



New and Promising Treatments for Bladder Cancer

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New Treatments and Promising Research in Bladder Cancer

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Conflicts of Interest

- UroGen Pharma (Speaker)

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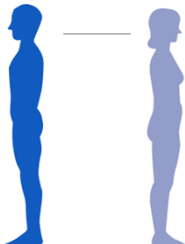
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Screening

- Goal: to diagnosis EARLY
- Current screening relies on:
 - PCP checking a urine sample
 - Microscopic hematuria
 - PCP to refer
- Most people with microscopic hematuria do not have bladder cancer
 - UTI
 - Nephrolithiasis
 - Enlarged prostate
 - Other malignancy – kidney cancer
 - Renal dysfunction

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	Male				Female		
Estimated New Cases	Prostate	288,300	29%		Breast	287,850	31%
	Lung & bronchus	117,550	12%		Lung & bronchus	118,830	13%
	Colon & rectum	81,860	8%		Colon & rectum	70,340	8%
	Urinary bladder	62,420	6%		Uterine corpus	65,950	7%
	Melanoma of the skin	58,120	6%		Melanoma of the skin	42,600	5%
	Kidney & renal pelvis	52,360	5%		Non-Hodgkin lymphoma	36,350	4%
	Non-Hodgkin lymphoma	44,880	4%		Thyroid	31,940	3%
	Oral cavity & pharynx	39,290	4%		Pancreas	29,240	3%
	Leukemia	35,670	4%		Kidney & renal pelvis	28,710	3%
	Pancreas	33,130	3%		Leukemia	24,840	3%
	All sites	1,010,310			All sites	934,870	

Epidemiology of bladder cancer

American Cancer Society 2022 Cancer Facts & Figures

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Screening in bladder cancer vs. other cancers

Bladder cancer

- US: 82, 290 new cases per year (M 62,000, F 18,000)
- 4th most common malignancy among men
- 8th most common cancer death among men
- **70% are non-muscle invasive at diagnosis**

Other cancers

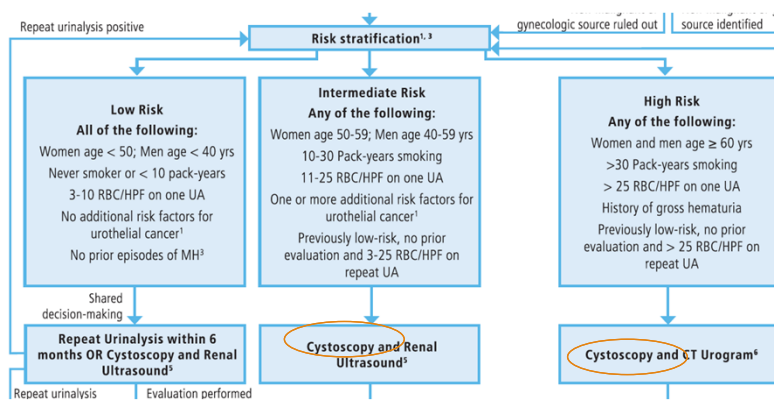
- Prostate – 288,300 new cases per year
- Breast – 297, 790 new cases per year
- Lung – 238, 340 new cases per year
- Colon 153, 020 new cases per year

•The more common the malignancy, the easier it is to justify screening for cancers.

American Cancer Society 2022 Cancer Facts & Figures

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AUA Guidelines - Screening



Only 5% of patients who see urologists are low risk

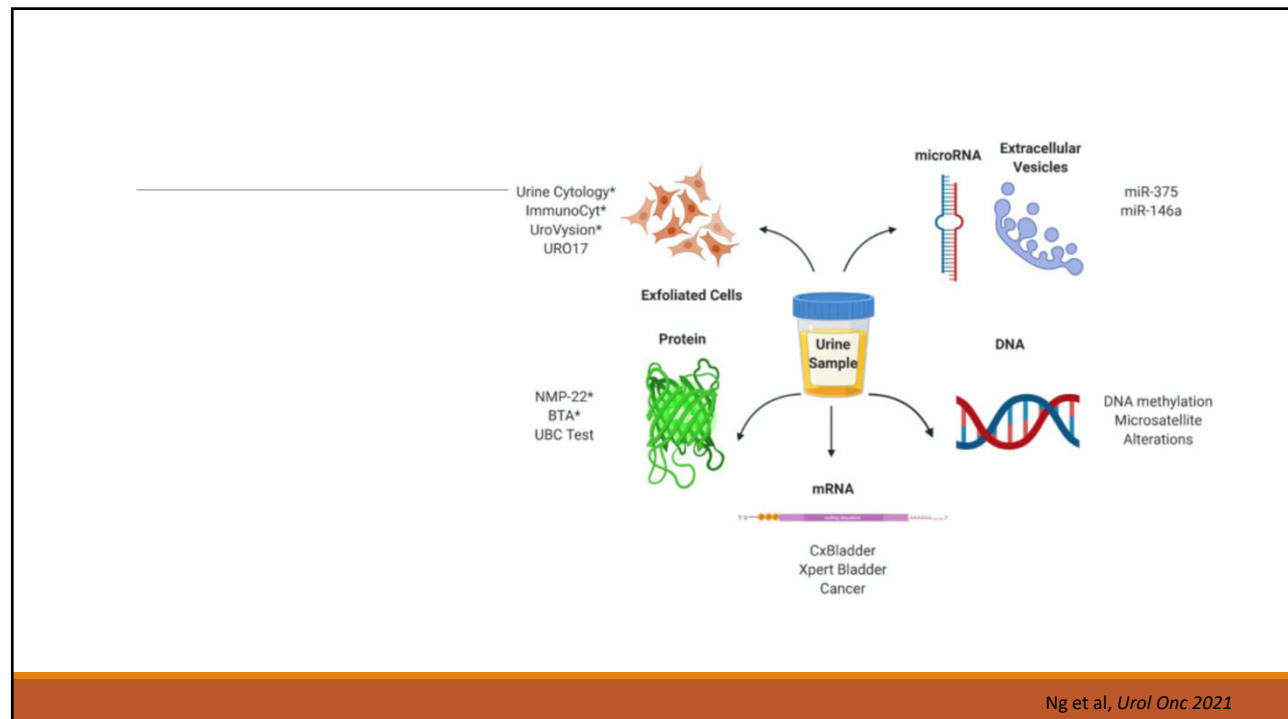
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New screening strategies

- Biomarkers
 - STRATA: Safe Testing of Risk for Asymptomatic Microhematuria
 - Randomized trial
 - Standard of care vs. biomarker for low risk patients
 - Low risk → CxBladder → + → cystoscopy
 - Enrolled: 554 patients
 - Results pending

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Biomarkers

- Advantages
 - Avoidance of cystoscopy
- Disadvantages
 - Missing a clinically significant cancer
 - False positives
 - Cost



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AUA Guidelines

Urine Markers after Diagnosis of Bladder Cancer

9. In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of cystoscopic evaluation. (Strong Recommendation; Evidence Strength: Grade B)

NMP22®	Protein-based; identifies nuclear matrix protein involved in the mitotic apparatus
BTA®	Protein-based; identifies a basement membrane antigen related to complement factor H
UroVysion® F ISH	Cell-based; identifies altered copy numbers of specific chromosomes using fluorescent probes
ImmunoCyt™	Cell-based; identifies three cell surface glycoproteins
Cxbladder™	Cell-based; identifies the presence of five mRNA fragments

AUA NMIBC Guidelines, 2020

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How good does it need to be to avoid cystoscopy?

Use of Urinary Biomarkers for Bladder Cancer Surveillance: Patient Perspectives

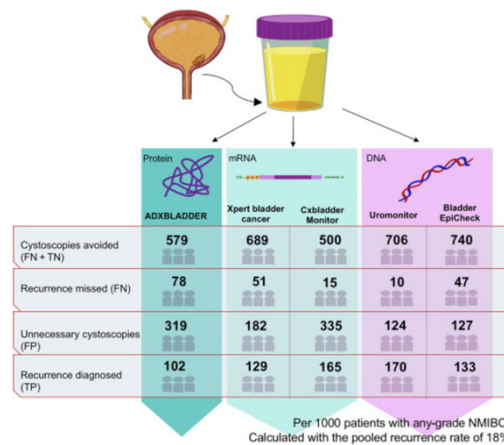
Ofer Yossepowitch, Harry W. Herr and S. Machele Donat*

From the Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, New York

- 75% of patients said it needed to diagnose $\geq 95\%$ of bladder tumors
- 21% said it needed to diagnose 90-95%

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Cystoscopies avoided



Laukhtina et al, *Eur Urol Onc* 2021

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Current markers

Test	Sensitivity	NPV
CxBladderMonitor	91%	96%
NMP22 (quant)	26%	87%
NMP22(qual)	11%	86%
Cytology	22%	87%
FISH	33%	92%

Lotan 2017

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Take Aways

- New biomarkers are **here** and **improving**
- Perform best for higher risk tumors
- When to use: atypical cytology, indeterminate cystoscopy
- Potentially avoid cystoscopy
- Unanswered questions:
 - Management of positive biomarker with negative cystoscopy – are you willing to go to the OR for these patients?
 - Risk/importance of deferred diagnosis of low grade disease
 - Cost

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Gemcitabine – Docetaxel

- N=276, median 73 years old, 22.9 months follow up
- **1 year recurrence free survival:** 60% (65% high grade RFS)
- **2 year recurrence free survival:** 46% (52%)
- 3.6% had disease progression
- 15.6% went on to cystectomy (4% had muscle invasion)
- Downside: requires sequential administration, increases time in clinic

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Adstiladrin (nadofaragene firadenovec/rAd-IFNalpha/Syn3)

CR for those with
HG Ta/T1 @ 3
months: 72.9%

@ 1 year **ALL**
patients: 30.5%
free from
recurrence

	Carcinoma in situ cohort (n=103)	High-grade Ta or T1 cohort (n=48)	All patients (n=151)
Patients with complete response at month 3*	55 (53.4%; 43.3-63.3)	35 (72.9%; 58.2-84.7)	40 (59.6%; 51.3-67.5)
Duration of complete response† or high-grade recurrence-free survival‡, months	9.69 (9.17-NE)	12.35 (6.67-NE)	7.31 (5.68-11.93)
Patients who were free from high-grade recurrence			
Month 6	42 (40.8%; 31.2-50.9)	30 (62.5%; 47.4-76.0)	72 (47.7%; 39.5-56.0)
Month 9	36 (35.0%; 25.8-45.0)	28 (58.3%; 43.2-72.4)	64 (42.4%; 34.4-50.7)
Month 12	25 (24.3%; 16.4-33.7)	21 (43.8%; 29.5-58.8)	46 (30.5%; 23.2-38.5)

Data are n (%; 95% CI) or median (95% CI) NE=not estimable. *Patients with a complete response included all patients who had both a complete response reported by the study investigator. †Patients in the carcinoma in situ cohort. ‡Patients in the high-grade Ta or T1 cohort.

Table 2: Complete response and freedom from high-grade recurrence in the efficacy population

Boorjian, et al, Lancet Oncology, 2021

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QUILT 3032 – ALT 803 + BCG

- Phase II/III clinical trial - BCG unresponsive disease
- ALT 803 – recombinant IL-15 super-agonist → upregulation of CD8 & NK cells
- Administered weekly x 6 weeks, and then maintenance
- Complete response rate for those with CIS: 71%
- Median duration of CR: 24.1 months
- Avoidance of cystectomy in responders: 91% at 24 months

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Low grade, intermediate risk urothelial carcinoma	Low grade, low or intermediate risk urothelial carcinoma	Intermediate risk urothelial carcinoma	High Risk BCG Naïve urothelial carcinoma
<p>Optima II: Phase 2b Trial <u>Agent:</u> UGN-102 (mitomycin reverse thermal gel)</p> <p><u>Study Design:</u> open label, single arm – 6 weekly instillations of UGN-102</p> <p><u>Population:</u> Biopsy proven low grade urothelial carcinoma, negative cytology - 63 patients</p> <p><u>Outcomes:</u> CR: 65% @ 3 months, 12 month CR: 61%</p> <p>Avoidance of TURBT in those with prior known LG UC Phase 3 ENVISION enrolling</p>	<p><u>Agent:</u> Pemigatinib</p> <p>Phase 2 trial</p> <p><u>Population:</u> recurrent low grade low or intermediate risk UC</p> <p><u>Mechanism of action:</u> FGFR3 inhibitor - FGFR3 mutations in low grade UC 87%</p> <p><u>Delivery:</u> given orally x 4-6 weeks prior to repeat TURBT</p> <p><u>Outcomes:</u> CR - Safety profile - RFS</p>	<p>ASCERTAIN <u>Agent:</u> APL-1202 oral vs. intravesical epirubicin</p> <p>Phase 3 randomized, open-label trial</p> <p><u>Population:</u> BCG naïve intermediate risk urothelial carcinoma</p> <p><u>Delivery:</u> APL 1202 = oral, epirubicin intravesical</p> <p><u>Primary outcome:</u> EFS <u>Secondary outcomes:</u> - EFS (locally) - OS - RFS, PFS - QOL outcomes</p>	<p>S1602 <u>Agent:</u> BCG TICE vs. BCG Tokyo +/- SQ BCG Phase 3 randomized, non-inferiority</p> <p>EA8212 <u>Agent:</u> BCG vs. gemcitabine/docetaxel Phase 3 randomized, non-inferiority</p> <p>SunRISe-3 <u>Agent:</u> TAR200 + cetrelimab vs. BCG CR: 72.7% @ 11 months median follow-up</p> <p>Many others BCG +/- immunotherapy (pembro, durvalumab, atezo)</p>

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Future directions

- Accurate alternatives to cystoscopy
- Precision medicine
 - Ex: Ertafitinib in TAR-200 pretzel for those with FGFR mutation
- Alternatives to BCG
- Further exploration in what matters to patients

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New Treatments and Promising Research in Bladder Cancer

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Conflicts of Interest

- Funding to the institution for preclinical research from BMS-IASLC-LCFA, Aravive, Pionyr, Arsenal
- Consultant for Alpine Bioscience, Aravive, Aveo, Astrazeneca, BMS, Merck, Eisai, Exelixis, Sanofi, Seagen

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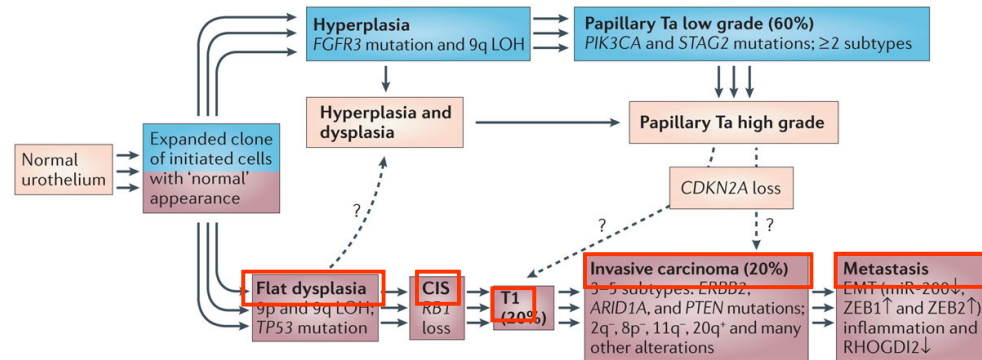


Exciting possibilities in bladder cancer

1. Immunotherapy
2. Targeted Therapies
3. Precision Medicine
4. Biomarkers
5. Non-invasive Tests
6. Bladder preservation
7. Minimally Invasive surgery
8. Neoadjuvant and adjuvant therapy
9. Radiation therapy innovations
10. Combination Therapy

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Biology of Bladder Cancer



Each stage comes with mutational changes and increased invasion

Nature Reviews | Cancer

(Knowles and Hurst 2014)

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Timeline History of Treatment for Bladder Cancer

Many single agents have activity

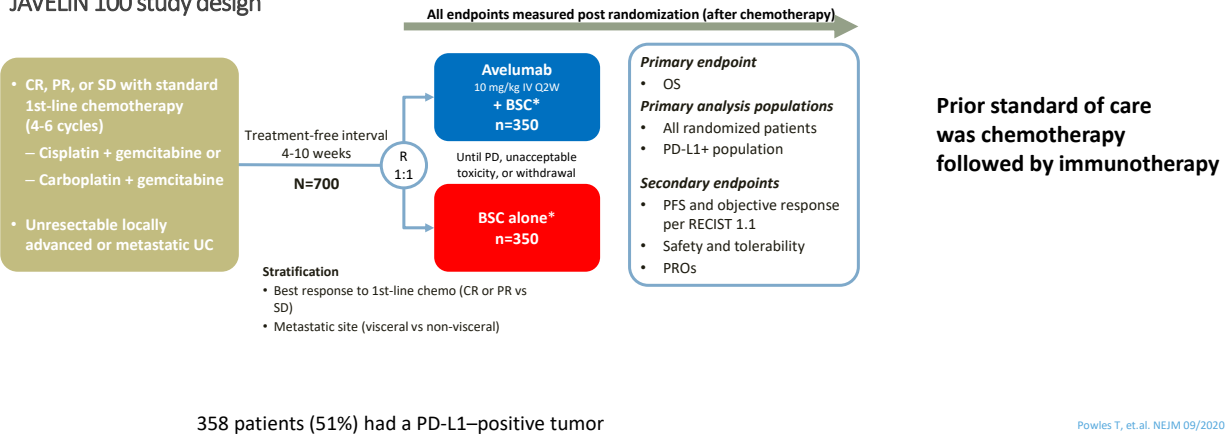
- CDDP (late 70s) > Carbo efficacy as single agent
- Combination > single agent
- CMV > MV
- MVAC (1995) > CMV
- M-VAC = dose escalated-MVAC (2001)
- M-VAC = GC (2006)
- Triplets < Doublets (2010)
- 2nd line IO therapy (2014)



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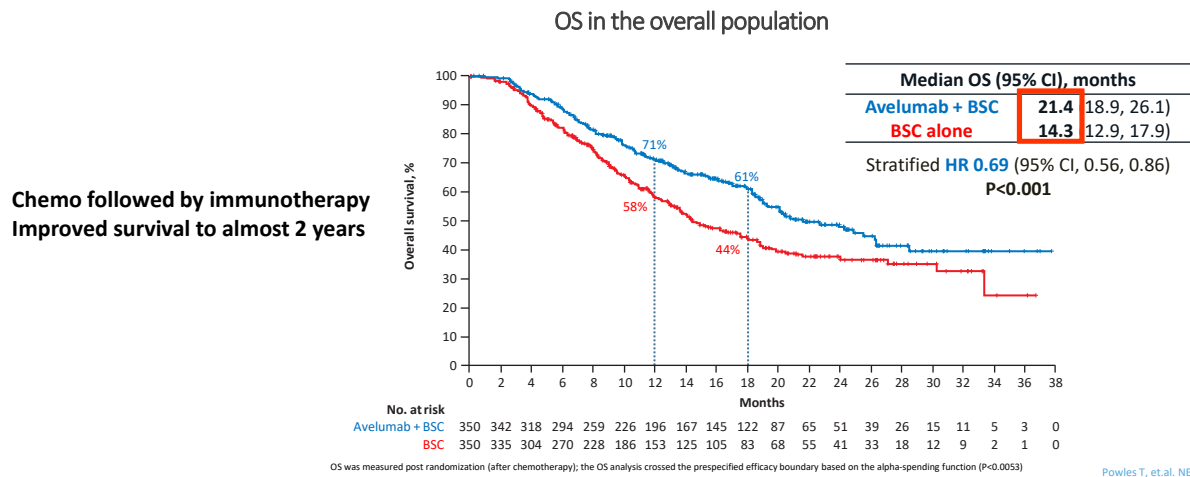
Standard of Care for systemic treatment for patients with bladder cancer, 2020-2023

JAVELIN 100 study design

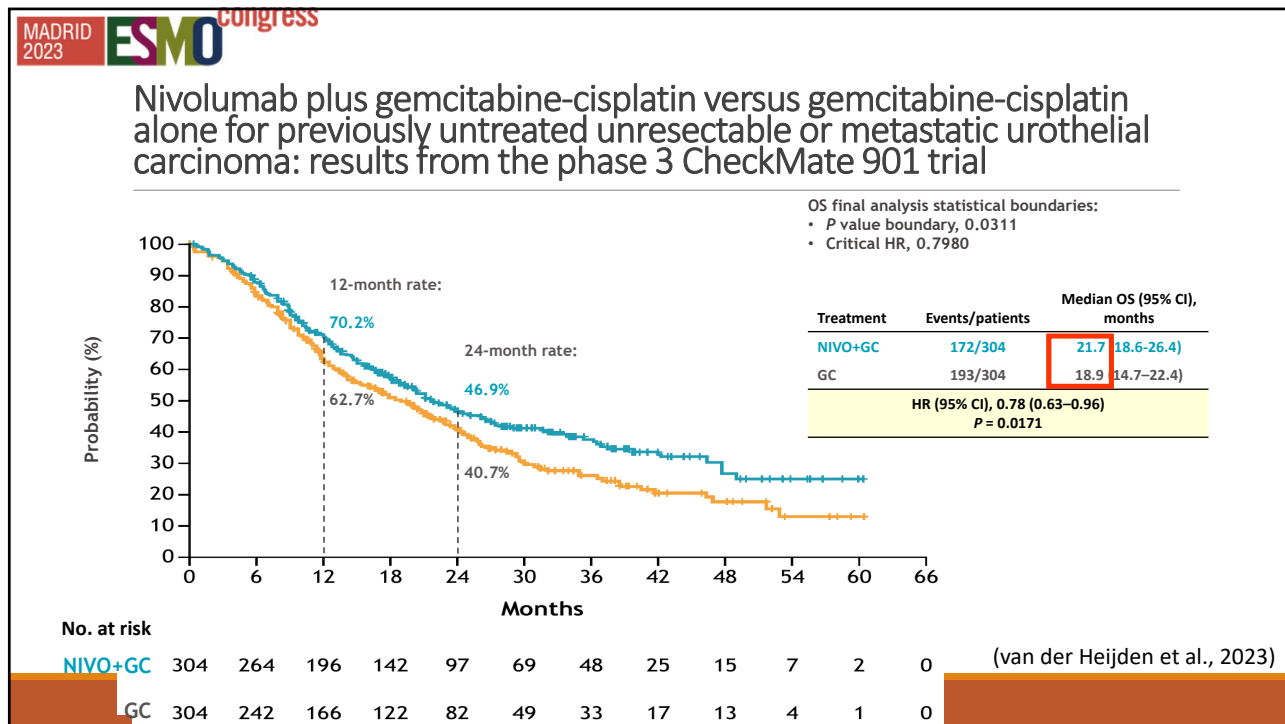


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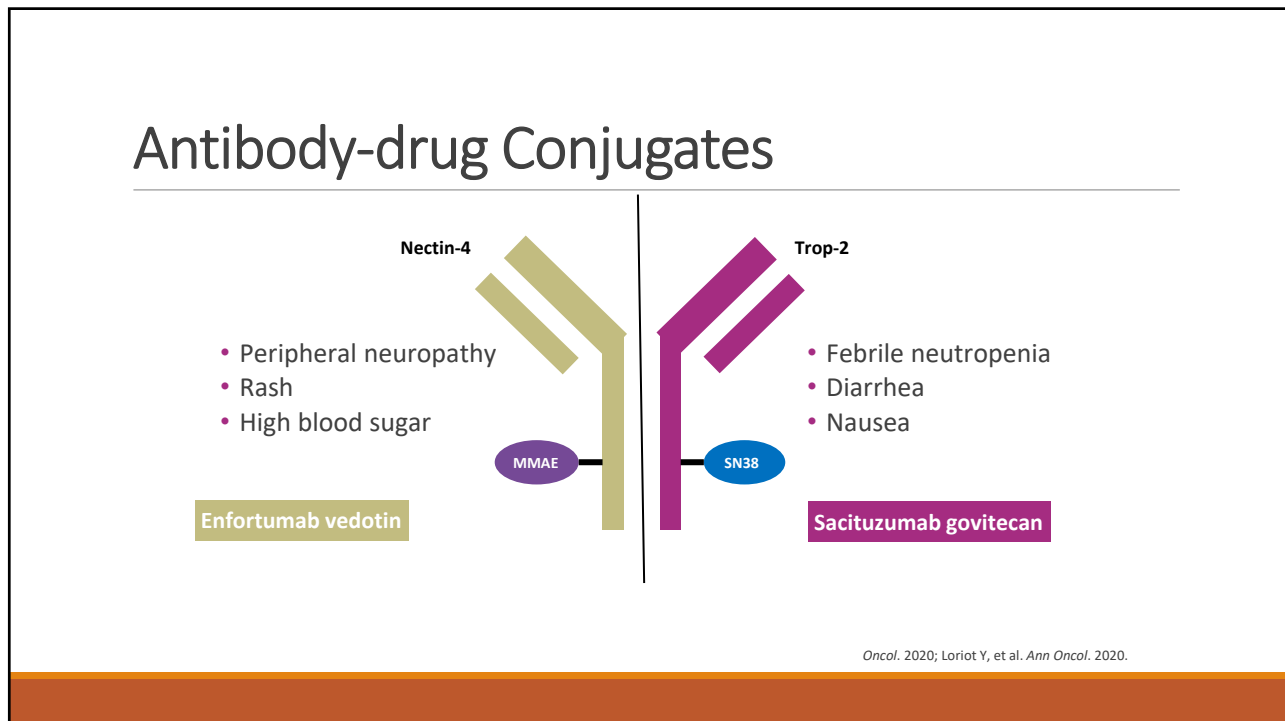
Current Standard of Care for systemic treatment for patients with bladder cancer



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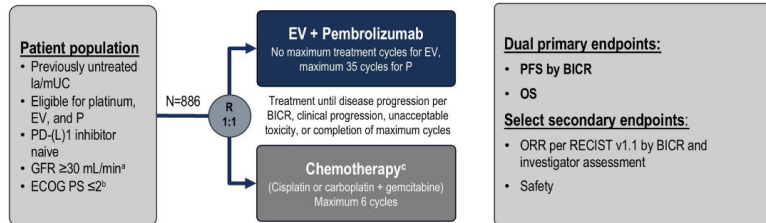


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Improving survival with novel combinations

Combining new antibody drug conjugate with immunotherapy

EV-302/KEYNOTE-A39 (NCT04223856)



Patient population

- Previously untreated la/mUC
- Eligible for platinum, EV, and P
- PD-(L)1 inhibitor naïve
- GFR ≥ 30 mL/min*
- ECOG PS ≤ 2

Dual primary endpoints:

- PFS by BICR
- OS

Select secondary endpoints:

- ORR per RECIST v1.1 by BICR and investigator assessment
- Safety

Stratification factors: cisplatin eligibility (eligible/ineligible), PD-L1 expression (high/low), liver metastases (present/absent)

Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol-defined; patients received 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and P (200 mg; IV) on Day 1

Statistical plan for analysis: the first planned analysis was performed after approximately 526 PFS (final) and 356 OS events (interim); if OS was positive at interim, the OS interim analysis was considered final

Data cutoff: 08 Aug 2023; FPI: 7 Apr 2020; LPI: 09 Nov 2022



Powles et al.

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; ORR, overall response rate; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors
*Measured by the Cockcroft-Gault formula. Modification of Diet in Renal Disease, or 24-hour urine
**Patients with ECOG PS of 2 were required to also meet the additional criteria: hemoglobin ≥ 10 g/dL, GFR ≥ 30 mL/min, may not have NYHA class III heart failure
***Maintenance therapy could be used following completion and/or discontinuation of platinum-containing therapy

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(Powles et al., 2023)

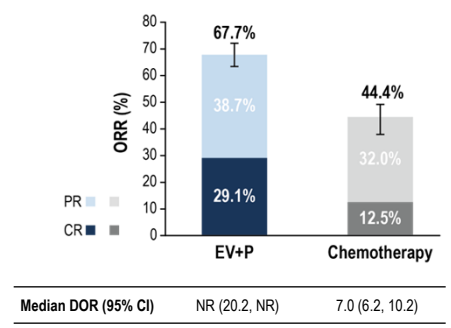
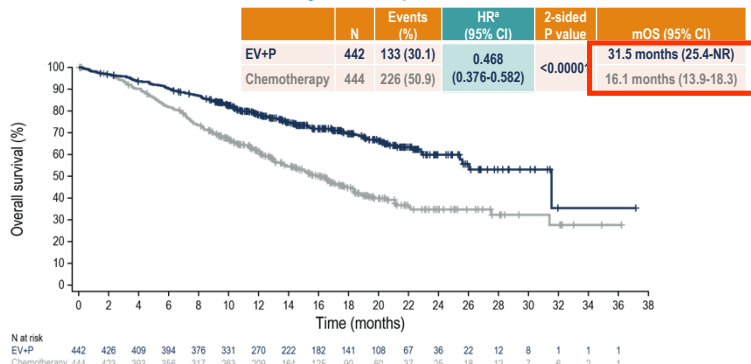
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Enfortumab vedotin + Pembrolizumab

Overall Survival

Risk of death was reduced by 53% in patients who received EV+P

EV+P: 68% confirmed ORR



N at risk

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38
EV+P	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	7	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1	1

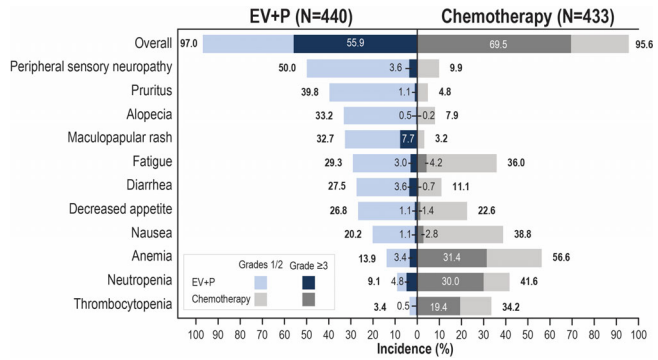
Data cutoff: 08 Aug 2023

(Powles et al., 2023)

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Enfortumab vedotin+ Pembrolizumab

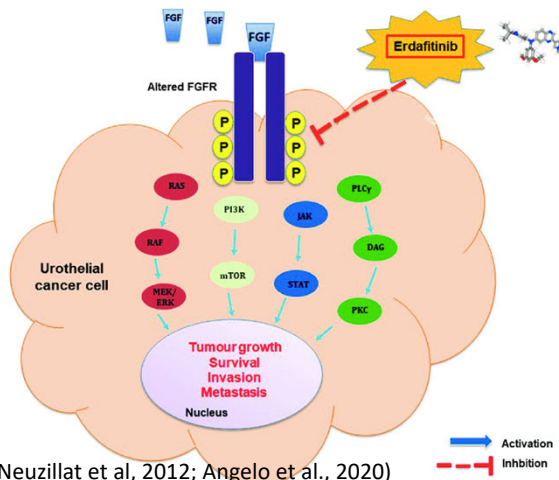
- Toxicities:
 - myelosuppression (neutropenia)
 - skin toxicity
 - Nausea
 - peripheral neuropathy
 - lung toxicity
- Toxicity prevention: antinausea



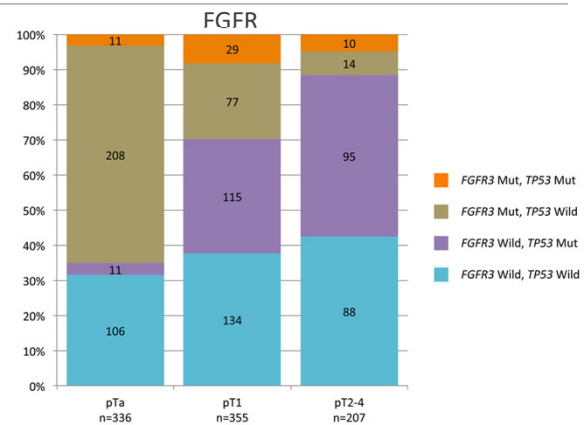
(Powles et al., 2023)

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Precision Medicine in Bladder Cancer



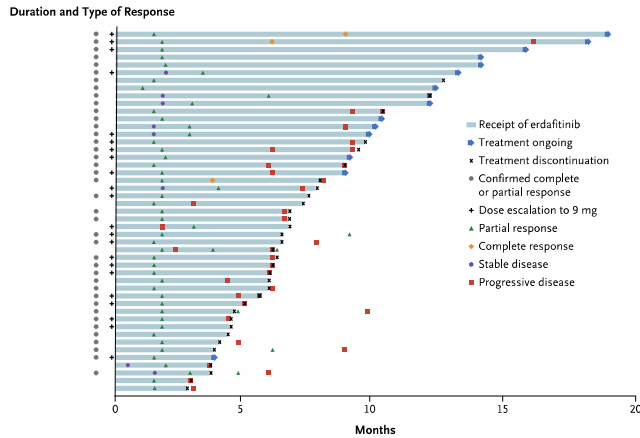
(Neuzillat et al, 2012; Angelo et al., 2020)



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Erdafitinib: metastatic urothelial carcinoma with FGFR3 or FGFR2 genetic alterations and progressed following prior chemotherapy

- FGFR Inhibitor
- Dose: 8 mg PO daily
- Toxicities:
 - Elevated phosphate
 - Eye/retina side effects
 - nail changes
 - Diarrhea
 - Dry mouth/dry skin
 - nausea



(Loriot et al., 2019)

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Biomarkers in Bladder Cancer

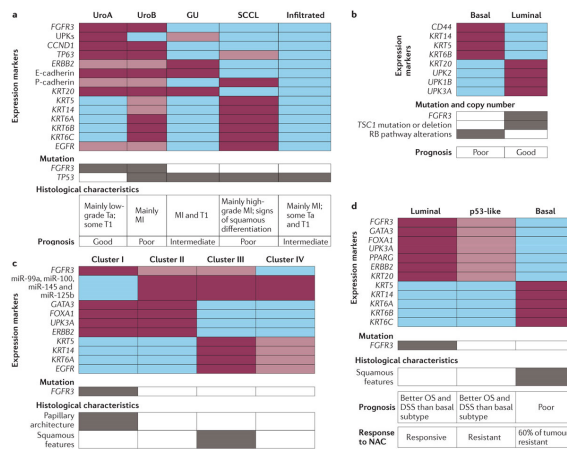
PD-L1

Genomics in bladder cancer

MSI

Microbiome

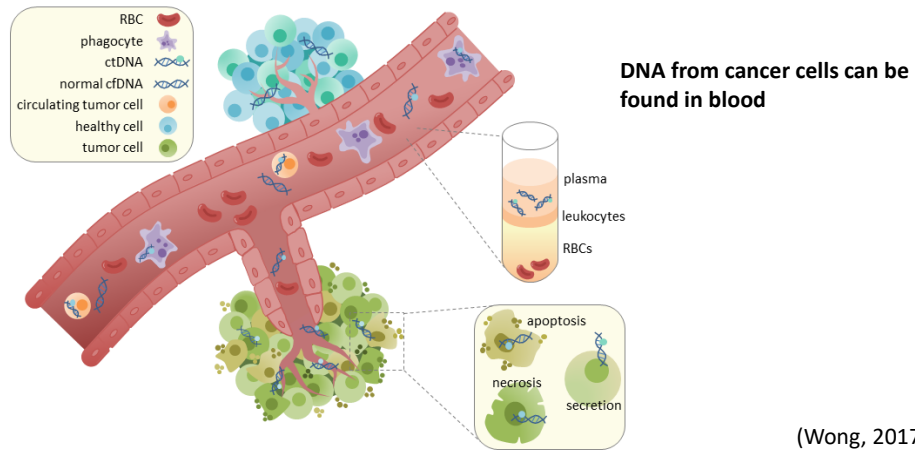
Urinary and serum based ctDNA



(Knowles and Hurst, 2014)

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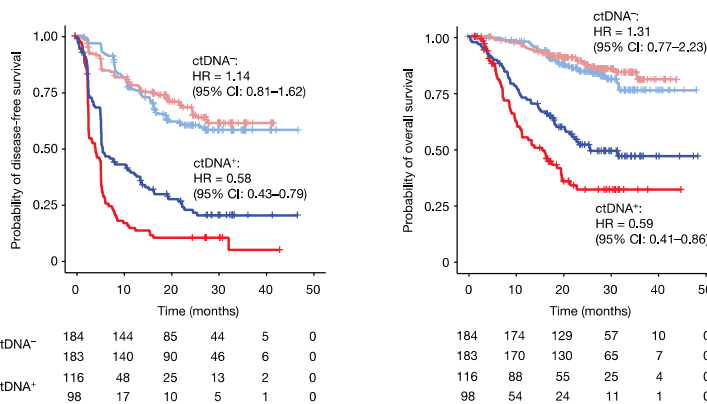
What is ctDNA and why might it be useful?



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Current data for ctDNA in patients with bladder cancer

Individuals + for ctDNA after surgery had improved cancer control with treatment



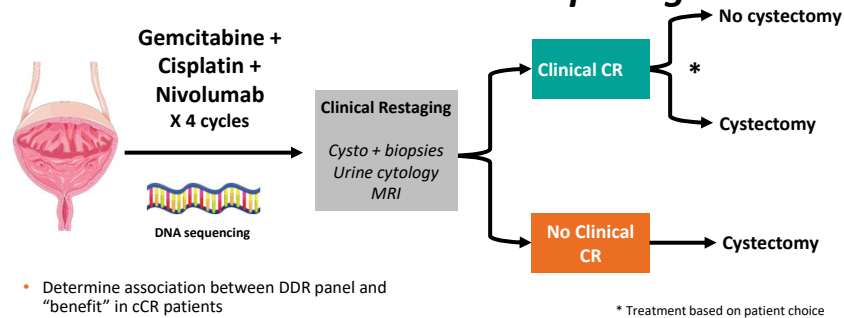
(Powles et al., 2021)

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Future clinical trials for patients with bladder cancer

HCRN GU16-257

GC + Nivo with Selective Bladder Sparing



- Determine association between DDR panel and “benefit” in cCR patients

Slide courtesy of Principal Investigator Matt Galsky, MD

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Resources for Patients with Bladder Cancer

- Bladder Cancer Advocacy Network (BCAN):**
 1. Website: bcan.org
 2. BCAN offers resources, educational materials, and support networks for bladder cancer patients and their families.
- American Cancer Society (ACS):**
 1. Website: cancer.org
 2. ACS provides comprehensive information on bladder cancer, treatment options, and support services.
- CancerCare:**
 1. Website: cancercares.org
 2. CancerCare offers free counseling, support groups, and educational resources for cancer patients, including those with bladder cancer.
- The Bladder Cancer WebCafé:**
 1. Website: blcwebcafe.org
 2. An online community and resource center that provides information, forums, and support for bladder cancer patients and caregivers.
- The American Bladder Cancer Society (ABCS):**
 1. Website: bladdercancersupport.org
 2. ABCS offers support, information, and advocacy for bladder cancer patients and their families.
- Patient Advocates for Advanced Bladder Cancer (PAABC):**
 1. Website: patientadvocatesforabc.org
 2. PAABC provides resources and support specifically focused on advanced bladder cancer.
- Cancer Support Community:**
 1. Website: cancersupportcommunity.org
 2. This organization offers a wide range of services, including support groups, educational programs, and online resources for cancer patients.

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