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How I Treat Metastatic Urothelial Cancer when IO Therapy Fails

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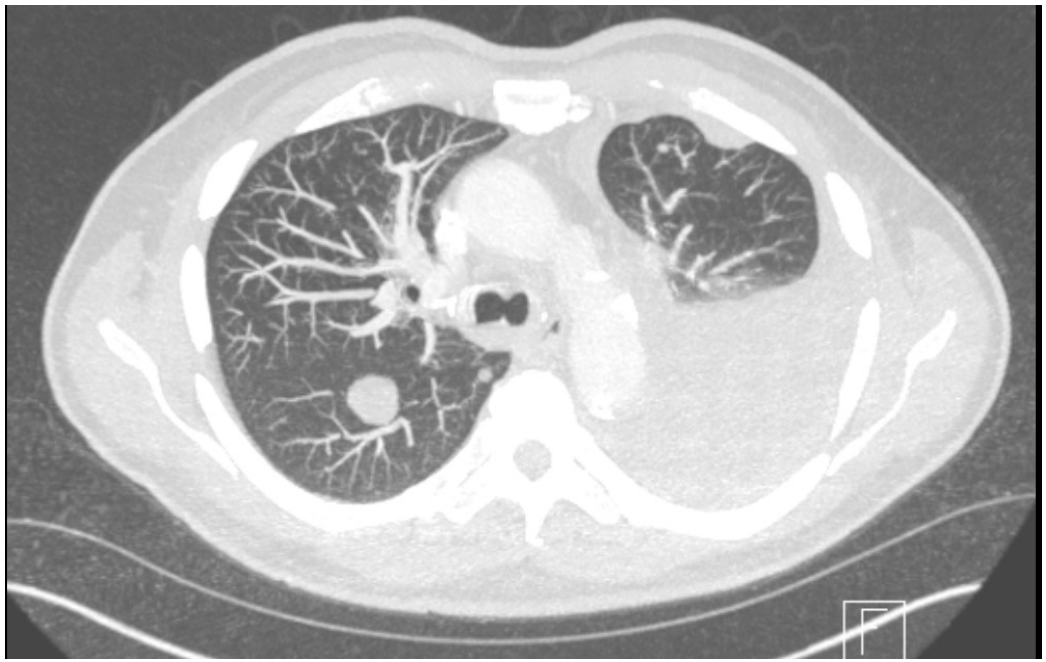
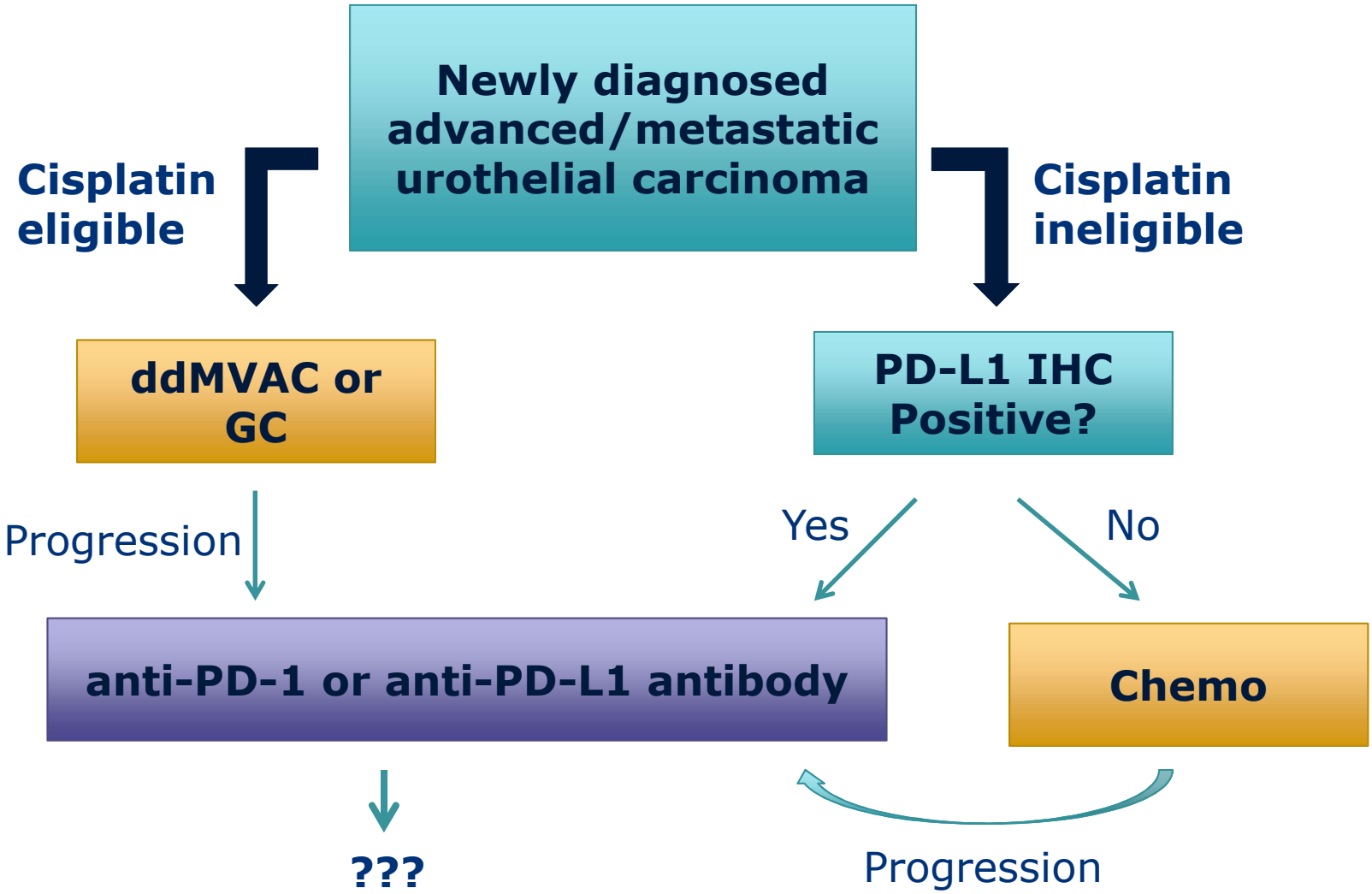
A Challenging (but familiar) case

- 78 year old previously healthy man diagnosed with muscle-invasive bladder cancer
- After 3 cycles of neoadjuvant ddMVAC, patient found to have biopsy-proven lung metastases
- PD-L1 IHC $\geq$ 70%
- After 3 cycles of pembrolizumab, SD
- After 6 cycles of pembrolizumab



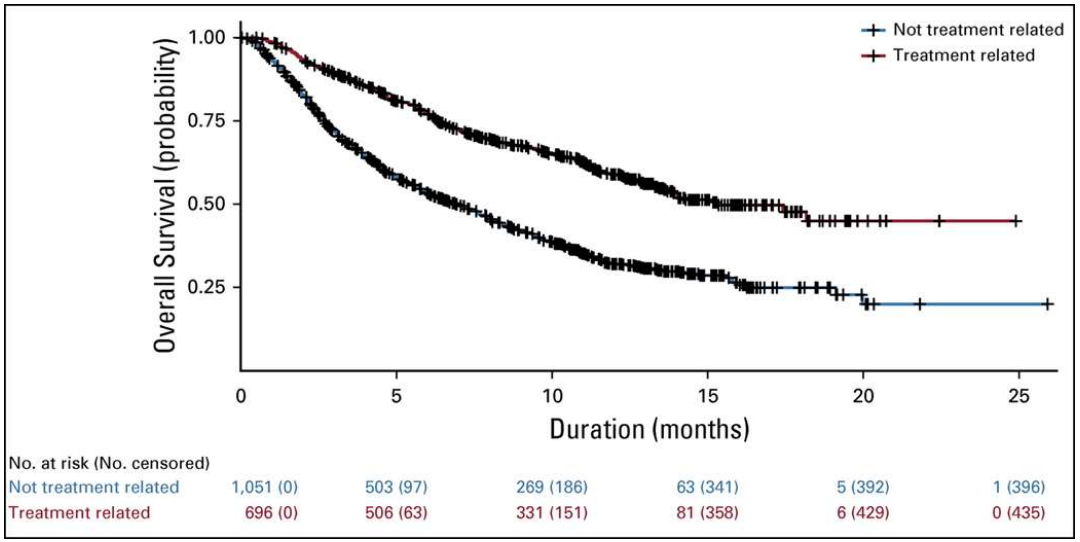
First- How Did We Get to Failure?



Why did we fail?

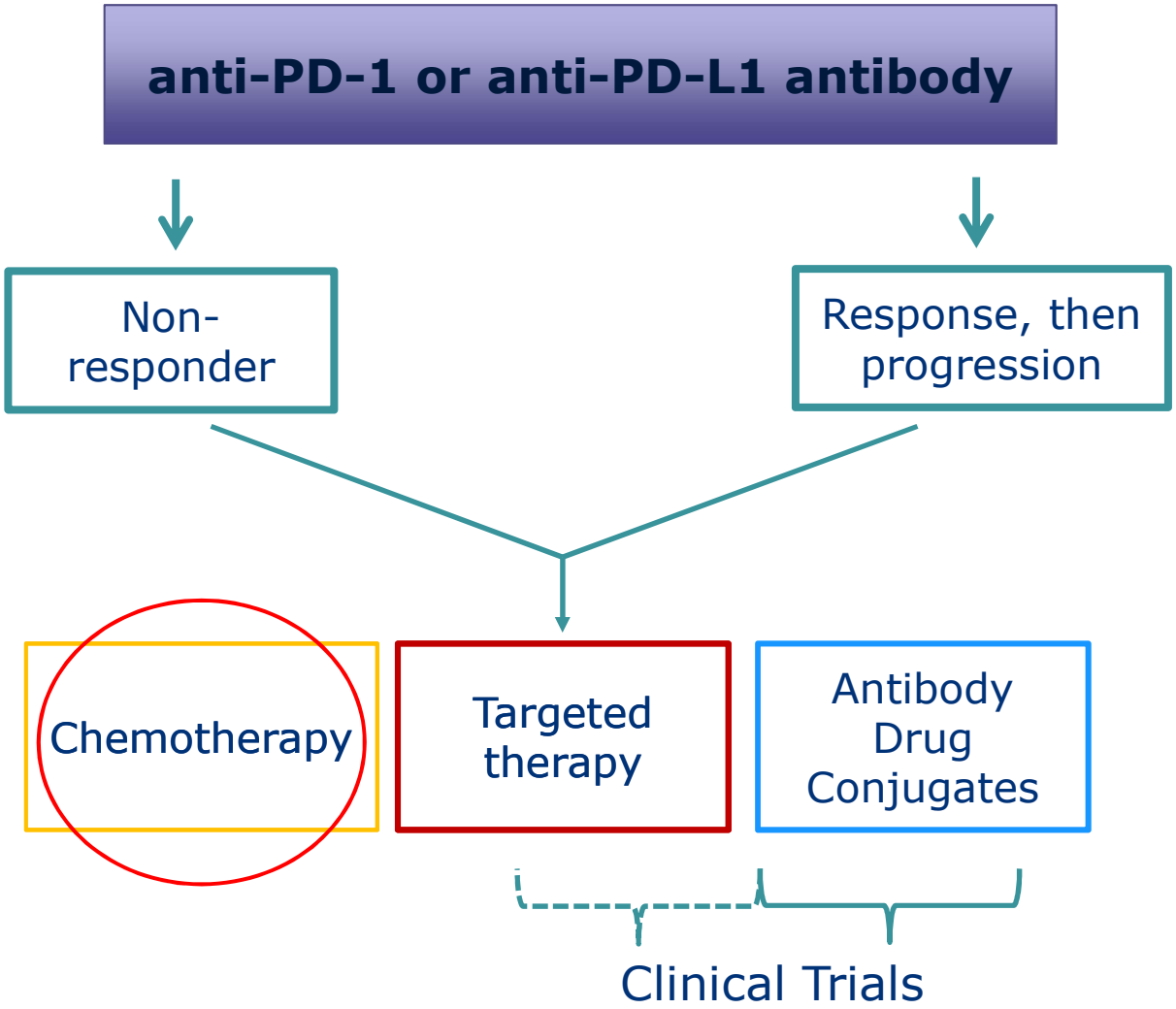
anti-PD-1 or anti-PD-L1 antibody

- Non-responder
- Treatment-related AE
- Response, then progression



VE Maher et al, J Clin Oncol 2019

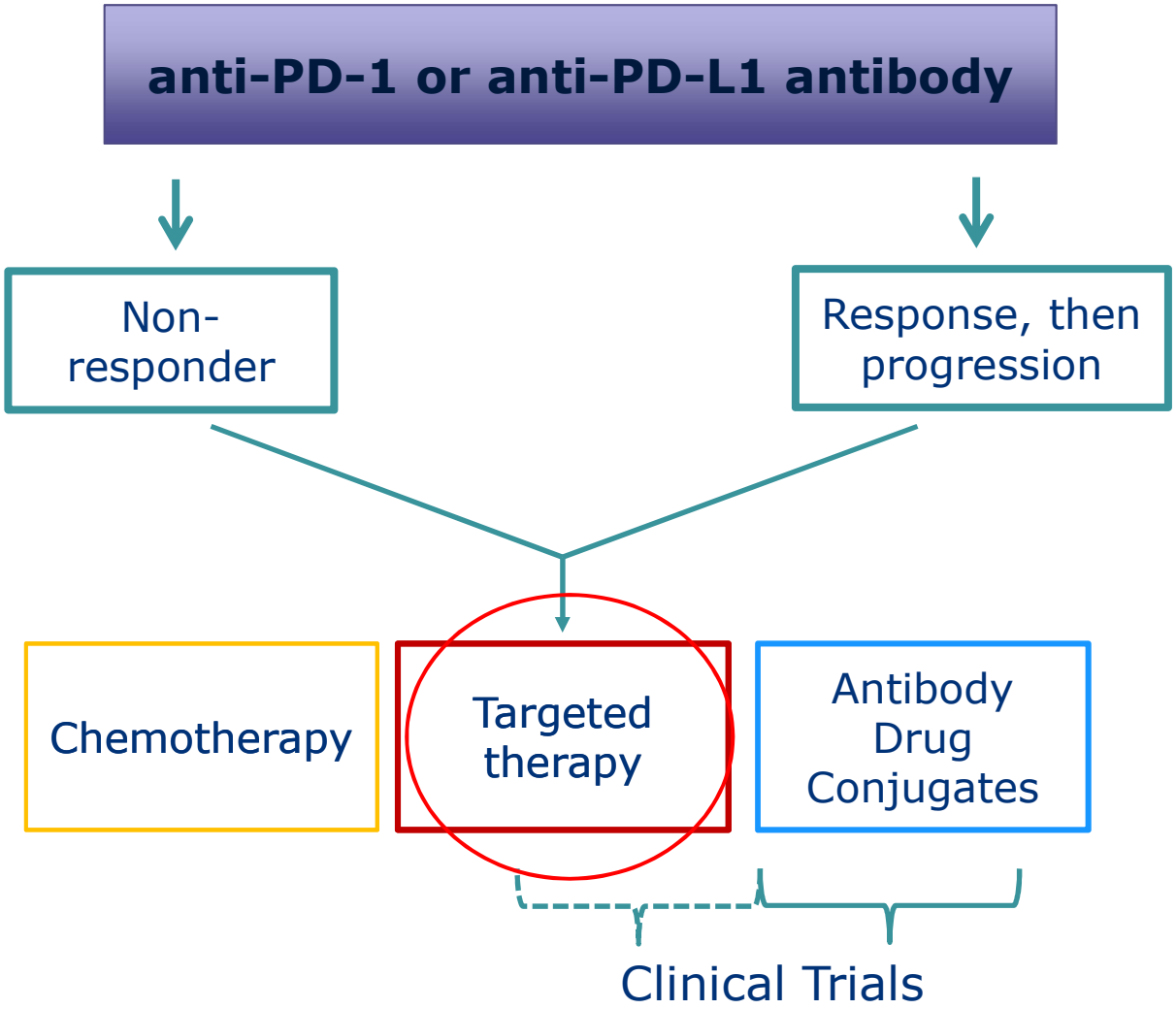
Options once Treatment is Indicated



Chemotherapy options

		Response Rate	Median OS
Platinum naive	MVAC with carboplatin	56%	10 months
	Gemicitabine + carboplatin	41%	9 months
	Gemcitabine + taxane	~50%	13-15 months
	Docetaxel	13-33%	9 months
	Docetaxel + Ramicurumab	24.5%	9.4 months
	Nab-paclitaxel	28%	--
	Pemetrexed	8-28%	9 months

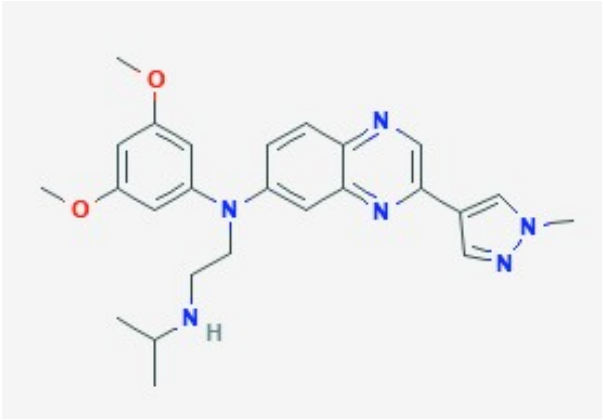
Options once Treatment is Indicated



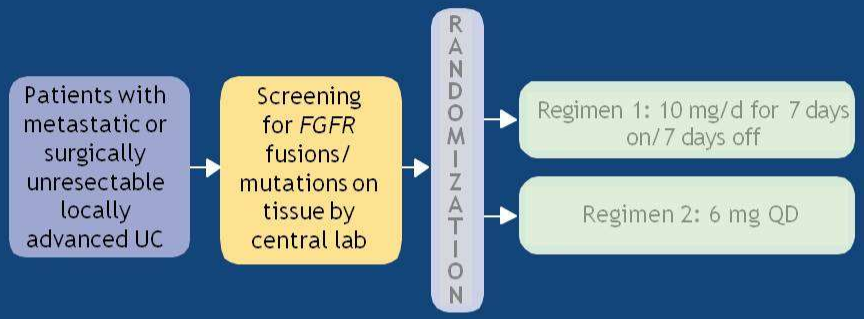
Targeted therapy- FGFR

Cancer Type	Frequency of FGFR alterations
Metastatic UC	15-20%
Upper Tract UC (FGFR3)	37%
NMIBC	40-70%

- **Erdafitinib** is an oral pan-FGFR (1-4) inhibitor



Phase 2 BLC2001 Study Design



Regimen 3[a]:
8 mg QD with PD
Uptitration to 9 mg QD
n = 99

Primary end point
ORR
Secondary end points
PFS, DoR, OS, safety, predictive biomarker evaluation, and PK

Patients
• Progression on ≥ 1 line prior systemic chemo or within 12 months of (neo)adjuvant chemo OR
• Chemo-naïve: cisplatin ineligible per protocol criteria[b] ← **53% GFR <60 mL/min**
• Prior immunotherapy was allowed ← **22%**

Primary hypothesis:
- ORR in Regimen 3 is > 25%
- One-sided α = 0.025
- 85% power

[a]Dose uptitration if ≥ 5.5 mg/dL target serum phosphate not reached by Day 14 and if no TRAEs.
[b]Ineligibility for cisplatin: impaired renal function or peripheral neuropathy.

Abbreviations: DoR, duration of response; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; QD, daily; TRAEs, treatment-related adverse events.

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Antitumor Activity

Study has met the primary objective

		[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.
[b]Response in 2 patients was unknown.

21.2% of patients remain on study treatment after 11 months of follow-up

- Of those treated with IO, 5% had response to IO
- Of those with prior IO, ORR was 59%

TRAEs of Clinical Importance or Special Interest

	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%).

- Majority of events were grade 1/2
- Few patients (n = 7) discontinued because of AEs of special interest
- All AEs of special interest were managed with supportive therapies, dose interruption, and/or modification
- CSR is a known class effect of inhibitors of the MAPK pathway[1,2]
- Patients were routinely monitored
- CSR rarely led to discontinuation (n = 3), and no patient had retinal vein or artery occlusion

Abbreviation: MAPK, mitogen activated protein kinase.

1. Renouf DJ, et al. *J Clin Oncol*. 2012;30:3277-3286
2. Stjepanovic N, et al. *Ann Oncol*. 2016;27:998-1005.

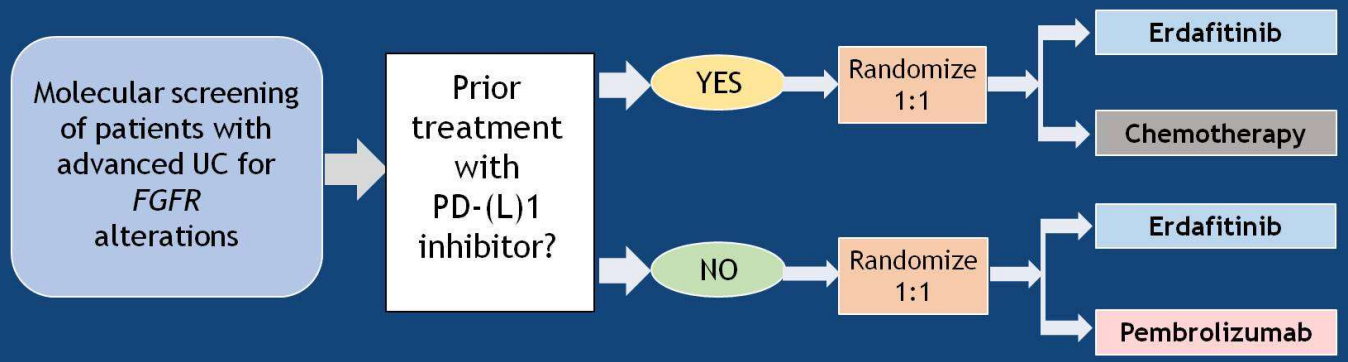
Is Response Rate Maintained Post-IO? Stay tuned…

FDA Grants Accelerated Approval to Erdafitinib for Metastatic Urothelial Carcinoma

By The ASCO Post
Posted: 4/12/2019 3:04:11 PM
Last Updated: 4/12/2019 3:04:11 PM

THOR

Ongoing Phase 3 Study (N = 630) of Erdafitinib Compared With Chemotherapy or Pembrolizumab



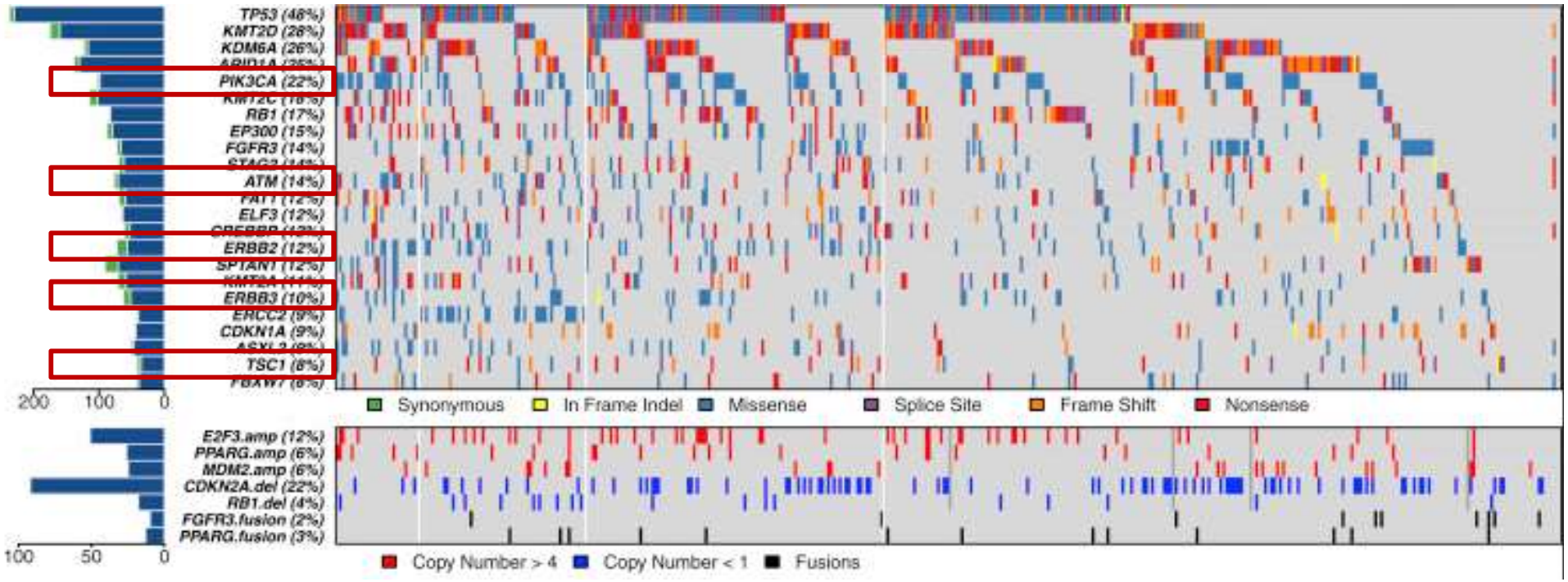
Primary end point: overall survival

The trial will run in 25 countries and 270 sites

Current status: open and enrolling patients

https://clinicaltrials.gov/ct2/show/NCT03390504

Other promising targets in Urothelial Carcinoma



Robertson et al Cell 2017

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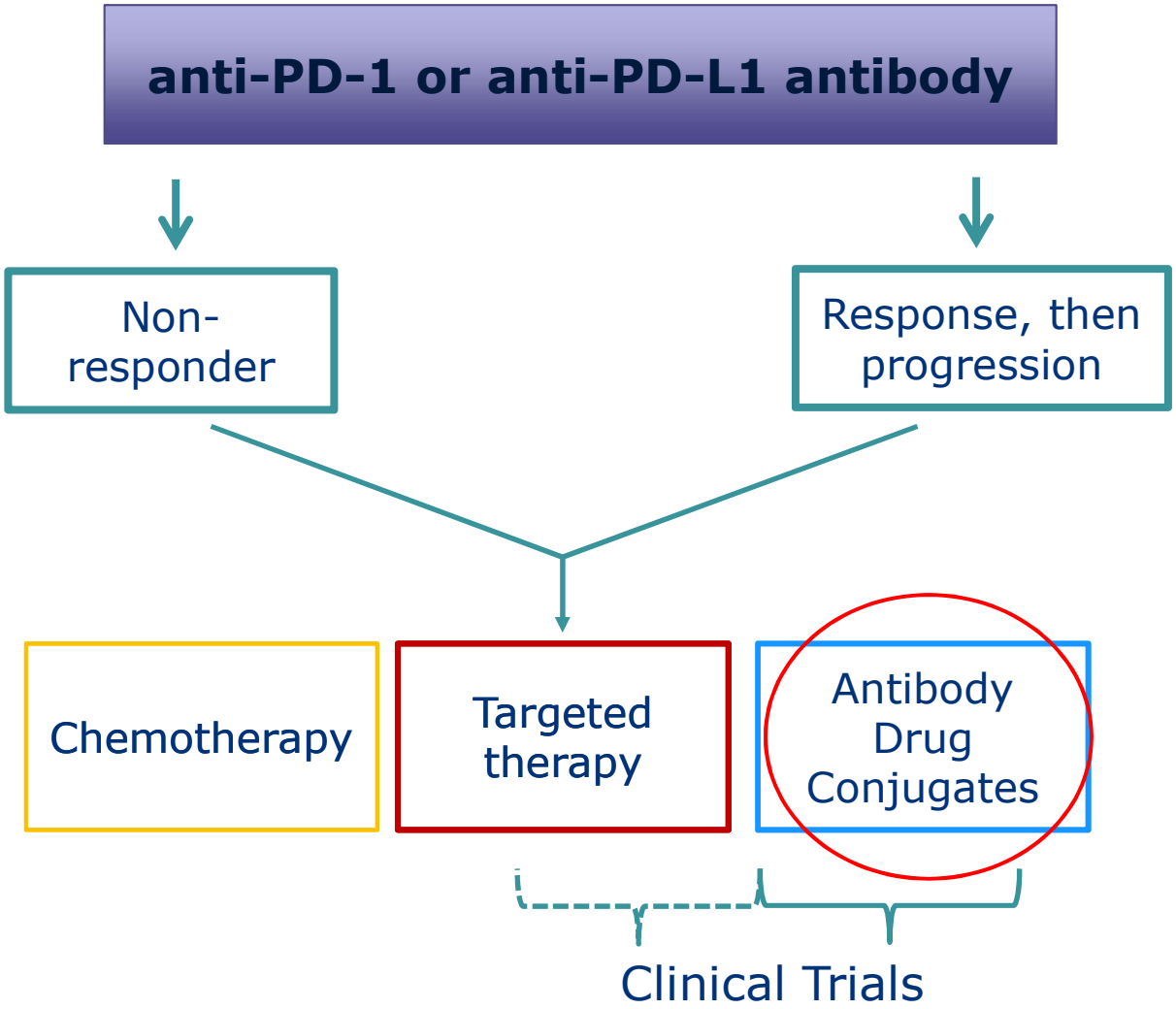
Targeted therapies in clinical trials

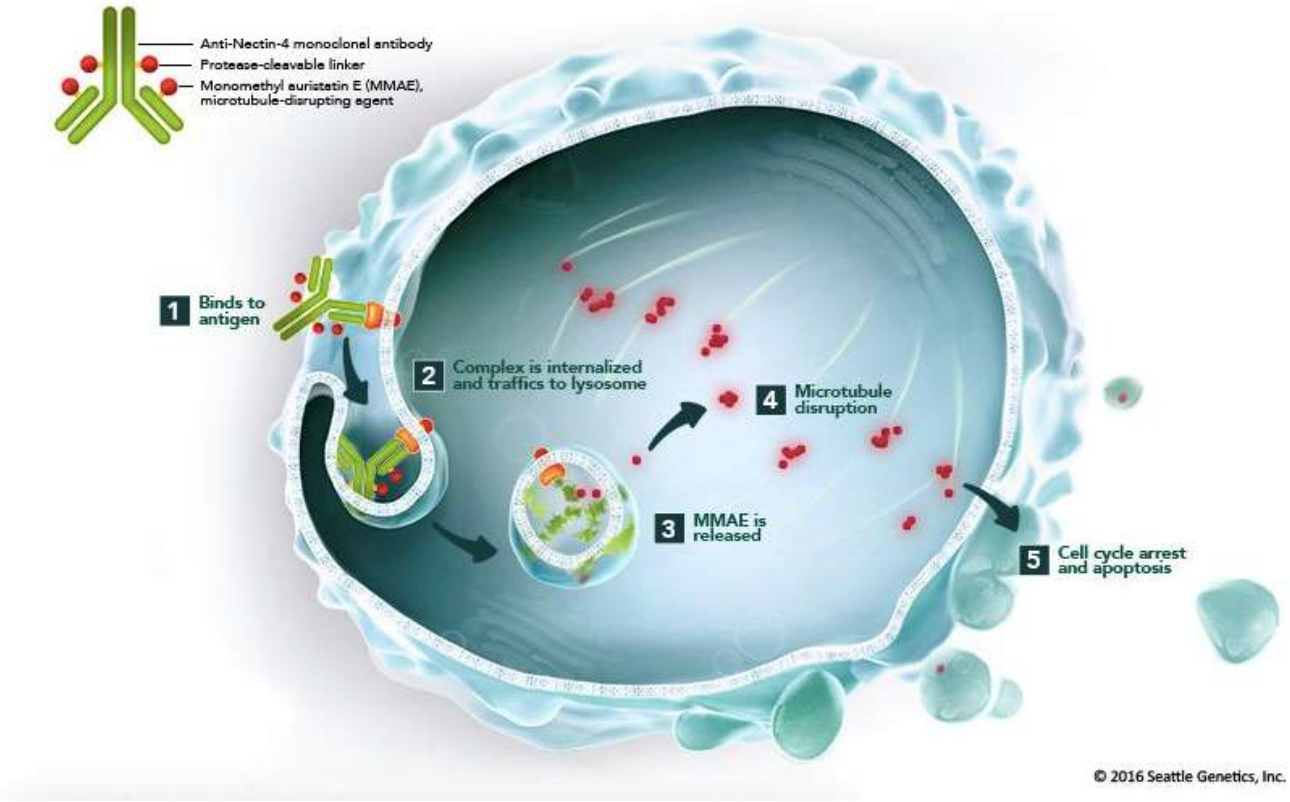
NCT #	Ph	Target	Treatment
02201212	II	TSC1, TSC2	Everolimus
03047213	II	TSC1, TSC2	Sapanisertib
02122172	II	HER	Afatinib
02546661 (BISCAY)	Ib		Durvalumab +/-
		FGFR	AZD4547
		PARP	Olaparib
		Wee-1	AZD1775
		mTOR1-2	Vistusertinib
		Stat3 ASO	AZD9150
		MEK	Selumetinib
03517956	I	FGFR	Rogaritinib + copanlisib
03523572	I/II	HER2	Trastuzumab deruxtecan + nivolumab
03330561	I	HER2, CD137	PRS-343 (bispecific)

Options once Treatment is Indicated

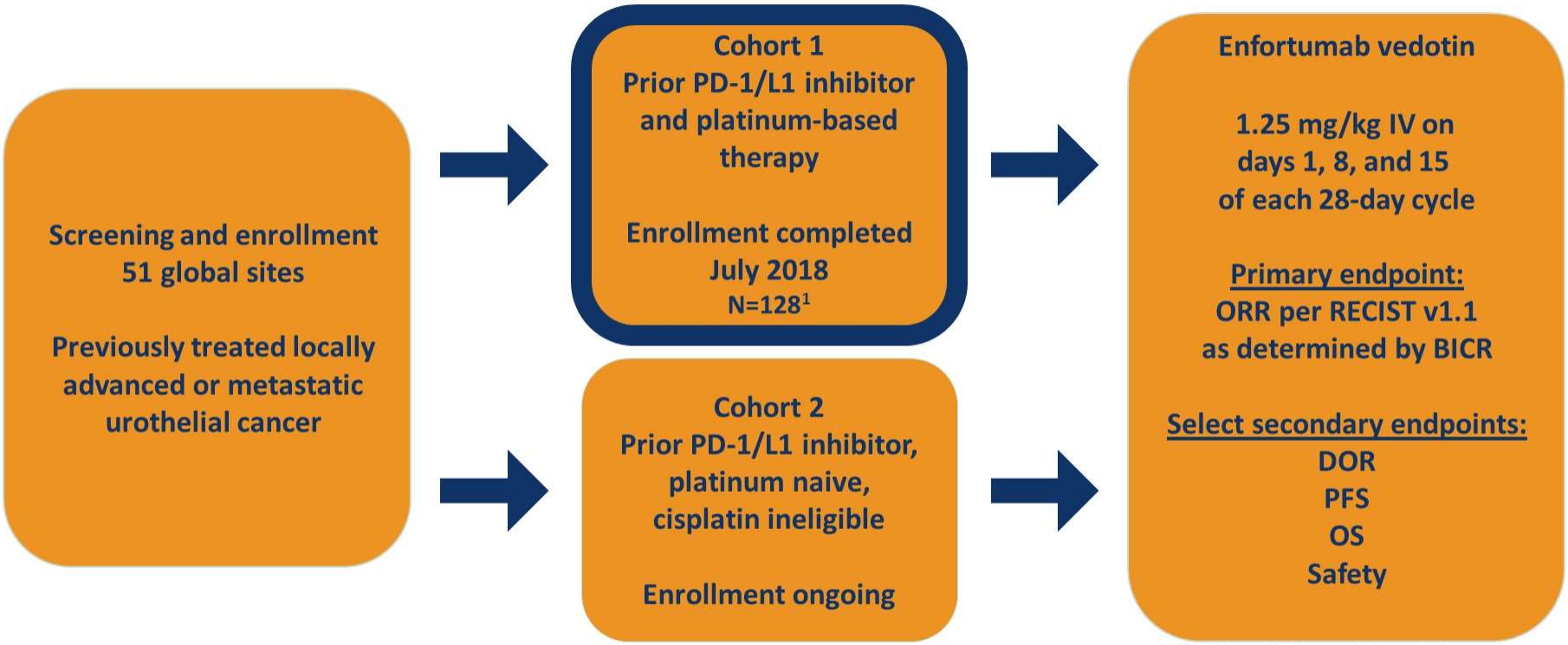


Antibody Drug Conjugates: Enfortumab vedotin

- Nectin 4 is overexpressed in mUC
- Enfortumab vedotin delivers MMAE to tumor cells with Nectin-4 expression



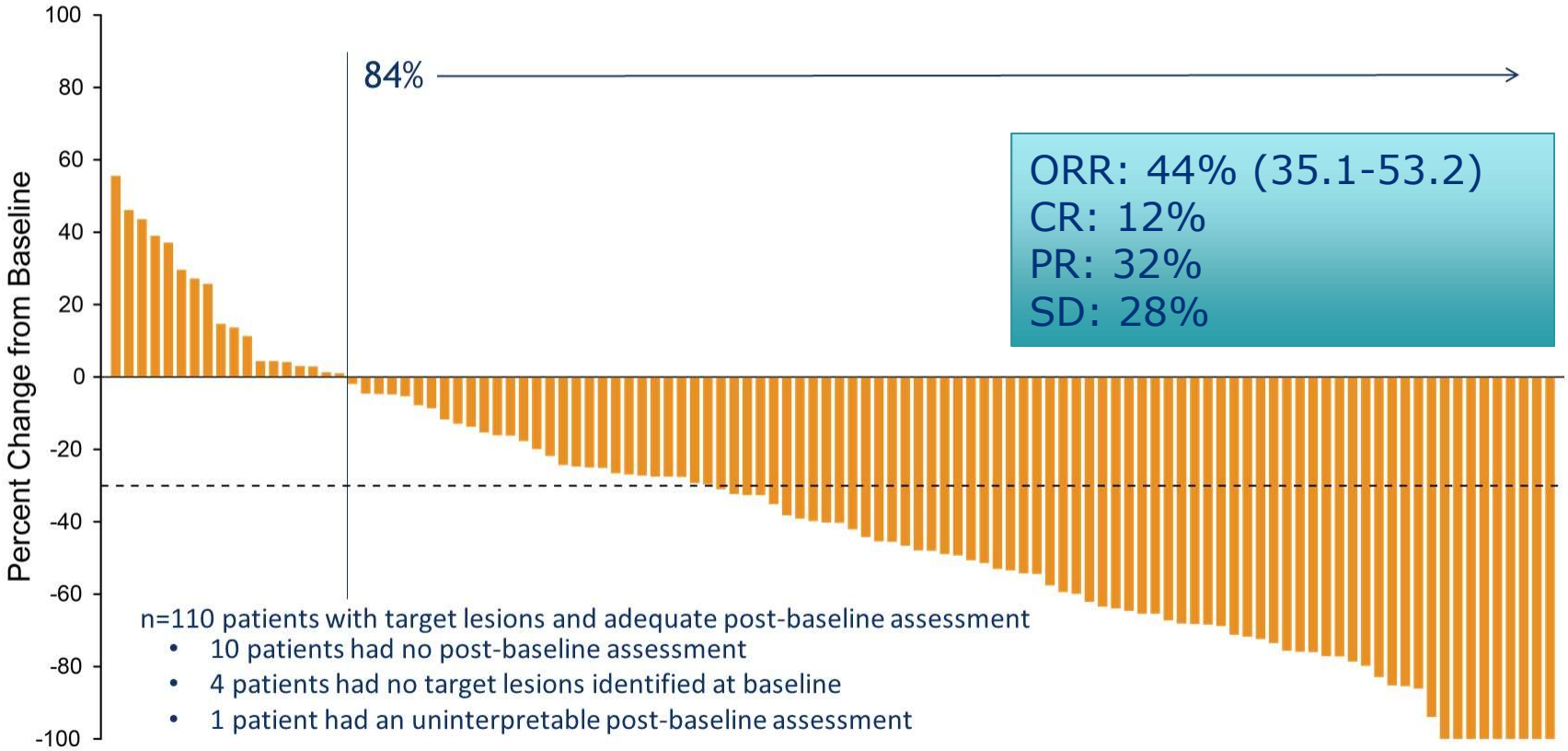
EV-201: Single-Arm, Pivotal Phase 2 Trial



[1] 3 patients did not receive enfortumab vedotin treatment:
one each due to clinical deterioration, patient decision, and low hemoglobin after enrollment

BICR=blinded independent central review; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

EV-201: Cohort 1 Change in Tumor Measurements per BICR



Presented By Daniel Petrylak at 2019 ASCO Annual Meeting

EV-301 Cohort A Results

- Most patients had PD-L1 IHC <10% (65%)
- 90% of patients had visceral disease
- 40% with liver metastases

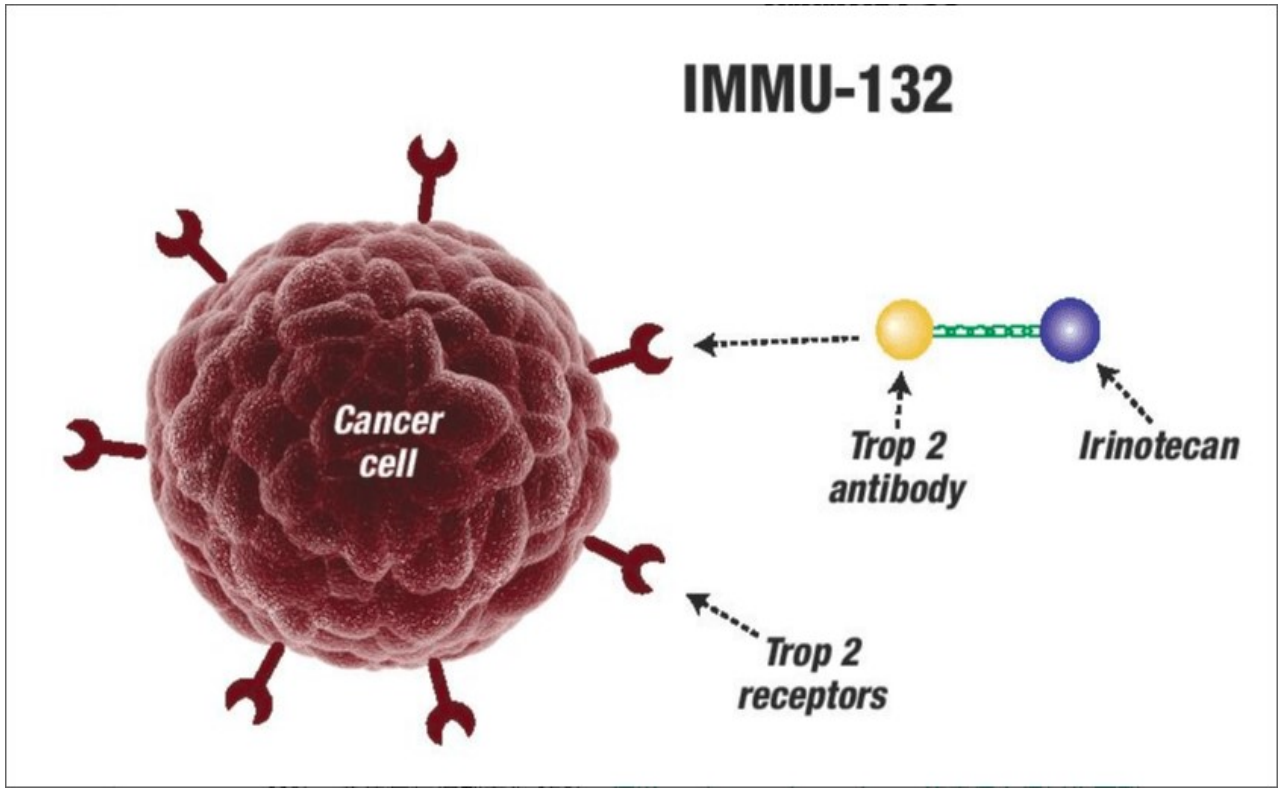
Efficacy endpoint (Median)	Months (95% CI)
Time on treatment	4.6 (0.5, 15.6)
Duration of Response	7.6 (0.95, 11.3+)
PFS	5.8 (4.9, 7.5)
OS	11.7 (9.1, NR)

- Peripheral neuropathy in 50% of patients (3% $\geq$ Grade 3)
- Rash in 48% (12% $\geq$ Grade 3)
- Hyperglycemia in 11% (6% $\geq$ Grade 3)
- 12% of patients discontinued due to AE (6% due to neuropathy)

D Petrylak ASCO 2019

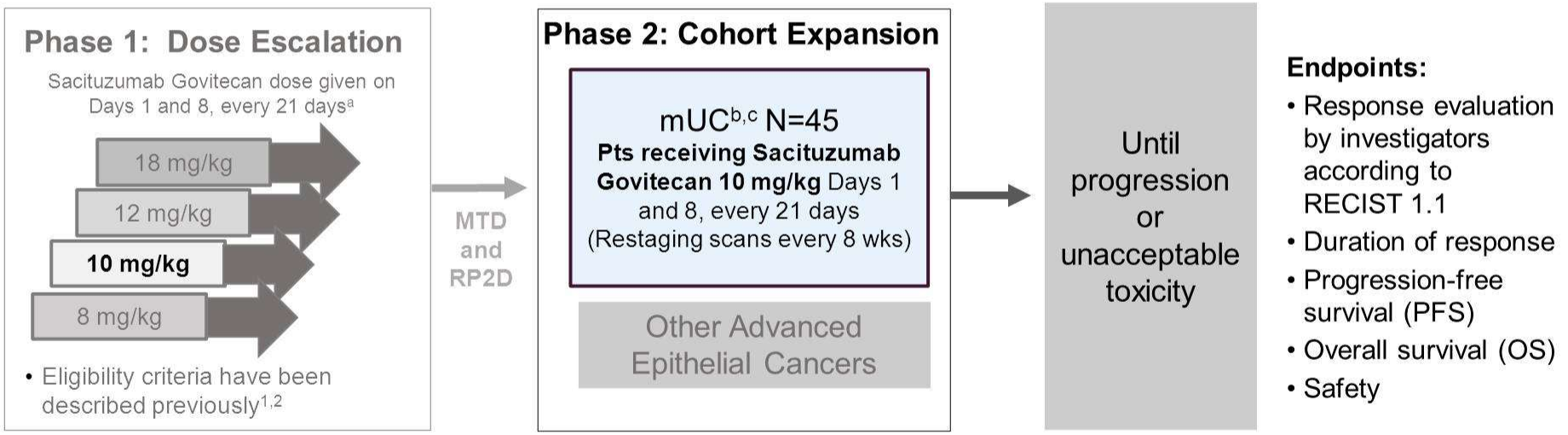
Antibody Drug Conjugates: Sacizituzumab govitecan

- Trop 2 is highly expressed in both normal urothelium and in ~80% of urothelial carcinoma patients



IMMU 132-01 Basket Study Design

- Study 01 was a phase I/II, open-label, single-arm, multicenter, basket trial (NCT01631552) investigated the activity of sacituzumab govitecan in patients with advanced epithelial cancers.



- mUC cohort: 45pts on 10 mg/kg dose, 3 on 8 mg/kg dose, 1 on 12 mg/kg dose
- Data cut-off: Sept 1, 2018

[1]Starodub AN, et al. *Clin Cancer Res*. 2015;21:3870-8; [2]Faltas B, et al. *Clin Genitourin Cancer*. 2016;14:e75-79. [a]All Phase I patients counted in Phase II Population; [b]One patient in this cohort had small cell carcinoma of the bladder; [c]Preliminary results were reported at ESMO 2017 (Tagawa et al. *Annals Oncol*. 2017;28(suppl 5):301 [Abstract 858P]).
MTD, maximum tolerated dose; mUC, metastatic urothelial cancer; RP2D, recommended phase 2 dose. clinicaltrials.gov: NCT01631552

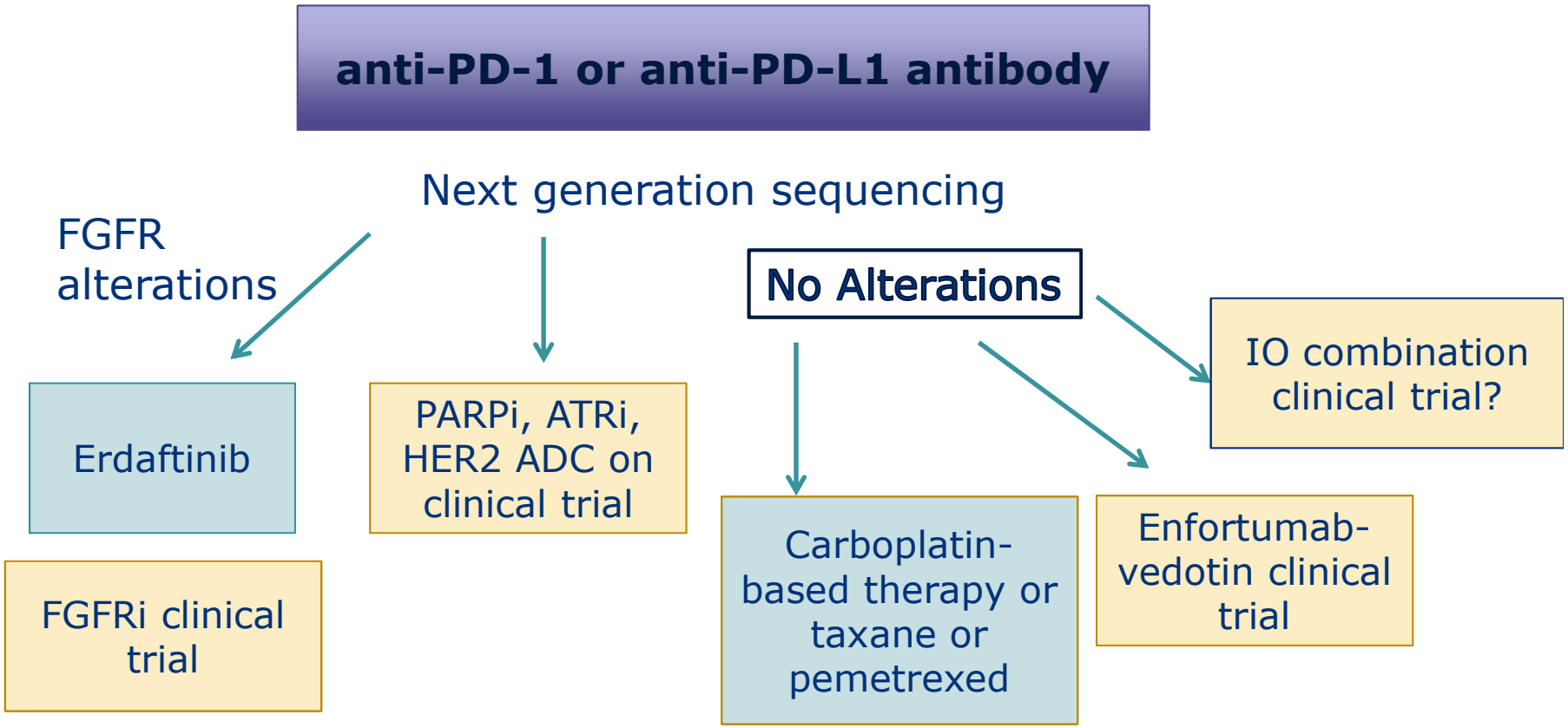
Summary of Results

- Objective Response Rate:
  - Total study population: 31.1% (14/45)
  - Prior checkpoint inhibitor: 23.5% (4/17)
  - Prior platinum, prior checkpoint inhibitor: 26.7% (4/15)

- Patients received median 8 cycles

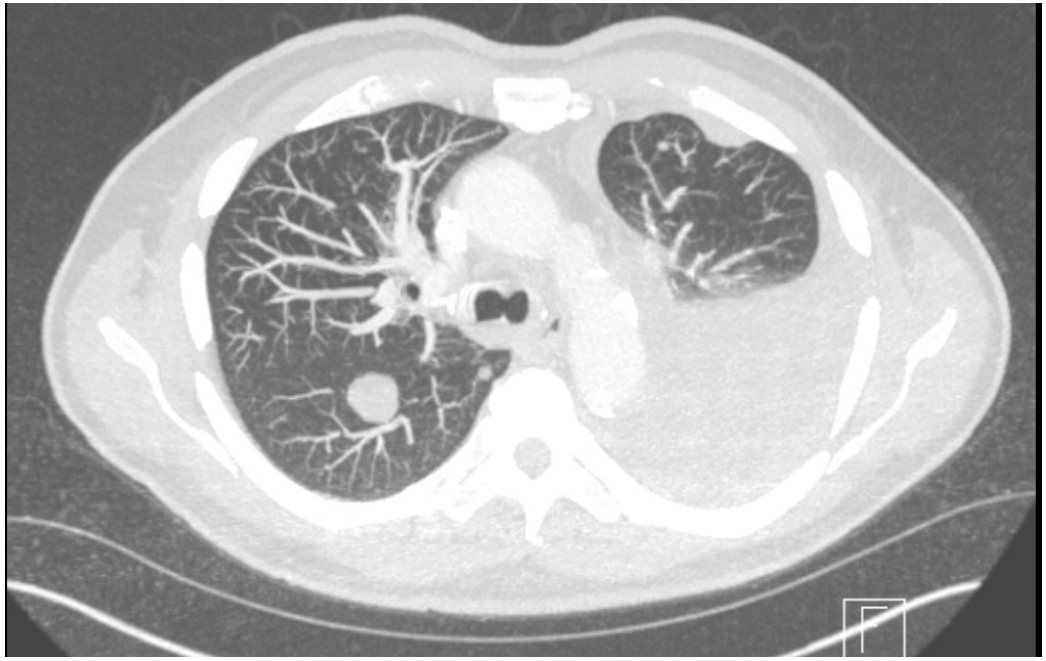
- Most frequent AEs:
  - Diarrhea → SAE
  - Nausea
  - Fatigue
  - Neutropenia → 24% needed G-CSF. SAEs of febrile neutropenia

Approach to the checkpoint inhibitor refractory patient



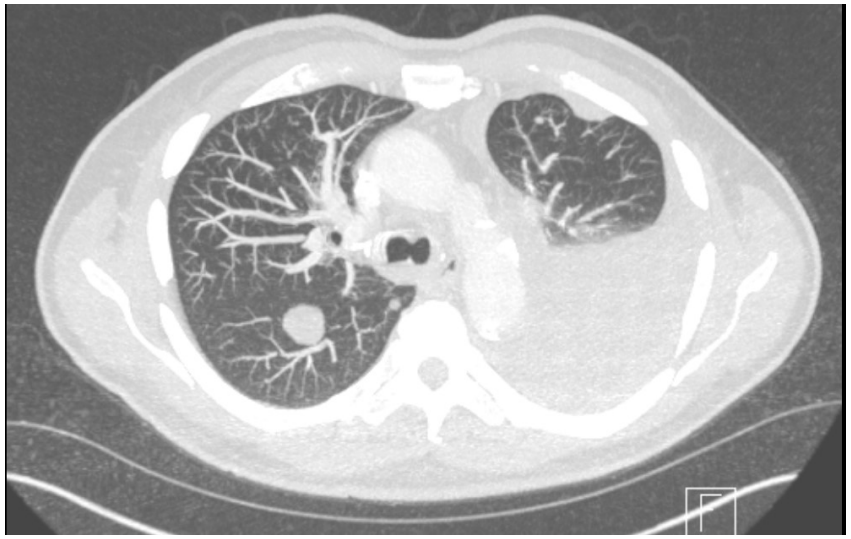
Back to the Patient

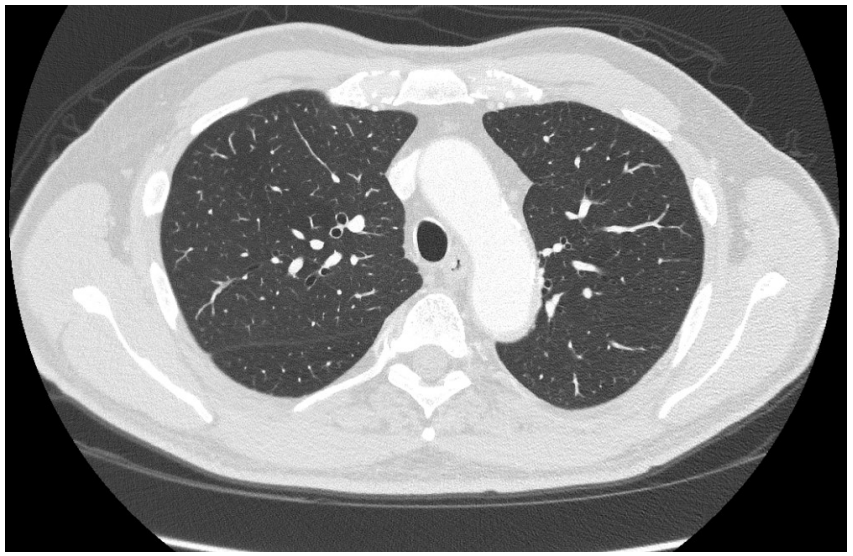
- 78 year old previously healthy man diagnosed with muscle-invasive bladder cancer
- After 3 cycles of neoadjuvant ddMVAC, patient found to have biopsy-proven lung metastases
- PD-L1 IHC $\geq$ 70%
- After 3 cycles of pembrolizumab, SD
- After 6 cycles of pembrolizumab



Clinical Course

- NGS mutations:
  - EGFR exon 20 insertion
  - TERT promoter
  - TMB low
- Patient enrolled to clinical trial of enfortumab vedotin v chemotherapy, randomized to enfortumab vedotin arm
- Continues on treatment, complicated by development of Grade 2 peripheral neuropathy





Questions