DATA-DRIVEN DEBATES ON THE EVOLVING BLADDER CANCER LANDSCAPE

Harnessing Novelty to Improve Outcomes

expert exchange 2022

CEC ONCOLOGY

BCAN Bladder Cancer Advocacy Network

Presented by Creative Educational Concepts, LLC, in collaboration with the Bladder Cancer Advocacy Network (BCAN).

Supported by an independent educational grant from AstraZeneca.

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Clinical Case 1

Neoadjuvant Setting

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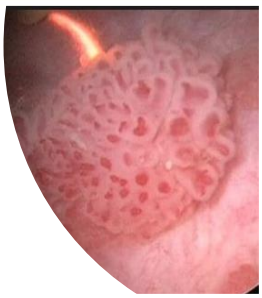
Case 1



A 69-year-old male has an 8-month history of irritative LUTS and microscopic hematuria (50 RBCs/HPF).

He has a history of DVT with PE 5 years ago, bilateral hearing loss, and a right hip replacement; HTN is well controlled on meds. He is a retired railroad worker and a former smoker with a 60 pack/year history (stopped yesterday).

Labs indicate his creatinine is 1.3 mg/dL, eGFR is 63 mL/min, and hemoglobin is 11.2 g/dL. CT urogram is without upper tract disease findings, no metastases; chest X-ray is within normal limits. In-office cystoscopy finds two 2 cm papillary lesions. Cytology is suspicious for high-grade urothelial carcinoma.

DVT, deep vein thrombosis; HPF, high-power field; HTN, hypertension; LUTS, lower urinary tract symptoms; PE, pulmonary embolism; RBC, red blood cell.

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Case 1 (…continued)

Pathology: CIS + high-grade Ta disease

Treatment:

- BCG induction x 6 weeks (instillations 1–6); surveillance cystoscopy (white light), NED; cytology negative
- BCG maintenance x 3 weeks (instillations 7–9); surveillance cystoscopy (blue light), NED; cytology atypical

Recurrence was found with CIS, verified with biopsy.

BCG, Bacillus Calmette-Guérin; CIS, carcinoma in situ; NED, no evidence of disease.

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Neoadjuvant Treatment

Subtitle

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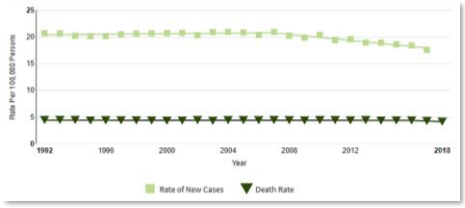
Localized Invasive Bladder Cancer

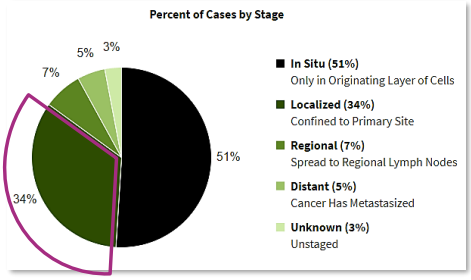
Estimated New Cases in 2020	81,400
% of All New Cancer Cases	4.5%
Estimated Deaths in 2020	17,980
% of All Cancer Deaths	3.0%

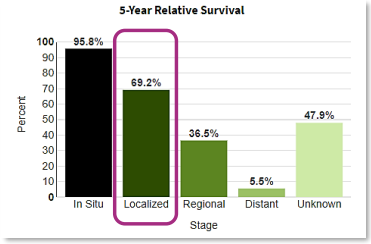
5-Year Relative Survival

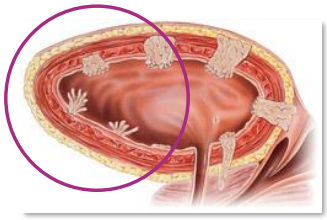
76.9%

2010–2016









http://seer.cancer.gov/statfacts/html/urinb.html.

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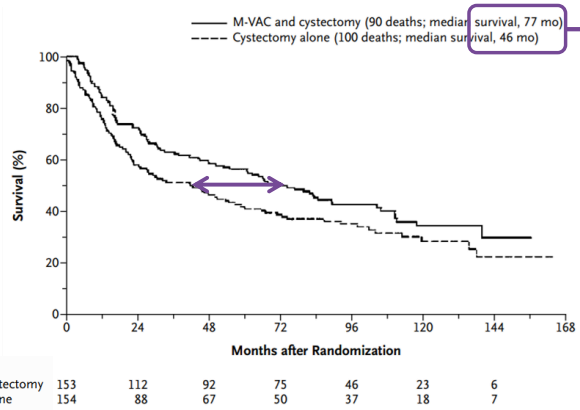
Neoadjuvant Chemotherapy Is Standard of Care for Muscle-invasive Bladder Cancer

3 cycles standard MVAC → cystectomy
vs
Cystectomy alone

SWOG-8710



No. at Risk							
M-VAC and cystectomy	153	112	92	75	46	23	6
Cystectomy alone	154	88	67	50	37	18	7

2.6-year median overall survival benefit

Magnitude of benefit similar to adjuvant 5FU therapy for colon cancer, which is widely accepted as international standard of care.

Grossman HE, et al. *N Engl J Med*. 2003.

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GC or ddMVAC? GETUG/AFU V05 VESPER Trial

Randomized Phase III Trial of 500 Patients

Table 3 – CTCAE grade ≥ 3 hematological toxicities reported for patients of the dd-MVAC and GC arms

	GC (n = 245)	dd-MVAC (n = 248)	p value
Anemia	19 (7.8%)	54 (22%)	<0.0001
Neutropenia	113 (46%)	97 (39%)	0.14
Febrile neutropenia	6 (2.4%)	16 (6.5%)	0.053
Thrombopenia	41 (17%)	49 (20%)	0.5
At least one grade ≥ 3 hematological toxicity	134 (55%)	129 (52%)	0.6

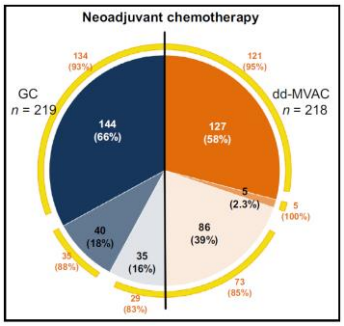

Table 4 – CTCAE grade ≥ 3 nonhematological toxicities reported for patients of the dd-MVAC and GC arms

	GC (n = 245)	dd-MVAC (n = 248)	p value
Nausea/vomiting	7 (2.9%)	24 (9.7%)	0.003
Diarrhea	2 (0.81%)	3 (1.2%)	–
Asthenia	10 (4.1%)	35 (14%)	<0.001
Cardiovascular	17 (6.9%)	16 (6.5%)	>0.9
Kidney	13 (5.3%)	15 (6.0%)	0.9
Liver	13 (5.3%)	7 (2.8%)	0.2
Neuropathy	0	2 (0.81%)	–
Chemotherapy-related deaths	1	3	–

Pfister C, et al. *Eur Urol.* 2021.

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GC or ddMVAC? GETUG/AFU V05 VESPER Trial

Table 5 – Pathological responses observed after neoadjuvant chemotherapy and cystectomy for the dd-MVAC and GC arms

	GC (n = 198)	dd-MVAC (n = 199)	p value
Complete response			
ypT0 pN0	71 (36%)	84 (42%)	0.021
ypTis or ypTa or ypT1 and ypN0		42 (21%)	
≥ypT2 and ypN0	63 (32%)	51 (26%)	
ypN+	35 (18%)	20 (10%)	
Uncertain staging	2	2	
Non-muscle invasive			
<ypT2 pN0	98 (49%)	126 (63%)	0.007
≥ypT2 or ypN+	99 (50%)	72 (36%)	
Uncertain staging	1	1	
Organ-confined disease			
<ypT3 pN0	124 (63%)	154 (77%)	0.001
≥ypT3 or ypN+	73 (37%)	43 (22%)	
Uncertain staging	1	2	

- pCR rate better for dd-MVAC

Pfister C, et al. *Eur Urol.* 2021.

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Does Neoadjuvant Checkpoint Inhibition Have a Role in Muscle-invasive Bladder Cancer?

	Pembrolizumab (n=80 UC)	Atezolizumab (n=95)
% patients cisplatin ineligible	0%	100%
% who also got neoadj. chemo	10%	0%
Duration of neoadjuvant therapy	3 cycles (9 weeks)	2 cycles (6 weeks)
Safe?	Yes	Yes
Pathologic complete response rate (pT0)	39%	31%

pT0 rates comparable to those seen with chemo

Gem Cis 15%–26%

DDMVAC 26%–43%

Despite multiple analyses, no predictive biomarker has emerged in this setting.

Necchi A, et al. *Eur Urol*. 2020; Powles T, et al. *Nat Med*. 2019.

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	Gem Cis				Dose Dense MVAC		
	Standard		Dose Dense				
	GC (Dash) n=42	GC (Tulley) n=154	DDGC (Anari) n=31	DDGC (Iyer) n=46	DD MVAC (Blick) n=80	DD AMVAC (Plimack) n=40	DD AMVAC (Choueiri) n=39
Prospective (P) vs Retrospe							P
# of cycle							4
# of week							8
Pathologi (pT0)							6%
Partial re							9%
Median d chemo to							98
Rate of gr Not collected							0%
Progression free @ 2 years	64%	~68%	~68%	~76%	65%	78%	~47%
Alive at 2 years (vs 58% cystectomy alone)	73%	~75%	~77%	~87%	77%	83%	≤80%

Phase II study of gemcitabine and split-dose cisplatin plus pembrolizumab as neoadjuvant therapy prior to radical cystectomy (RC) in patients with muscle-invasive bladder cancer (MIBC).

Rose TL, Harrison MR, Deal AM, Osterman CK, Ramalingam S, Whang YE, Brower BY, Bjurlin M

Abstract 396; ASCO GU 2021

AMVAC (aka DDMVAC) is safe, effective, and allows for the shortest time to surgery.

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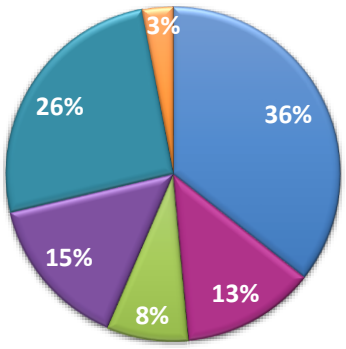
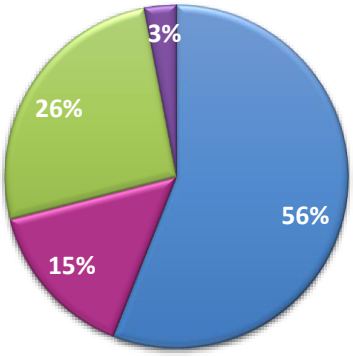
Pembrolizumab + Gem/Cis



Pathologic response

Pathologic Stage
- T0 N0
- Tis or Ta N0
- T1 N0
- T2 N0
- Tany N+
- No cystectomy



- Downstaged
- No change
- Upstaged
- No cystectomy

Pathologic downstaging at the time of cystectomy (pathologic stage compared with pretreatment clinical stage)

Rose T, et al. *J Clin Oncol*. 2022.

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Atezolizumab + Gem/Cis

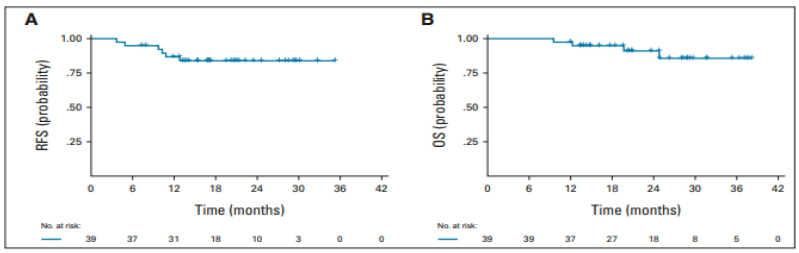

FIG 1. (A) RFS and (B) OS in 39 response-evaluable patients who were treated with neoadjuvant GC with atezolizumab. GC, gemcitabine and cisplatin; OS, overall survival; RFS, relapse-free survival.

Pathologic Response at the Time of RC

Pathologic Response	No. (%)
Responders (<pT2N0)	27 (69.2; 95% CI, 55.0–79.0)
pT0N0/pT0NX	16 (41.0)
pTaN0	2 (5.1)
pTisN0	7 (17.9)
pT1N0	2 (5.1)

Funt SA, et al. *J Clin Oncol*. 2022.

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Phase III MIBC IO Trials in Progress

Design	n	Study Name/NCT#
SWOG/NRG: Radiation +/- Atezo	475	SWOG/NRG 1806 NCT03775265
Gem Cis + Durva → Cystectomy → Durva adjuvant vs Gem Cis → Cystectomy	1050	NIAGRA NCT03732677
Gem Cis + Pembro→ Cystectomy → Pembro adjuvant vs Gem Cis → Cystectomy	790	KEYNOTE-866 NCT03924895
Pembro (Cis ineligible)→ Cystectomy → Pembro adjuvant vs Cystectomy	610	KEYNOTE-905 NCT03924895
Gem Cis vs Gem Cis + Nivo vs Gem Cis + Nivo + BMS-986205 (IDO inhibitor)	1200	CA017-078 NCT03661320

Clinicaltrials.gov.

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Enfortumab + Lots of Options

- In neoadjuvant setting
- Cisplatin eligible
  - Pembrolizumab combination vs chemotherapy combination
- Cisplatin ineligible
  - Alone
  - Durvalumab combination
  - Pembrolizumab combination

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Will We Need to Perform Cystectomy after Successful Neoadjuvant Therapy?

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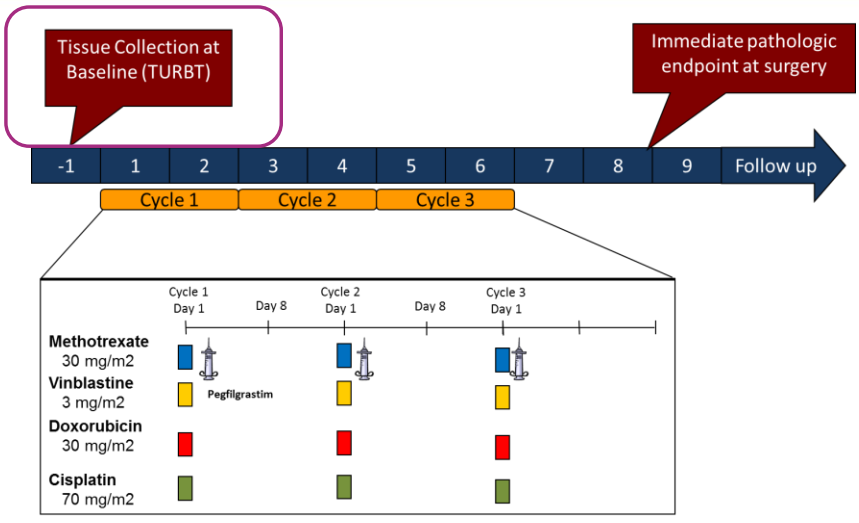
Neoadjuvant Platform Is Optimal for Predictive Biomarker Discovery



Plimack ER, et al. *J Clin Oncol*. 2014.

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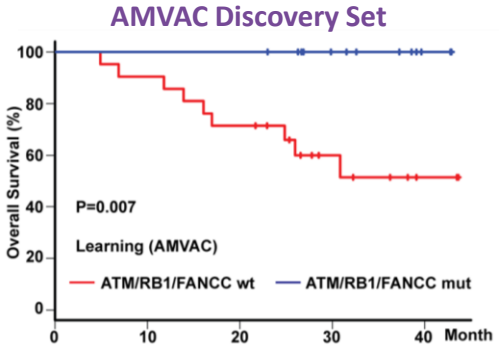
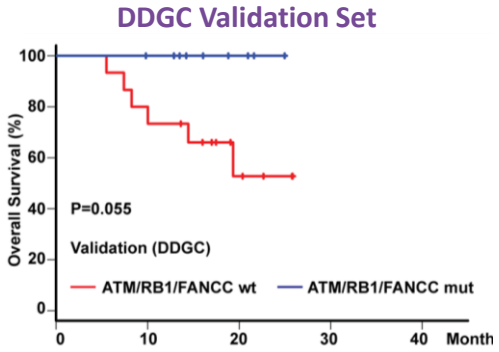
ATM/RB1/FANCC Mutation Correlates with Improved Response and Survival in Discovery and Validation Sets

DNA





ATM, RB1, FANCC	n	Sensitivity for response	Specificity for response	PPV for response	NPV for response
Discovery: Philadelphia AMVAC	34	87%	100%	100%	90%
Validation: Philadelphia DDGC	24	64%	85%	78%	73%

Plimack ER, et al. *Eur Urol*. 2015.

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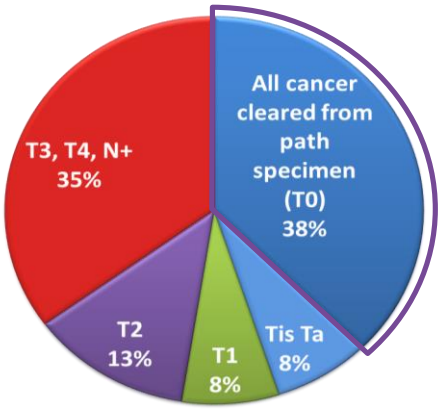
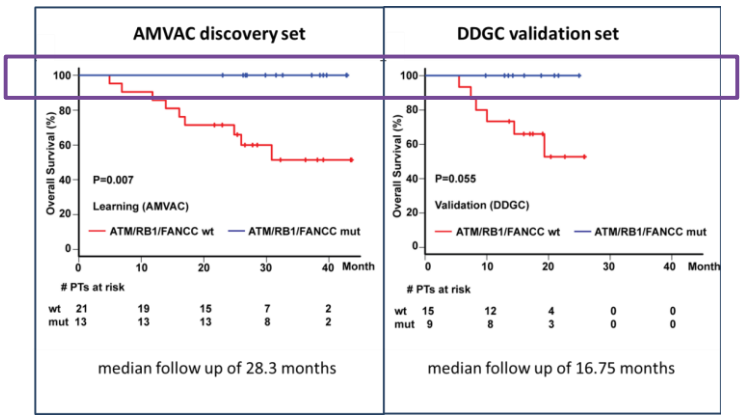
Using a Predictive Marker of *Sensitivity* to Test Novel Approaches to Bladder Sparing

DNA





Plimack ER, et al. *Eur Urol*. 2015.

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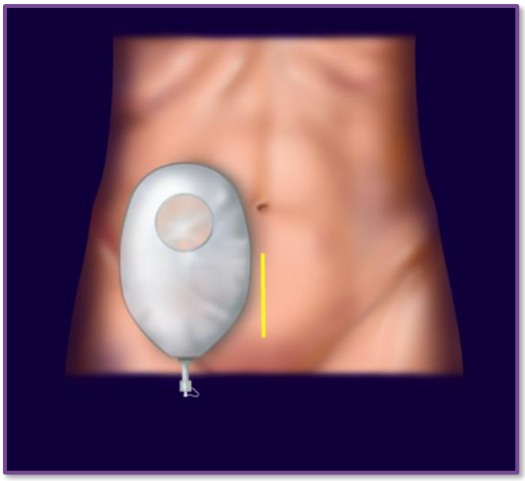
Radical Cystectomy with Ileal Conduit



Slide courtesy of A. Kutikov MD, www.drawmd.com.

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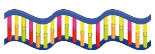
HCRN GU16-257

DNA

GC + Nivo with Selective Bladder Sparing

Gemcitabine + Cisplatin + Nivolumab
X 4 cycles



DNA sequencing

Clinical Restaging

Cysto + biopsies
Urine cytology
MRI

Clinical CR

No cystectomy

*

Cystectomy

* Treatment based on patient choice

No Clinical CR

Cystectomy

- Determine association between DDR panel and "benefit" in cCR patients

Slide courtesy of Principal Investigator Matt Galsky, MD.

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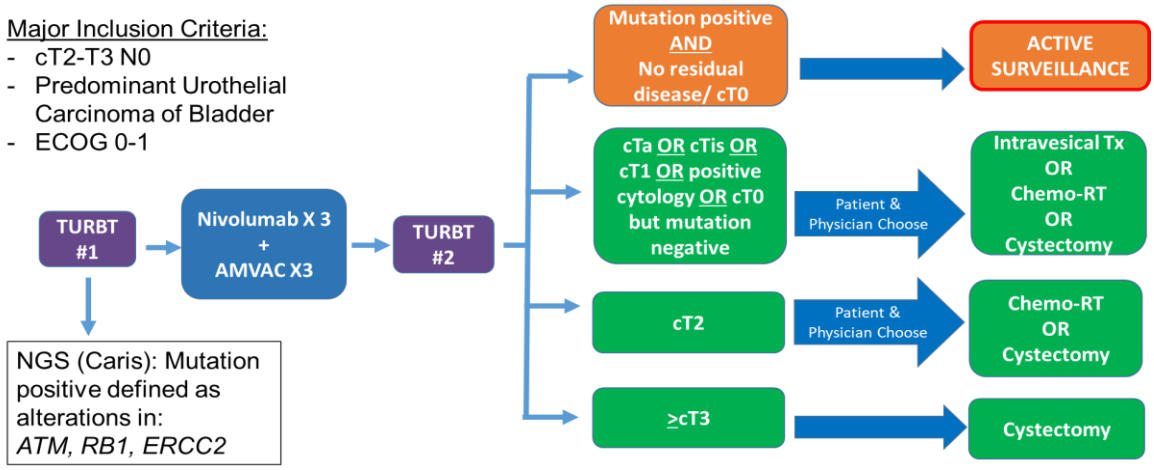
RETAIN-2: A Phase II Trial of Risk-enabled Therapy after Neoadjuvant Immuno-chemotherapy for Bladder Cancer



Primary endpoint: metastases-free survival at 2 years

Slide courtesy of Elizabeth Plimack, MD.

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Conclusions

- Neoadjuvant therapies continue to expand
- Improving outcomes will likely evolve to tailor treatments to avoid cystectomy
- Predictive biomarkers and identifying genetic characteristics of an individual's tumors will influence treatment choices and success

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Case 1 (…continued)

The patient received 6 cycles of pembrolizumab, which he tolerated well.

TURBT demonstrates persistent CIS, with new findings of HG T1. Lab results include a creatinine of 1.5 mg/dL, an eGFR of 58 mL/min, and a hemoglobin of 11.2 g/dL. A chest/abdomen/pelvis CT found no evidence of metastases.

HG, high grade; TURBT, trans urethral resection of bladder tumor.

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Non-muscle Invasive Bladder Cancer

Options for BCG Unresponsive Disease

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Goals of Therapy

- Appropriate, aggressive therapy for high-risk tumors
  - Prevent tumor progression
  - Save lives
- Modified and, perhaps, reduced therapy and management for low-risk patients who do not need aggressive therapy or intensive surveillance

Makes Sense to See What Guidelines Recommend

Diagnosis and Treatment of Non-muscle Invasive Bladder Cancer

AUA/SUO Guideline

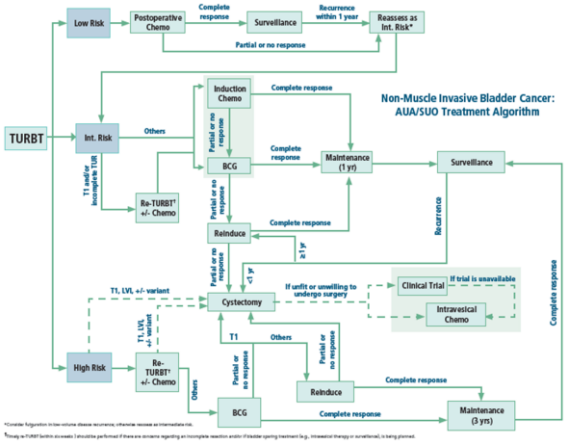
Chang S, Boorjian SA, Chou R, Clark PE, Daneshmand S, Konety BR, Pruthi R, Quale DZ, Ritch CR, Seigne JD, Skinner EC, Smith ND, McKiernan JM

American Urological Association | SUO Society of Urologic Oncology, Inc.

"This guideline provides a risk-stratified clinical framework for the management of NMIBC."

2020–2021 Update

https://www.auanet.org/guidelines/bladder-cancer-non-muscle-invasive-guideline



Chang S, et al. *J Urol.* 2016.

Use and Validation of the AUA/SUO Risk Grouping for Non-muscle Invasive Bladder Cancer in a Contemporary Cohort

Ritch CR, Velasquez MC, Kwon D, Becerra MF, Soodana-Prakash N, Atluri VS, Almengo K, Alameddine M, Kineish O, Kava BR, Punnen S, Parekh DJ, Gonzalgo ML

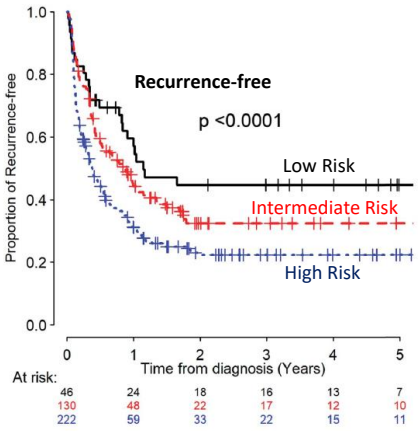


Figure 1. Kaplan-Meier analysis of RFS by low (black curve), intermediate (red curve) and high (blue curve) risk groups.

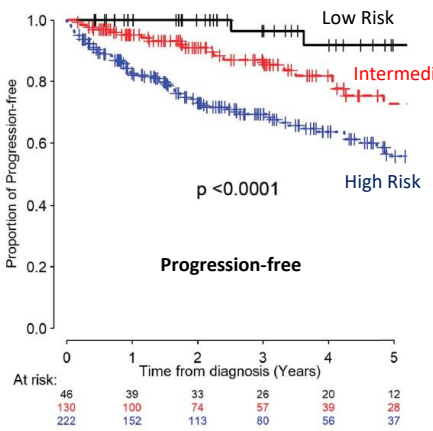


Figure 2. Kaplan-Meier analysis of PFS by low (black curve), intermediate (red curve) and high (blue curve) risk groups.

Ritch CR, et al. *J Urol.* 2020.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 6.2021
Non-Muscle Invasive Bladder Cancer

AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer*

Low Risk	Intermediate Risk	High Risk
• Papillary urothelial neoplasm of low malignant potential • Low grade urothelial carcinoma ▸ Ta and ▸ ≤3 cm and ▸ Solitary	• Low grade urothelial carcinoma ▸ T1 or ▸ >3 cm or ▸ Multifocal or ▸ Recurrence within 1 year • High grade urothelial carcinoma ▸ Ta and ▸ ≤3 cm and ▸ Solitary	• High grade urothelial carcinoma ▸ CIS or ▸ T1 or ▸ >3 cm or ▸ Multifocal • Very high risk features (any): ▸ BCG unresponsive[k] ▸ Variant histologies[l] ▸ Lymphovascular invasion ▸ Prostatic urethral invasion

Reproduced with permission from Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol 2016;196:1021.
*Within each of these risk strata an individual patient may have more or less concerning features that can influence care.

https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf

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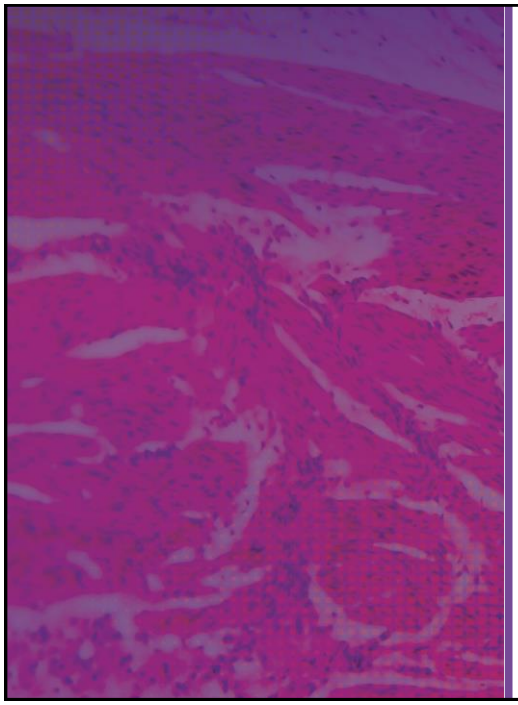

What Do We Do if BCG Has Not Worked?

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Treatment Options for BCG Unresponsive NMIBC

	Options	Pro	Con
PRESENT	**Radical cystectomy with LND and diversion**	• Definitive • LUTS addressed	• Morbidity (competing risks, frailty for this patient)
PRESENT	**Intravesical chemotherapy**	• Avoid major surgery, doublet preferred (gem/docetaxel: 42% 2-year RFS)	• Already has severe LUTS (? tolerability) • Efficacy/durability
PRESENT	**Systemic therapy Pembrolizumab FDA approved 2020**	• Not intravesical therapy (i.e., minimize LUTS) • Avoid major surgery	• Efficacy/durability • Rare, but severe side effects • Cost
FUTURE	? **Intravesical therapy** (e.g., nadofaragene, oportuzumab monatox-qqrs) ***Clinical trial**	• Avoid major surgery, early phase data good!	• Already has severe LUTS (? tolerability) • Efficacy/durability

* Clinical trials available at time of discussion

Slide courtesy of Sima Porten, MD.

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Intravesical "Salvage" Chemotherapy

Single Agent

Agent	Study	#	Schedule	1-year CRR	2-year CRR
Valrubicin	Steinberg 2000	90	6 weekly	14%	(8%, 30 months)
Gemcitabine	Skinner 2013	47	6 weekly, monthly x 12	28%	21%
Docetaxel	Barlow 2013	54	6 weekly, monthly x 9	40%	—
Nab-paclitaxel	McKiernan 2014	28	6 weekly, monthly x6	36%	—

Only FDA approved is valrubicin.

Combination of Agents

Agent	Study	#	Schedule	1-year CRR	2-year CRR
Gem/mito	Breyer 2010 Lightfoot 2014 Cockerill 2016	10–47	6 weekly, monthly x 12 (or no maintenance)	48%–70%	38%–41%
Gemcitabine/ Docetaxel	Steinberg 2015 Milbar 2017	45	6 weekly	54%–56%	34%–42%
BCG/IFN/IL2/GM-CSF	Steinberg 2017	52	6 weekly	55%	53%
Cab/Gem/Cis	McKiernan 2019	18	6 weekly, maintenance	78%	—

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IOWA

Long-term Follow-up for Gem/Docetaxel for BCG Unresponsive

Survival Outcome	1 Year	2 Years	5 Years
Overall HG-RFS	60%	51%	31%
BCG unresponsive HG-RFS	67%	53%	33%
PFS	86%	79%	68%
CFS	89%	86%	75%
CSS	99%	97%	91%
OS	96%	87%	64%

With permission, Chevuru PT, et al.

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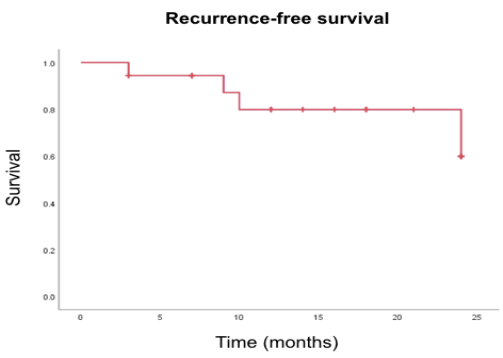
Combination Intravesical Chemotherapy for BCG Unresponsive Cabazitaxel + Gemcitabine + Cisplatin (CGC)

- Recurrence-free survival rates (RFS)
- 17/18 (94%) tumor free at 3-month follow-up
  - 12 months = 83%
  - 24 months = 78%
- Received treatment Mon, Wed, every other Fri x 6 weeks, then every month maintenance up to 24 months
- 2/4 recurrences in prostatic urethra if excluded, 2-year *intravesical* RFS 89%



DeCastro J, et al. *J Urol.* 2020.

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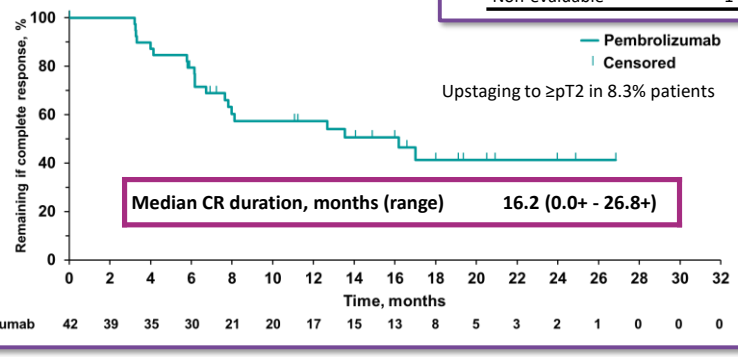
KEYNOTE-057

BCG Unresponsive CIS Patients Achieving CR with Pembrolizumab

Best response	N=96 n (%)	95% CI
CR	39 (40.6)	30.7–51.1
Non-CR	56 (58.3)	47.8–68.3
Progression to T2	0	NA–NA
Non-evaluable	1 (1.0)	0–5.7

@ 3 months

No progression to T2 disease



- Number of patients with an observed DOR ≥12 months was
  - 19% of all treated patients (n=96)

CR, complete response. [a]1 month = 30.4367 days; [b]Month 0 = time point when initial CR was achieved.
Database cutoff: February 20, 2019.

FDA Oncologic Drugs Advisory Committee (ODAC) Meeting, 2019.

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As a Result
FDA Approved IV Pembrolizumab

- January 2020
- Pembrolizumab is approved for the treatment of patients with BCG-unresponsive, high-risk NMIBC with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for, or who have elected not to undergo, cystectomy

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Intravesical Therapy
What's Next?

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Intravesical Nadofaragene Firadenovec Gene Therapy for BCG-unresponsive Non-muscle Invasive Bladder Cancer

A Single-arm, Open-label, Repeat-dose Clinical Trial

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Single-arm, Open-label Study Evaluating Nadofaragene Firadenovec in High-grade, BCG-unresponsive NMIBC

Replication-deficient recombinant adenovirus that delivers human interferon alfa-2b cDNA into the bladder epithelium

Patient Population

High-grade BCG-unresponsive NMIBC[a]

N=157

Cohorts

1. CIS±Ta/T1
2. High-grade Ta/T1

Treatment

Nadofaragene firadenovec

3 x 10^{11} vp/mL (75 mL) intravesically every 3 months with a planned 1-hour dwell time

Endpoints

Primary

CR in patients with CIS±Ta/T1 at any time after the first instillation

Key Secondary

- Durability of CR in patients with CIS±Ta/T1 who achieved a CR
- HGRFS rate in patients with high-grade Ta/T1
- Durability of HGRF survival in patients with high-grade Ta/T1
- Time to cystectomy[b]
- Overall survival[b]

Key Inclusion Criteria

- High-grade, BCG-unresponsive NMIBC patients ≥18 years
  - CIS±Ta/T1 (CIS with or without high-grade Ta/T1)
  - High-grade Ta/T1 (without concomitant CIS)

Key Exclusion Criteria

- Current or previous evidence of muscle-invasive (muscularis propria) or metastatic disease
- Intravesical therapy within 8 weeks prior to beginning study treatment

[a]BCG-unresponsive NMIBC is defined as: 1) persistent high-grade T1 recurrence ≤12 months after BCG initiation; 2) relapse with CIS after initial complete response ≤12 months after last BCG treatment; or 3) relapse with high-grade Ta/T1 NMIBC ≤6 months after last BCG treatment[3]; [b] Results for time to cystectomy and overall survival are not yet presented due to insufficient follow-up as of this data cut off.

BCG, Bacillus Calmette-Guérin; NMIBC, non-muscle invasive bladder cancer; CIS, carcinoma in situ; CR, complete response; HGRFS, high-grade recurrence-free survival.

Boorjian SA, et al. *Lancet Oncol*. 2020; ClinicalTrials.gov. Identifier: NCT02773849; https://www.fda.gov/media/101468/download.

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Primary Endpoint
Incidence of CR At Any Time in CIS ±Ta/T1 Cohort

Patients Who Have Achieved a CR (n, %)	CIS±Ta/T1 (N=103)	% of CR (N=55)
By 3 months	**55 (53.4)**	**100**
During 4–6 months	0 (0.0)	0
During 7–9 months	0 (0.0)	0
During 10–12 months	0 (0.0)	0
Total	**55 (53.4)**	**—**

All CRs occurred within 3 months

Boorjian SA, et al. *Lancet Oncol*. 2020.

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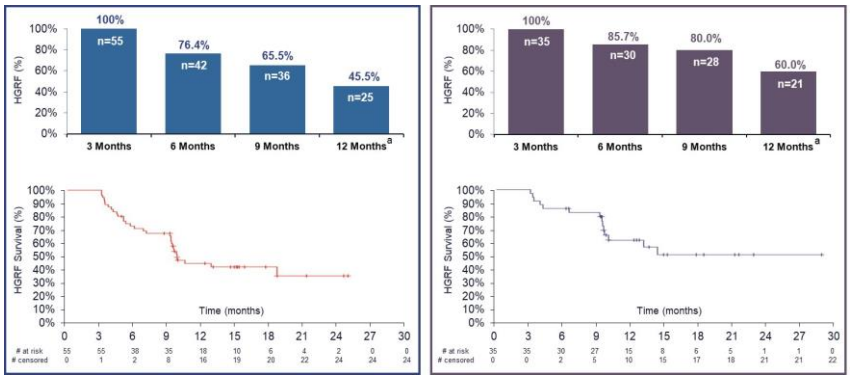
Secondary Endpoint
Durability of Response High-grade Recurrence-free Survival in Patients Who Achieved CR

CIS Cohort | **High-grade Ta/T1 Cohort**



Overall at 12 months: high-grade DFS

24.3% of the CIS±Ta/T1 cohort **43.8% of the Ta/T1 cohort**

74% of patients were free of cystectomy

Boorjian SA, et al. *Lancet Oncol*. 2020.

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FerGene Provides Update on BLA for **Nadofaragene Firadenovec**

by FerGene | May 17, 2020 | Media | 0 comments

The U.S. Food and Drug Administration (FDA) has issued a response to the Biologics License Application (BLA) for investigational gene therapy, nadofaragene firadenovec, which was submitted by FKD Therapies Oy, the company leading the development and regulatory filing for the therapy.

In its response letter, the FDA indicated there are outstanding questions that our manufacturing partner needs to further address regarding its CMC and manufacturing processes. There are no outstanding questions regarding the clinical data for nadofaragene firadenovec. The application for nadofaragene firadenovec was granted Priority Review, Fast Track and Breakthrough Therapy Designati[illegible] by the FDA.

CMC: Chemistry Manufacturing and Controls

BLA, biologics license application.

https://fergene.com/media/fergene-provides-update-on-bla-for-nadofaragene-firadenovec/

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Intravesical Therapy

What's Next?

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Vista Trial

Phase 3 Registration Study of Vicineum for BCG-unresponsive NMIBC

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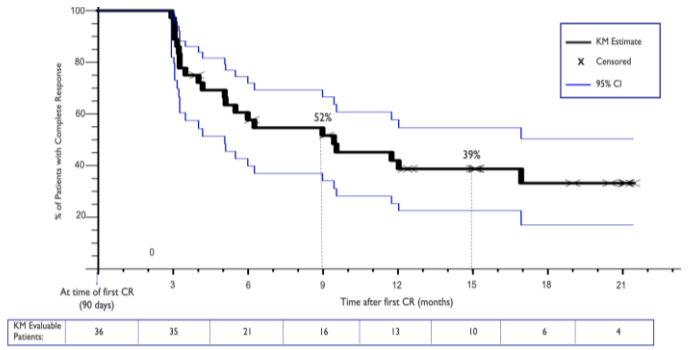
Vista Trial

Phase 3 Registration Study of Vicineum for BCG-unresponsive NMIBC

Duration of response: 52% of CIS patients who had a CR at 3 months remained disease free for a total of 12 months after starting treatment.

- 40% CR with CIS at 3 months
- Durability of response
  - 52% retain CR at 9 months
  - 39% retain CR at 15 months

Median duration of response is 287 days (95% CI, 154–NE* days) (9.4 months)**



Duration of response defined as the time of complete response to treatment failure.
*Not estimable, the upper bound for the 95% confidence interval has not reached the median.
**Note: data reflect an ad hoc analysis of pooled results of patients in cohorts 1 and 2. Median duration of response for the primary endpoint, Cohort 1 (n=86) is 273 days (95% CI, 122–NE), and duration of response for Cohort 2 (n=7) is 290 days (95% CI, 167–NE), based on the Kaplan-Meier method.

Dickstein RJ, et al. *J Urol*. 2018.

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BUT…Another Complete Response Letter (CRL)

https://www.urologytimes.com/view/fda-does-not-approve-vicineum-for-bladder-cancer

65

The FDA has determined that it cannot approve the BLA for Vicineum in its present form and has provided recommendations specific to additional clinical/statistical data and analyses in addition to Chemistry, Manufacturing and Controls (CMC) issues pertaining to a recent pre-approval inspection and product quality.

https://ir.sesenbio.com/news-releases/news-release-details/sesen-bio-receives-complete-response-letter-fda-vicineumtm

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What Does This Mean?

- Discouraging at the least
- Will there need to be a comparator arm now for patients with BCG-unresponsive disease?
- Does the FDA consider other disease subtypes as the “current unmet need”?
- Does the next study for BCG-unresponsive disease have to be after pembrolizumab “unresponsiveness”? If so, how would this be defined?

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Just Reported at AUA 2021

September 2021

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QUILT-3.032: A Multicenter Clinical Trial of Intravesical Bacillus Calmette-Guérin (BCG) in Combination with ALT-803 (N-803) in Patients with BCG-unresponsive High-grade Non-muscle Invasive Bladder Cancer

NIH U.S. National Library of Medicine
ClinicalTrials.gov

QUILT 3.032

N-803 + BCG: primary endpoint met

- Complete response at 3 or 6 months, biopsy confirmed
- 81 patients enrolled
- 58 out of 81 patients have achieved a CR at any time
- CR rate at any time of 72% (95% CI, 61%–81%)

Chamie K, et al. AUA 2021. Abstract 510.

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Partial Listing
Current Clinical Trials

Systemic Therapy + BCG

- KEYNOTE-676
- ALBAN trial
- CREST trial
- CheckMate 9UT
- New agents and new delivery systems are being formulated and studied

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KEYNOTE-676 Study Design Schema
Pembro + BCG vs BCG

Eligibility
- Has histologically-confirmed diagnosis of non-muscle invasive (T1, high-grade Ta, and/or CIS) transitional cell carcinoma (TCC) of the bladder
- Has been treated with one adequate course of BCG induction therapy for the treatment of HR NMIBC

Estimated enrollment: 550

Randomization 1:1

- Pembro + BCG
- BCG

Treatment discontinuation → Post-treatment follow-up

Primary Endpoint
- CR rate by BICR

Key Secondary Endpoints
- EFS
- RFS
- OS
- DOR
- Time to cystectomy
- Safety
- Time to true deterioration
- QLQ-C30, QLQ-NMIBC24, etc.

BICR, blinded independent central review; EFS, event-free survival; RFS, recurrence-free survival; DOR, duration of response.

ClinicalTrials.gov.

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ALBAN Study
BCG + Atezolizumab vs BCG

Objective: to investigate whether atezolizumab improves the outcome of patients treated with BCG for high-risk NMIBC

Inclusion Criteria High-risk NMIBC defined as
- High-grade

OR
- T1

OR
- In situ carcinoma

Primary Endpoint
- RFS

Secondary Endpoints
- PFS, OS
- Cancer specific survival
- Disease worsening
- QoL, safety

TURBT → Randomization (N=614 patients)

- Control: BCG: 6 (induction) + 3 (maintenance, 1 year)
- Experimental: BCG: 6 + 3 (1 year) + atezolizumab IV (1 year)

NCT03799835

Roupret M, et al. *J Clin Oncol*. 2019.

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CREST Trial

- Study of sasanlimab (PF-06801591) in combination with Bacillus Calmette-Guérin (BCG) in participants with high-risk non-muscle invasive bladder cancer
- A subcutaneous monoclonal antibody (mAb) that blocks the interaction between PD-1 and PD-L1/PD-L2

Three arm trial:

A. SASANLIMAB (PF-06801591) + BCG (induction and maintenance)
B. SASANLIMAB (PF-06801591) + BCG (induction alone)
C. BCG alone (induction and maintenance)

Primary endpoint: event-free survival

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CheckMate 9UT

- Phase 2 randomized trial in BCG-unresponsive bladder cancer BMS-986205—oral IDO1 inhibitor that reduces kynurenine
  - Nivolumab +/- BCG

  vs

  - Nivolumab and BMS-986205 +/- BCG in BCG
- Primary endpoint: complete response rate

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Conclusions

- Multiple options currently exist for BCG unresponsive disease
  - Intravesical options
  - Systemic therapy
  - Radical cystectomy
- Multiple clinical trials open
  - Intravesical options +/- BCG
  - Systemic options +/- BCG

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Adjuvant Therapy

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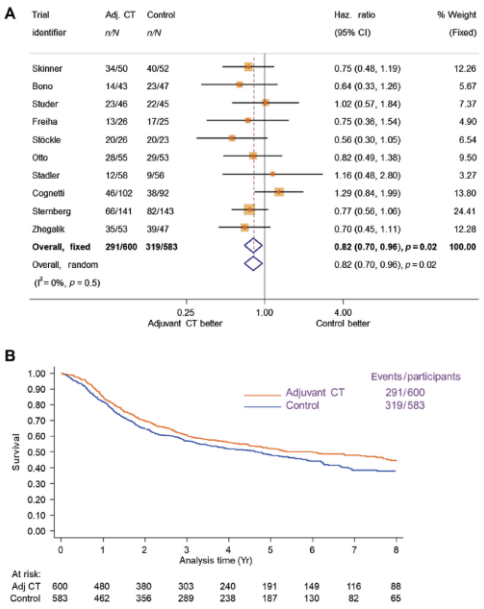
Case 1 (…continued)

The patient undergoes radical cystectomy with ileal conduit. He has a relatively uneventful recovery.

Now 3 months post op, he has an ECOG PS of 1. Pathology finds invasive high-grade urothelial cancer pT3b, N+ (3 of 15 notes involved). Lab results include a creatinine of 1.6 mg/dL, an eGFR of 50 mL/min, and a hemoglobin of 10.3 g/dL. A chest/abdomen/pelvis CT finds no evidence of metastases.

Benefit of Adjuvant Chemotherapy for Bladder Cancer *Meta-analysis*

- Overall survival results were based on 10 RCTs (1,183 participants and 610 deaths)
- There was a clear benefit of adjuvant chemotherapy (HR=0.82; 95% CI, 0.70–0.96; *P*=0.02),



CI, confidence interval; HR, hazard ratio; RCT, randomized controlled trial.

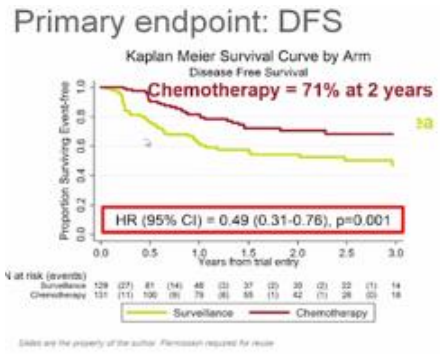
Advanced Bladder Cancer Meta-analysis Collaborators Group. *Eur Urol*. 2022.

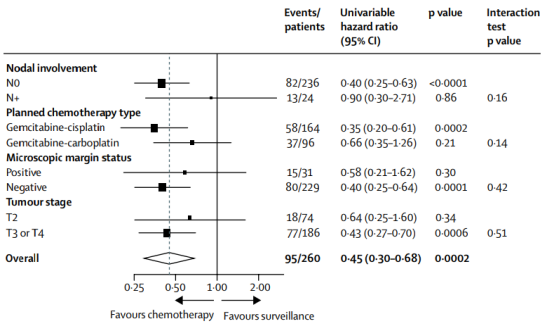
Adjuvant Chemotherapy for Upper Tract TCC

Results of POUT

A Phase III Randomised Trial of Peri-operative Chemotherapy versus Surveillance in Upper Tract Urothelial Cancer (UTUC)

Birtle AJ, Chester JD, Jones R, Johnson M, Hill M, Bryan RT, Catto J, Donovan J, French A, Harris C, Keeley F, Kockelbergh R, Powles T, Todd R, Tregelias L, Wilson C, Winterbottom A, Lewis R, Hall E; on behalf of POUT Investigators





Birtle AJ, et al. *J Clin Oncol.* 2018; Birtle A, et al. *Lancet*. 2020.

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IMvigor010 Study Design

Key eligibility[a]

- **High-risk MIUC (bladder, renal pelvis, ureter)**
- **Radical cystectomy/nephroureterectomy with LN dissection** within ≤14 weeks
  - **ypT2-T4a or ypN+** for patients treated with **NAC**[b]
  - **pT3-T4a or pN+** for patients **not treated with NAC**[b]
- No postsurgical radiation or AC
- If no prior NAC given, patient had to be ineligible for, or declined, cisplatin-based AC
- ECOG PS 0-2
- **Tissue sample for PD-L1 testing**

Stratification factors

- Number of LNs resected (<10 vs ≥10)
- Prior NAC (Yes vs No)
- LN status (+ vs –)
- Tumor stage (≤pT2 vs pT3/pT4)
- PD-L1 status[a] (IC0/1 vs IC2/3)

R 1:1

Atezolizumab 1200 mg q3w *(16 cycles or 1 year)*

No crossover allowed

Observation[c] **q3w**

Disease recurrence/ survival follow-up

Tumor assessments: q12w for years 1–3, (q24w for years 4–5 and at year 6)

Primary endpoint

DFS (ITT population)

Secondary endpoints

OS (ITT population)

Exploratory analyses

Biomarkers including PD-L1
Safety

[a] Protocol amendments broadened eligibility to "all-comers" (initially, only PD-L1–selected patients were enrolled [IC2/3: PD-L1 expression on tumor-infiltrating immune cells (IC) ≥5% of tumor area [VENTANA SP142 IHC assay]) and to patients with MIUC (initially, only patients with muscle-invasive bladder cancer were enrolled). [b] Upper-tract UC staging: ypT2-4 or ypN+ (with NAC) and pT3-4 or pN+ (without NAC). [c] Alternating clinic visits and phone calls.

AC, adjuvant chemotherapy; DFS, disease-free survival; ITT, intention to treat; LN, lymph node; MIUC, muscle-invasive UC.

Hussain M, et al. *J Clin Oncol*. 2020.

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IMvigor010
Phase III Randomized Study of Adjuvant Atezolizumab vs Observation in High-risk Muscle-invasive Urothelial Carcinoma

- No DFS benefit (HR 0.89)
- No DFS benefit across all subgroups including PD-L1+
- No OS benefit at median 22 months follow up (HR 0.85)
- Tolerable (16% disc due to AEs)

AE, adverse event; OS, overall survival.

Hussain M, et al. *J Clin Oncol*. 2020.

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CheckMate 274 Study Design

CheckMate 274 : phase 3, randomized, double-blind, multicenter study of adjuvant nivolumab versus placebo in patients with high-risk MIUC

N = 709

Key Inclusion Criteria

- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of dosing

Stratification Factors

- PD-L1 status (<1% vs ≥1%)[a]
- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status

R 1:1

- NIVO IV 240 mg Q2W
- PBO IV Q2W

Treat for up to 1 year of adjuvant therapy

Minimum follow-up: 5.9 months
Median follow-up in ITT population: 20.9 months (NIVO) and 19.5 months (PBO)

Primary endpoints: DFS in ITT population and DFS in all randomized patients with tumor PD-L1 ≥ 1%
Secondary endpoints: NUTRFS, DSS, and OS[b]
Exploratory endpoints included: DMFS, safety, HRQoL

DMFS, distant metastasis-free survival; DSS, disease specific survival; HRQoL, health-related quality of life; NUTRFS, non-urothelial tract recurrence-free survival.

Bajorin DF, et al. *J Clin Oncol*. 2021.

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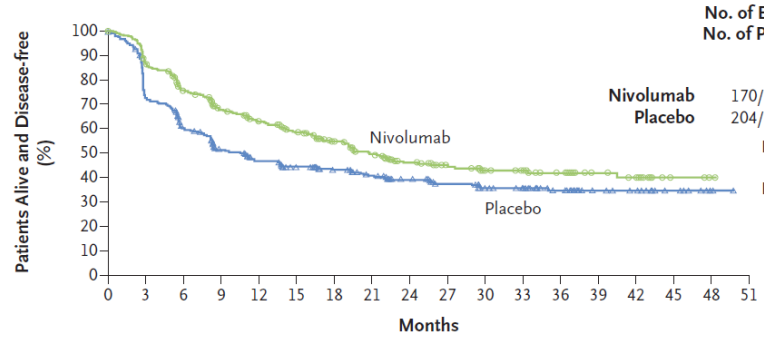
Disease-free Survival

Intention-to-Treat Population



	No. of Events/ No. of Patients	Disease-free Survival at 6 Mo (95% CI)	Disease-free Survival at 12 Mo (95% CI)
		%	
Nivolumab	170/353	74.9 (69.9–79.2)	62.8 (57.3–67.8)
Placebo	204/356	60.3 (54.9–65.3)	46.6 (41.1–51.9)

Hazard ratio for disease recurrence or death, 0.70 (98.22% CI, 0.55–0.90)
P<0.001

No. at Risk

Nivolumab	353	296	244	212	178	154	126	106	85	68	57	51	36	23	20	3	1	0
Placebo	356	248	198	157	134	121	105	94	80	65	54	50	37	22	19	10	2	0

Bajorin DF, et al. *N Engl J Med.* 2021.

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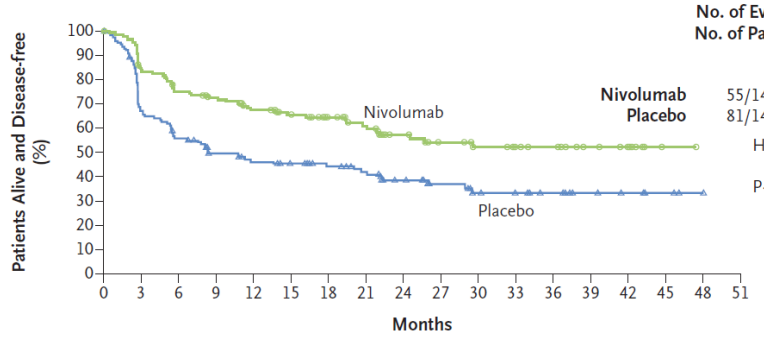
Disease-free Survival PD-L1 Positive

Patients with a PD-L1 Expression Level of ≥1%



	No. of Events/ No. of Patients	Disease-free Survival at 6 Mo (95% CI)	Disease-free Survival at 12 Mo (95% CI)
		%	
Nivolumab	55/140	74.5 (66.2–81.1)	67.2 (58.4–74.5)
Placebo	81/142	55.7 (46.8–63.6)	45.9 (37.1–54.2)

Hazard ratio for disease recurrence or death, 0.55 (98.72% CI, 0.35–0.85)
P<0.001

No. at Risk

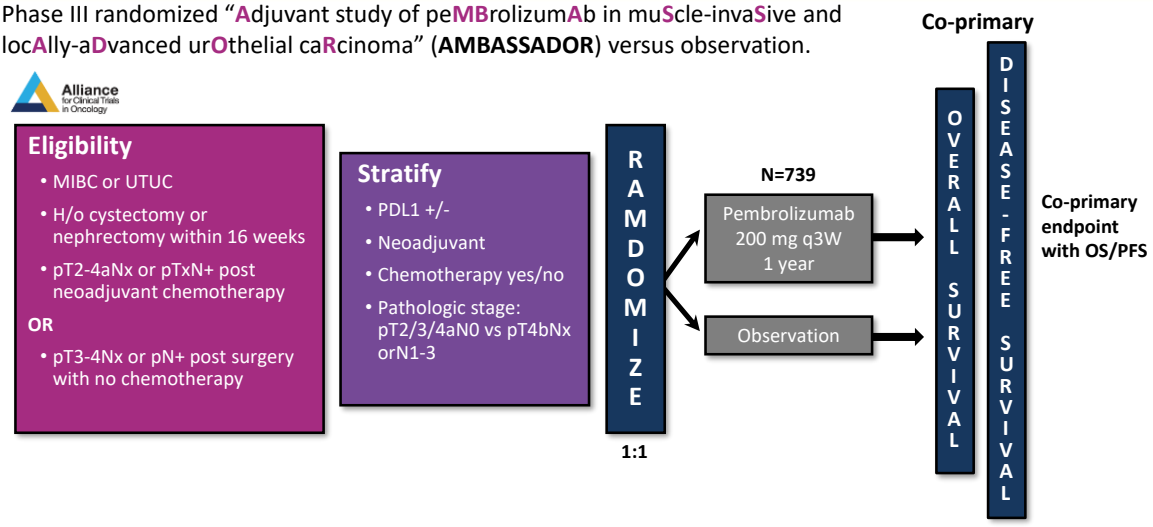
Nivolumab	140	113	98	91	76	68	58	50	38	31	27	24	21	12	10	1	0	0
Placebo	142	90	73	59	53	49	42	37	28	22	17	16	12	7	5	3	1	0

Bajorin DF, et al. *N Engl J Med.* 2021.

96

Closed to Accrual

Phase III randomized "**A**djuvant study of pe**MB**rolizum**Ab** in mu**S**cle-inva**S**ive and loc**A**lly-a**D**vanced ur**O**thelial ca**R**cinoma" (**AMBASSADOR**) versus observation.



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Selected Phase III Adjuvant IO Trials in Progress

Design	n	Study Name/NCT#
SWOG/NRG: Radiation +/- Atezo	475	SWOG/NRG 1806 NCT03775265
Gem Cis + Durva → Cystectomy → Durva adjuvant vs Gem Cis → Cystectomy	1,050	NIAGRA NCT03732677
Gem Cis + Pembro→ Cystectomy → Pembro adjuvant vs Gem Cis → Cystectomy	790	KEYNOTE-866 NCT03924895
Pembro (Cis ineligible)→ Cystectomy → Pembro adjuvant vs Cystectomy	610	KEYNOTE-905 NCT03924895
Gem Cis vs Gem Cis + Nivo vs Gem Cis + Nivo + BMS-986205 (IDO inhibitor)	1,200	CA017-078 NCT03661320

Clinicaltrials.gov.

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Metastatic Disease

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Case 2

A 67-year-old female presents with hematuria. Evaluation reveals muscle-invasive high-grade urothelial cancer. Metastatic evaluation reveals liver/lung metastases. A liver biopsy is positive for metastatic urothelial cancer (PD-L1+, *FGFR*3 mutation), and her ECOG PS is 1.

Her creatinine is 1.62 mg/dL (43 mL/min), and CBC and LFT are within normal limits.

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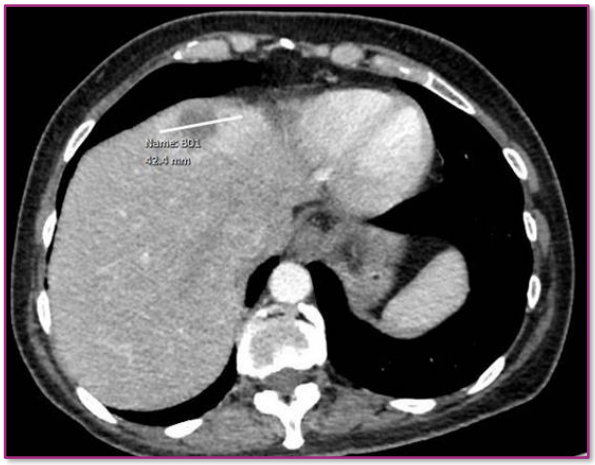
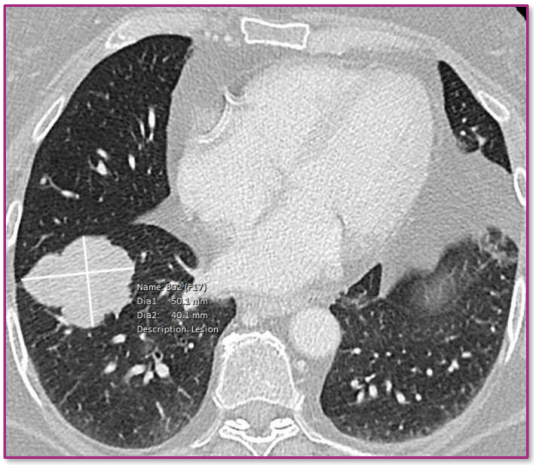
Case 2 (…continued)





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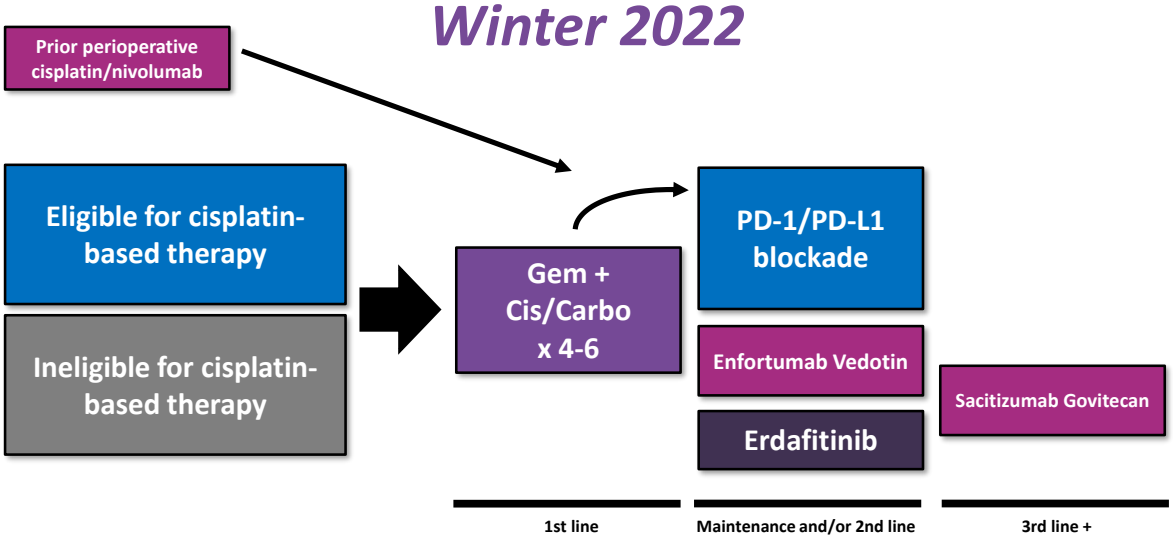
Advanced Bladder Cancer
Winter 2022



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Drug Approvals in Urothelial Cancer

FDA-approved Drugs for Bladder Cancer

Non-muscle Invasive

- Valrubicin 1998
- BCG 1998
- Pembrolizumab 2020

Advanced

- Cisplatin 1993
- Gemcitabine 2008 (European Medicine Agency harmonization)
- Vinflunine 2009 (European Medicine Agency)
- Atezolizumab 2016 (2020 switch maintenance)
- Nivolumab, durvalumab, pembrolizumab, avelumab 2017
- Erdafitinib 2019
- Enfortumab vedotin 2019
- Sacituzumab govitecan 2021

FDA Prescribing Information.

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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.

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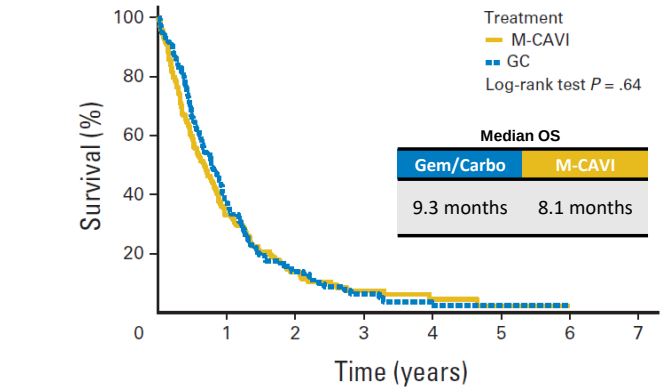
Carboplatin Combinations for Advanced Bladder Cancer Patients

EORTC Study 30986

- Randomized phase 2/3 trial in patients with advanced urothelial cancer deemed unfit for cisplatin-based chemotherapy (n=238)
- Gemcitabine/carboplatin vs methotrexate/ carboplatin/vinblastine



De Santis M, et al. *J Clin Oncol*. 2012.

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First-line Pembrolizumab in Cisplatin-ineligible Patients with Locally-advanced and Unresectable or Metastatic Urothelial Cancer (KEYNOTE-052)

A Multicenter, Single-arm, Phase 2 Study

Balar AV, Castellano D, O'Donnell PH, Grivas P, Vuky J, Powles T, Plimack ER, Hahn NM, de Witt R, Pang L, Savage MJ, Perini RF, Keefe SM, Bajorin D, Bellmunt J

Baseline Characteristics

Characteristic, n (%)	n=370
Age, median (range), y	74 (34–94)
75–84	139 (38)
≥85	40 (11)
Men	286 (77)
ECOG performance status	
0	80 (22)
1	133 (36)
2	156 (42)
Primary tumor location	
Upper tract	69 (19)
Lower tract	300 (81)
Liver metastases	78 (21)

Characteristic, n (%)	n=370
Metastases location	74 (34–94)
Lymph node only	51 (14)
Visceral disease	315 (85)
Prior adjuvant/neoadjuvant platinum-based chemotherapy	36 (10)
Reasons for cisplatin ineligibility	
Renal dysfunction	182 (49)
ECOG PS 2	120 (32)
ECOG PS 2 + renal dysfunction	35 (9)
Other reasons	33 (9)

Balar AV, et al. *Lancet Oncol*. 2017.

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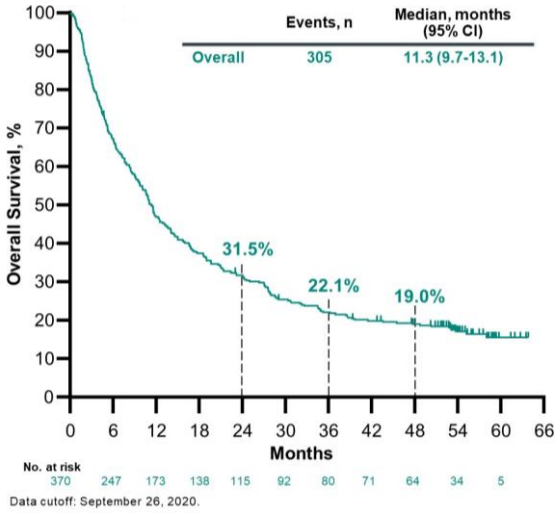
KEYNOTE-052
Confirmed Objective Response Rate

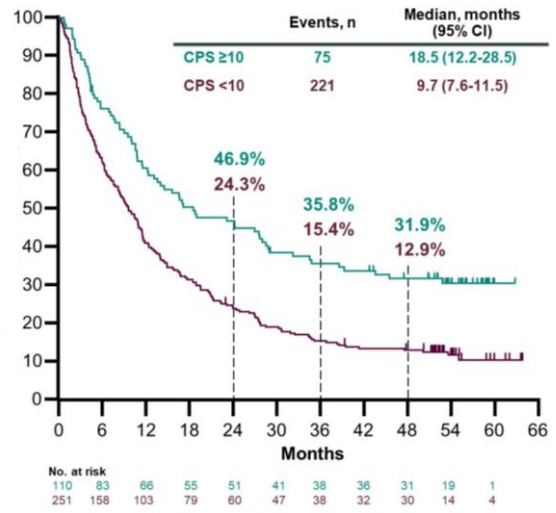
	Total Population (n=370)	
	n	% (95% CI)
Objective response rate	108	29 (25–34)
Complete response	25	7 (5–10)
Partial response	81	22 (18–27)
Stable disease	69	19 (14–22)
Progressive disease	156	42 (37–47)

Balar AV, et al. *Lancet Oncol.* 2017; O'Donnell PH, et al. ASCO Annual Meeting. 2017. Abstract 4502.

109

Kaplan-Meier Estimates of OS





O'Donnell P, et al. *J Clin Oncol.* 2021.

110

Conclusions

- First-line pembrolizumab monotherapy continued to show durable antitumor activity up to 5 years after the last patient was enrolled
  - ORR: 28.9%
  - Median DOR: 33.4 months
  - Median OS 11.3 months
- Patients with CPS ≥10 were more likely to respond than those with CPS <10, and this response was durable, supporting the current FDA indication
  - ORR: 47.3% (CPS ≥10), 20.7% (CPS <10)
  - Median DOR: NR (CPS ≥10), 21.2 months (CPS <10)
  - Median OS: 18.5 months (CPS ≥10), 9.7 months (CPS <10)
- Safety was consistent with the known profile of pembrolizumab
- These data support the use of pembrolizumab in cisplatin-ineligible patients with locally advanced or metastatic UC

O'Donnell P, et al. *J Clin Oncol.* 2021.

111

Standards of Care for Initial Therapy in Advanced Urothelial Cancer

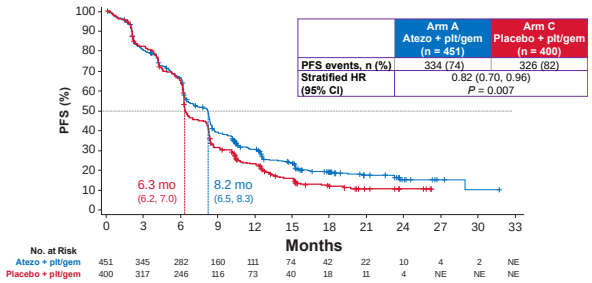
Setting		Regimen	Response Rate	Median Survival
First line	Cisplatin-eligible	MVAC Gem/cis PGC	40%–50%	12–15 months
	Cisplatin-ineligible	Gem/carbo	36%–56%	7–9 months
		Atezolizumab pembrolizumab	~24%	~15.9 months (atezolizumab)
Switch maintenance	SD or better from platinum-based chemotherapy	Avelumab	9.7%	21.4 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.

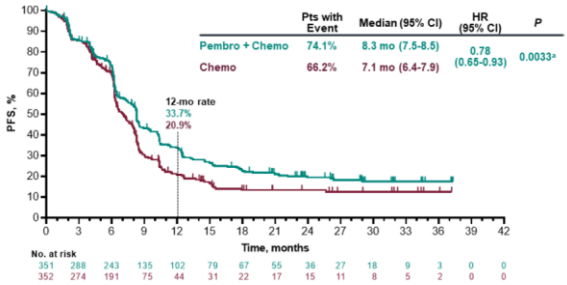
112

Platinum-based Chemo + Immune Checkpoint Inhibitors Leads to Minor Improvements in PFS in ITT

IMvigor 130



Keynote 361

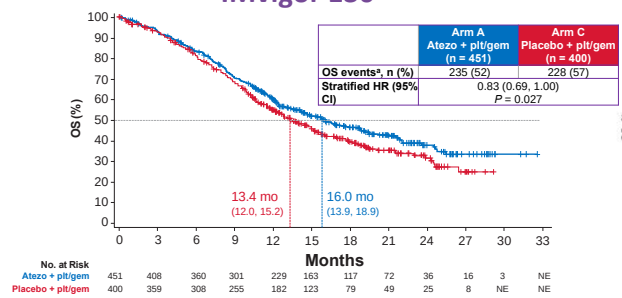


Galsky MD, et al. *Lancet*. 2020; Alva A, et al. *Ann Oncol.* 2020.

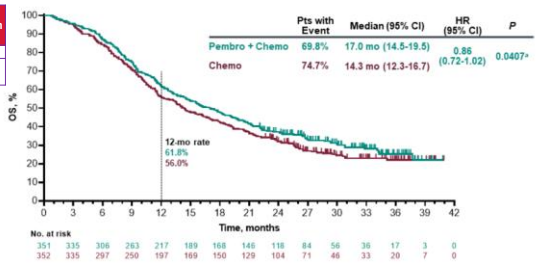
113

Platinum-based Chemo + Immune Checkpoint Inhibitors Leads to Non-significant Improvements in OS in ITT

IMvigor 130



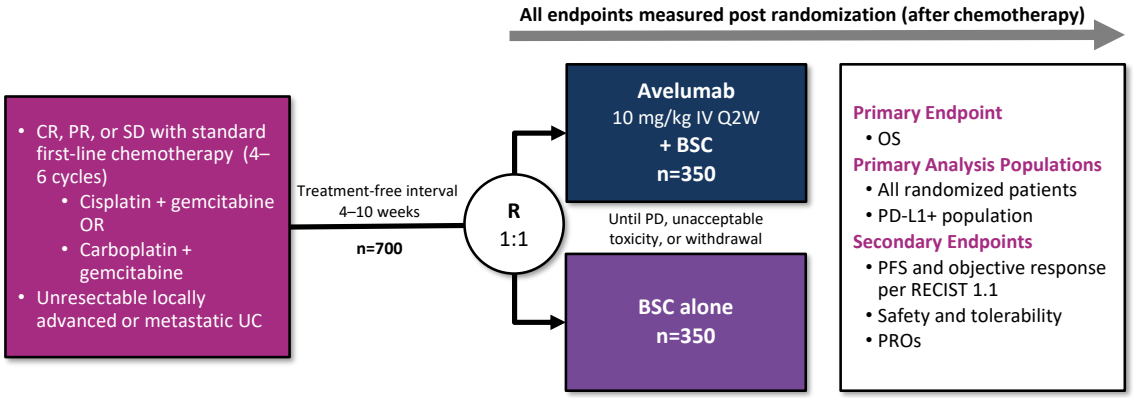
Keynote 361



Galsky MD, et al. *Lancet*. 2020; Alva A, et al. *Ann Oncol.* 2020.

114

JAVELIN Bladder 100 Study Design (NCT02603432)



Powles T, et al. *N Engl J Med.* 2020.

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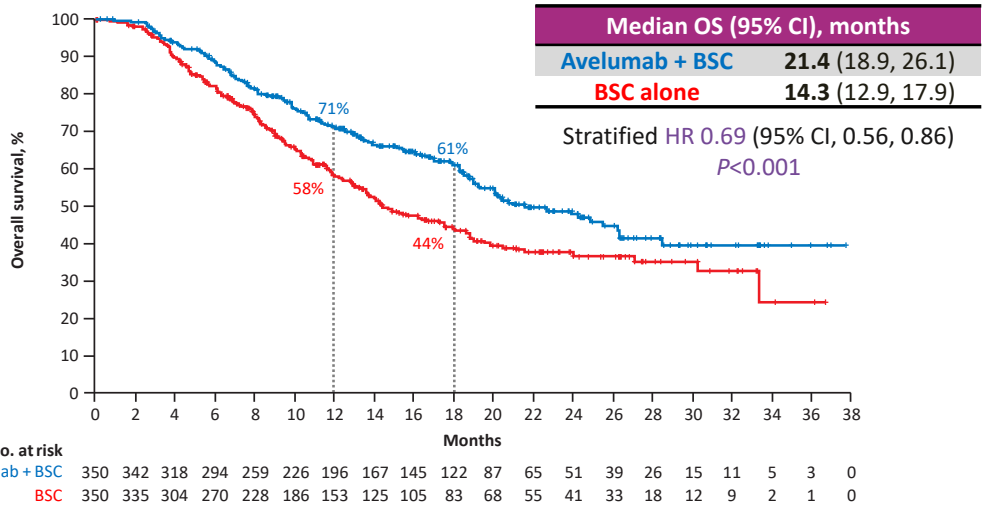
OS in the Overall Population

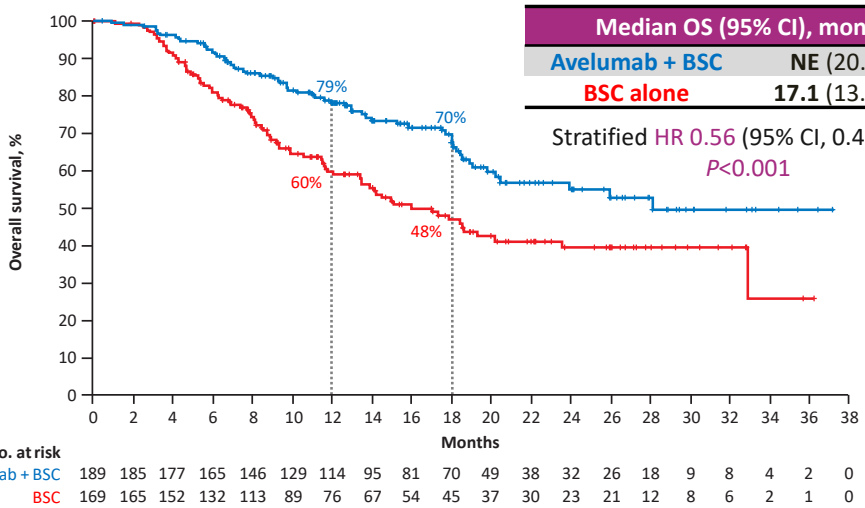


OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0053).

Powles T, et al. *N Engl J Med.* 2020.

116

OS in the PD-L1+ Population



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

OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0014). **NE**, not estimable.

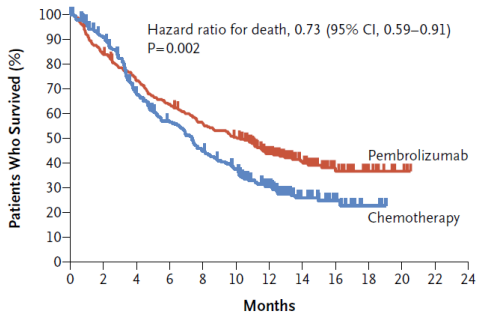
Powles T, et al. *N Engl J Med.* 2020.

117

Pembrolizumab as Second-line Therapy for Advanced Urothelial Carcinoma

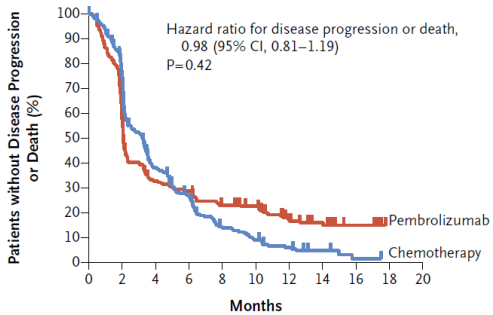
Overall Survival

10.3 mo in P vs 7.4 mo C



No. at Risk													
Pembrolizumab	270	226	194	169	147	131	87	54	27	13	4	0	0
Chemotherapy	272	232	171	138	109	89	55	27	14	3	0	0	0

Progression-free Survival



No. at Risk												
Pembrolizumab	270	165	85	73	56	51	23	16	7	0	0
Chemotherapy	272	188	85	56	27	17	10	5	1	0	0

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

118

Case 2 (…continued)

The patient received 5 cycles of gemcitabine/carboplatin (persistent thrombocytopenia caused discontinuation). Her liver and lung lesions decreased by approximately 30%. Avelumab maintenance was initiated.

Following 5 months of therapy, she presents now with overt radiographic disease progression. ECOG PS 1–2

Her creatinine is 1.6 mg/dL (40 mL/min), hemoglobin is 11.4 g/dL, and platelet count is 102K. Her WBC and LFT are within normal limits.

119

Erdafitinib in Locally-advanced or Metastatic Urothelial Carcinoma

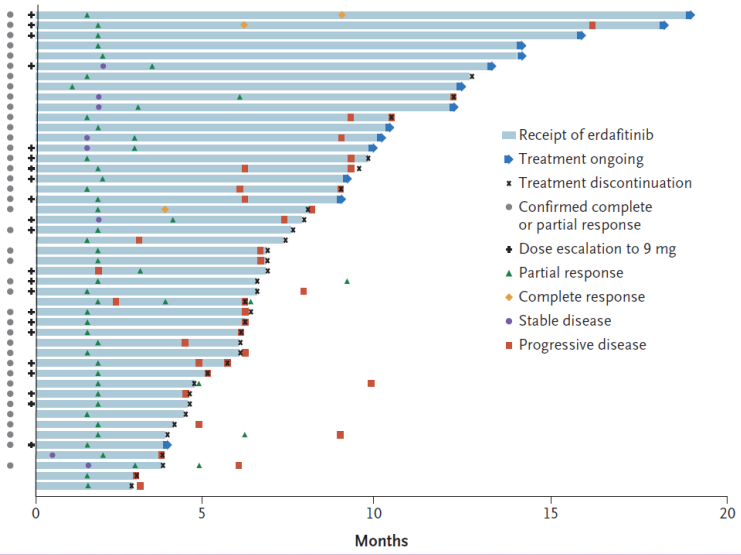
Loriot Y, Necchi A, Park SH, Garcia-Donas J, Huddart R, Burgess E, Fleming M, Rezazadeh A, Mellado B, Varlamov S, Joshi M, Duran I, Tagawa ST, Zakharia Y, Zhong B, Stuyckens K, Santiago-Walker A, De Porre P, O'Hagan A, Avadhani A, Siefker-Radtke AO

- Erdaftinib potent tyrosine kinase inhibitor of FGFR1–4
- Open label phase II trial
- 99 patients with at least 1 F*GFR3* mutation or *FGFR2/3* fusion

Loriot Y, et al. *N Engl J Med.* 2019.

121

Duration and Type of Response

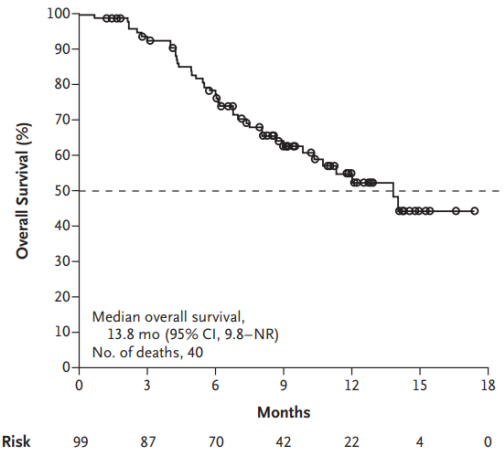


Loriot Y, et al. *N Engl J Med.* 2019.

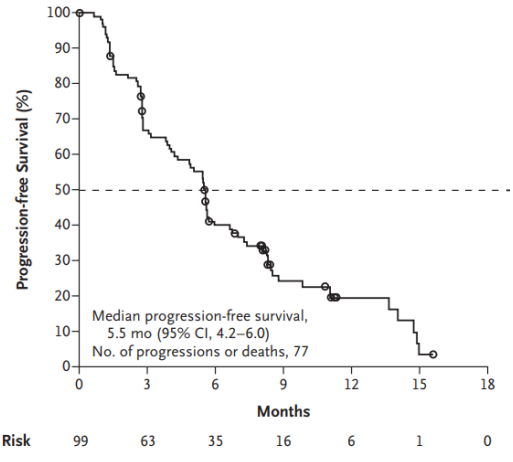
122

Characterizing PFS and OS

Overall Survival



Progression-free Survival



Loriot Y, et al. *N Engl J Med.* 2019.

123

Adverse Events in the 99 Patients in the Selected-regimen Group

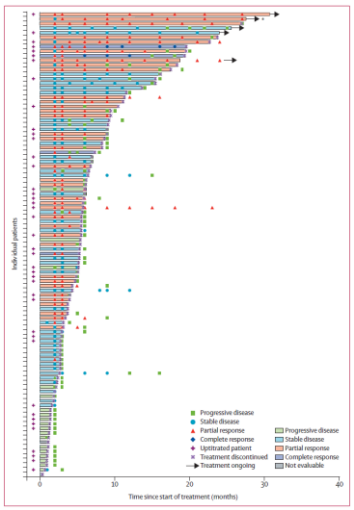
Adverse Event	Any Grade	Grade 1	Grade 2	Grade 3
		Number of patients (percent)		
Hyperphosphatemia	76 (77)	53 (54)	21 (21)	2 (2)
Stomatitis	57 (58)	21 (21)	26 (26)	10 (10)
Diarrhea	50 (51)	31 (31)	15 (15)	4 (4)
Dry mouth	46 (46)	34 (34)	11 (11)	0
Decreased appetite	38 (38)	18 (18)	20 (20)	0
Dysgeusia	37 (37)	23 (23)	13 (13)	1 (1)
Fatigue	32 (32)	12 (12)	18 (18)	2 (2)
Dry skin	32 (32)	24 (24)	8 (8)	0
Alopecia	29 (29)	23 (23)	6 (6)	0
Constipation	28 (28)	19 (19)	8 (8)	1 (1)
Hand-foot syndrome	23 (23)	6 (6)	12 (12)	5 (5)
Anemia	20 (20)	9 (9)	7 (7)	4 (4)
Asthenia	20 (20)	2 (2)	11 (11)	7 (7)
Nausea	20 (20)	13 (13)	6 (6)	1 (1)
Dry eye	19 (19)	14 (14)	4 (4)	1 (1)
Onycholysis	18 (18)	6 (6)	10 (10)	2 (2)

Loriot Y, et al. *N Engl J Med.* 2019

124

Efficacy and Safety of Erdafitinib in Patients with Locally-advanced or Metastatic Urothelial Carcinoma

Long-term Follow-up of a Phase 2 Study



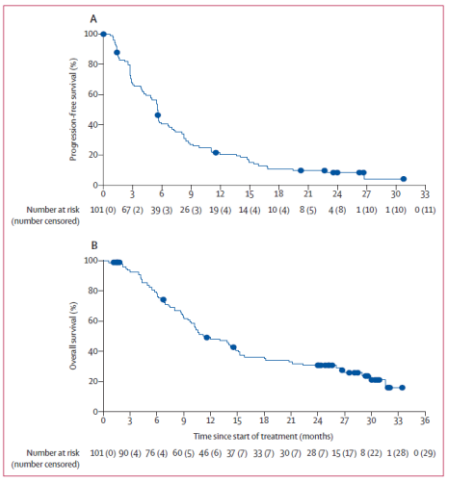
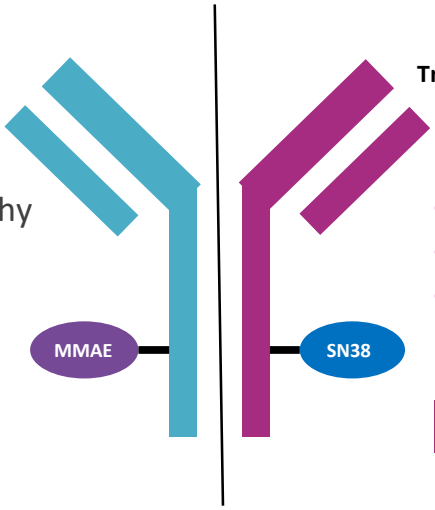


Figure 2: **Investigator-assessed progression-free survival and overall survival for patients treated with the selected 8 mg/day erdafitinib UpT regimen**

Siefker-Radtke A, et al. *Lancet Oncol.* 2022.

125

Antibody-drug Conjugates in Advanced Urothelial Cancer



- Peripheral neuropathy
- Rash
- Hyperglycemia

Enfortumab vedotin

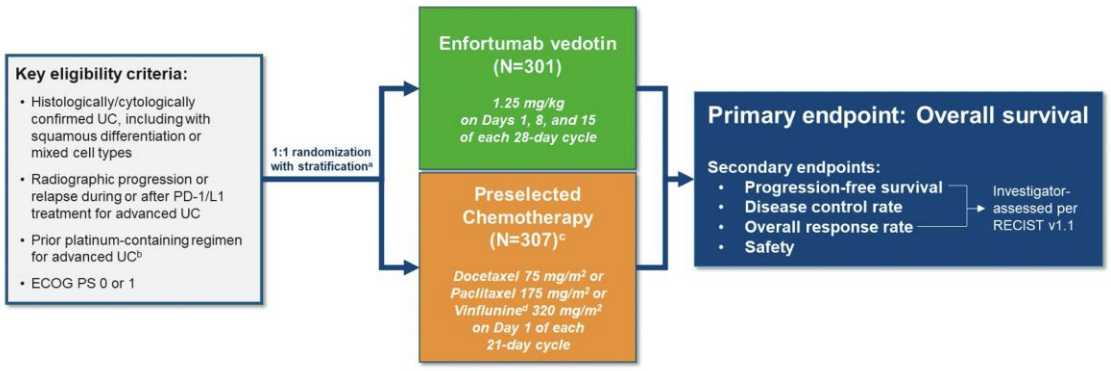
- Febrile neutropenia
- Diarrhea
- Nausea

Sacituzumab govitecan

O'Donnell PH, et al. *Ann Oncol*. 2020; Loriot Y, et al. *Ann Oncol*. 2020.

126

EV-301: Phase 3 Trial of EV vs Chemotherapy in Previously Treated Locally-advanced or Metastatic UC

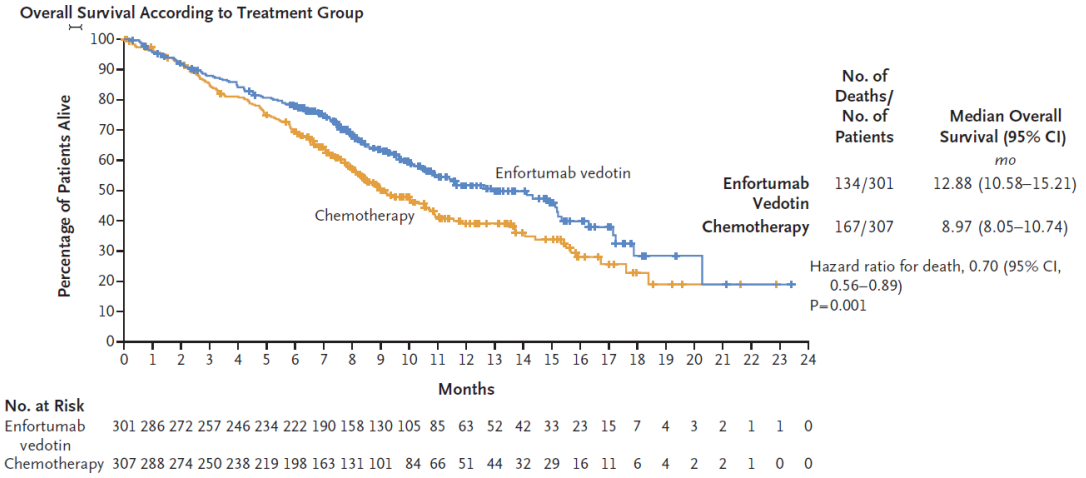


[a]Stratification variables were ECOG performance status (0 or 1), regions of the world (United States, western Europe, or rest of world), liver metastasis (yes or no).
[b]If used in the adjuvant/neoadjuvant setting, progression must be within 12 months of completion.
[c]Investigator selected prior to randomization.
[d]In countries where approved; overall proportion of patients receiving vinflunine capped at 35%.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1/L1, programmed cell death protein-1/programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; UC, advanced urothelial carcinoma.

Powles T, et al. GU ASCO 2021. Abstract 393.

127

EV-301: Phase 3 Trial of EV vs Chemotherapy in Previously Treated Locally-advanced or Metastatic UC



Powles T, et al. *N Engl J Med*. 2021.

128

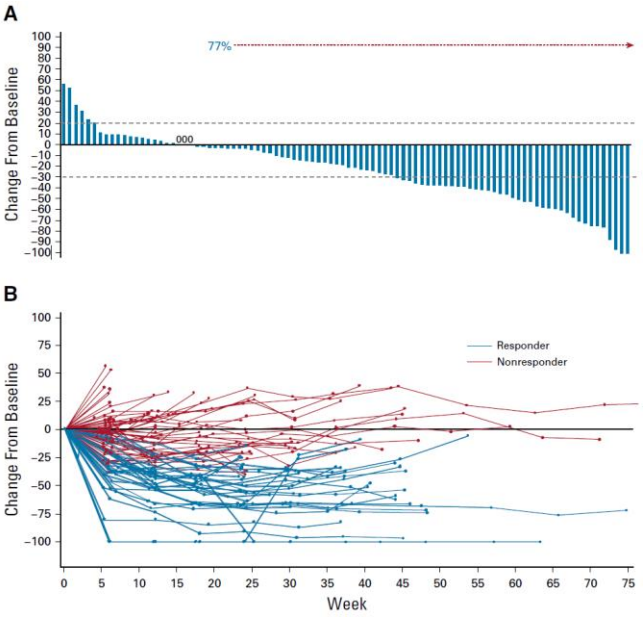
Treatment-Related Adverse Events (Safety Population)

Adverse Event	Enfortumab Vedotin Group (N=296)		Chemotherapy Group (N=291)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	278 (93.9)	152 (51.4)	267 (91.8)	145 (49.8)
Alopecia	134 (45.3)	0	106 (36.4)	0
Peripheral sensory neuropathy†	100 (33.8)	9 (3.0)	62 (21.3)	6 (2.1)
Pruritus	95 (32.1)	4 (1.4)	13 (4.5)	0
Fatigue	92 (31.1)	19 (6.4)	66 (22.7)	13 (4.5)
Decreased appetite	91 (30.7)	9 (3.0)	68 (23.4)	5 (1.7)
Diarrhea	72 (24.3)	10 (3.4)	48 (16.5)	5 (1.7)
Dysgeusia	72 (24.3)	0	21 (7.2)	0
Nausea	67 (22.6)	3 (1.0)	63 (21.6)	4 (1.4)
Maculopapular rash	48 (16.2)	22 (7.4)	5 (1.7)	0
Anemia	34 (11.5)	8 (2.7)	59 (20.3)	22 (7.6)
Decreased neutrophil count	30 (10.1)	18 (6.1)	49 (16.8)	39 (13.4)
Neutropenia	20 (6.8)	14 (4.7)	24 (8.2)	18 (6.2)
Decreased white-cell count	16 (5.4)	4 (1.4)	31 (10.7)	20 (6.9)
Febrile neutropenia	2 (0.7)	2 (0.7)	16 (5.5)	16 (5.5)

Powles T, et al. *N Engl J Med*. 2021.

129

TROPHY-U-01
A Phase II Open-label Study of Sacituzumab Govitecan in Patients with Metastatic Urothelial Carcinoma Progressing after Platinum-based Chemotherapy and Checkpoint Inhibitors



Tagawa ST, et al. *J Clin Oncol.* 2021.

130

TROPiCS-04
Phase 3 Trial of SG in Previously Treated Metastatic or Locally-advanced Unresectable UC

Study population

- Locally advanced unresectable or mUC
- Upper/lower tract tumors
- Mixed histologic types are allowed if urothelial is predominant
- Progression after platinum-based **and** anti–PD-1/PD-L1 therapy

OR

- Platinum in neoadjuvant/adjuvant setting if progression within 12 months and subsequent CPI

N=482

SG
Sacituzumab govitecan
10 mg/kg
day 1/8 of 21-day cycle

TPC
- Docetaxel @ 75 mg/m²
OR
- Paclitaxel @ 175 mg/m²
OR
- Vinflunine @ 320 mg/m² on day 1 of 21-day cycle

Continue treatment until loss of clinical benefit or unacceptable toxicity

Primary endpoint

Overall survival

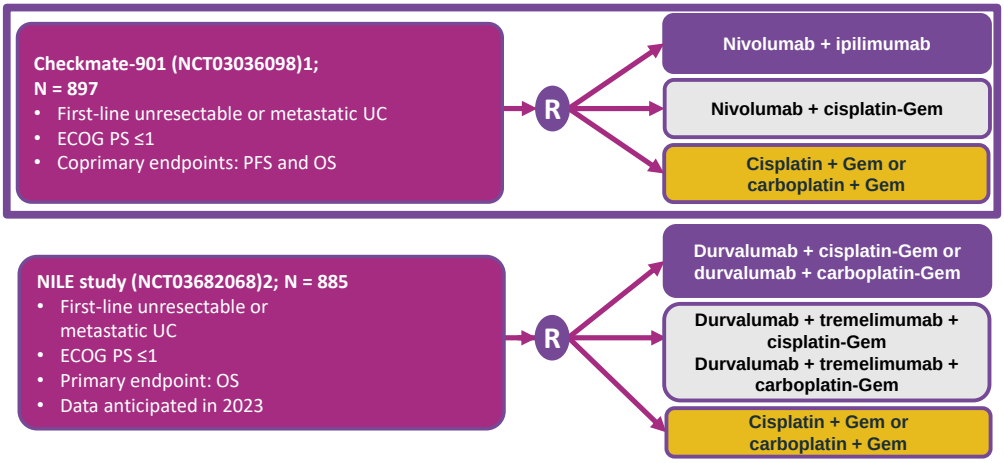
Secondary endpoints

- PFS by PI assessment using RECIST v1.1
- ORR, DOR, and CBR by PI assessment using RECIST v1.1
- EORTC QLQ C30 score and EuroQOL EQ-5D-5L QoL score

Grivas P, et al. ASCO GU 2021. Abstract TPS498.

131

Ongoing Phase 3 Trials in the Metastatic Setting



NOTE: ipilimumab and tremelimumab are off-label use for bladder cancer.

[1]https://clinicaltrials.gov/ct2/show/NCT03036098?term=NCT03036098&draw=2&rank=1;
[2]https://clinicaltrials.gov/ct2/show/NCT03682068?term=NCT03682068&draw=2&rank=1.

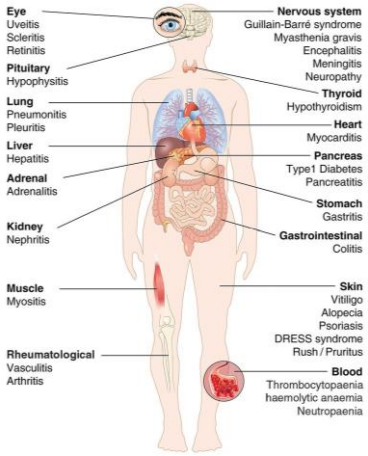
132

Immune Related Adverse Events (irAEs)

133

Immune-related Adverse Events (irAEs)

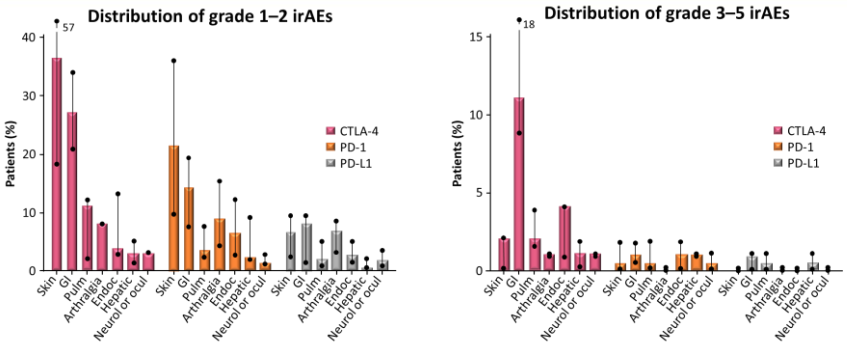
- ICIs introduce the potential for transformative, durable responses in multiple malignancies
- ICIs also introduce the potential for new toxicity
- irAEs
  - Activation of immune cells in non-tumor compartments
  - Can mimic autoimmune conditions



Varricchi G, et al. *ESMO Open*. 2017.

134

irAEs with ICI Monotherapy

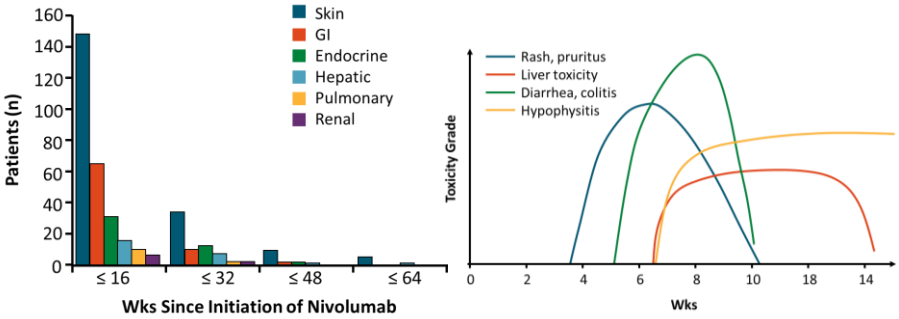


- Incidence of irAEs can vary among malignancies
  - Retrospective review found an overall incidence of colitis in 6% and pneumonitis in 3.84% of patients with multiple cancer types at a single institution
  - Colitis was significantly more common in melanoma (P=0.016), pneumonitis significantly more common in NSCLC (P=0.004)

Michot JM, et al. *Eur J Cancer*. 2016; Owen DH, et al. ESMO 2018 Congress. Abstract 4304.

135

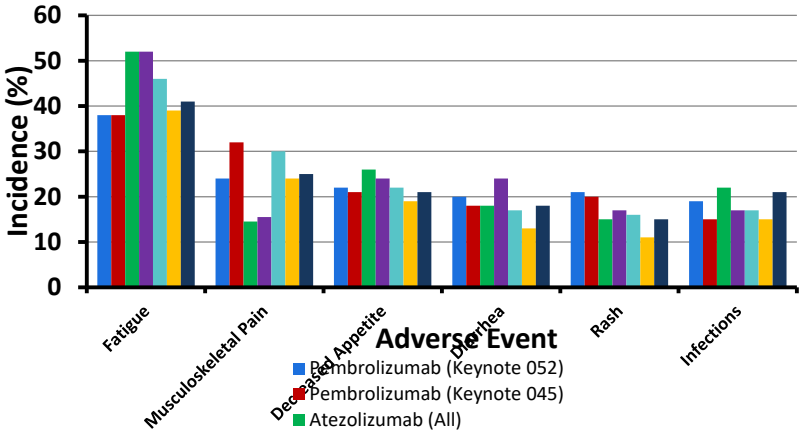
Onset of irAEs



Weber JS, et al. *J Clin Oncol*. 2017.

136

Select All Grade AEs in ≥10% of Patients with UC



FDA Prescribing Information.

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PD-1/PD-L1 Safety (Grade III–IV Toxicity)
Per UC Trials

Pembrolizumab	Atezolizumab	Nivolumab	Durvalumab	Avelumab
Fatigue (4%)	Urinary tract infection (9%)	Fatigue (1.9%)	Increased LFTs (2.6%)	Hyponatremia (16%)
Muscle spasms (2%)	Anemia (8%)	Diarrhea (1.9%)	Hypertension (1%)	Fatigue (7%)
Decreased appetite (1%)	Fatigue (6%)	Asthenia (1.5%)	Diarrhea (0.5%)	Anemia (6%)
Diarrhea (1%)	Dyspnea (4%)	Rash (1.1%)	Anemia (0.5%)	Hypertension (5%)

Balar A, et al. *Lancet Oncol.* 2017; Sharma P, et al. *Lancet Oncol*. 2017; Bellmunt J, et al. *N Engl J Med*. 2017; Apolo A, et al. ESMO 2017 Congress. Abstract 4042; Balar A, et al. 2016 ASCO Annual Meeting. Abstract LBA4500; Heery C, et al. *Lancet Oncol*. 2017; Powles T, et al. *JAMA Oncol*. 2017; Rosenberg J, et al. *Lancet*. 2016.

138

Generic Toxicity Management of irAEs

- Corticosteroids remain cornerstone of care for immune-mediated adverse events
  - Resolved most irAEs among UC trials
  - Mild skin reactions can be treated with topical steroids
  - Higher grade/persistent toxicity requires systemic steroids
  - Oral preferred; IV may be used when absorption compromised (i.e., colitis)
- Moderate cases (Grade II)
  - Hold drug, redose if toxicity improves, consider low-dose steroids (prednisone 0.5–1 mg/kg/day)
- Severe cases (Grade III/IV)
  - Start high-dose steroids (prednisone 1–2 mg/kg/day) with a slow taper (≥1 month)
  - Infliximab 5 mg/kg once every 2 weeks can be used
- Endocrine side effects
  - Hormonal replacement

CTCAE Grade	Corticosteroids	Other Adjunctive Therapies	Immunotherapy Action
1	Not required	Not required	Continue
2	Topical or systemic steroids	Not required	Hold temporarily
3	Systemic steroids	If no response to steroids after 3–5 days	Discontinue and may consider resuming therapy* based on risk/benefit
4	Systemic steroids	If no response to steroids after 3–5 days	Discontinue

*Doses are either given or held. There are no dose reductions.

Petrylak DP. *Clin Genitourin Cancer.* 2017; Weber J, et al. *J Clin Oncol*. 2012; Brahmer JR, et al. *J Clin Oncol*. 2018.

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Resources for Management of irAEs
Guidelines

NCCN Guidelines in Oncology for Management of Immunotherapy-related Toxicities:
https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

ASCO Clinical Practice Guideline on Management of Immune-related Adverse Events:
https://ascopubs.org/doi/full/10.1200/JCO.21.01440

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Conclusions

- "Relative" wealth of therapeutic options creates challenges
- No data to support CPI/chemotherapy combo upfront
- Switch maintenance data is compelling
- Available data supports a risk/benefit discussion regarding adjuvant nivolumab for high-risk patients
- Impact of adjuvant immune checkpoint therapy on management paradigm in flux
- NGS needs to become part of management paradigm
- Single-agent "salvage" chemotherapy's time has gone
- Novel non-chemotherapy combinations for upfront therapy being evaluated in phase III trials

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Notes

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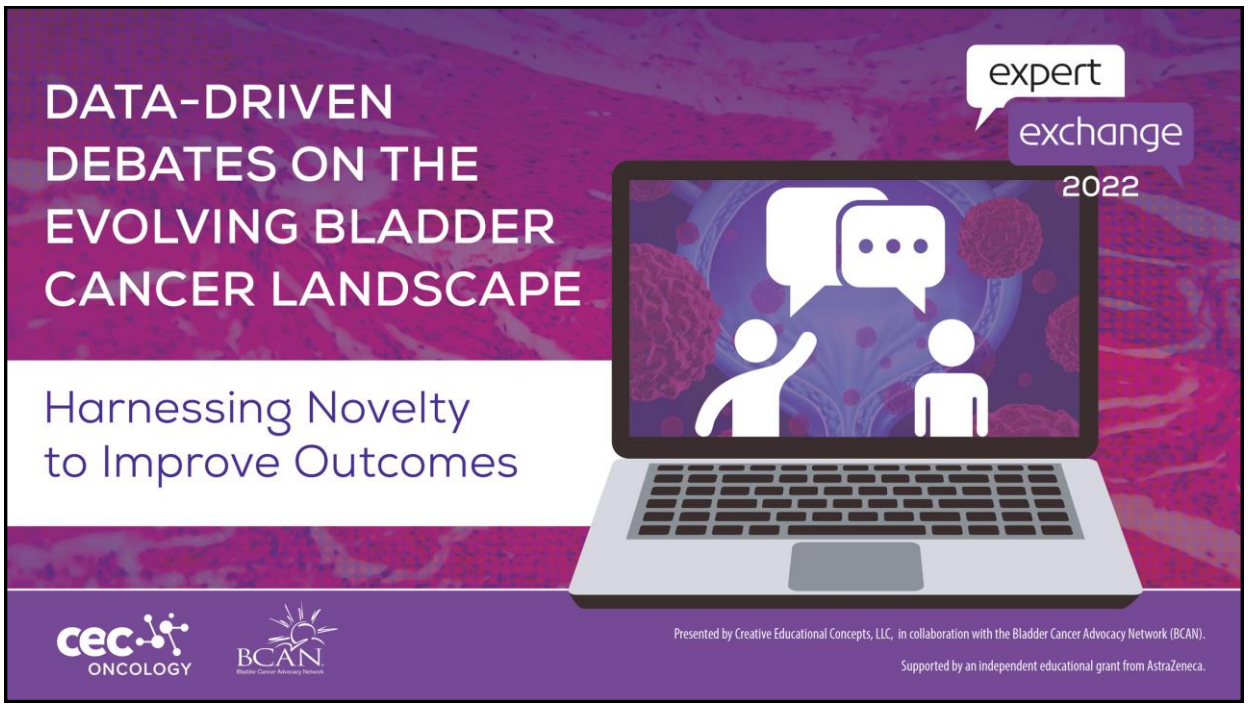

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