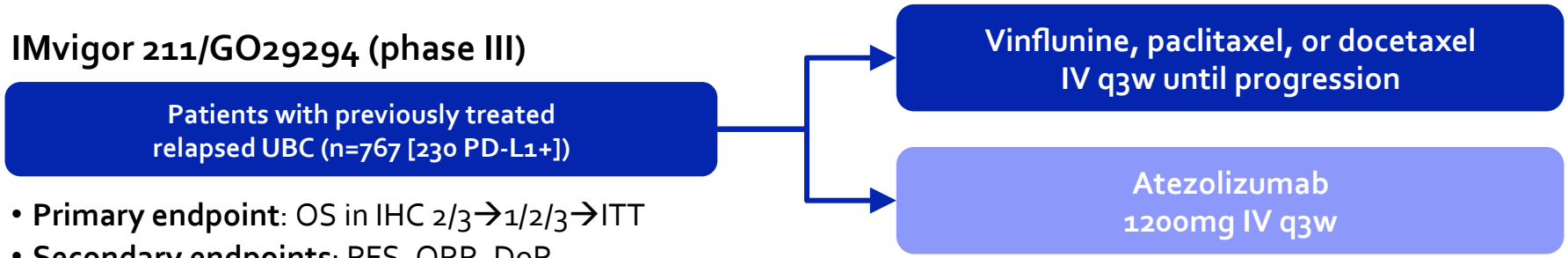
Atezolizumab: two studies in first-line/second-line UC are under way

IMvigor 210/GO29293 (phase II)



- **Primary endpoint**: ORR in IHC 2/3→1/2/3→ITT
- **Secondary endpoints**: DoR, PFS, OS
- FPI: May 2014

IMvigor 211/GO29294 (phase III)



- **Primary endpoint**: OS in IHC 2/3→1/2/3→ITT
- **Secondary endpoints**: PFS, ORR, DoR
- FPI: Q4 2014

http://www.clinicaltrials.gov/ct2/show/NCT02108652

FPI=first patient in; ITT=intent-to-treat

Atezolizumab in Patients with Locally-Advanced or Metastatic Urothelial Carcinoma (mUC): Results from a Pivotal Multicenter Phase II Study (IMvigor 210)

Jonathan E. Rosenberg,[1] Daniel P. Petrylak,[2] Oyewale Abidoye,[3] Michiel S. van der Heijden,[4] Jean Hoffman-Censits,[5] Andrea Necchi,[6] Peter H. O'Donnell,[7] Ani Balmanoukian,[8] Yohann Loriot,[9] Margitta Retz,[10] Jose Luis Perez-Gracia,[11] Nancy A. Dawson,[12] Arjun V. Balar,[13] Matthew D. Galsky,[14] Mark T. Fleming,[15] Thomas Powles,[16] Na Cui,[3] Sanjeev Mariathasan,[3] Gregg D. Fine,[3] Robert Dreicer[17]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Yale Cancer Center, New Haven, CT, USA; Genentech, Inc., South San Francisco, CA, USA; [4]Netherlands Cancer Institute, Amsterdam, Netherlands; [5]Thomas Jefferson University Hospital, Philadelphia, PA, USA; [6]Istituto Nazionale dei Tumori, Milan, Italy; [7]University of Chicago, Chicago, IL, USA; [8]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [9]Gustave Roussy, Villejuif, France; [10]Urologische Klinik und Poliklinik, Technische Universität München, Munich, Germany; [11]Clinica Universidad de Navarra, Pamplona, Spain; [12]Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA; [13]Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY, USA; [14]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [15]Virginia Oncology Associates, Norfolk, VA, USA; [16]Barts Cancer Institute, Queen Mary University of London, London, UK; [17]Division of Hematology/Oncology, University of Virginia, Charlottesville VA USA

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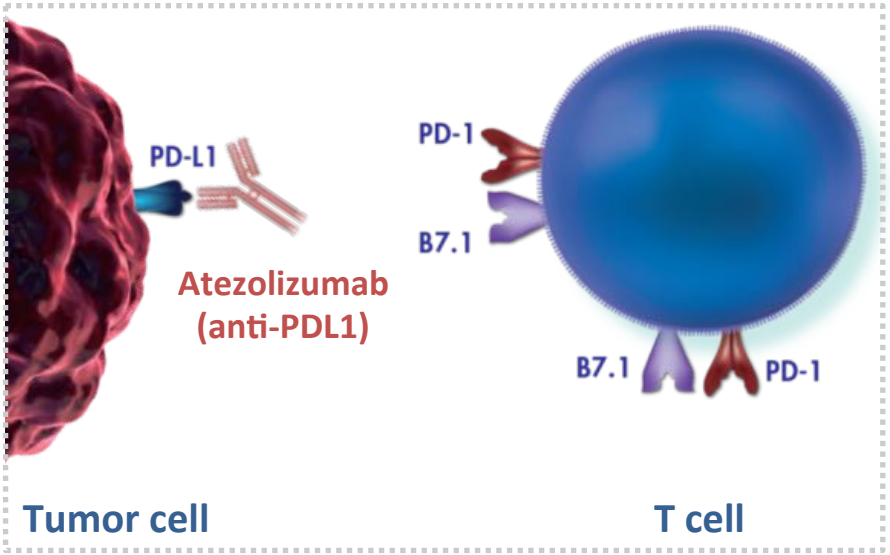
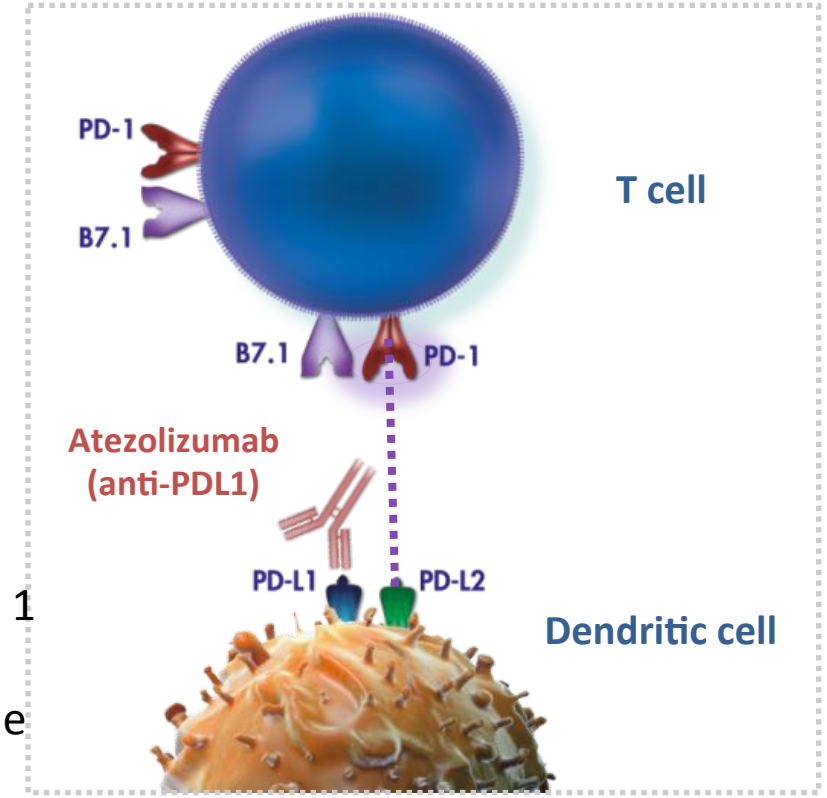
Atezolizumab (MPDL3280A):

A Humanized Anti-PDL1 Antibody





- Signaling through programmed death-ligand 1 (PD-L1), which is expressed in many cancers including mUC, can inhibit antitumor immune responses
- Atezolizumab can enhance T-cell priming and reinvigorate suppressed immune cells by inhibiting binding of PD-L1 to PD-1 and B7.1
- By leaving the PD-L2/PD-1 interaction intact, atezolizumab has the potential to preserve peripheral immune homeostasis[1,2]

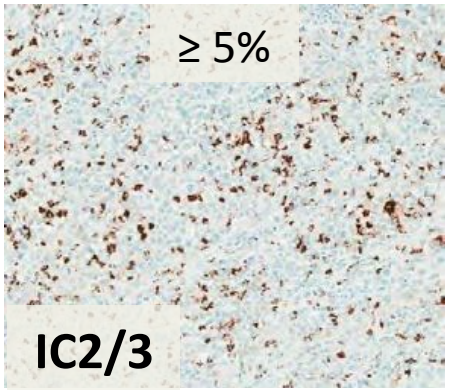
References: 1. Akbari et al. *Mucosal Immunol*. 2010. **2.** Matsumoto et al. *Biochem Biophys Res Commun*. 2008.

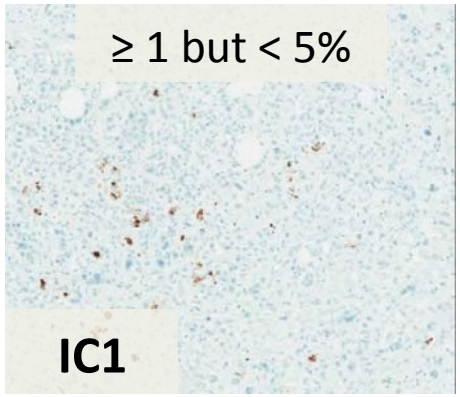
Rosenberg JE et al, ECC2015

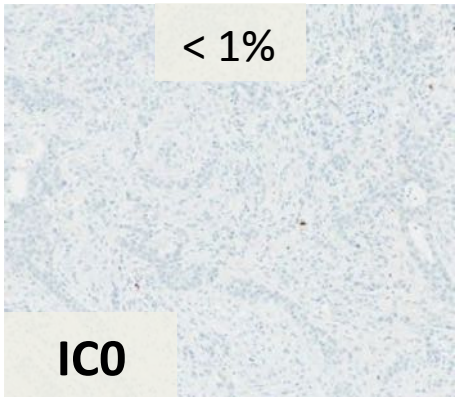
IMvigor 210: PD-L1 IHC

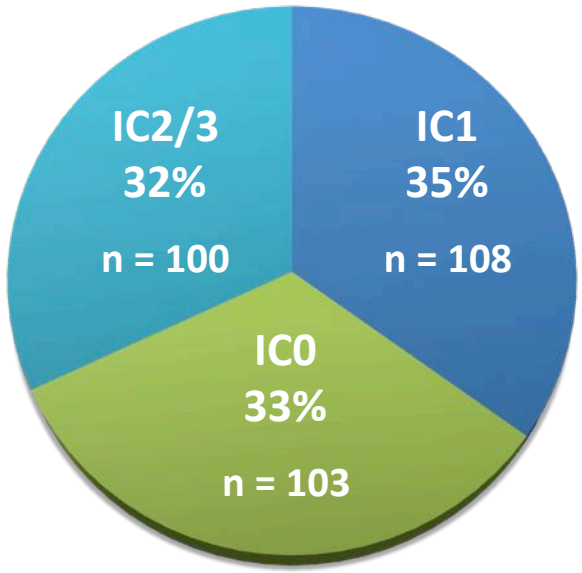
PD-L1 Immune Cell Expression and Prevalence

IHC Status of Treated Patients in IMvigor 210 Study (N = 311)









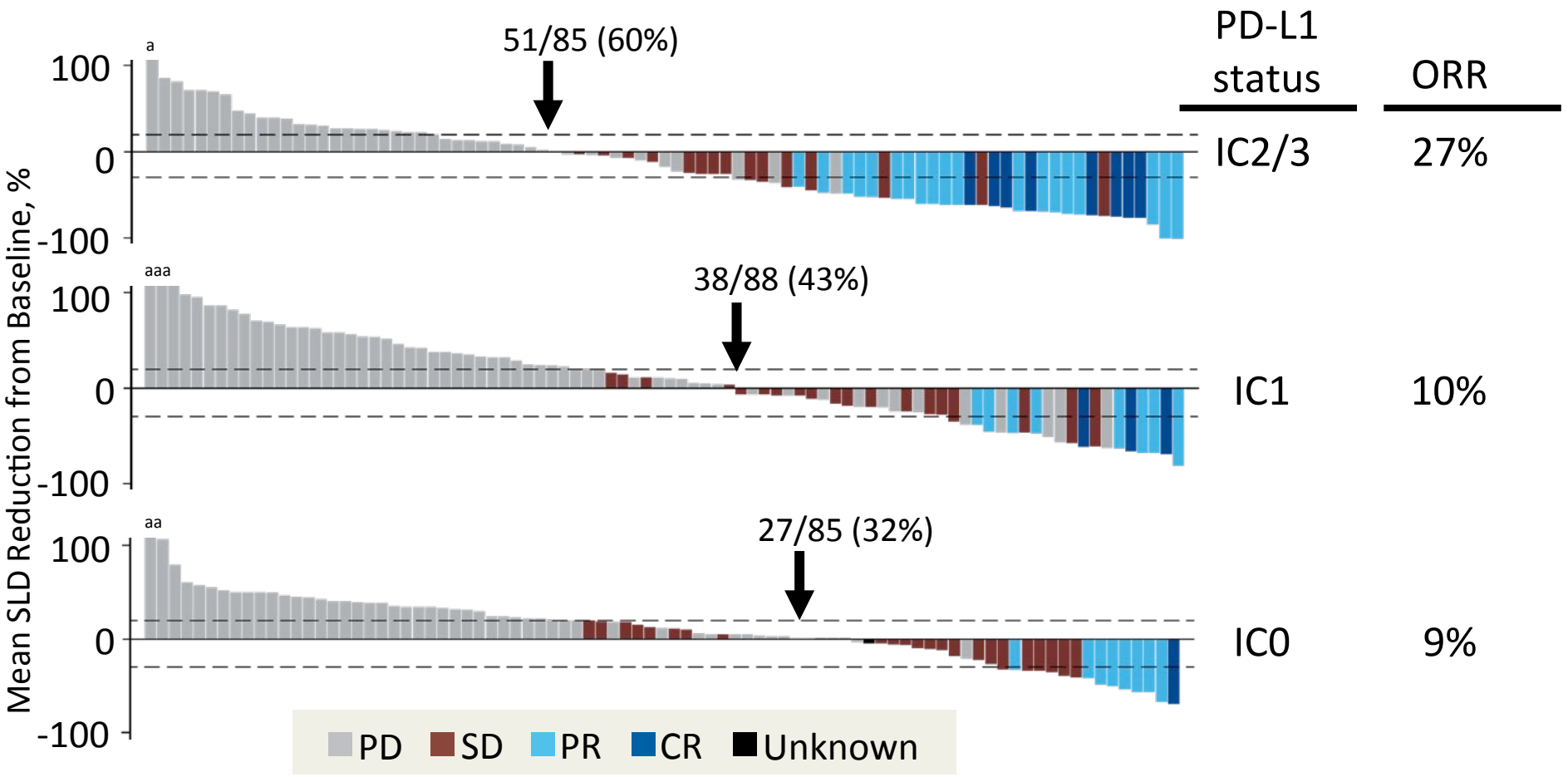
- IMvigor 210 enrolled an all-comer population
- VENTANA PD-L1 (SP142) CDx Assay was used to prospectively measure tumor-infiltrating immune cell (IC) PD-L1 expression based on 3 IHC scoring levels

Images at 10x magnification.

Rosenberg JE et al, ECC2015

IMvigor 210: Efficacy

Changes in Target Lesions by PD-L1 Subgroup

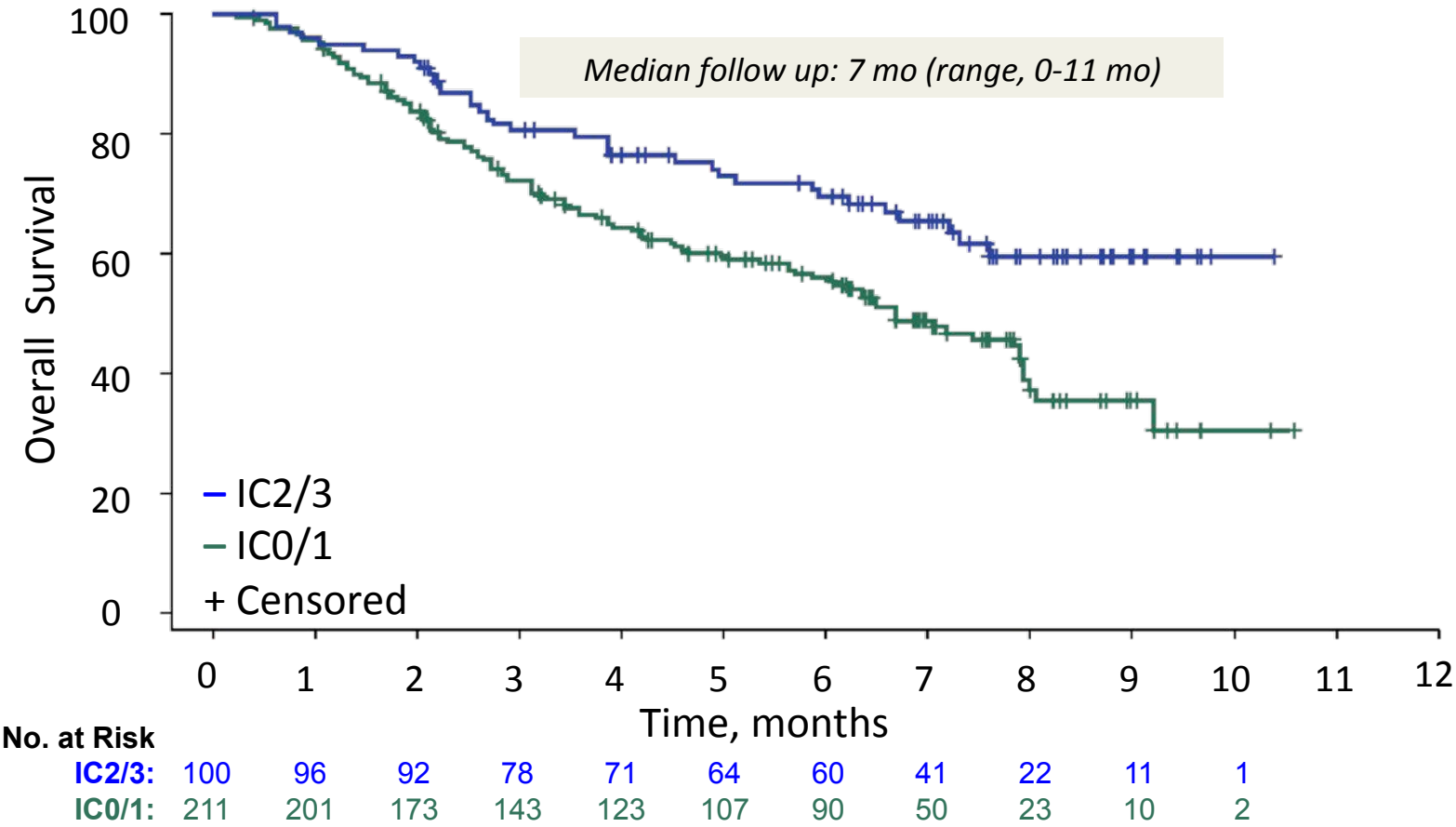


111/258 (43%) patients with tumor assessments had SLD reduction

IMvigor 210: Efficacy

Preliminary Analyses of Overall Survival

Survival	IC2/3 n = 100	IC0/1 n = 211	All N = 311
Median OS, mo (95% CI)	NR (7.6, NE)	6.7 (5.7, 8.0)	7.9 (6.7, NE)



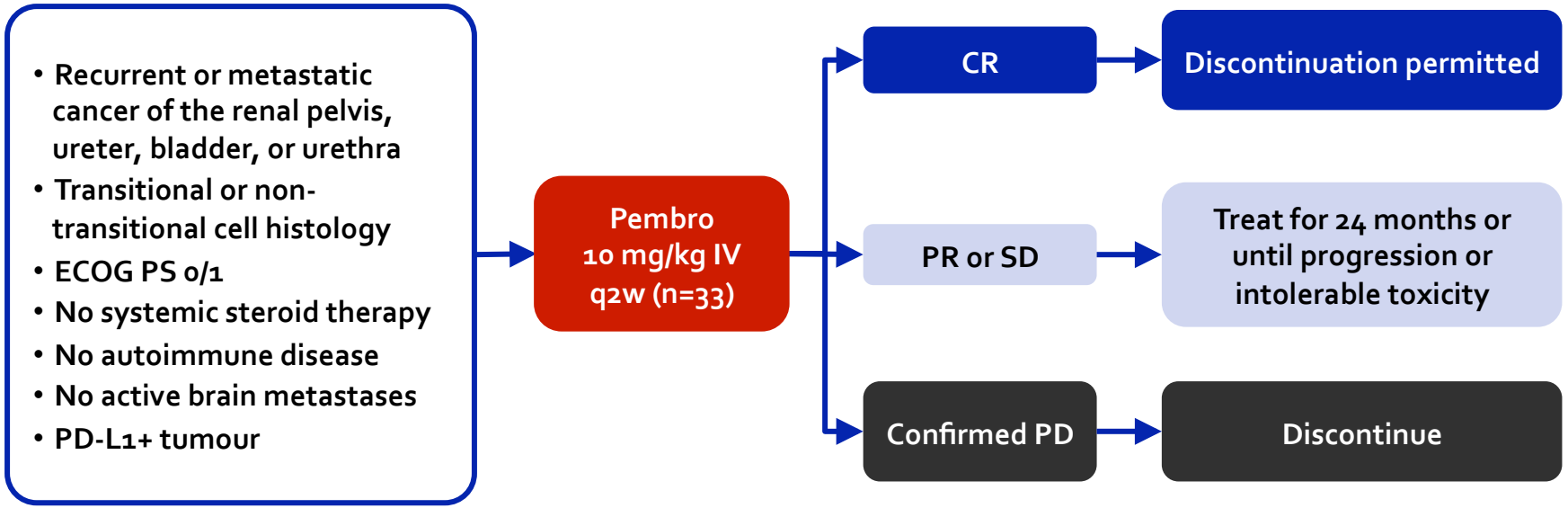
No. at Risk

IC2/3:	100	96	92	78	71	64	60	41	22	11	1
IC0/1:	211	201	173	143	123	107	90	50	23	10	2

NR, not reached; NE, not estimable. Data cutoff May 5, 2015. Follow up ≥ 24 weeks.

Rosenberg JE et al, ECC2015

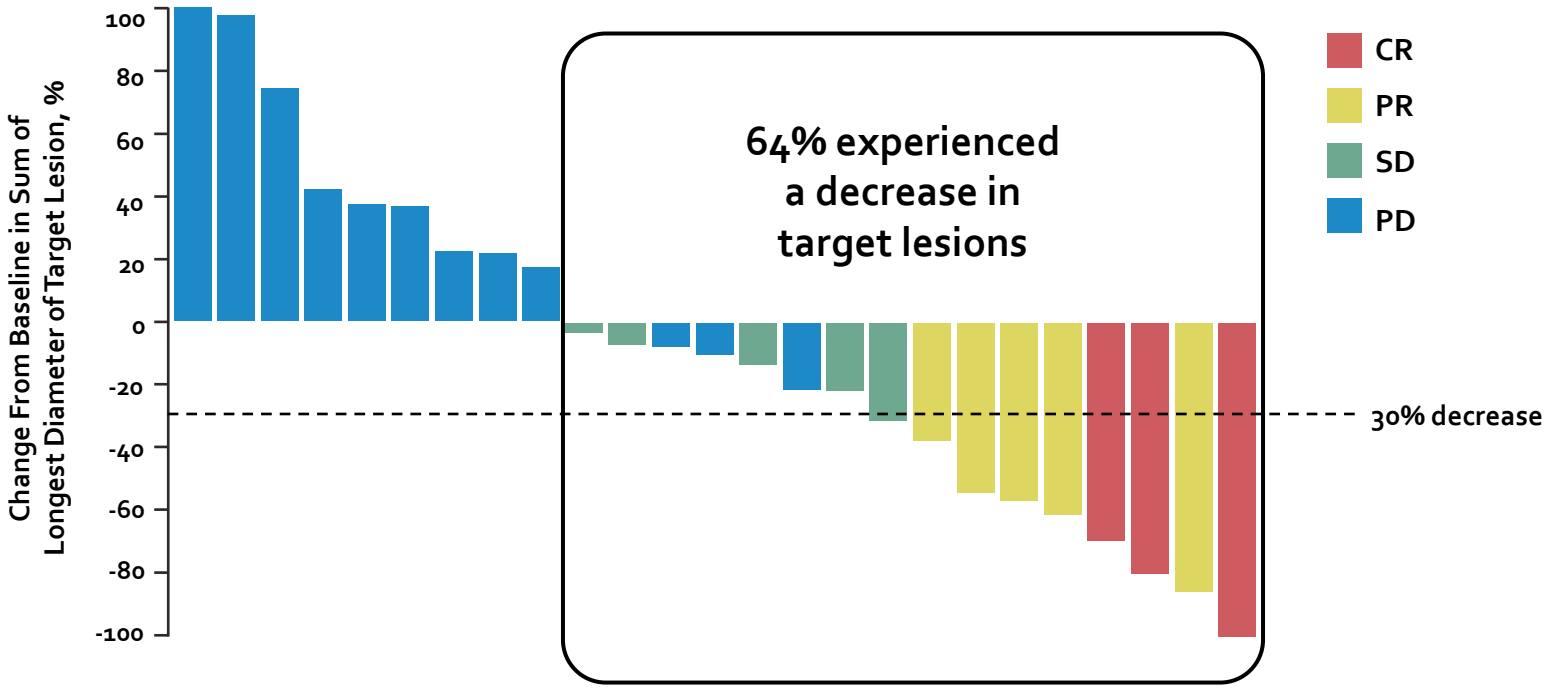
KEYNOTE-012: study design



- Screening for PD-L1
- PD-L1 positivity was defined as any staining in the stroma or in ≥1% of tumour cells, using a prototype IHC assay and the 22C3 antibody clone
- 61 of 95 (64.2%) patients screened were found to be PD-L1 positive
- Response assessment: performed every 8 weeks per RECIST v1.1

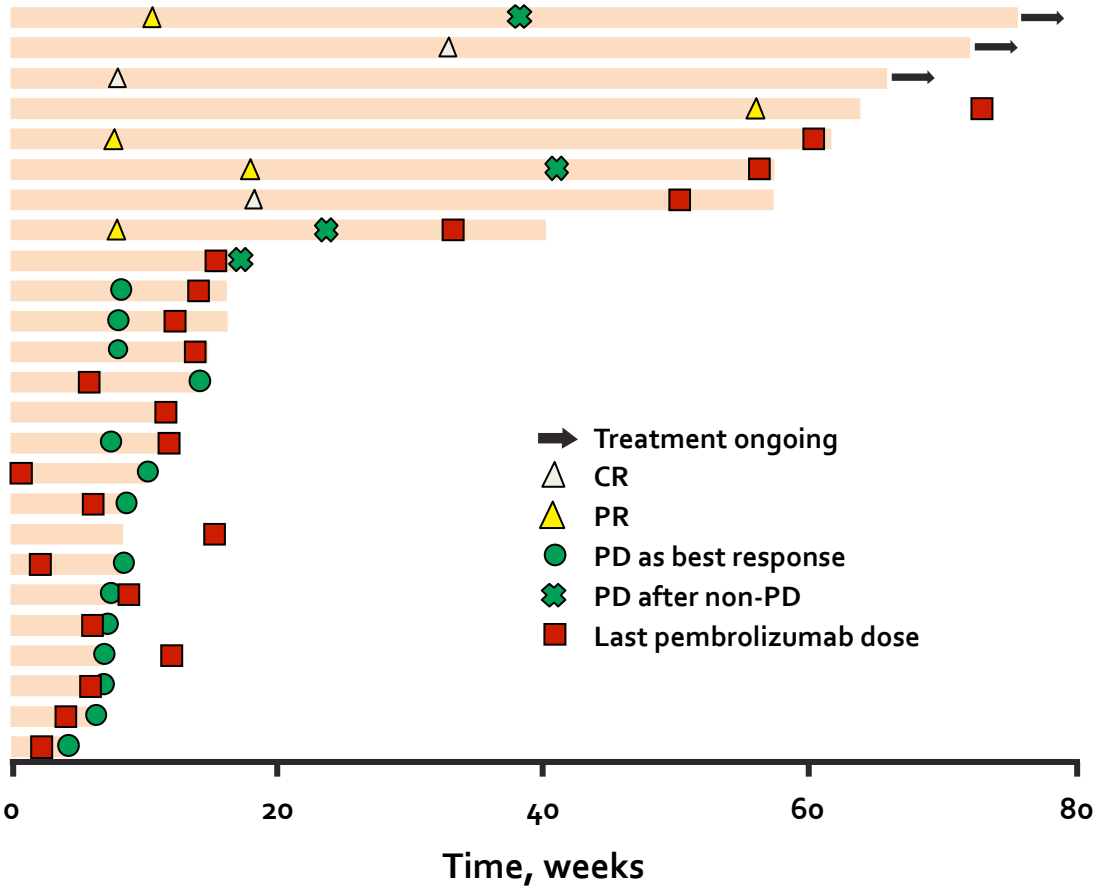
At the discretion of the investigator, patients who received pembrolizumab for ≥24 weeks and for ≥2 treatments beyond confirmed complete response may discontinue therapy. Patients who experience progression may be eligible for up to 1 year of additional pembrolizumab if no other anticancer therapy was received. If clinically stable, patients are to remain on pembrolizumab until progresive disease is confirmed on a second scan performed ≥4 weeks later
Plimack, et al. ASCO 2015.https://clinicaltrials.gov/show/NCT01848834

KEYNOTE-012: maximum percent change from baseline in target lesions



Analysis includes patients with measurable disease per central review at baseline who received ≥1 pembro dose and
had ≥ 1 post-baseline tumour assessment (n=25)
RECIST v1.1, Central Review
Analysis cutoff date: March 23, 2015
Plimack, et al. ASCO 2015

KEYNOTE-012: treatment exposure and response duration



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

RECIST v1.1, Central Review
Analysis cutoff date: March 23, 2015
Plimack, et al. ASCO 2015

Summary: pembrolizumab and atezolizumab in UC

	Pembrolizumab KEYNOTE-012 (phase Ib)[1]	Atezolizumab	
		PCD4989g (phase Ia)[2]	IMvigor 210 (phase II)[3]
Target	PD-1	PD-L1	PD-L1
Number of evaluable patients	29	87 (IC2/3 = 46)	311 (IC2/3 = 100)
Study population	PD-L1+*	All comers**	All comers**
Schedule	q2wk	q3wk	q3wk
Grade 3–4 toxicity	15%	8%	15%
ORR	28%	IC2/3 = 50%	IC2/3 = 27%
Median OS	13 months	IC2/3 = NR (1 to 20+ months)	IC2/3 = NR (7.6, NE)
12-month OS rate	53%	57%	–

*Defined as any staining in the stroma or in ≥1% of tumour cells

**IHC status defined as IC3: ≥10% of IC expressing PD-L1; IC2: ≥5% but <10% of IC expressing PD-L1; IC1: ≥1% but <5% of IC expressing PD-L1; IC0: <1% of IC expressing PD-L1 (SP142 IHC assay)

1. Plimack, et al. ASCO 2015
2. Petrylak, et al. ASCO 2015
3. Rosenberg, et al. ECC 2015

Urothelial Bladder Cancer: Next Development Steps in I-O

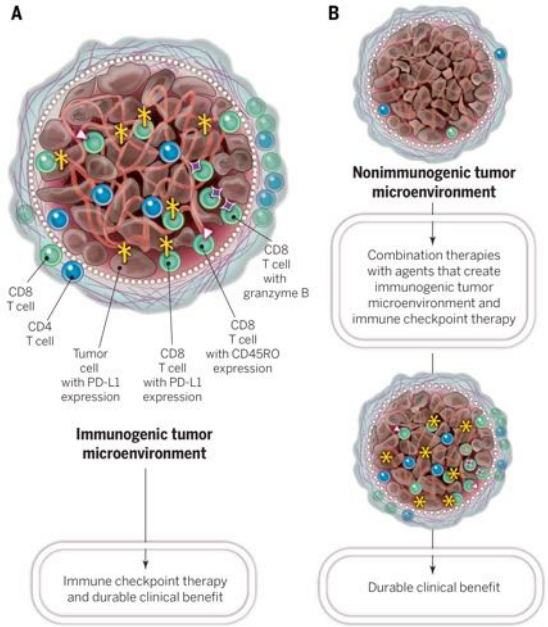
Biomarker-driven approach

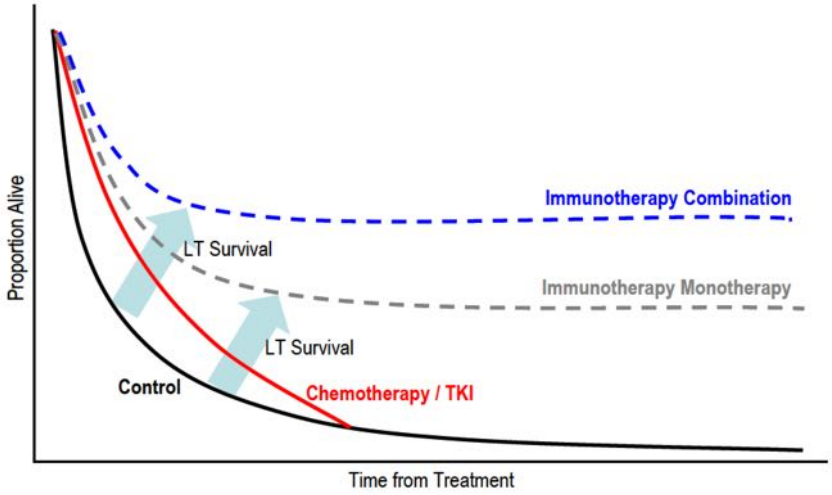
- P53 53%
- FGFR3 19%
- RAS 4%
- PI3KCA 25%
- FGFR1 12%

Potential 2nd gen I-O combos

- Pan-FGFR inh/aPD1-PD-L1
- Parp Inh/aPD1-PD-L1
- Rad223/Atezolizumab
- aPD1-PD-L1/aCTLA4
- .....

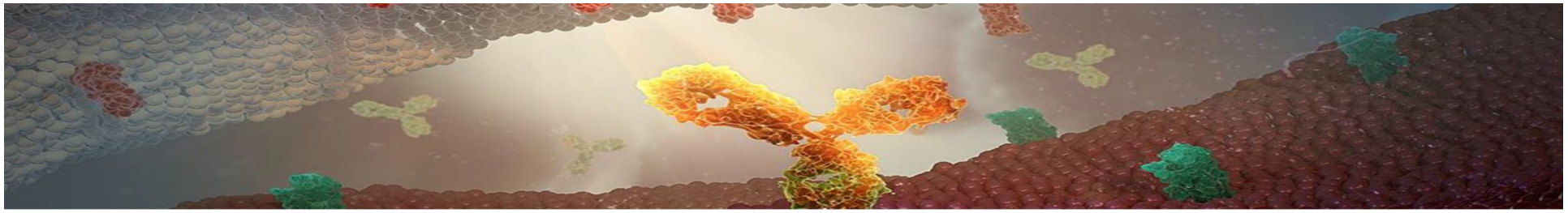
Non-biomarker-driven approach





- Improving frequency of sustained responses
- Improving responses in PD-L1 negative cohort

Sharma P & Allison JP, Science 2015



A myriad of next generation I-O trials with mono- or combination therapy are underway in almost all clinical settings

Non-muscle Invasive | Muscle Invasive | 1L Metastatic cis-eligible | 1L Metastatic cis-ineligible | 2L Metastatic | 3L Metastatic

BCG Refractory

- Pembrolizumab
- Everolimus +intravesical GEM (NCT01259063)

NEOADJUVANT

Pembrolizumab+RT (NCT02560636)
PURE01: Pembrolizumab>Cystectomy (EudraCT: 2015-002055-10)
MIRTOS: Atezolizumab>Cystectomy

ADJUVANT

Phase III: Atezolizumab (NCT02450331)
Phase III: Pembrolizumab (AMBASSADOR)
Phase III: Avelumab (EudraCT 2015-003262-86)
Phase III: Nivolumab (CA209-274)

Phase II: KEYNOTE-052, Pembrolizumab (NCT02335424)

Phase III: MEDI4736 vs MEDI4736+Tremelimumab vs ChemoTx (DANUBE, NCT02516241)

Phase III: KEYNOTE-045, Pembrolizumab (NCT02256436)
Phase III: Atezolizumab (GO29294), NCT02302807

MAINTENANCE Tx

Phase III: Avelumab (EudraCT 2015-003262-86)
Phase II: Regorafenib (NCT02459119)

REFRACTORY

Atezo+Bevacizumab
Atezo+Rad223
AD4547/MEDI4736
AZD8186/MEDI4736
Olaparib/MEDI4736
Wee1/MEDI4736
Olaparib/MEDI4736/Tremelimumab
Etc.

Sources: http://ClinicalTrials.gov; http://www.bcan.org

Durvalumab (MEDI4736): phase III study of first-line durvalumab with or without tremelimumab vs SOC CT in patients With unresectable stage IV UBC

Key eligibility

- First-line histologically or cytologically confirmed unresectable stage IV UBC
- Eligible or ineligible for cisplatin-based CT
- Cisplatin ineligible defined as meeting 1 of the below criteria:
  - Creatinine clearance <60 mL/min; CTCAE grade ≥2 audiometric hearing loss; CTCAE grade 2 peripheral neuropathy; NY Heart Association class III heart failure
- Tumor PD-L1 status (IHC confirmed by reference laboratory) is required prior to randomisation

N=525

R

1:1:1

- **Durvalumab + tremelimumab**
- **Durvalumab**
- **SOC CT: Cisplatin + gemcitabine or Carboplatin + gemcitabine**

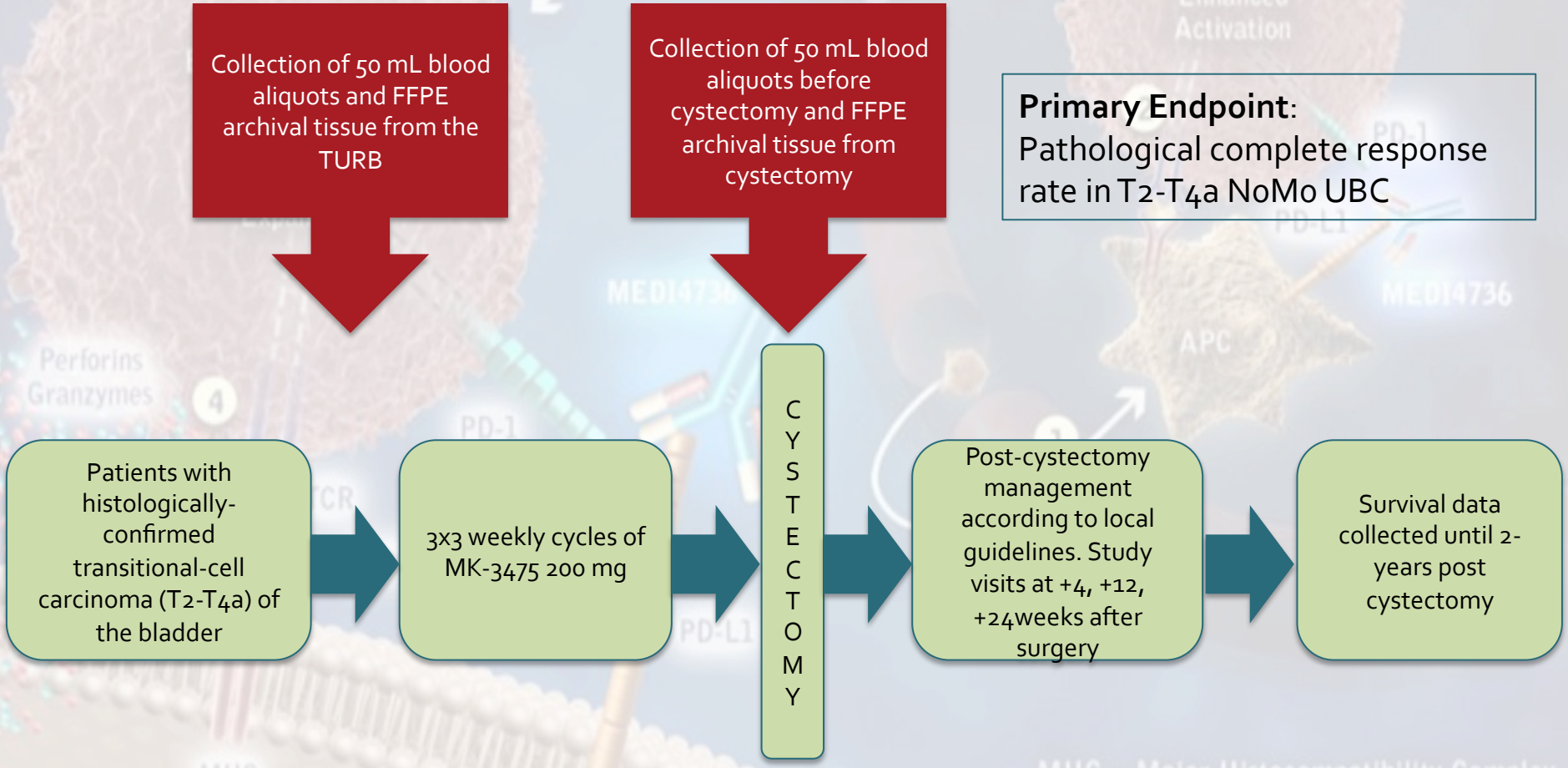
- Primary endpoint: PFS of combination therapy vs SOC CT
- Secondary endpoint: PFS in PD-L1-negative patients, OS, safety and tolerability, ORR, functional assessment of cancer therapy- bladder cancer (FACT-BL), immunogenicity, pharmacokinetics
- Study start date: October 2015
- Estimated study completion date: August 2019
- Estimated primary completion date: November 2017

https://clinicaltrials.gov/ct2/NCT02516241

AstraZeneca

PURE-01 - Window pre-operative study of aPD-1 MK-3475 (Pembrolizumab) in urothelial bladder cancer patients who are candidates for surgery.

EudraCT: 2015-002055-10



Study sponsor: Fondazione IRCCS Istituto Nazionale dei Tumori
Principal Investigator: A. Necchi

Fondazione IRCCS
Istituto Nazionale dei Tumori
via Venezian, 1 20133 Milano

Fondazione IRCCS Istituto Nazionale dei Tumori
via Venezian, 1 20133 Milano

Umbrella Study for molecularly informed salvage therapy of Urothelial Cancer

Inclusion criteria:
- Failure of ≥1 prior chemotherapy regimen
- Adequate organ function
- Measurable disease
- TCC histology
- Availability of sufficient archival tumor tissue for analyses

Industry-sponsored NGS or Ion Ampliseq™ Comprehensive Cancer Panel (+ customized additional analyses)

	Industry-sponsored vs Academic planned/ongoing trials
E2F amplification Rb amplification/mutation CDKN2A mutation	**CDK4/6 inhibitor** **MILCICLIB Ph2**
FGFR3 fusion/mutation/ amplification	**Pan FGFR TKI** **JNJ-42756493 Ph2**
Androgen Receptor +ve	**ARN509 Ph2**
CREBBP, EP300 mutation	**HDAC inhibitor** **MOCETINOSTAT Ph2**
EGFR mutation	**Panitumumab + Paclitaxel vs Paclitaxel randomized Ph 2**
None of the above	**Anti PD1/PDL1:** - **Nivolumab Ph2** - **Pembrolizumab Ph3** - **MPDL3280A Ph3**

Primary Endpoint (descriptive):
Overall survival (benchmark of 6 months)
[Global and according to study arm]

Bladder Cancer White Paper EU action recommendations

- **Education** and **information** for patients and broad public, including policy makers
- **Prevention**: smoking cessation and occupational cancer
- **More research funding and centralised data** to better understand the risk factors and the disease
- **Early diagnosis**: screening programme for high-risk groups
- **Money and resources** should always be readily available but austerity measures
- **Training urologists** when cancer manifested long after initial exposure
- **Access** to novel technological solutions

Group consensus document launch in December 2015 in EU Parliament

Opportunity for the community to **contribute** and further **cascade** the initiative

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