Urothelial Cancers- New Strategies

Sandy Srinivas.MD

Stanford University

Relevant financial relationships in the past twelve months by presenter or spouse/partner.

Consultant: Genentech, Astra Zeneca

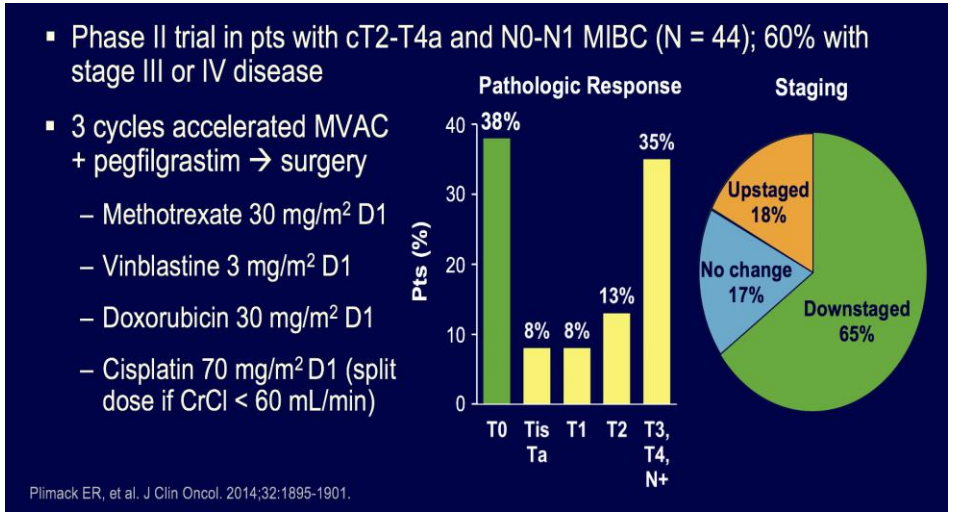
The speaker will directly disclosure the use of products for which are not labeled (e.g., off label use) or if the product is still investigational.

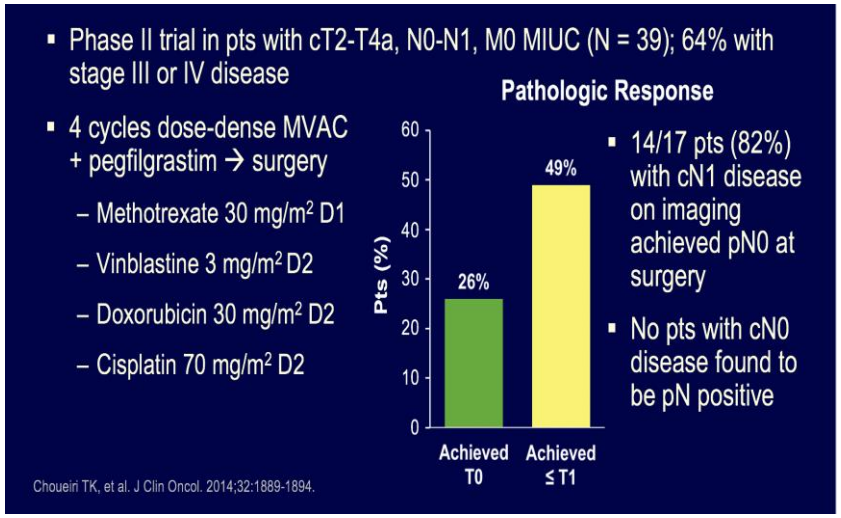
Outline

- Chemotherapy
- Targeted therapy
- Immunotherapy
- Adjuvant/Neoadjuvant

Neoadjuvant chemotherapy in UC

- Standard of care in cT2 Bladder cancer
- Goal is to achieve a pT0
- <pT2 results have better outcomes and are acceptable endpoints
- Cis/gem or DD MVAC commonly used



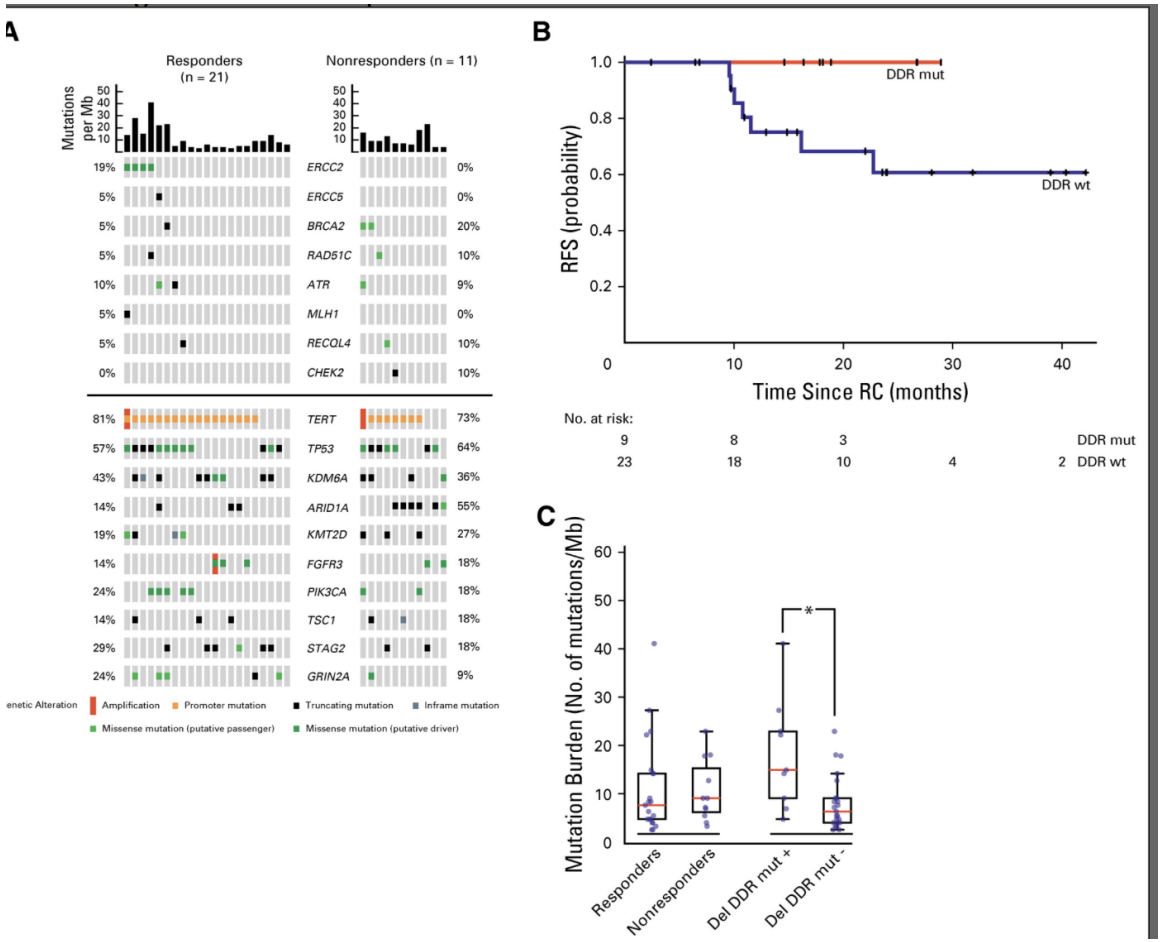


Dose Dense Gemcitabine/Cisplatin

Gemcitabine :2500mg/m2 Day 1.
Cisplatin: 35mg/m2 days 1,2; Q 2 weeks X 6 cycles

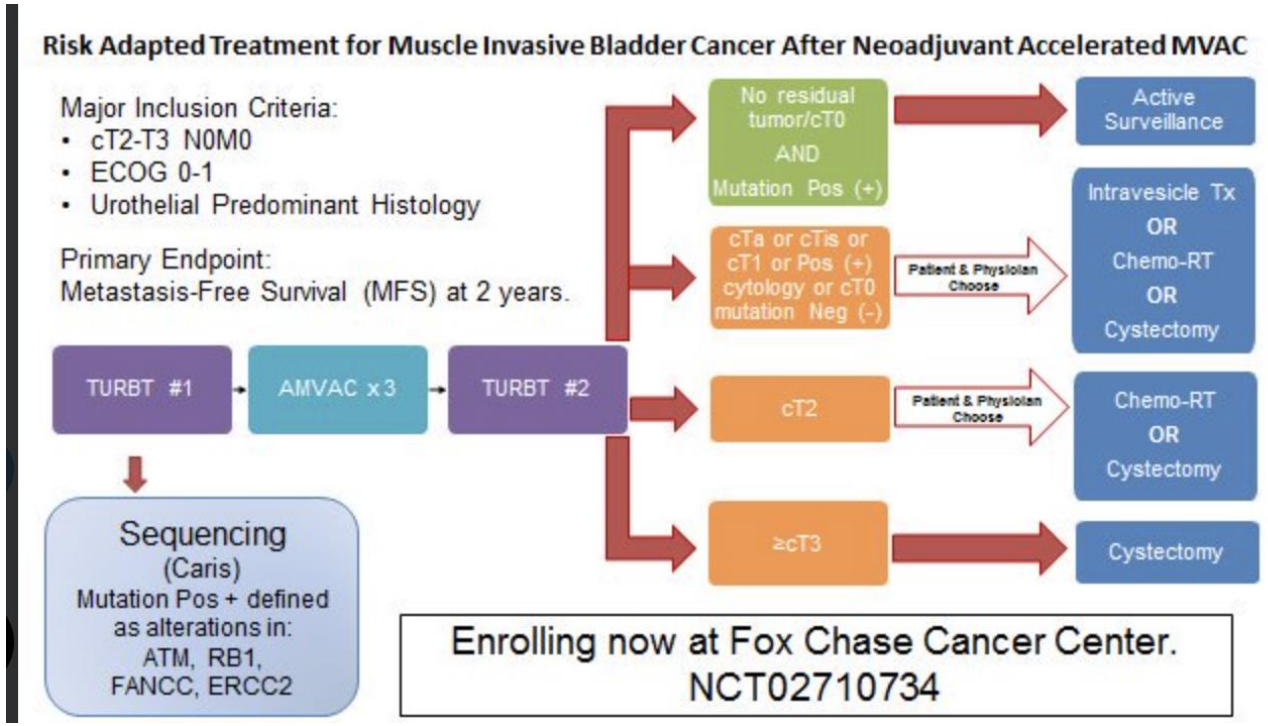
RESULTS

N=49	(%)
P<T2	57
pT0	15
Dose modifications	39
Grade3/4	37
6 cycles	67



Iyer, JCO 2018

Risk adapted strategies to spare cystectomy



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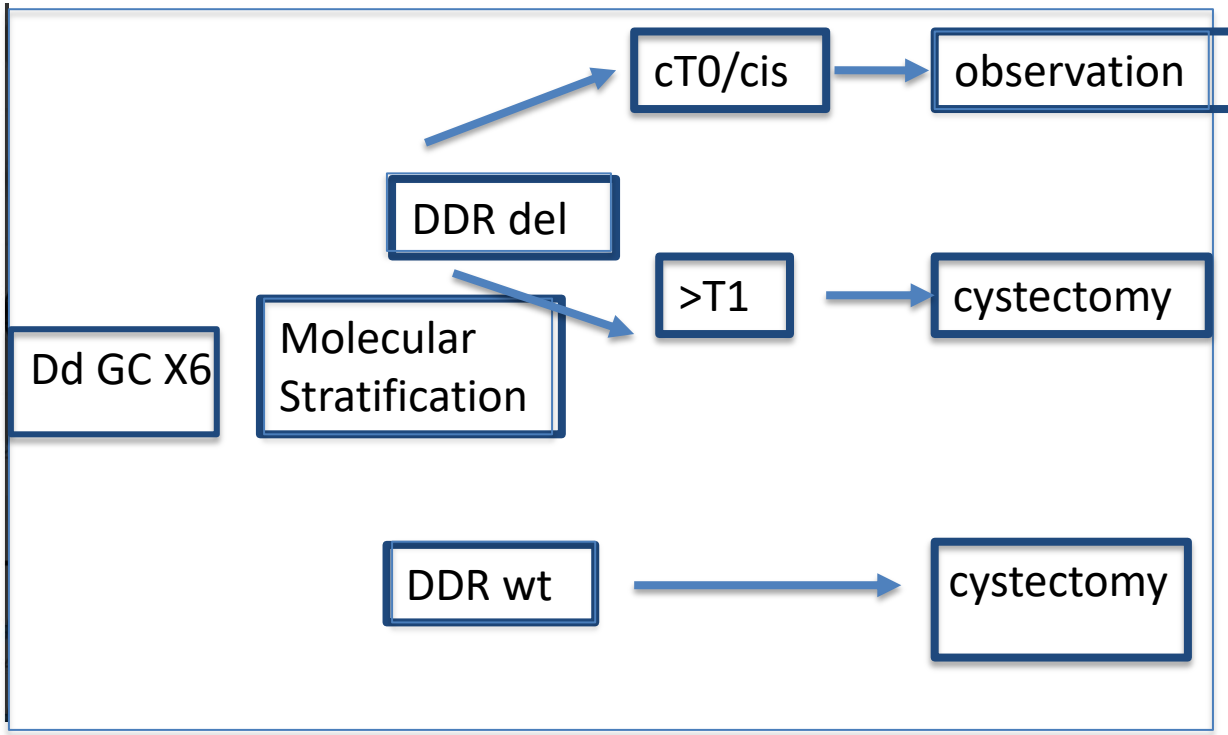
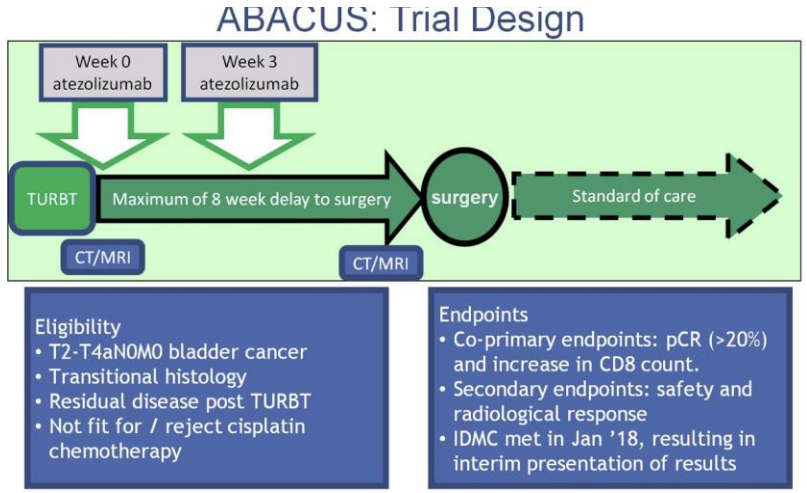
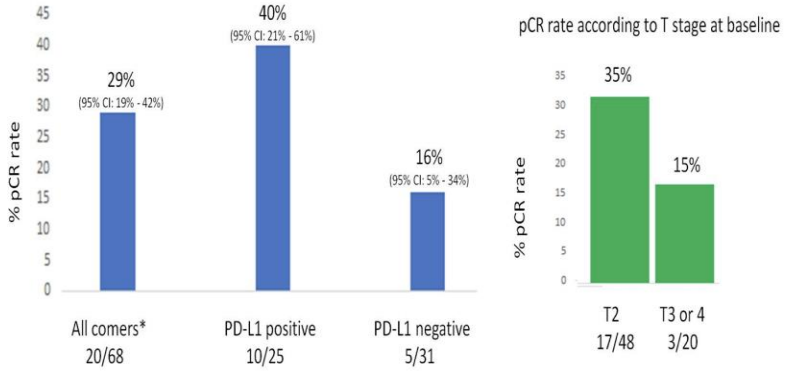


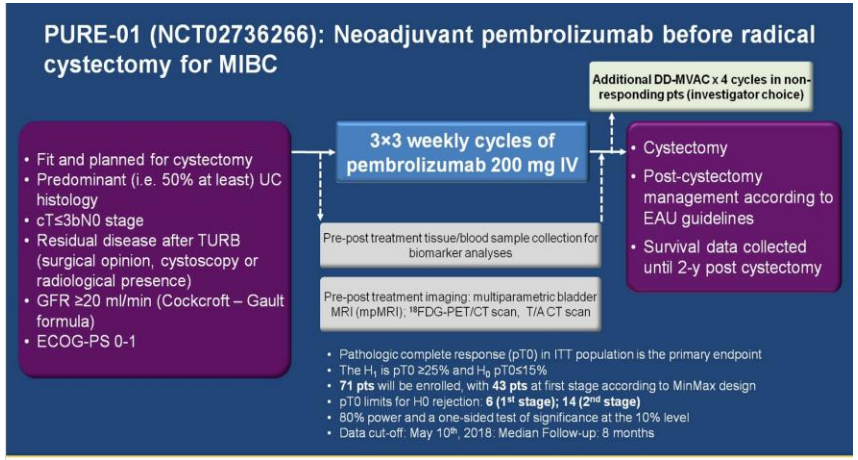
Neoadjuvant Check point inhibitors in UC

Cis Ineligible





Cis Eligible

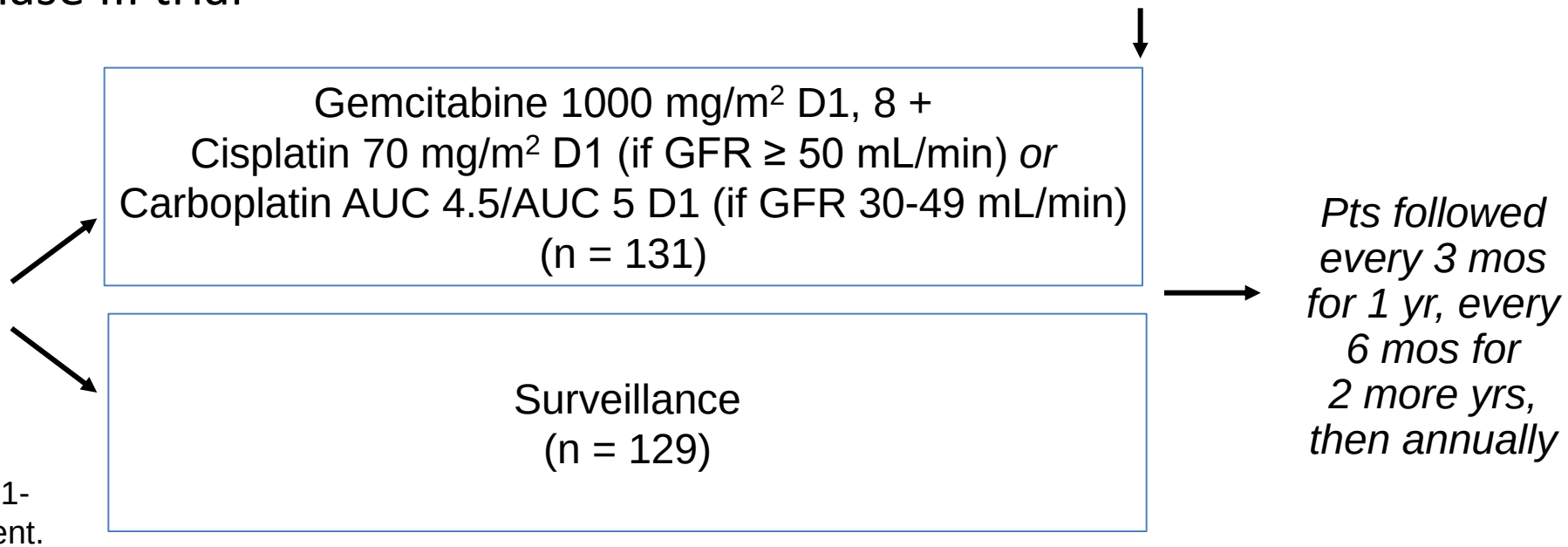


Pathologic response to pembrolizumab

	All treated patients N=43
Pathologic complete response, n (%), 95% CI	17 (39.5) 26.3–54.4
Secondary endpoint, n (%) Pathologic downstaging to pT<2	22 (51.2) (2 pTis; 2pTa; 1pT1)
Treatment failure, n (%)	
ypT2-4 ypN0	7 (16.3)
ypTany ypN+	9 (20.9)
"Clinical" failure (additional NAC*)	5 (11.6)
Clinical PD (RECIST v.1.1)	0 (-)

POUT: Perioperative Chemotherapy vs Surveillance in Upper Tract Urothelial Cancer

- Randomized phase III trial



*pT2-4, pN0, M0 or pTany, N1-3, M0. †n = 1 withdrew consent.

- Primary endpoint: DFS
- Secondary endpoints including: acute and late toxicity, metastasis-free survival, treatment compliance, feasibility of recruitment, OS

Birtle AJ, et al. ASCO GU 2018. Abstract 407.

POUT: Disease-Free Survival (Primary Endpoint)

- 2-yr DFS: 71% with chemotherapy vs 54% with surveillance
  - HR: 0.49 (95% CI: 0.31-0.76; *P* = .001)
  - HR adjusted for nodal involvement, microscopic margin status, planned chemotherapy type: 0.47 (95% CI: 0.30-0.74; *P* = .001)

Variable	n	Univariable HR	*P* Value
Overall	260	0.49 (0.31-0.76)	.001
Nodal involvement			
▪ N0	236	0.45 (0.28-0.73)	.001
▪ N+	24	0.85 (0.24-2.95)	.80
Planned chemotherapy			
▪ Gem-Cis	**166**	**0.40 (0.23-0.73)**	**.003**
▪ Gem-Carbo	**94**	**0.67 (0.33-1.38)**	**.28**
Microscopic margin status			
▪ Positive	31	0.56 (0.19-1.71)	.31
▪ Negative	229	0.44 (0.27-0.73)	.001

Birtle AJ, et al. ASCO GU 2018. Abstract 407.

POUT: Key Secondary Endpoints

- 2-yr metastasis-free survival: 74% with chemotherapy vs 60% with surveillance
  - HR: 0.49 (95% CI: 0.30-0.78; *P* = .002)
  - HR adjusted for nodal involvement, microscopic margin status, planned chemotherapy type: 0.47 (95% CI: 0.30-0.76; *P* = .002)
- OS data immature (HR: 0.55)
- 67.9% of pts in chemotherapy arm received maximum number of cycles (4) with 6 pts still undergoing treatment
  - 12.9% of pts who received cisplatin at start of treatment switched to carboplatin

Birtle AJ, et al. ASCO GU 2018. Abstract 407.

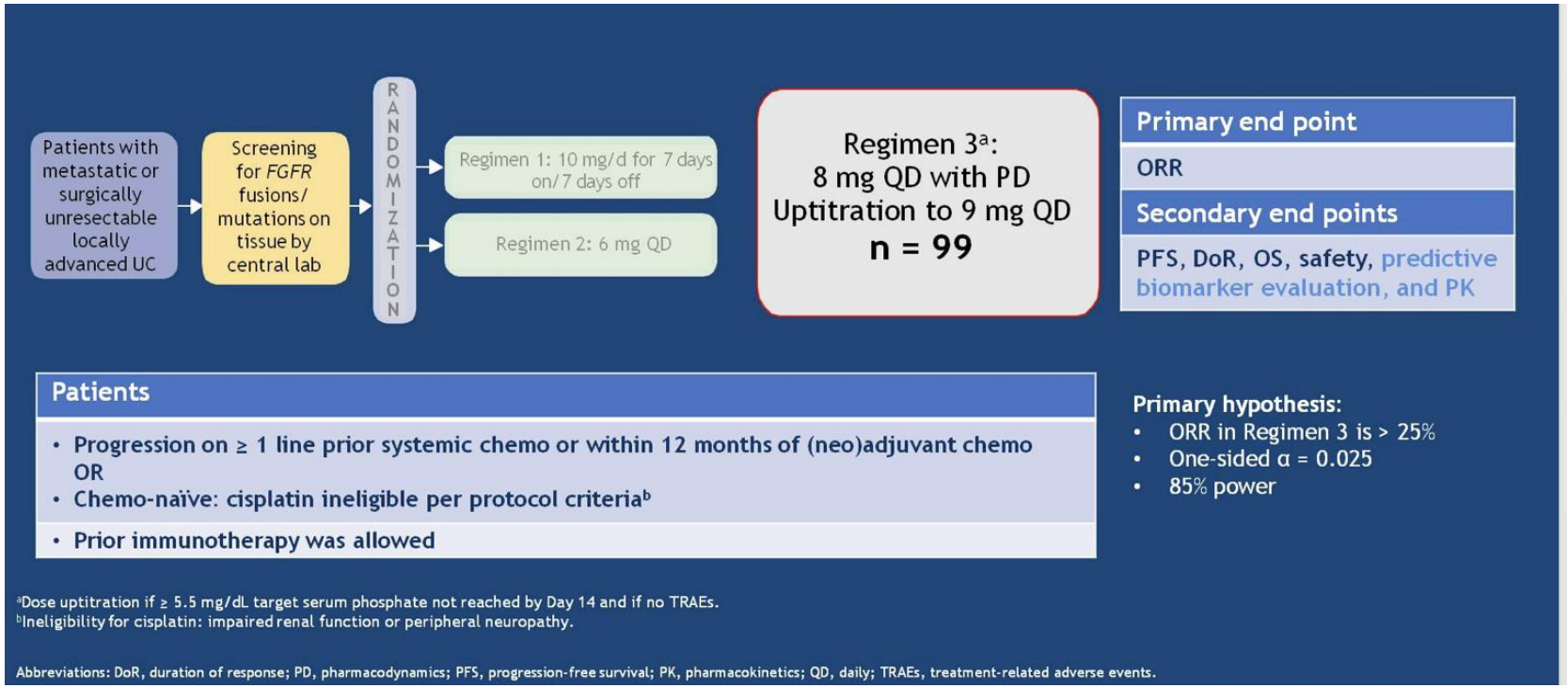
Outline

- Targeted therapy

Phase 2 study of Erdafitinib (ERDA; JNJ-42756493) in patients (pts) with metastatic or unresectable urothelial carcinoma (mUC) and *FGFR* alterations

FGFR alterations
mUC-15-20%
Upper tract- 30-40%
NMIBC-40-70%

Erdafitinib is a Pan FGFR inhibitor 1-4

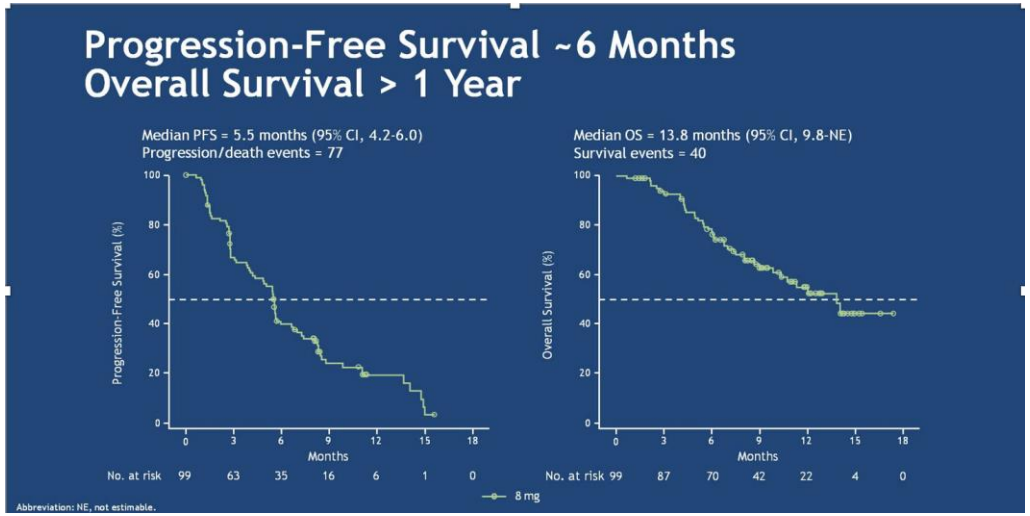


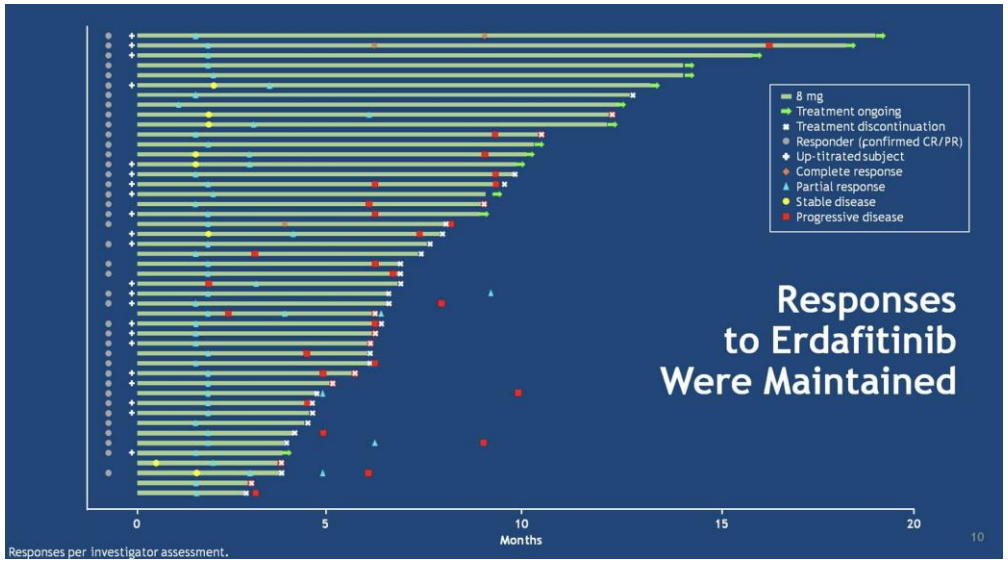
Patient Characteristics/Results

Patients, n (%)		8 mg continuous dose (n = 99)
Age, median years (range)		68 (36-87)
ECOG performance status	0	50 (51)
	1	42 (42)
	2	7 (7)
Pre-treatment	Progressed or relapsed after chemo	87 (88)
	Chemo-naïve	12 (12)
	Prior immunotherapy	22 (22)
Number of lines of prior treatment	0	11 (11)
	1	45 (46)
	2	29 (29)
	≥ 3	14 (14)
Visceral metastases	Present	78 (79)
	Absent	21 (21)
Hemoglobin Level	≥10	84 (85)
	<10	15 (15)
Tumor location	Upper tract	23 (23)
	Lower tract	76 (77)
Creatinine clearance rate	< 60 mL/min	52 (53)
	≥ 60 mL/min	47 (47)
FGFR alterations	*FGFR2* or *FGFR3* fusion	25 (25)
	FGFR3 mutation	74 (75)

		[95% CI]
Patients, n	99	
Response per investigator assessment[a,b], n (%)		
ORR	40 (40.4)	[30.7-50.1]
Complete response	3 (3.0)	
Partial response	37 (37.4)	
Stable disease	39 (39.4)	
Progressive disease	18 (18.2)	
Median time to response	1.4 months	
Median duration of response	5.6 months	[4.2-7.2]
ORR among patient subgroups, n (%)		
Chemo-naïve vs progressed/relapsed after chemo	5/12 (41.7) vs 35/87 (40.2)	
With vs without visceral metastases	30/78 (38.5) vs 10/21 (47.6)	

[a]Confirmed with second scan at least 6 weeks following the initial observation of response.



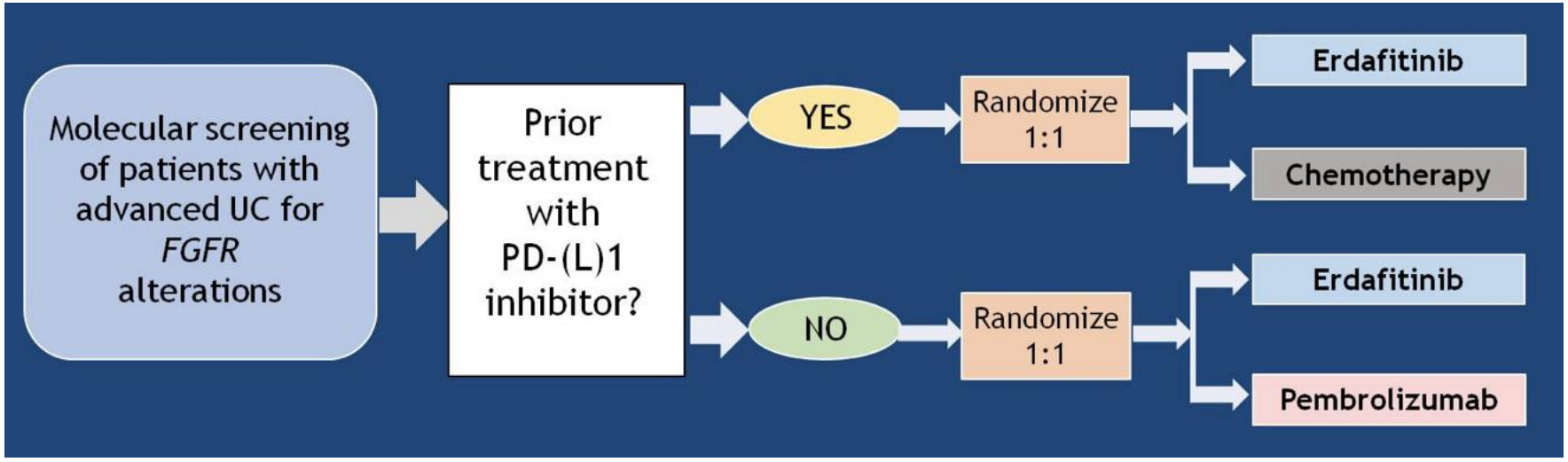


Adverse Events/Future Directions

Reported in >20% of patients	8 mg continuous dose (n = 99)	
Patients with TRAEs, n (%)	Any grade	Grade 3
Hyperphosphatemia	72 (73)	2 (2)
Stomatitis	54 (55)	9 (9)
Dry mouth	43 (43)	0
Diarrhea	37 (37)	4 (4)
Dysgeusia	35 (35)	1 (1)
Dry skin	32 (32)	0
Alopecia	27 (27)	0
Decreased appetite	25 (25)	0
Hand-foot syndrome	22 (22)	5 (5)
Fatigue	21 (21)	2 (2)

	8 mg continuous dose (n = 99)	
Patients with AEs, n (%)	Any grade	Grade ≥ 3
Hyperphosphatemia	72 (73)	2 (2)
Skin events	48 (49)	6 (6)
Dry skin	32 (32)	0 (0)
Hand-foot syndrome	22 (22)	5 (5)
Nail events	51 (52)	14 (14)
Onycholysis	16 (16)	2 (2)
Paronychia	14 (14)	3 (3)
Nail Dystrophy	16 (16)	6 (6)
Central serous retinopathy (CSR)	21 (21)	3 (3)
Non-CSR ocular events[a]	51 (52)	5 (5)

[a]Most common non-CSR ocular events included dry eye (19%), blurry vision (16%), increased lacrimation (11%), and conjunctivitis (9%).



Enfortumab vedotin phase 1 (EV-101) study in patients with metastatic urothelial cancer (mUC).

Enfortumab vedotin is an investigational agent, and its safety and efficacy

EV-101: Demographics and Disease Characteristics

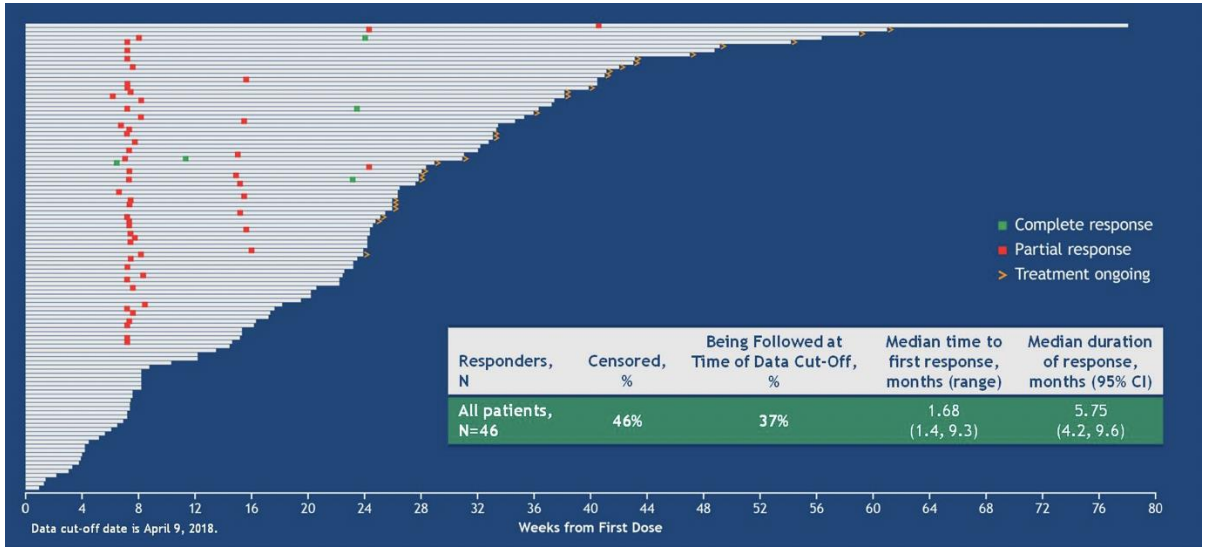
	Patients With mUC 1.25 mg/kg (N=112)
Median age, years (range)	67 (24-86)
Male	73%
Race	
Caucasian	92%
Asian	5%
Other	3%
ECOG score	
0	32%
1	68%
Hemoglobin levels <10 g/dL	21%
GFR <60 mL/min	50%

	Patients With mUC 1.25 mg/kg (N=112)
Primary tumor site bladder	77%
Site of metastases at baseline	
Liver	29%
Lung	48%
Lymph node only	19%
≥2 prior therapies in the metastatic setting	63%
Prior therapy	
Prior platinum-based therapy	94%
Prior taxane treatment	29%
Prior CPI treatment	79%
CPI was most recent therapy	58%

Data cut-off date is April 9, 2018.

	Patients With mUC 1.25 mg/kg (N=112)	
	All Grades	Grade ≥3
Fatigue	54%	1%
Alopecia	45%	0
Decreased appetite	40%	1%
Dysgeusia	38%	0
Nausea	36%	1%
Pruritus	35%	1%
Peripheral neuropathy	35%	0
Diarrhea	32%	1%
Maculo-papular rash	25%	3%

Adverse events listed are individual preferred terms.



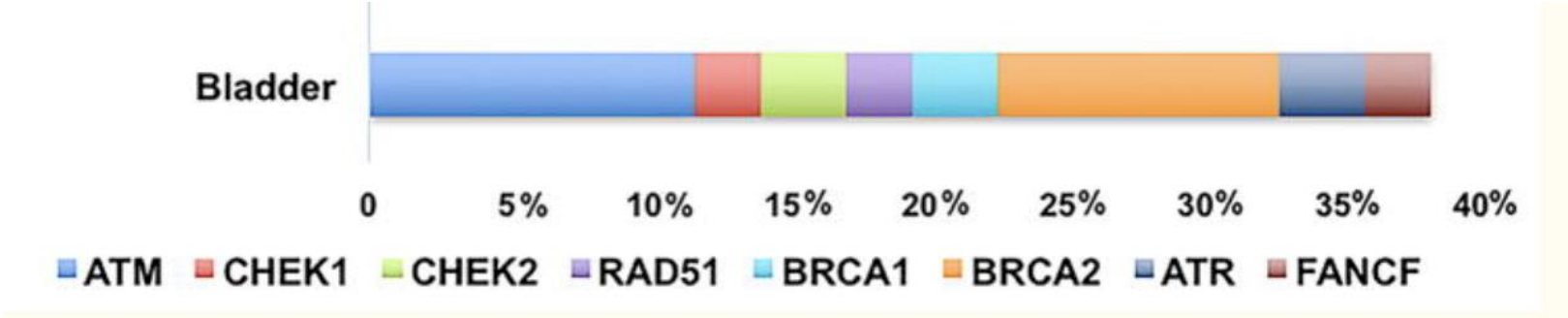
	Prior CPI Treatment[a]	CPI-Naive[a]	Liver Metastases[a]
	1.25 mg/kg (n=89)	1.25 mg/kg (n=23)	1.25 mg/kg (n=33)
Confirmed complete response	3%	9%	0
Confirmed partial response	37%	35%	39%
Confirmed ORR[b] (95% CI)	40% (30.2, 51.4)	43% (23.2, 65.5)	39% (22.9, 57.9)
Stable disease	34%	17%	21%
DCR[b] (95% CI)	74% (63.8, 82.9)	61% (38.5, 80.3)	61% (42.1, 77.1)

Abbreviations: CPI, checkpoint inhibitor; DCR, disease control rate (DCR=CR+PR+SD); ORR, overall response rate (ORR=CR+PR).
Data rounded to the nearest whole percent.
[a]Evaluable patients must have at least one post-baseline assessment or discontinued treatment without any disease assessment; responses assessed per RECIST 1.1.
[b]Data presented as % (95% CI); 95% CI based on the Clopper-Pearson method.

Population	Median OS, Months (95% CI)
All patients	13.6 (11.0, 15.4)
Patients with prior CPI	14.0 (11.0, 16.1)
Estimated Overall Survival Rates	
OS rate at 6 months, %	
All patients	74.4
Patients with prior CPI	75.6
OS rate at 12 months, %	
All patients	56.3
Patients with prior CPI	54.2

Data cut-off date is April 9, 2018.

PARP inhibitors



Rucaparib	ATLAS	Non enriched	NCT03397394
Olaparib		Enriched	NCT03375302
Olaparib+Durvalumab	BISCAY	Cis- Eligible	NCT0254661
Olaparib +Durvalumab	BAYOU	Cis-ineligible	NCT02516241

Rimar Cancer 2017

Outline

- Immunotherapy

CPI in Cisplatin Refractory Disease

Drug	Target	N	ORR (%)	CR (%)	PFS (mos)	OS (mos)	1yr Sur (%)	FDA approval
Atezolizumab	PDL1	310	**15**	6	2.1	7.9	36	Accelerated 2016
Pembrolizumab	PD1	27	**26**	11	2	13	50	2017
Nivolumab	PD1	265	**20**		2	8.7		Accelerated 2017
Durvalumab	PDL1	191	**18**	4		18.2		Break through2017
Avelumab	PDL1	161	**17**	6	3	13.7	51	Accelerated 2017

Summary- All CPI inhibitors active in Post platinum disease; ORR-15-26%; Small fraction with CR; Pembrolizumab demonstrating superiority to chemotherapy

Rosenberg JE, et al. Lancet. 2016;387:1909-1920.Sharma P, et al. Lancet Oncol. 2017;18:312-322; Apolo AB, et al. J Clin Oncol. 2017;35:2117-2124. ;Powles T, et al. JAMA Oncol. 2017;3:e172411.

CPI in cis ineligible Patients

- Best Chemotherapy Regimen: Carboplatin/Gemcitabine
  - ORR- 36%; PFS-5.8 mos; OS-9.3 mos

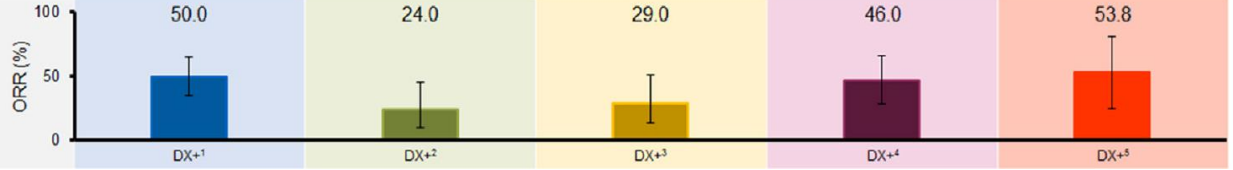
Drug	N	ORR (%)	CR (%)	PFS	OS
Atezolizumb ImVigor 210	119	24	7	2.7	**14.8**
Pembrolizumab KN 052	370	29	7		**6 mos OS- 67%**

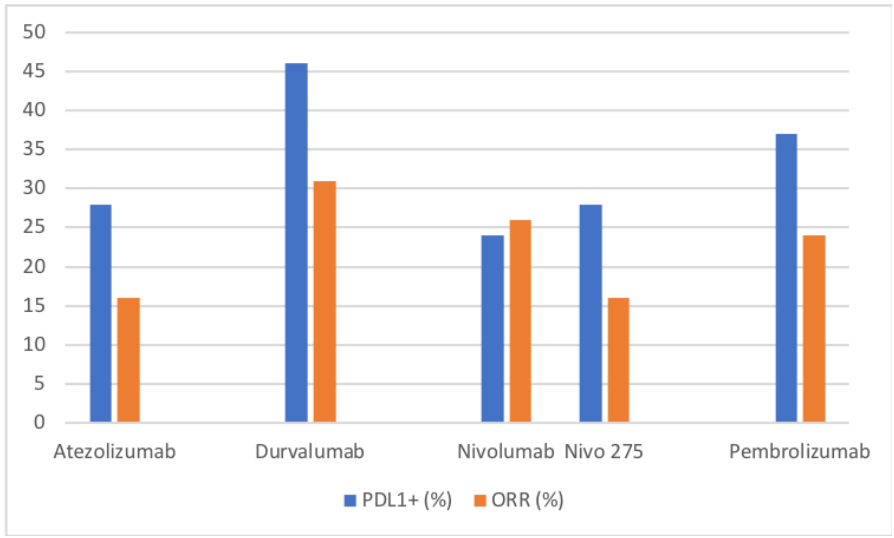
- Performance status ≥ 2
- Hearing loss grade ≥ 2
- Peripheral neuropathy grade ≥ 2
- NYHA Class III
- CrCl < 60 mL/min

Bellmunt Ann 2017 ; Balar Lancet 2017

PDL 1 as a biomarker

	Atezolizumab[1]	Nivolumab[2]	Pembrolizumab[3]	Durvalumab[4]	Avelumab[5]
Detection antibody	SP142	28-8	22C3	SP263	73-10
IHC platform	Ventana	Dako	Dako	Ventana	Dako
Cell types scored for urothelial cancer	IC and TC	TC	TC	IC and TC	IC and TC
Cut-off definitions for urothelial cancer	PD-L1+ (IHC 2/3) as ≥5% of ICs PD-L1+	PD-L1+ ≥1% TC expression	PD-L1+ ≥1% TC staining	PD-L1+ as ≥25% of ICs and TCs with membrane PD-L1 staining	PD-L1+ as ≥5% TC staining or ≥10% IC staining
Estimated PD-L1 prevalence in urothelial cancer trials	~32[1]	~37[2]	~62%[3]	~65%[4]	~36%[5]
PD-L1+ ORR (phase I trials)	50.0	24.0	29.0	46.0	53.8



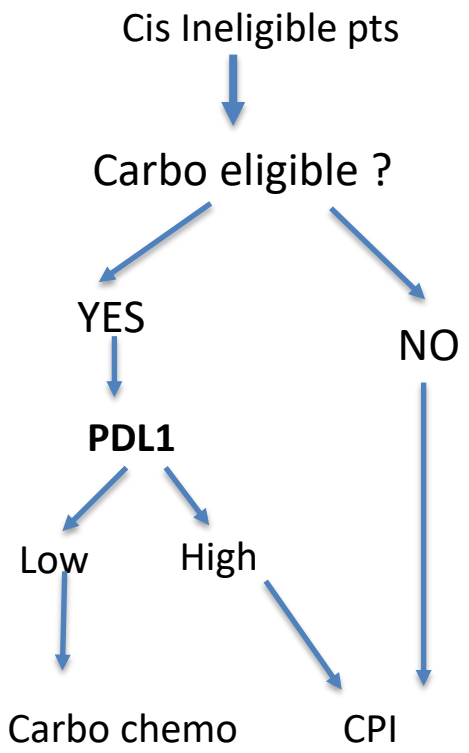


Issues with PDL1
Multiple assays
Primary vs met
Timing of testing
Patients with negative tests achieve CR
Cut off for positivity
Test on TC vs IC

FDA alert May 18, 2018- Label Change- Atezolizumab/Pembrolizumab

"FDA issued an alert that preliminary data analysis shows a decrease in **survival** for bladder cancer patients with low PDL1 receiving mono- immunotherapy with pembrolizumab in KN 361or atezolizumab in Imvigor 130 versus chemotherapy as first-line therapy",

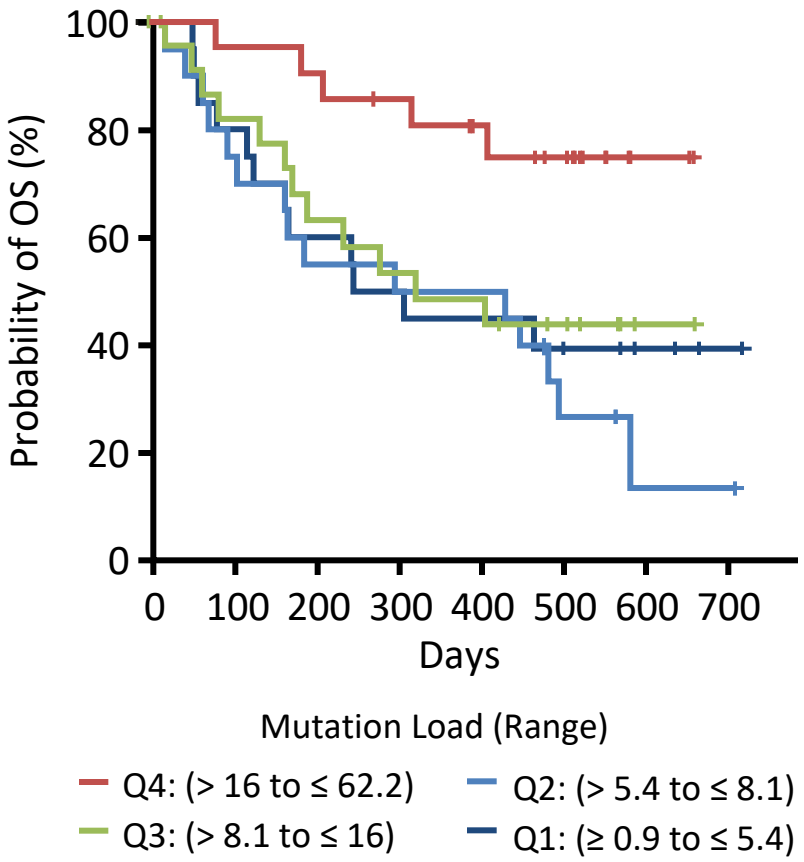
Cis eligible patients: **CISPLATIN**



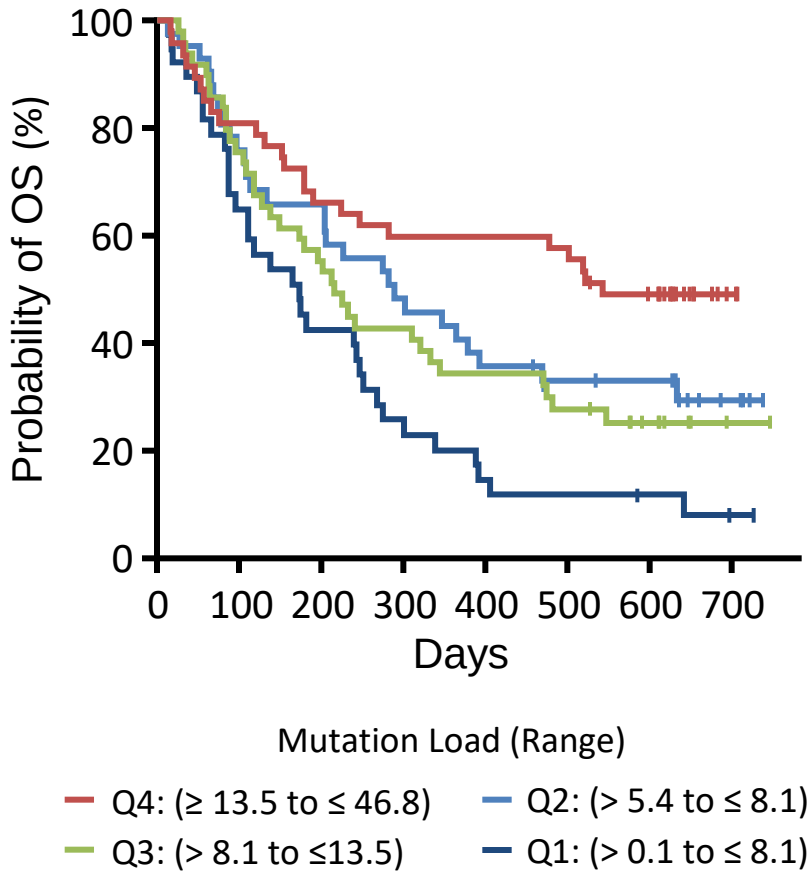
Trial	N	Opened Est. Complete	End Point
▪ Atezolizumab [2] ▪ Atezolizumab + cisplatin or carboplatin/gemcitabine ▪ Cisplatin or carboplatin/gemcitabine	1200	June 2016 July 2020	PFS/OS/AE
▪ Pembrolizumab [3] ▪ Pembrolizumab + cisplatin or carboplatin/gemcitabine ▪ Cisplatin or carboplatin/gemcitabine	990	September 2016 May 2020	PFS/OS

Mutation Load and Survival With Immunotherapy

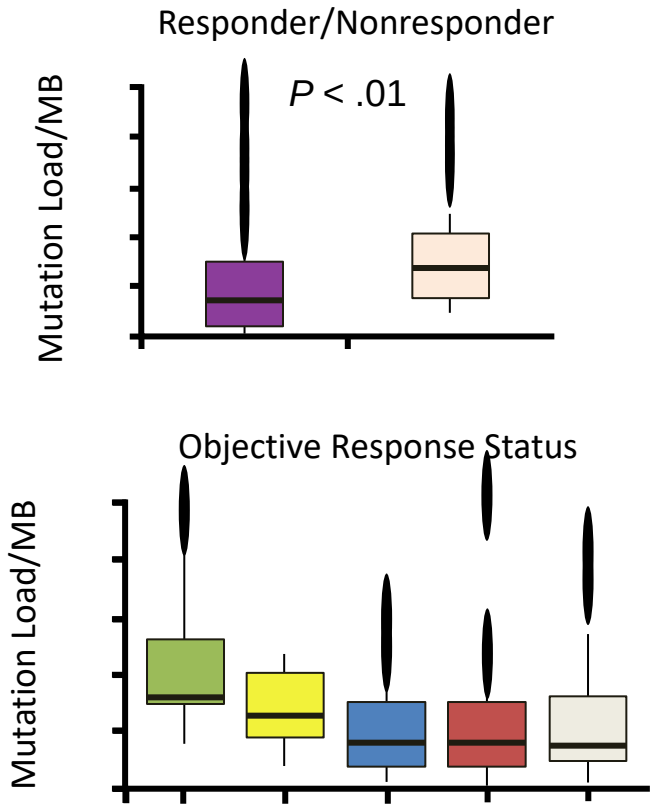
IMvigor210 Cohort 1[1]



IMvigor210 Cohort 2[2]

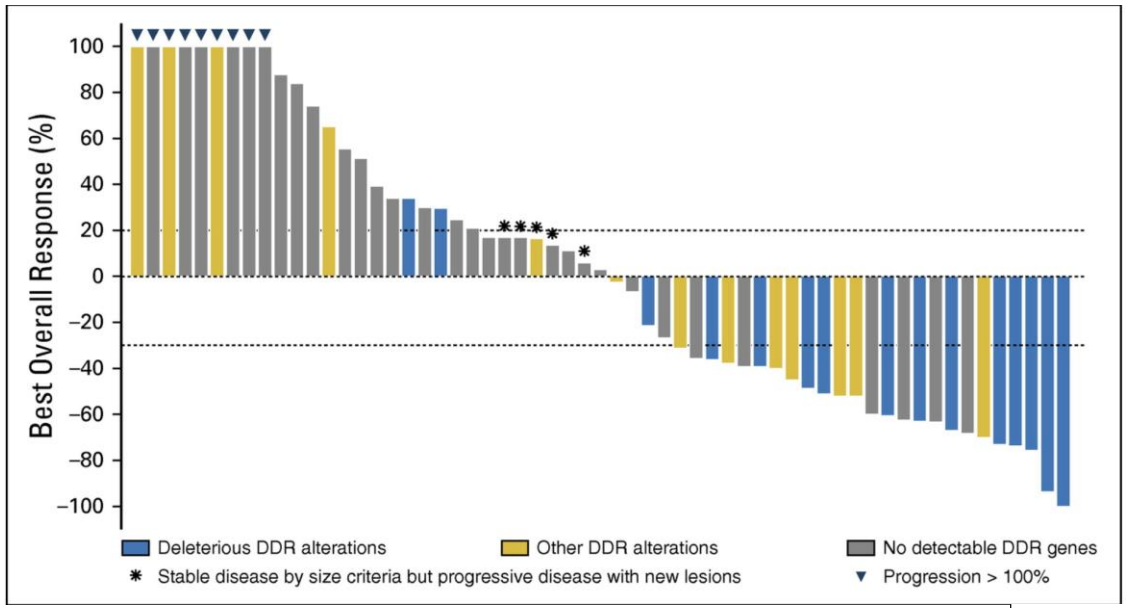


Responses by Mutation Load[2]

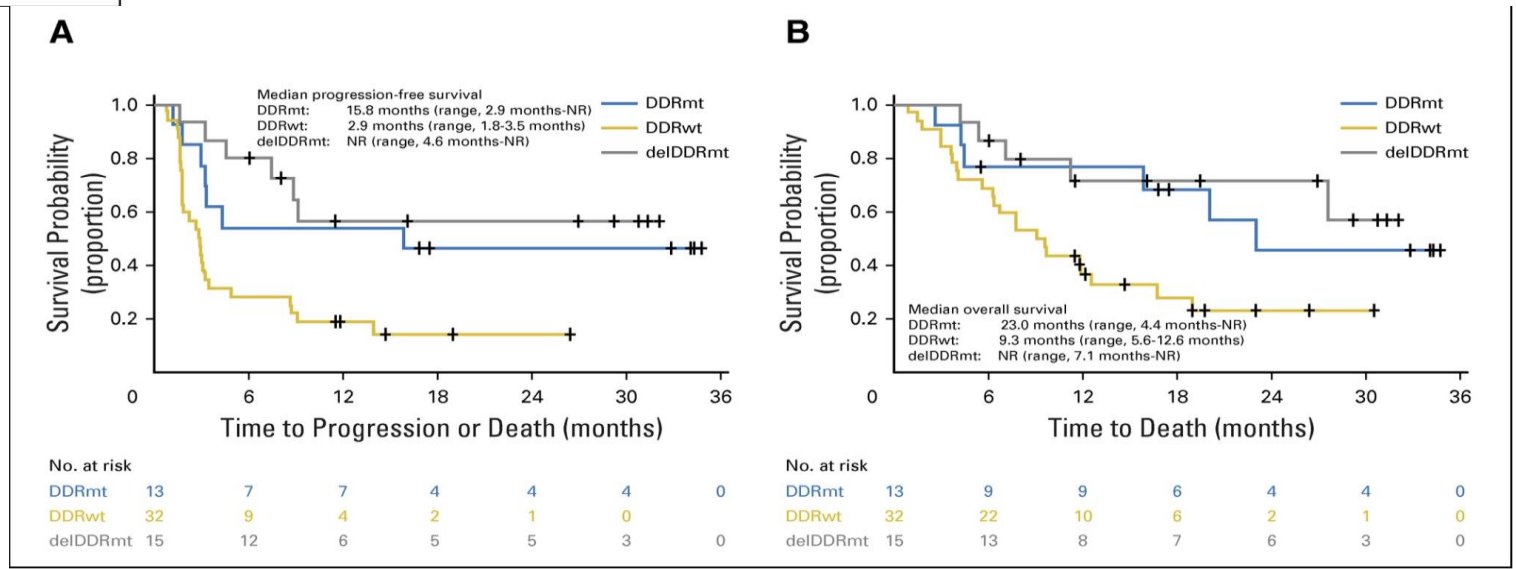


1. Balar AV, et al. Lancet. 2017;389:67-76. 2. Loriot Y, et al. ESMO 2016. Abstract 783P.

Deletrious DDR Alterations and Response to CPI



N=60	(%)	ORR (%)	PFS (mos)	OS (mos)
Any DDR	47	68 vs 18	15.8 vs 2.9	23 vs 9.3
Likely deleterious	25	80 vs 19	NR	NR



Teo JCO 2018;

Adjuvant Therapy : Clinical Trials With CPI

Trial Name	Treatments	# patients	Population	Primary Endpoint
IMvigor0101[1]	Atezolizumab vs observation	800	With neoadjuvant: ypT2−4a or ypN+ (ypT2-4 or ypN+ for UTUC) Without neoadjuvant: pT3−T4a or pN+ (pT3-4 or pN+ for UTUC)	DFS
CheckMate 274[2]	Nivolumab vs placebo	640	With neoadjuvant: ypT2-pT4a or ypN+ Without neoadjuvant: ypT3-pT4a or ypN+	DFS
AMBASSADOR[3]	Pembrolizumab vs observation	739	With neoadjuvant: ≥ pT2 and/or N+ Without neoadjuvant: ≥ pT3 or pN+	DFS, OS

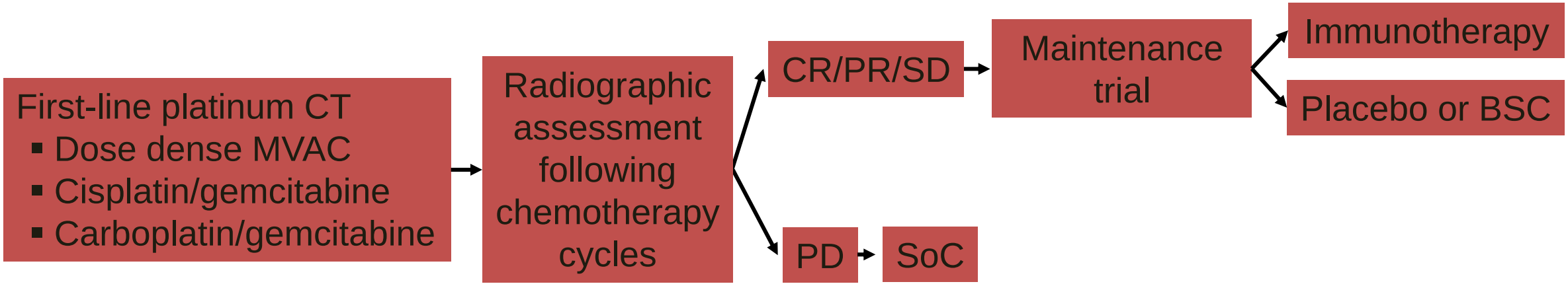
1. NCT02450331. 2. NCT02632409. 3.NCT03244384.

First-line Combination Trials in Platinum-Eligible/Ineligible Pts

Trial	N	Opened Est. Complete	End Point
▪ Durvalumab (MEDI4736) [1] ▪ Durvalumab/tremelimumab ▪ Cisplatin or carboplatin/gemcitabine	1200	November 2015 September 2019	OS
▪ Atezolizumab [2] ▪ Atezolizumab + cisplatin or carboplatin/gemcitabine ▪ Cisplatin or carboplatin/gemcitabine	1200	June 2016 July 2020	PFS/OS/AE
▪ Pembrolizumab [3] ▪ Pembrolizumab + cisplatin or carboplatin/gemcitabine ▪ Cisplatin or carboplatin/gemcitabine	990	September 2016 May 2020	PFS/OS
▪ Ipilimumab + nivolumab [4] ▪ Nivolumab + cisplatin/gemcitabine* ▪ Cisplatin or carboplatin/gemcitabine†	897	March 2017 December 2022	PFS/OS

1.NCT02516241;2. NCT02807636; 3.NCT02853305; 4.NCT03036098

Maintenance Immunotherapy Following First-line Platinum-Based CT



Trial	N	Chemotherapy Duration	Primary Endpoint	Estimated Completion
Phase II NCT02500121[1] ▪ Pembrolizumab vs ▪ Placebo (up to 24 mos)	200	Up to 8 cycles	6-mo PFS	November 2019
Phase III JAVELIN Bladder 100[2] ▪ Avelumab vs ▪ BSC	668	4-6 cycles	OS	July 2019

1. ClinicalTrials.gov. NCT02500121. 2. ClinicalTrials.gov. NCT02603432.

Challenges

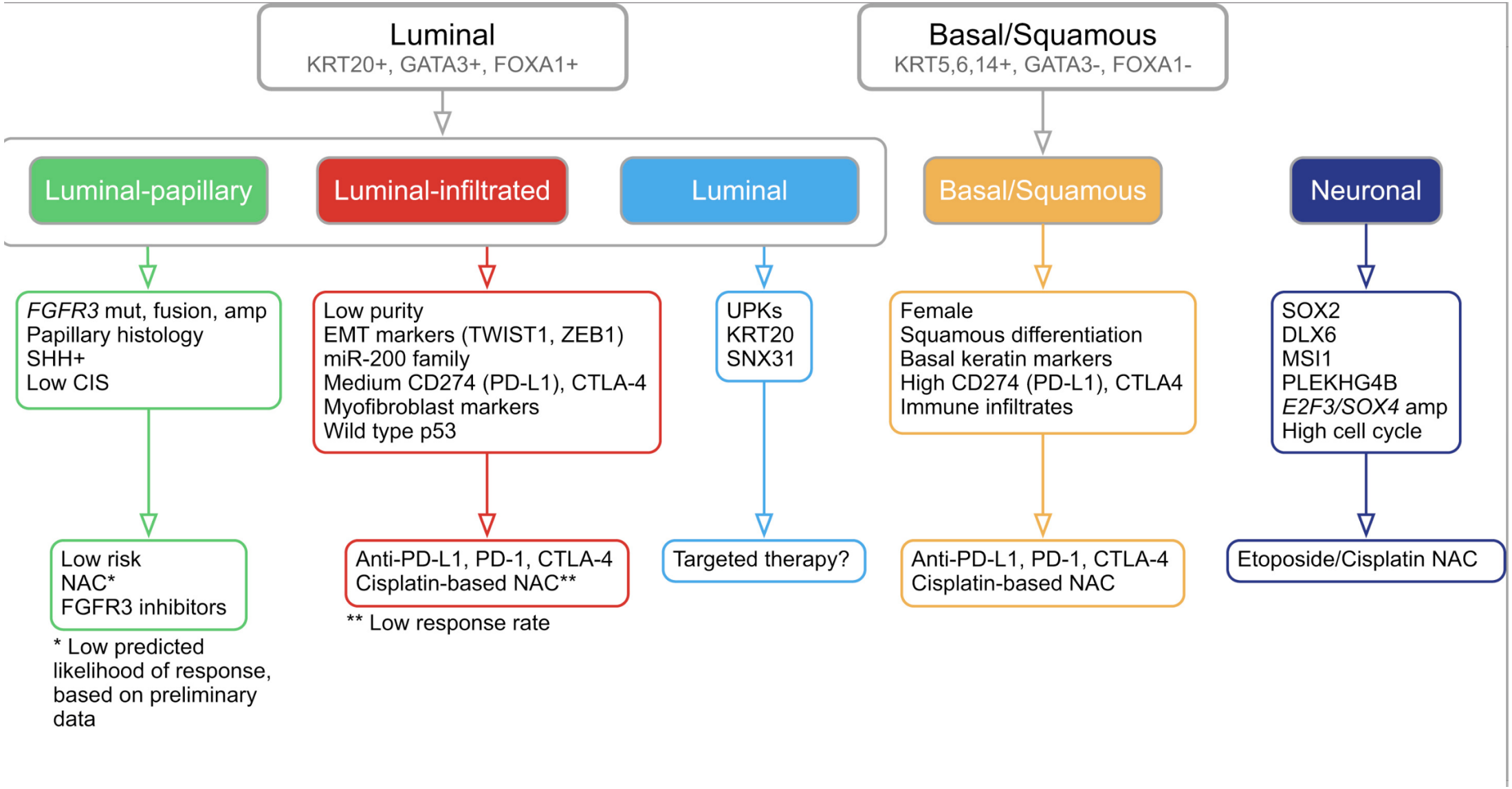
- No predictive biomarker
- Low responses
- Unclear duration of therapy in responders
- Best setting to use-
  - First line chemo? Adjuvant? Neoadjuvant?
- Will sequence of therapy matter
- Is re-treatment an option?
- Post CPI – unmet need?
- Combination

Looking Forward

	CISPLATIN ELIGIBLE		CISPLATIN INELIGIBLE	
	NOW	FUTURE	NOW	FUTURE
FIRST LINE	CIS/GEM DD MVAC	IO +IO IO+ CHEMO	Atezo/Pembro Carbo/Gem	IO +Novel agent
SECOND LINE	IO	IO+ NOVEL AGENT	Carbo/gem IO	IO +Novel agent
NEOADJUVANT	CIS/GEM DD MVAC	IO+IO IO + CIS/GEM IO+ DD MVAC	NONE	IO +Novel agent
ADJUVANT	NONE	IO IO+IO	NONE	IO +Novel agent

Novel agents: TKI- FGFRI; VEGFRI; PARPI, immuno-drug conjugate

Molecular Classification- pick therapies



Roberston Cell 2017

Systemic Treatments in UC-2018

NMIBC	Neo adjuvant	First Line	Second Line	Third Line ???
BCG				
	DD MVAC Cis-Gem			
		Cis eligible: MVAC DD MVAC Cis/gem		
		Cis-ineligible Carbo/gem PDL1 high: atezo/pembro		
			Atezolizumab Pembrolizumab Nivolumab Durvalumab Avelumab	
				FGFR Immune Drug-conj PARPI TKI's

Thank You

@sandysrimd