



# Debate: Neoadjuvant vs. Adjuvant Chemotherapy in Localized Upper Tract Urothelial Cancer

## *Neoadjuvant*

Jacqueline T. Brown, MD

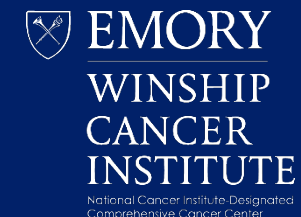
Assistant Professor

Genitourinary Medical Oncology

2022 Debates and Didactics in Hematology and Oncology

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# DISCLOSURES

**None**

# UPPER TRACT UROTHELIAL CARCINOMA (UTUC) AT A GLANCE

- UTUC anatomically denotes involvement of the renal pelvis, calyces or ureters
- Rare but aggressive disease
  - From SEER data, 5-year cancer specific mortality is 21% (pT2), 35% (pT3) and 59% (pT4)
- Treatment depends on risk stratification

Low risk
<ul style="list-style-type: none"><li>• Low grade on biopsy</li><li>• Negative cytology</li><li>• Unifocal</li><li>• ≤ 1 cm tumor size</li><li>• Hydronephrosis absent</li><li>• CTU without findings of invasive disease</li></ul>

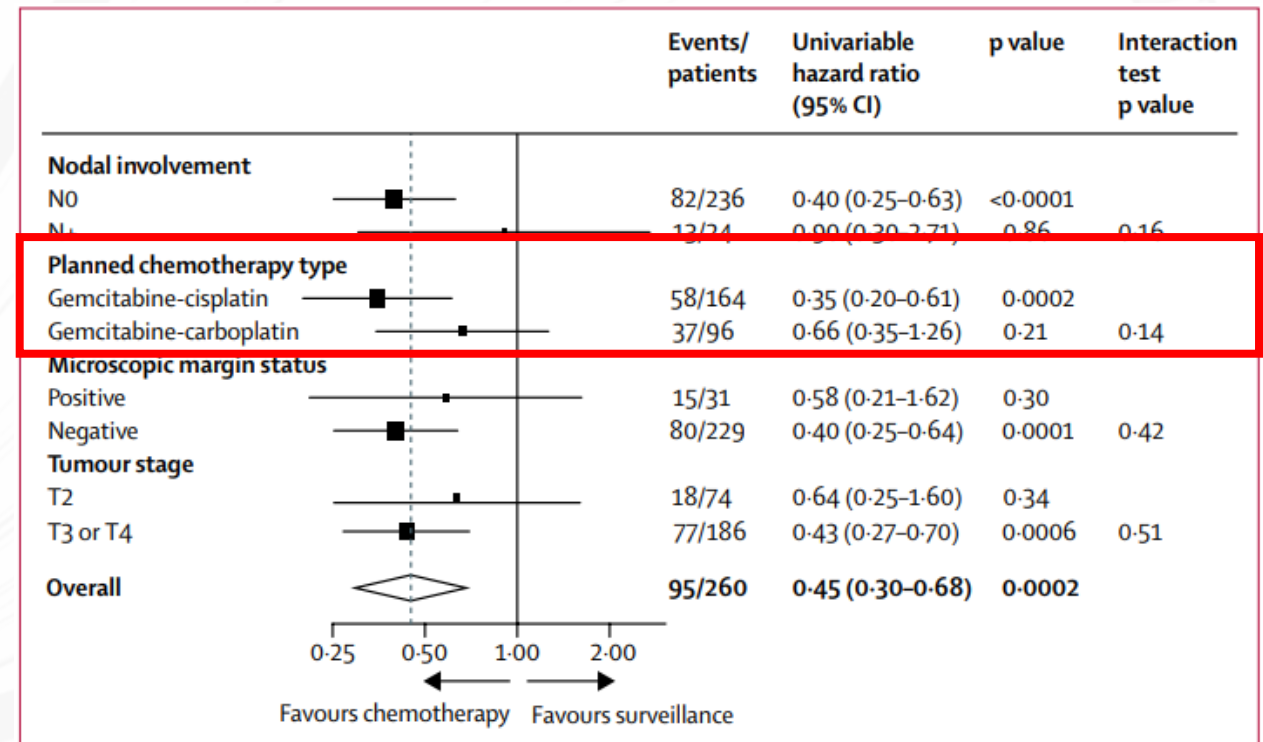
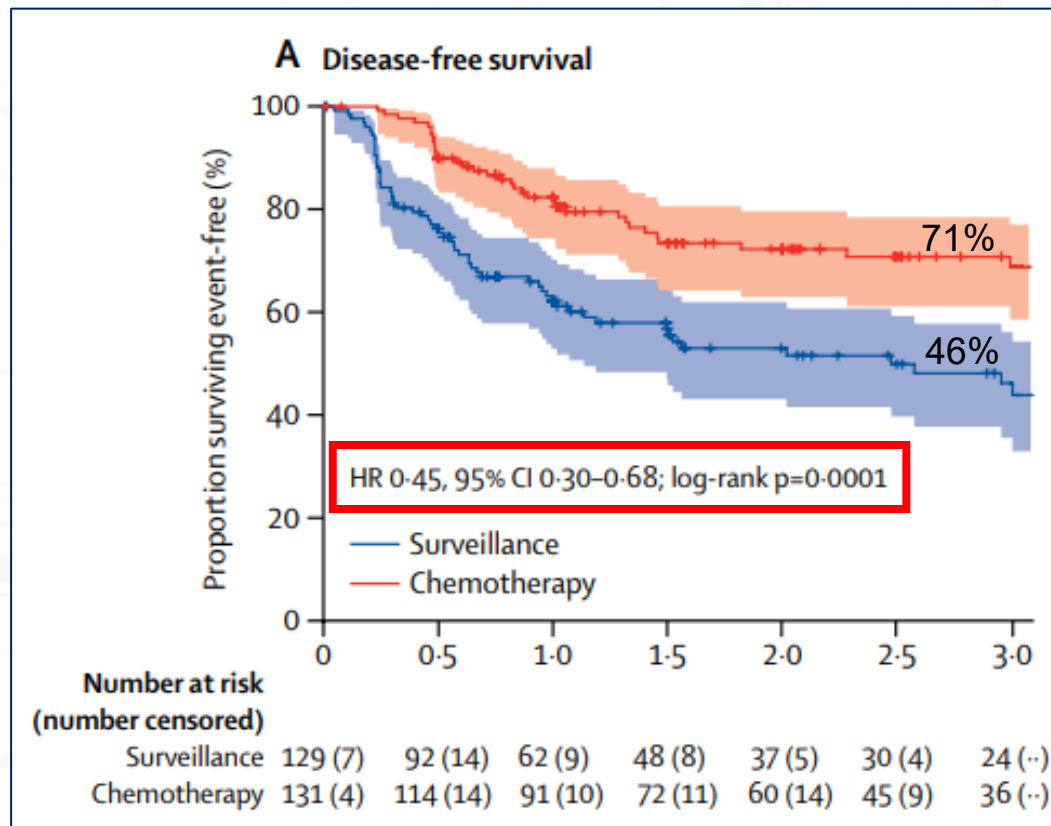
High risk
<ul style="list-style-type: none"><li>• High grade on biopsy</li><li>• Positive/HG cytology</li><li>• Multifocal</li><li>• Unknown</li><li>• Hydronephrosis present</li><li>• CTU with parenchymal/fat invasion, LAD</li></ul>

Amin et al. (2015) and Roupret et al. (2014)

- **Gold standard for high-risk disease is radical nephroureterectomy (RNU) with excision of bladder cuff and regional lymphadenectomy**

# PERIOPERATIVE CHEMOTHERAPY IS EFFECTIVE IN UTUC...

- POUT trial showed benefit of adjuvant platinum-based chemotherapy in UTUC<sup>1</sup>
  - Greatest benefit in patients who received cisplatin



<sup>1</sup>Birtle et al. (2020). Lancet 398(10232): 1268-1277.





**...IF YOU CAN GIVE IT**

# CISPLATIN INELIGIBILITY PER GALSKY CRITERIA (2011)

## Performance status

- ECOG  $\geq 2$
- KPS  $\leq 60-70\%$

## Renal function

- CrCl  $< 60$  mL/min

## Hearing

- CTCAE grade  $\geq 2$

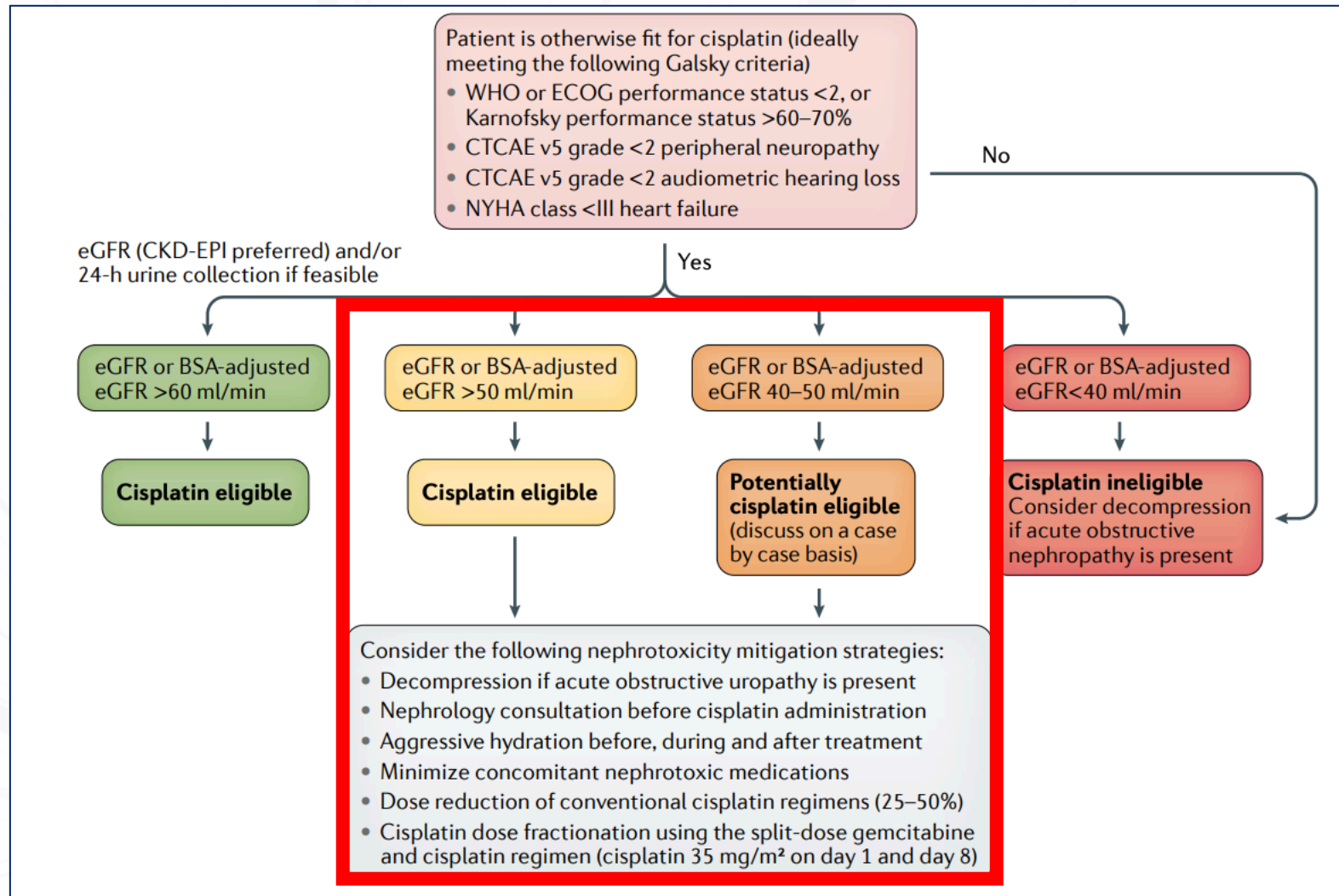
## Neuropathy

- CTCAE grade  $\geq 2$

## Cardiac function

- NYHA class  $\geq III$

# ACKNOWLEDGEMENT OF CISPLATIN ELIGIBILITY IN THE REAL WORLD



# IMPLICATION OF RNU ON RENAL FUNCTION

- *RNU involves removal of a renal unit*
  - In a population enriched for male sex, significant smoking history and medical comorbidities like chronic kidney disease
- Renal function examined in 118 patients with UTUC<sup>1</sup>
  - Pre-operative GFR 58.4
  - CKD stage 0-1 (12%), II (37%), IIIA (29%), IIIB (14%), IV (6%) and V (3%)
- Analysis of 666 patients treated with RNU for UTUC<sup>2</sup>
  - eGFR decreased by 18.2% after RNU

GFR ≥ 60

GFR ≥ 45

Pre-op

37%\*

72%\*

Post-op

16%\*

52%\*

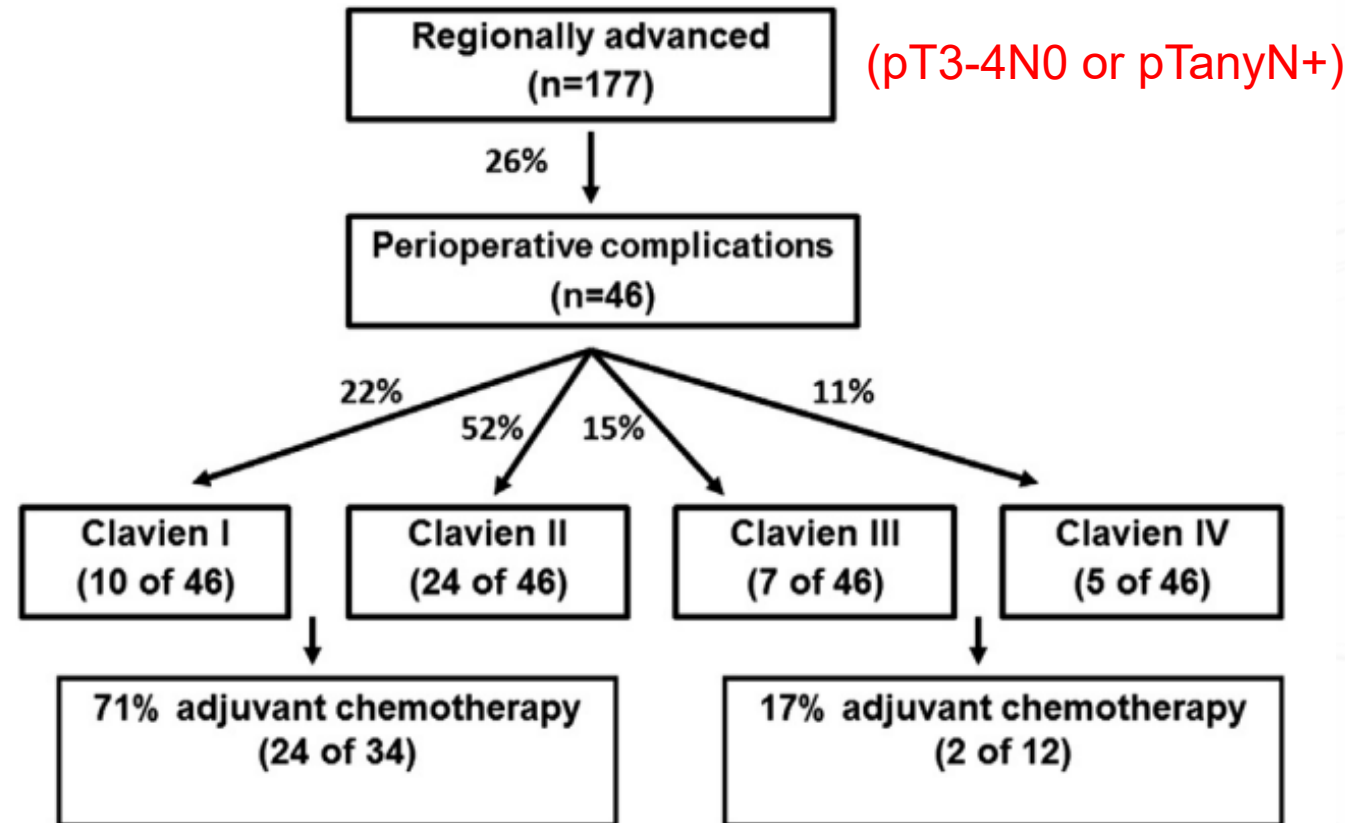
\* P<0.001

<sup>1</sup>Singla et al. (2016). Urology 96: 44-53., <sup>2</sup>Xylinas et al. (2013); BJU Int 112(3): 453-61.



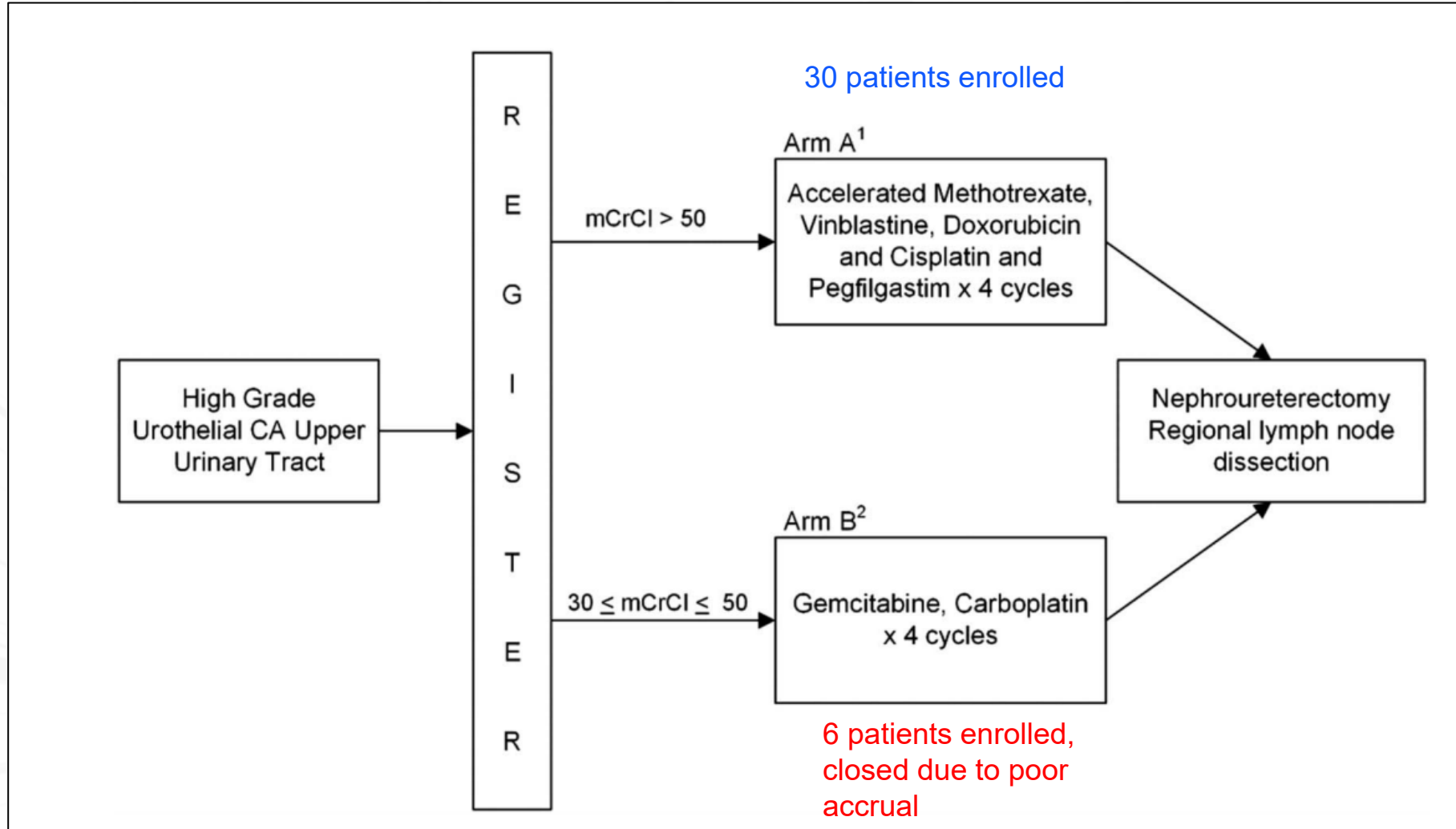
# PERIOPERATIVE COMPLICATIONS OF RNU

- Less morbid compared to radical cystectomy, but not benign



Only 31% went on to receive adjuvant chemotherapy

# ECOG-ACRIN 8141: PHASE II TRIAL OF NAC FOLLOWED BY SURGERY IN PATIENTS WITH HG UTUC



# EA 8141

## Primary endpoint: pCR

- ypT0N0 rate in ddMVAC arm: 4/29 patients (14%, 90% CI 4.9-28.8)
  - ≤ ypT1 rate: 18/29 (62%)
  - Zero patients with PD at end of chemotherapy

## Therapy completed

- Median of 4 chemotherapy cycles were received in each arm
- 24/30 patients (80%) completed all 4 ddMVAC cycles
- 5/6 (83%) completed all 4 gem/carbo cycles



POUT adjuvant trial:

- 68% successfully completed the 4 planned chemotherapy cycles
- 58% of those who started on gem/cis completed 4 cycles

## Impact on renal function

Arm	Baseline		After NAC		Postop
1 (aMVAC):					
No. measured	30		30		29
Median ml/min CrCl (range)	82.0 (53.7–170.0)		75.5 (23.6–203.0)		48.0 (25.9–173.4)
No. CrCl less than 60 ml/min	2		6		20
% CrCl less than 60 ml/min (90% CI)	6.7 (1.2–19.5)		20.0 (9.1–35.7)		69.0 (52.1–82.8)
No. CrCl less than 30 ml/min	0		1		2
% CrCl less than 30 ml/min (90% CI)	0.0 (0.0–9.5)		3.3 (0.2–14.9)		6.9 (1.2–20.2)
Median % change from baseline (range)	—		−1.4 (−64.5–71.1)		−40.8 (−61.8–17.2)

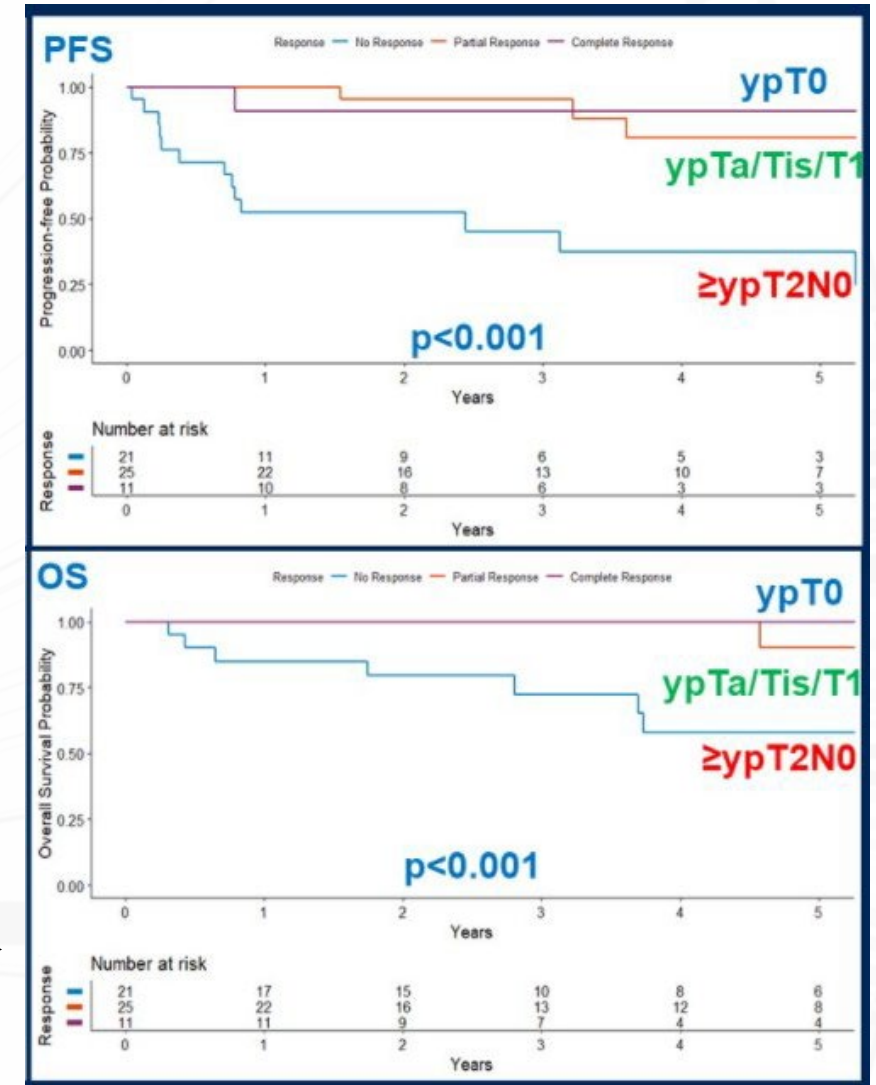
Margulis et al. (2020). J Urol 203(4): 690-698.

## GU ASCO 2022: NAC WITH GEM/CIS IN HG UTUC (YIP ET AL)

- Multicenter, prospective, single-arm Phase II design
- Key eligibility criteria:
  - High-risk UTUC as evidenced by HG biopsy and/or imaging (cT2-T4a) and + cytology
  - eGFR  $\geq$  55 ml/min
- 57 patients enrolled, received 4 cycles of **split-dose gemcitabine/cisplatin** followed by extirpative surgery
- 89% of patients underwent at least 3 cycles
  - All patients underwent surgery (median 7 weeks)

# YIP ET AL (GU ASCO 2022): ONCOLOGIC OUTCOMES BY PATHOLOGIC RESPONSE

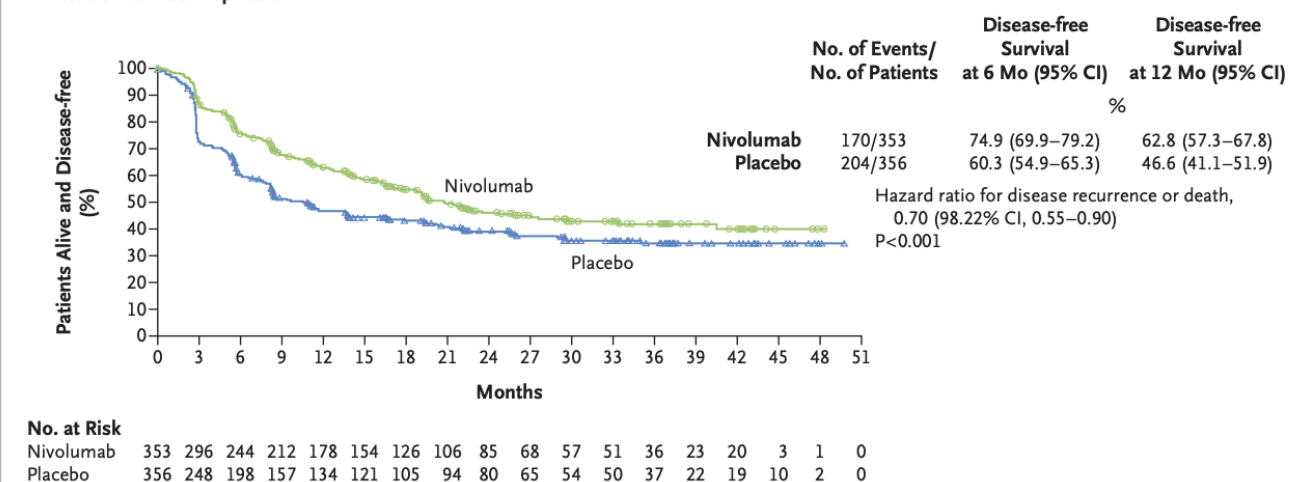
- Pathologic response rate (<ypT2N0): 36/57 (62%)
  - Complete response rate (ypT0): 11/57 (19%)
  - Progression prior to surgery: 0%
- Median follow-up 3.1 years
  - 2-year PFS 78%, OS 93%
  - 5-year PFS 65%, OS 79%
  - Improved compared to POUT (but beware of across trial comparisons)
- Pathologic response corresponds to PFS and OS →
  - *In vivo* chemosensitivity testing



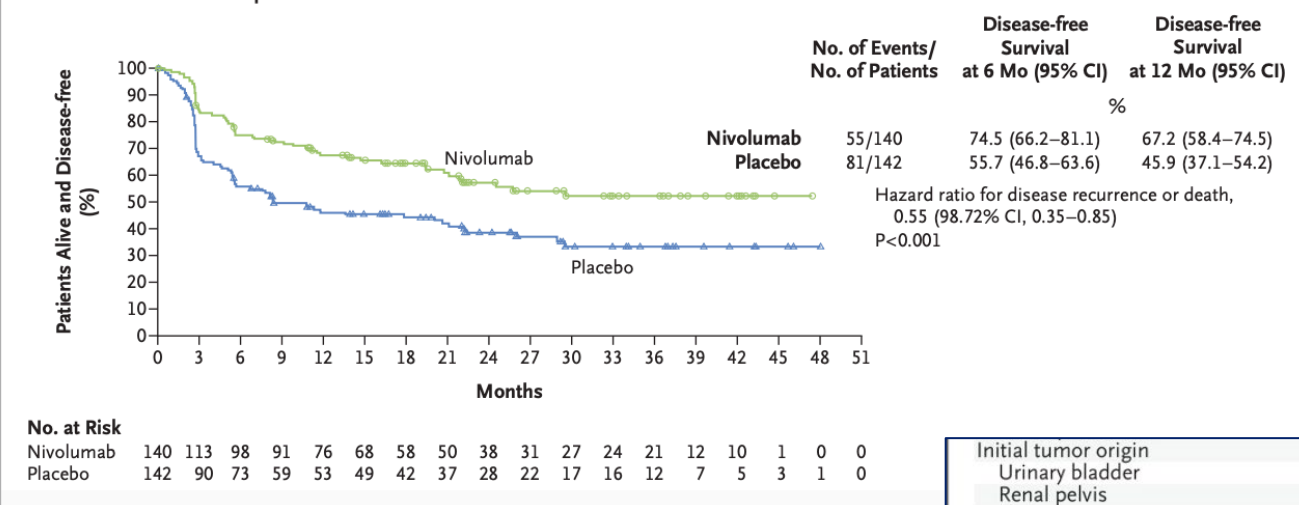


# ADJUVANT LANDSCAPE MORE COMPLEX AFTER CHECKMATE-274

**A Intention-to-Treat Population**



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

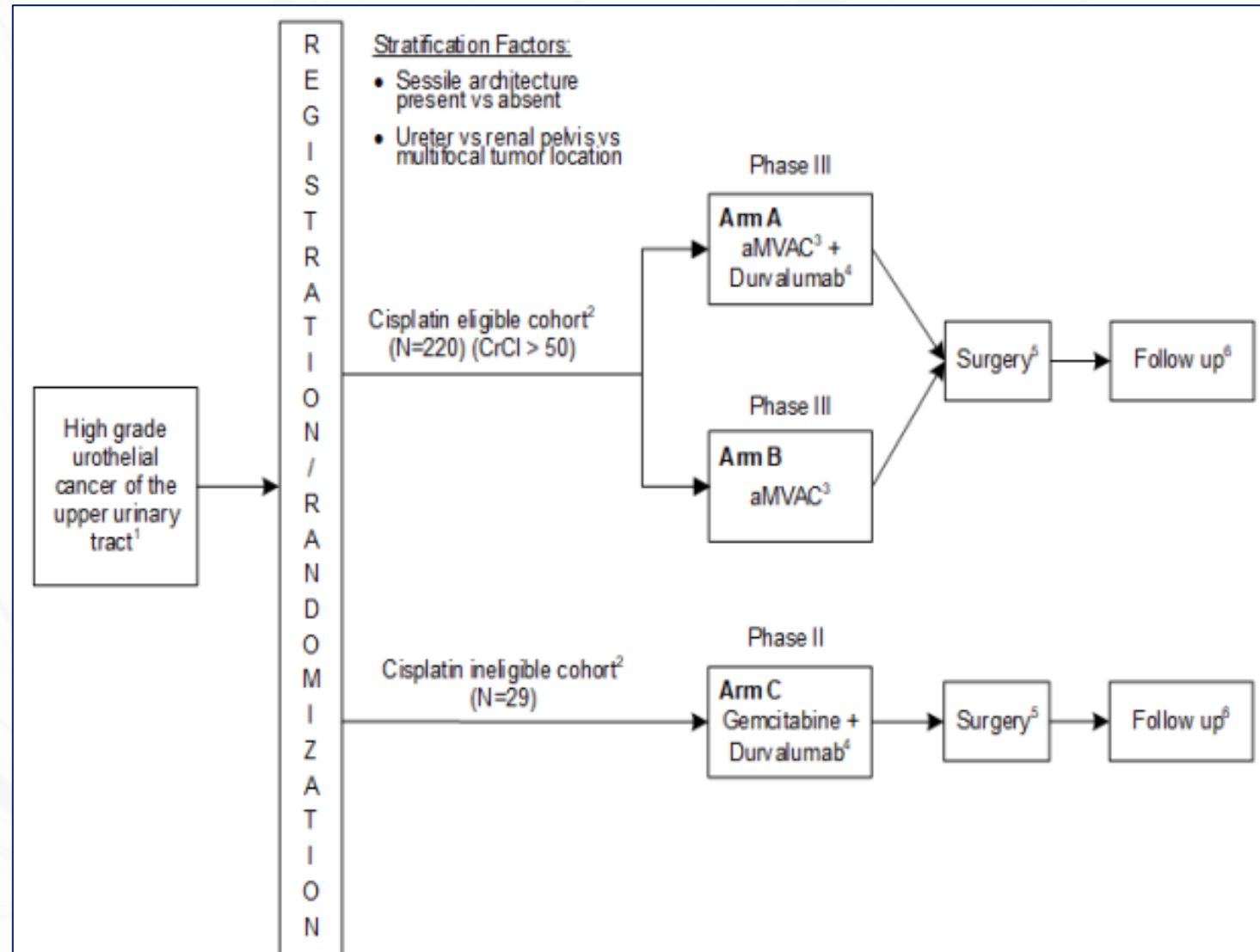


- Adjuvant nivolumab showed DFS improvement over placebo in urothelial carcinoma
- UTUC represented ~ 20%
- UTUC did not benefit to the same degree in subgroup analysis as lower tract disease
- Still a consideration if PD-L1 elevated in high-risk disease after surgery
- Administered within 90 days of surgery

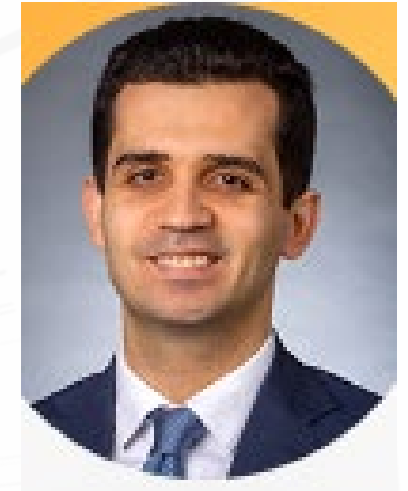
Ordering of adjuvant therapies more complicated in high-risk patients if neoadjuvant chemotherapy was not administered

Initial tumor origin	560	129/279	166/281	0.62 (0.49–0.78)
Urinary bladder	96	24/44	25/52	1.23 (0.67–2.23)
Renal pelvis	53	17/30	13/23	1.56 (0.70–3.48)
Ureter				
Minor histologic variants				

# EA8192: PHASE II/III TRIAL OF DURVALUMAB + CHEMO IN HG UTUC PRIOR TO RNU



Emory PI:



## TAKE-HOME POINTS

- UTUC is a rare and aggressive disease that stage for stage has poorer outcomes compared to lower tract disease
- Radical nephroureterectomy is accompanied by both risk of perioperative complications and *promise* of decreased GFR
- There is prospective data supporting the use of neoadjuvant chemotherapy
- Adjuvant landscape now includes nivolumab which may have a role in patients with high-risk UTUC after surgery (especially with high PD-L1)
- EA8192 trial (ongoing) utilizes neoadjuvant chemotherapy +/- immunotherapy and may provide additional rationale for this approach
- **The best perioperative chemotherapy approach is the one your patient can actually receive**

**THANK YOU!**

[jacqueline.theresa.brown@emory.edu](mailto:jacqueline.theresa.brown@emory.edu)



**@jackiebrown\_MD**