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CHALLENGING CASES

Bladder Cancer

Challenging Cases in Bladder Cancer

Presented by Dr. Eric Schaefer

Program Disclosures

The information presented is consistent with FDA Guidelines and includes the latest clinical trial data

This program has been provided as an opportunity for discussion and learning, with insights from key opinion leaders

Sponsored by:

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Challenging Cases in Bladder Cancer

Presented virtually
on December 20th, 2023

Bladder Cancer

Patient case: untreated metastatic disease

- *What is the optimal first line therapy? Second line therapy?*
- *How to incorporate new clinical trial data and FDA approvals?*
- *Sequencing considerations to provide the best outcomes for patients?*

Note: Aggregated results and discussion are based on 6 oncologists and do not necessarily reflect the views and opinions of the moderator or Cornerstone Specialty Network unless otherwise stated

Patient History

59-year-old male with urothelial cancer of the bladder

Other medical history includes DM with both DM neuropathy and DM retinopathy

Diagnosis

Metastatic disease 11/2022

What first-line metastatic treatment do you recommend?

CPS=combined positive score

Open-text Response Results from HCP Participants

What first-line metastatic treatment do you recommend?

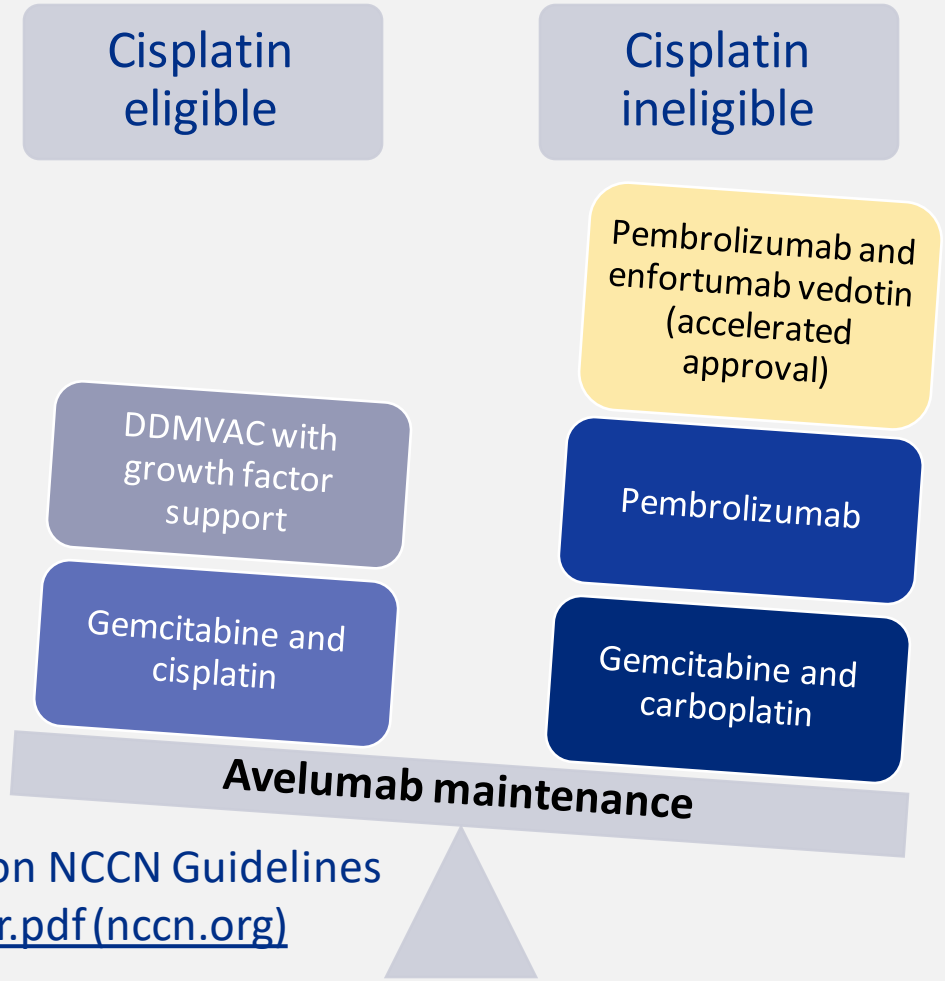
- *Pembrolizumab and EV*
- *Chemotherapy followed by IO*
- *Padcev + Keytruda*

Discussion with HCP Participants

How does cisplatin eligible versus cisplatin ineligible impact treatment decisions?

- *In general, if stage 4 disease and younger patient tend to avoid cisplatin, unless in the neoadjuvant curative setting*
- *General criteria for determining cisplatin ineligibility include performance status, age, hearing loss, neuropathy, and cardiac issues but now less important*
- *Previously cisplatin eligibility/ineligibility was less important but now the data with Padcev is better, so it is more impactful*
- *Swayed now to say all patients are cisplatin ineligible based on the Padcev data*

1L Metastatic Treatment Options



Based on NCCN Guidelines
bladder.pdf (nccn.org)

Choice of treatment

- Some patients cannot receive cisplatin-based chemotherapy due to renal-impairment or other comorbidities
- Non-nodal metastases
- ECOG performance status
- Accelerated approval versus full approval

On April 3, 2023, the Food and Drug Administration granted accelerated approval to enfortumab vedotin-ejfv (Padcev, Astellas Pharma) with pembrolizumab (Keytruda, Merck) for patients with locally advanced or metastatic urothelial carcinoma who are ineligible for cisplatin-containing chemotherapy based on EV-103/KEYNOTE-869.

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NCCN Guidelines for Bladder Cancer: 1L

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Bladder Cancer

NCCN Guidelines Index
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PRINCIPLES OF SYSTEMIC THERAPY

First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)	
Cisplatin eligible	**Preferred regimens** • Gemcitabine and cisplatin[4] (category 1) followed by avelumab maintenance therapy (category 1)[a,11] • DDMVAC with growth factor support (category 1)[2,8] followed by avelumab maintenance therapy (category 1)[a,11]
Cisplatin ineligible	**Preferred regimens** • Gemcitabine and carboplatin[12] followed by avelumab maintenance therapy (category 1)[a,11] • Pembrolizumab[14] (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy) • Pembrolizumab and enfortumab vedotin-ejfv[17] **Other recommended regimens** • Gemcitabine[15] • Gemcitabine and paclitaxel[16] • Atezolizumab[13] (only for patients whose tumors express PD-L1[b]) (category 2B) **Useful under certain circumstances** • Ifosfamide, doxorubicin, and gemcitabine[18] (for patients with good kidney function and good performance status) • Atezolizumab[13] (only for patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 3)

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Recent clinical trial data from ESMO will be practice changing

COMPARISON

Untreated locally advanced or metastatic urothelial carcinoma

	EV302/KEYNOTE-A39		CheckMate 901	
Inclusion Criteria	Patients with locally advanced/mUC, No prior systemic therapy except for (neo)adjuvant chemo pre/post cystectomy and recurrence >12 mo after end of therapy, Eligible for platinum, enfortumab vedotin, and pembrolizumab, PD-1/PD-L1 inhibitor naïve, GFR ≥30 mL/min ECOG PS 0-2		Adults with previously untreated unresectable or metastatic UC of renal pelvis, bladder, urethra, or ureter Eligible for cisplatin ECOG PS 0/1	
N	886		608	
Study design	Enfortumab Vedotin-ejfv + Pembro	Gemcitabine + Cisplatin or Carboplatin	Nivolumab + Gemcitabine + Cisplatin	Gemcitabine + Cisplatin
Median OS	31.5 (25.4-NR)	16.1 (13.9-18.3)	21.7 (18.6-26.4)	18.9 (14.7-22.4)
	HR: 0.47 (0.38-0.58; **P < 0.00001**)		**HR: 0.78** (0.63 – 0.96) *P* = 0.0171	
Median PFS	12.5 (10.4-16.6)	6.3 (6.2-6.5)	7.9 (7.6-9.5)	7.6 (6.1-7.8)
	HR: 0.45 (0.38-0.54; **P < 0.00001**)		**HR: 0.72** (0.59 – 0.88) *P* = 0.0012	
ORR | CR	67.7% | 29.1%	44.4% | 12.5%	57.6% | 21.7%	43.1% | 11.8%
TRAE Grade ≥3	56%	70%	62%	52%
Other considerations	How to sequence treatments?		Financial considerations?	
Reference	ESMO 2023. Abstr LBA6		ESMO 2023. Abstr LBA7	

Discussion with HCP Participants

What will be your new standard of care for bladder cancer in the 1L setting?

- *Confident of the data from both CheckMate-901 and EV302 against Gem/Cis; both demonstrate superiority to chemotherapy*
- *Double OS (in EV302 trial) is really good*
- *CR is most impactful*
- *EV302 data is practice changing; sad it took so long to bypass Gem/Cis, no one gets Gem/Cis and goes into remission*
- *EV + IO provides a long-term durable response but can be patient dependent; have a young patient that is progressing while 90-year-old patient is doing well*
- *Cost of EV + IO can be a problem but will still recommend for all eligible patients based on impactful data; insurance is there for a reason*
- *So far used EV only in the 2L setting*
- *Dose reduction or dose interruption in the 2L setting cuts cost of EV*

Discussion with HCP Participants

What will be your new standard of care for bladder cancer in the 1L setting?

Side effects with Padcev + Keytruda

- *Start on lower dose of EV and titrate up; don't get to full dose; multiple delays*
- *Challenges with neuropathy, rash, GI, and eye issues; start patients on EV at 7.5 mg/kg (second dose reduction level) then go up to 1.0 mg/kg (first dose reduction level)*
- *For skin rash it can be difficult to know if it is caused by Padcev or Keytruda; treat with topical steroids, generally don't dose reduce for rash*
- *Start patients at lower dose*
- *Recommended dose is too harsh*
- *Not used Padcev yet, hard to tolerate; preference for another treatment regimen*

1L Treatment

Keytruda

Initially was treated with single agent Keytruda due to CKD and not eligible for cisplatin

Progression

Progressed in 6 months

Solitary brain mets

Treated with SRS

How often do you test metastatic lesions on first tumor progression?

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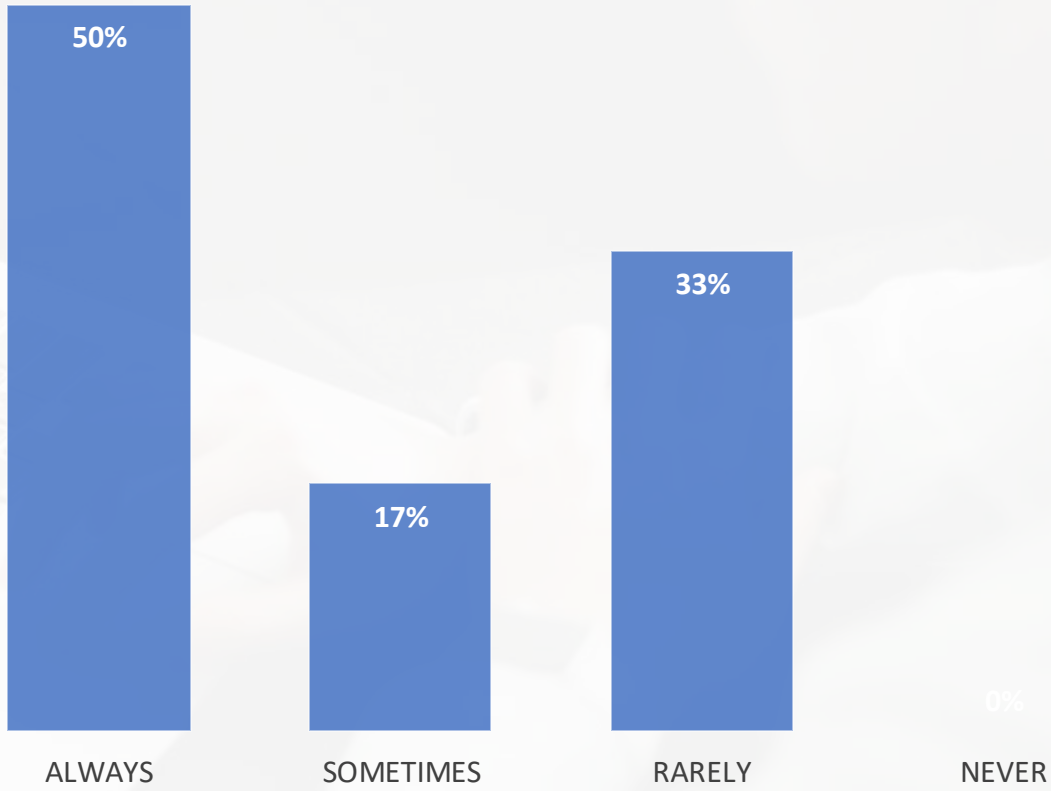
Open-text Response Results from HCP Participants

How often do you test metastatic lesions on first tumor progression?



Discussion with HCP Participants

How often do you test metastatic lesions on first tumor progression?

General view that both tissue and liquid biopsy are done on first tumor progression

- *Tissue and liquid on first progression*
- *Do both tissue and liquid*
- *Tissue and liquid*

Progression

1L treatment: Keytruda

Site of Metastases:

Solitary brain mets

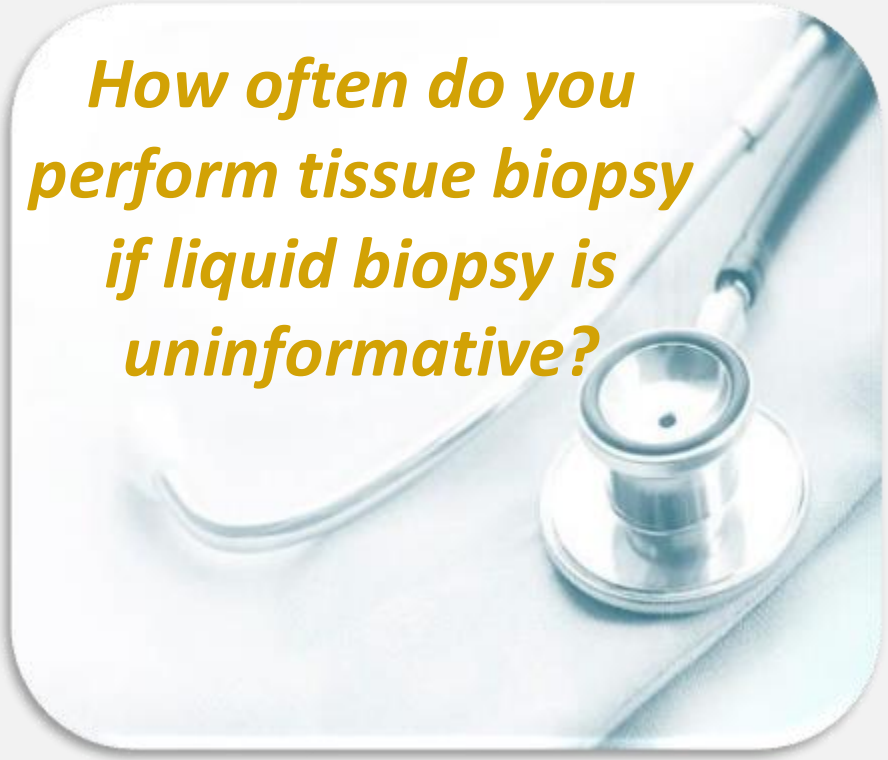
Treated with SRS

Diagnostics

Testing Results:

Liquid NGS testing did not reveal any actionable mutations

How often do you perform tissue biopsy if liquid biopsy is uninformative?



Open-text Response Results from HCP Participants

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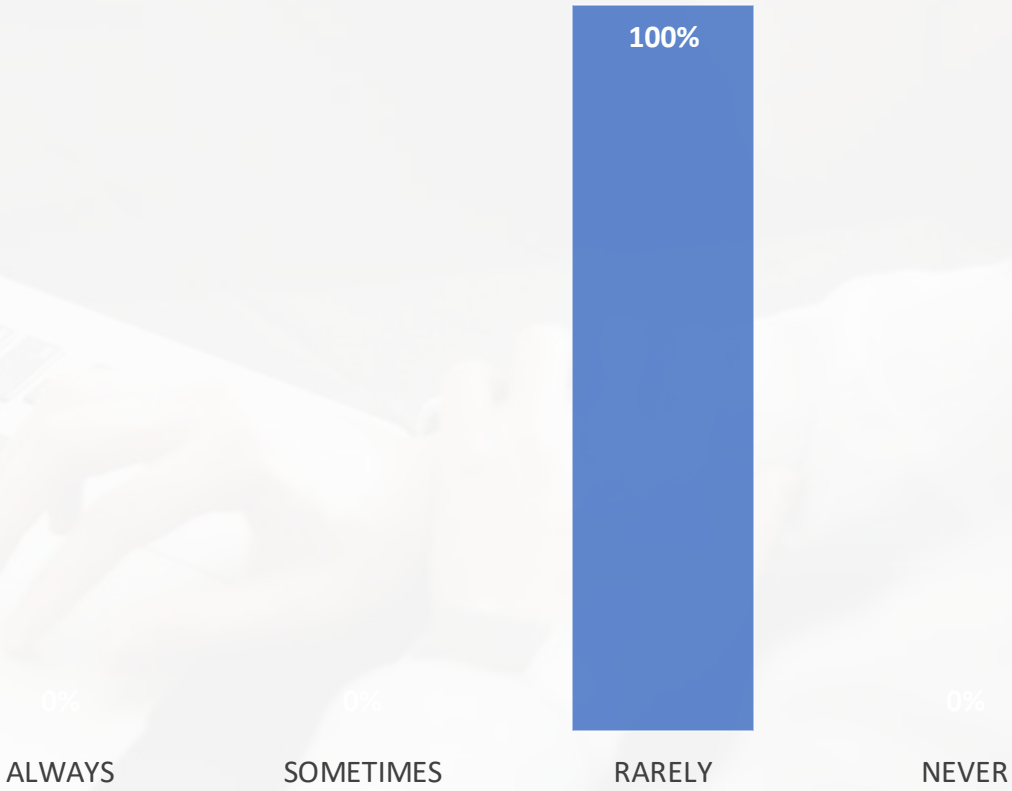


Progression

1L treatment: Keytruda

Site of Metastases:

Solitary brain mets

Treated with SRS

Diagnostics

Testing Results:

Liquid NGS testing did not reveal any actionable mutations

What treatment do you recommend next?

Open-text Response Results from HCP Participants

What treatment would you recommend next?

- *Padcev or single-agent chemo*
- *Trodelvy*
- *Carbo taxol*

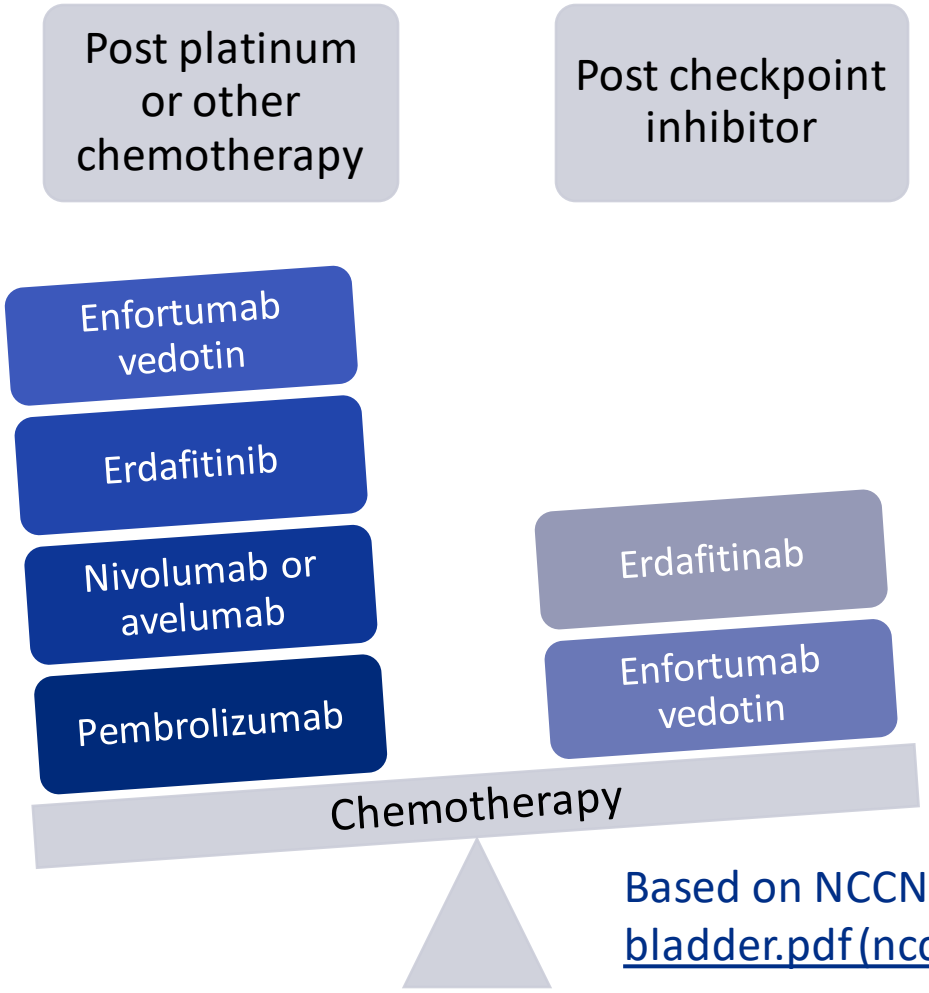
Discussion with HCP Participants

What treatment would you recommend next?

Trodelvy in the 2L setting?

- *Use Trodelvy in the 2 L setting; use of Trodelvy in later lines makes it harder to tolerate*
- *Have used Trodelvy in breast cancer but not in bladder cancer*
- *Limited use of Trodelvy in bladder cancer in a phase 1 trial*
- *Diarrhea and neutropenia with Trodelvy are challenging*
- *Lot of GI issues with Trodelvy with breast cancer patients*

2L Metastatic Treatment Options



Based on NCCN Guidelines
bladder.pdf (nccn.org)

Choice of treatment

- Length of time of progression-free survival
- Cisplatin-eligible versus cisplatin-ineligible patients
- Lack of actionable mutations

NCCN Guidelines for Bladder Cancer: 2L

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Bladder Cancer

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PRINCIPLES OF SYSTEMIC THERAPY

Second-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV) (post-platinum or other chemotherapy)[c] Participation in clinical trials of new agents is recommended.	
Preferred regimen • Pembrolizumab (category 1 post-platinum)[20]	**Other recommended regimens** • Paclitaxel[26] or docetaxel[27] • Gemcitabine[15] • Pembrolizumab and enfortumab vedotin-ejfv (category 2B)[17]
Alternative preferred regimens • Immune checkpoint inhibitor ▸ Nivolumab[21] ▸ Avelumab[22,23] • Erdafitinib[d,24] • Enfortumab vedotin-ejfv[e,25]	**Useful in certain circumstances based on prior medical therapy** • Ifosfamide, doxorubicin, and gemcitabine[18] • Gemcitabine and paclitaxel[16] • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]

Second-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV) (post-checkpoint inhibitor) Participation in clinical trials of new agents is recommended.	
Preferred regimens for cisplatin ineligible, chemotherapy naïve • Enfortumab vedotin-ejfv[25] • Gemcitabine and carboplatin	**Other recommended regimens** • Erdafitinib[d,24] • Paclitaxel or docetaxel[27] • Gemcitabine[15]
Preferred regimens for cisplatin eligible, chemotherapy naïve • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]	**Useful in certain circumstances based on prior medical therapy** • Ifosfamide, doxorubicin, and gemcitabine[18] • Gemcitabine and paclitaxel[16]

*On **July 9, 2021**, the FDA approved enfortumab vedotin-ejfv (Padcev) for adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 or programmed death-ligand inhibitor and platinum-containing chemotherapy, or are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy*

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Treatment

Enfortumab vedotin

Progression

Unfortunately, after 3 cycles was diagnosed with CNS disease requiring WBRT

Stopped PADCEV

Patient refused hospice

How often do you test new metastatic lesions on subsequent progression(s)?

Discussion with HCP Participants

How often do you test new metastatic lesions on subsequent progression(s)?

- *Just liquid*
- *Recheck liquid*
- *On second progression, liquid biopsy*
- *Liquid on subsequent progression as could qualify for clinical trial(s)*
- *Occasionally subsequent liquid biopsy(s) result in changes*

Progression

Repeat MRI revealed new CNS lesions

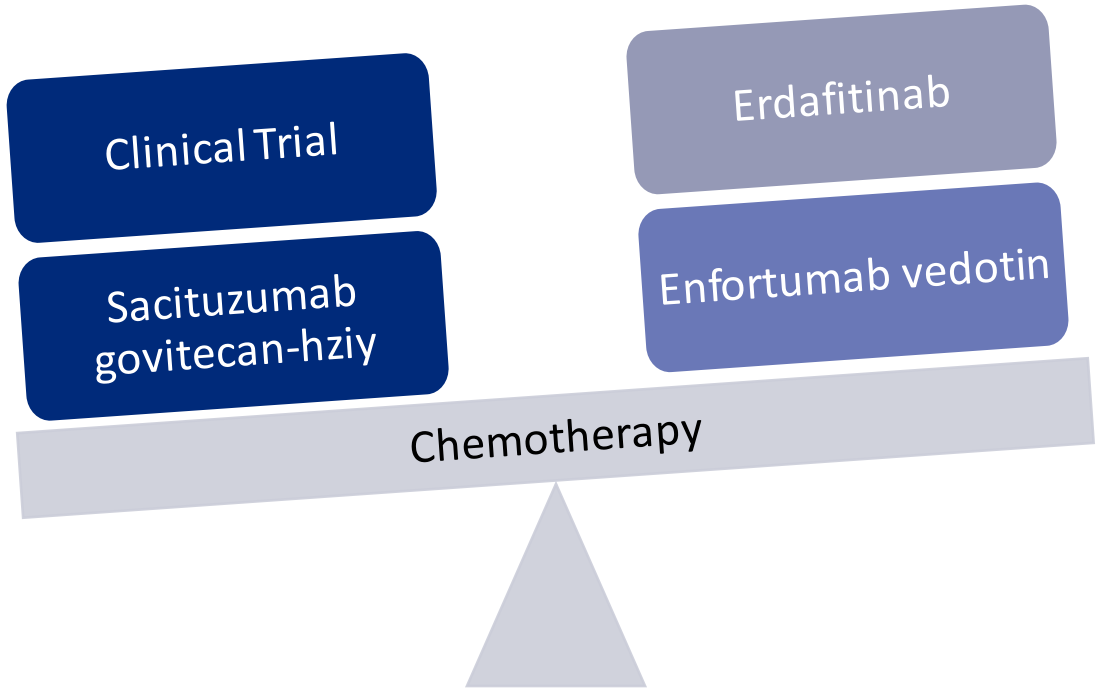
Diagnostics

Not a candidate for more XRT

Rebiopsy revealed FGFR mutation

What treatment would you recommend next?

3L+ Metastatic Treatment Options



Choice of treatment

- No head-to-head comparisons between the agents
- Limited data to support sequencing of therapies
- Discussion of hospice care

Discussion with HCP Participants

What treatment would you recommend next?

- *If patient is able, potential for a clinical trial*
- *Taxol*
- *Taxol*
- *If prior use of EV, compromises 2L treatment but, in general, use most potent treatment as early as possible to achieve maximum response (improved OS and PFS with earlier use)*

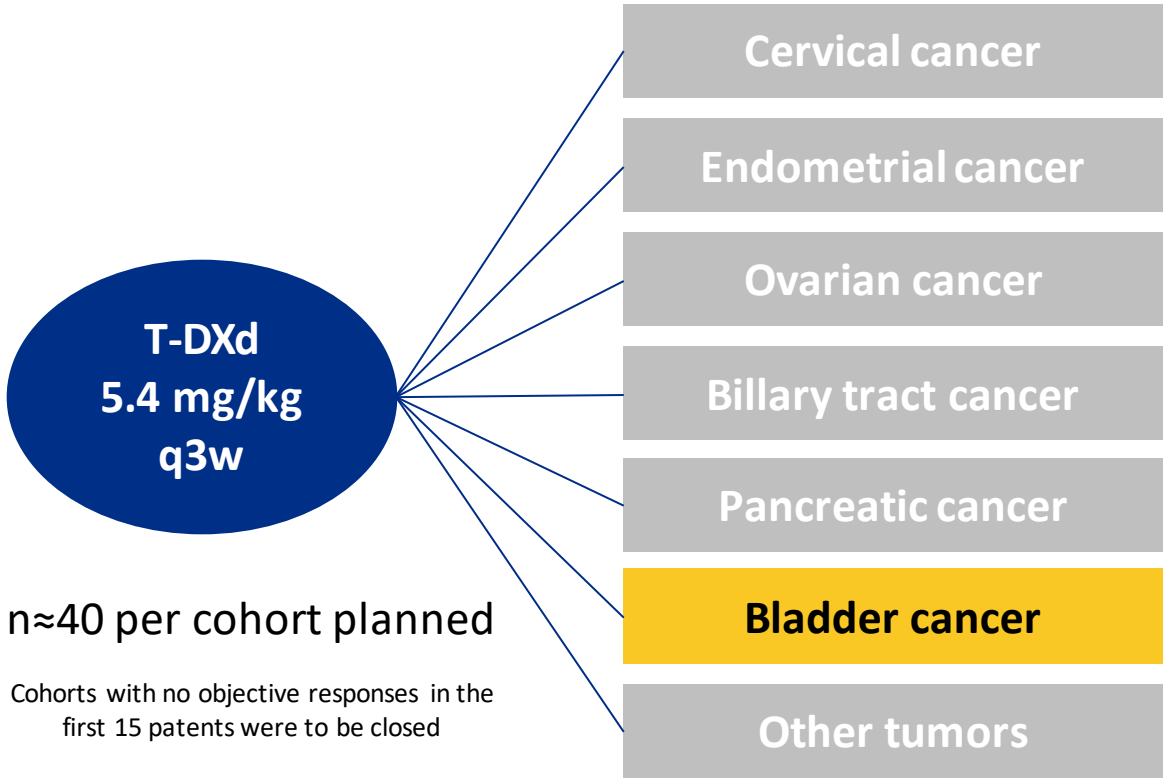
KEY DATA

DESTINY-PanTumor02

Study Design: Open-label, multicenter, Phase II study

- Patients with advanced solid tumor not eligible for curative therapy
- 2L + patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by Hercep test if local test not feasible (ASCO/CAP gastric cancer guidelines)*
- Prior HER2-targeting therapy allowed
- ECOG / WHO PS 0-1

*All patients centrally confirmed



n≈40 per cohort planned

Cohorts with no objective responses in the first 15 patents were to be closed

Primary endpoints: Confirmed ORR (investigator)
Secondary endpoints: DOR, DCR, PFS, OS, Safety
Exploratory endpoint: Subgroup analyses by HER2 status

Data cutoff : June 8, 2023

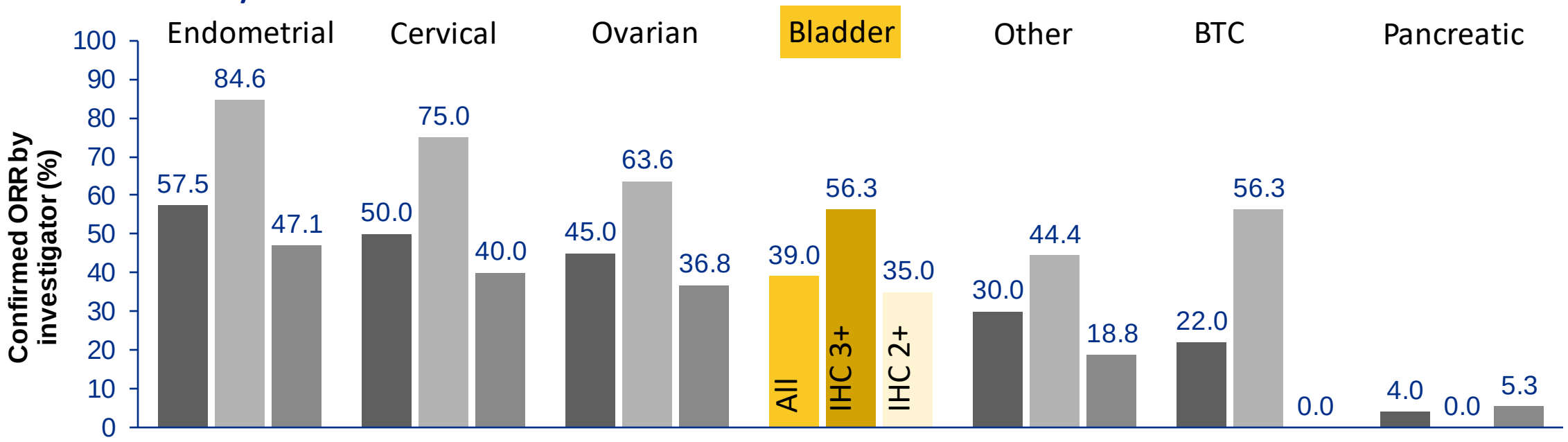
[a] Patients were eligible for either test. All patients were centrally confirmed. [b] Cohorts with no objective responses in the first 15 patients were to be closed. [c] Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non–small cell lung cancer, gastric cancer, and colorectal cancer. [d] Investigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1.

1. Meric-Bernstam F, et al. Presented at: ESMO Congress; October 20-24, 2023; Madrid, Spain. LBA34. 2. Meric-Bernstam F, et al. *J Clin Oncol*. October 2023. Online ahead of print. doi:10.1200/JCO.23.02005
3. Hofmann M, et al. *Histopathology.* 2008;52(7):797-805.

KEY DATA

DESTINY-PanTumor02

ORR and DoR by HER2 Status



Median DoR, months (95% CI)[b]	**NR (9.9-NR)**	**14.2 (4.1-NR)**	**11.3 (4.1-22.1)**	**8.7 (4.3-11.8)**	**22.1 (4.1-NR)**	**8.6 (2.1-NR)**	**5.7 (NR-NR)**

	All patients (N =267)	IHC 3+ (n =75)	IHC 2+ (n =125)
ORR, % (95% CI)	37.1 (31.3-43.2)	61.3 (49.4-72.4)	27.2 (19.6-35.9)
Median DoR, months (95% CI)[b]	11.3 (9.6-17.8)	22.1 (9.6-NR)	9.8 (4.3-12.6)

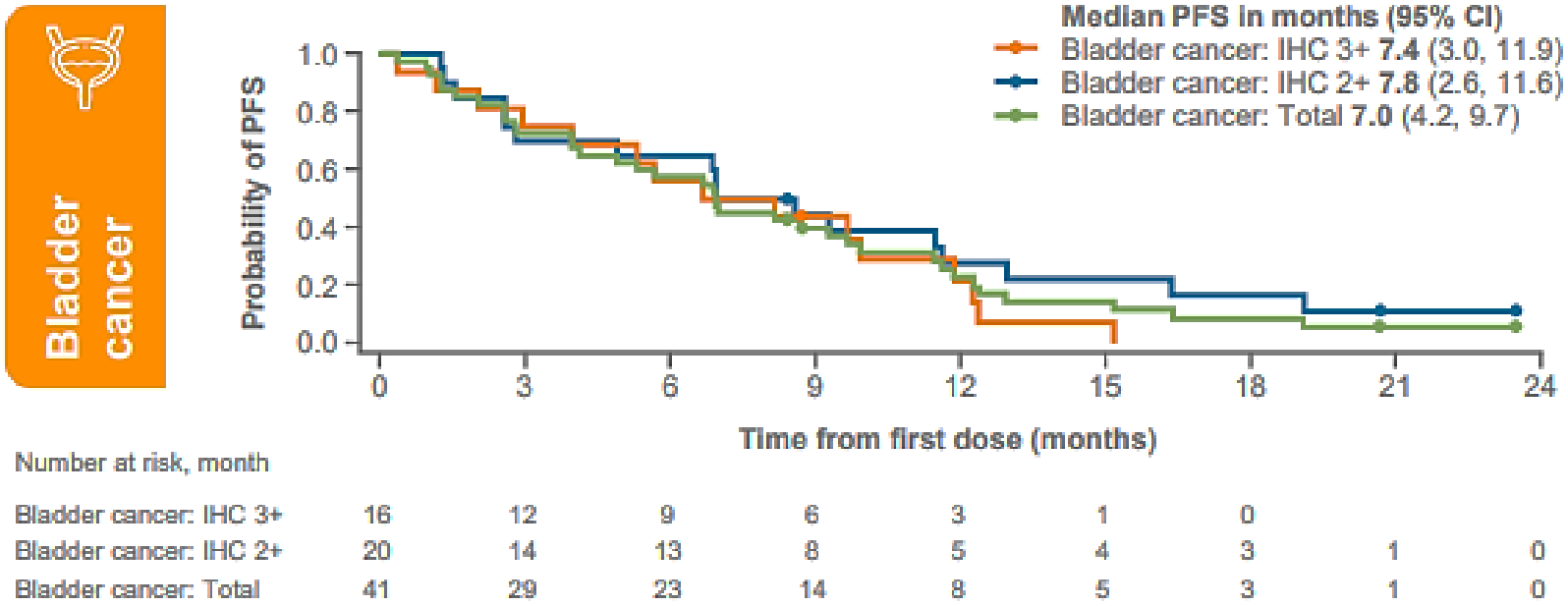
Analysis of ORR by investigator was performed in patients who received ≥ 1 dose of T-DXd; all patients (N = 267; including 67 patients with IHC 1+ [n = 25], IHC 0 [n = 30], or unknown IHC status [n = 12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n = 75) or IHC 2+ (n = 125) status. Analysis of DoR was performed in patients with objective response who received ≥ 1 dose of T-DXd; all patients (n = 99; including 19 patients with IHC 1+ [n = 6], IHC 0 [n = 9], or unknown IHC status [n = 4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n = 46) or IHC 2+ (n = 34) status.

[a] Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer. [b]Includes patients with a confirmed objective response only.

1. Meric-Bernstam F, et al. Presented at: ESMO Congress; October 20-24, 2023; Madrid, Spain. LBA34. 2. Meric-Bernstam F, et al. *J Clin Oncol*. 2023. doi:10.1200/JCO.23.02005

DESTINY-PanTumor02

Bladder Cancer: PFS by HER2 status



Discussion with HCP Participants

How will new clinical trial data fit into the treatment algorithm?

- *Based on DESTINY-PanTumor02, will talk to pathologist about HER2 testing for patients with bladder cancer*
- *Already do NGS, PD-L1 and HER2 testing on every metastatic patient in order to have access to clinical trials or compassionate use*
- *Intriguing information with IHC3+ appearing to be better*
- *NGS testing for ERBB2 is always worth doing; example of a patient with metastatic breast cancer that was diagnosed as IHC negative but was strongly ERBB2 positive with NGS testing and facilitated insurance approval*

Key Takeaways

Bladder Cancer

Patient case: untreated metastatic disease

- *Testing and retesting drives treatment strategies*
- *Awareness of clinical trial data provides new treatment options for patients*
- *FDA approvals and NCCN Guidelines play a pivotal role in directing treatment pathways*