Improving Outcomes for Patients With Advanced Urothelial Carcinoma of the Bladder

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Welcome and Introductions

Financial Disclosures

Petros Grivas, MD, PhD

- AstraZeneca, Bavarian Nordic, Bayer, Bristol-Myers Squibb, Clovis Oncology, Debiopharm, EMD Serono, Foundation Medicine, Genzyme, Heron Therapeutics, Immunomedics, Janssen, Merck & Co., Mirati Therapeutics, Pfizer, QED Therapeutics, Seattle Genetics

Jeannette Hammond, PA-C

- Nothing to disclose

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Product Disclosure

This activity may include discussion of agents that have not yet been approved by the U.S. Food and Drug Administration and investigational uses of approved products. Please consult prescribing information and practice guidelines for detail regarding safe and effective use of therapeutic agents.

Learning Objectives

At the conclusion of this continuing education activity, the oncology advanced practice provider will be better able to:

- Evaluate data regarding mechanistic activity, efficacy, and safety of approved and emerging therapeutic options for advanced or metastatic UC
- Plan strategies for managing adverse events associated with approved therapies for UC
- Select appropriate lines of therapy for treatment of advanced or metastatic UC in accordance with evidence-based best practices

Introduction

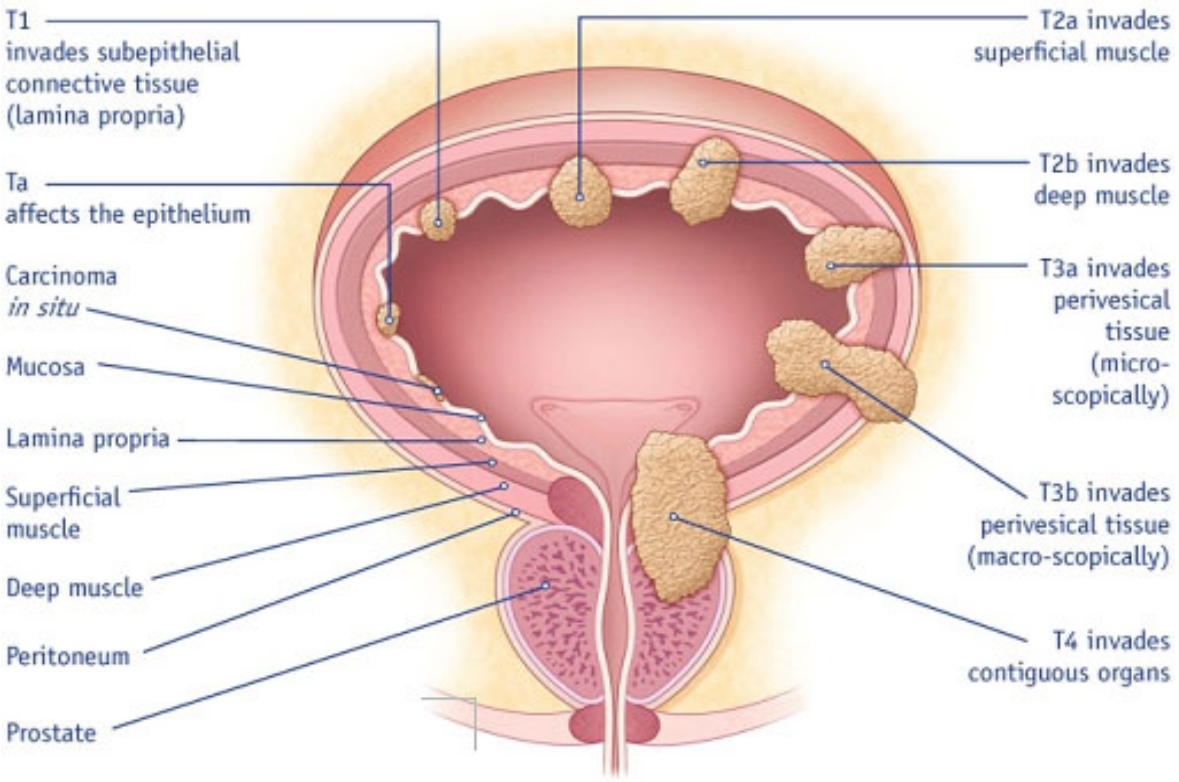
- Urothelial carcinoma is 6th most common cancer
- In 2019, estimated 80,470 new cases in US and 17,670 deaths
- Average age at diagnosis 73
- Most originate in bladder; can involve renal pelvis, ureter, urethra
- Urothelial carcinoma is most common histology
- Lifetime risk is 1:26 for men and 1:90 for women
- In 2016, nearly 700,000 people in the US were living with urothelial cancer

Risk Factors and Presentation

- Cigarette smoking is most widely recognized risk factor
- Various industrial chemicals, printing material, hair dyes, etc.
- Family history of bladder and other cancers, DDR genes, Lynch syndrome
- Certain chemotherapies and radiation
- Parasite Schistosoma haematobium linked to squamous histology in endemic areas
- Microscopic or gross hematuria most common presenting sign/symptom, prompting evaluation

DDR, DNA damage repair.

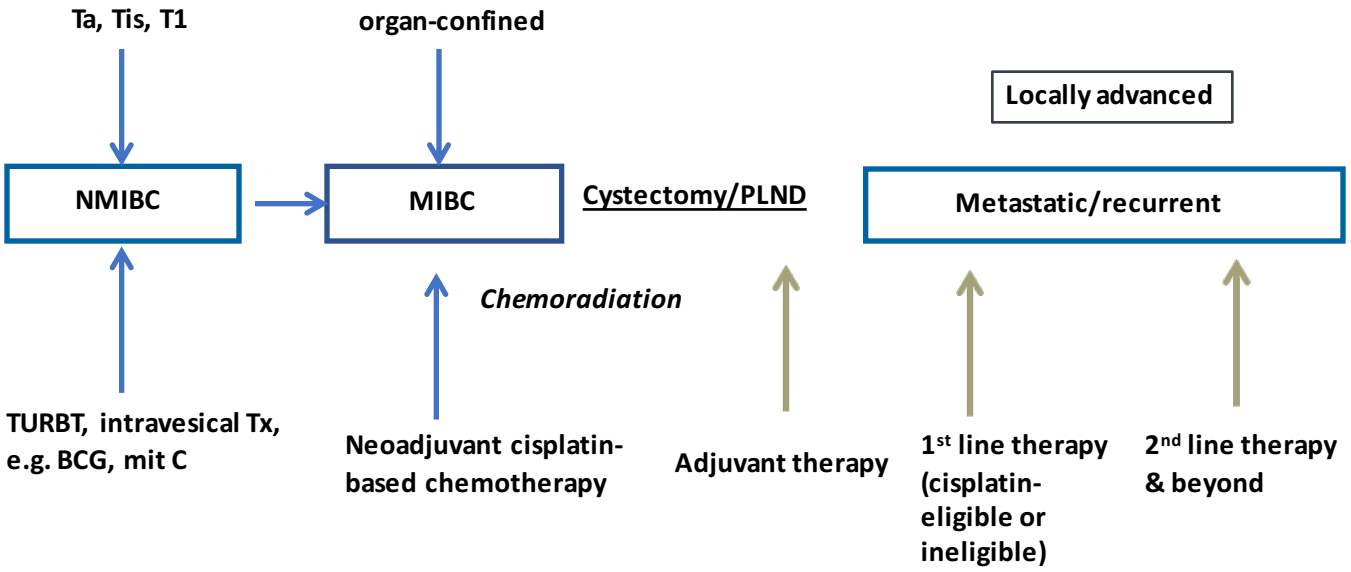
Urothelial Ca: NMIBC vs MIBC



http://www.actiononbladdercancer.org/content.php?id=159g=2/Types.

MIBC, muscle-invasive bladder cancer;
NMIBC, non–muscle-invasive bladder cancer.

Disease/Treatment Settings



PLND, pelvic lymph node dissection.

Non–Muscle-Invasive Bladder Cancer

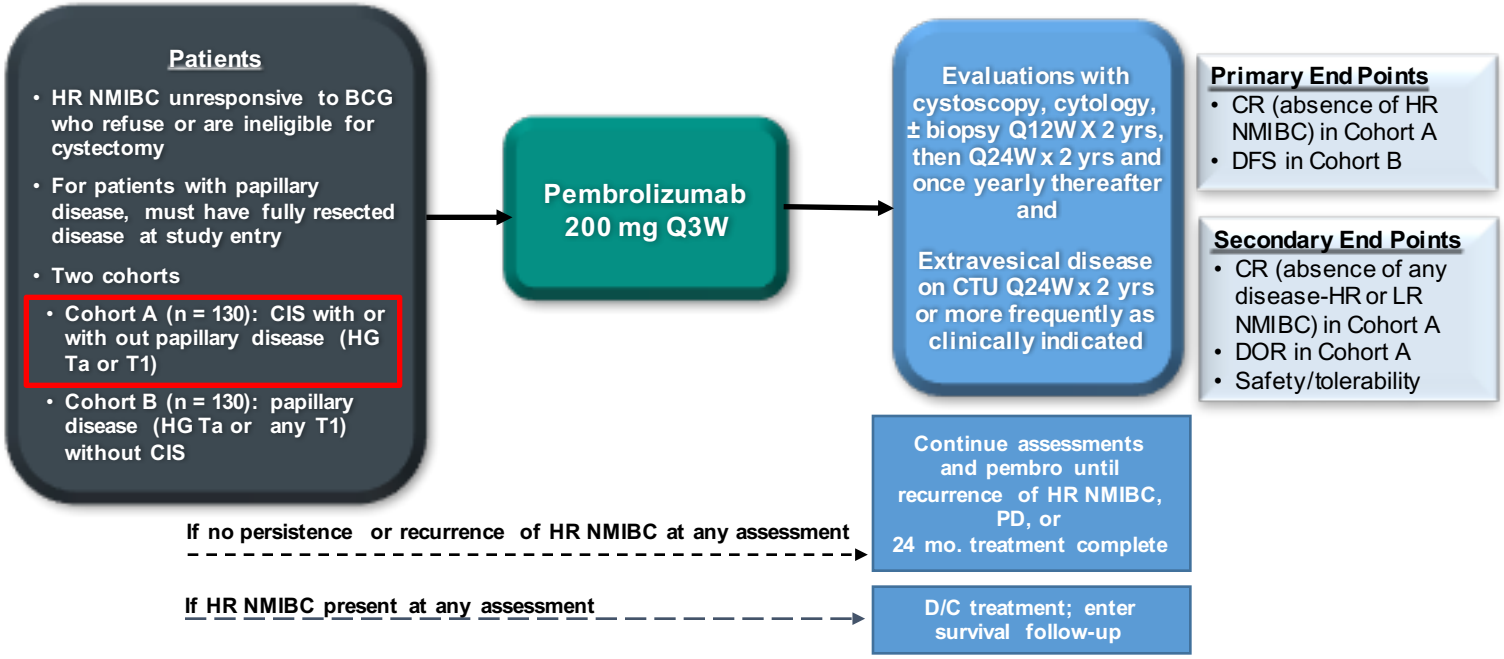
- Three quarters of new cases of bladder cancer
- Sample must have muscularis propria present but uninvolved; however, risk of under-staging is significant and common
- 30–80% will recur within 5 years
- Majority are papillary and confined to the mucosa (Ta)
- Typically managed by our urology colleagues with TURBT and intravesical therapies
- Intra-vesicular BCG main therapy, intra-vesicular chemotherapies
- Evidence that immediate postoperative intravesical gemcitabine or mitomycin decreases risk of recurrence in certain cases

BCG, Bacillus Calmette Guerin; TURBT, transurethral resection bladder tumor.

BCG

- Inactivated *tuberculosis* bacteria
- Causes inflammation in the bladder, which in turn recruits immune cells to the area to take action against the tumor cells
- Induction therapy (weekly x6)
- Maintenance therapy (q 3 weeks for 1-3 years)
- Flu-like symptoms as well as local side effects
- Manufacturing shortage is a long-term problem and hard to solve

KEYNOTE-057: Single-Arm, Open-Label Phase II Trial (NCT02625961) in BCG-Unresponsive High-Risk NMIBC



CIS, carcinoma in situ; CR, complete response; CTU, computed topography urography; DFS, disease-free survival; D/C, discontinue; DOR, duration of response; HG, high grade; HR, high-risk; LR, low-risk; PD, disease progression; Q3W, every 3 weeks; Q12W, every 12 weeks; Q24W, every 24 weeks.

Baseline Characteristics

Characteristic	N = 103
Age, median (range), years	73.0 (44-92)
≥65	72 (69.9)
<65	31 (30.1)
Male	86 (83.5)
Female	17 (16.5)
Race	
White	70 (68.0)
Asian	27 (26.2)
Missing	6 (5.8)
ECOG performance status	
0 (normal activity)	76 (73.8)
1 (symptomatic but ambulatory)	27 (26.2)

Characteristic	N = 103
No. of prior BCG instillations, median (range)	12.0 (6.0-45.0)
Tumor histology: urothelial (transitional cell) carcinoma	103 (100.0)
Tumor pattern at study entry (pretreatment bladder cancer stage)	
CIS with T1	13 (12.6)
CIS (TIS) with high-grade Ta	16 (15.5)
CIS (TIS) alone	74 (71.8)
PD-L1 status[a]	
CPS ≥10	39 (37.9)
CPS <10	59 (57.3)
Not evaluable	5 (4.9)

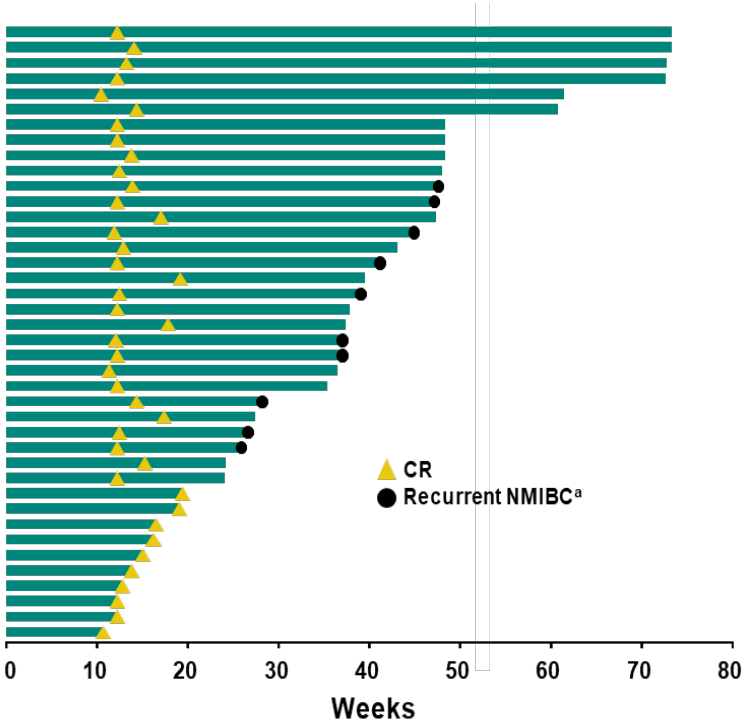
[a]Percentages do not sum to 100 because of rounding.
Values are n (%) unless specified otherwise.
Database cutoff: July 18, 2018.

Overall Response Rate at Month 3[a]

Response	N = 103		
	N	%	95% CI
CR	**40**	**38.8**	**29.4–48.9**
Non–CR	**57**	**55.3**	**45.2–65.1**
Persistent[b]	47	45.6	35.8–55.7
NMIBC stage progression[c]	9	8.7	4.1–15.9
Extravesical disease[d]	1	1.0	0.0–5.3
Progression to T2	0	0	–
Nonevaluable[e]	**6**	**5.8**	2.2–12.2

[a]Summary of overall responses of high-risk NMIBC per central assessment at month 3 in all patients who received ≥1 dose of trial treatment, had baseline evaluations, and also had ≥1 post-baseline disease assessment. [b]Defined as patients with CIS at baseline who at month 3 also had CIS +/- papillary tumor. [c]Increase in stage from CIS and/or high-grade Ta at baseline to T1 disease. [d]Defined as presence of lesions suspicious for locally advanced or metastatic bladder cancer on imaging. [d]Patient developed new liver lesions on imaging and was later found to have a second primary malignancy of pancreatic cancer. Subsequent review of the baseline scan showed subtle findings that, in retrospect, could be attributed to pancreatic cancer. [e]Patients missing protocol-specified efficacy assessments or have discontinued from the trial for reasons other than PD are considered not evaluable for efficacy.
Database cutoff: July 18, 2018

Time to CR and Development of Recurrent HR NMIBC

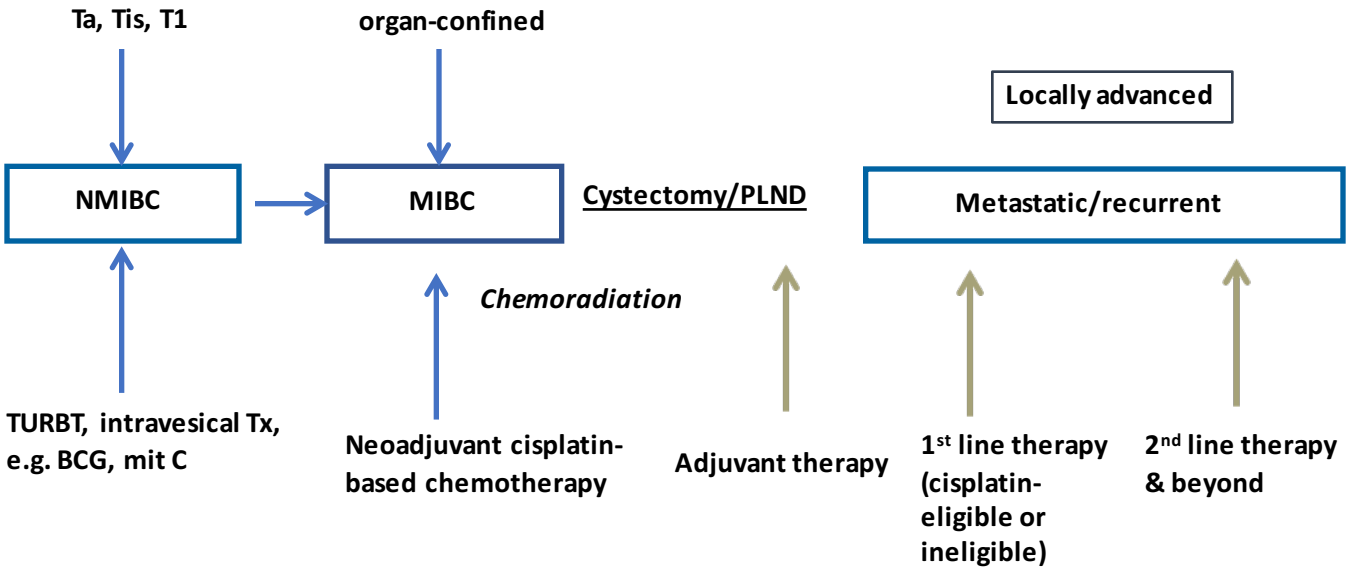


- Median follow-up in cohort A: 14.0 months (range, 4.0-26.3 months)
- Treatment ongoing in 32/103 (31.1%) patients
- 29 (72.5%) patients in CR had an ongoing response
- 10 (25.0%) patients experienced recurrent NMIBC after CR
- 1 patient in CR underwent cystectomy
- No patient developed muscle-invasive or metastatic disease

[a]Reappearance of high-risk NMIBC (CIS and/or high-grade Ta and/or T1 disease) after a disease-free interval (at each month or afterward).
Database cutoff: July 18, 2018

No new safety signal / regulatory fate to be defined

Disease/Treatment Settings



Muscle-Invasive Bladder Cancer

- 25% of cases at presentation
- Combination of aggressive local therapy with systemic therapy
- Decision points:
  - Is there locally advanced/unresectable or metastatic disease?
  - Are they a candidate for radical surgery?
  - Is bladder preservation an option?
  - Are they eligible for cisplatin-based chemotherapy?
  - Clinical trials relevant and available?

Rationale for Neoadjuvant Chemotherapy

- Earlier attempt for eradication of micro-metastasis, which can be the most common cause of cancer-related morbidity and mortality
- Downstaging of bladder tumor → higher pCR ~ better outcomes
- Pts do not need to recover after radical cystectomy to receive systemic therapy
- Opportunity to assess tumor biology and behavior *in vivo* real time; this has treatment and prognostic implications for overall management
- Interrogation of biomarkers in tumor tissue, blood, urine, stool for research (retrospective studies, biorepositories, and clinical trials)
- Level I evidence supported by Phase III trials, meta-analysis, and all guidelines

Cisplatin Eligibility

- ECOG PS 0-1
- No ≥ G2 hearing loss or peripheral neuropathy
- No Class III/IV CHF
- CrCl ≥ 60cc/min
  - Most pts ≥ 50cc/min get all planned doses
  - Consider 24-hour urine collection and/or nephrostomy tube

Galsky MD, et al. *J Clin Oncol*. 2011;29:2432-8.

CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Cisplatin Regimens for Neoadjuvant Therapy

- Gemcitabine/cisplatin
- Accelerated (dose-dense) MVAC

The Case for Neoadjuvant Chemotherapy (NAC)

- Lancet meta-analysis of 10 randomized trials (2,688 pts) comparing:
  - Cisplatin-based combination neoadjuvant chemotherapy plus local therapy vs definitive local therapy alone
- Improved OS for pts with NAC
  - 5- year OS 50%vs 45%, HR 0.87, 95% CI 0.78-0.98
- Lower recurrence risk for pts with NAC (HR for recurrence 0.81, 95% CI 0.74-0.90), translating into absolute disease-free survival benefit of 7%

Advanced Bladder Cancer Meta-analysis Collaboration. *Lancet*. 2003;361:1927-34.

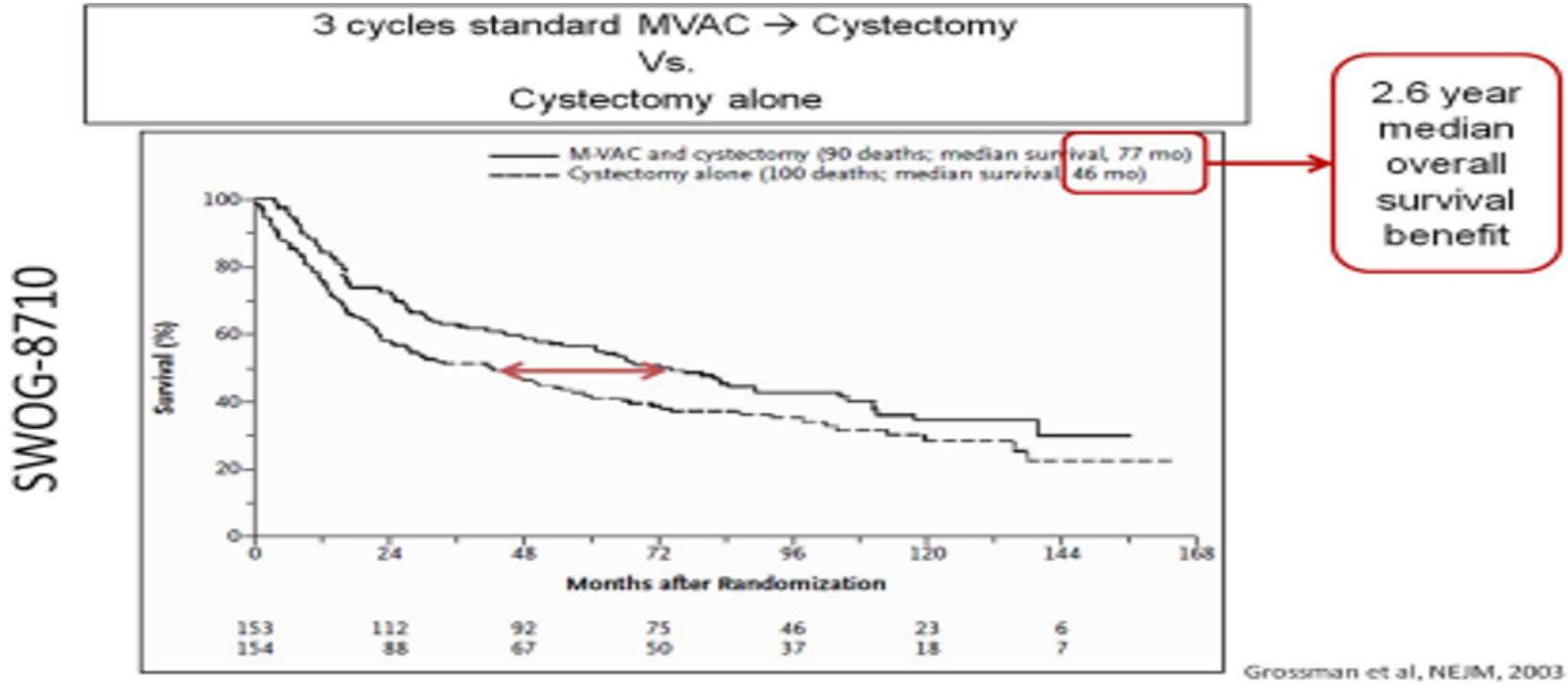
HR, hazard ratio; OS, overall survival.

Take-Home Points: NAC

- Disease-free and overall survival benefit from neoadjuvant chemotherapy with cisplatin-based combinations in patients who can tolerate cisplatin
- Non–cisplatin-based chemotherapy in neoadjuvant or adjuvant setting has no proven benefit
- Accelerated/dose-dense MVAC may have less toxicity, shorter time to surgery
- Retrospective datasets and S1314/COXEN Phase II trial: comparable pCR % between gemcitabine/cisplatin and (a)MVAC
- Novel trials focus on immunotherapy and biomarkers of response

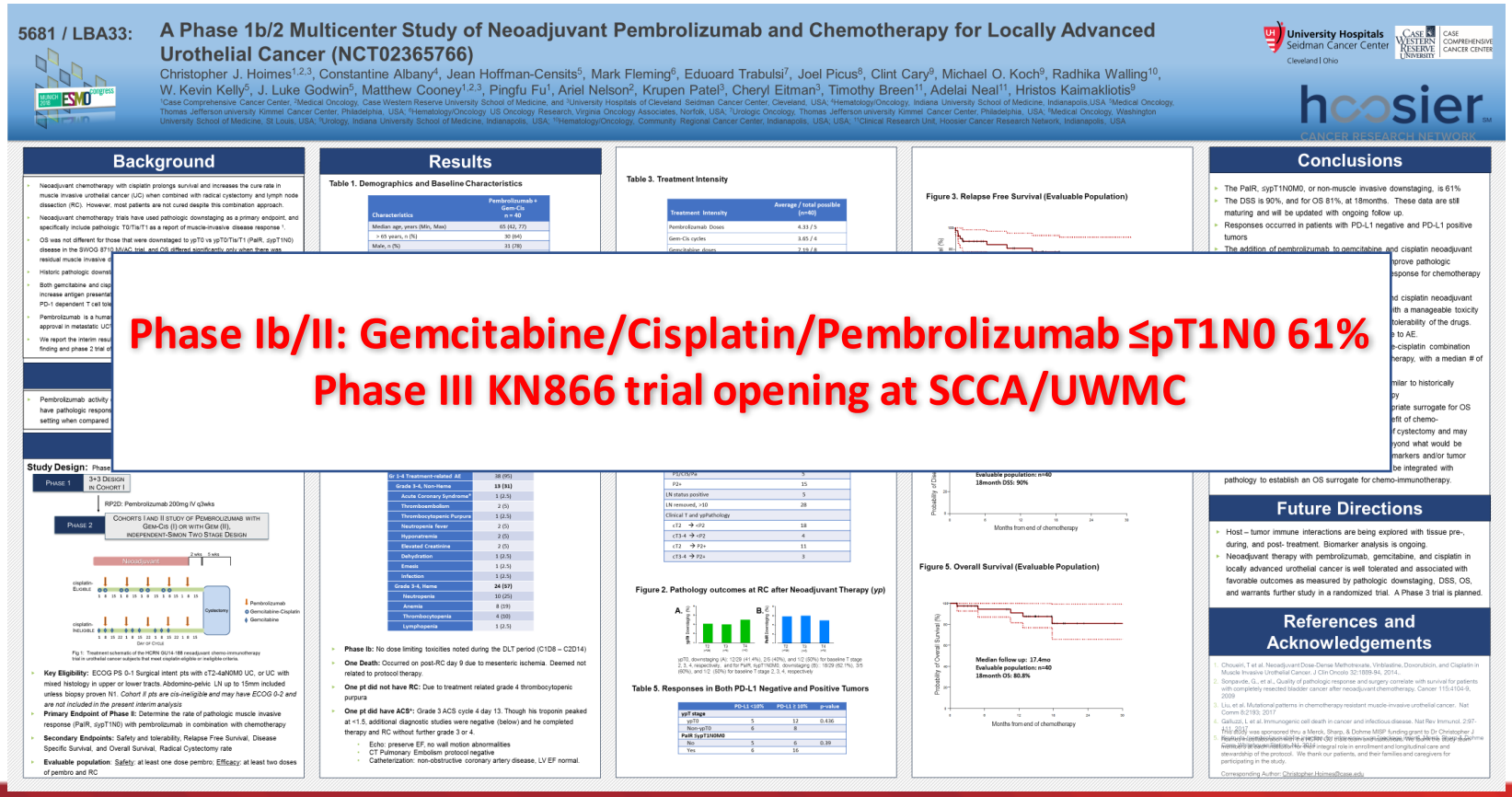
Smith DC, et al. *J Urol*. 2008;180:2384-8; Grivas PD, et al. *Urology*. 2013;82:111-7; Choueiri TK, et al. *J Clin Oncol*. 2014;32:1889-94; Plimack ER, et al. *J Clin Oncol*. 2014;32:1895-901; Blick C, et al. *Cancer*. 2012;118:3920-7.

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



Plimack ER. ASCO 2018 (discussant).

Chemoimmunotherapy Combination?



5681 / LBA33:

A Phase 1b/2 Multicenter Study of Neoadjuvant Pembrolizumab and Chemotherapy for Locally Advanced Urothelial Cancer (NCT02365766)

Christopher J. Hoimes[1,2,3], Constantine Albany[4], Jean Hoffman-Censits[5], Mark Fleming[6], Eduoard Trabulsi[7], Joel Picus[8], Clint Cary[9], Michael O. Koch[9], Radhika Walling[10], W. Kevin Kelly[5], J. Luke Godwin[5], Matthew Cooney[1,2,3], Pingfu Fu[1], Ariel Nelson[2], Krupen Patel[3], Cheryl Eitman[3], Timothy Breen[11], Adelai Neal[11], Hristos Kaimakliotis[9]

[1]Case Comprehensive Cancer Center, [2]Medical Oncology, Case Western Reserve University School of Medicine, and [3]University Hospitals of Cleveland Seidman Cancer Center, Cleveland, USA; [4]Hematology/Oncology, Indiana University School of Medicine, Indianapolis,USA [5]Medical Oncology, Thomas Jefferson university Kimmel Cancer Center, Philadelphia, USA; [6]Hematology/Oncology US Oncology Research, Virginia Oncology Associates, Norfolk, USA; [7]Urologic Oncology, Thomas Jefferson university Kimmel Cancer Center, Philadelphia, USA; [8]Medical Oncology, Washington University School of Medicine, St Louis, USA; [9]Urology, Indiana University School of Medicine, Indianapolis, USA; [10]Hematology/Oncology, Community Regional Cancer Center, Indianapolis, USA; USA; [11]Clinical Research Unit, Hoosier Cancer Research Network, Indianapolis, USA

University Hospitals Seidman Cancer Center, Cleveland | Ohio

Case Western Reserve University, Case Comprehensive Cancer Center

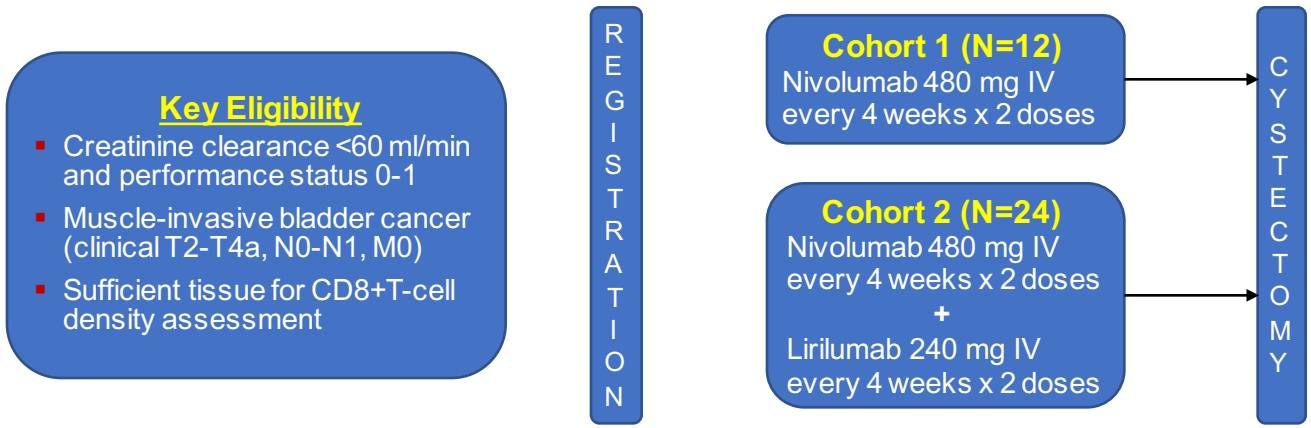
hoosier CANCER RESEARCH NETWORK

Phase Ib/II: Gemcitabine/Cisplatin/Pembrolizumab ≤pT1N0 61%

Phase III KN866 trial opening at SCCA/UWMC

Hoimes CJ, et al. ESMO 2018. Abstract LBA33.

Neoadjuvant Trial in Cisplatin-Unfit Patients



- Treatment should begin within 10 working days of study entry (registration)
- Accrual goal: 43 patients enrolled for 36 eligible, treated patients
- Cohort 1: 12 eligible, treated patients
- Cohort 2 (after Cohort 1 completes accrual): 24 eligible, treated patients
- Number of sites: ~8

https://clinicaltrials.gov/ct2/show/NCT03532451.

Percutaneous Nephrostomy vs. Ureteral Stent

Stenting Prior to Cystectomy is an Independent Risk Factor for Upper Urinary Tract Recurrence

Bernhard Kiss,*,† Marc A. Furrer,† Patrick Y. Wuethrich, Fiona C. Burkhard, George N. Thalmann and Beat Roth

From the Departments of Urology and Anaesthesiology and Pain Medicine (PYW), University Hospital of Bern, University of Bern, Bern, Switzerland

- 114 pts with ureteral obstruction by tumor
  - 53 with ureteral stents
  - 61 with nephrostomy tubes
- All underwent cystectomy
- Upper-tract recurrence developed (median time to recurrence, 17 months)
  - 13% of pts with ureteral stents
  - 0% of pts with nephrostomy tubes
  - 3% in those without obstruction (n = 891)
- Ureteral stenting associated with upper-tract recurrence (HR 4.54, 95% CI 1.43-14.4)

Candidate for Bladder Preservation

- Ideal Candidate
  - Small/unifocal tumor (cT2/3)
  - Location away from UV junctions
  - Maximal/optimal TURBT
  - Node negative
  - No extensive CIS
  - No hydronephrosis
  - Good bladder function
  - ? Variant histology ?

UV, ureterovesical.

Chemoradiation

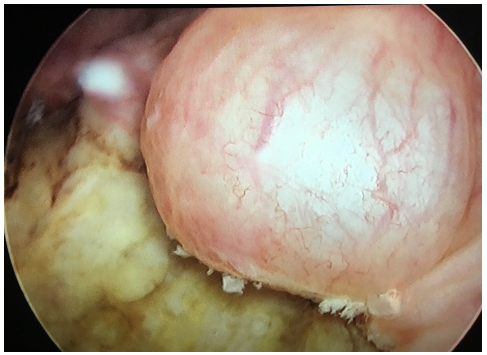
- Cisplatin 35-40 mg/m2 weekly (ideally Monday), or mitomycin-C/5-FU, or gemcitabine as radiosensitizer
- Radiation alone inferior to chemoradiation
- TraceIT study at UWMC
- Patient selection is key (ideal chemoRT candidates vs “poor surgical candidates due to medical issues, ECOG PS, etc.”)

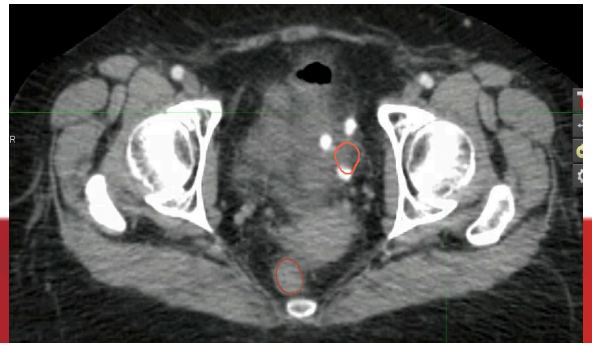
Giacalone NJ, et al. *Eur Urol*. 2017;71:952-60.

Temporary Intravesical Fiducial Marker for Bladder Cancer Radiation: A Pilot Study

Goal: Improve radiotherapy planning and daily image guidance

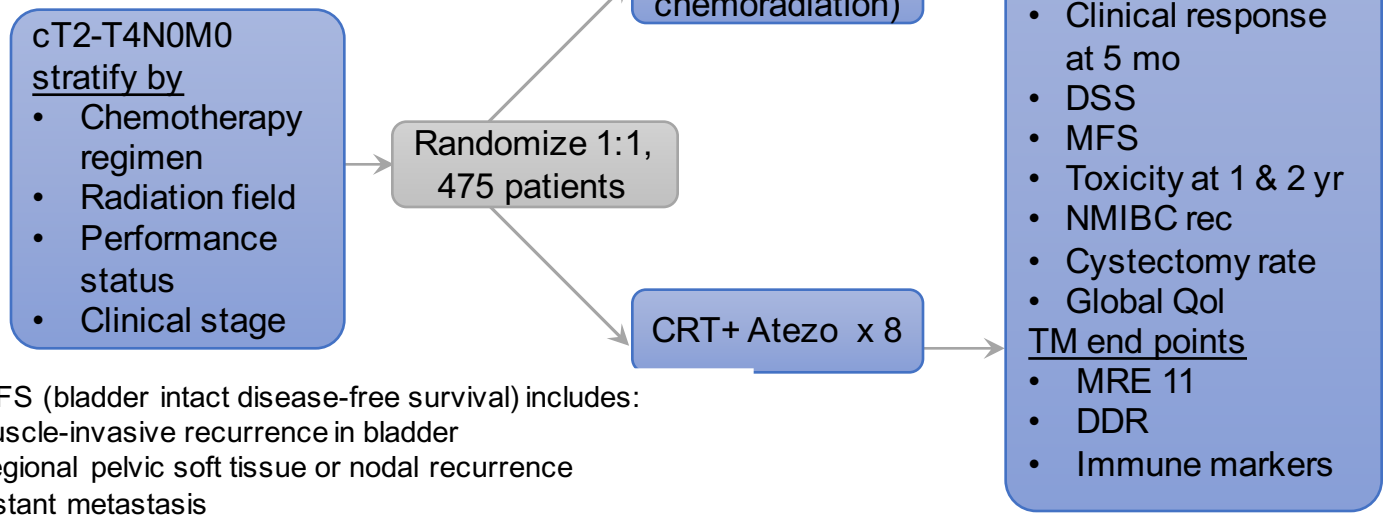
- TraceIT® hydrogel (*Augmentix*)
  - Injectable biocompatible hydrogel (iodinated polyethylene glycol)
    - > Visible on CT and dissolves after 3 months
  - Injected circumference around tumor bed
- To date:
  - Well tolerated, with no notable adverse effects
  - Modifications
    - > Increase amount injected at each site (0.5cc)
    - > Repeat injection at mid-cycle TURBT
- Conclusion:
  - Safe and feasible
  - Future study of clinical impact





SN1806 Trial for Bladder Preservation

- Cisplatin 35 mg/m^2 weekly (ideally Monday)
- 5-FU (500 mg/m^2 x 5 days 1st & 4th week during RT) and mitomycin-C (day 1)
- Gemcitabine 27 mg/m^2 twice per week



*BIDFS (bladder intact disease-free survival) includes:
- Muscle-invasive recurrence in bladder
- Regional pelvic soft tissue or nodal recurrence
- Distant metastasis
- Bladder cancer or toxicity-related death or cystectomy

PI: Dr. Parminder Singh

Atezo, atezolizumab.

Adjuvant Chemotherapy for Invasive Bladder Cancer: A 2013 Updated Systematic Review and Meta-Analysis of Randomized Trials

- 945 patients included in 9 randomized trials
- OS: pooled HR (9 trials) 0.77 (95% CI 0.59–0.99; p=0.049)
- DFS: pooled HR (7 trials) 0.66 (95% CI 0.45–0.91; p=0.014)
- DFS benefit more apparent in nodal metastasis (p=0.010)

EORTC Intergroup trial 30994: planned 660 pts; only 284 enrolled!

- Within 90 days of cystectomy, randomized to immediate adjuvant chemotherapy (4 cycles of Gem/Cis or MVAC) or 6 cycles of deferred chemotherapy at relapse
- 5-yr DFS: 47.6 vs. 31.8%, (HR 0.54, 95% CI 0.40-0.73)
- 5-yr OS: 53.6 vs. 47.7%; (HR 0.78, 95% CI 0.56-1.08)
- Lot of flaws and under-accrual in the adjuvant chemotherapy trials

Leow JJ, *Eur Urol.* 2014;66:42-54; Sternberg CN, et al. *Lancet Oncol.* 2015;16:76-86.

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EDITORIAL

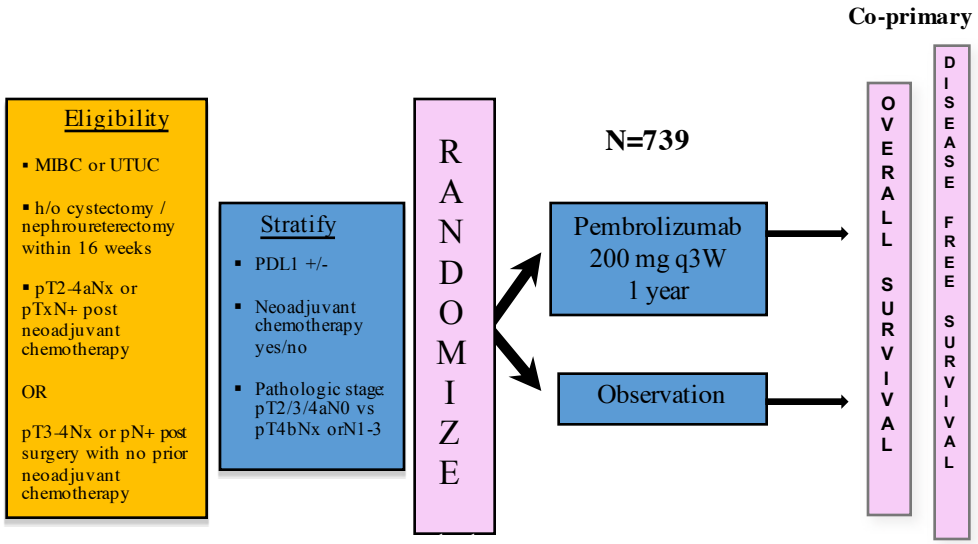
Consider gemcitabine/cisplatin or accelerated/dose dense MVAC X 4 cycles for pT3/4 and/or pN+ who are cisplatin-fit and did not receive neoadjuvant chemoTx

Adjuvant Chemotherapy for Bladder Cancer: Using Population-Based Data to Fill a Void of Prospective Evidence

Sumanta K. Pal, *City of Hope Comprehensive Cancer Center, Duarte, CA*
Neeraj Agarwal, *Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*
Petros Grivas, *Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH*
Toni Choueiri, *Dana-Farber Cancer Institute, Boston, MA*

AMBASSADOR Trial Schema

Phase III randomized "Adjuvant study of peMBrolizumAb in muScle invaSive and locAlly aDvanced urOthelial carcinoma" (AMBASSADOR) vs. observation



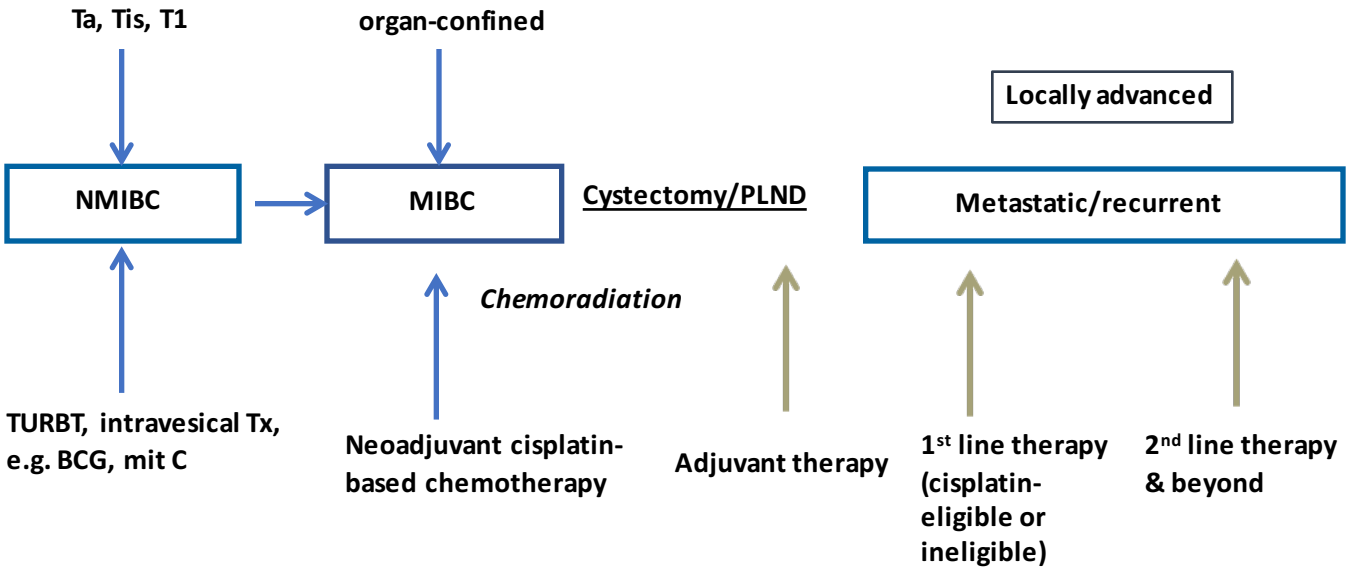
PI: Dr. Andrea B. Apolo

https://clinicaltrials.gov/ct2/show/NCT03244384.

Clinical Pearls: MIBC

- Cisplatin-based chemotherapy is standard of care
- Cisplatin ineligibility criteria
- No high-level evidence for non–cisplatin-containing regimens in the neoadjuvant or adjuvant setting
- Multidisciplinary team approach invaluable to successful development and implementation of treatment plans
- Nephrostomy tubes preferred if needed for obstruction (not stent)
- Immunotherapy and combination chemo/immunotherapy being investigated in this space

Disease/Treatment Settings



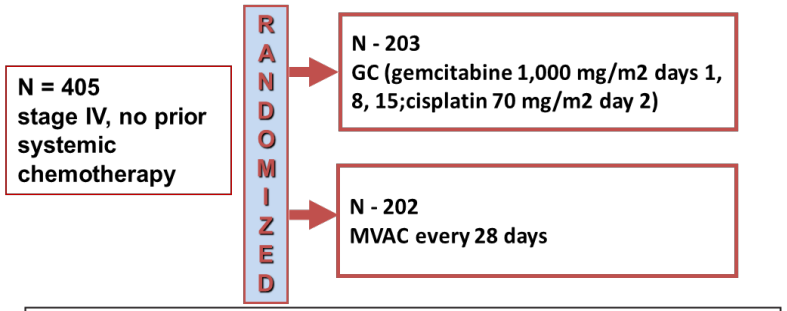
Metastatic Urothelial Carcinoma

- 4% of pts present with metastatic disease
- Half of all pts relapse after cystectomy, depending on initial stage
- Distant metastases and/or locoregional recurrences
- Median OS with platinum-based chemotherapy 9-15 months

Metastatic Disease: 1st Line

- Comparable ORR between GC and 'classic' MVAC
- Median PFS: 7.7 mo (GC) vs 8.3 mo (MVAC)
- Median OS: 14 mo vs 15 mo)
- Similar 5-yr OS rate (13–15%) (p=0.53)
- Less Grade 3/4 AEs with GC, e.g. neutropenia (71% vs 82%), neutropenic sepsis (2% vs 14%), mucositis (1% vs 22%)
- Trial was designed to assess if GC is superior and was not powered to demonstrate non-inferiority

Most patients get GC (dose-dense MVAC easier and better than older 'classic' MVAC)



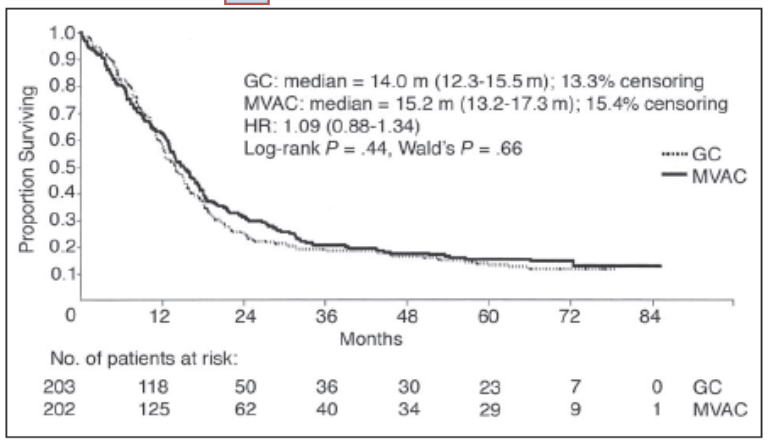


Fig 1. Kaplan-Meier curves for overall survival. GC, gemcitabine/cisplatin; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; HR, hazard ratio; Pts, patients.

von der Maase H, et al. *J Clin Oncol.* 2000;18:3068-77.

mUC 1st Line, Cisplatin-Ineligible: Immune Checkpoint Inhibitors

	Atezolizumab[1]	Pembrolizumab[2]
Phase	Phase II (IMvigor Cohort 1)	Phase II (Keynote-052)
N	119	370
Dosing	1200 mg every 3 weeks	200 mg every 3 weeks
ORR	23% (9% CR)	29% (7% CR)
Duration of response	70% of responses ongoing at 17.2 months	82% of responses ongoing at ≥ 6 months
Median OS	15.9 months	Not reached
Median PFS	2.7 months	2 months
Rate of Grade 3/4 treatment-related AEs	16%	19%

[1]Balar AV, et al. *Lancet*. 2017;389:67-76; [2]Balar AV, et al. *Lancet Oncol*. 2017;18:1483-92.

Atezolizumab

- FDA approval in 2016
- First drug approved in urothelial cancer space in 3 decades
- PD-L1 inhibitor
- First-line therapy in pts with locally advanced/unresectable or metastatic disease who are cisplatin ineligible
- Salvage therapy in pts who progressed post-platinum therapy

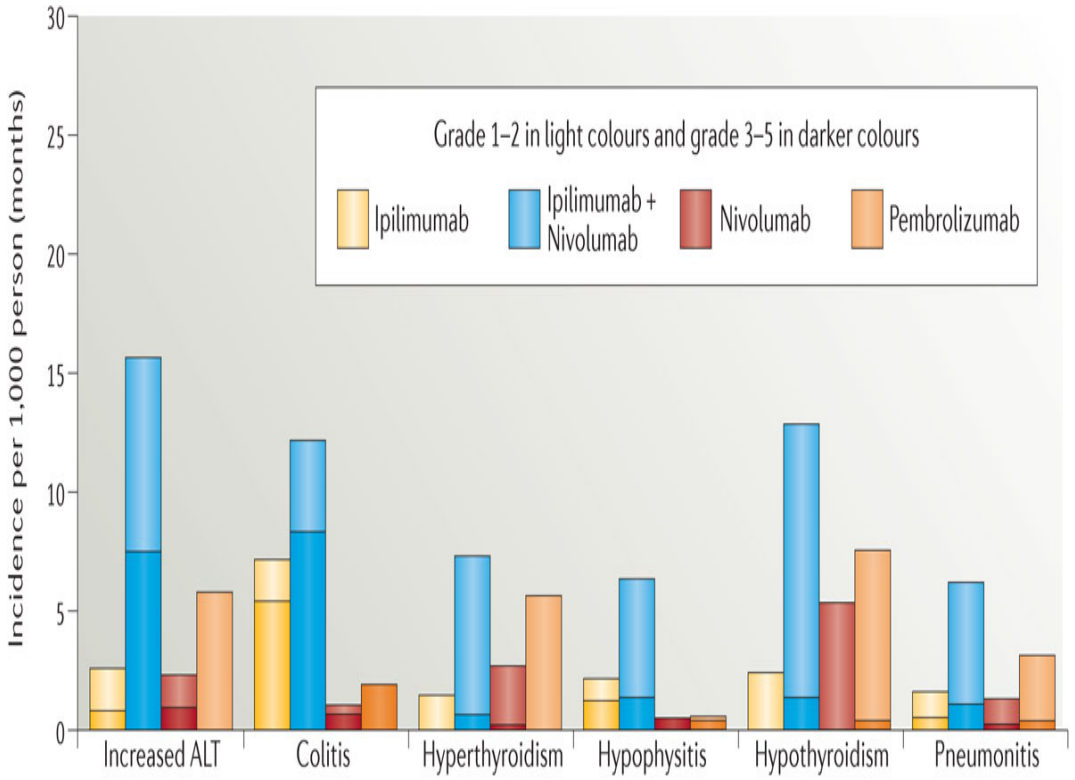
mUC: Immune Checkpoint Inhibitors in Salvage Setting

	Atezolizumab[1]	Nivolumab[2]	Pembrolizumab[3]	Avelumab[4]	Durvalumab[5]
Phase	Phase III randomized vs chemotherapy	Phase II single-arm	Phase III randomized vs chemotherapy	Phase Ib	Phase I/II
N	931	265	542	249 (161 pts ≥ 6 mo F/U)	191
Dosing	1200 mg every 3 wks	3 mg/kg every 2 wks	200 mg every 3 wks	10 mg/kg every 2 wks	10 mg/kg every 2 wks
ORR	13.4%	19.6%	21.1%	17%	17.8%
Duration of response	63% of responses ongoing at median F/U of 21.7 mo	77% of responses ongoing at median F/U of 7 mo	72% of responses ongoing at median F/U of 14.1 mo	96% of responses ongoing at 6-mo F/U	50% of responses lasting ≥ 6 mo
Median OS, mo	8.6	8.7	10.3	6.5	18.2
Median PFS, mo	2.1	2.0	2.1	1.5	1.5
Grade 3/4 treatment-related AEs	20%	18%	15%	8%	6.8%

[1]Powles T, et al. *Lancet*. 2018;391:748-57; [2]Sharma P, et al. *Lancet Oncol*. 2017;18:312-22; [3]Bellmunt J, et al. *N Engl J Med*. 2017;376:1015-26; [4]Patel MR, et al. *Lancet Oncol*. 2018;19:51-64; [5]Powles T, et al. *JAMA Oncol*. 2017;3:e172411.

Incidence of irAEs Depends on the ICI

CA-184-002
KEYNOTE-001
KEYNOTE-002
KEYNOTE-006
CheckMate-037
CheckMate-066
CheckMate-067
CheckMate-069



Presented by: Allison Betof Warner, MD, PhD

Nature Reviews | Clinical Oncology

Boutros C, et al. *Nat Rev Clin Oncol*. 2016;13:473-86.

ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events.

How Should We Manage irAEs?

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

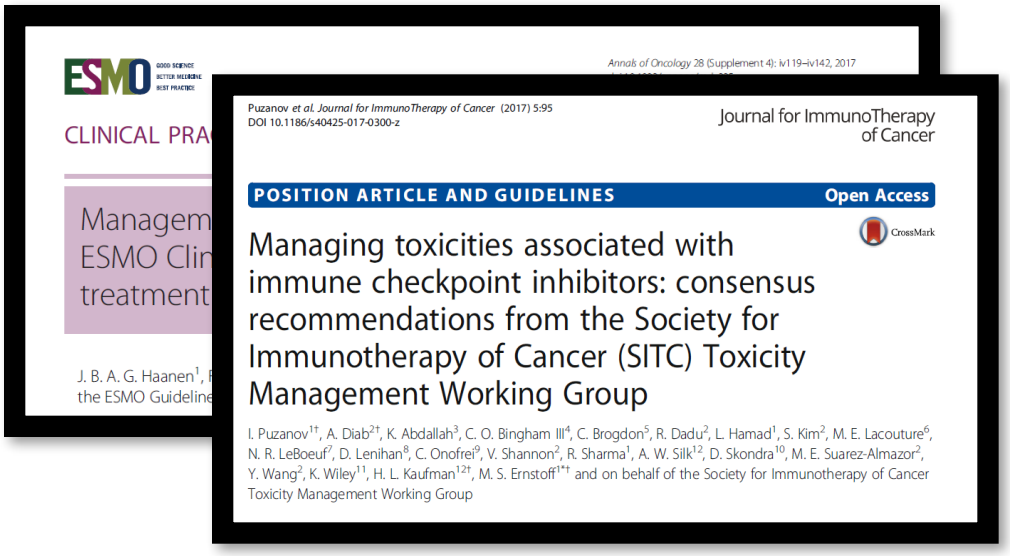
Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

Presented by: Allison Betof Warner, MD, PhD

Haanen JB, et al. *Ann Oncol*. 2017;28(suppl 4):iv119-iv142; Puzanov I, et al. *J Immunother Cancer*. 2017;5:95; Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-68.

How Should We Manage irAEs?



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Haanen JB, et al. *Ann Oncol*. 2017;28(suppl 4):iv119-iv142; Puzanov I, et al. *J Immunother Cancer*. 2017;5:95; Brahmer JR, et al. *J Clin Oncol*. 2018;36:1714-68.

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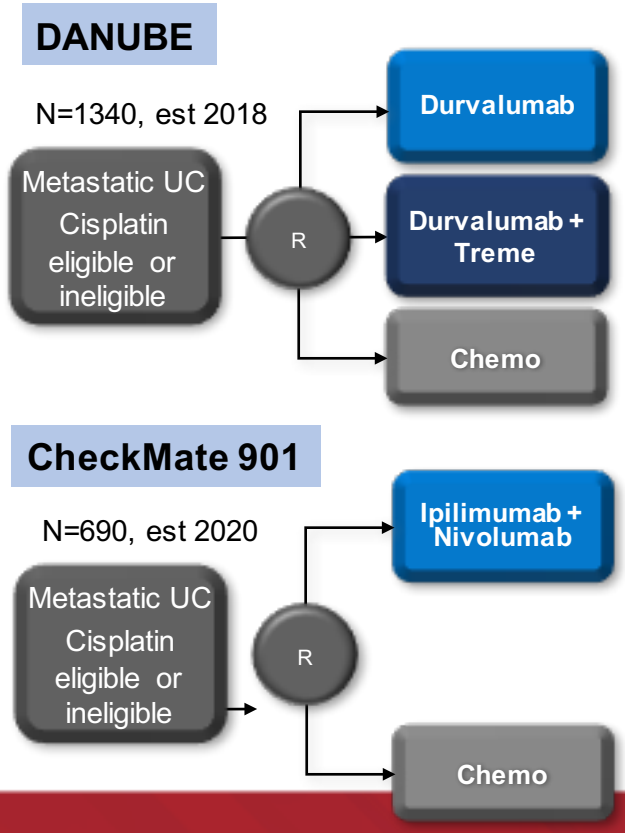
IO Doublet vs Chemotherapy as First-line Treatment for Metastatic UC



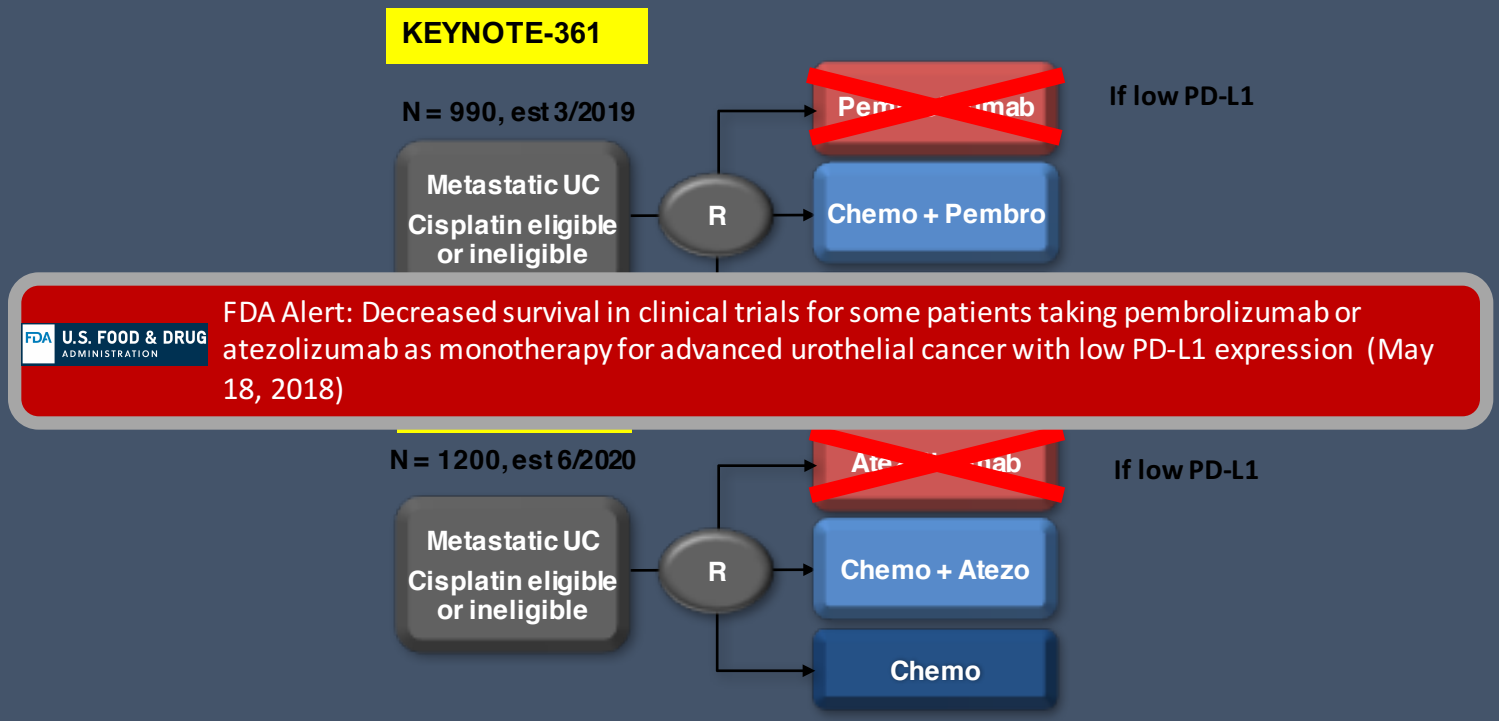
Primary endpoints:
PFS and OS of durva-treme combo vs standard of care

Primary endpoints:
PFS and OS in cisplatin-ineligible pts

Secondary:
PFS and OS in all pts; EORTC QLQ-C30

Durva, durvalumab; EORTC, European Organisation for Research and Treatment of Cancer; Treme, tremelimumab.

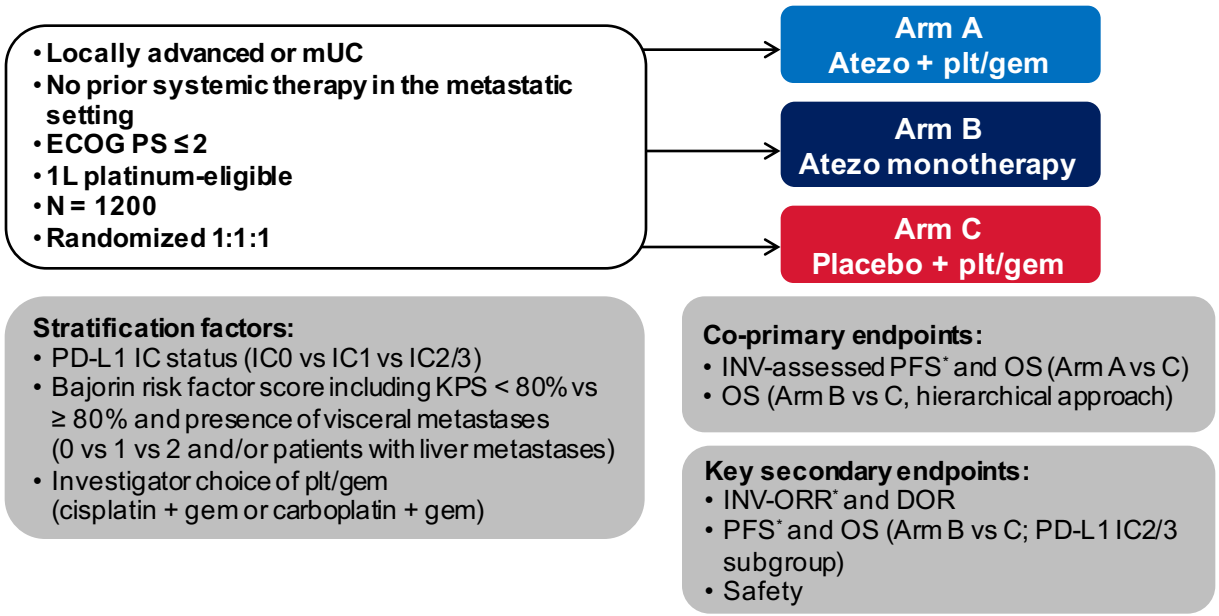
Chemotherapy Plus CPI as First-line Treatment for aUC



Grande E, et al. ESMO 2019. Abstract LBA14_PR.

CPI, checkpoint inhibitor.

IMvigor130 Study Design



* per RECIST 1.1.

Grande E, et al. ESMO 2019. Abstract LBA14_PR.

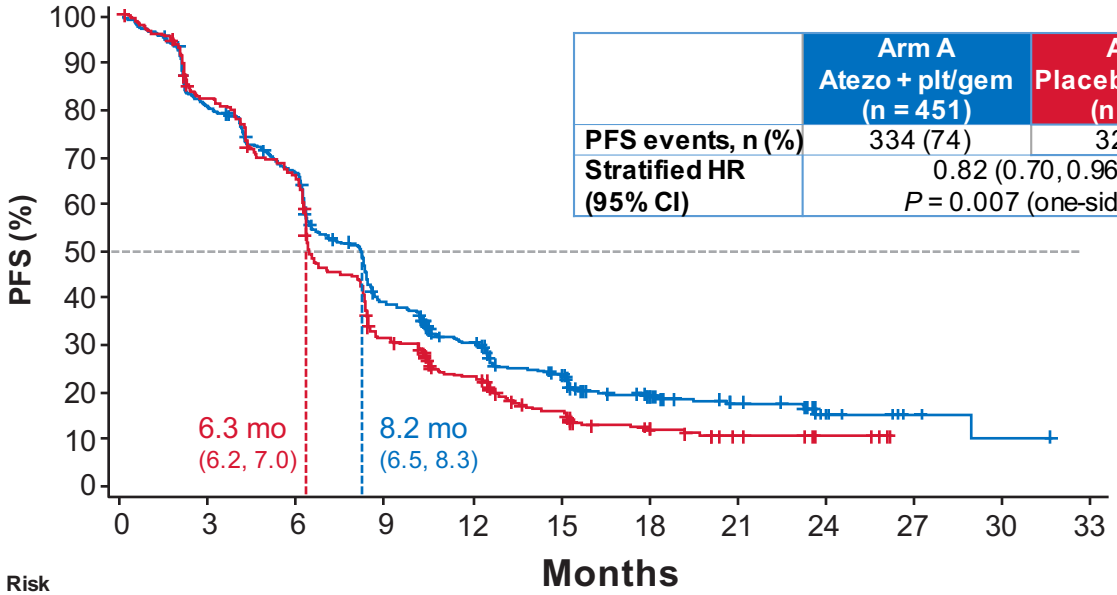
Gem, gemcitabine; KPS, Karnofsky performance status; Plt, platinum.

IMvigor130 Baseline Characteristics

Characteristic	Atezo + plt/gem (n = 451)	Placebo + plt/gem (n = 400)[a]	Atezo (n = 362)
Median age (range), y	69 (31-87)	67 (33-89)	67 (36-87)
ECOG PS, n (%)			
0	182 (40)	173 (43)	157 (43)
1	209 (46)	187 (47)	174 (48)
2	60 (13)	40 (10)	31 (9)
Bajorin risk factor score, n (%)			
0	176 (39)	162 (41)	151 (42)
1	169 (37)	149 (37)	134 (37)
2 and/or liver mets	106 (24)	89 (22)	77 (21)
PD-L1 status on IC, n (%)			
IC2/3	108 (24)	91 (23)	88 (24)
IC1	195 (43)	179 (45)	160 (44)
IC0	148 (33)	130 (33)	114 (31)
Cisplatin ineligibility[b]	204 (45)	140 (35)	107 (30)
Renal impairment	113 (25)	94 (24)	65 (18)
Investigator choice of chemotherapy[c]			
Carboplatin	314 (70)	264 (66)	227 (63)
Cisplatin	137 (30)	136 (34)	135 (37)

[a] n = 359 for comparisons to atezo monotherapy arm. [b] Per Galsky criteria per protocol, excluding New York Heart Association functional classification.
[c] Of the patients considered cisplatin eligible at study entry, 52% received carboplatin, while 10% of patients who were cisplatin ineligible received cisplatin.

Final PFS: ITT (Arm A vs Arm C)

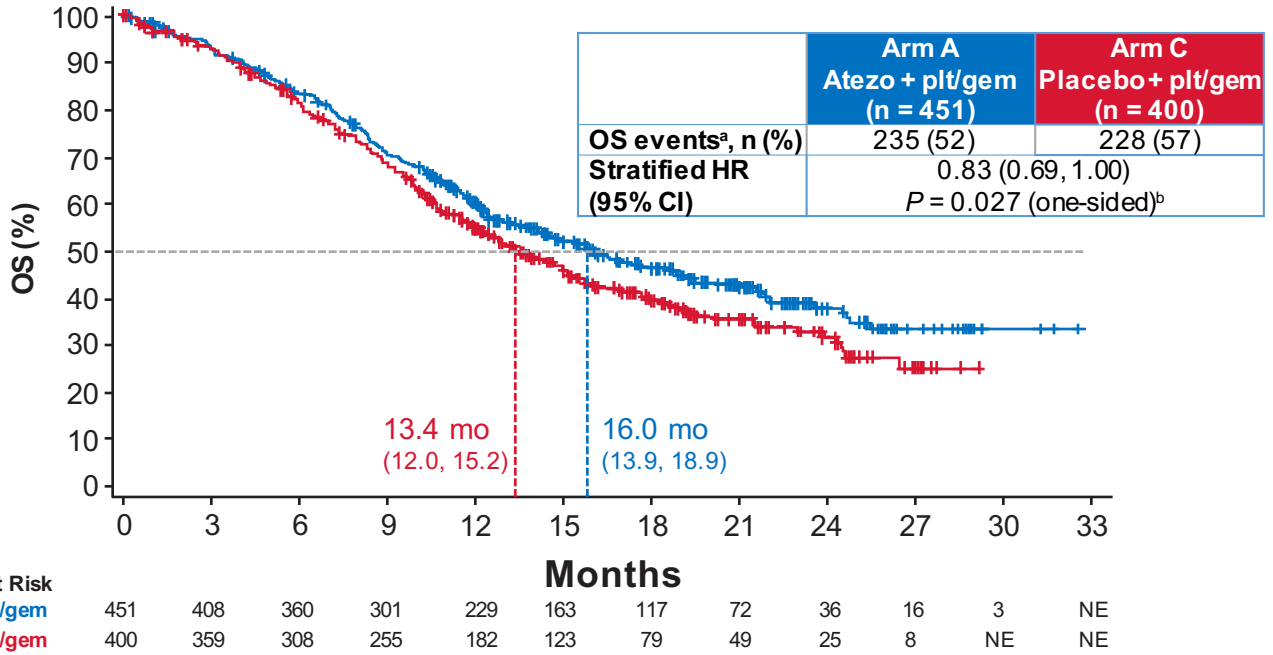


	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
PFS events, n (%)	334 (74)	326 (82)
Stratified HR (95% CI)	0.82 (0.70, 0.96) *P* = 0.007 (one-sided)	

No. at Risk												
Atezo + plt/gem	451	345	282	160	111	74	42	22	10	4	2	NE
Placebo + plt/gem	400	317	246	116	73	40	18	11	4	NE	NE	NE

NE, not estimable. Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients).

Interim OS: ITT (Arm A vs Arm C)

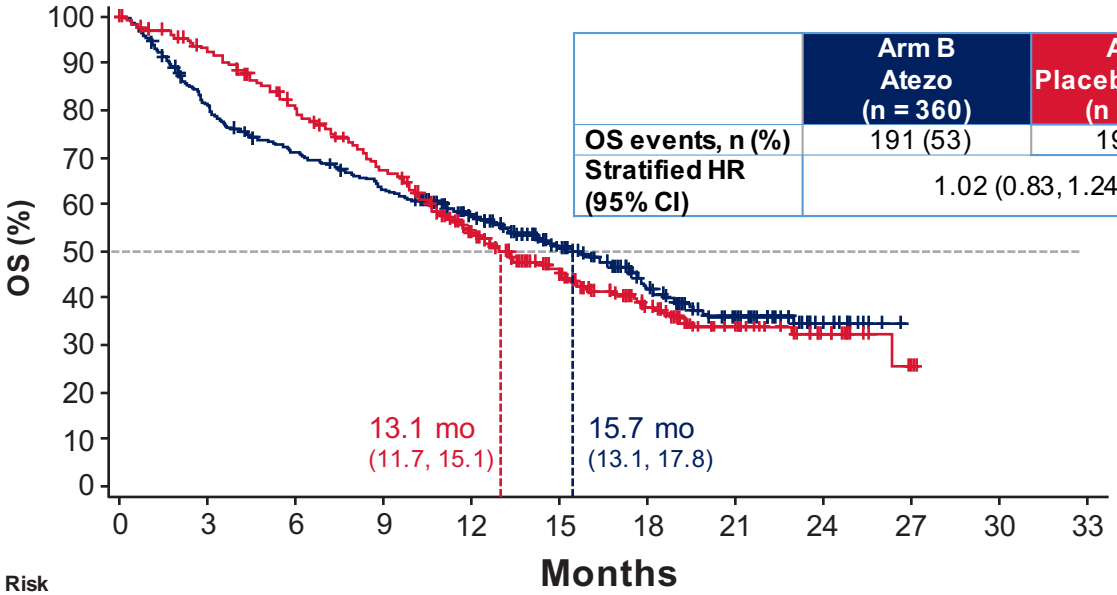


	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
OS events[a], n (%)	235 (52)	228 (57)
Stratified HR (95% CI)	0.83 (0.69, 1.00) *P* = 0.027 (one-sided)[b]	

No. at Risk												
Atezo + plt/gem	451	408	360	301	229	163	117	72	36	16	3	NE
Placebo + plt/gem	400	359	308	255	182	123	79	49	25	8	NE	NE

Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients). [a] 5% of patients from Arm A and 20% of patients from Arm C received non-protocol immunotherapy. [b] Did not cross the interim efficacy boundary of 0.007 per the O'Brien-Fleming alpha spending function.

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

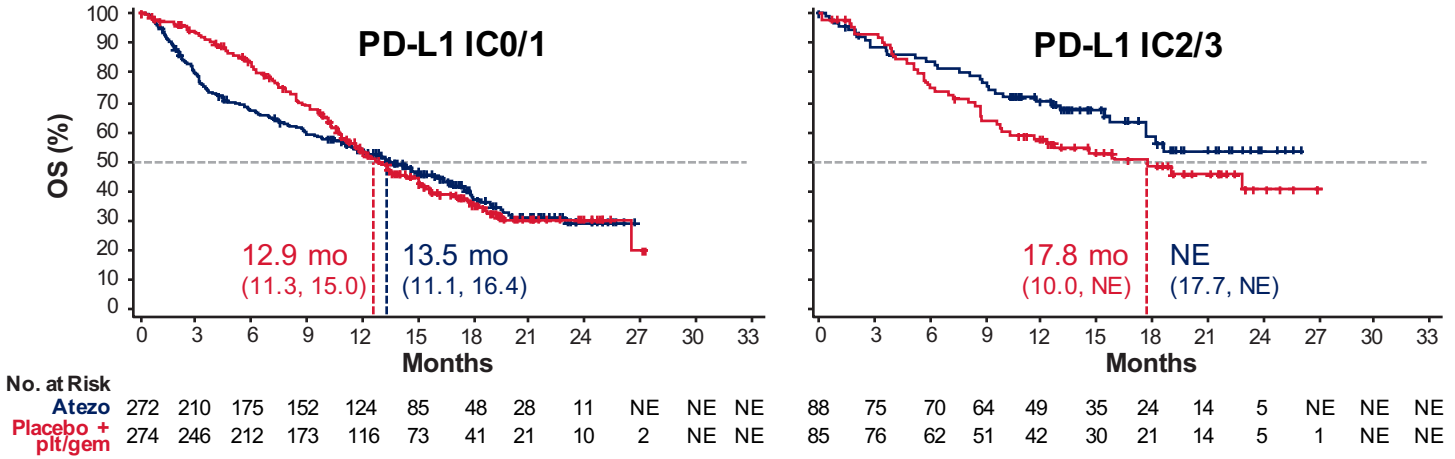


	Arm B Atezo (n = 360)	Arm C Placebo + plt/gem (n = 359)[a]
OS events, n (%)	191 (53)	198 (55)
Stratified HR (95% CI)	1.02 (0.83, 1.24)	

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

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

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



No. at Risk												
Atezo	272	210	175	152	124	85	48	28	11	NE	NE	NE
Placebo + plt/gem	274	246	212	173	116	73	41	21	10	2	NE	NE

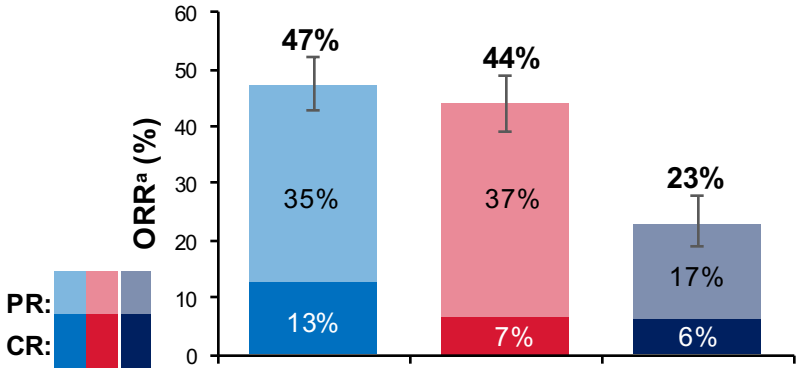
No. at Risk												
Atezo	88	75	70	64	49	35	24	14	5	NE	NE	NE
Placebo + plt/gem	85	76	62	51	42	30	21	14	5	1	NE	NE

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

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

Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients).

Confirmed ORR and DOR



	Atezo + plt/gem	Placebo + plt/gem	Atezo
DOR[b], median (95% CI), mo	8.5 (7.2,10.4)	7.6 (6.3, 8.5)	NE (15.9, NE)

Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients).
[a] Objective response–evaluable patients: n = 447 in atezo + plt/gem, n = 397 in placebo + plt/gem, n = 359 in atezo.

[b] n = 212 in atezo + plt/gem, n = 174 in placebo + plt/gem, n = 82 in atezo.

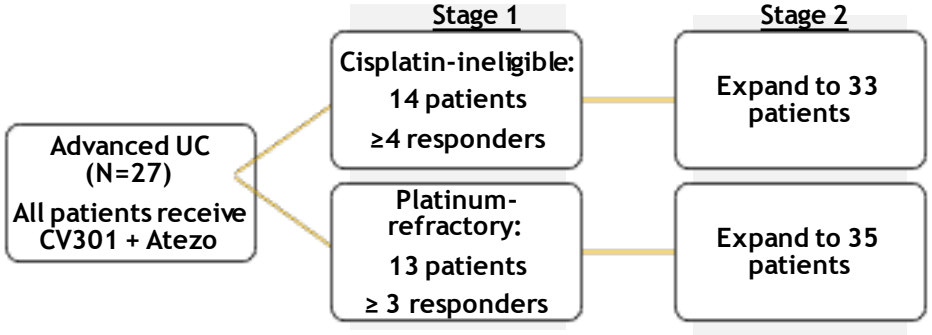
Safety Summary

AE, n (%)	Atezo + plt/gem (n = 453)	Placebo + plt/gem (n = 390)	Atezo (n = 354)
Any grade, all cause	451 (100)	386 (99)	329 (93)
Grade 3-4	383 (85)	334 (86)	148 (42)
Grade 5	29 (6)	20 (5)	28 (8)
Any grade, treatment related	434 (96)	373 (96)	211 (60)
Grade 3-4	367 (81)	315 (81)	54 (15)
Grade 5	9 (2)	4 (1)	3 (1)
Any grade, serious	234 (52)	191 (49)	152 (43)
Treatment-related serious AEs	144 (32)	101 (26)	44 (12)
Any grade leading to any treatment discontinuation	156 (34)	132 (34)	22 (6)
Atezo or placebo discontinuation	50 (11)	27 (7)	21 (6)
Cisplatin discontinuation	53 (12)	52 (13)	0
Carboplatin discontinuation	90 (20)	79 (20)	1 (< 1)[a]
Gemcitabine discontinuation	117 (26)	100 (26)	1 (< 1)[a]
Any grade leading to any dose reduction or interruption	363 (80)	304 (78)	112 (32)

AE, adverse event. Safety-evaluable population.
Data cutoff, 31 May 2019; median survival follow-up 11.8 months (all patients).
[a] This patient was randomised to atezo + plt/gem and received atezo; they had an AE of pyrexia that day, and gemcitabine and carboplatin were marked as 'drug withdrawn'. Since no chemotherapy was given, this patient was included in the atezo monotherapy arm for safety analysis.

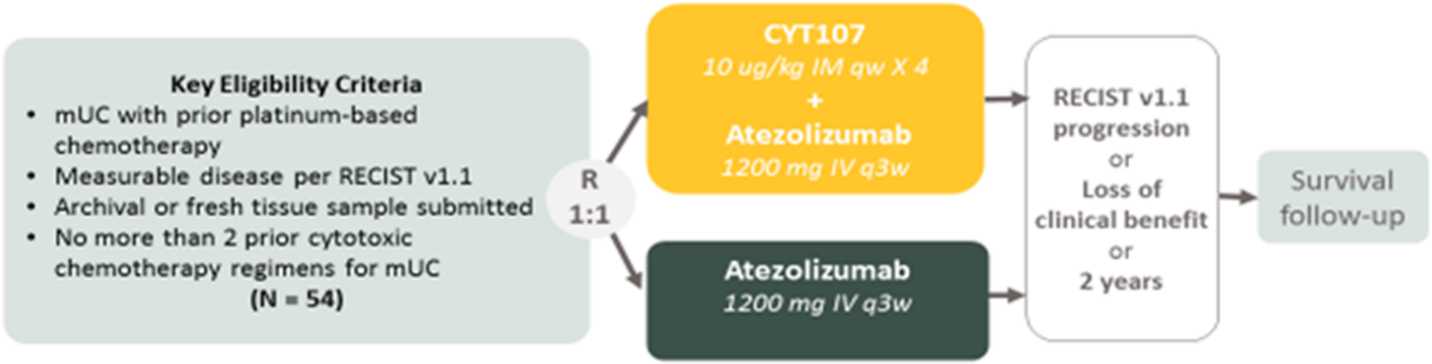
CV301 + Anti-PD-L1 in Advanced UC

- Primary endpoint: objective response rate
- 2 cohorts: 1st and 2nd line: locally advanced/unresectable or metastatic
- Secondary endpoints:
  - Progression-free survival, overall survival, duration of response, safety
- Exploratory endpoints: biomarker discovery and validation
  - Inform future trial design and other indications



Co-PIs:
Petros Grivas
Guru Sonpavde

CITN-14 Trial Design – A Randomized Phase II Study of Atezolizumab Plus Recombinant Human IL-7 (CYT107) in Patients with Locally Advanced or Metastatic Urothelial Carcinoma



- **Primary endpoint**
  - ORR by RECIST 1.1
- 6 patient safety run-in then wait 4 weeks after last patient entered to ensure <2 DLTs before randomization begins for 74 additional patients
- H_{null}=0.173, H_{alt}=0.45; alpha 0.05; power 76.9%

- **Additional endpoints**
  - Efficacy: CBR, PFS, DOR, OS in all patients and by PD-L1 expression
  - Safety and tolerability
  - Tumor biopsy for tumor infiltrating cells, PD-L1 expression, IFNY gene expression
  - Peripheral blood for tumor specific T cells, TCR repetoire, RNAseq neoantigens

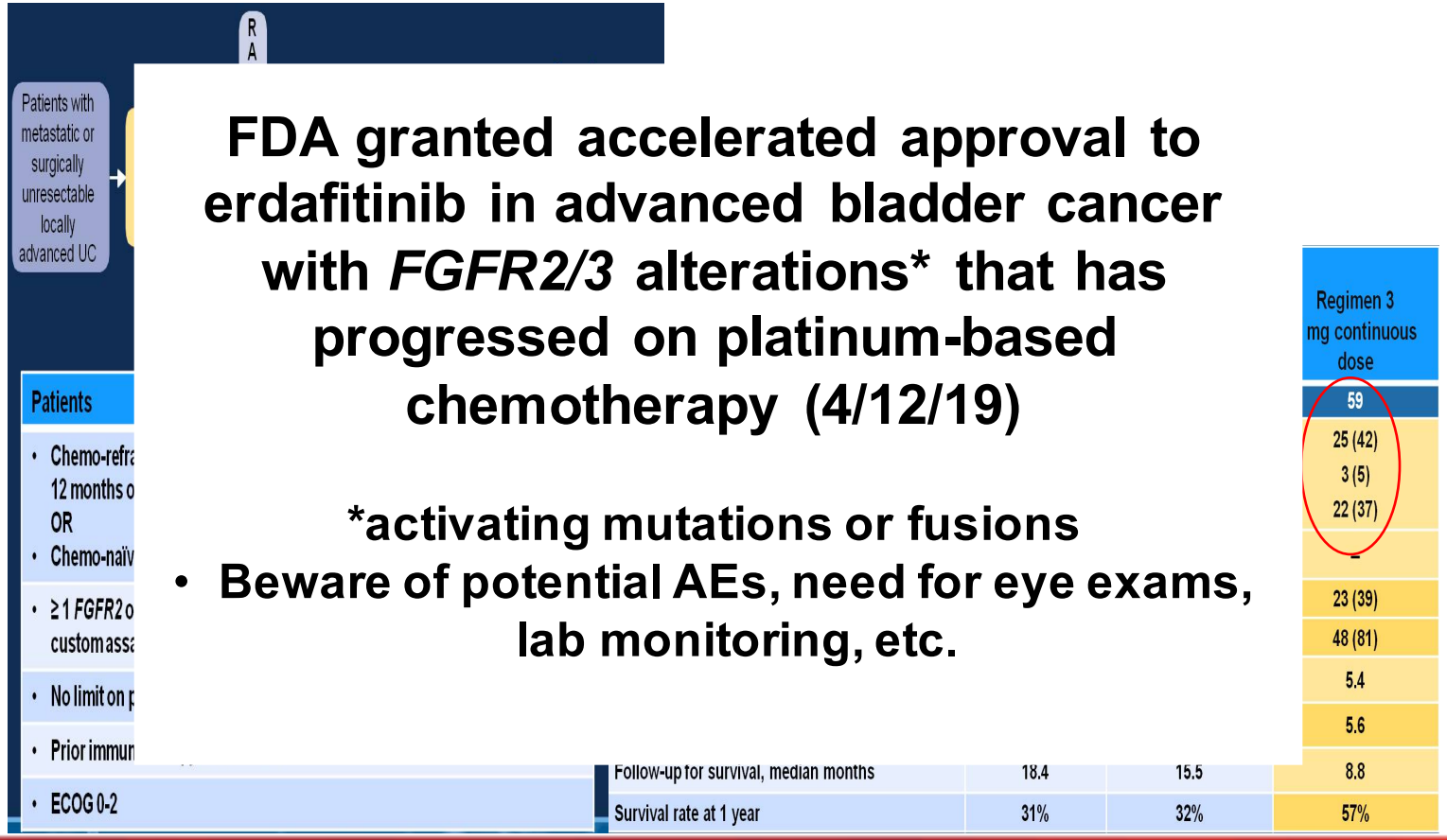
PIs: E.Y. Yu, R.K. Pachynski

Salvage Therapy for Urothelial Cancer

Drug	N	RR, %	Median PFS (mo)	Median OS (mo)
Ifosfamide	56	20	2.4	5.5
Gemcitabine	30	11	4.9	8.7
Weekly paclitaxel	31	10	2.2	7.2
Docetaxel	30	13	-	9.0
Nab-paclitaxel	35	44	6.0	10.8
Pemetrexed	47	27.7	2.9	9.6
Irinotecan	40	5	2.1	5.4
Ixabepilone	42	11.9	2.7	8.0
Vinflunine	175	15	2.8	8.2
Volasertib	50	14	1.5	-
Gefitinib	31	3	-	3.0
Everolimus	45	4.5	3.3	10.5
Aflibercept (VEGF-trap)	22	4.5	2.8	Not reported
Lapatinib	59	3	2	4.5
Sorafenib	27	0	-	6.8
Pazopanib	30	22	-	-
Sunitinib	45	7	2.4	6.9

Sonpavde G, et al. *Lancet Oncol*. 2010;11:861-70.

Erdafitinib BLC2001 Phase II Trial



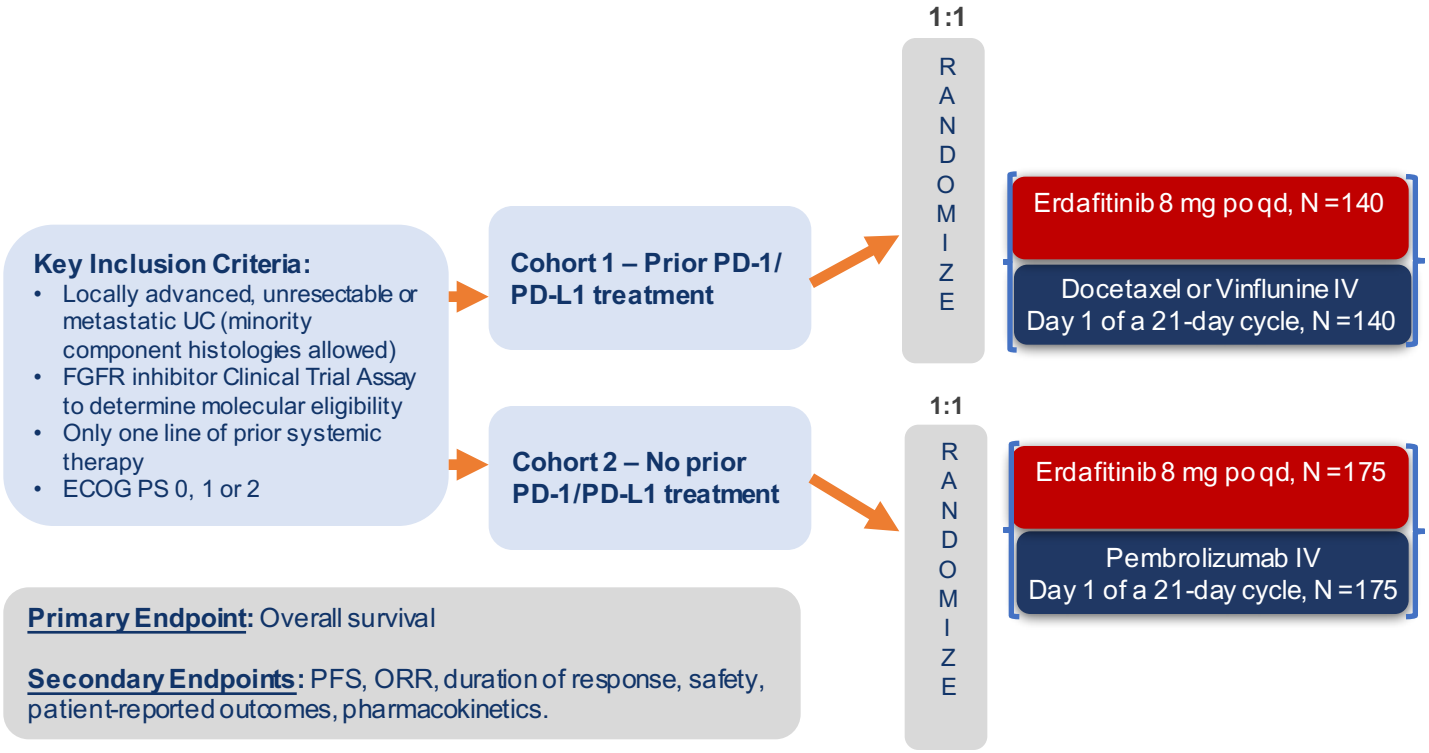
FDA granted accelerated approval to erdafitinib in advanced bladder cancer with *FGFR2/3* alterations* that has progressed on platinum-based chemotherapy (4/12/19)

***activating mutations or fusions**

- **Beware of potential AEs, need for eye exams, lab monitoring, etc.**

Loriot Y, et al. ASCO 2018. Abstract 411.

Erdafitinib Phase III Trial



Numerous Agents Being Evaluated in mUC: Combos vs Sequential Tx

Conventional Cytotoxic Agents	Immunotherapy	Targeted Therapies
• Chemotherapy • Antibody-Drug Conjugates • Radiation Tx	• Checkpoint inhibitors • Vaccines • Cytokines • Adoptive cell-based therapy • Other immuno-modulating agents	• Anti-angiogenesis • FGFR inhibitors • HER family inhibitors • PARP inhibitors • Chromatin remodeling, i.e. HDAC inhibitors • Other, i.e. mAbs, TKIs, etc.

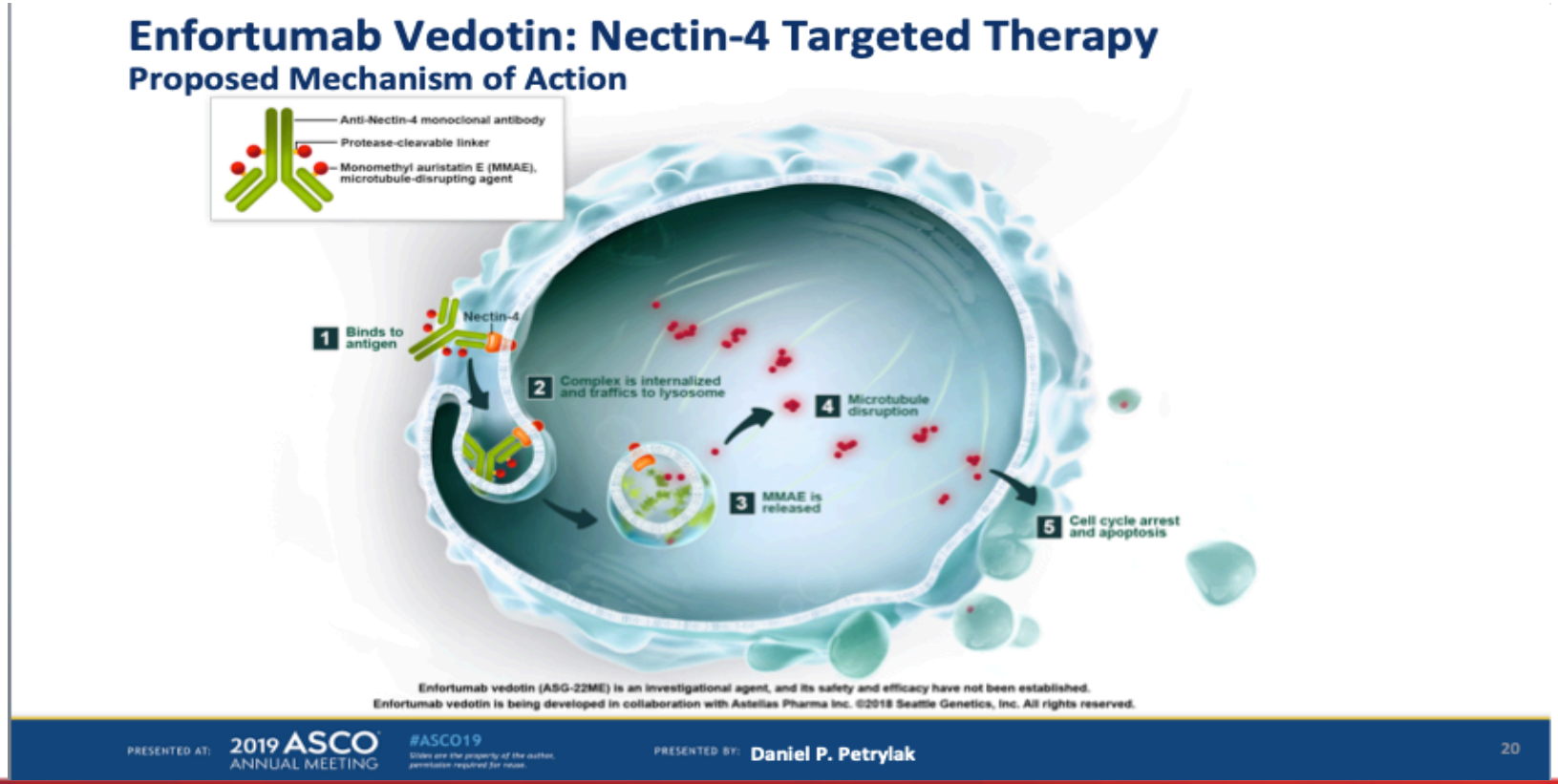
- Patient selection / precision oncology
- Tumor tissue and ctDNA analysis
- Targets and predictive biomarkers with:
  - Analytical validity
  - Clinical validity (biological relevance)
  - Clinical utility

Advanced Urothelial Cancer Treatment Algorithm

Disease State	Setting	Preferred Option	Standard Options
Metastatic, no prior chemotherapy	Cisplatin-eligible	Cisplatin-based combination chemotherapy	
Metastatic, no prior chemotherapy			arboplatin
Metastatic, prior platinum chemotherapy or relapse within 1 year of perioperative cisplatin-based therapy		Pembrolizumab OR Erdafitinib (tumors with *FGFR2/3* alterations)	Atezolizumab Nivolumab Durvalumab Avelumab
Metastatic, prior chemotherapy and immunotherapy (and erdafitinib in some pts)			Taxane (US) Vinflunine (EU)

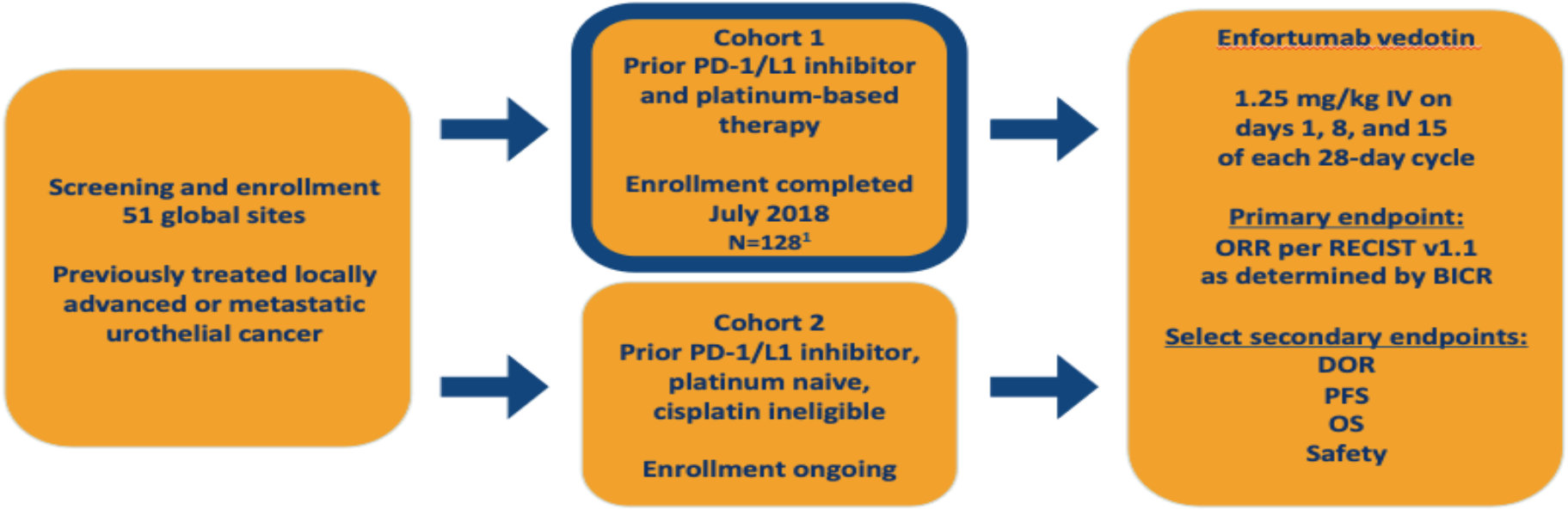
Clinical trials are critical throughout disease spectrum and treatment settings!

Enfortumab Vedotin: Mechanism of Action



Enfortumab Vedotin: Cohort 1 Data

Abstract LBA4505 - EV-201: Single-Arm, Pivotal Phase 2 Trial



[1] 3 patients did not receive enfortumab vedotin treatment: one each due to clinical deterioration, patient decision, and low hemoglobin after enrollment

BICR=blinded independent central review; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

Enfortumab Vedotin: Cohort 1 Data

Abstract LBA4505 - EV-201: Cohort 1 Summary and Conclusions

- High unmet need for patients with advanced and metastatic urothelial carcinoma
- Enfortumab vedotin: First novel therapeutic to demonstrate substantial clinical activity in patients who progressed after platinum chemotherapy and a PD-1/L1 inhibitor
  - 44% response rate (CR 12%) and 7.6 months median duration of response
  - Responses observed across all subgroups and irrespective of response to prior PD-1/L1 inhibitor or presence of liver metastases
  - Tolerable with a manageable safety profile
  - EV-201 results are highly consistent with the phase 1 EV-101 trial in the same patient population
  - These data support submission to the FDA for accelerated approval
- If approved, enfortumab vedotin may have the potential to become a new standard of care in patients who have progressed after platinum and PD-1/L1 inhibitors

Ongoing enfortumab vedotin trials: **EV-201:** Cohort 2 enrolling cisplatin-ineligible patients without prior platinum (NCT03219333); **EV-301:** Randomized phase 3 trial of EV vs. SOC post-platinum and a PD-1/L1 inhibitor (NCT03474107); **EV-103:** EV in combination with pembrolizumab and/or chemotherapy (NCT03288545)

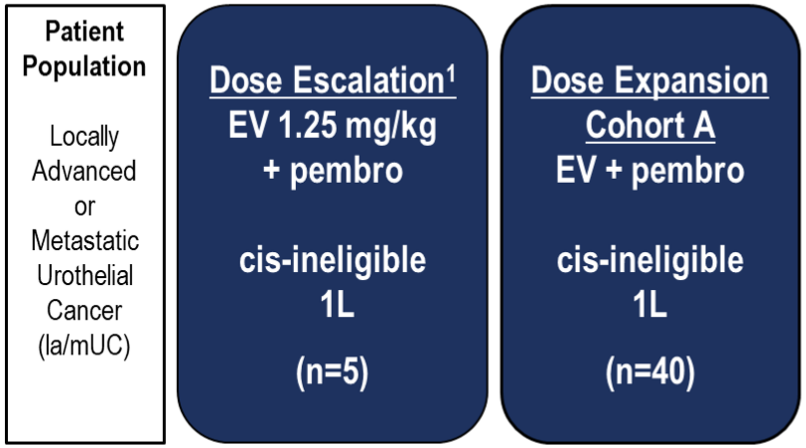
EV-201: Cohort 1 Treatment-Related Adverse Events of Interest

Events categorized based on queries for related MedDRA terms

- **Peripheral neuropathy: 50% any grade, 3% ≥Grade 3**
  - No Grade 4 events
  - Sensory events most common (44%, all pts)
  - Of pts with peripheral neuropathy at enrollment, 48% did not worsen
  - 76% had resolution or events ongoing at Grade 1 at last follow-up
- **Rash: 48% any grade, 12% ≥Grade 3**
  - No Grade 4 events
  - 1 case of Grade 3 Stevens-Johnson Syndrome was reported by the investigator
  - 93% resolution or improvement at last follow-up
  - Of those with ongoing rash, most (75%) were Grade 1
- **Hyperglycemia: 11% any grade, 6% ≥Grade 3**
  - 68% of pts with pre-existing hyperglycemia did not develop treatment-related event
  - 1 Grade 4 event, resolved, no need for ongoing medication
  - 71% resolution or improvement at last follow-up

Enfortumab Vedotin + Pembrolizumab Cohorts

EV 1.25 mg/kg + pembrolizumab (200 mg) in 1L la/mUC patients



Dosing: EV days 1 and 8 of 3-wk cycle to align with pembro (day 1 of 3-wk cycle)

EV exposure: Comparable to EV monotherapy on 4-wk schedule (EV Days 1, 8, and 15)[2]

Primary endpoints: AEs, lab abnormalities

Key secondary endpoints: DLTs, ORR, DCR, DOR, OS

[1] Not included in the current analysis: three 1L patients treated with EV 1 mg/kg + pembro 200 mg and two 2L patients treated with EV 1.25 mg/kg + pembro 200 mg

[2] Rosenberg et al. *J Clin Oncol. Epub July* 2019

Hoimes CJ, et al. ASCO 2019 (Abstract TPS4593).

EV, enfortumab vedotin; pembro, pembrolizumab.

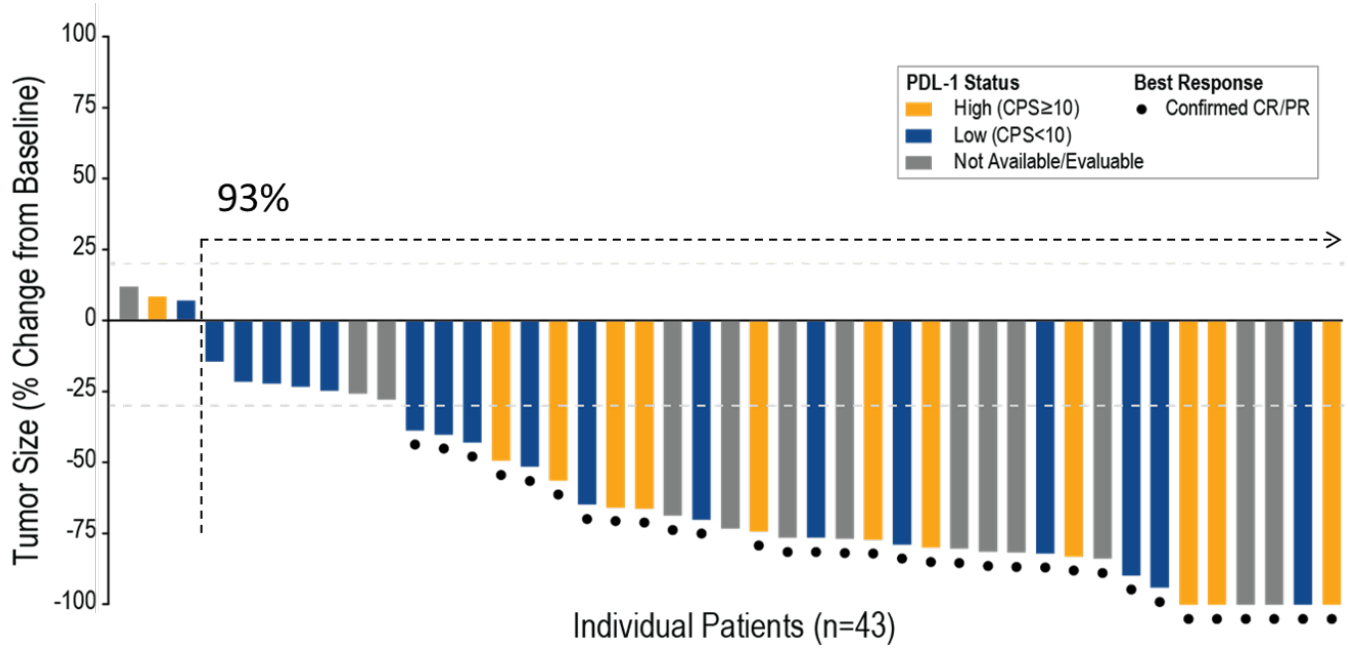
Objective Response Rate

ORR per RECIST v1.1 by investigator 18 Jun 2019 data cut-off	Patients (N=45) n (%)
Confirmed Objective Response Rate (ORR)	**32 (71)**
95% confidence interval	(55.7, 83.6)
Best Overall Response per RECIST v. 1.1	
Complete response	6 (13)
Partial response	26 (58)
Stable disease	10 (22)
Progressive disease	1 (2)
Not evaluable[1]	2 (4)

[1] Two patients did not have post-baseline response assessments before end-of-treatment: 1 withdrew consent and 1 died before any post-baseline response assessment

Hoimes CJ, et al. ASCO 2019 (Abstract TPS4593).

Maximum Percent Reduction from Baseline in Sum of Diameters of Target Lesions



*Per investigator.

Treatment-related Adverse Events (TRAE)

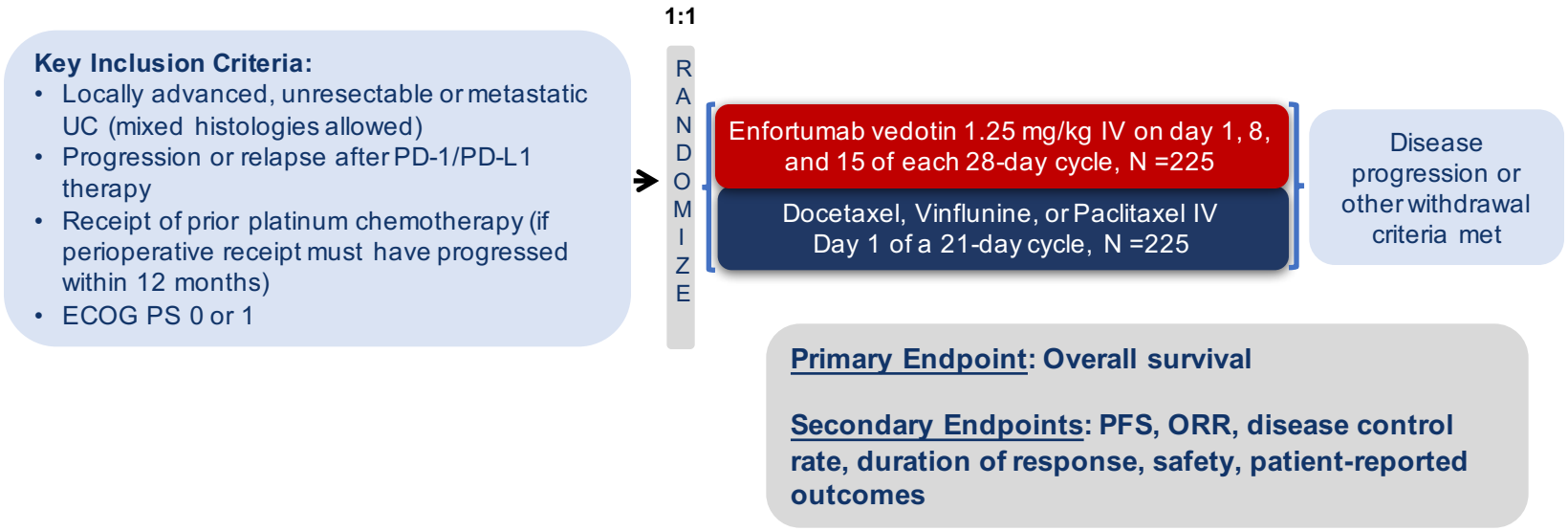
TRAEs by preferred term Any grade in ≥20% of patients and ≥Grade 3 in ≥10% of patients	Patients (N=45) n (%)	
	Any Grade	≥Grade 3
Overall	43 (96)	23 (51)
Fatigue	22 (49)	4 (9)
Alopecia	21 (47)	N/A
Peripheral sensory neuropathy	21 (47)	2 (4)
Diarrhea	18 (40)	2 (4)
Decreased appetite	15 (33)	0
Dysgeusia	14 (31)	N/A
Nausea	13 (29)	0
Pruritus	12 (27)	1 (2)
Rash maculo-papular	12 (27)	3 (7)
Weight decreased	10 (22)	0
Anemia	9 (20)	2 (4)
Lipase increased	7 (16)	6 (13)

N/A: Non-applicable

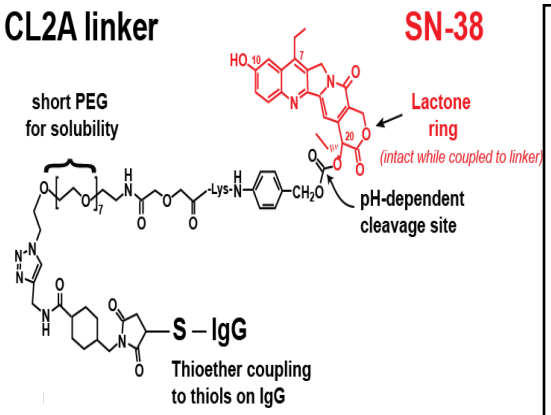
- **7 patients had treatment-related serious AEs (16%)**
- **4 treatment-related discontinuations of EV + pembro due to AEs (9%)**
  - Peripheral sensory neuropathy most common: 2 patients
- **1 treatment-related death as reported by investigator (2%)**
  - Multiple organ dysfunction syndrome
  - Confounded by concomitant acute onset of atrial fibrillation, corticosteroids, and amiodarone

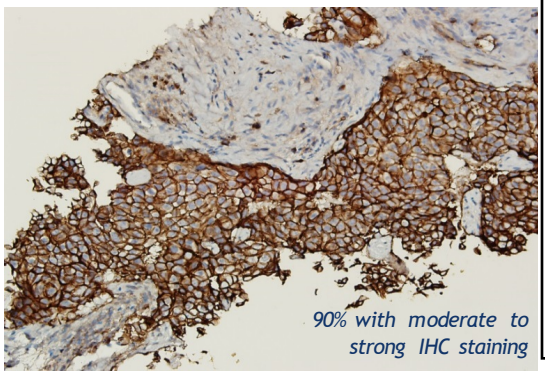
Hoimes CJ, et al. ASCO 2019 (Abstract TPS4593).

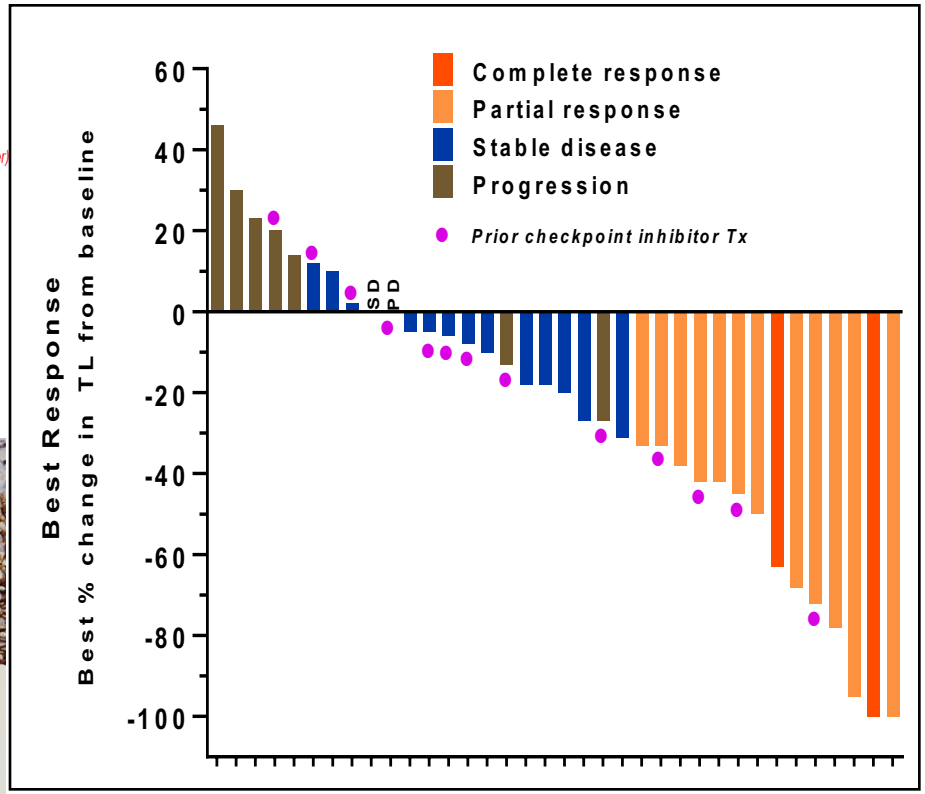
Enfortumab Vedotin Phase III Trial Design



Sacituzumab Govitecan (IMMU-132): ADC to TROP-2





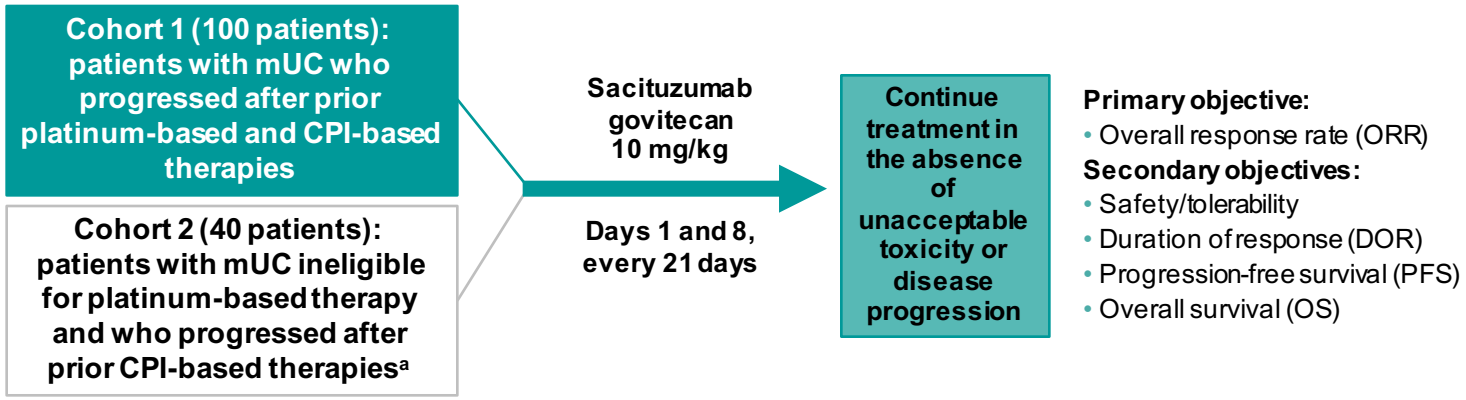


14/41 (34%) ORR; 10/33 (30%) ≥3rd line; 4/14 (29%) prior IO

Tagawa ST, et al. *Ann Oncol*. 2017;28(suppl 5):v295-v329.

ADC, antibody–drug conjugate.

TROPHY-U-01: Study Design



[a]CPI, immune checkpoint inhibitor therapy (includes anti PD-1/anti PD-L1-based therapies).
EudraCT Number: 2018-001167-23; ClinicalTrials.gov Number: NCT03547973; IMMU-132-06 study.

Tagawa ST, et al. ESMO 2019. Abstract LBA55.

PD-1, programmed death-1; PD-L1, programmed death-ligand 1.

Demographic and Baseline Characteristics

Characteristic	N=35
Age (y), median (range)	64 (43-90)
≥75 y	7 (20)
Male, n (%)	28 (80)
Race,[a] n (%)	
White	29 (83)
Black	1 (3)
Asian	2 (6)
Other	1 (3)
ECOG PS 0, n (%)	15 (43)
ECOG PS 1, n (%)	20 (57)
Visceral metastatic sites,[b] n (%)	22 (63)
Lung	14 (40)
Liver	8 (23)
Other	4 (11)

Characteristic	N=35
Prior anticancer regimens, median (range)	3.0 (2.6)
Median duration of last anticancer regimen, mo (range)	1.6 (1-60)
Lines of prior therapies, n (%)	
2	11 (31)
≥3	24 (69)
Median time since diagnosis of metastatic cancer, mo (range)	21.1 (3-71)
Bellmunt risk factors, n (%)	
0	8 (23)
1	21 (60)
2	5 (14)
3	1 (3)

[a]Information on race was not collected in 2 patients; [b]visceral metastases included only target and non-target lesions (metastatic sites are not mutually exclusive).

Tagawa ST, et al. ESMO 2019. Abstract LBA55.

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Treatment-Related Adverse Events ≥20%: Any Grade or ≥5% Grade ≥3 (N=35)

Category	Event	All Grades (%)	Grades 3 (%)	Grade 4 (%)
Hematologic[a,b]	Neutropenia[c]	66	29	26
	Leukopenia[d]	40	20	9
	Anemia	34	17	0
	Febrile neutropenia	11	9	3
	Lymphocyte count decreased	11	6	3
Gastrointestinal	Diarrhea	57	6	3
	Nausea	43	0	0
	Abdominal pain	20	3	0
General disorders and administrative site conditions	Fatigue	54	6	0
Infections and infestations	Urinary Tract infection	14	11	0
Skin & subcutaneous tissue	Alopecia	74	0	0
Metabolism and nutrition	Decreased appetite	20	0	0

- 3 patients discontinued due to TRAEs[e]
- Other key TRAEs:
  - 5 pts with rash (≤G 2)
  - No cases of ILD, ocular toxicities, or hyperglycemia
  - No G >2 peripheral neuropathy
- **No treatment-related deaths**

Median treatment cycles: 5 (range: 1-11); worst grade CTCAE reported; data cut-off for the interim analysis: 05Aug2019

[a]Prophylactic growth factor support was permitted per protocol, at the discretion of the investigator; [b]included SOC terms Blood and lymphatic system disorders and Investigations; [c]combined term includes neutropenia and neutrophil count decreased; [d]combined term includes leukopenia and WBC count decreased; [e]discontinuations due to TRAEs: G3 febrile neutropenia, G3 neutrophil count decreased; G4 leukopenia/G3 anemia/G3 thrombocytopenia.

Tagawa ST, et al. ESMO 2019. Abstract LBA55.

CTCAE, Common Toxicity Criteria for Adverse Events; G, grade; ILD, interstitial lung disease; SOC, system organ class; TRAE, treatment-related adverse event; WBC, white blood cell.

Patients With Objective Responses

Response Outcomes

Endpoint	Cohort 1 (N=35)
Median follow-up, mon	4.1
Patients continuing treatment, n (%)	20 (57)
ORR, n (%) [95% CI]	10 (29) [15, 46]
CR, n (%)	2 (6)
PR, n (%)	6 (17)
uPR pending confirmation,[a] n (%)	2 (6)
Median time to onset of response, mon (range)	1.5 (1.2, 2.8)

ORR in Patient Subgroups

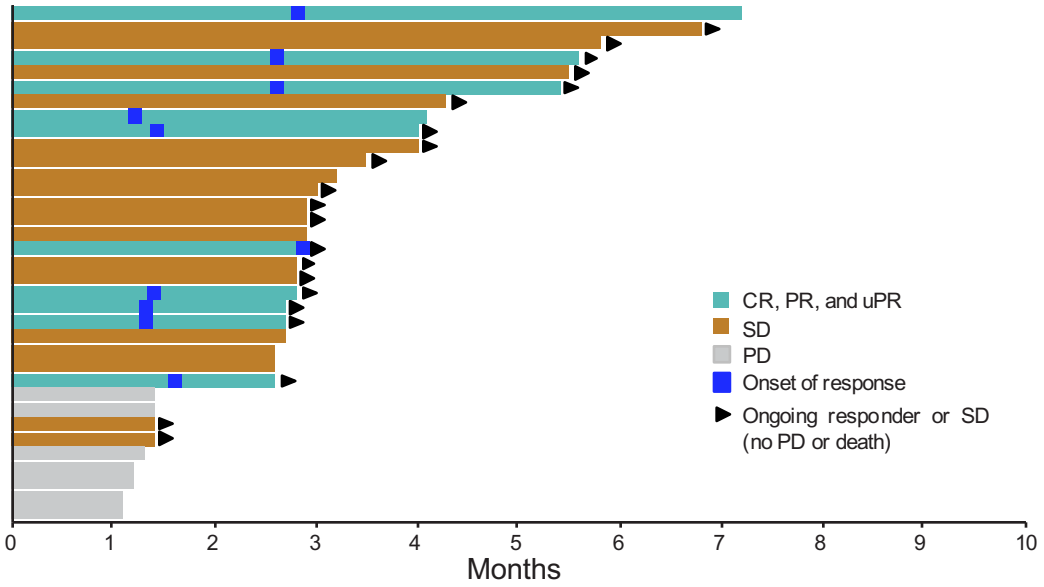
Category	Subgroup	ORR, % (n/N)
Overall	N/A	29 (10/35)
Age	<75	29 (8/28)
	≥75	29 (2/7)
ECOG PS	0	33 (5/15)
	1	25 (5/20)
No. prior anticancer regimens	2	18 (2/11)
	≥3	33 (8/24)
Visceral involvement at study entry	Yes	23 (5/22)
	Liver	25 (2/8)
	No	39 (5/13)
Bellmunt risk factors	0-1	35 (10/29)
	2-3	0 (0/6)

[a]Follow-up scan is pending.

Tagawa ST, et al. ESMO 2019. Abstract LBA55.

CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; PR, partial response; uPR, unconfirmed partial response.

Treatment Duration and Response (N=35)

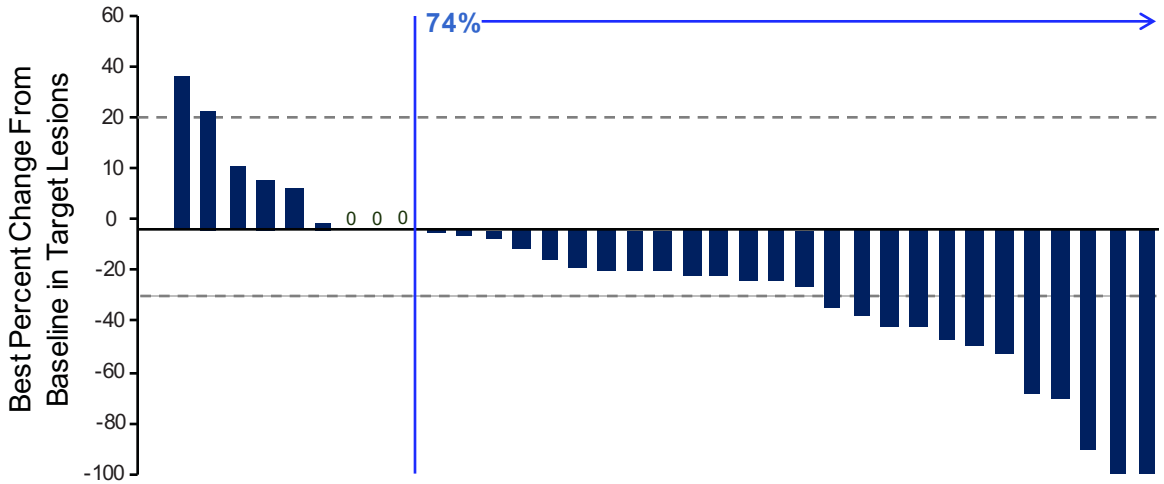


- 8 of 10 responders have ongoing response at data cutoff

Tagawa ST, et al. ESMO 2019. Abstract LBA55.

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; uPR, unconfirmed partial response.

74% of Patients Demonstrated a Reduction in Tumor Size



Tagawa ST, et al. ESMO 2019. Abstract LBA55.

Clinical Pearls in the Metastatic Setting

- Platinum-based chemotherapy and immune checkpoint inhibitors are SOC options
- Nephrostomy tube care
- Clinician vigilance and patient education keys to recognizing and managing irAEs
- FDA-approved erdafitnib and future antibody–drug conjugates can offer new treatment options
- ISTH guidance statement suggests use of LMWH for patients with VTE and high risk of bleeding – including patients at risk for bleeding from the GU tract
  - Edoxaban and rivaroxaban are specific DOACs that are acceptable alternatives if no drug-drug interactions; discuss with experts!

Khorana AA, et al. *J Thromb Haemost*. 2018;16:1891-4.

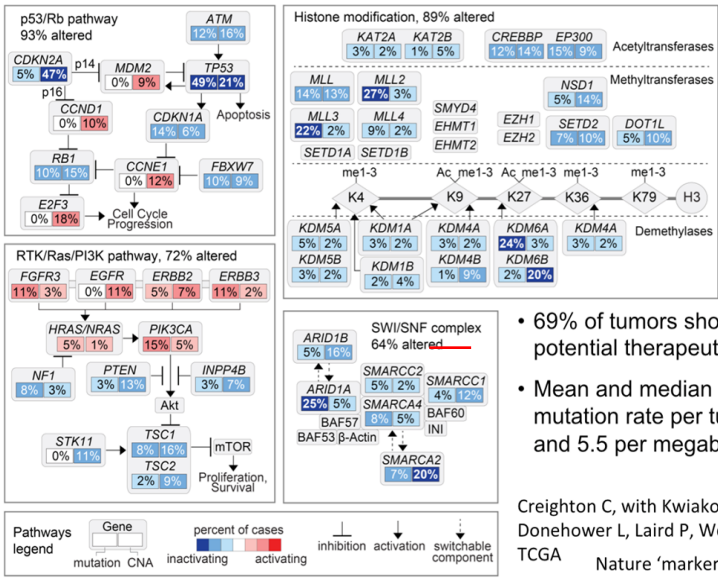
DOACs, direct oral anticoagulants; ISTH, International Society on Thrombosis and Haemostasis; LMWH. Low-molecular-weight heparin; VTE, venous thromboembolism.

TCGA Profiling

238 MIBC tumors assessed for:

- gene mutations
- DNA copy number variants
- mRNA/mi-RNA expression
- protein expression/phosphorylation
- DNA methylation
- transcript splicing
- gene fusion
- viral integration
- pathway perturbation
- clinical correlates
- histopathology

Altered Pathways in Urothelial Bladder Cancer (mutation/CNV)



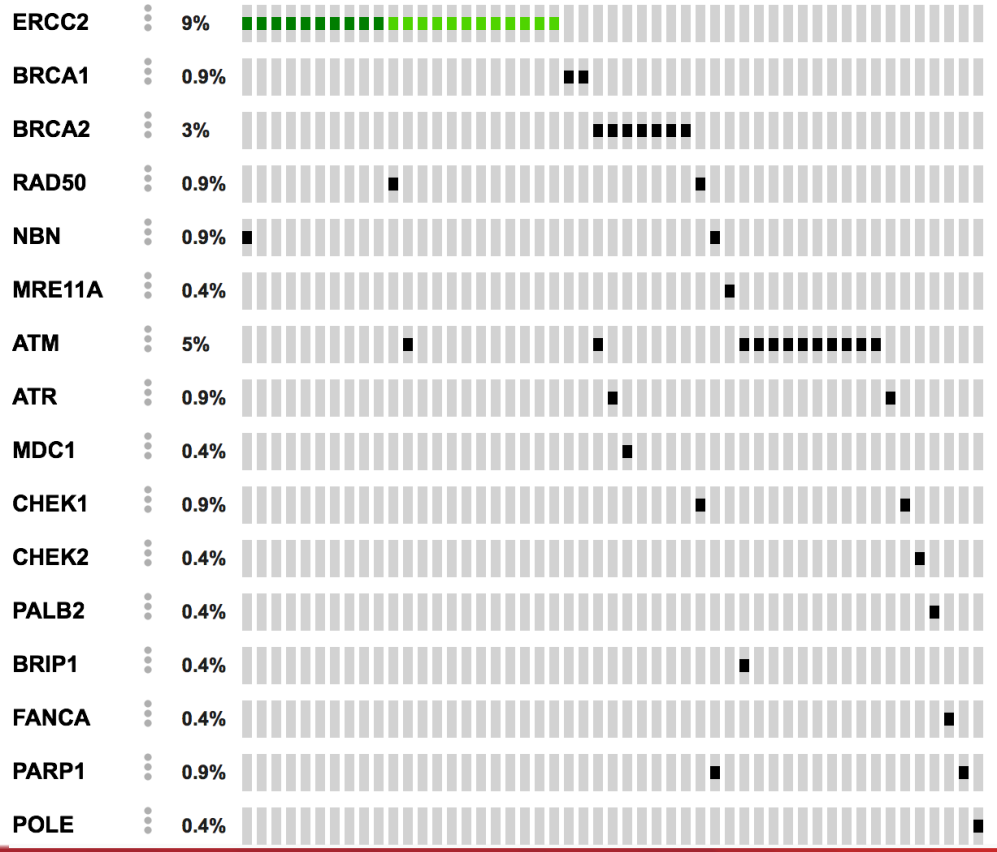
- 69% of tumors showed potential therapeutic targets
- Mean and median somatic mutation rate per tumor 7.7 and 5.5 per megabase

Creighton C, with Kwiakowski D, Donehower L, Laird P, Weinstein J, TCGA
Nature 'marker' paper, 2014

- 29 recurrently mutated genes
- 27 focal copy number variants [*CDKN2A* (p16) deletion 47%]
- 3 tumors with *FGFR3-TACC3* fusions
- Cell cycle regulation (93%), kinase/PI3-K signaling (72%), histone-modifiers (89%), SWI/SNF nucleosome remodeling complex (64%)
- PI3-K/AKT/mTOR (42%), RTK/RAS (44%) pathways: actionable?

Presented by: Petros Grivas, MD, PhD at ASCO 2014 Annual Meeting

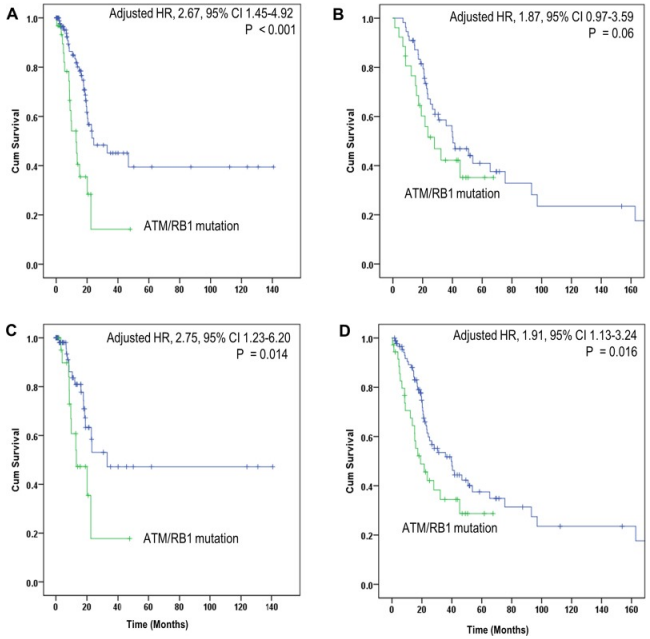
DDR Alterations in Urothelial Cancer



Cancer Genome Atlas Research Network. *Nature*. 2014;507:315-22; Robertson AG, et al. *Cell*. 2017;171:540-56.

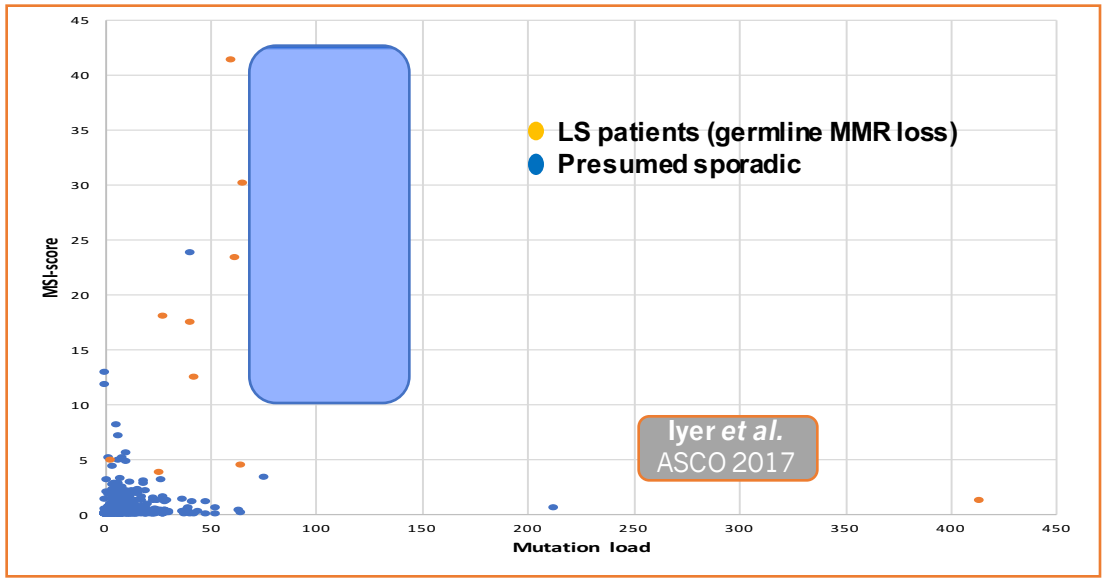
~22% incidence in TCGA

ATM and *Rb1* Mutations May Have Negative Prognostic Role in Advanced Urothelial Cancer



Yin M, et al. *Oncotarget.* 2018;9:16891-8.

Germline *MMR* Mutations in UC: Uncommon but Important and May Be Associated with HNPCC

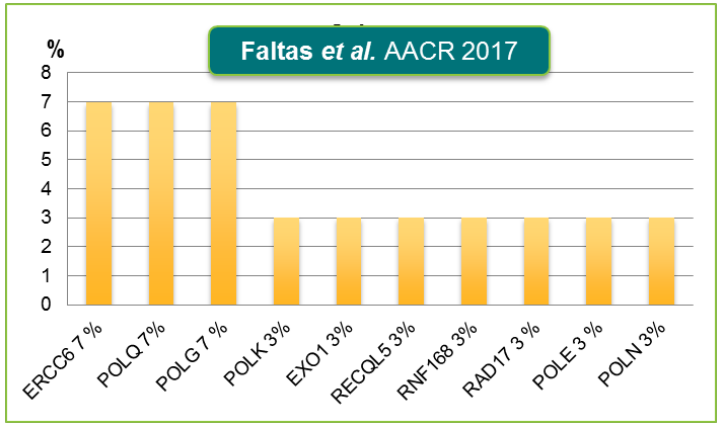


Iyer G, et al. ASCO 2017. Abstract 4511.

Courtesy: Bishoy Faltas

HNPCC, hereditary nonpolyposis colorectal cancer.

Germline DDR SNVs: Common in UC Patients



22% germline DDR mutations

MSK-IMPACT (targeted)
UTUC in 31% of cohort

48% germline DDR SNPs

EXaCT-1 (WES)
UTUC in 19% of cohort

Carlo MI, et al. ASCO 2017. Abstract 4510; Faltas BM, et al. AACR 2017. Abstract 1115.

Courtesy: **Bishoy Faltas**

Should We Test Patients with UC for Germline Mutations?

For all pts with upper tract UC:

- Yes

For pts with bladder UC:

- In the clinic, consider screening in presence of family history and younger patients, e.g. < 50 yo
  - Germline testing should trigger referral to genetic counselor
  - Need to integrate into clinic workflow and assess capacity
  - Implications for patient and broader family members

Conclusions

- Clinical trials or cisplatin-based chemotherapy are SOC for cisplatin-eligible pts
- FDA approval of PD-L1 (atezolizumab, durvalumab, avelumab) and PD-1 inhibitors (pembrolizumab, nivolumab); *level I evidence for pembrolizumab* in post-platinum setting
- Atezolizumab & pembrolizumab: similar level of evidence in 1st line cisplatin-ineligible setting (*for PD-L1+ or 'platinum-unfit' pts*)
- Erdafitinib received accelerated approval for platinum-resistant advanced bladder cancer with *FGFR2/3* alterations (Phase III trial ongoing); other FGFRi and targeted Tx in clinical trials; variable biomarkers for patient selection
- Several Phase III 1st line trials and switch maintenance trials (Phase II pembrolizumab vs placebo; Phase III avelumab vs observation) will help define the optimal combos / sequences of chemoTx and IO agents
- Need for biomarkers to select right treatment for right patient at right time

FGFRi, fibroblast growth factor receptor inhibitor.

Q&A

Improving Outcomes for Patients With Advanced Urothelial Carcinoma of the Bladder

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Twitter: @PGrivasMDPhD

Thank you for joining us!

Please complete your evaluation.