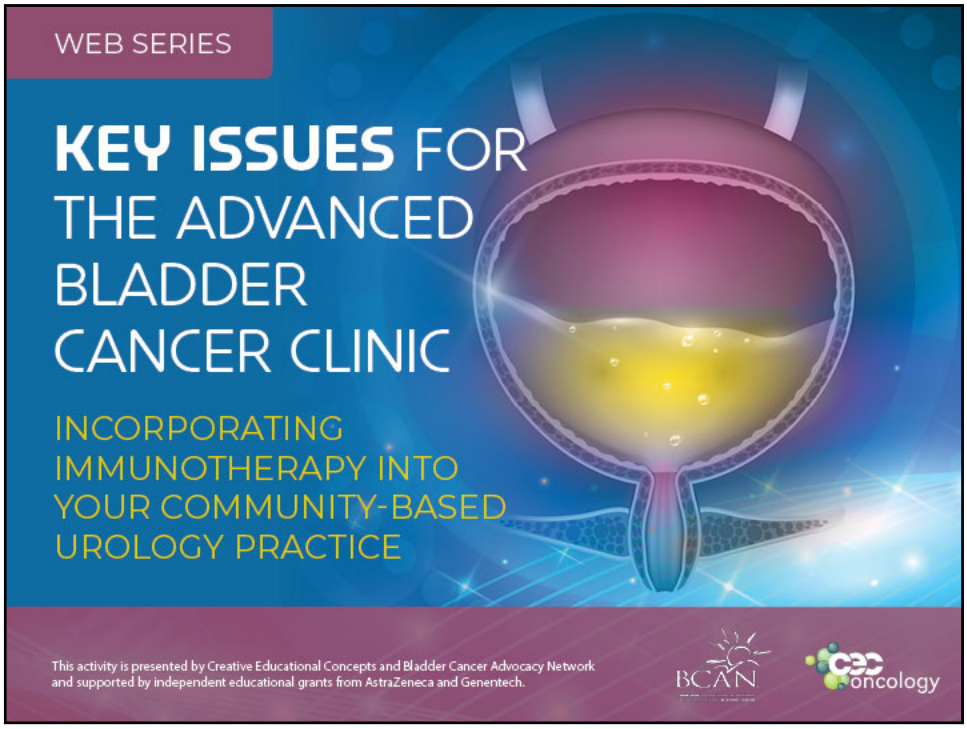

2020 and Beyond: How Immunotherapy is Changing the Game in Bladder Cancer Management

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Learning Objectives

At the conclusion of this on-demand internet activity, participants will be able to:

- Review conventional therapies for mUBC currently employed in community urology practice.
- Explore FDA-approved immune checkpoint inhibitors (ICIs) used in mUBC regarding mechanism of action, dosing, and applications for use.

Patient Case

A 65-year-old male underwent neoadjuvant chemotherapy with DD-MVAC x 4 cycles and radical cystectomy for treatment of MIBC. Ten months after radical cystectomy, he developed mid-back pain.

MRI revealed multilevel vertebral body osseous metastases, including a destructive lesion with no cord involvement.

PET scan revealed diffuse osseous metastases and multiple bilateral lung lesions measuring up to 2 cm, consistent with metastatic disease

Standard Therapy in Advanced Urothelial Cancer
The Current Paradigm

Setting		Regimen	Response Rate	Median Survival
First Line	Cisplatin-eligible	ddMVAC Gem/Cis PGC	40%–50%	12–15 months
	Cisplatin-ineligible	Gem/Carbo	36%–56%	7–9 months
	Platinum-ineligible or PD-L1 positive	Atezolizumab Pembrolizumab	~24%	~15.9 months (atezolizumab)
Second Line		Atezolizumab, Nivolumab, Durvalumab, Avelumab, Pembrolizumab	15%–19%	7.9–10.3 months
		Single-agent chemo	~10%	5–8 months
Second/Third Line		Erdafitinib	40%	13.8 months
Third Line		Enfortumab Vedotin	44%	Median DOR 7.6 months

Loehrer PJ Sr, et al. *J Clin Oncol*. 1992; von der Maase H, et al. *J Clin Oncol*. 2000; Bellmunt J, et al. *J Clin Oncol*. 2012; De Santis M, et al. *J Clin Oncol*. 2012; Linardou H, et al. *Urology.* 2004; Nogué-Aliguer M, et al. *Cancer.* 2003; Rosenberg JE, et al. *Lancet*. 2016; Loriot Y, et al. *N Engl J Med.* 2019; Rosenberg J, et al. *J Clin Oncol.* 2019.

Patients "Unfit" for Cisplatin-based Chemotherapy

- Represents 40%–60% of patients with advanced urothelial cancer
- Widely accepted definition includes
  - ECOG 2 or greater
  - Creatinine clearance ≤60 mL/min
  - Grade 2 or greater peripheral neuropathy/hearing loss
  - NYHA Class III heart failure

Galsky MD, et al. *J Clin Oncol*. 2011.

Systemic Chemotherapy

	Median Survival	Response Rates	Deaths (Toxicity)	Neutropenic Sepsis*	Mucositis* (Grade 3/4)
Gemcitabine/ Cisplatin	13.8 months	49.4%	1%	1%	1%
MVAC	14.8 months	45.7%	3%	12%	22%

- GC vs MVAC (Category 1)
  - OS and TTP similar at 19 months and 5 years

	CR*	Overall Response	Median Survival	TTP	FN*
ddMVAC	21%	62%	15.5 months	11.1 months	10%
MVAC	9%	50%	14.1 months	9.6 months	26%

*p<0.05

- ddMVAC vs MVAC (Category 1)
  - 24.6% vs 13.2% alive at 7.3 years
  - Require growth factor support

FN, febrile neutropenia.

von der Maase, et al. *J Clin Oncol*. 2000; von der Maase, et al. *J Clin Oncol*. 2005; Sternberg, et al. *Eur J Cancer*. 2006; Sternberg, et al. *J Clin Oncol*. 2001; Hayes TG, et al. *Handbook of Prostate Cancer and Other Genitourinary Malignancies*. 2017.

Systemic Chemotherapy

	ORR	ORR*
Gemcitabine/Carboplatin	42%	26%
Methotrexate/Carboplatin/ Vinblastine	30%	20%

*ECOG PS 2 and GFR <60mL/min

- Carboplatin may be substituted
  - Glomerular filtration rate (GFR) <60mL/min
  - Significant drop in efficacy in unfit patients and GFR <60mL/min

	OS*	ORR*	FN*
Gemcitabine/ Cisplatin	12.7 months	43.6%	4.3%
Gemcitabine/ Cisplatin/Paclitaxel	15.8 months	55.5%	13.2%

*p<0.05

- Taxane-containing chemotherapy
  - 3-drug regimens: OS benefit, increased toxicities
  - 2-drug regimens: modest benefit

De Santis, et al. *J Clin Oncol*. 2009; Bellmunt, et al. *J Clin Oncol*. 2012.

Immune Checkpoint Inhibitors Currently FDA Approved for UC after Platinum-based Therapy

Agent	Target	Dosing Schedule	Post Platinum
Atezolizumab	PD-L1	840 mg Q2W 1200 mg Q3W 1680 mg Q4W	Accelerated
Nivolumab	PD-1	240 mg Q2W 480 mg Q4W	Accelerated
Durvalumab	PD-L1	10 mg/kg Q2W	Accelerated
Avelumab	PD-L1	800 mg Q2W	Accelerated
Pembrolizumab	PD-1	200 mg Q3W 400 mg Q6W	Level 1*

*Dosing regimen of 400 mg every 6 weeks is approved under accelerated approval.

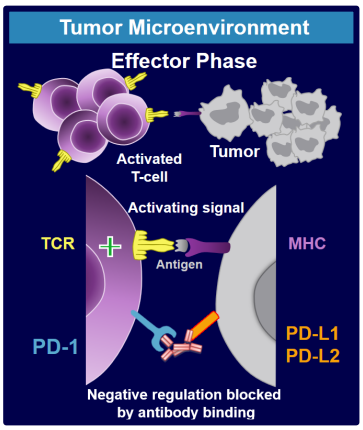


Image adapted from Ribas A. *N Engl J Med*. 2012.

Select ICI Trials

	IMvigor 210	CheckMate 275	Study 1108	JAVELIN Solid Tumor	Keynote 045	Keynote 052
Sample Size (n)	310	270	191	242	521	370
Population	Adults (≥18 years), locally advanced or metastatic UC, RECIST v1.1 measurable disease					Adults, platinum-ineligible
Primary Endpoint	ORR	ORR	ORR	ORR	PFS, OS	ORR
ECOG PS	0, 1	0, 1*	0, 1	0, 1	0, 1, 2**	0, 1, 2*
Liver Metastasis	31%	28%	43%	34%	34%	21%
Prior therapy	0– ≥4	0– ≥3	0– ≥4	0– ≥3	1–2	0***

*One patient had an ECOG PS of 3
**Patients with liver metastases (ECOG PS <2 required)
***Patients who had adjuvant or neoadjuvant platinum-based chemotherapy with recurrence more than 12 months from completion of that therapy were eligible for the trial (10%).

Front-line Pembrolizumab

KEYNOTE 052[1]

- Open-label, multicenter, single-arm, phase 2 trial
  - Cisplatin-ineligible patients, treatment naïve
  - Recurrence >12 months after platinum-based chemotherapy
- Accelerated first-line approval for cisplatin-ineligible patients

Outcomes	N=370
ORR, %	24 (95% CI: 20, 29)
Median DOR	NR (9 mo to NR)
CR, % **PR, %**	6 22
PFS (6 mo), %	31
OS (6 mo), %	67

KEYNOTE 361 (ongoing)[2]

- Phase 3 randomized, controlled clinical trial
- Pembrolizumab with or without platinum-based combination chemotherapy vs chemotherapy alone
- Primary outcomes: PFS and OS
- Preliminary findings
  - PD-L1–low status has decreased overall survival in the single-agent immunotherapy vs chemotherapy
  - Stopped enrolling patients with PD-L1–low status to the monotherapy arms

Limited indication for the treatment of patients with locally advanced or mUC who are not eligible for cisplatin-containing therapy and whose tumors express PD-L1 (Combined Positive Score ≥10), or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

[1]Balar A, et al. *Lancet Oncol*. 2017; [2]ClinicalTrials.gov. Identifier: NCT02853305.

Front-line Atezolizumab

IMvigor 210[1,2]

- Multicenter, single-arm, 2-cohort, phase 2 trial
  - Cisplatin-ineligible patients, treatment naive
  - Patients who had progressed on platinum-based chemotherapy
- Accelerated first-line approval for cisplatin-ineligible patients

Outcomes	N=119 (Cisplatin Ineligible)
ORR, %	19 (95% CI: 13, 28)
Tumor response per PD-L1 expression	
≥5%	22 (95% CI: 9, 40) (n=32)
<1% to <5%	19 (95% CI: 11, 29) (n=80)
Median DOR, mo	NR (3.7+ to 16.6+)
CR, %	6.7
PR, %	16.8

IMvigor 130 (ongoing)[3]

- Phase 3 randomized, controlled clinical trial
- Atezolizumab alone and in combination with chemotherapy vs chemotherapy
- Primary outcomes: PFS, OS, and AEs
- Preliminary findings: same as Keynote 361

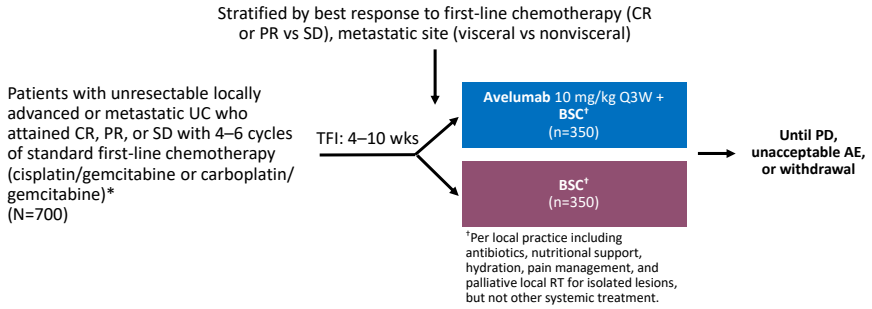
Limited indication for the treatment of patients with locally advanced or mUC who are not eligible for cisplatin-containing therapy, and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells covering ≥5% of the tumor area or are not eligible for any platinum-containing therapy regardless of PD-L1 status).

PD-L1 testing IS required for front-line treatment with checkpoint inhibitor unless ineligible for platinum-therapy.

[1]Rosenberg JE, et al. *Lancet*. 2016;
[2]Balar A, et al. ASCO Annual Meeting. 2016. Abstract LBA4500; [3]Galsky M, et al. ASCO Annual Meeting 2018. Abstract TPS4589.

Avelumab Maintenance *(Approved 07/2020)*

- Randomized, open-label phase III trial (data cutoff: October 21, 2019)

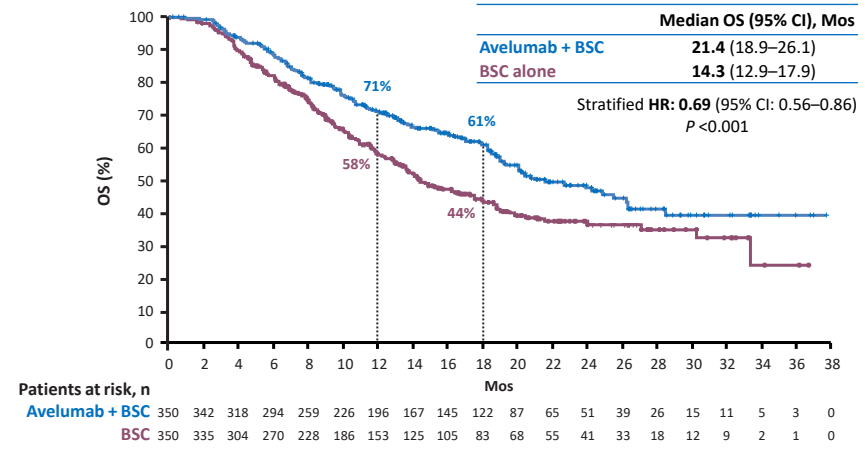


- Primary endpoint: OS in all randomized patients, PD-L1+ population
- Secondary endpoints: PFS (RECIST v1.1), ORR (RECIST v1.1), safety and tolerability, PROs

*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

Powles T, et al. 2020 ASCO Annual Meeting (virtual). Abstract LBA1.

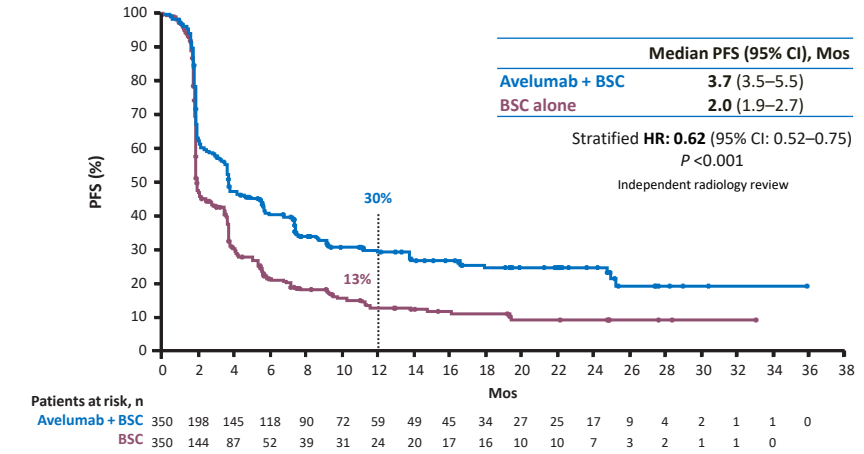
Avelumab Maintenance OS



OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (*P* <0.0053).

Powles T, et al. 2020 ASCO Annual Meeting (virtual). Abstract LBA1.

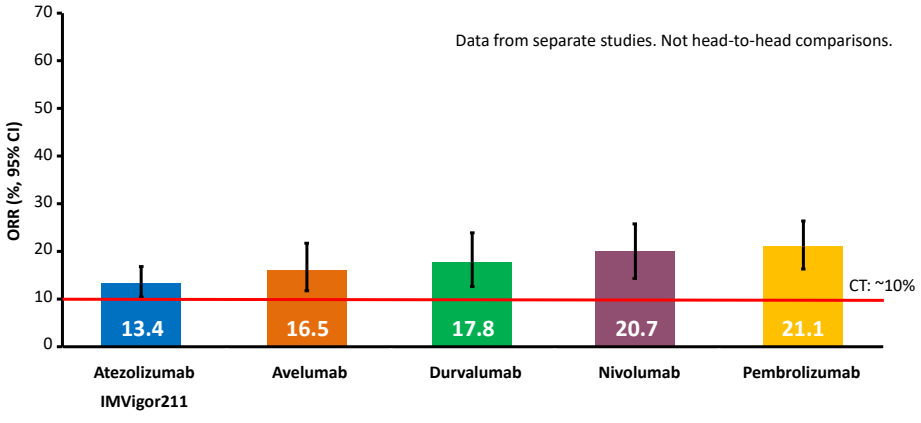
Avelumab Maintenance PFS



OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (*P* <0.0053).

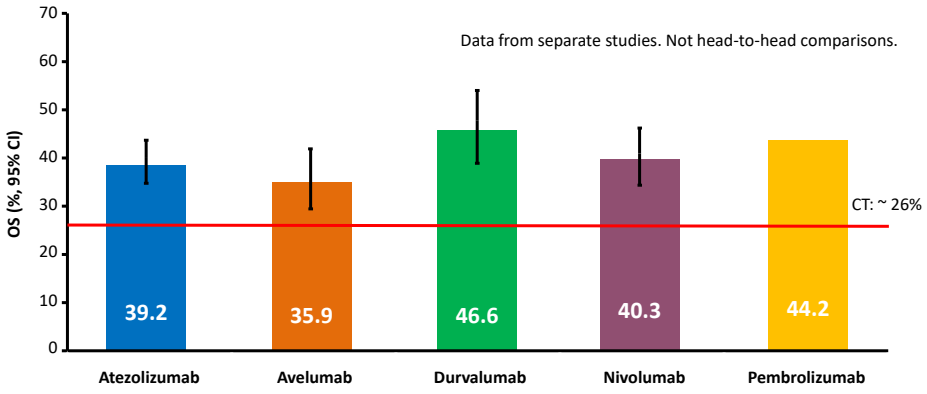
Powles T, et al. 2020 ASCO Annual Meeting (virtual). Abstract LBA1.

Second-line Setting
Overall Response after Platinum Therapy



Powles T, et al. *Lancet*. 2018; Apolo AB, et al. Genitourinary Cancers Symposium. 2019. Abstract 425; Powles T, et al. *JAMA Oncol*. 2017; Siefker-Radtke AO, et al. 2019 ASCO Annual Meeting. Abstract 4524; Fradet Y, et al. *Ann Oncol*. 2019.

Second-line Setting
12-Mo OS after Platinum Therapy



Powles T, et al. *Lancet*. 2018;
Apolo AB, et al. Genitourinary Cancers Symposium. 2019. Abstract 425; O'Donnell P, et al. 2018 AACR Annual Meeting. Abstract CT031;
Siefker-Radtke AO, et al. 2019 ASCO Annual Meeting. Abstract 4524; Fradet Y, et al. *Ann Oncol*. 2019.

Atezolizumab
IMvigor211 Results

- Randomized, phase III trial of atezolizumab vs chemotherapy (n=931)
- Endpoints
  - Primary: OS benefit in the second-line setting for patients with locally advanced or metastatic UC
  - Secondary: ORR, PFS, DOR
- Results
  - OS: failed to meet primary endpoint (11.1 vs 10.6 months)
    - HR 0.87, 95% CI 0.63–1.21, p=0.41
  - PFS: longer with chemotherapy
    - 4.0 months (95% CI 3.4–4.2) vs 2.1 months (95% CI 2.1–2.2)
  - DOR: longer with atezolizumab
    - 15.9 months (95% CI 10.4–NR) vs 8.3 months (95% CI 5.3–13.2)
  - ORR: similar in both groups

Powles T, et al. *Lancet*. 2018.

Pembrolizumab
Keynote-045 Results

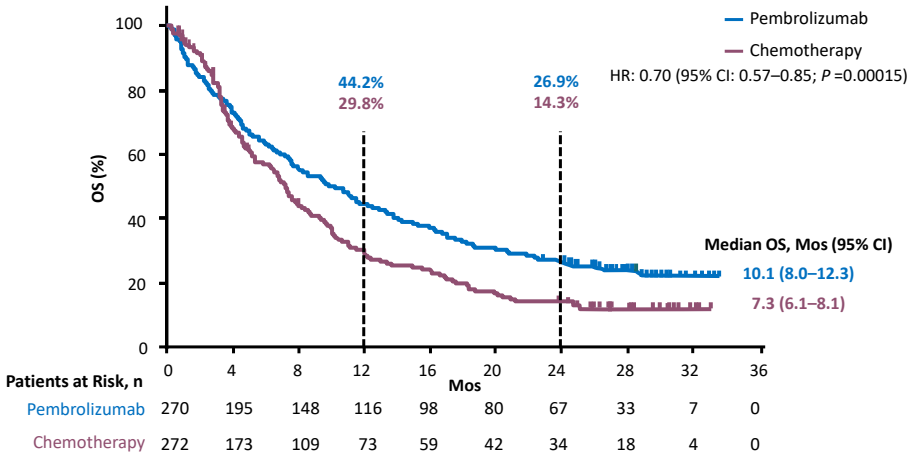
- International, randomized, open-label, phase III trial
  - Patients who had progressed on platinum-based chemotherapy or within 12 months for muscle-invasive disease
  - Pembrolizumab versus investigators choice of chemotherapy (paclitaxel, docetaxel, or vinflunine) for 2 years

Outcomes	Pembrolizumab (n=266)*	Chemotherapy (n=255)*
OS (months) **PD-L1 expression ≥10%**	10.3 (95% CI 8.0–11.8; p=0.002) 8.0 (95% CI, 5.0–12.3; p=0.005)	7.4 (95% CI 6.1–8.3) 5.2 months (95% CI, 4.0–7.4)
Median PFS	2.1 months (95% CI, 2.0–2.2; p=0.42)	3.3 months (95% CI, 2.3–3.5)
ORR	21.1% (95% CI, 16.4–26.5%; p=0.001)	11.4% (95% CI, 7.9–15.8%)
Median DOR	NR (1.6+ to 15.6+ months)	4.3 months (1.4+ to 15.4+)
CR	7%	3.3%

*Regular second-line approval after chemotherapy.

Bellmunt J, et al. *N Engl J Med*. 2017.

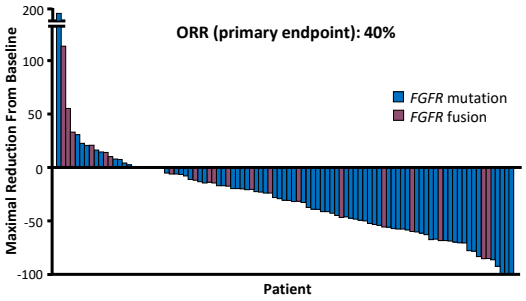
Phase III KEYNOTE-045
OS with Pembrolizumab in Recurrent UC at 24-months Follow-up

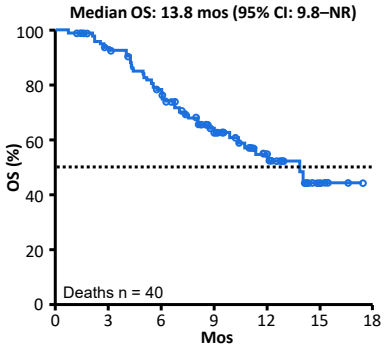


Fradet Y, et al. *Ann Oncol*. 2019.

Pivotal Phase II Erdafitinib Study in *FGFR*-positive Metastatic UC after ≥1 Line Platinum-based Chemo

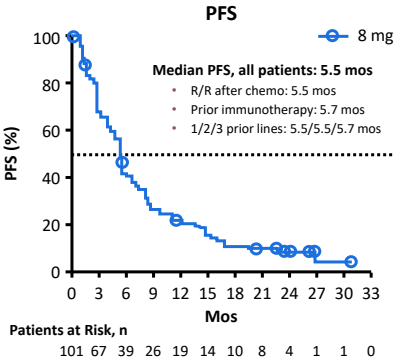
- Erdafitinib: oral pan-FGFR (1–4) inhibitor
- Patients with metastatic UC and *FGFR* mutation or fusion (prevalence in metastatic UC: 15%– 20%)
  - At least 1 prior systemic therapy; prior ICI allowed

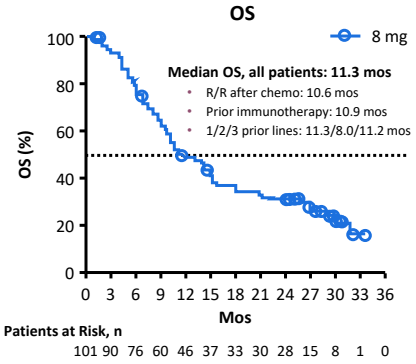




Siefker-Radtke AO, et al. 2018 ASCO Annual Meeting. Abstract 4503; Loriot Y, et al. *N Engl J Med*. 2019.

Pivotal Phase II Erdafitinib Study
Updated PFS and OS





Siefker-Radtke AO, et al. 2020 ASCO Annual Meeting (virtual). Abstract 5015.

Novel Therapy
Erdafitinib Clinical Pearls

- Novel mechanism of action, first targeted therapy and orally available option in UC treatment
  - MOA: Pan-FGFR inhibitor (FGFR 1–4)
  - **Approved** for FGFR 2–3 mutations or fusions
- 8 mg PO daily (w/ or w/o food) with dose increase to 9 mg daily if criteria are met
  - Day 14 to 21 phosphorus <5.5 mg/dL
  - No ocular disorders
  - No grade ≥2 AEs
- Increase occurred in **41% of patients**
- Restricted distribution (US Bioservices specialty pharmacy): tablets: 3 mg, 4 mg, 5 mg

Adverse Reaction (8 mg/day)	All Grade (%)	Grade 3–4 (%)
Any	100	67
Gastrointestinal disorders	92	24
Metabolism and nutrition disorders	90	16
General disorders and admin site conditions	69	13
Skin and subcutaneous disorders	75	16
Eye disorders	62	11
Nervous system disorders	57	5
Infections and infestations	56	20
Respiratory, thoracic, and mediastinal disorders	40	7
Renal and urinary tract disorders	38	10
Musculoskeletal and connective tissue disorders	31	0

FDA Prescribing Information.

Erdafitinib Ocular Toxicity

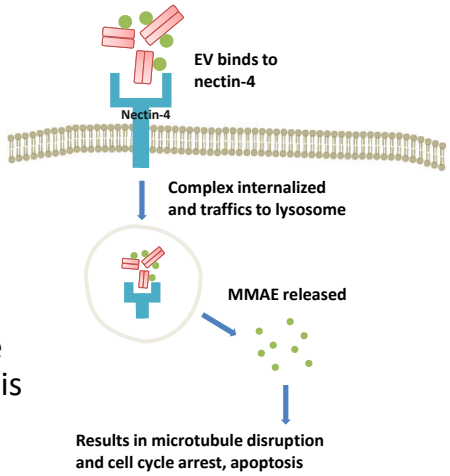
- Central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED) were reported in 25% of patients
  - First onset of 50 days
  - Grade 3 in 3% of patients
  - Usually resolve or improve after dose hold
  - Ongoing in 13% of patients at the study cutoff
  - 9% dose interruptions, 14% reductions, 3% discontinuations
- Dry eye symptoms occurred in 28% of patients with grade 3 in 6% of patients
  - All patients should receive dry eye prophylaxis with ocular demulcents as needed
- Monthly ophthalmological examinations during the first 4 months of treatment and every 3 months afterward, and urgently at any time for visual symptoms
  - Assessment of visual acuity, slit lamp examination, fundoscopy, optical coherence tomography

FDA Prescribing Information.

Enfortumab Vedotin

An Antibody–drug Conjugate Targeting Nectin-4

- Enfortumab vedotin[1]
  - A fully humanized monoclonal antibody against nectin-4
  - Conjugated with microtubule-disrupting agent, monomethyl auristatin E (MMAE), by a protease-cleavable linker
- Nectin-4 is a transmembrane cell adhesion molecule[2] that is highly expressed in 97% of mUC patient samples[3]



[1]Challita-Eid PM, et al. *Cancer Res*. 2016. [2]Samanta D, Almo SC. *Cell Mol Life Sci*. 2015; [3]Petrylak DP, et al. *J Clin Oncol*. 2017.

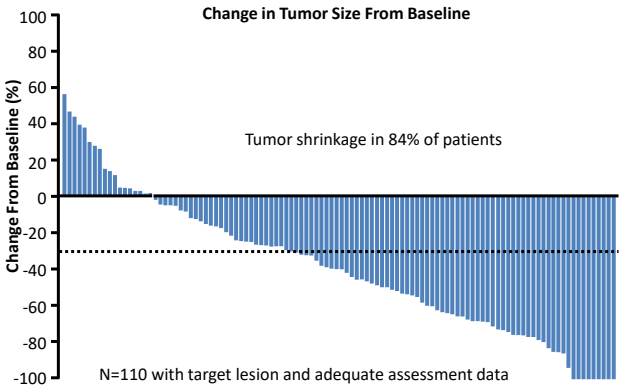
EV-201 Cohort 1

Response to Enfortumab Vedotin Monotherapy in Metastatic UC

Pivotal phase II trial of enfortumab vedotin 1.25 mg/kg in mUC after platinum-based chemo and immune checkpoint inhibitor.

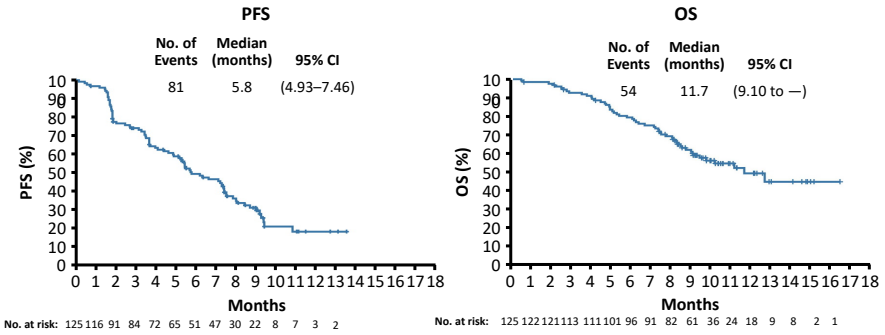
Response, n (%)	Cohort 1 (n = 125)
Confirmed ORR	55 (44)
Best overall response per RECIST 1.1	
• **CR**	15 (12)
• **PR**	40 (32)
• **SD**	35 (28)
• **PD**	23 (18)

All patients had previous platinum and checkpoint therapy



Rosenberg JE, et al. *J Clin Oncol*. 2019.

EV-201 Cohort 1
PFS and OS with Enfortumab Vedotin



Rosenberg JE, et al. *J Clin Oncol*. 2019.

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

*No treatment-related deaths were reported during the 30-day safety reporting period; 1 death, as a result of interstitial lung disease, that occurred outside the reporting period was reported as treatment-related.

Rosenberg J, et al. *J Clin Oncol.* 2019.

Patient Case

What is the next most appropriate step in his management?

What is the role of potential biomarkers and molecular testing?

- PD-L1 expression
- *FGFR* mutation status
- Tumor mutational burden
- Nectin-4 expression
- NGS to evaluate for other tumor-agnostic biomarkers