Memorial Sloan Kettering Cancer Center

Emerging data for treatment of metastatic urothelial carcinoma

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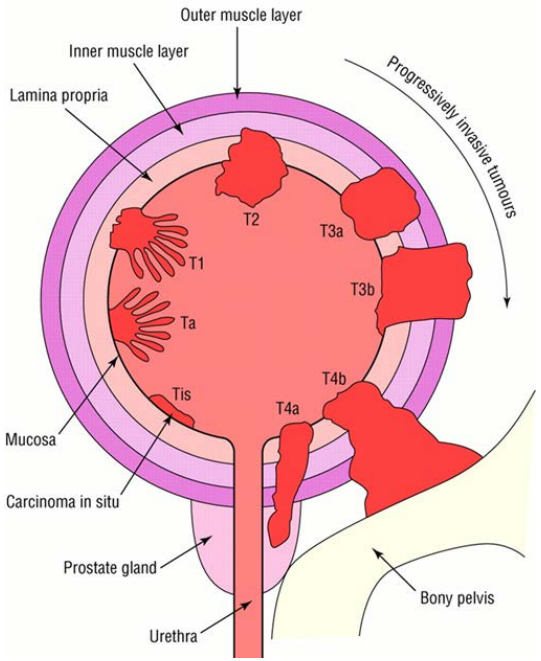
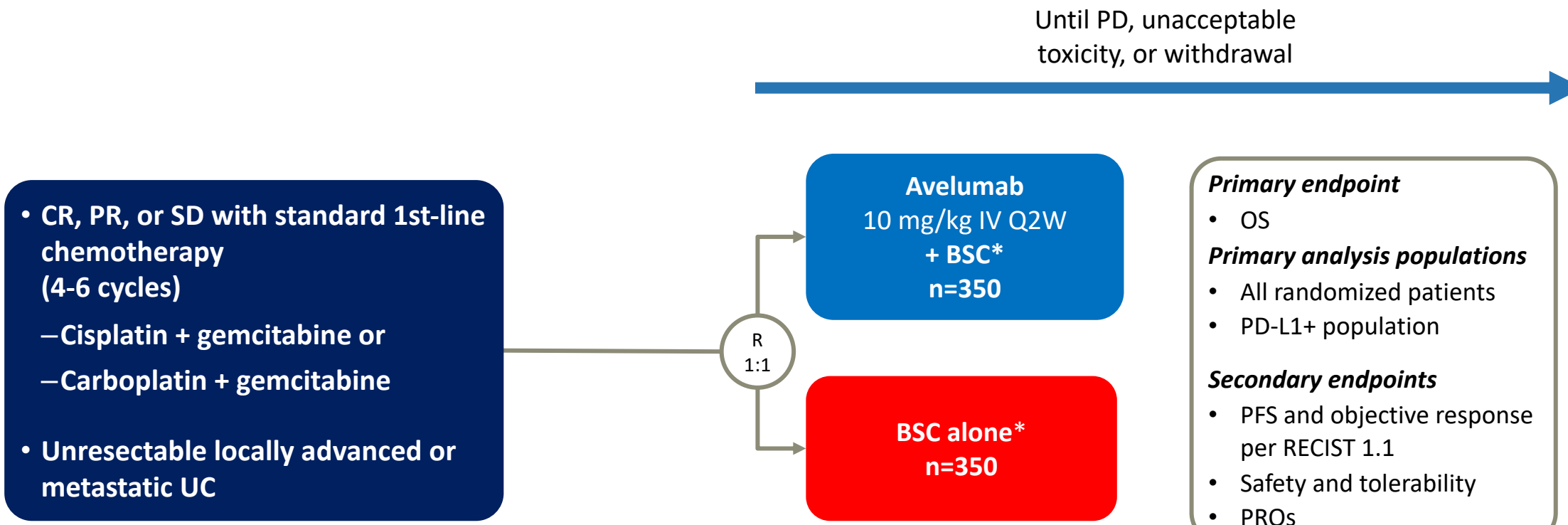


Current treatment of metastatic urothelial cancer

- First-line cisplatin-based chemotherapy has been the standard of care for patients with adequate organ function and performance status
  - Median survival historically has been 14 months[1]
  - Low rates of long-term survival, primarily in node-only, good performance status patients
- Carboplatin-based therapy has a median survival of about 9 months in cisplatin-ineligible patients[2]
  - Almost no complete responses or long-term survivors in this patient population

1. Von der Maase et al. Ann Oncol 2006. 2. De Santis et al. J Clin Oncol 2012

JAVELIN Bladder 100 study design (NCT02603432)



Stratification

- Best response to 1st-line chemo (CR or PR vs SD)
- Metastatic site (visceral vs non-visceral)

PD-L1+ status using SP263 assay, defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively

Courtesy of Jonathan E Rosenberg, MD

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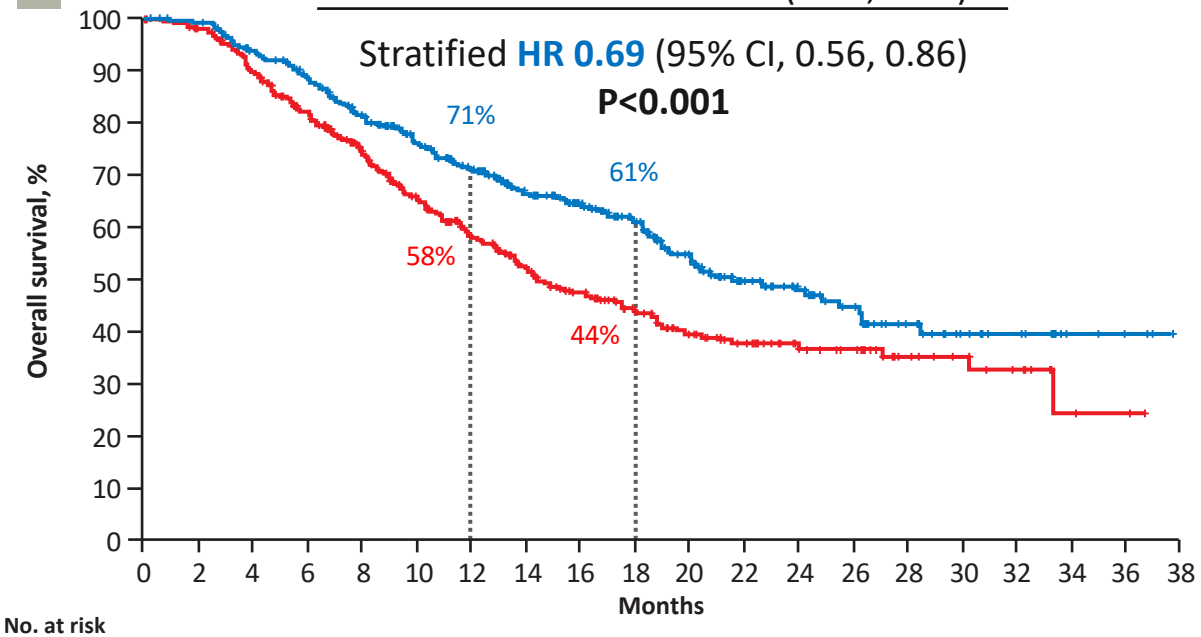
Adapted from Powles et al. ASCO 2020

JAVELIN Bladder 100: Avelumab improves OS in the overall study population and PD-L1+ population

Median OS (95% CI), months	
Avelumab + BSC	**21.4** (18.9, 26.1)
BSC alone	**14.3** (12.9, 17.9)

Stratified **HR 0.69** (95% CI, 0.56, 0.86)

P<0.001

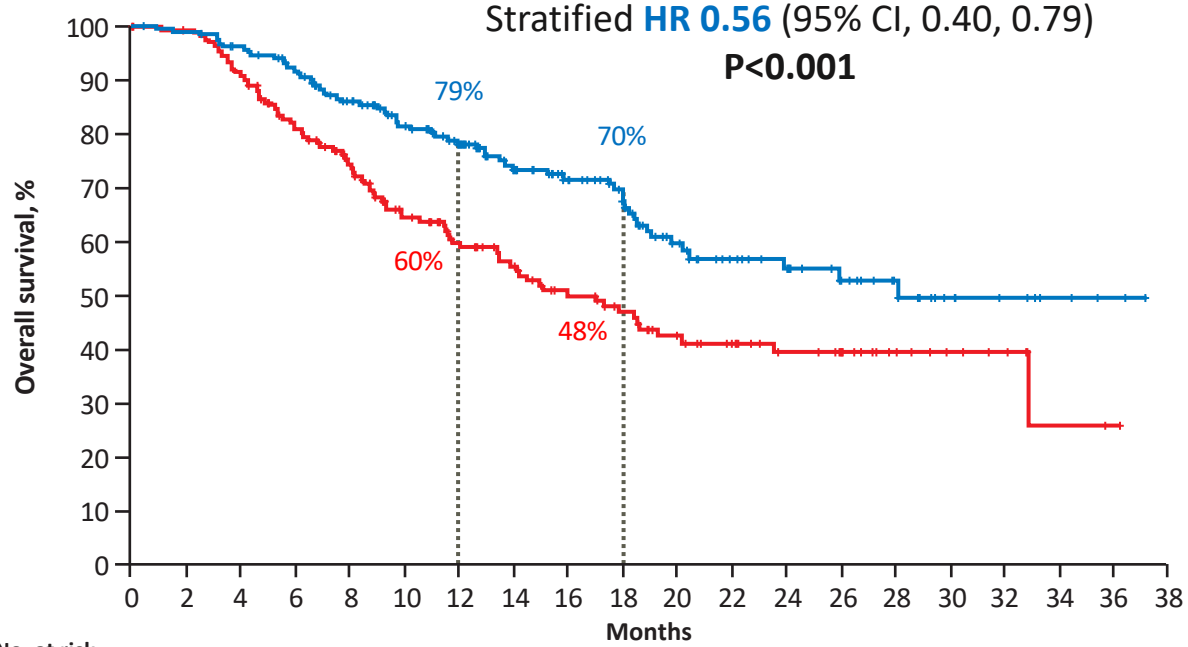


No. at risk																				
Avelumab + BSC	350	342	318	294	259	226	196	167	145	122	87	65	51	39	26	15	11	5	3	0
BSC	350	335	304	270	228	186	153	125	105	83	68	55	41	33	18	12	9	2	1	0

Median OS (95% CI), months	
Avelumab + BSC	**NE** (20.3, NE)
BSC alone	**17.1** (13.5, 23.7)

Stratified **HR 0.56** (95% CI, 0.40, 0.79)

P<0.001



No. at risk																				
Avelumab + BSC	189	185	177	165	146	129	114	95	81	70	49	38	32	26	18	9	8	4	2	0
BSC	169	165	152	132	113	89	76	67	54	45	37	30	23	21	12	8	6	2	1	0

Adapted from Powles et al. ASCO 2020

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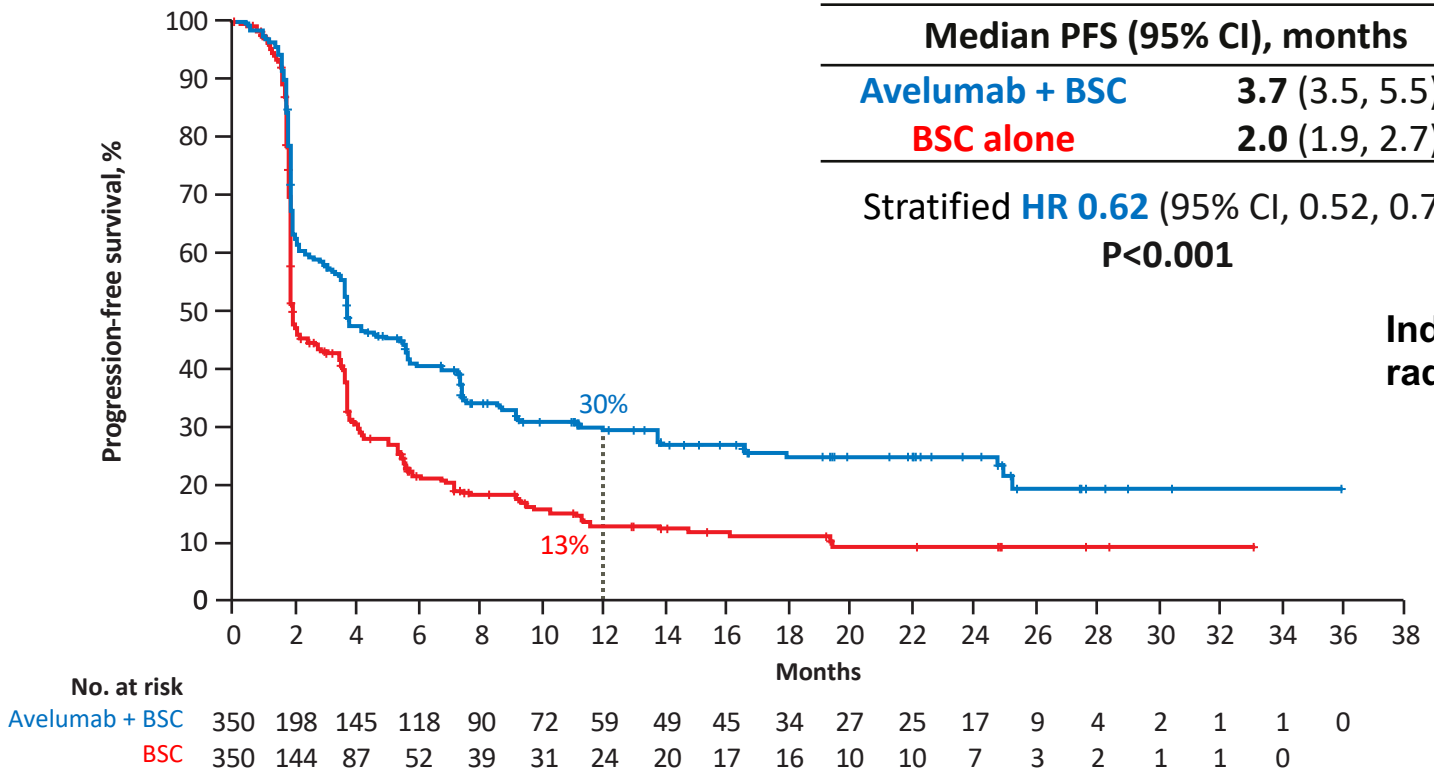
JAVELIN Bladder 100: Avelumab improves PFS in the overall population



Median PFS (95% CI), months	
Avelumab + BSC	**3.7** (3.5, 5.5)
BSC alone	**2.0** (1.9, 2.7)

Stratified **HR 0.62** (95% CI, 0.52, 0.75)

P<0.001

Independent radiology review

- The incidence of adverse events from any cause was 98% in the avelumab group and 77.7% in the control group.
- The incidence of Grade 3 or higher adverse events was 47.4% in the avelumab group and 25.2% in the control group

PFS was measured post randomization (from end of chemotherapy)

Courtesy of Jonathan E Rosenberg, MD

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Adapted from Powles et al. ASCO 2020

Select patients may be eligible for treatment with immune checkpoint inhibitors as first-line therapy for mUC

Courtesy of Jonathan E Rosenberg, MD

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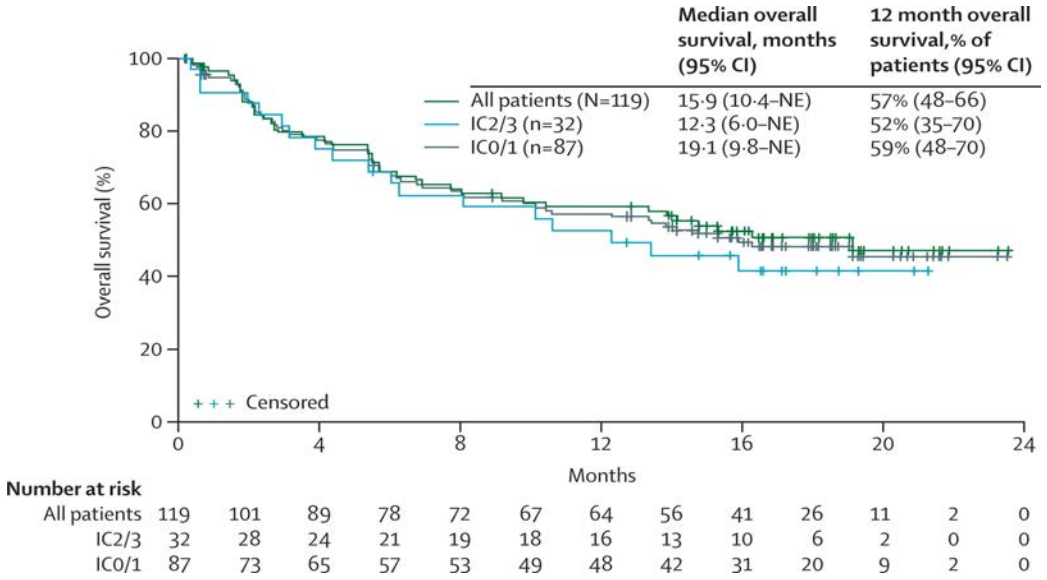
IMvigor210 Cohort 1: accelerated FDA approval

Atezolizumab: cisplatin-unfit (n=119)

	IC2/3 (n = 32)	IC1/2/3 (n = 80)	All Patients (N = 119)	IC1 (n = 48)	IC0 (n = 39)
ORR[a] (95% CI)	28% (14, 47)	24% (15, 35)	23% (16, 31)	21% (10, 35)	21% (9, 36)
CR	12%	10%	9%	8%	8%
PR	16%	14%	14%	13%	13%

Cohort 1–specific inclusion criteria

- No prior treatment for mUC (> 12 mo since perioperative chemo)
- ECOG PS 0-2
- Cisplatin ineligibility[1] based on ≥ 1 of the following:
  - Renal impairment: GFR < 60 and > 30 mL/min
  - ≥ Grade 2 hearing loss or peripheral neuropathy
  - ECOG PS 2



Median duration of response not reached

Median OS 15.9 months

Adapted from Balar et al. Lancet 2017

Courtesy of Jonathan E Rosenberg, MD

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KEYNOTE-052: Anti-tumor activity (RECIST 1.1) (N=370)

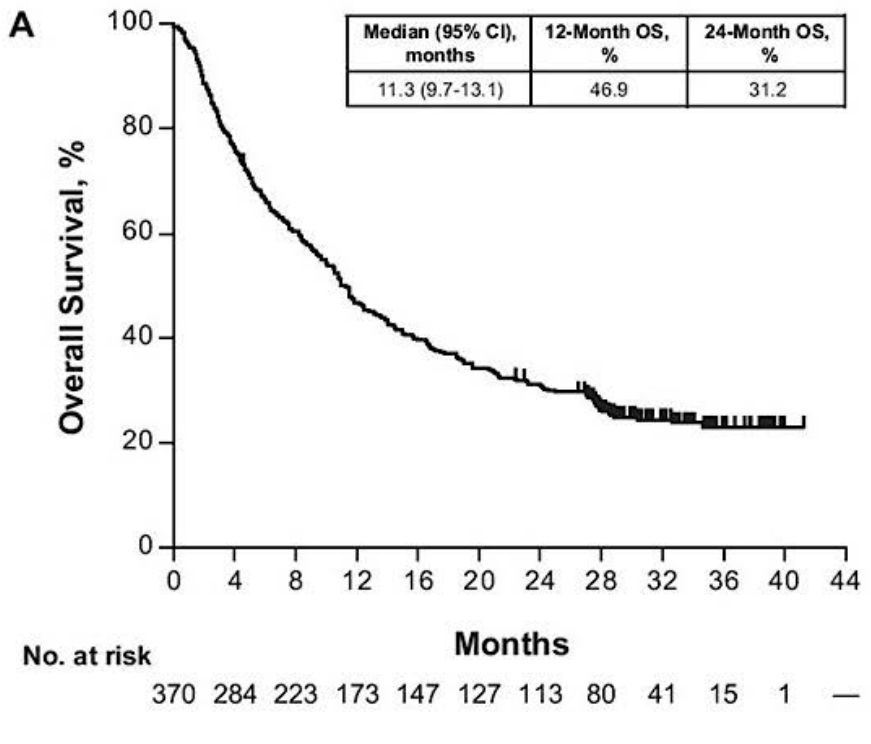
	All Treated Patients % (95% CI) N=370	CPS ≥10 % (95% CI) N=110
Objective response	28.6 (24.1-33.5)	47.3 (37.7-57.0)
Complete response	8.9 (6.2-12.3)	20.0 (13.0-27.7)
Partial response	19.7 (15.8-24.2)	27.3 (19.2-36.6)

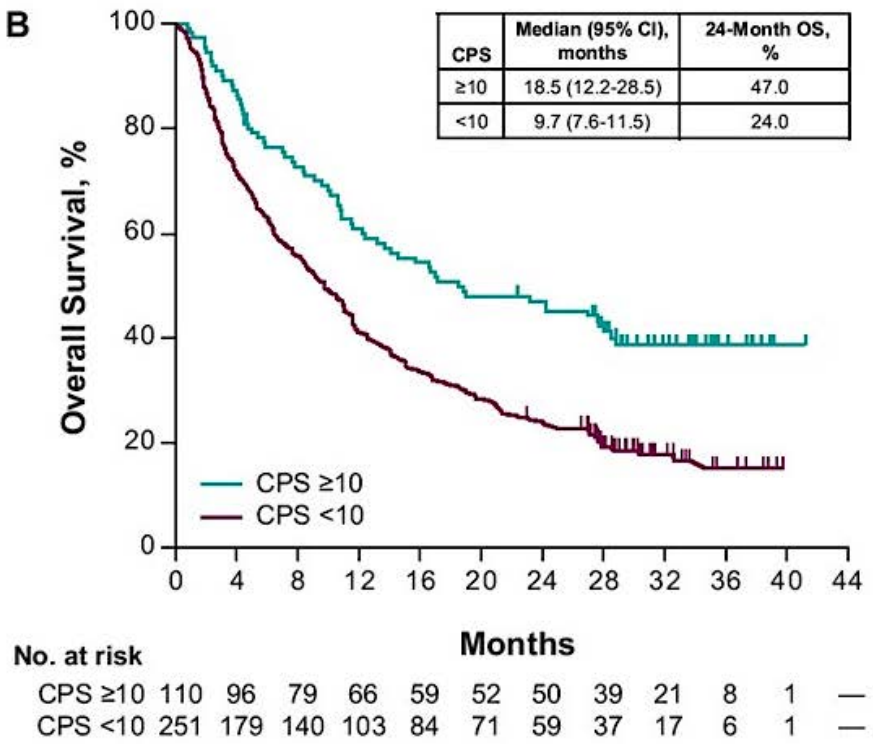
Median OS 11.3 months

CPS ≥10% OS 18.5 months

Inclusion Criteria

- Advanced urothelial cancer
- No prior chemotherapy for metastatic disease
- ECOG PS 0-2
- Ineligible for cisplatin based on ≥ 1 of the following:
- CrCl <60 mL/min
- ECOG PS 2
- ≥ grade 2 neuropathy or hearing loss
- NYHA class III CHF



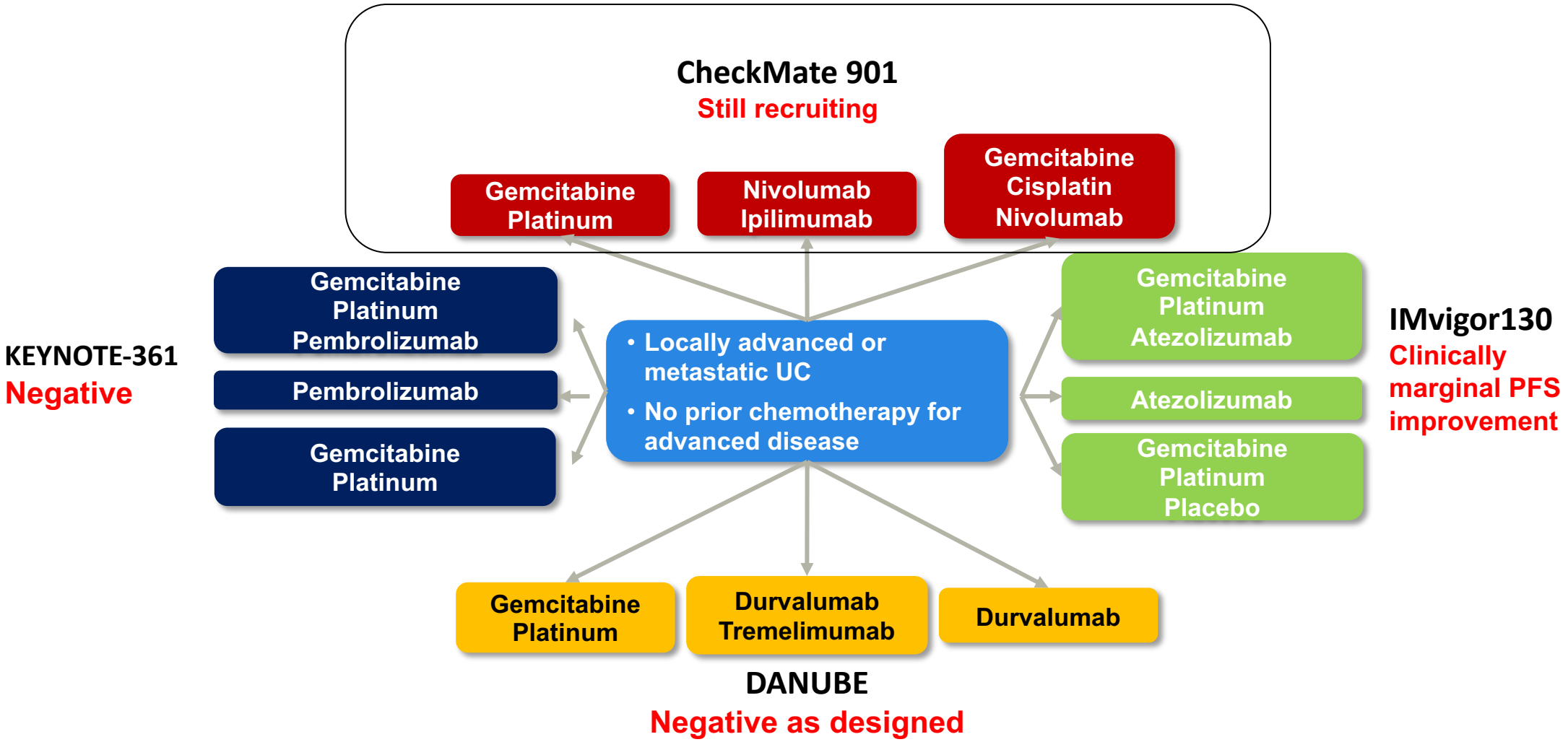


Courtesy of Jonathan E Rosenberg, MD

CPS, combined positive score; OS, overall survival; PD-L1, programmed death ligand 1.

O'Donnell, et al. ASCO 2019

First-line metastatic UC trials have started to read out



Courtesy of Jonathan E Rosenberg, MD

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IMvigor130: Interim OS for Monotherapy: ITT (Arm B vs Arm C)

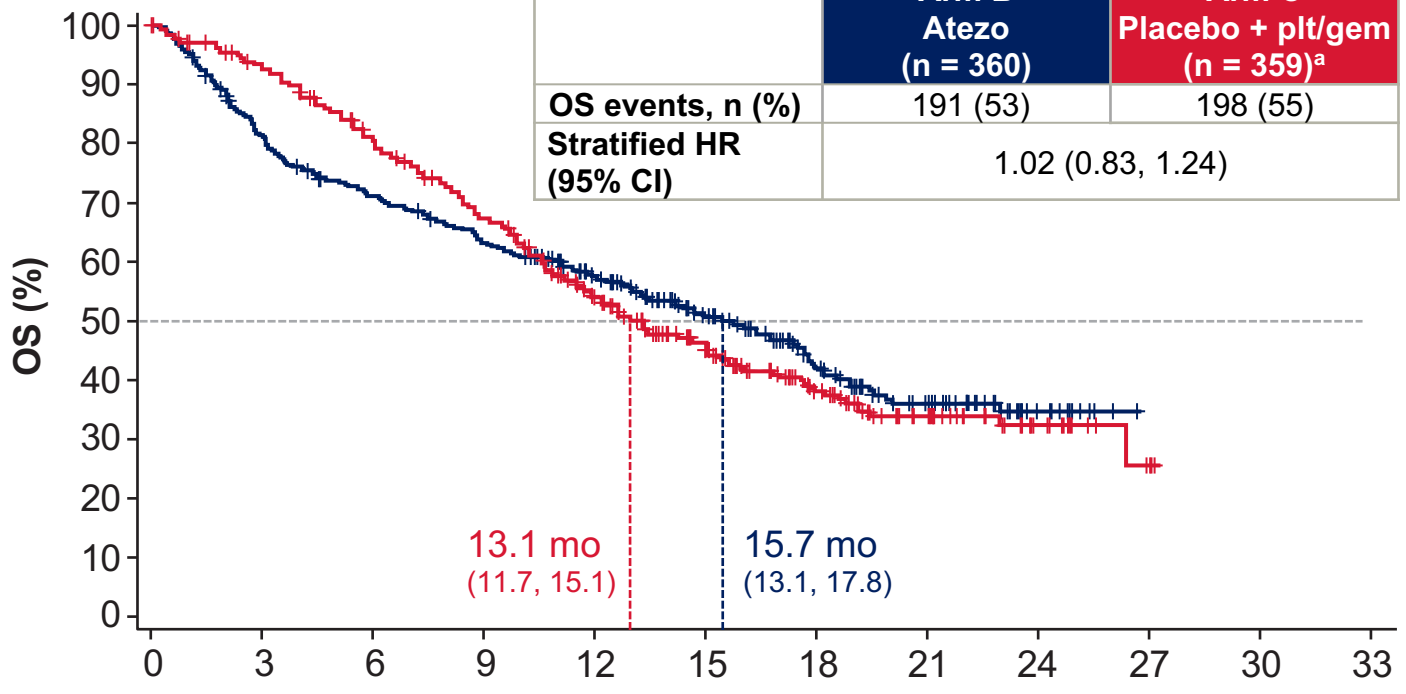
- Locally advanced or metastatic UC
- No prior chemotherapy for advanced disease

→ Gemcitabine Platinum Atezolizumab

→ Atezolizumab

→ Gemcitabine Platinum Placebo

	Arm B Atezo (n = 360)	Arm C Placebo + plt/gem (n = 359)[a]
OS events, n (%)	191 (53)	198 (55)
Stratified HR (95% CI)	1.02 (0.83, 1.24)	



No. at Risk												
Atezo	360	285	245	216	173	120	72	42	16	NE	NE	NE
Placebo + plt/gem	359	322	274	224	158	103	62	35	15	3	NE	NE

Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients). [a] Comparison only includes patients concurrently enrolled with Arm B.

Adapted from Grande et al. ESMO 2019

Courtesy of Jonathan E Rosenberg, MD

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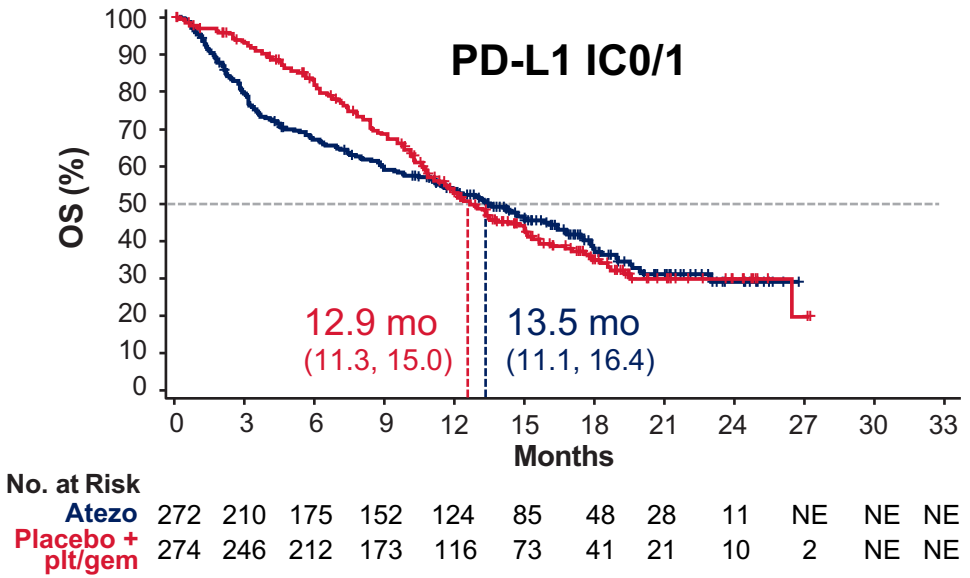
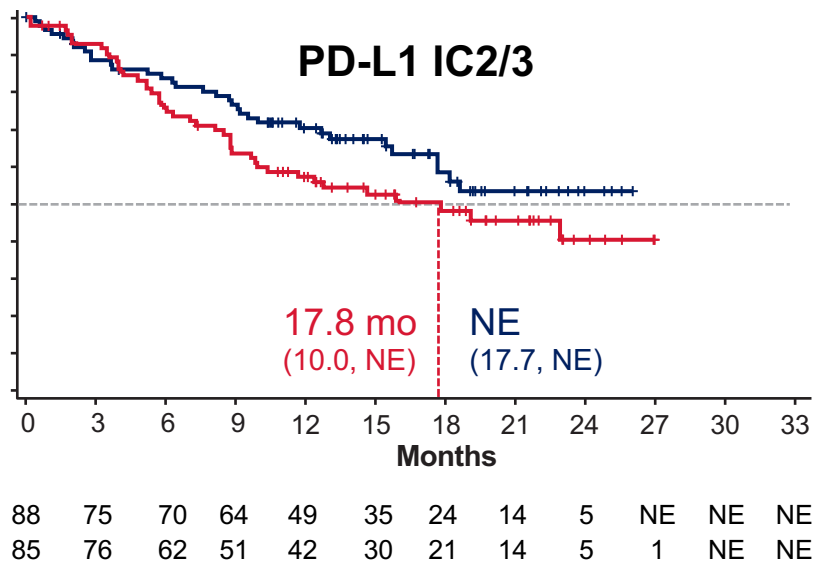
IMvigor130: Interim OS: PD-L1 status (Arm B vs Arm C)



	Arm B Atezo (n = 272)	Arm C Placebo + plt/gem (n = 274)
OS events, n (%)	158 (58)	156 (57)
Unstratified HR (95% CI)	1.07 (0.86, 1.33)	

Chemotherapy treated patients do better initially but curves cross at about 1 year



	Arm B Atezo (n = 88)	Arm C Placebo + plt/gem (n = 85)
OS events, n (%)	33 (38)	42 (49)
Stratified HR (95% CI)	0.68 (0.43, 1.08)	

Immunotherapy patients do better but not statistically significant

Adapted from Grande et al. ESMO 2019

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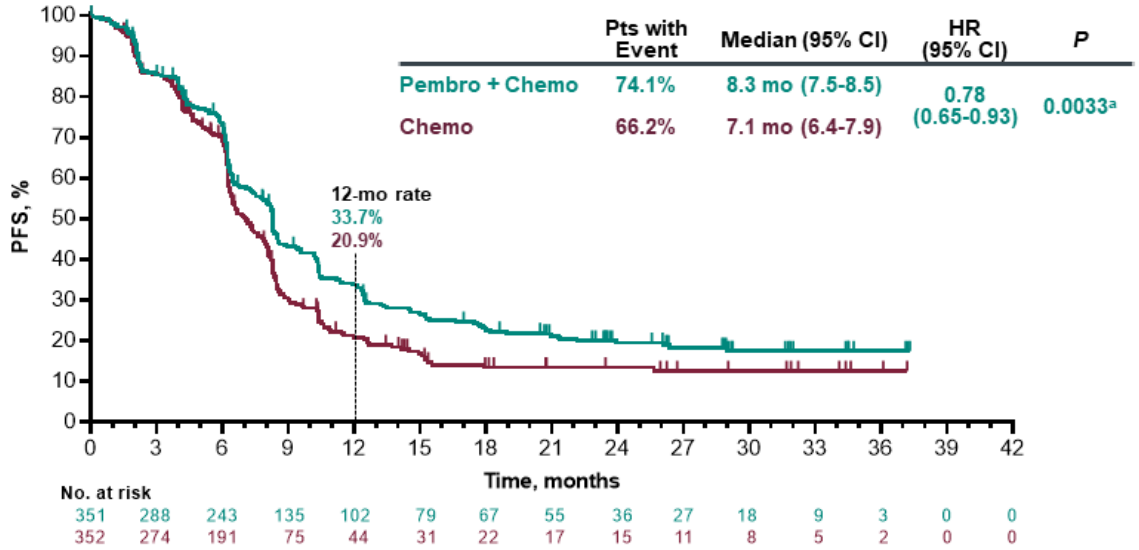
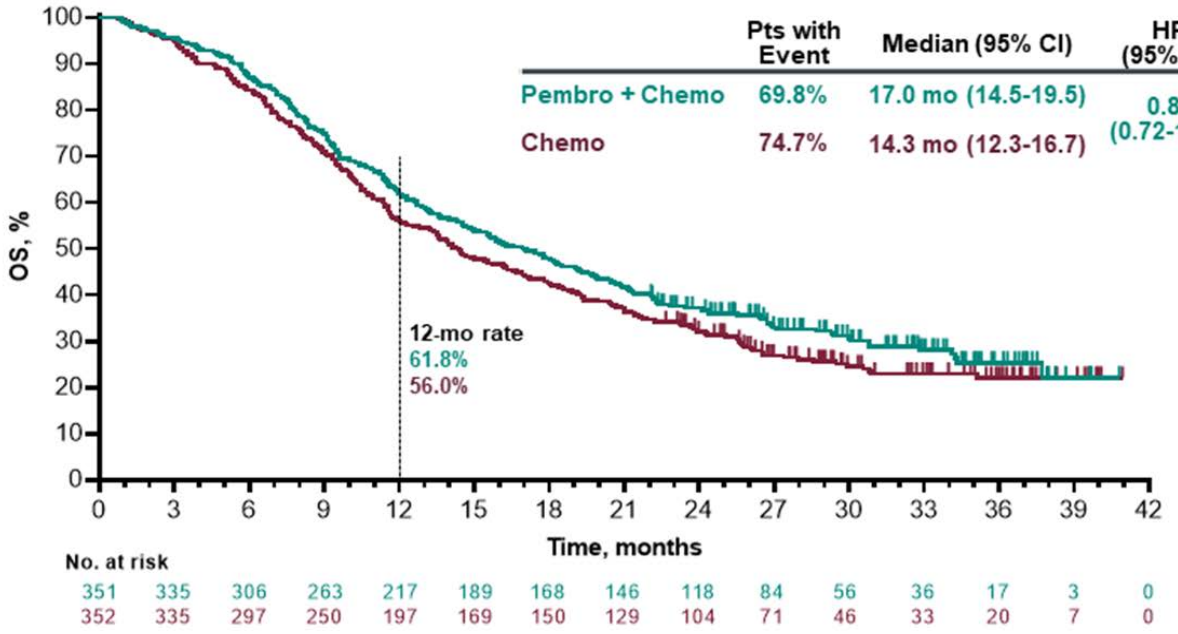
KEYNOTE-361: Pembrolizumab + chemo vs chemo



	Pts with Event	Median (95% CI)	HR (95% CI)	P
Pembro + Chemo	74.1%	8.3 mo (7.5-8.5)	0.78 (0.65-0.93)	0.0033[a]
Chemo	66.2%	7.1 mo (6.4-7.9)		

PFS

PFS (primary endpoint) and OS negative (p=NS per analysis plan)



	Pts with Event	Median (95% CI)	HR (95% CI)	P
Pembro + Chemo	69.8%	17.0 mo (14.5-19.5)	0.86 (0.72-1.02)	0.0407[a]
Chemo	74.7%	14.3 mo (12.3-16.7)		

OS

Gemcitabine Platinum Pembrolizumab

Pembrolizumab

Gemcitabine Platinum

- **Locally advanced or metastatic UC**
- **No prior chemotherapy for advanced disease**

Adapted from Aijai Alva, ESMO 2020

Courtesy of Jonathan E Rosenberg, MD

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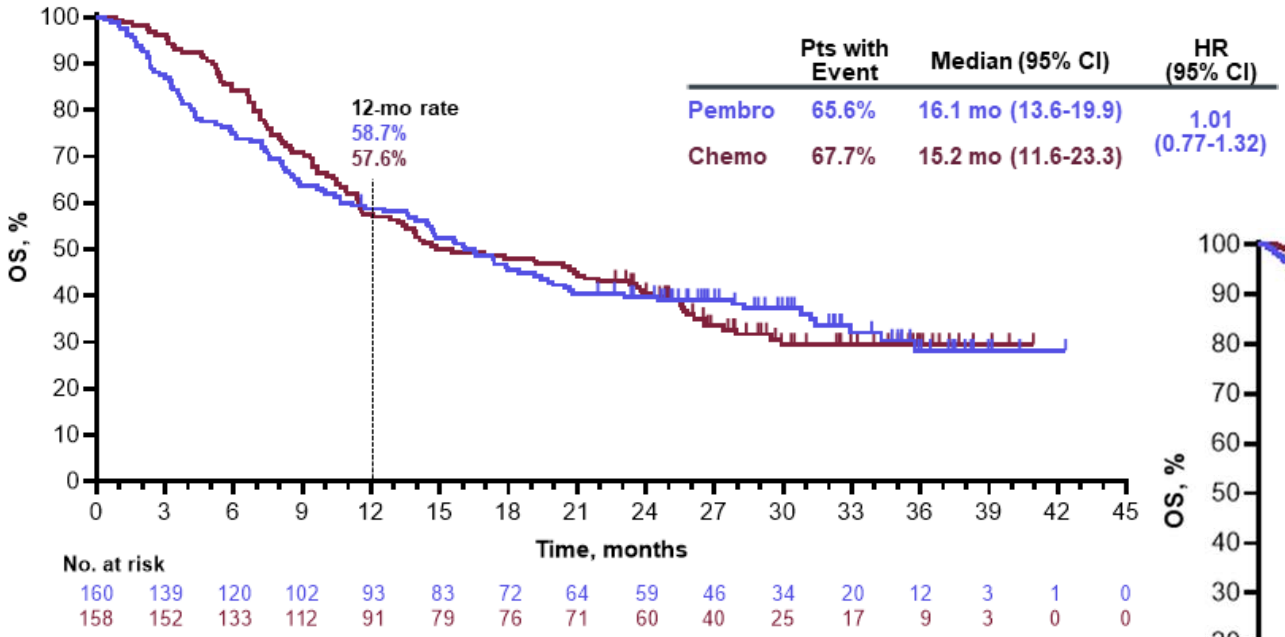
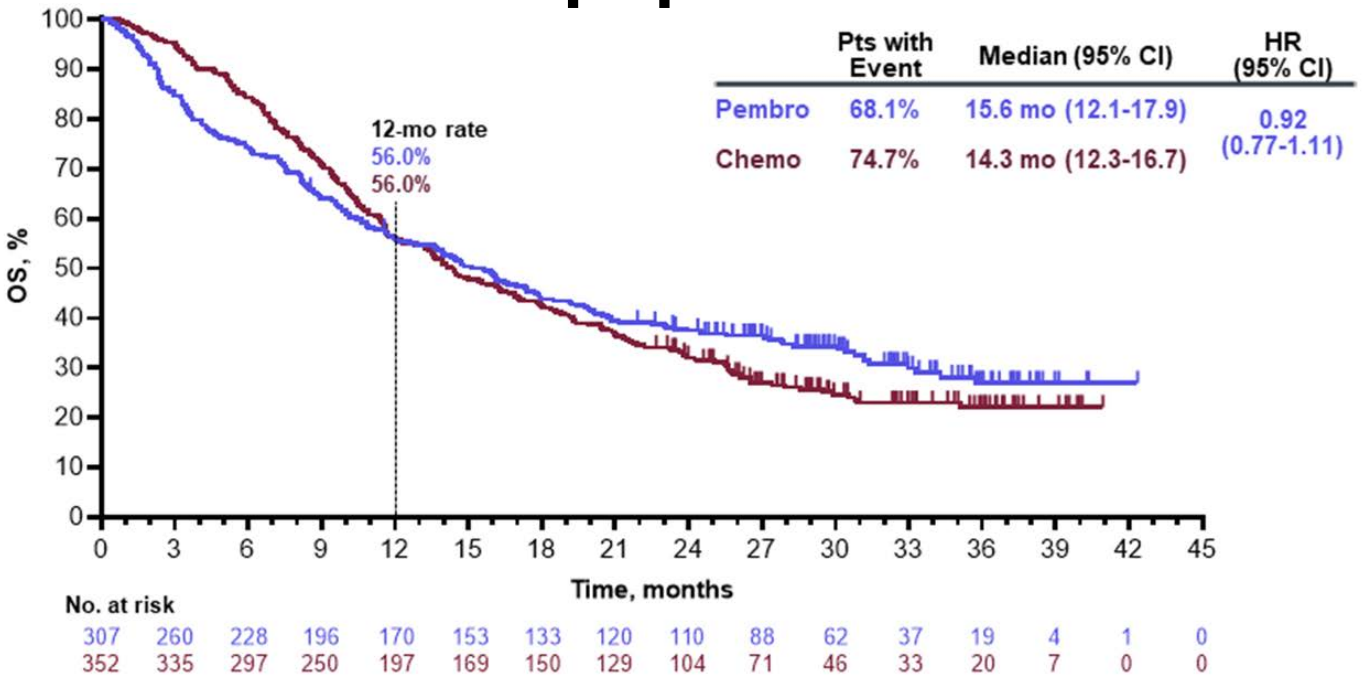
KEYNOTE-361: Pembrolizumab vs chemotherapy



CPS >10



ITT population

Gemcitabine
Platinum
Pembrolizumab

Pembrolizumab

Gemcitabine
Platinum

- Locally advanced or metastatic UC
- No prior chemotherapy for advanced disease

Adapted from Aijai Alva, ESMO 2020

No improvement in OS either with CPS>10 or ITT population; curves cross at ~1 year timepoint

Courtesy of Jonathan E Rosenberg, MD

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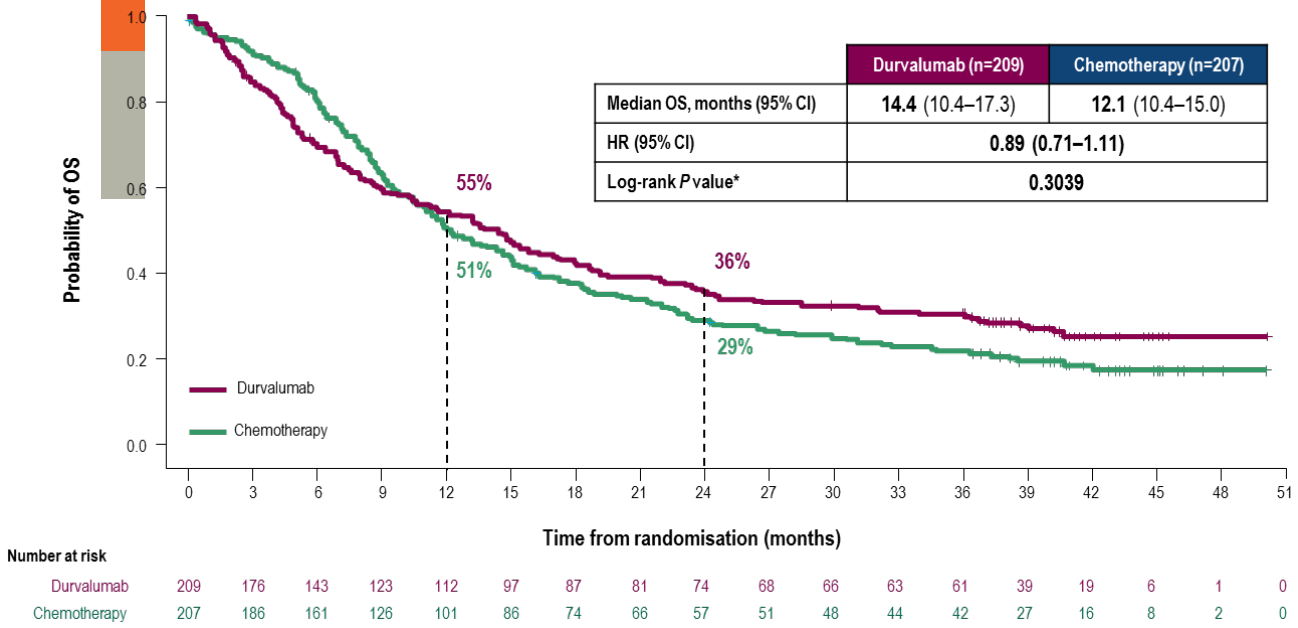
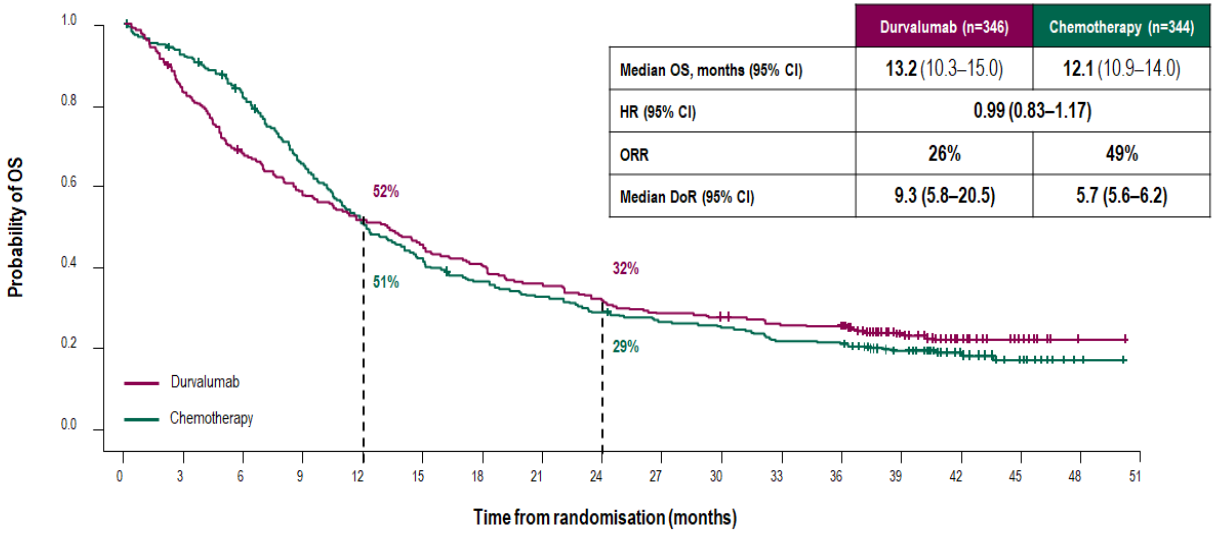
DANUBE: Durvalumab does not improve OS compared to chemotherapy



	Durvalumab (n=209)	Chemotherapy (n=207)
Median OS, months (95% CI)	**14.4** (10.4–17.3)	**12.1** (10.4–15.0)
HR (95% CI)	**0.89 (0.71–1.11)**	
Log-rank *P* value*	**0.3039**	

OS in PD-L1 high population

OS curves cross and chemotherapy treated patients do better initially



	Durvalumab (n=346)	Chemotherapy (n=344)
Median OS, months (95% CI)	**13.2** (10.3–15.0)	**12.1** (10.9–14.0)
HR (95% CI)	**0.99 (0.83–1.17)**	
ORR	**26%**	**49%**
Median DoR (95% CI)	**9.3 (5.8–20.5)**	**5.7 (5.6–6.2)**

OS in ITT population

- **Locally advanced or metastatic UC**
- **No prior chemotherapy for advanced disease**

Gemcitabine Platinum | **Durvalumab Tremelimumab** | **Durvalumab**

Adapted from Powles, ESMO 2020

Courtesy of Jonathan E Rosenberg, MD

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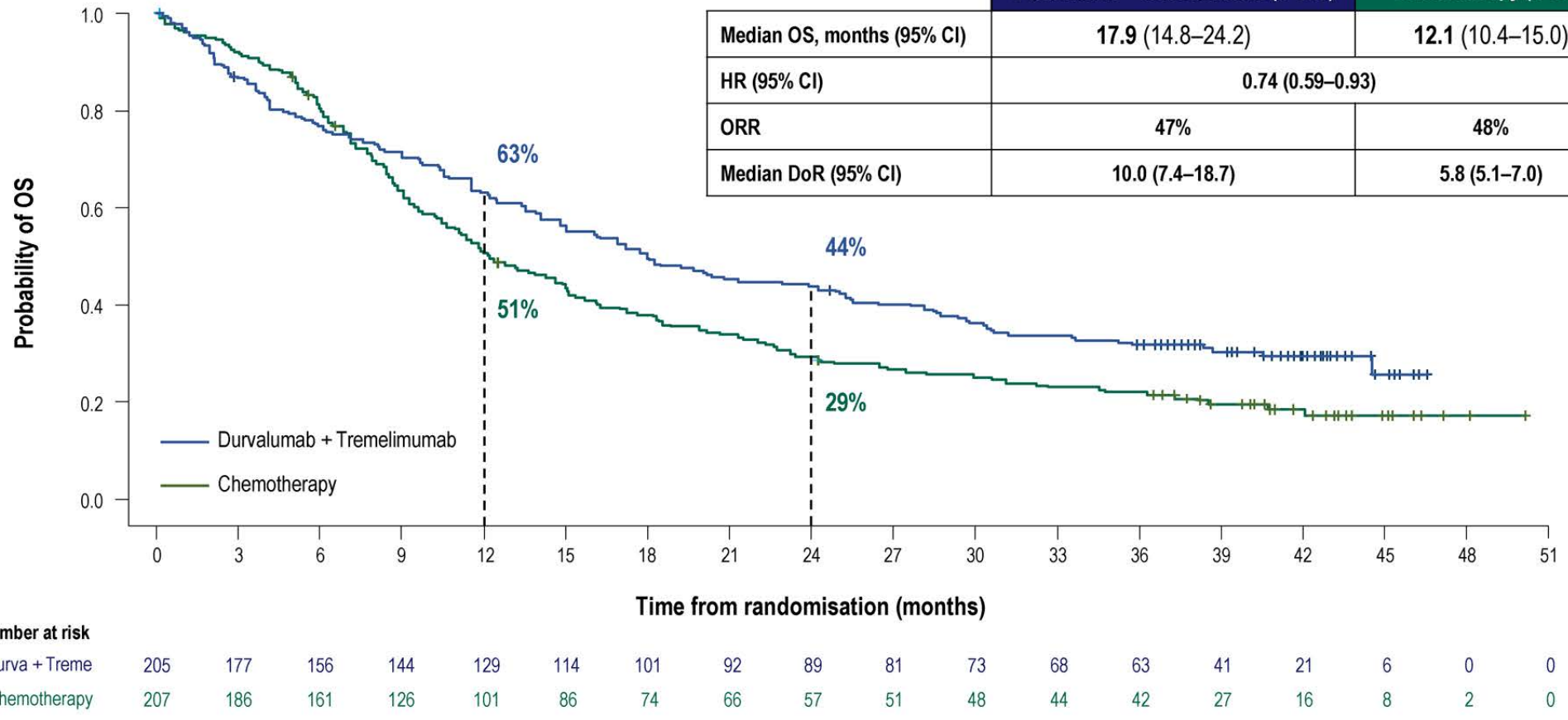
DANUBE

Secondary endpoint: Durvalumab/tremelimumab shows improved OS compared to chemotherapy in PD-L1 high patients but not in all patients

	Durvalumab + Tremelimumab (n=205)	Chemotherapy (n=207)
Median OS, months (95% CI)	**17.9** (14.8–24.2)	**12.1** (10.4–15.0)
HR (95% CI)	0.74 (0.59–0.93)	
ORR	47%	48%
Median DoR (95% CI)	10.0 (7.4–18.7)	5.8 (5.1–7.0)



- Locally advanced or metastatic UC
- No prior chemotherapy for advanced disease

Gemcitabine Platinum | **Durvalumab Tremelimumab** | **Durvalumab**

Adapted from Powles, ESMO 2020

Courtesy of Jonathan E Rosenberg, MD

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Current standard for first-line therapy

- First-line standard remains cisplatin-based chemotherapy in eligible patients

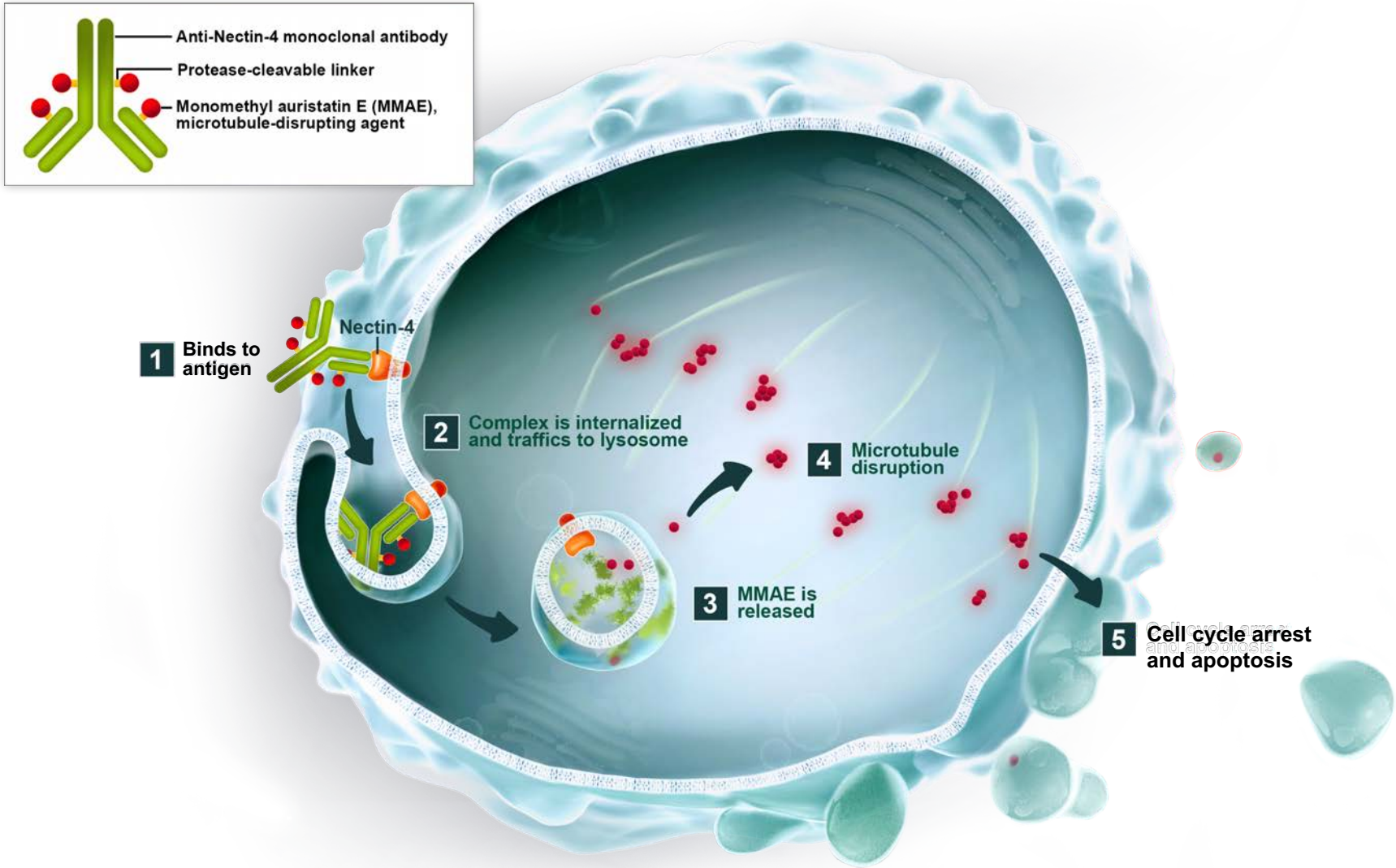
- Pembrolizumab or atezolizumab are FDA approved for PD-L1+ cisplatin-ineligible patients
  - IC 2/3 by SP142 (atezolizumab)
  - CPS ≥10% (pembrolizumab)

- Pembrolizumab and atezolizumab are also approved for platinum-ineligible patients regardless of PD-L1 status

- Less than 50% of patients who progress on first-line therapy receive 2nd-line treatment, and may partly explain results of JAVELIN Bladder 100
  - Early immunotherapy treatment improves outcomes

Courtesy of Jonathan E Rosenberg, MD

Enfortumab Vedotin: Nectin-4 Targeted Therapy



Courtesy of Jonathan E Rosenberg, MD

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EV-201 Trial: Enfortumab Vedotin has high antitumor activity in refractory patients

- Single arm phase II study in mUC patients previously treated with platinum-based chemotherapy and immunotherapy
- ORR 44%
  - Similar to phase I data
- 12% complete responses
- Responses seen in patients with liver metastases
- Median TTR is 1.8 months
- Median DOR is 7.6 months

Response	Patients (N = 125)
Objective response rate	55 (44)
95% CI*	35.1 to 53.2
Best overall response†	
Complete response	15 (12)
Partial response	40 (32)
Stable disease	35 (28)
Progressive disease	23 (18)
Not evaluable‡	12 (10)

Rosenberg et al. J Clin Oncol. 2019; 29; 2592-2600

Courtesy of Jonathan E Rosenberg, MD

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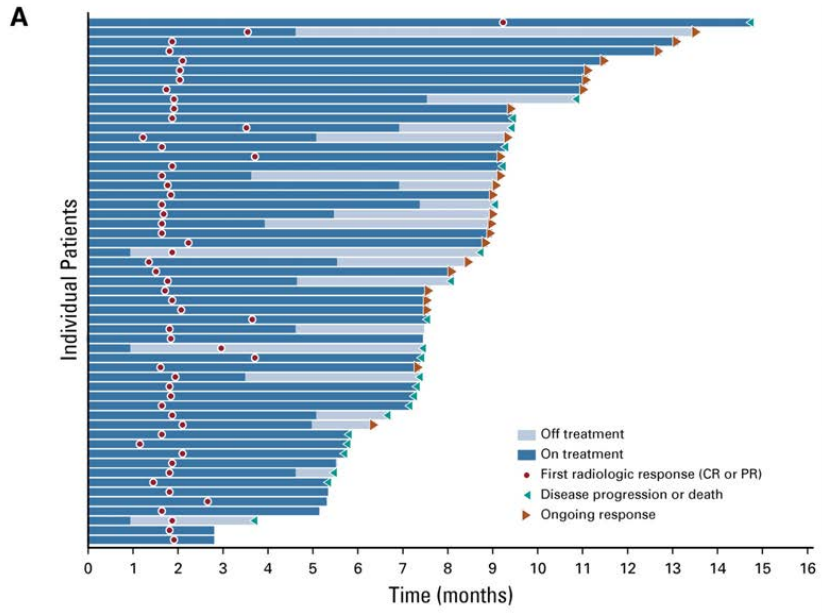
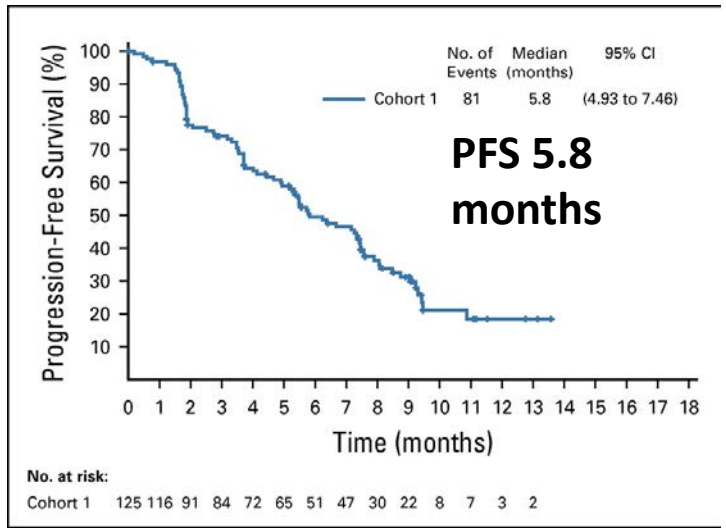
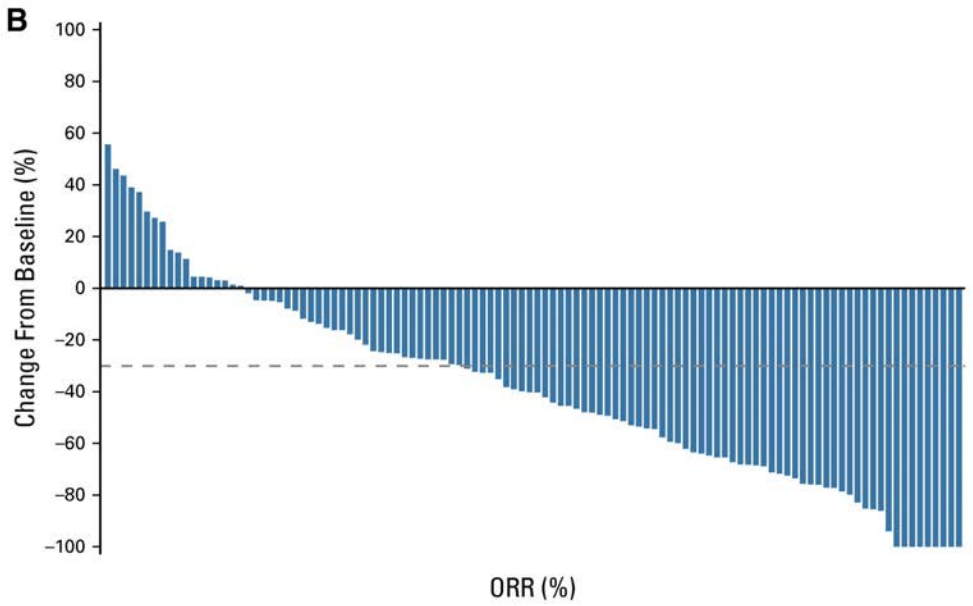
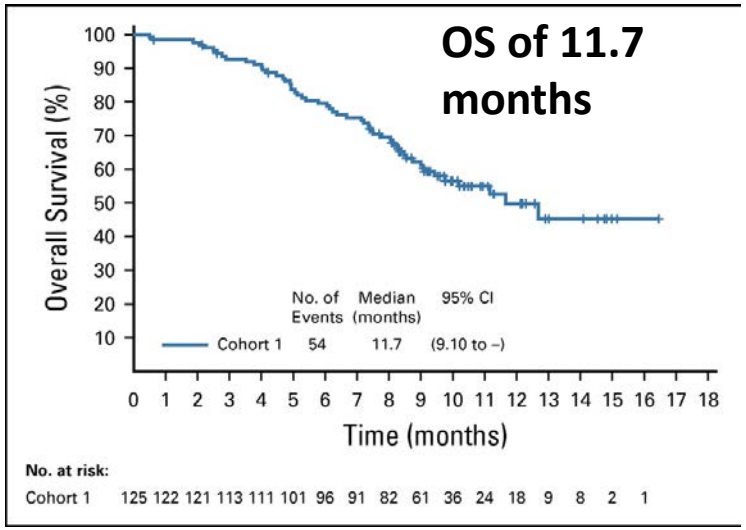
EV-201: Majority of patients have tumor reduction, many responses ongoing









Courtesy of Jonathan E Rosenberg, MD

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Rosenberg et al. J Clin Oncol. 2019; 29; 2592-2600

EV-201: Common Enfortumab Vedotin toxicities include fatigue, rash, neuropathy; hyperglycemia occurs and rarely may be severe

TABLE 3. Summary of Adverse Events in Patients Receiving Enfortumab Vedotin

Variable		Patients (N = 125)
Any adverse event		125 (100)
Treatment-related adverse events		117 (94)
Grade ≥ 3 treatment-related adverse events		68 (54)
Treatment-related serious adverse events		24 (19)
Treatment-related adverse events resulting in treatment discontinuation		15 (12)
Treatment-related adverse events leading to death*		0 (0)
Treatment-related adverse events occurring in ≥ 20% (preferred term)	Any Grade	Grade ≥ 3
Fatigue	62 (50)	7 (6)
Alopecia	61 (49)	0
Decreased appetite	55 (44)	1 (1)
Dysgeusia	50 (40)	0
Peripheral sensory neuropathy	50 (40)	2 (2)
Nausea	49 (39)	3 (2)
Diarrhea	40 (32)	3 (2)
Rash maculopapular	27 (22)	5 (4)
Weight decreased	28 (22)	1 (1)
Dry skin	28 (22)	0

NOTE. Data are presented as No. (%).

*There were no treatment-related deaths during the 30-day safety reporting period. One death as a result of interstitial lung disease that occurred outside the safety reporting period was reported as treatment related.

Courtesy of Jonathan E Rosenberg, MD

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Rosenberg et al. J Clin Oncol. 2019; 29; 2592-2600

EV-301: Randomized phase III trial of EV vs dealers choice chemotherapy (taxane or vinflunine)

- Enfortumab vedotin significantly improved overall survival compared to chemotherapy
  - 30% reduction in risk of death (Hazard Ratio [HR]=0.70; [95% Confidence Interval (CI): 0.56, 0.89]; p=0.001).
- Enfortumab vedotin also significantly improved PFS, a secondary endpoint
  - 39% reduction in risk of disease progression or death (HR=0.61 [95% CI: 0.50, 0.75]; p<0.00001).

Press release, September 18, 2020

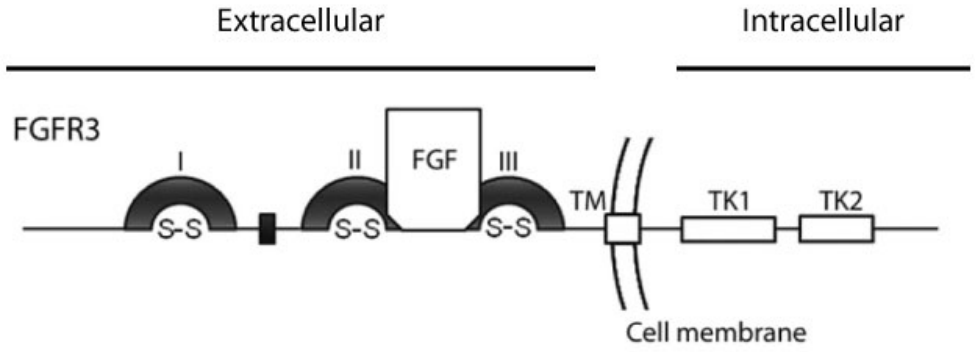
- FDA approved for platinum- and IO-previously treated patients
- Randomized phase III EV-301 shows improved overall survival compared to conventional chemotherapy
- First-line studies are ongoing alone and in combination with pembrolizumab

Courtesy of Jonathan E Rosenberg, MD

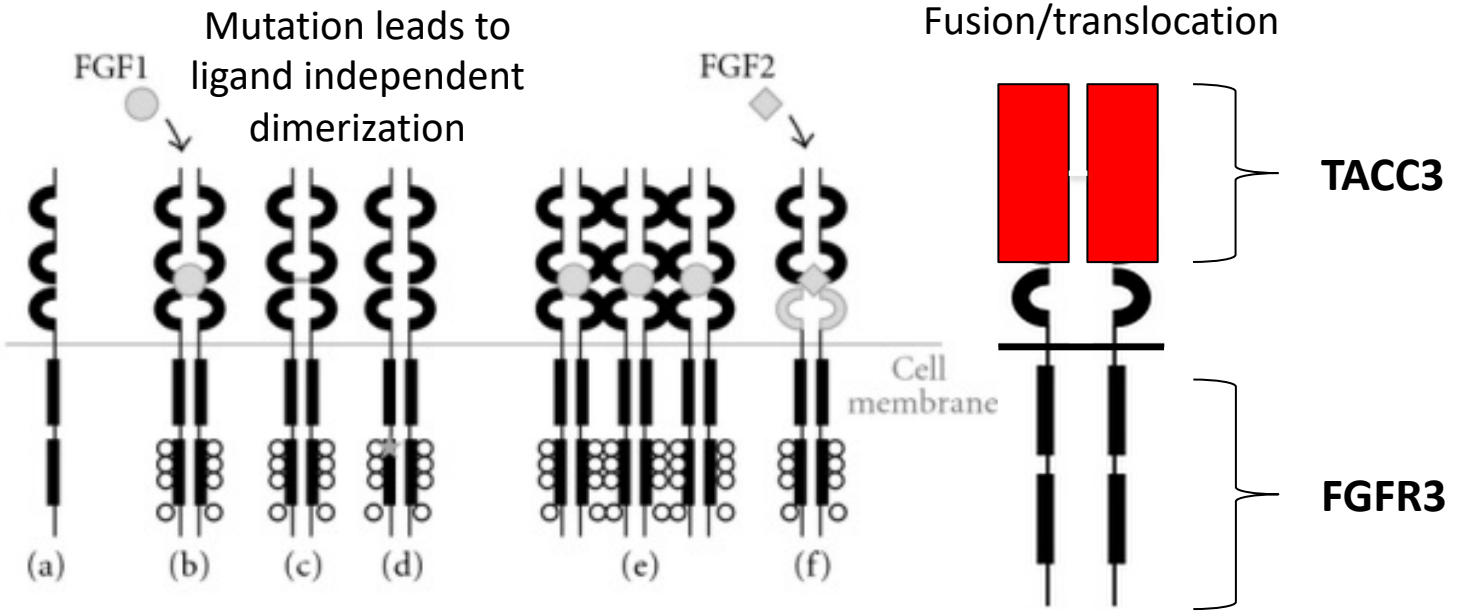
Fibroblast Growth Factor Receptor 3 is a therapeutic target in mUC

- Mutation frequency in non-invasive disease is >50% in Stage Ta tumors
- Mutations and fusions are less common in advanced UC
  - Mutation 5-15%
  - Fusion 3-5% using NGS

FGFR3 signals via PI3K, PKC, RAS/MAP kinase pathways



FGFR3 activation can occur by mutation, overexpression or gene fusion



Overexpression

Courtesy of Jonathan E Rosenberg, MD

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Erdafitinib is the first targeted therapy approved for advanced bladder cancer

- Accelerated approval: April 12, 2019
- Indicated in tumors with FGFR3 or FGFR2 alterations
  - Progression during or following prior platinum-containing chemotherapy
- Dosing:
  - 8 mg daily
  - Increase to 9mg daily if serum phosphorus level is <5.5 mg/dL (and no ocular disorders or ≥ grade 2 toxicity) at days 14-21 of therapy
  - Continue until disease progression or unacceptable toxicity occurs
  - Monthly ophthalmologic exams x 4 then q3 months

Courtesy of Jonathan E Rosenberg, MD

Memorial Sloan Kettering Cancer Center

BLC2001 Trial of Erdafitinib

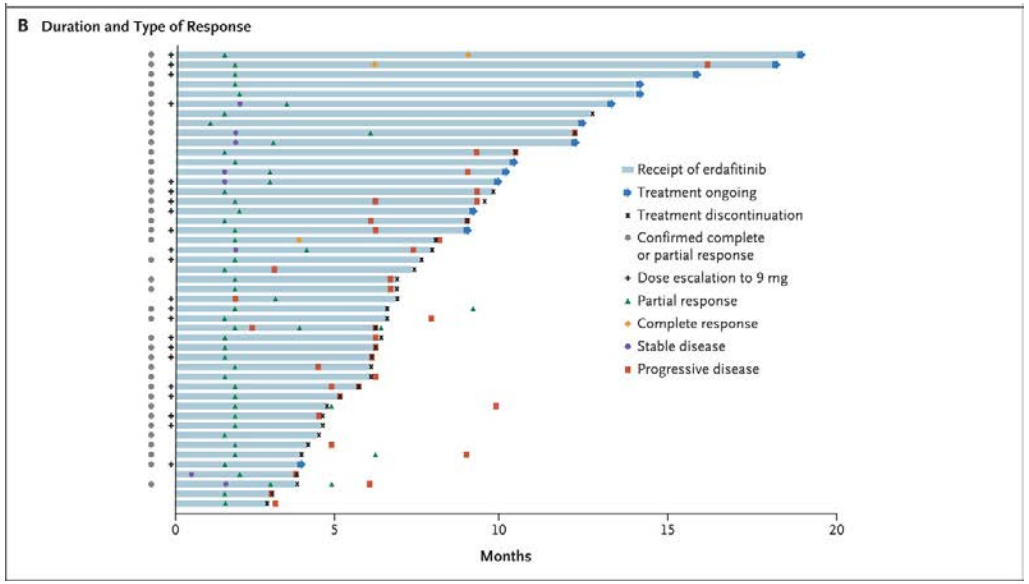
- Enrolled 99 patients with FGFR 1-3 alterations
- 88% had prior chemotherapy, 22% prior immunotherapy
- 12% had no prior systemic therapy
- Majority had visceral metastases
- Objective response rate 40% with 3% CR rate (per investigator)
  - Median TTR 1.4 months
  - Median DOR 5.6 months
- 5/12 patients without prior therapy responded (not FDA approved population)

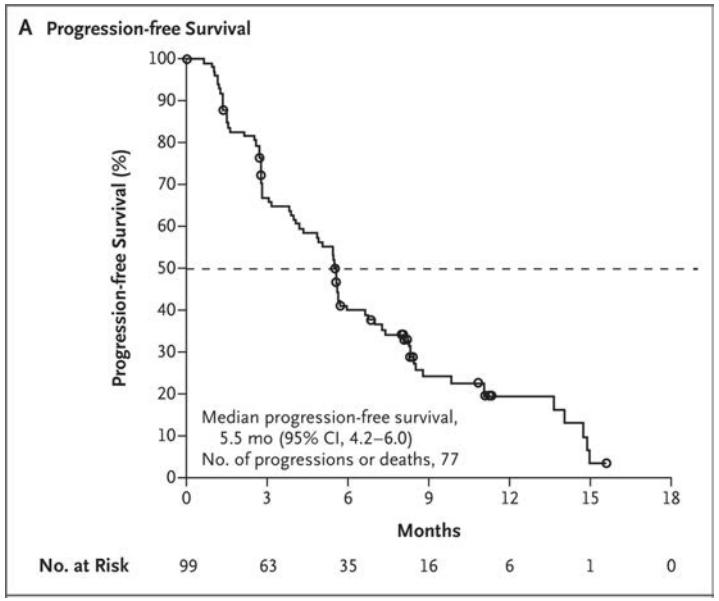
Y Loriot et al. N Engl J Med 2019;381:338-348.

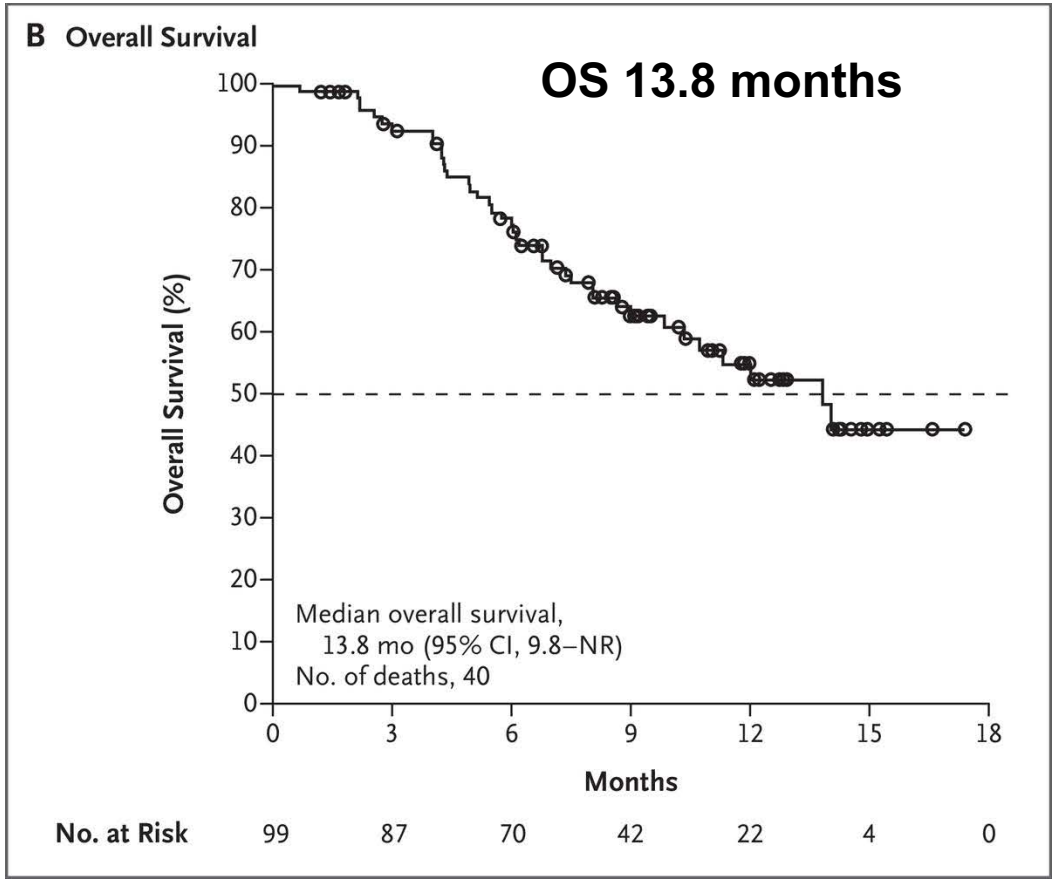
Courtesy of Jonathan E Rosenberg, MD

Memorial Sloan Kettering Cancer Center

BLC2001: Some patients treated with erdafitinib have responses >1 year







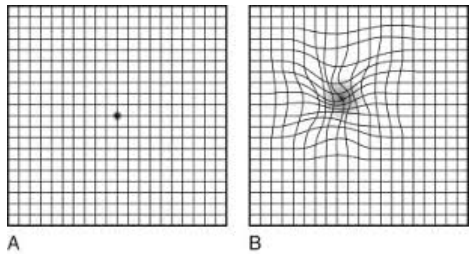
PFS 5.5 months

Y Loriot et al. N Engl J Med 2019;381:338-348.

Courtesy of Jonathan E Rosenberg, MD

BLC2001: Toxicity of erdafitinib

- 55% of patients required dose reductions
- 41% of patients were able to escalate to 9mg daily
- 59% required subsequent dose reductions
- 46% of patients had grade 3 or higher AE attributable to treatment
- Most common toxicities are hyperphosphatemia (on-target effect), stomatitis, and diarrhea
- Central serious retinopathy in 21% of patients, 3% grade 3
  - Generally reversible
  - Amsler grid testing



Y Loriot et al. N Engl J Med 2019;381:338-348.

Courtesy of Jonathan E Rosenberg, MD

Conclusions

- Platinum-based chemotherapy remains the first-line standard of care
- Avelumab maintenance in responders or for stable disease
- Pembrolizumab or atezolizumab monotherapy in selected patients
  - PD-L1 high
  - Platinum ineligible
- Enfortumab vedotin is FDA approved for immunotherapy and chemotherapy refractory tumors
- Erdafitinib is approved post-chemotherapy for FGFR2 and FGFR3 mutant tumors
  - Combinations with IO agents ongoing
- Despite dramatic advances, much work remains

Case 1

72 yo woman with history of DM2 and gross hematuria and renal insufficiency. She underwent radical cystectomy in 2017 with pT3bN0 tumor, negative margins.

One year later she presented with lung and lymph node metastases, and was treated with atezolizumab for 11 months with a minor response/stable disease as her best response.

Her course was notable for grade 2 transaminase elevation that resolved after a short course of corticosteroids

After 9 months, she developed symptomatic progressive disease and agreed to chemotherapy treatment with gemcitabine and carboplatin.

Case 1 (continued)

Gemcitabine and carboplatin was initiated with excellent palliative and radiographic response. Tumor next generation sequencing revealed the presence of an FGFR3 mutation (Y373C).

6 months following completion of chemotherapy, imaging showed progressive disease in the pelvis, liver, and lungs.

She was started on erdafitinib 8 mg daily. At 4 weeks, her phosphorus was 5.0 and her dose was escalated to 9mg daily.

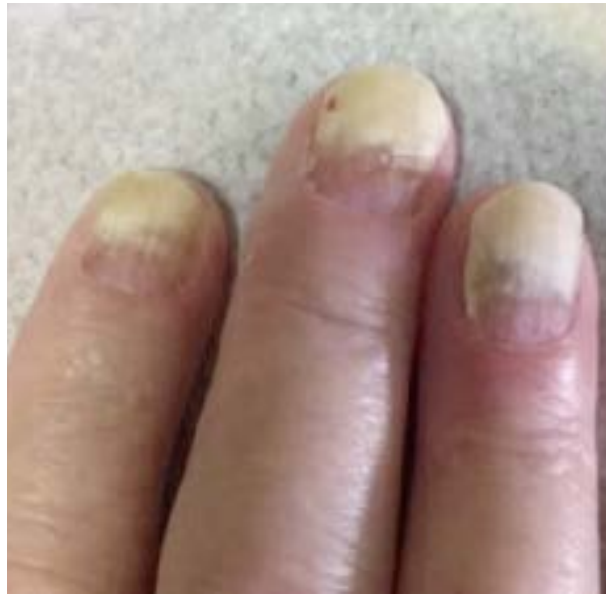
Case 1 (continued)

3 weeks later, she called with mucositis interfering with eating and was dose reduced back to 8 mg daily

6 weeks later, she presented with severe onycholysis of all her fingernails with pus, and grade 2 mucositis.

Erdafitinib was held and she received oral antibiotics and topical therapies for her fingernails.

Erdafitinib was dose reduced to 6mg and tolerated without incident until progressive disease 3 months later.



Courtesy of Jonathan E Rosenberg, MD

Case 2

59 yo woman initially presented with T1 bladder cancer s/p BCG, then developed metastatic disease 1 year later to lymph nodes.

She was treated with gemcitabine and cisplatin with a partial response.

She was observed after 6 cycles of treatment but developed progressive disease 8 months later.

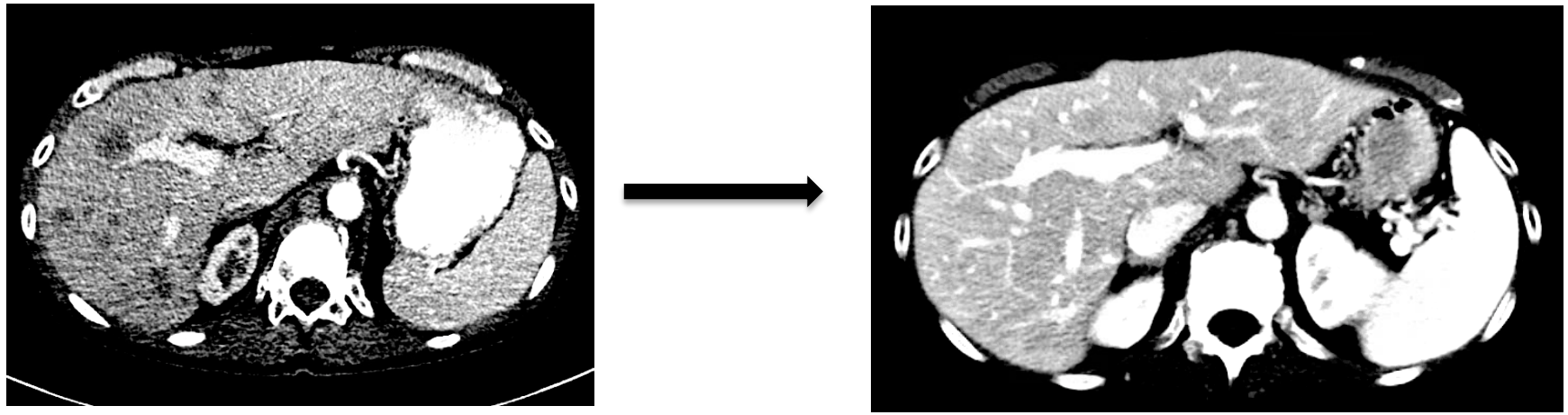
Mutation profiling showed an FGFR3 mutation and she was referred for a trial of a checkpoint inhibitor and an FGFR inhibitor. She developed rapidly progressive disease after 2 months of therapy.

She developed back and RUQ pain and was found to have large liver metastases and multiple new sclerotic lumbar spine lesions as well as enlarged lymph nodes.

Case 2 (continued)

Pt was treated with enfortumab vedotin. After 1 cycle, pain disappeared and she was no longer requiring opiates.

Imaging after 2 months showed dramatic regression of liver metastases and sclerosis of bone metastases consistent with treatment response.



Pt continued on therapy for 2 years. Treatment was complicated by grade 2 neuropathy managed with dose holding and dose reduction, along with physical and occupational therapy, with reduction to grade 1.

She experienced disease progression after 2 years.

Courtesy of Jonathan E Rosenberg, MD