

# Adjuvant treatment in localized upper tract urothelial cancer

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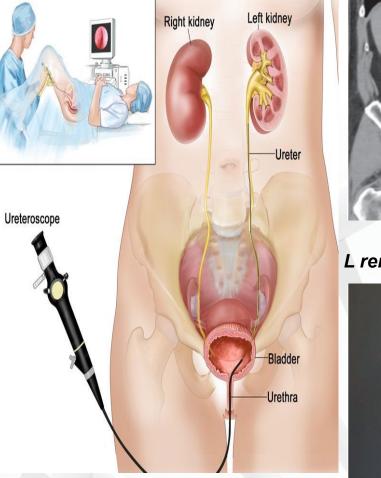


#### **Disclosures:**

#### Member of advisory board for Exelixis

#### Paid Participant in Case Discussion, AmerisourceBergen

## **Upper Tract Urothelial Cancer (UTUC): Rare and Difficult to Stage**







Tumor in L renal pelvis/promixal ureter



Papillary appearance of mass on ureteroscopy

**RARE 5-7% of urothelial cancer** 

**ELDERLY 73 y average age at Dx** 

## **BIOPSIES ARE SCANT**

- Technically difficult
- Low-grade vs. high-grade only

**LARGELY SUBOPTIMAL** preop staging:

- As low as 58.6 % (Vashistha et al. 2013)

- ≈ 70% in predictive models

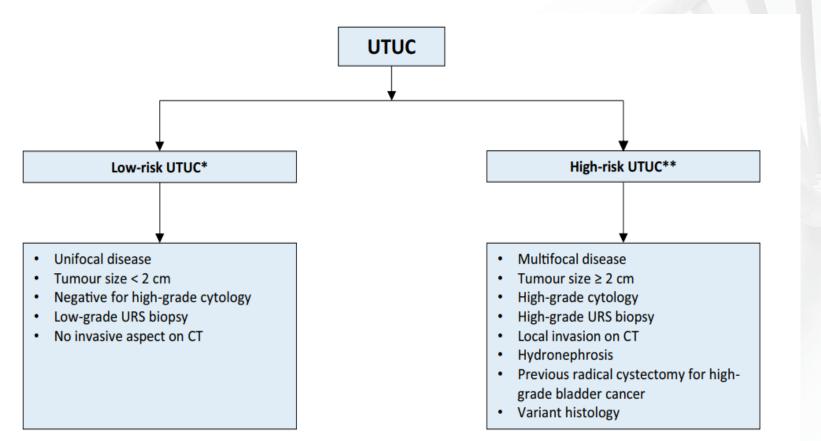
(Mbeutcha et al., 2016)

Images: NCI visual online; Olsen et al., 2022

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## UTUC tumor grade (and not invasion into urinary tract wall)

#### guides pre-operative evaluation



*CT* = computed tomography; *URS* = ureteroscopy; *UTUC* = upper urinary tract urothelial carcinoma.

\* All these factors need to be present.

\*\*Any of these factors need to be present.

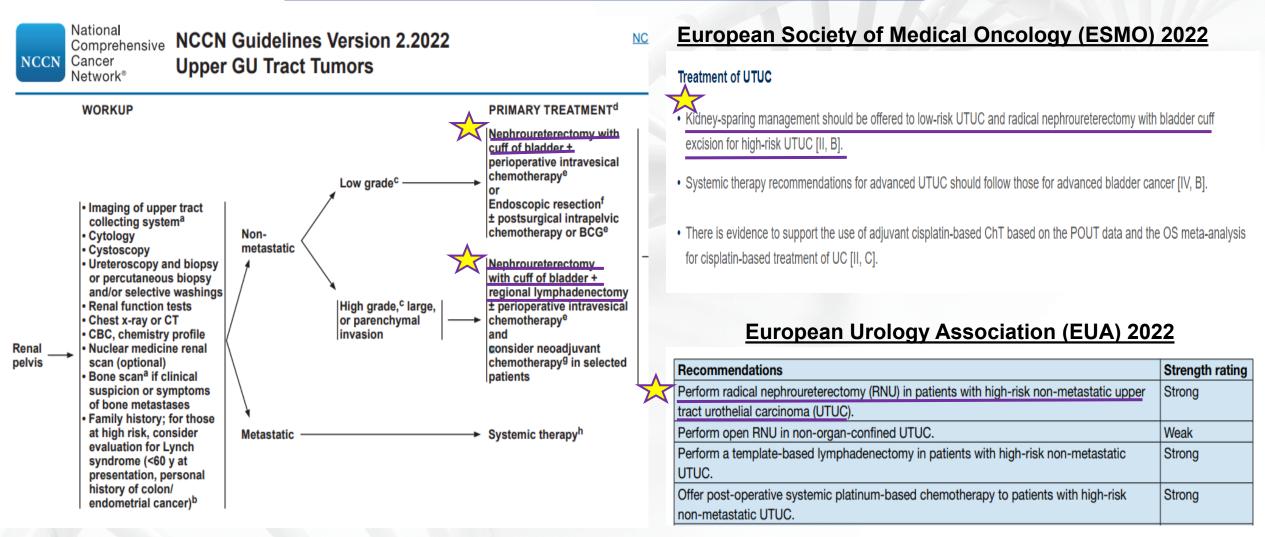
European Urology Association (EUA) guidelines 2022

Degree of muscle invasiveness is difficult to establish before definitive surgery

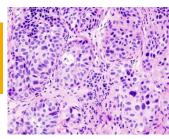


Flexible ureteroscope

#### <u>Upfront Radical Nephroureterectomy (RNU):</u> Standard of Care for Most Patients with UTUC



#### even if upstaging is common



# Urothelial Bladder Cancer and UTUC: share many features but are distinct diseases

	Bladder Cancer	UTUC
Published RCT	Over 100	1 ( <b>POUT</b> )
Molecular studies	TP53, RB1, ERBB2, and KDM6A	FGFR3, HRAS, and KMT2D
Microsatellite instability/ Aristolochic Acid Exposure	Very minor	Major role
Tissue for diagnosis	More available	Scant
Discordance between biopsy and surgical pathology	Lower	Higher
Level 1 data for chemotherapy perioperative setting	Neoadjuvant	Adjuvant only ( <b>POUT</b> )



- Singla N, Margulis V. Differences between Upper Tract Urothelial Carcinoma and Bladder Cancer. AUA News. 2021 - Adapted from Roupert, M (2019) with permission

## **Kidney function after RNU**

#### Preoperative predictors of renal function decline after radical nephroureterectomy for upper tract urothelial carcinoma

Matthew Kaag, Landon Trost\*, R. Houston Thompson\*, Ricardo Favaretto<sup>†</sup>, Vanessa Elliott, Shahrokh F. Shariat<sup>‡</sup>, Alexandra Maschino<sup>†</sup>, Emily Vertosick<sup>†</sup>, Jay D. Raman and Guido Dalbagni<sup>†</sup>

Penn State Hershey Medical Center, Hershey, PA, \*Mayo Clinic, Rochester, MN, †Memorial Sloan-Kettering Cancer Center, New York, NY, USA, and †Medical University of Vienna, Vienna, Austria

# Retrospective evaluation of 374 patients treated with RNU 1995-2010

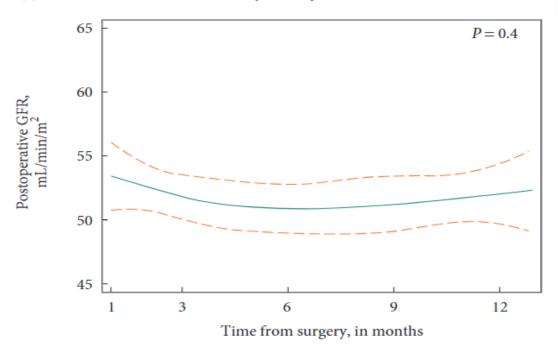
Baseline eGFR ≥60 (cisplatin-eligible)

**Outcome: eGFR 1-5 months after RNU** 

 $\rightarrow$  eGFR declined by 32%

→ post-RNU median eGFR 49 (early), 50 (later)

Fig. 1 Change in estimated GFR after radical nephroureterectomy for upper tract urothelial carcinoma (n = 198).



#### Good enough for cisplatin in clinical practice (fractionated approach if needed)

Carboplatin is an option for eGFR>30

**Neoadjuvant chemotherapy in UTUC** 

# "If one can, does it mean one should?"

#### The danger of overtreating patients is significant 5- year cancer-specific survival (CSS) based on pathological staging\* pT1 >90% pT2 70-80% pT3 50-55% pT4 0-35%

Extrapolation from bladder urothelial cancer treatment approach

### The advantages are theoretical

- in-vivo test of chemosensitivity
- Facilitate surgery
- Micrometastasis treatment

#### **RETROSPECTIVE + small Phase II data**

# Yet to be proven prospectively in a randomized trial

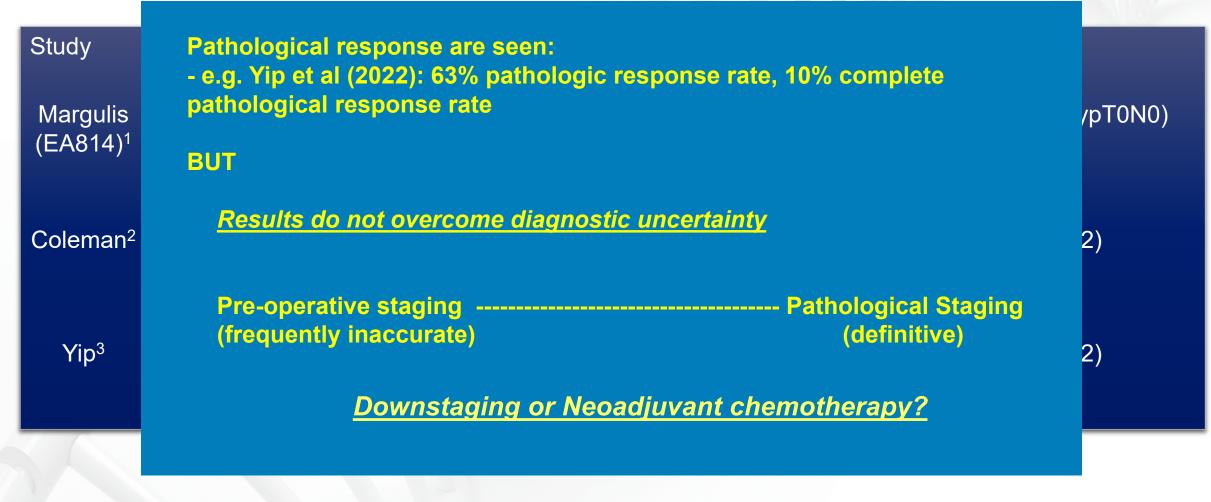
\*Olson K et al., Treatment of Upper Tract Urothelial Carcinoma, Springer Nature, 2022

# Prospective Data on Neoadjuvant Chemotherapy: Small, Non-Randomized Phase II, Level 2

Study	N	Regimen	Cr Clearance	Primary Endpoint
Margulis (EA814) <sup>1</sup>	29	Accelerated MVAC x 4 (Gemcitabine and Carboplatin if Cr clearance 30-50)	≥ 50	Pathological complete response (ypT0N0)
Coleman <sup>2</sup>	53	Gemcitabine and cisplatin (Days 1/8) x 4	≥ 55	Pathological response ( <pt2)< td=""></pt2)<>
Yip <sup>3</sup>	57	Gemcitabine and cisplatin (Days 1/8) x 4	≥ 55	Pathological response ( <pt2)< td=""></pt2)<>

1. Margulis. J Urol. 2020;203:690. 2. Coleman. AUA 2019. LBA-17. 3. Yip ASCO GU Abstract 440

## Prospective Data on Neoadjuvant Chemotherapy: Small, Non-Randomized Phase II, Level 2



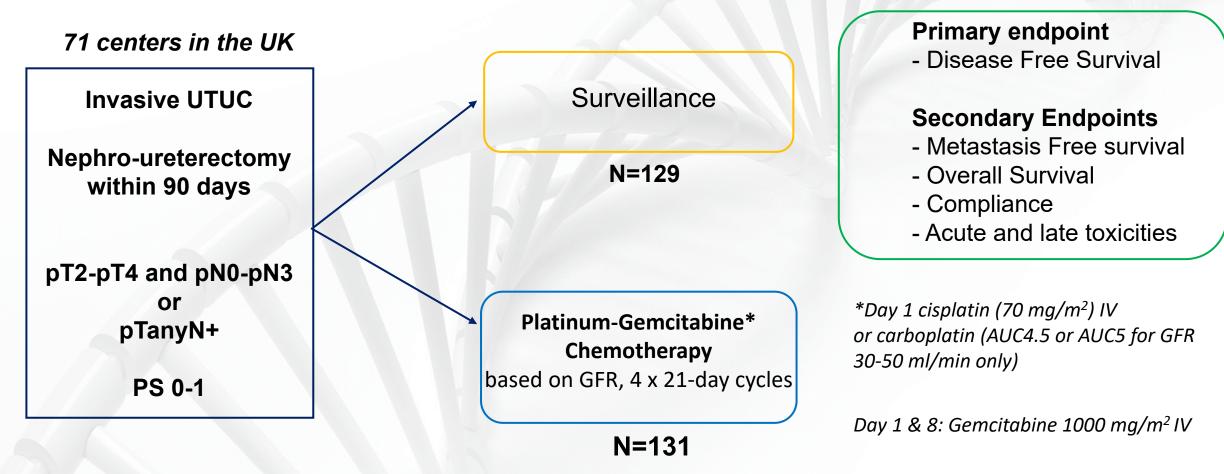
Britle A, Adjuvant chemotherapy in UTUC, EUA 2022

# Level 1 data for adjuvant chemotherapy in upper tract urothelial cancer

# **POUT PHASE III TRIAL**

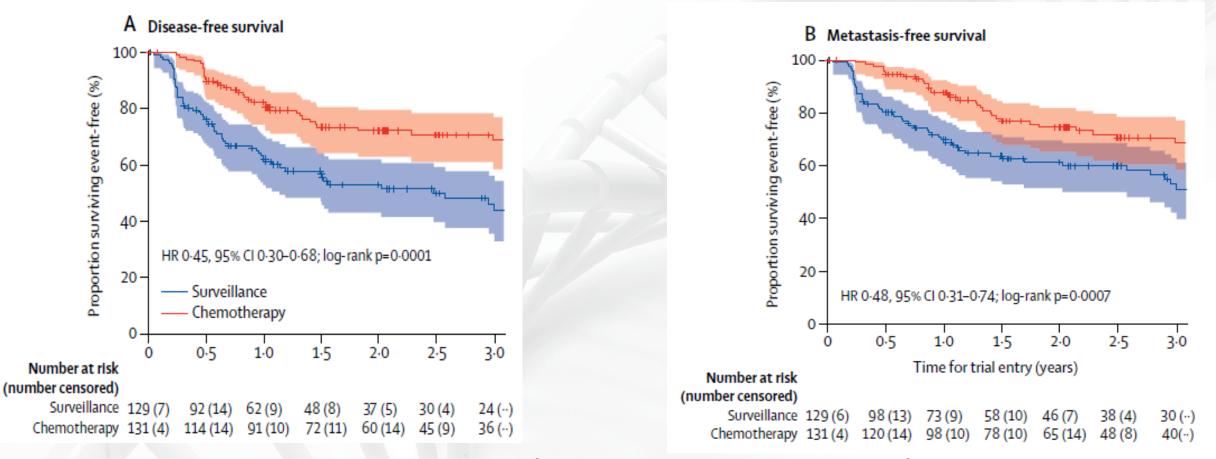
#### **POUT TRIAL:**

Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a <u>phase 3</u>, open-label, randomized controlled trial



#### First dedicated randomized phase 3 trial of perioperative chemotherapy for UTUC

#### POUT CLOSED EARLY due to strong efficacy signal with adjuvant chemotherapy



DFS hazard ratio 0.45, (95% CI 0.30-0.68; p=0.0001)

#### 3-year DFS 71% (95% CI 61–78) for chemotherapy and 46% (36–56) for surveillance

Birtle, A et al. "Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial." The Lancet (2020)

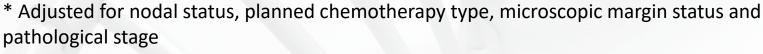
# **POUT showed overall survival improvement**

#### **Overall Survival**

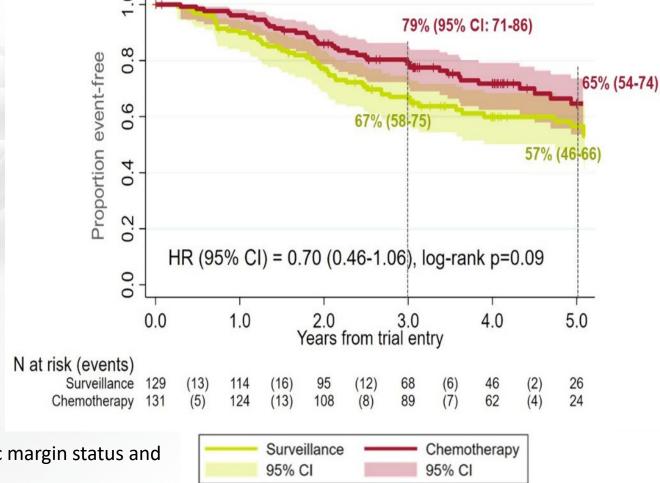
#### OS improvement: HR 0.70 (NS)

Adjusted HR\*: 0.77 (95% CI: 0.50-1.17, *P* = 0.21)

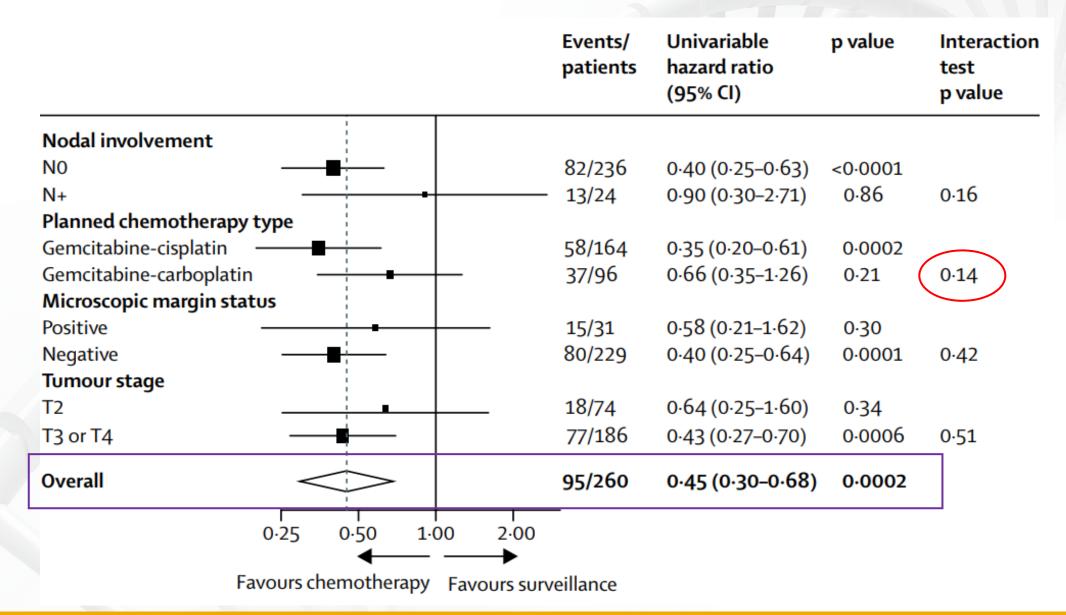
- Study not powered for OS: RARE CANCER, would require very large study.
- Met primary endpoint (DFS)
  → trial closed early
  (261 out of 345 planned)



Birtle A et al., 2021 GU ASCO Hoffman-Censits 2021 Perioperative Systemic Therapy for High-Grade, Invasive UTUC

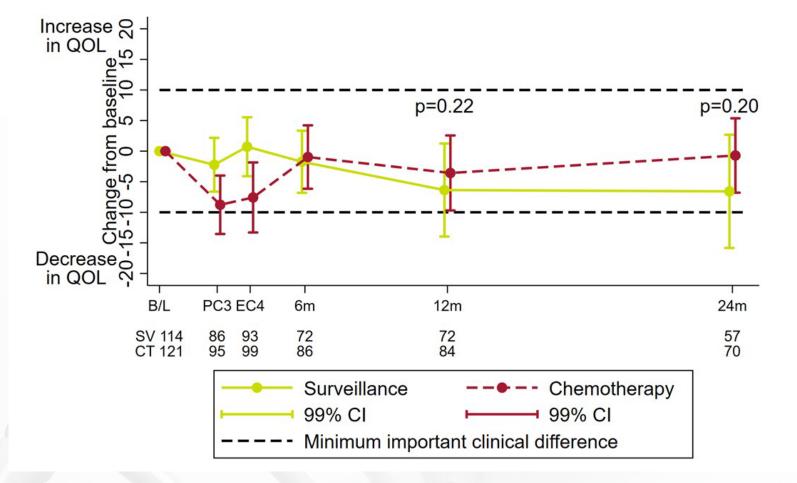


#### POUT: Benefit of adjuvant platinum-gemcitabine in UTUC is across groups



## Adjuvant platinum-gemcitabine is safe and effective in UTUC

EORTC QLQ-C30 Global Health Status/Quality of Life



No evidence of long-term toxicity with chemotherapy

Birtle, A et al. "Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial." The Lancet (2020)

# Real-life use of adjuvant platinum-gemcitabine in UTUC

75 year old man with intermittent hematuria and flank pain \*

Past medical history: hypertension, diabetes, LE DVT

Baseline GFR>60

High-grade UTUC with right renal pelvis mass



\*Details were adjusted to preserve confidentiality

Upfront right nephro-ureterectomy

Surgical staging pT2N0

**Post-operative GFR 55** 

- Presenting symptoms were immediately managed
- ✓ No delay in definitive treatment
- Less concern for overtreatment
- ✓ Chemotherapy discussion based on true/final pathology
- ✓ Better informed decision on balance of risk/benefits

→ 4 cycles of cisplatin/gemcitabine per POUT, followed by active surveillance

# Adjuvant nivolumab in high-risk UTUC: data from Checkmate 274

Subgroup	No. of Patients	Nivolumab	Placebo	Hazard Ratio for Disease Recurr	ence or Death (95% C
no. of events/no. of patients				•	
Initial tumor origin		-1 -	-1-		
Urinary bladder	560	129/279	166/281		0.62 (0.49-0.78
Renal pelvis	96	24/44	25/52		1.23 (0.67-2.23
Ureter	53	17/30	13/23		1.56 (0.70-3.48
viinor histologic variants			,		
Yes	286	70/145	76/141		0.73 (0.53-1.02
No	423	100/208	128/215	<b>_</b> _	0.69 (0.53-0.90
Nodal status			•		•
N+	335	95/167	116/168	_ <b>_</b>	0.64 (0.48-0.85
N0 or NX with <10 nodes removed	193	46/94	50/99		0.85 (0.57-1.28
N0 with ≥10 nodes removed	179	29/91	37/88		0.67 (0.41–1.10
Not reported	2	0/1	1/1		NA
Pathological tumor stage		•	•		
pT0-2	166	35/80	40/86		0.88 (0.54-1.43
pT3	410	97/206	120/204		0.63 (0.48–0.82
pT4a	119	36/57	40/62		0.77 (0.47–1.25
Other	12	1/9	3/3		` NA
Not reported	2	1/1	1/1		NA
Pathological tumor stage and nodal status		,	,		
pT2N-	54	6/25	10/29	← ●	0.54 (0.16-1.86
pT3,4N-	317	68/158	78/159		0.75 (0.54-1.05
pT0-4N1	143	39/71	45/72		0.74 (0.47-1.15
pT0-4N2,3	192	56/96	71/96	:	0.57 (0.40-0.83
pTisN-	1	0/1	Ó		NA
Not reported	2	1/2	0		NA
Previous neoadjuvant cisplatin therapy		-/-			
Yes	308	70/153	100/155	<b>_</b>	0.52 (0.38-0.71
No	401	100/200	104/201		0.92 (0.69-1.21
ny previous neoadjuvant systemic therap					0.52 (0.05 1.121
Yes	319	75/160	104/159		0.53 (0.39-0.72
No	390	95/193	100/197		0.91 (0.69-1.21
Days from surgery to randomization					0.52 (0.05 1.12
0-30	5	0/2	2/3		NA
>30-60	149	43/79	40/70		0.66 (0.40-1.06
>60-90	342	78/165	93/177		0.76 (0.55–1.03
>90-120	198	47/103	62/95		0.67 (0.44-1.00
>120	15	2/4	7/11	-	NA
		-/ ·	.,		
				0.25 0.50 1.00 2.00	4.00
				<u> </u>	→
				Nivolumab Better Placebo Bett	or

↓ benefit for UTUC from adjuvant nivolumab compared with bladder tumors

#### OS data unavailable

#### Would not recommend nivolumab yet in this setting

Bajorin DF et al. N Engl J Med 2021;384:2102-2114

#### Adjuvant Phase III trials of immunotherapy and targeted therapy in high-risk urothelial cancer after surgery

AMBASSADOR TRIAL NCT03244384 Adjuvant pembrolizumab vs. observation	Completed accrual
<b>Checkmate 274</b> <i>NCT02632409</i> Adjuvant nivolumab vs. placebo	Completed accrual Further analysis planned for effect on UTUC subgroup
<b>PROOF 302</b> <i>NCT04197986</i> Adjuvant Infigratinib (FGFR1-3 inhibitor) vs placebo in patients with actionable FGFR3 alterations	Enrolling

Subgroup analyses for high-risk UTUC patients are anticipated

NOT ready for prime time

#### TAKE HOME MESSAGES

 Upfront radical nephro-ureterectomy is the standard of care in most patients with localized UTUC

✓ Adjuvant therapy based on POUT Phase III data: the standard to beat

→ Accurate pathological staging + Level 1 evidence allow communicating risk and benefit of adjuvant platinum-gemcitabine Tx

→ UTUC is rare: DFS is an appropriate primary endpoint

→ Can substitute cisplatin for carboplatin when needed

# THANK YOU

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# **Questions?**

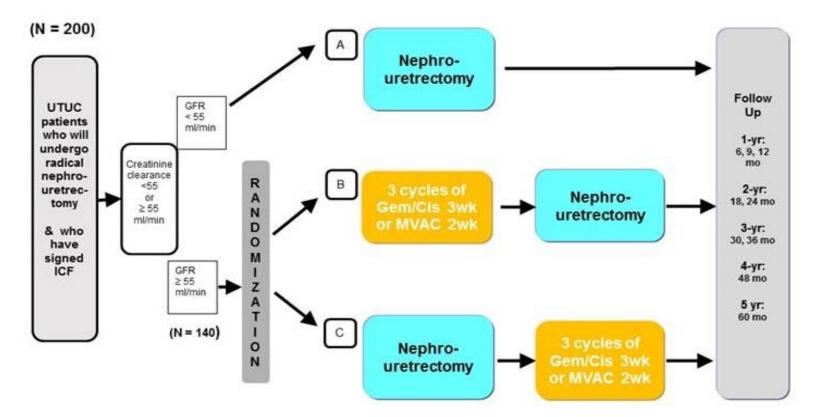
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# Supplementary



Feasibility of Neo-adjuvant Versus Adjuvant Chemotherapy in Upper Tract Urothelial Carcinoma: A Feasibility Phase II Randomized Clinical Trial (URANUS)

# **URANUS DESIGN**



ClinicalTrials.gov #: NCT02969083