Checkpoint Inibitors for Bladder Cancer

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II CONGRESO PANAMEÑO DE UROLOGIA
IX CONGRESO CENTROAMERICANO Y DEL
CARIBE DE UROLOGIA
Panamá, 21 al 23 de Enero 1993

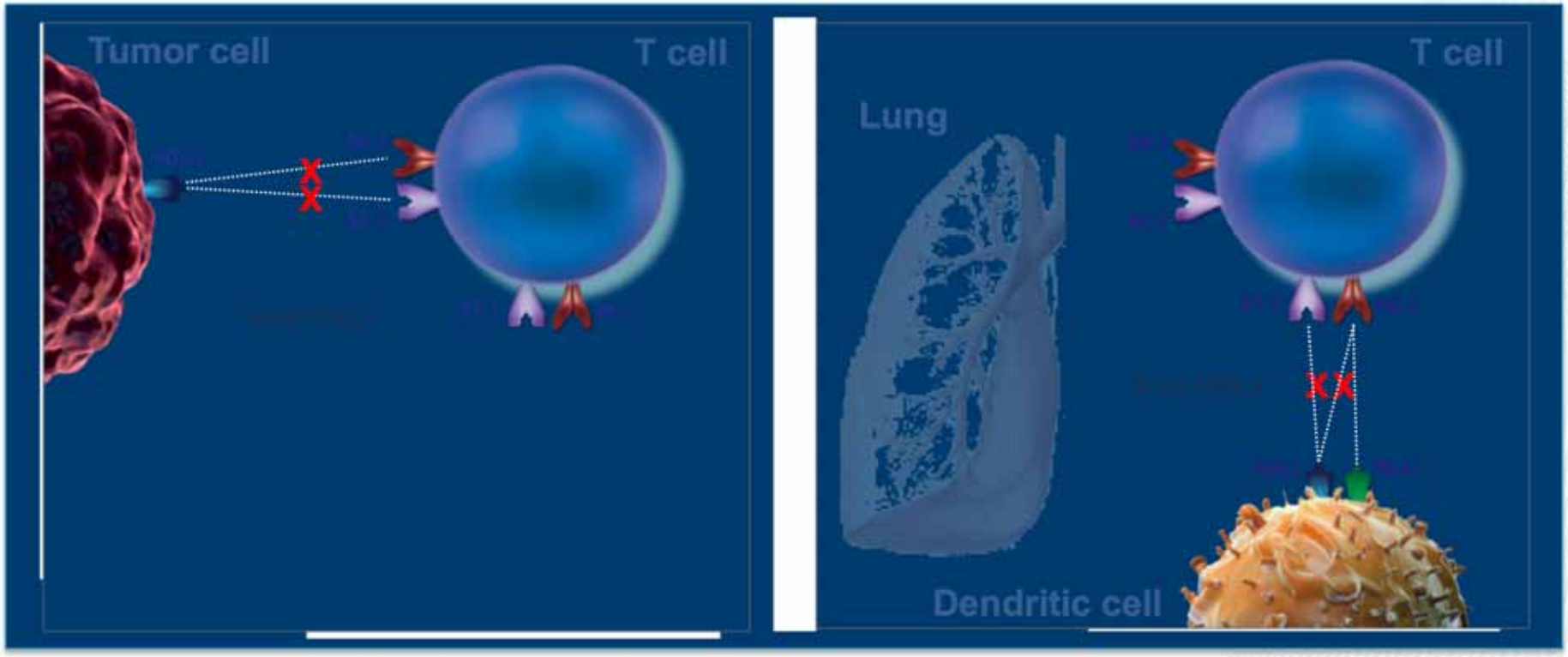
M-VAC vs Cisplatin Phase III
Long term survival

	Cisplatin	M-VAC
Evaluable	122	133
3 years	4	17
6 years*	2	9

*6 patients died of TCC, 1 2nd Ca, 2 other, 1 lost to F/U

Saxman, JCO, 15:2564, 1997

MPDL3280A is an Engineered Anti-PD-L1 Antibody that Inhibits the Binding of PD-L1 to PD-1 and B7.1

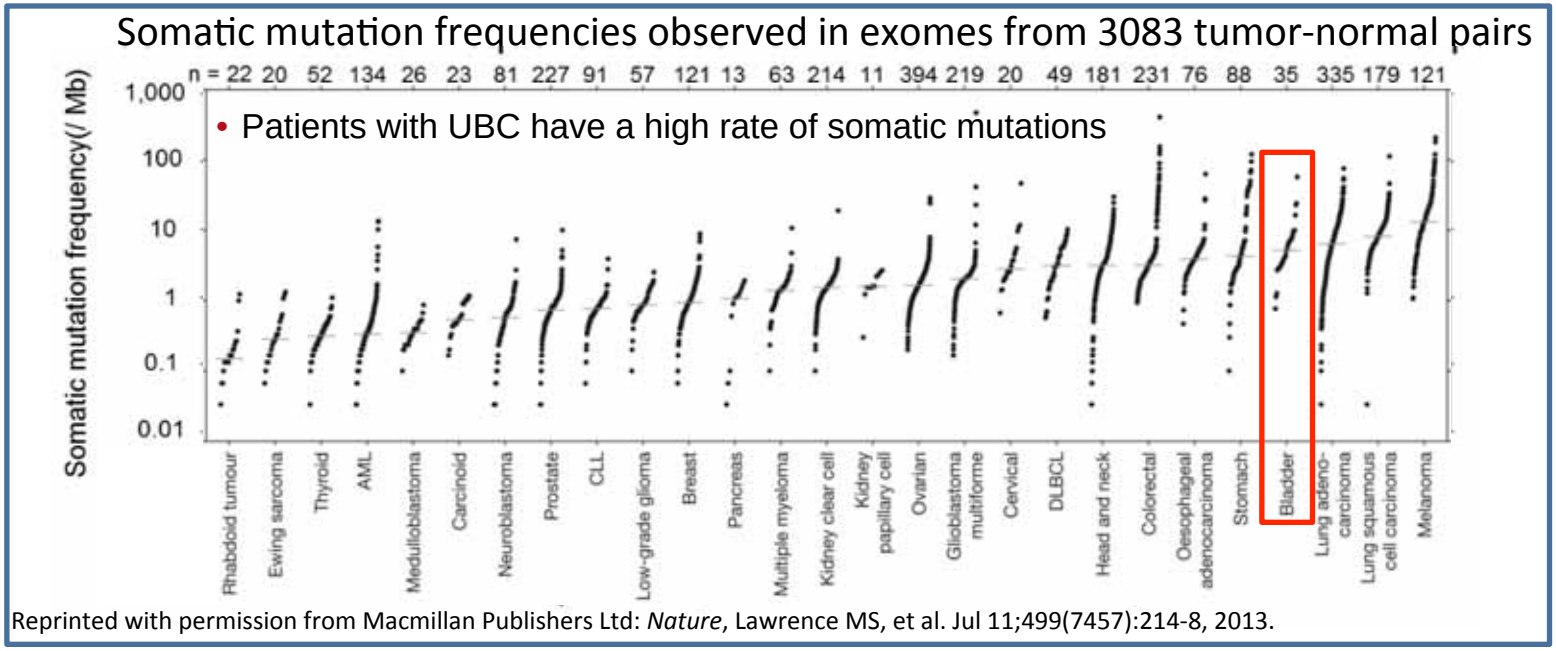


- Inhibiting PD-L1/PD-1 and PD-L1/B7.1 interactions can restore antitumor T-cell activity and enhance T-cell priming

- MPDL3280A leaves the PD-L2/PD-1 interaction intact – maintaining immune homeostasis and potentially preventing autoimmunity

1. Akbari, *Mucosal Immunol,* 2010; Matsumoto, *Biochem Biophys Res Commun*, 2008.

Metastatic UBC



Reprinted with permission from Macmillan Publishers Ltd: *Nature*, Lawrence MS, et al. Jul 11;499(7457):214-8, 2013.

- High unmet need with no FDA-approved therapies for relapse after platinum chemo
  - Vinflunine approved in EU with no significant OS benefit in ITT population
- Median OS ≈ 7 months, PFS ≈ 3 months for 2L UBC[1]
- Patients tend to be elderly with impaired renal function
- High mutational complexity rates similar to tobacco/environmental carcinogen exposure[2-4]
- Potential for many neo-antigens to be seen as foreign by host immune system[2-4]

1. Bellmunt. *Ann Oncol*. 2013; 2. Hodi FS, *Nature*. 2014; 3. Lawrence. *Nature*. 2013; 4. Kandoth. *Nature*. 2013


OUTLOOK
Haemophilia
nature
THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE
Antitumour immunity enhanced by inhibiting PD-L1/PD-1 and identifying mutant neo-antigens
IMMUNE-CHECKPOINT BLOCKADE IN CANCER
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ACCEPT YOUR OWN PAPER
How some scientists are duping the system
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Atomic resolution is there for the taking
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New materials enable radiative cooling in sunlight
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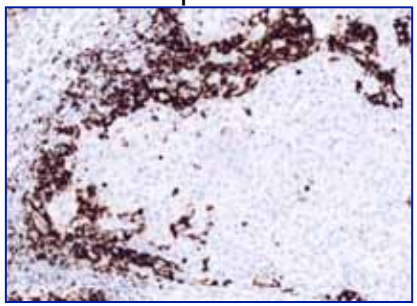
IHC Characteristics of Prescreened Patients: PD-L1 Expression in the UBC Tumor Microenvironment

- The Genentech/Roche SP142 assay measures PD-L1 expression based on 4 IHC scoring levels[a]
- This assay is optimized for detection of PD-L1 expression in both tumor cells (TC) and tumor-infiltrating immune cells (IC)
  - In UBC, prevalence of PD-L1 on TC is low,[1,2] and patients who express PD-L1 on TC are captured within IC cutoffs
  - In UBC, PD-L1 expression on IC is correlated with response,[1,2] while TC expression is not predictive
  - PD-L1 expression is associated with atezolizumab clinical activity in other cancers, including NSCLC[3-6]

PD-L1 Prevalence in UBC[b]	
IHC Level (N = 205)	**IC Scored as PD-L1+, n (%)**
IC3	18 (9%)
IC2	37 (18%)
IC1	89 (43%)
IC0	61 (30%)

PD-L1 Expression in IC



[a] IC scoring criteria: **IC3**: ≥ 10% of IC PD-L1+; **IC2**: ≥ 5% but < 10% of IC PD-L1+; **IC1**: ≥ 1% but < 5% of IC PD-L1+; **IC0**: < 1% of IC PD-L1+.
[b] Based on staining of archival tumor tissue from patients prescreened in atezolizumab Phase Ia study.

References: **1.** Bellmunt et al. ESMO, 2014. **2.** Powles et al. *Nature*. 2014. **3.** Spira et al. ASCO 2015. **4.** Horn et al., ASCO 2015. **5.** Liu et al., ASCO 2015. **6.** Spigel et al., ASCO 2015.

Atezolizumab (MPDL3280A): Baseline Characteristics in UBC *(safety evaluable)*

Characteristic	Patients N = 92[a]
Median age, y (range)	66 (36-89)
Male, n (%)	69 (75%)
ECOG PS, n (%)	
0	37 (40%)
1	55 (60%)
Site of primary tumor	
Bladder	73 (79%)
Renal pelvis	5 (5%)
Ureter	9 (10%)
Urethra	5 (5%)
Site of metastases at baseline, n (%)	
Visceral[b]	73 (79%)
Liver	34 (37%)

Characteristic	Patients N = 92[a]
Prior treatments, n (%)	
Cystectomy or nephroureterectomy	56 (61%)
Platinum-based chemotherapy	86 (94%)
Cisplatin-based	69 (75%)
Carboplatin-based	35 (38%)
≥ 2 prior systemic therapies (metastatic)	66 (72%)
≤ 3 months from last chemotherapy	37 (42%)[c]
Hemoglobin levels < 10 g/dL	16 (17%)
GFR < 60 mL/min	38 (41%)

- Poor prognostic factors included visceral mets, low hemoglobin levels, ECOG PS 1 and short time (≤ 3 months) from prior chemo[1,2]

[a] Safety-evaluable patients received at least 1 dose of atezolizumab. [b] Includes lung, liver, non-lymph or soft tissue. [c] n = 89. Data cutoff, Dec 2, 2014.

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Atezolizumab (MPDL3280A): Treatment-Related AEs in UBC

Treatment-Related AEs Occurring in ≥ 5% of Patients (All Grade) or in ≥ 2 Patients (Grade 3-4)		
N = 92[a]	**All Grade**	**Grade 3-4[b]**
Any AE	60 (65%)	7 (8%)
Fatigue	15 (16%)	0
Asthenia	12 (13%)	1 (1%)
Nausea	10 (11%)	0
Decreased appetite	9 (10%)	0
Pruritus	9 (10%)	0
Pyrexia	6 (7%)	0
Rash	7 (8%)	0
Diarrhea	5 (5%)	0
Increased AST	2 (2%)	2 (2%)

- Atezolizumab was generally well tolerated
  - Median safety follow-up was 16+ wk (range, 3 to 86+ wk)
    - Median duration of treatment was 3 mo (range, 0 to 19 mo)
  - No treatment-related deaths
  - 1 discontinuation due to a treatment-related AE
  - 5% of patients had a Grade 3-4 immune-mediated AE per investigator assessment
    - Grade 3 AEs: increased AST (n = 3); increased ALT (n = 2); increased blood bilirubin (n = 1); hypophysitis (n = 1)
  - 37 patients (40%) had a Grade 3-4 AE of any cause[c]

[a] Safety-evaluable patients received at least 1 dose of atezolizumab. [b] Additional Gr 3-4 AEs (1% each) included anemia, confusional state, decreased blood phosphorus, hypophysitis, increased ALT, increased GGT and thrombocytopenia. [c] In addition, 2 Grade 5 AEs not related to treatment were seen (acute respiratory failure and alcohol overdose). Data cutoff, Dec 2, 2014.

Atezolizumab (MPDL3280A): ORR in UBC by IC Status

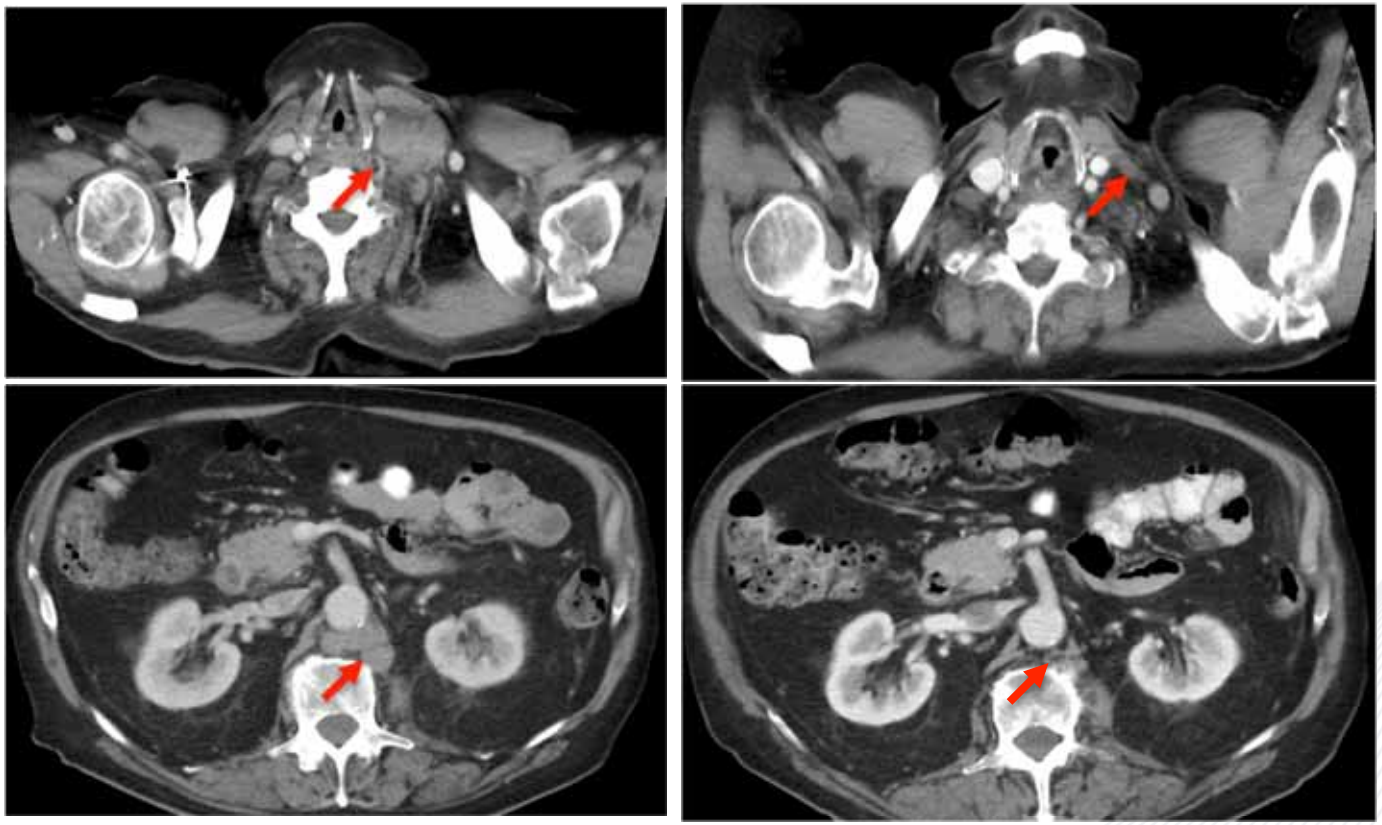
PD-L1 IHC n = 87[b]	ORR (95% CI), %[a]		CR, n (%)		PR, n (%)	
IC3 (n = 12)	**67%** (35%-90%)	**50%** (35, 65)	4 (33%)	9 (20%)	4 (33%)	14 (30%)
IC2 (n = 34)	**44%** (27%-62%)		5 (15%)		10 (29%)	
IC1 (n = 26)	19% (7%-39%)	17% (7, 32)	-	-	5 (19%)	7 (17%)
IC0 (n = 15)	13% (2%-40%)		-		2 (13%)	

- 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

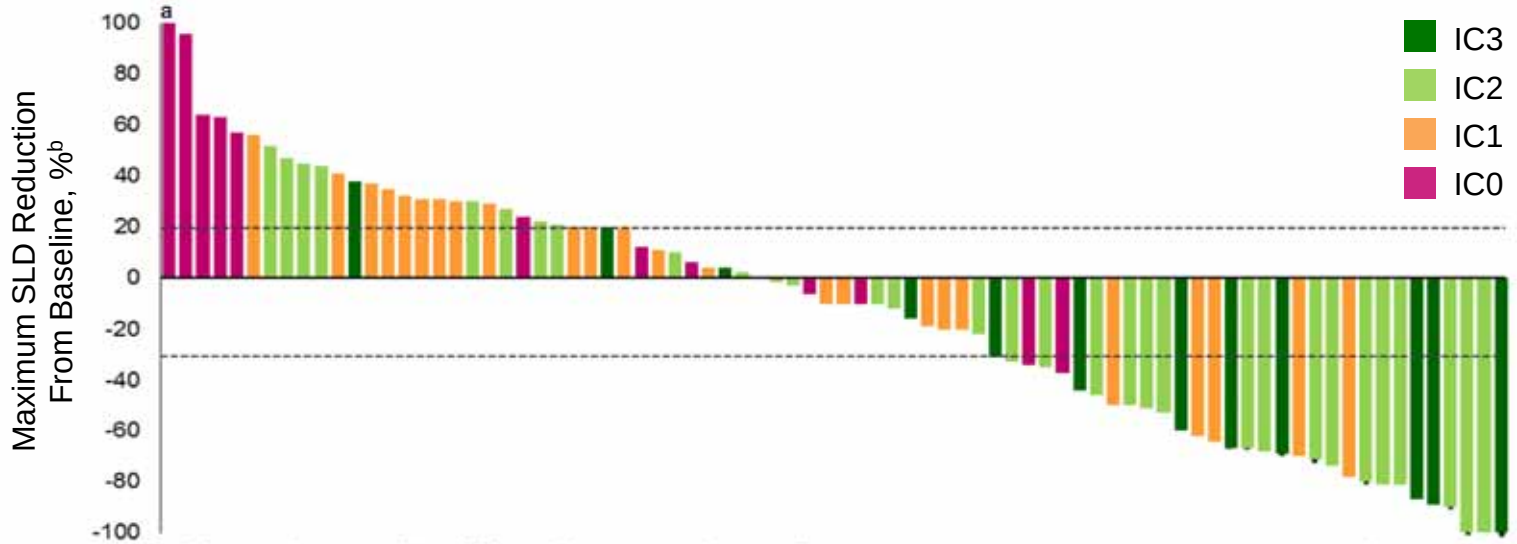
[a] Efficacy-evaluable patients with measurable disease at baseline per RECIST v1.1. Responses are investigator assessed (unconfirmed); of 30 unconfirmed responses, 24 have been confirmed by the cutoff date. [b] 4 IC2/3 patients and 7 IC0/1 patients missing or unevaluable. Data cutoff, Dec 2, 2014.

MPDL3280A: Response in Patient with UBC

Baseline **Post-cycle 6**



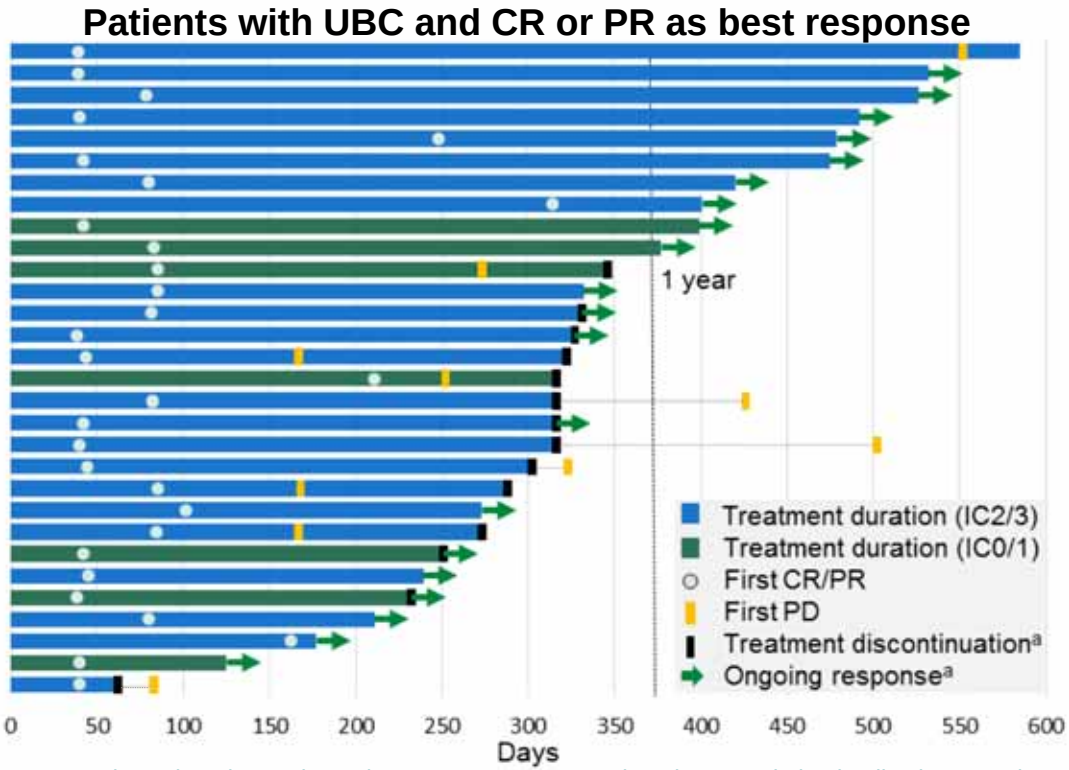
Atezolizumab (MPDL3280A): Response in UBC by IC status



- 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

[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 (MPDL3280A): Duration of Treatment and Response in UBC

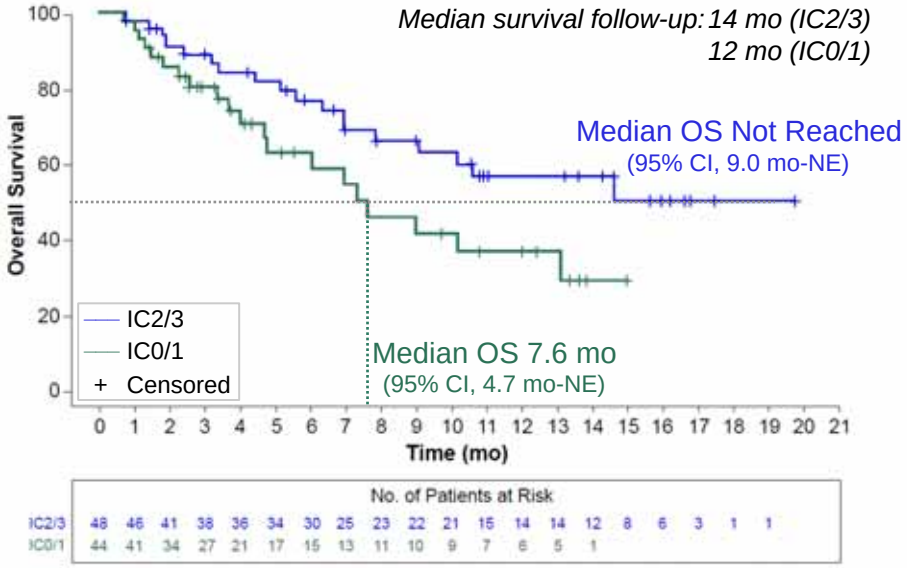


- Median duration of response has not yet been reached in either IC group (range, 0+ to 43 mo)
- Median time to response was 62 days
  - IC2/3 patients: range, 1+ to 10+ mo
  - IC0/1 patients: range, 1+ to 7+ mo
- 20 of 30 responding patients had ongoing responses at the time of data cutoff
- 10 patients have been treated for over 1 year, including 3 retreated following protocol amendment

[a] Discontinuation and ongoing response status markers have no timing implication. 4 patients discontinued treatment after cycle 16 prior to 1 year per original protocol. Responses plotted are investigator assessed and have not all been confirmed by the data cutoff (Dec 2, 2014).

Atezolizumab (MPDL3280A): Survival in UBC

Survival[a] N = 92	IC2/3 n = 48	IC0/1 n = 44
PFS		
Median PFS (range)	6 mo (0+ to 18)	1 mo (0+ to 14+)
1-y PFS (95% CI)	39% (24-54)	10% (0-21)
OS		
Median OS (range)	Not reached (1 to 20+ mo)	8 mo (1 to 15+ mo)
1-y survival (95% CI)	57% (41-73)	38% (19-56)



- PD-L1 IC status appeared to be predictive of benefit from atezolizumab treatment
  - mPFS and 1-year PFS rates were higher in atezolizumab-treated patients with higher PD-L1 IC expression
  - The same association was observed for 1-year OS rates, and mOS for IC2/3 patients was not yet reached
- Preliminary analysis using SP142 from an independent sample set (n = 110) suggests that PD-L1 IC status is not *prognostic* for OS in UBC[1]

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

IMvigor 210

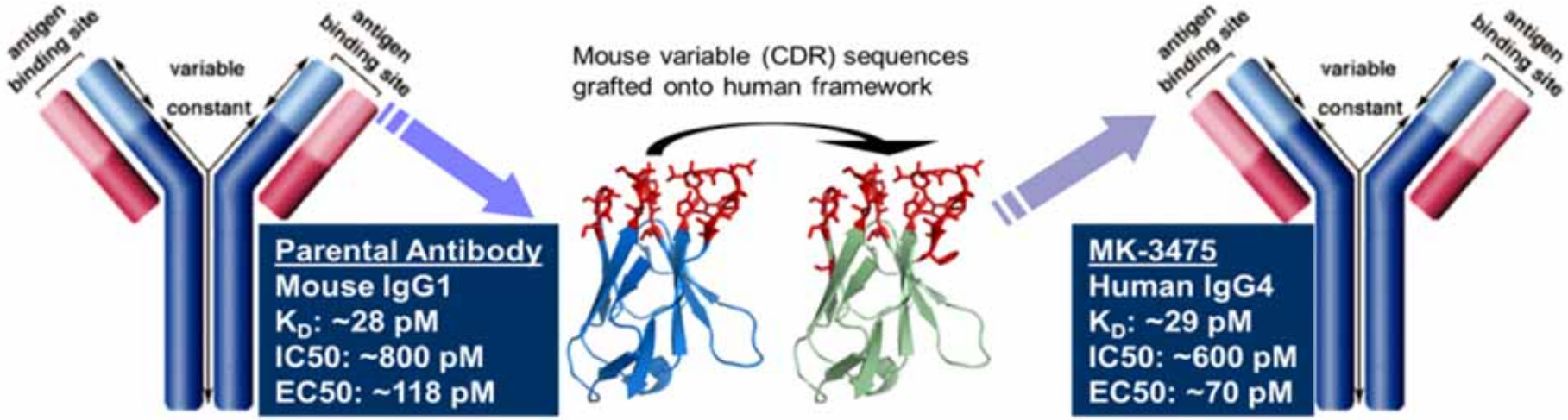
- MPDL3280A 1200 mg Q 21 days for up to 16 cycles
- Prospective collection of tissue
- No requirement for PDL 1 IHC
- 400 patients
  - 300 cisplatin refractory
  - 100 platinum ineligibhle.

Press Release Genetech July 12, 2015

- “We are encouraged by the number of people who responded to atezolizumab and maintained their response during the study because minimal progress has been made in advanced bladder cancer for nearly 30 years," said Sandra Horning, M.D., chief medical officer and head of Global Product Development. "We plan to present results at an upcoming medical meeting, and will discuss next steps with health authorities to bring a new treatment option to patients as soon as possible."

Pembrolizumab (MK-3475)

Humanized IgG4, High-Affinity, Anti-PD-1 Antibody



- Dual blockade of PD-L1 and PD-L2
- No cytotoxic (ADCC/CDC) activity
- Pharmacokinetics: dosing every 2 weeks (Q2W) or every 3 weeks (Q3W)
- Low occurrence of anti-drug antibodies; therefore no impact on pharmacokinetics

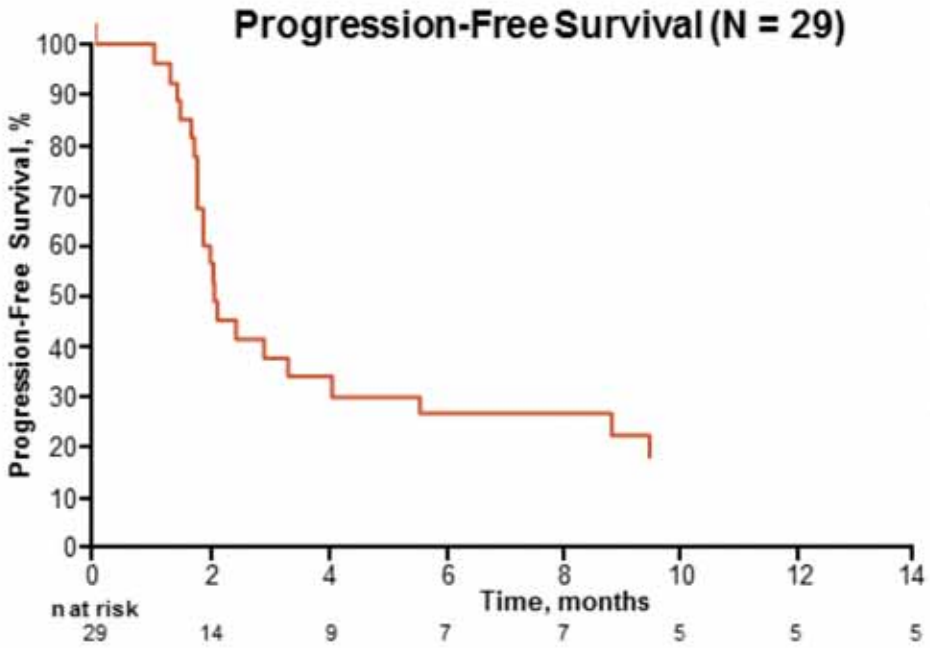
Baseline Characteristics

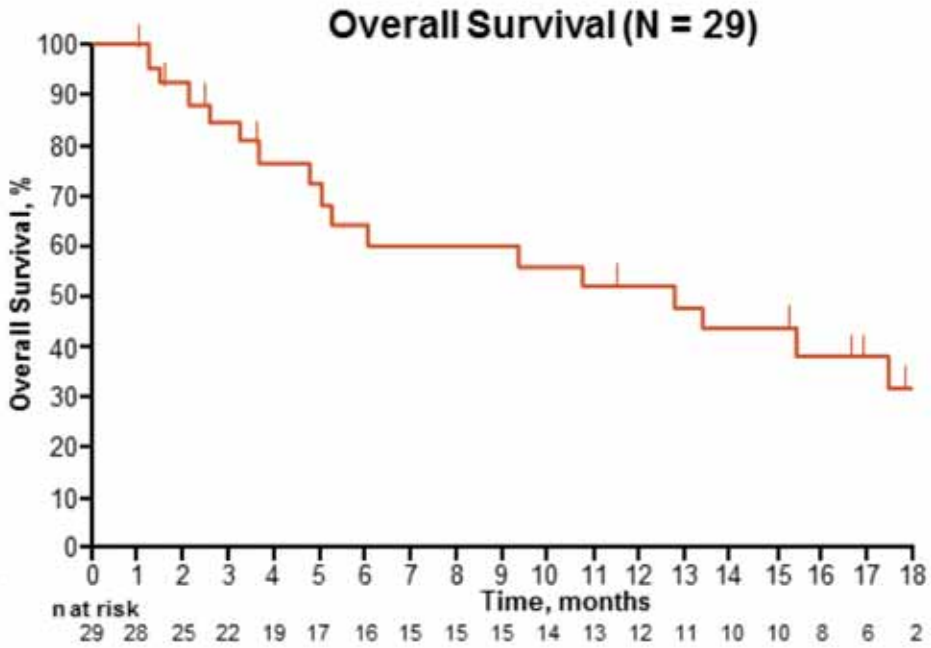
Characteristic	Total (N = 33) N (%)
Age, yr, median (range)	70 (44–85)
Male	23 (69.7)
ECOG performance status	
0	9 (27.3)
1	24 (72.7)
Histology	
Transitional cell	30 (91)
Non-transitional cell/mixed	3 (9)
Location of metastasis	
Any liver	8 (24)
Lymph node only	3 (9)

Characteristic	Total (N = 33) N (%)
No. of prior therapies for advanced disease	
0	8 (24.2)
1	8 (24.2)
2	6 (18.2)
≥3	11 (33.3)
Prior adjuvant/neoadjuvant therapy	
Yes	20 (60.6)

Analysis cutoff date: Mar 23, 2015.

Survival (Central Radiology Assessment)





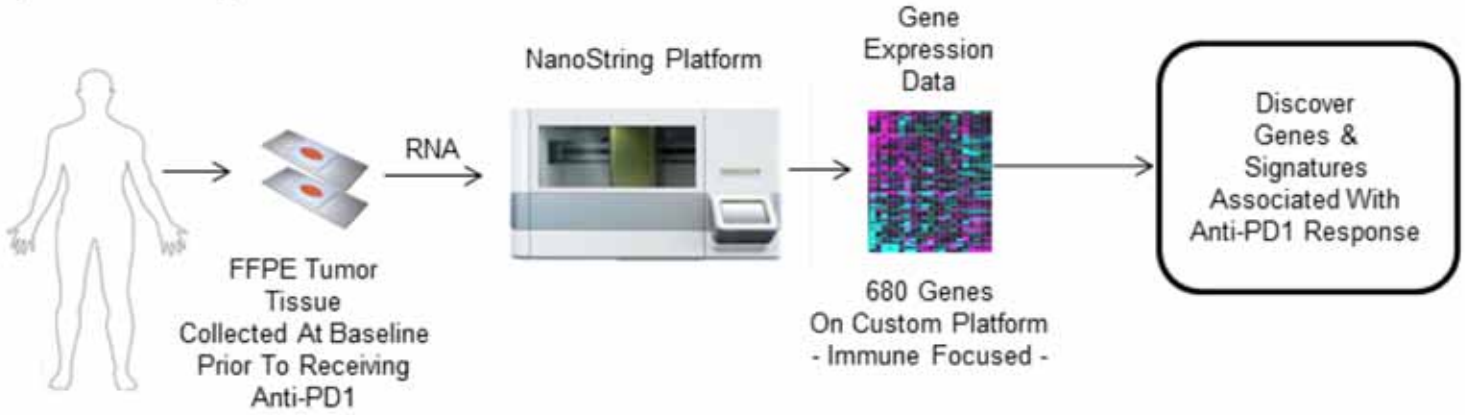
- Median PFS: 2 months (95% CI, 1.7−4.0)
- PFS rate at 12 months: 19.1%

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

Analysis cutoff date: March 23, 2015.

Association Between Immune-Related Gene Expression Signatures and Clinical Outcome

- Immune-related gene expression signature data, using NanoString platform, obtained from tumor tissue was an exploratory objective in KEYNOTE-012
- Four signatures discovered and refined in melanoma were independently tested in bladder cancer[1]



1. Ribas A, et al. ASCO 2015; Abstract No: 3001.

E. Plimack, June 1, 2015

Immune-Related Gene Expression Signatures Identified in Melanoma Patients

INFγ	Expanded Immune		T-Cell Receptor Signaling	De-Novo		
IDO1	CD3D	NKG7	CD27	IKZF3	SAMHD1	CD38
CXCL10	IDO1	HLA-E	TIGIT	HLA-DPB1	TIGIT	CRTAM
CXCL9	CIITA	CXCR6	CD8a	CD27	IL2RB	CD8a
HLA-DRA	CD3E	LAG3	CD3D	AMICA1	TARP	CXCL9
STAT1	CCL5	TAGAP	GRAP2	CD74	CD3D	HLA-C
IFNG	GZMK	CXCL10	LCK	LY9	CD3G	GPR18
	CD2	STAT1	PTPRCAP	CD4	HLA-B	IL18
	HLA-DRA	GZMB	CD4	HLA-DRA	IGJ	CX3CR1
	CXCL13		CCL5	B2M	IRF1	CXCL10
	IL2RG		IL2RB	IGSF6	BST2	SIT1
			IKZF3	FASLG	PTPN7	
			CD3G	LCK		
			CD74			

Exploratory Analysis of the Association Between Immune-related Gene Expression Signatures and Response

	Nominal One-sided *P*-value*			
Signature	ORR N = 25	Clinical Benefit (CR+PR+SD) N = 25	PFS N = 29	OS N = 29
IFNγ-induced (6-gene)	0.698	0.722	0.406	0.184
Expanded Immune (18-gene)	0.616	0.342	0.115	0.193
T-Cell Receptor Signaling (13-gene)	0.405	0.073	0.024	0.322
De-Novo (33-gene)	0.702	0.322	0.131	0.315

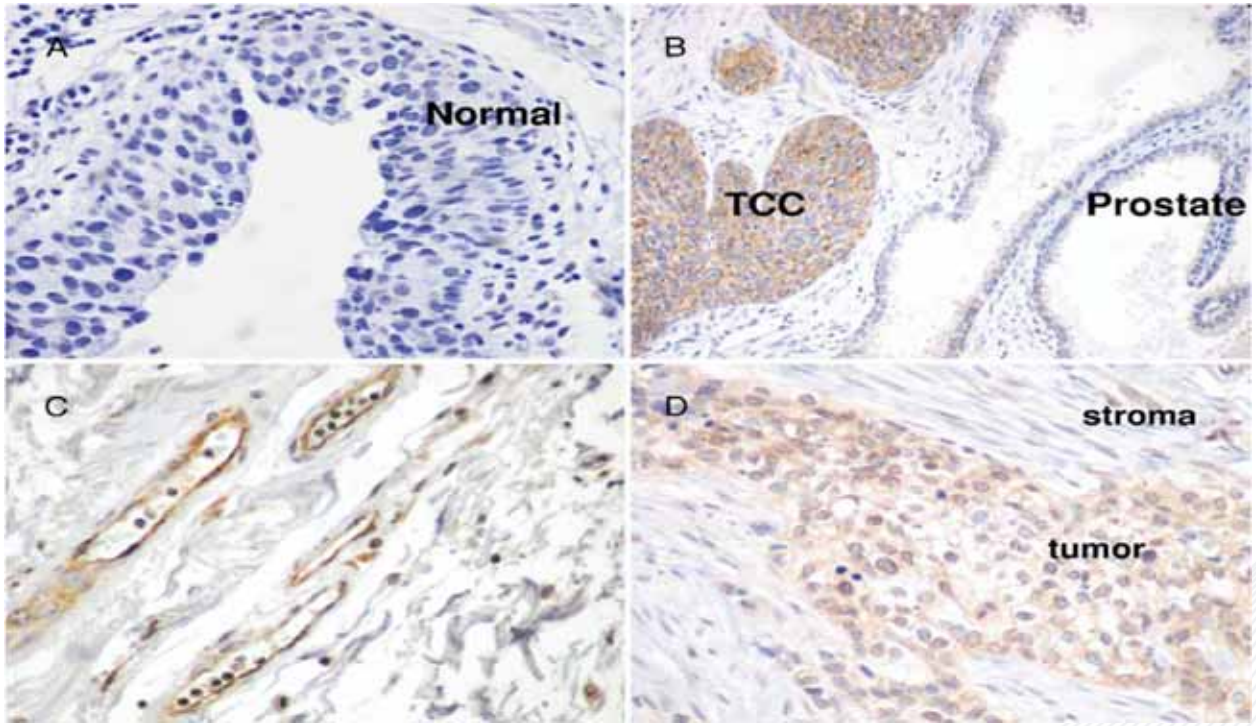
*Using one-sided test from logistic regression for best overall response or Cox regression for PFS.

Rational for VEGF Blockade in Bladder Cancer

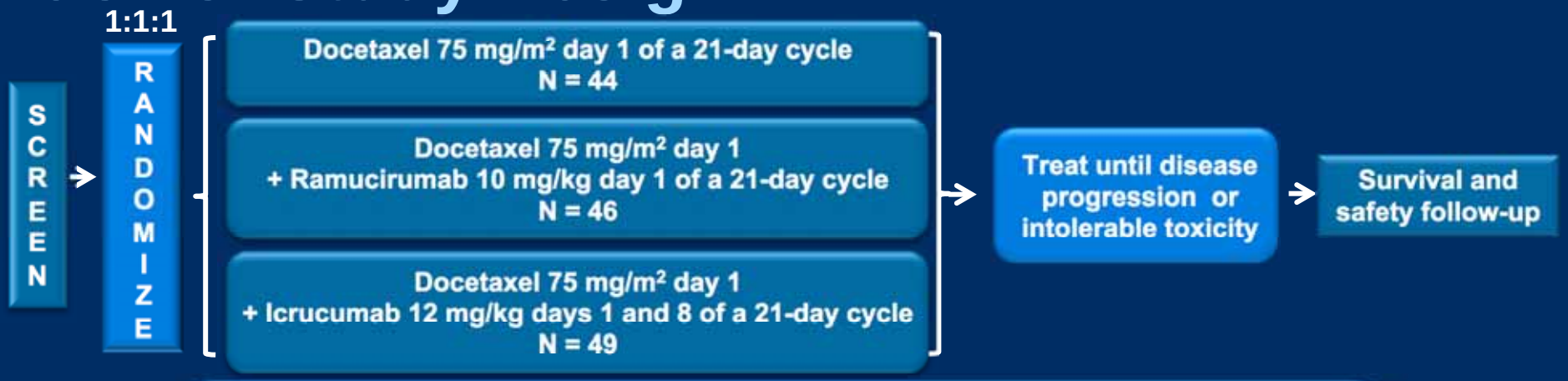
– Antiangiogenic agents, particularly anti-VEGFR-2 monoclonal antibodies (MAbs), may be capable of acting as chemosensitizing agents when given in combination with docetaxel, since this effect was demonstrated in mice when an anti-VEGFR-2 MAb, DC101, was combined with paclitaxel

– Anti-VEGFR-1 MAbs may inhibit metastasis, based on the observed impact of the anti-VEGFR-1 MAb, MF1, on VEGFR-1-positive circulating hematopoietic progenitor cells in mice

Expression of VEGFR-2 in bladder cancer but not in normal urothelium



JCDC: Study Design



Primary Endpoint:

- Progression-free survival (PFS)

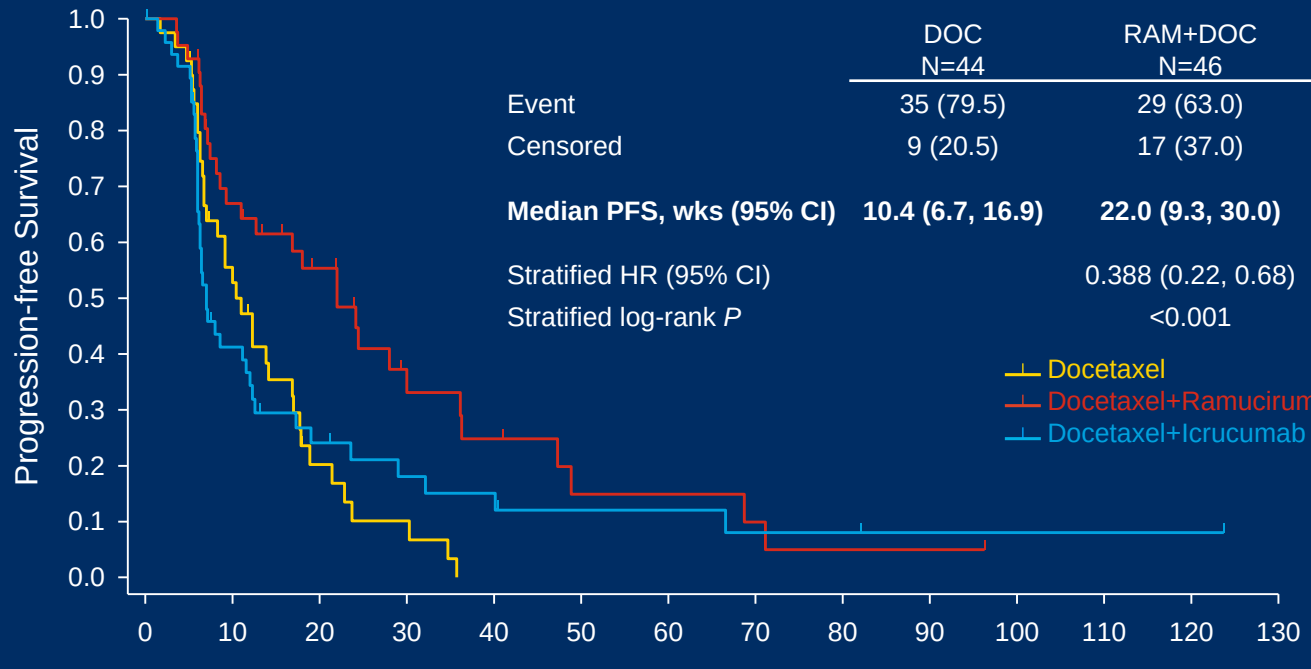
Secondary Endpoints:

- Overall survival, objective response rate, duration of response, safety, PK/PD and immunogenicity profile

Stratification factors:

- Visceral metastasis (yes vs. no)
- Prior antiangiogenic therapy (yes vs. no)

Progression-free Survival - Interim Analysis

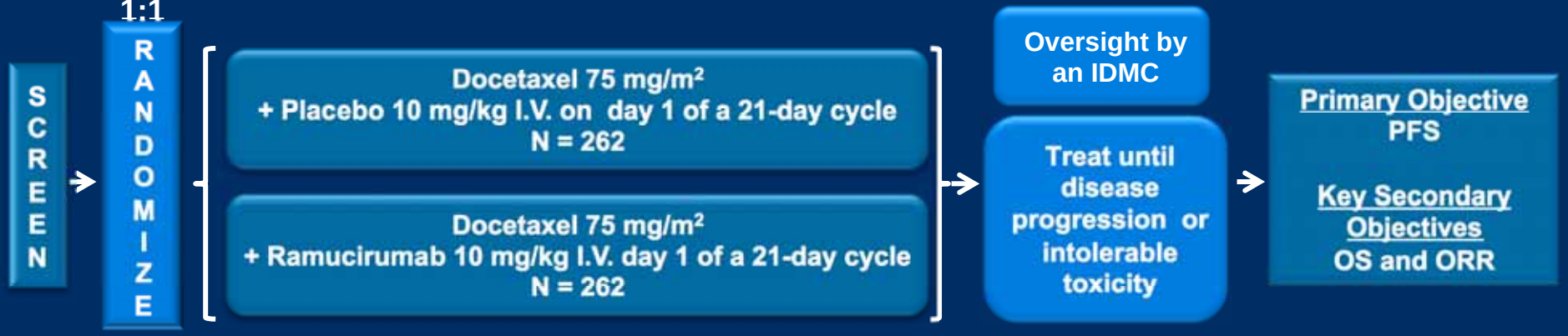


	DOC N=44	RAM+DOC N=46	ICR+DOC N=49
Event	35 (79.5)	29 (63.0)	39 (79.6)
Censored	9 (20.5)	17 (37.0)	10 (20.4)
Median PFS, wks (95% CI)	**10.4 (6.7, 16.9)**	**22.0 (9.3, 30.0)**	**7.0 (6.0, 12.0)**
Stratified HR (95% CI)		0.388 (0.22, 0.68)	0.988 (0.61, 1.59)
Stratified log-rank *P*		<0.001	0.932

Number at Risk

DOC	44	19	6	3	0	0	0	0	0	0	0	0	0	0
DOC+RAM	46	25	17	8	6	3	3	2	1	1	0	0	0	0
DOC+ICR	49	18	9	6	5	3	3	2	2	1	1	1	1	0

RANGE (trial I4T-MC-JVDC): Study Design



Important Inclusion Criteria:

- Locally advanced or unresectable or metastatic UC and ECOG PS 0 or 1
- Progression on or after first-line platinum-based chemotherapy (≤ 14 months; or ≤ 24 months if prior treatment with one immune checkpoint inhibitor)

Key Exclusion Criteria:

- Hemoglobin < 9 g/dL
- Uncontrolled bleeding or thrombotic disorder
- Known untreated brain metastasis

Phase I trial Pembrolizumab + Ramicurimab in Metastatic Cancer

- PI Overall Roy Herbst
  - Bladder Petrylak
  - Fuchs Gastric

Conclusions

- Checkpoint inhibition therapy demonstrates significant antitumor activity in cisplatin treated metastatic urothelial carcinoma
- Phase II and III trials are ongoing to confirm initial observations of anti PD-1 and PDL-1 in metastatic urothelial carcinoma
- A thorough understanding of the markers of resistance and response will help to designing future trials in earlier disease.