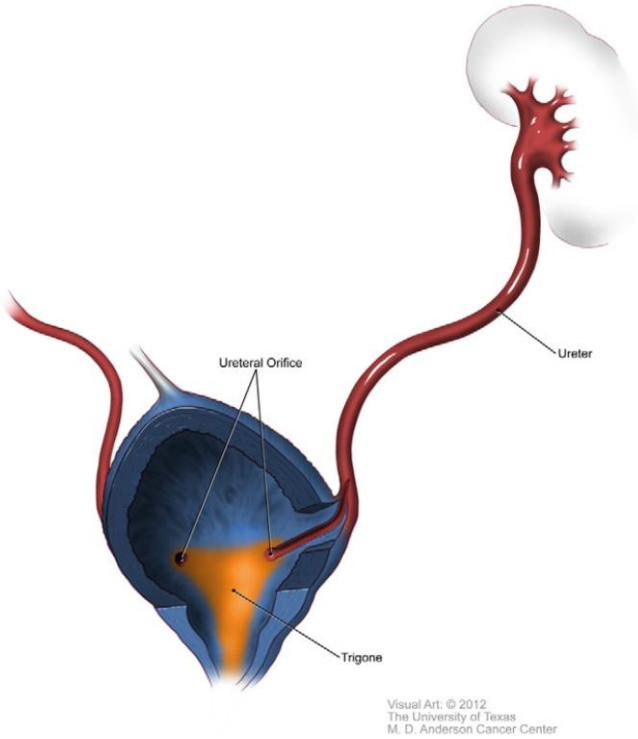
SIU UPDATES

ASCO GU

ASCO GENITOURINARY CANCER SYMPOSIUM

Treatment of high-risk UTUC



Andrea Necchi

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European Association of Urology – Research Foundation

eaurf Research Foundation

Fondazione IRCCS Istituto Nazionale dei Tumori

Sistema Socio Sanitario

Regione Lombardia

Disclosures

Andrea Necchi:

Consulting or Advisory Role: Company: Roche, Bayer, Merck & Co. Inc., Astra Zeneca, Janssen, Astellas/Seattle Genetics, Clovis Oncology, BioClin Therapeutics

Travel, Accommodations, Expenses: Company: Roche, Merck & Co. Inc., Janssen, PeerVoice

Research Funding (Institution): Company: Merck & Co. Inc., Astra Zeneca

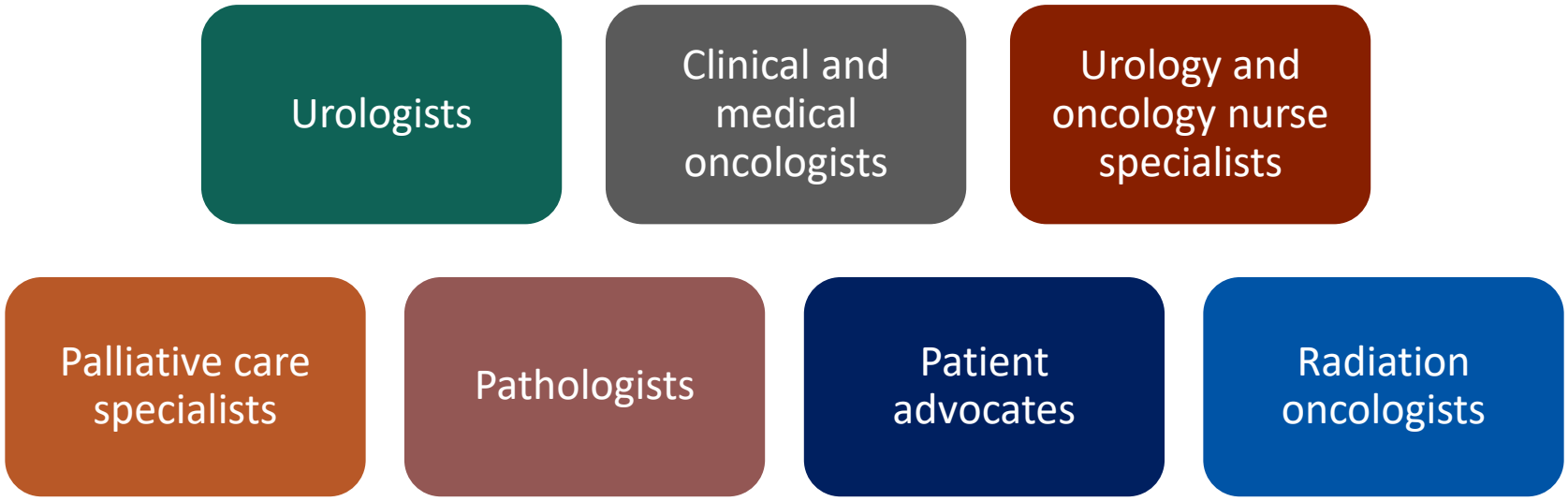
Thomas Powles:

Honoraria: Bristol-Myers Squibb, Merck, Roche/Genentech

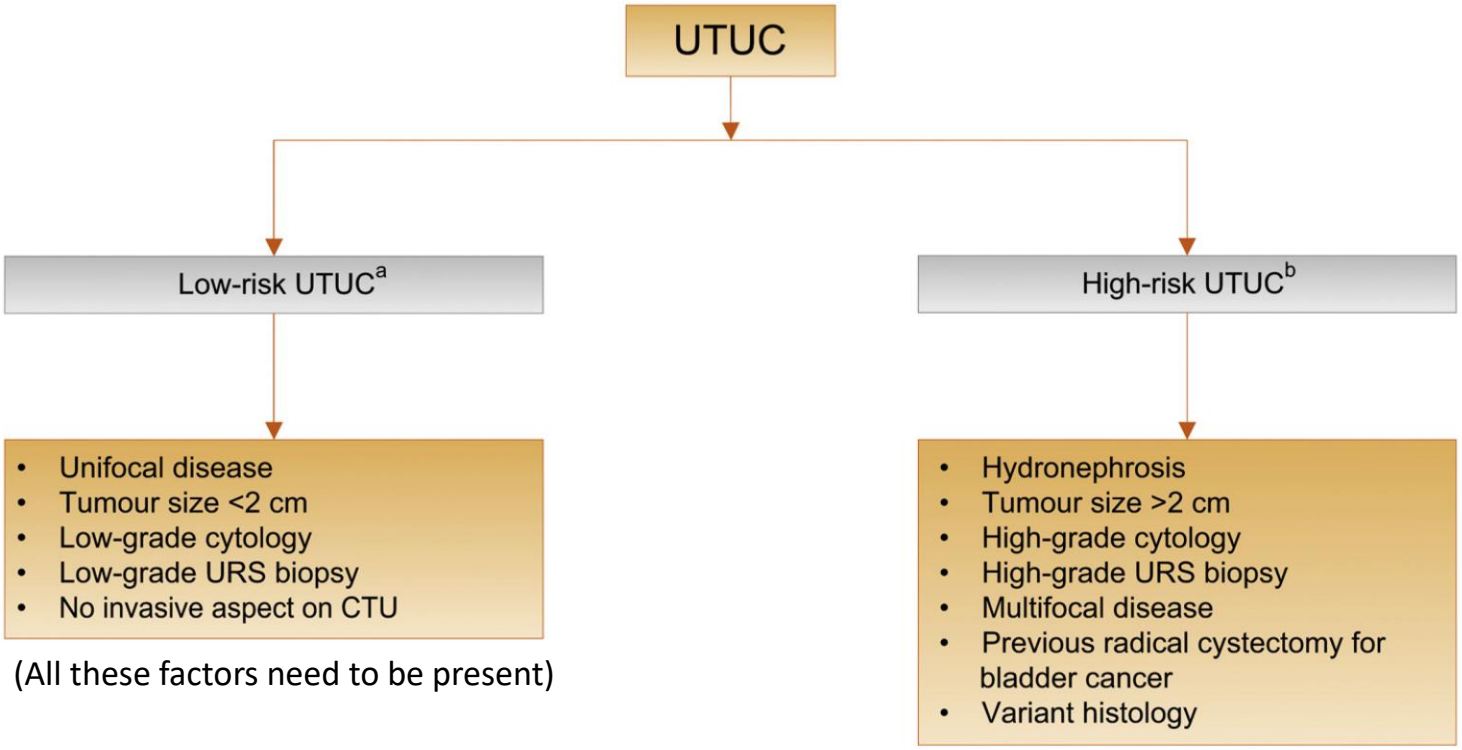
Consulting or Advisory role: Astra Zeneca, Bristol-Myers Squibb, Roche/Genentech, Merck, Novartis

Other relationship: Bristol-Myers Squibb, Ipsen

MULTIDISCIPLINARY Approach to Advanced Bladder Cancer



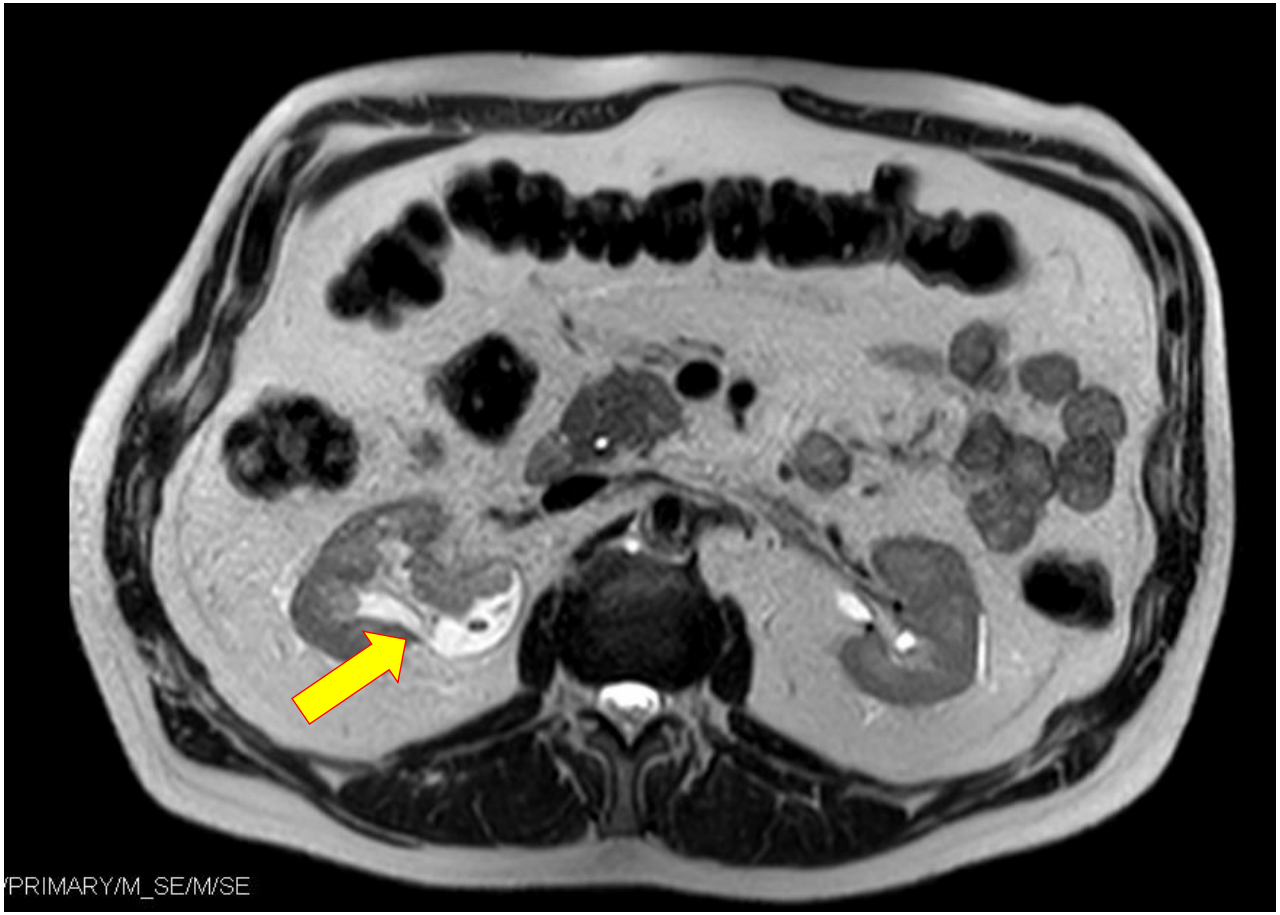
Adapted from MDT Guidance for Managing Bladder Cancer, 2nd edition. http://www.baus.org.uk/_userfiles/pages/files/Publications/MDT%20Guidance%20For%20Managing%20Bladder%20Cancer%202013.pdf . Published January 2013. Accessed February 15, 2017.



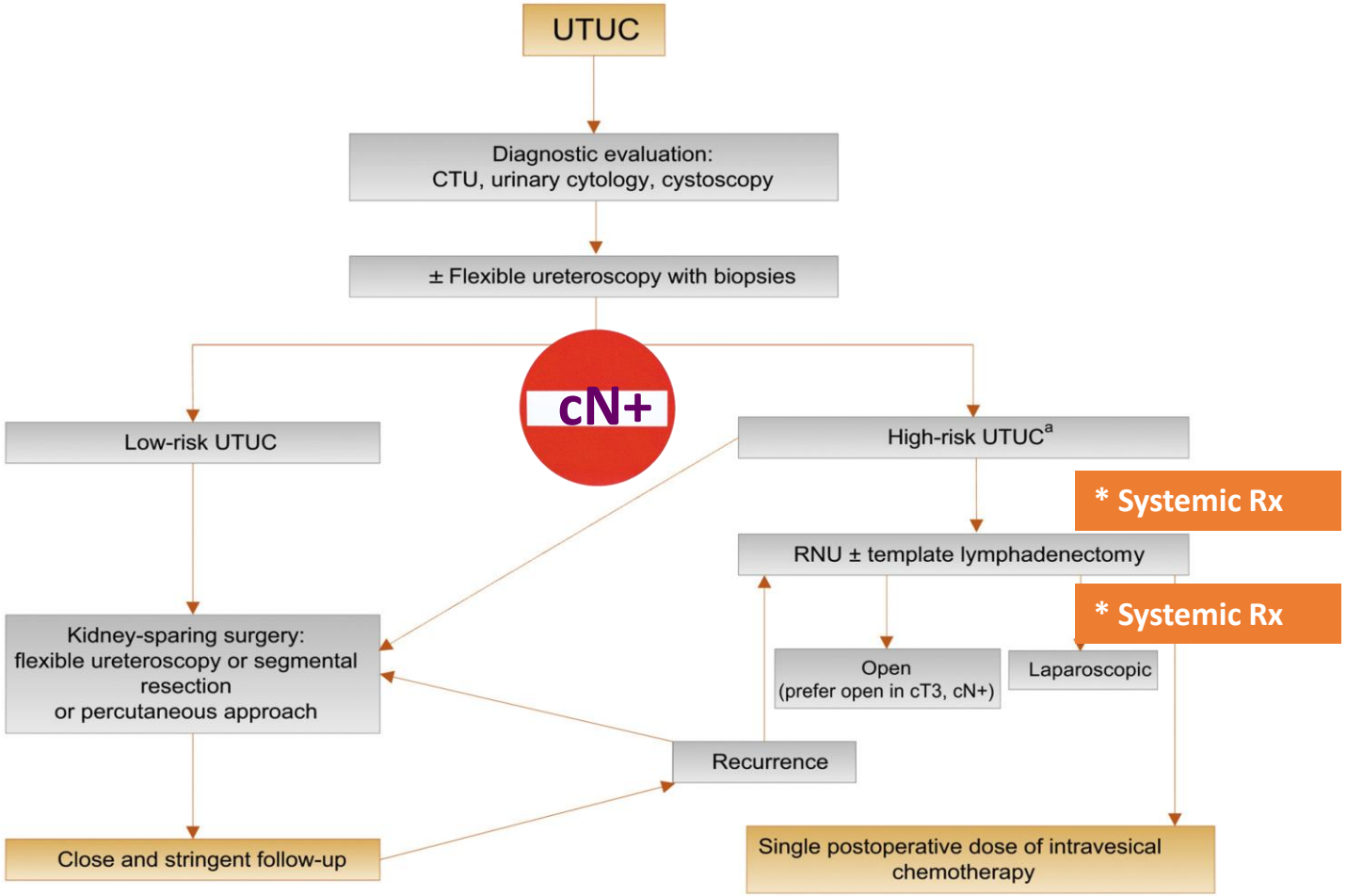
(All these factors need to be present)

(Any of these factors need to be present)

EAU Guidelines, 2017 Update. Eur Urol 2018

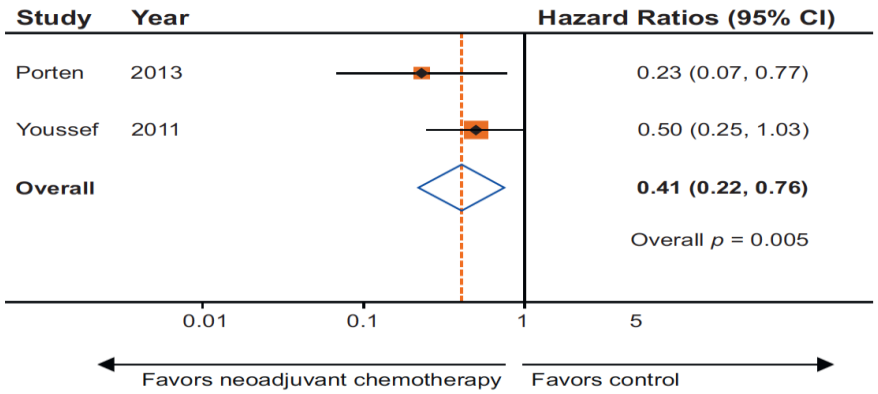


PURE-01 study (NCT02736266), UTUC cohort, ID#01
Baseline pre-therapy urinary tract mpMRI



EAU Guidelines, 2017 Update. Eur Urol 2018

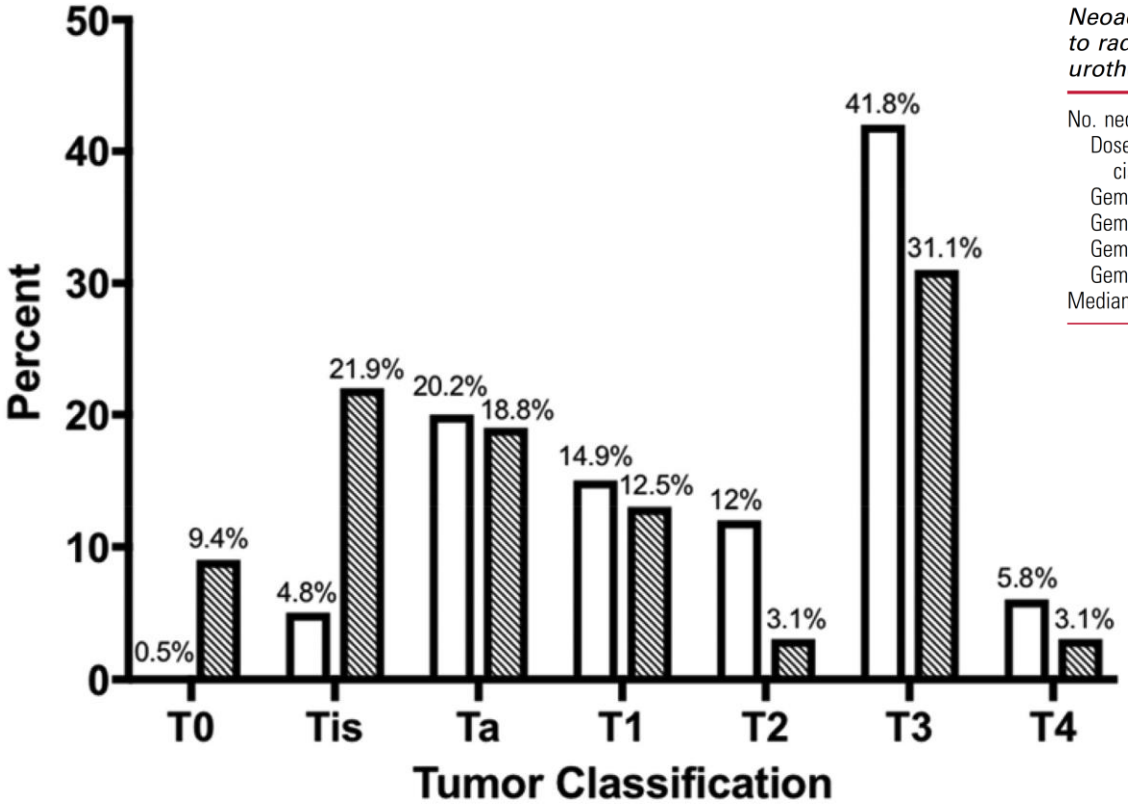
Pooled results from 2 retrospective studies found a 59% benefit in disease-specific survival (HR=0.41, P= .005)



Leow JJ et al, Eur Urol 2014

Author	Year	Study Type	N	Regimen	pT0 %
Porten	2014	Retrospective	29	Various	**13.8**
Matin	2010	Retrospective	43	Various	**14**
Youssef	2011	Retrospective	18	MVAC/GC	**27.8**
Igawa	1995	Retrospective	15	Various	**13**
Margulis	2009	Retrospective	47	Various	**10.6**
McConkey	2015	Prospective	16	DD-MVAC+Beva	**38**
Hoffman-Censits	2014	Prospective	10	Accelerated MVAC	**10**

Retrospective study from the Johns Hopkins University

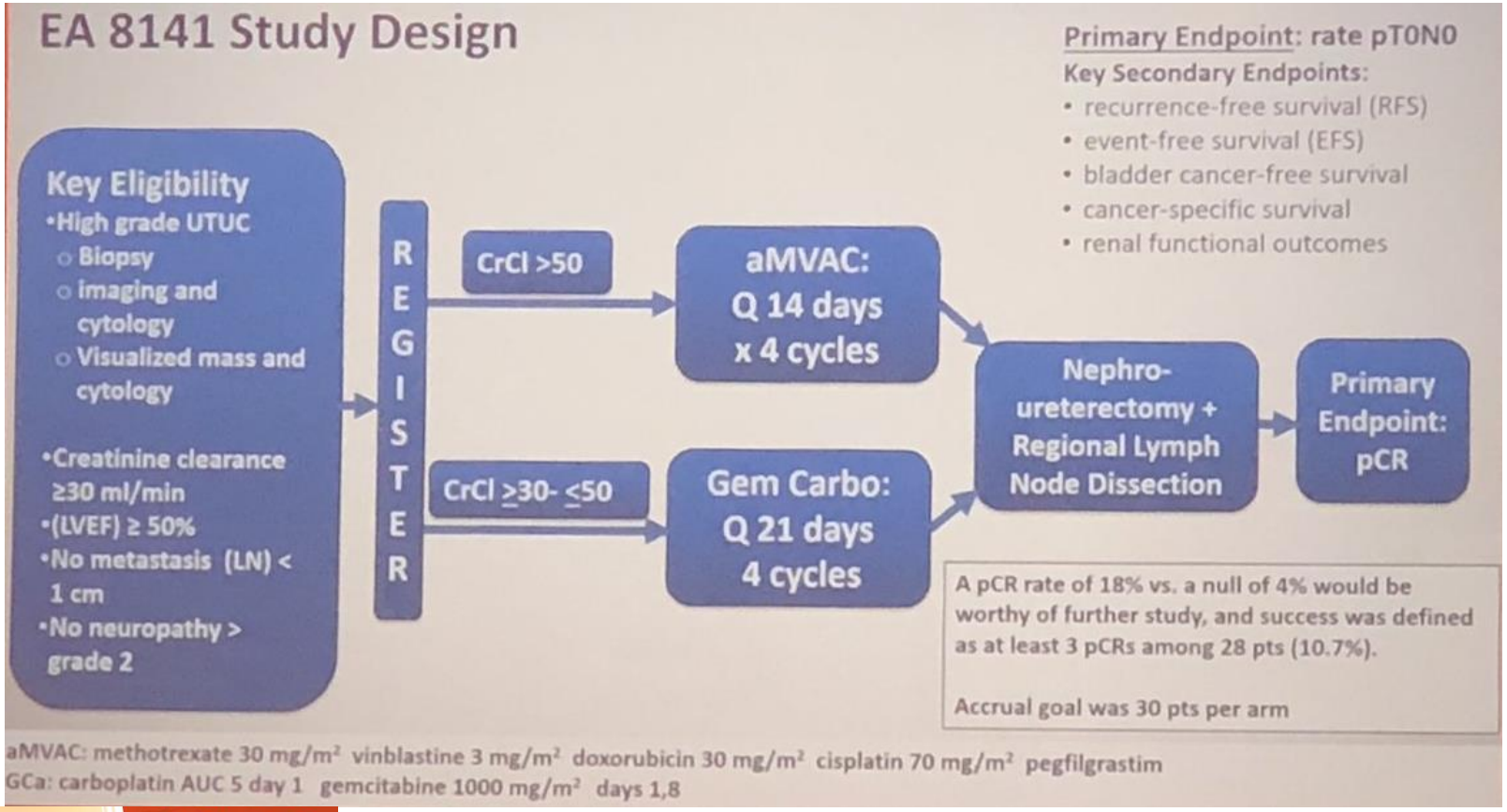


Neoadjuvant chemotherapy administered in 32 patients prior to radical nephroureterectomy of high risk upper tract urothelial carcinoma

No. neoadjuvant chemotherapy regimen (%):		
Dose dense methotrexate, vinblastine, doxorubicin + cisplatin	12	(37.5)
Gemcitabine + cisplatin	17	(53.1)
Gemcitabine + docetaxel	1	(3.1)
Gemcitabine, cisplatin + bevacizumab	1	(3.1)
Gemcitabine	1	(3.1)
Median ± SD No. chemotherapy cycles (range)	4 ± 1 (3–6)	

N=208 RNU alone
N=32 NAC+RNU

Liao RS, et al. J Urol 2018;200:68-73



Hoffman-Censits J, et al. AUA 2018

Pathologic Response at Nephroureterectomy

aMVAC Response Rate

pCR: 4/29 (14%)
90% CI [4.9 - 28.8])

≤pT1: 18/29 (62%)

Pathologic response	aMVAC (n=29) Responses	%	GemCarbo (n=6) Responses	%
T0N0	3	10%	1	20%
T0Nx	1	3%	0	
TaN0	3	10%	2	33%
TisN0	3	10%	0	
T1N0	7	24%	0	
T1Nx	1	3%	0	
T2N0	1	3%	0	
T2Nx	0		1	20%
T3N0	6	21%	1	20%
T3Nx	2	7%	0	
T3N2	0		1	20%
TaN2	1	3%	0	
NA -Pt refused surgery	1	3%	0	

ECOG-ACRIN cancer research group

Hoffman-Censits J, et al. AUA 2018

Neoadjuvant trials for upper tract urothelial carcinoma

Agents	Sponsor	ClinicalTrials.gov Identifier	Patient Selection	Design	Primary Endpoint	Sample Size
Gem-Cis	Xiangya Hospital of Central South University	NCT02876861	High grade UTUC	Single arm Phase 2	OS	50
Durvalumab + Tremelimumab	MDACC, MedImmune	NCT02812420	High risk UTUC, CDDP-ineligible	Single arm Phase 2	Safety	15
Gem-Cis	MSKCC	NCT01261728	High grade UTUC	Single arm Phase 2	Path Response	54
Gem-Carbo; DD-MVAC	ECOG-ACRIN	NCT02412670	High grade UTUC	Non-randomized Phase 2	pCR	60
Pembrolizumab	INT Milano	NCT02736266	High grade UTUC	Single arm Phase 2	pCR	20

Cytologically of histologically-confirmed diagnosis of high-grade UC
Clinical stage cN0 cM0
“High risk” per modified EAU guidelines (i.e., excluding the previous radical cystectomy factor), defined
No prior systemic therapies.
No prior of concomitant evidence of UC of the bladder (i.e., negative cystoscopy is mandatory)
ECOG performance status 0 to 2.
Adequate end-organ function tests.

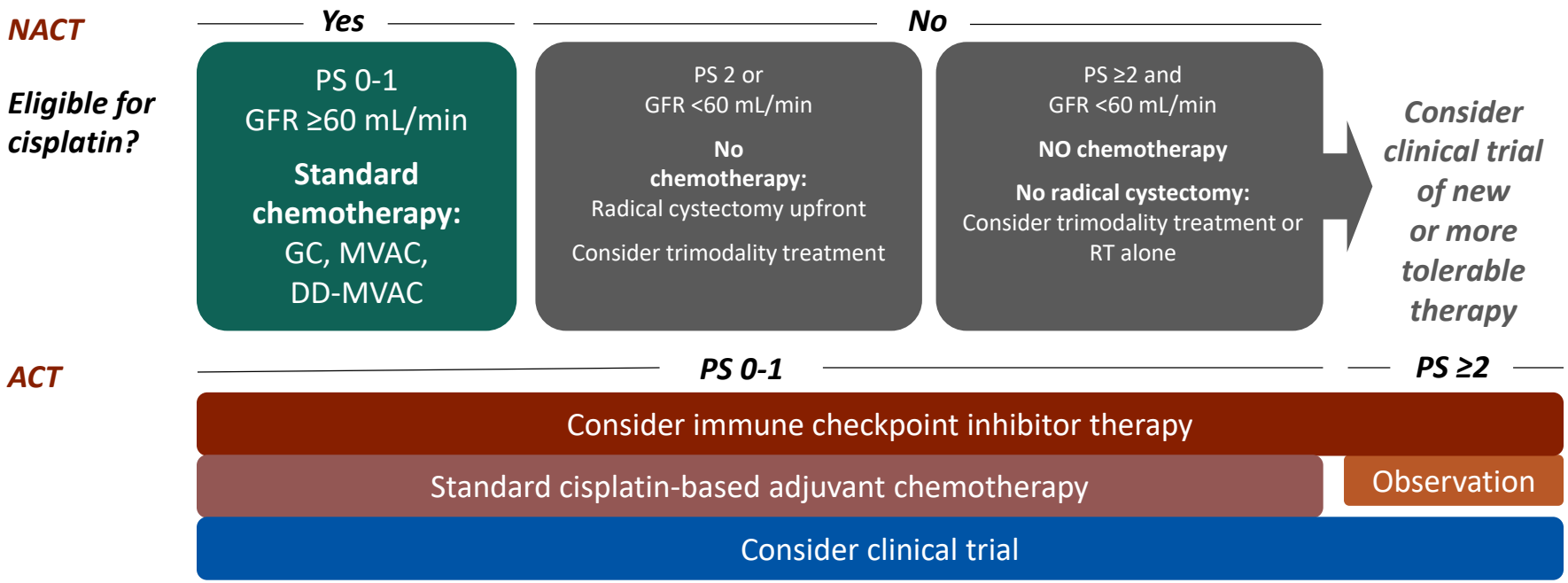
3×3 weekly cycles of pembrolizumab 200 mg IV

Pre-post treatment tissue/blood sample collection for biomarker analyses

Pre-post treatment imaging: multiparametric bladder MRI (mpMRI); ^{18}FDG-PET/CT scan, T/A CT scan

- RNU
- Post-RNU management according to EAU guidelines
- Survival data collected until 2-y post cystectomy

How Emerging Clinical Data Will Impact the European Treatment Algorithm for MIBC

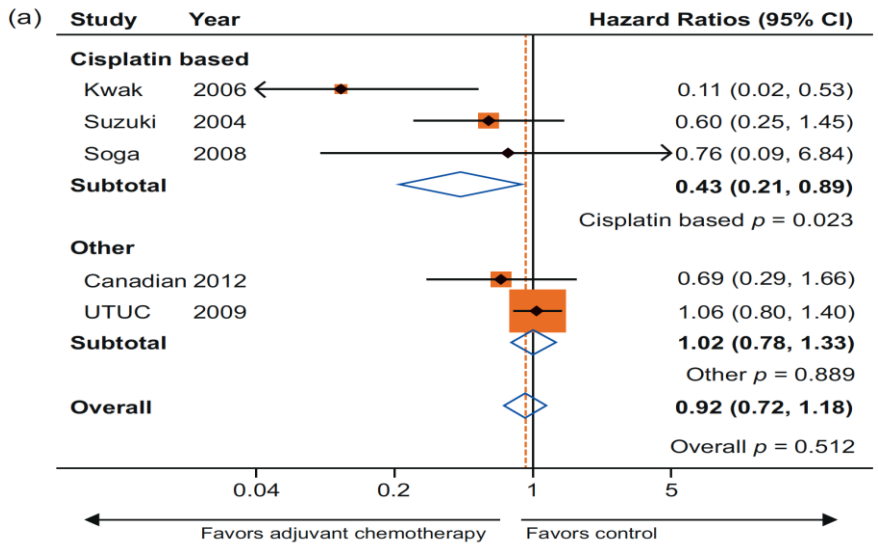


Available at: http://ime.peervoice.com/v/index.html?collection=505202977-2-2&presentationid=p1&Promocode=860#main

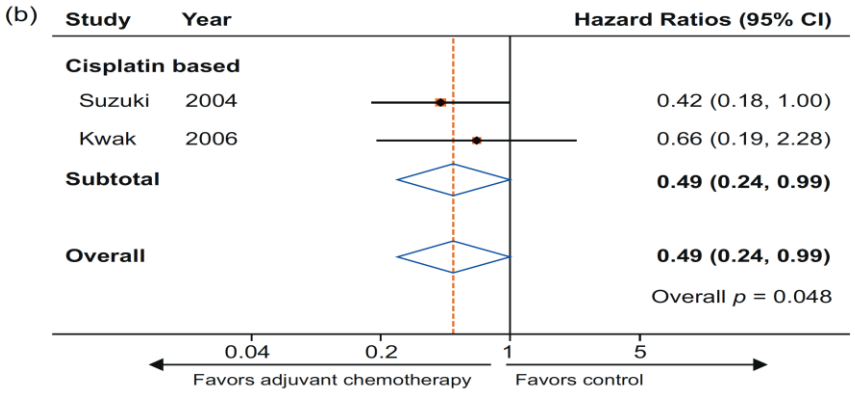
Adjuvant chemotherapy for Upper Tract UC:

- Pooled overall survival benefit (HR=0.43, 95% CI: 0.21–0.89, P= .023), across 3 cisplatin-based studies.
- 57% benefit in OS among those treated with adjuvant chemotherapy compared with controls.

OS



DFS



Leow JJ, Eur Urol 2014

VOLUME 22 · NUMBER 11 · JUNE 1 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Adjuvant Chemotherapy With Paclitaxel and Carboplatin in Patients With Advanced Carcinoma of the Upper Urinary Tract: A Study by the Hellenic Cooperative Oncology Group

A. Bamias, Ch. Deliveliotis, G. Fountzilas, D. Gika, A. Anagnostopoulos, M.P. Zorzou, E. Kastritis, C. Constantinides, P. Kosmidis, and M.A. Dimopoulos

N=36

Unique prospective study of adjuvant chemotherapy for UTUC

Table 2. 5-Year Survival According to Stage and Grade in Patients With Upper Urinary Tract Carcinoma

Study	No. of Patients	T Stage			Grade	
		T2	T3	T4	2	3/4
Hall et al[3]	252	73	41	0	—	—
Guinan et al[2]	611	87	54	19	—	—
Morioka et al[25]	93	89	62	0	87	57
Mufti et al[26]	185	80	80	27	76	40
Masuda et al[27]	64	79	54		76	46
Rey et al[28]	83	83	60	21	89	47-80
Racioppi et al[29]	100	—	—	—	46	29
Corrado et al[30]	127	72	51	16	75	0-52
Present study	36	54		43	100	43

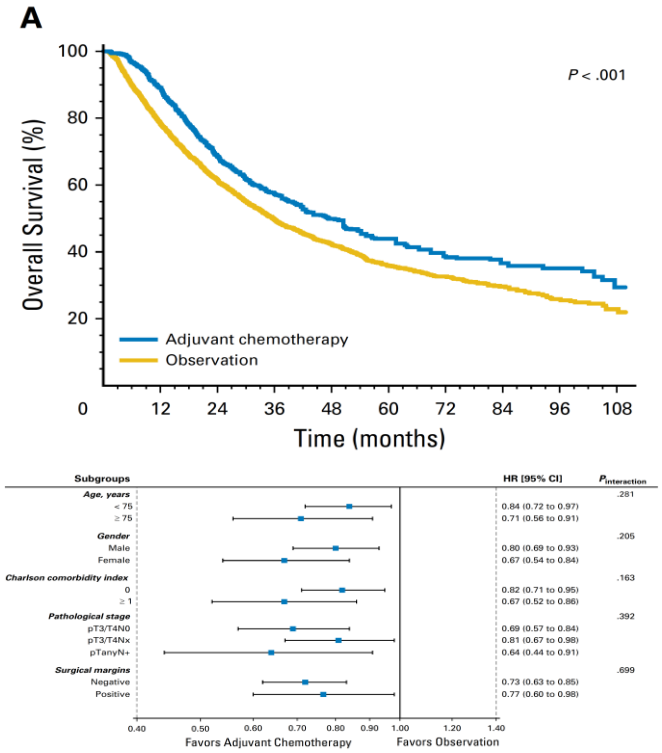
Table 3. Local Failure Rate and Distant Metastases After Radical Surgery for Upper Urinary Tract Carcinoma

	No. of Patients	Local	Metastatic
No treatment/radiotherapy			
Cozad et al[4]	30/67*	8	22
Hall et al[3]	21/252	6	15
Hall et al[35]	51/74†	6	45
Maulad-Durdux et al[34]	15/26‡	1	14
Chemotherapy			
Present study	17/36	11	6

*Ten patients received adjuvant radiotherapy.

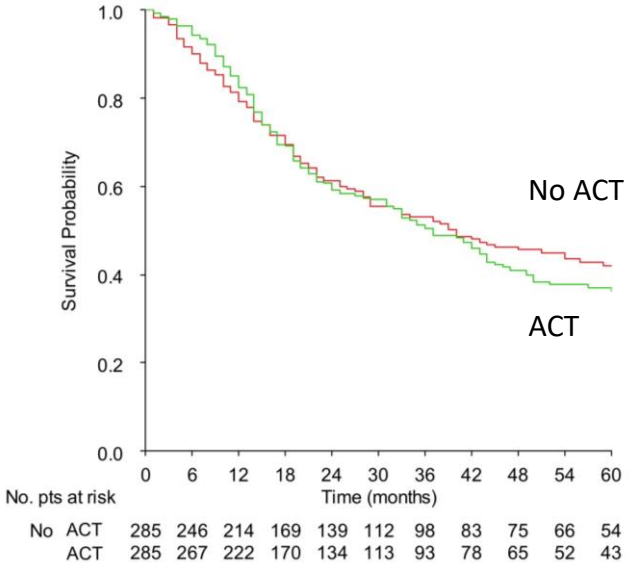
Local control is a concern
Any role for Adjuvant chemoradiation?

Conflicting results with the use of adjuvant chemotherapy after RNU



Seisen T, et al. J Clin Oncol 2017;35:852-860

Propensity score-matched overall survival curves according to the study group



Necchi A, et al. ESMO 2017, abstr. 865P

ICR The Institute of Cancer Research

POUT

CANCER RESEARCH UK

Results of POUT - A phase III randomised trial of peri-operative chemotherapy versus surveillance in upper tract urothelial cancer (UTUC)

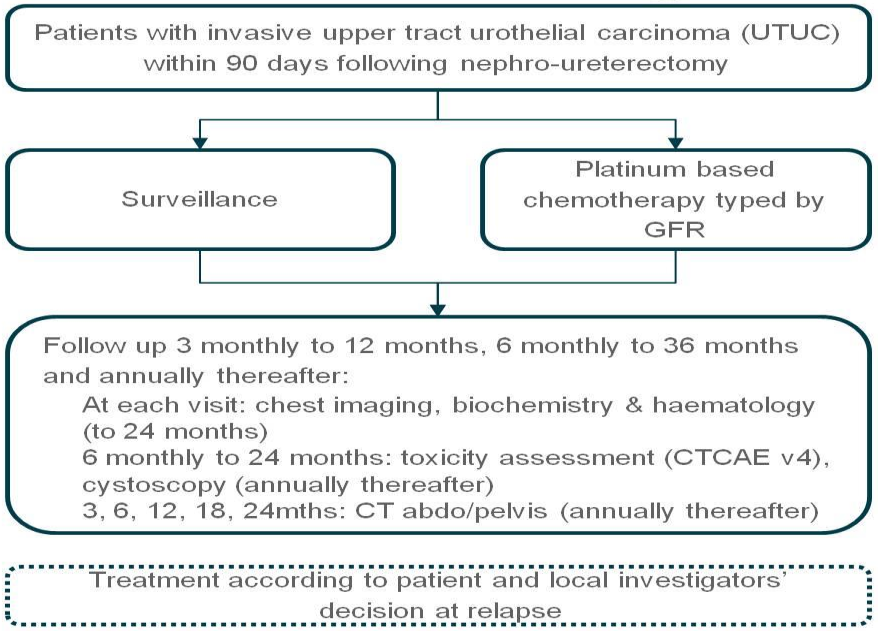
Alison Jane Birtle*, John David Chester, Robert Jones, Mark Johnson, Michaela Hill, Richard T Bryan, James Catto, Jenny Donovan, Ann French, Chris Harris, Francis Keeley, Roger Kockelbergh, Thomas Powles, Rachel Todd, Lucy Tregellas, Caroline Wilson, Andrew Winterbottom, Rebecca Lewis, Emma Hall, on behalf of the POUT Investigators

*Chief Investigator

PRESENTED AT: **2018 Genitourinary Cancers Symposium**

Presented By Alison Birtle at 2018 Genitourinary Cancers Symposium: Translating Evidence to Multidisciplinary Care

POUT Trial design



Inclusion criteria:

- En-bloc radical nephro-ureterectomy
- UTUC pT2-pT4 pN0 M0 or pTany N1-3 M0 (abnormal nodes resected at surgery)
- Satisfactory haematology profile & liver function tests
- WHO performance status 0-1
- Fit to receive chemotherapy within 90 days following nephro-ureterectomy

Exclusion criteria:

- GFR <30ml/min
- Distant metastases
- Un-resected macroscopic nodal disease
- Concurrent MIBC (concurrent NMIBC acceptable)
- Other malignancy in previous 5 years
- Significant co-morbidities

POUT chemotherapy regimen

Four 21 day cycles:

All patients:

Gemcitabine

- 1000mg/m^2 day 1 & 8

With:

If GFR ≥ 50 ml/min:

Cisplatin

- 70mg/m^2 day 1

OR

If GFR 30-49ml/min:

Carboplatin*

- AUC 4.5/AUC 5 day 1

*only permitted for impaired renal function

Supportive care according to local practice

Presented By Alison Birtle at 2018 Genitourinary Cancers Symposium: Translating Evidence to Multidisciplinary Care

POUT endpoints

Endpoints in red presented here

Primary endpoint:

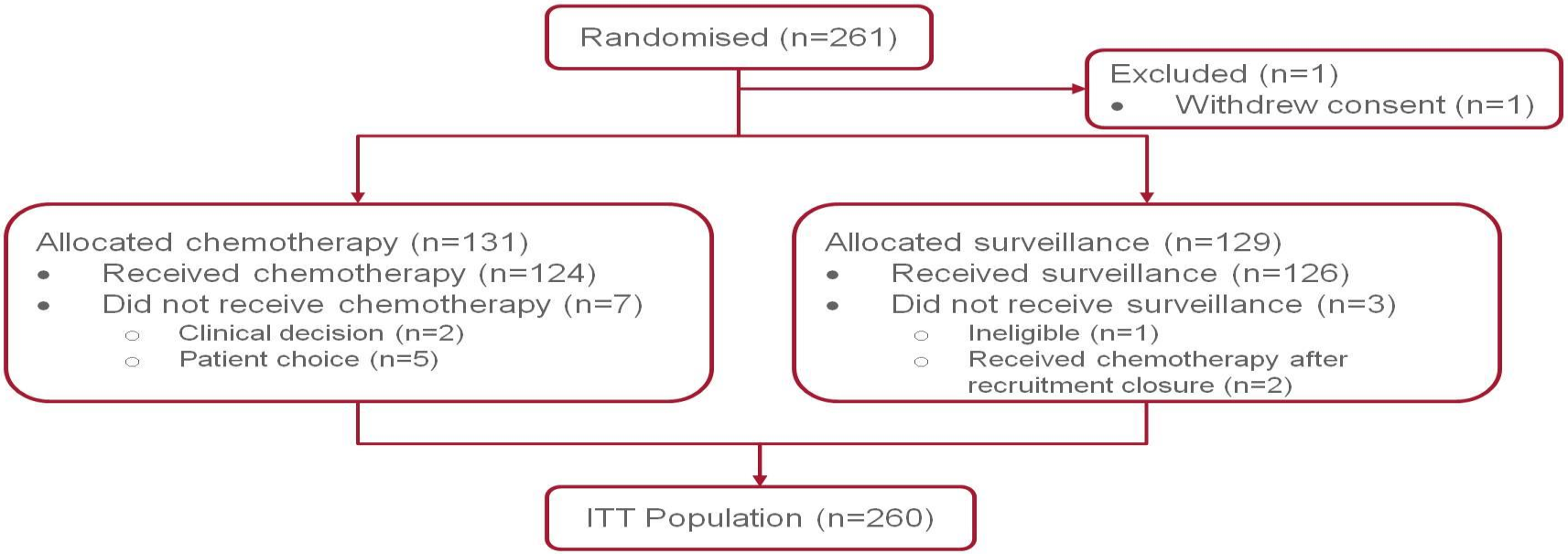
- Disease free survival (DFS)

Secondary endpoints:

- Acute and late toxicity
- Metastasis free survival
- Treatment compliance
- Feasibility of recruitment
- Overall survival
- Incidence of contralateral primary tumours
- Incidence of bladder and second primary tumours
- Quality of life

Presented By Alison Birtle at 2018 Genitourinary Cancers Symposium: Translating Evidence to Multidisciplinary Care

POUT CONSORT diagram



Presented By Alison Birtle at 2018 Genitourinary Cancers Symposium: Translating Evidence to Multidisciplinary Care

Baseline characteristics

		Surveillance N=129		Chemotherapy N=131		Total N=260	
		N	%	N	%	N	%
Pathological stage	pT2	30	23.3%	45	34.4%	75	28.8%
	pT3	88	68.2%	82	62.6%	170	65.4%
	pT4	11	8.5%	4	3.1%	15	5.8%
Nodal involvement*	N0	117	90.7%	119	90.8%	236	90.8%
	N1	8	6.2%	7	5.3%	15	5.8%
	N2	4	3.1%	4	3.1%	8	3.1%
	N3	0	0.0%	1	0.8%	1	0.4%
Microscopic margin status*	Positive	14	10.9%	17	13.0%	31	11.9%
	Negative	115	89.1%	114	87.0%	229	88.1%
Planned chemotherapy type*	Gem-cis	85	65.9%	81	61.8%	166	63.8%
	Gem-carb	44	34.1%	50	38.2%	94	36.2%

*Balancing factors for minimisation

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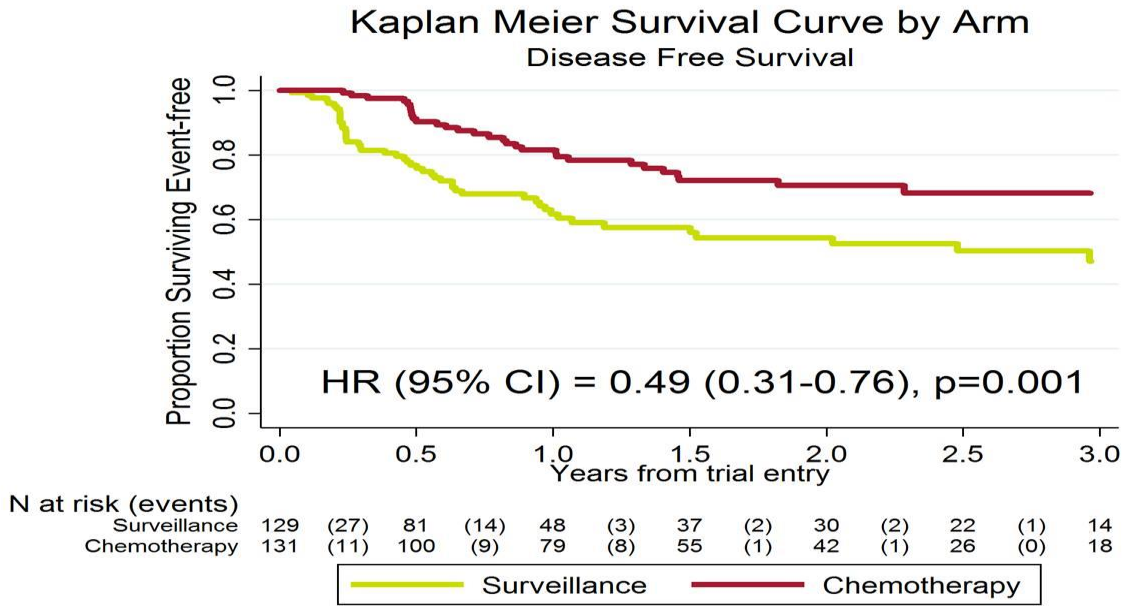
Treatment compliance

Number of cycles of chemotherapy received	Treatment on-going N=6		No further treatment expected N=125		Total N=131	
	N	%	N	%	N	%
0	3	50.0%	7	5.6%	10	7.6%
1	0	0%	12	9.6%	12	9.2%
2	1	16.7%	8	6.4%	9	6.9%
3	2	33.3%	9	7.2%	11	8.4%
4 (max)	0	0%	89	71.2%	89	67.9%

- 9/70 (12.9%) patients who received Gemcitabine-Cisplatin at the start of treatment switched to Gemcitabine-Carboplatin during treatment

Presented By Alison Birtle at 2018 Genitourinary Cancers Symposium: Translating Evidence to Multidisciplinary Care

Primary endpoint: DFS



DFS defined as time from randomisation to first of death from any cause, metastases or any ureteric or renal bed recurrence

Proportion event free at 2 years:

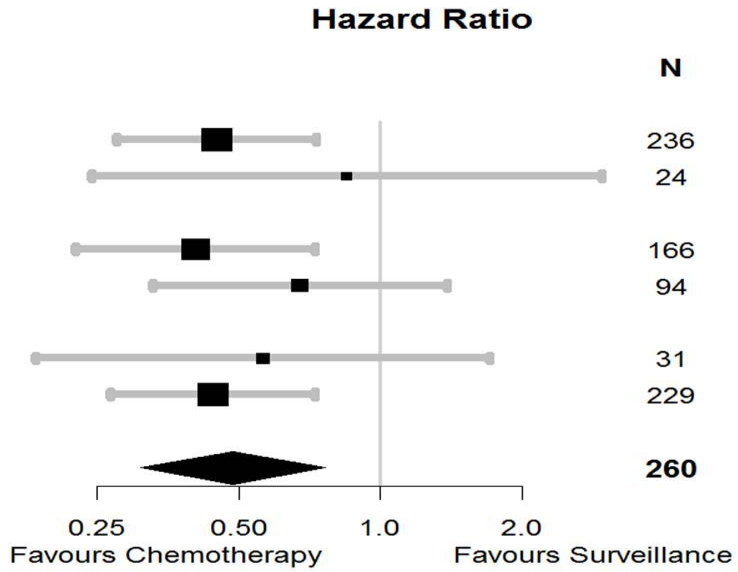
Chemotherapy: 0.71 (95% CI: 0.60, 0.79)

Surveillance: 0.54 (95% CI: 0.43, 0.64)

After adjustment for nodal involvement, microscopic margin status and planned chemotherapy type:

HR (95% CI) = 0.47 (0.30-0.74); p=0.001

Primary: DFS



Variable	N	Univariable Hazard Ratio	p-value
Nodal involvement			
N0	236	0.45 (0.28, 0.73)	0.001
N+	24	0.85 (0.24, 2.95)	0.80
Planned chemotherapy type			
Gem-Cis	166	0.40 (0.23, 0.73)	0.003
Gem-Carbo	94	0.67 (0.33, 1.38)	0.28
Microscopic margin status			
Positive	31	0.56 (0.19, 1.71)	0.31
Negative	229	0.44 (0.27, 0.73)	0.001
Overall	**260**	**0.49 (0.31, 0.76)**	**0.001**

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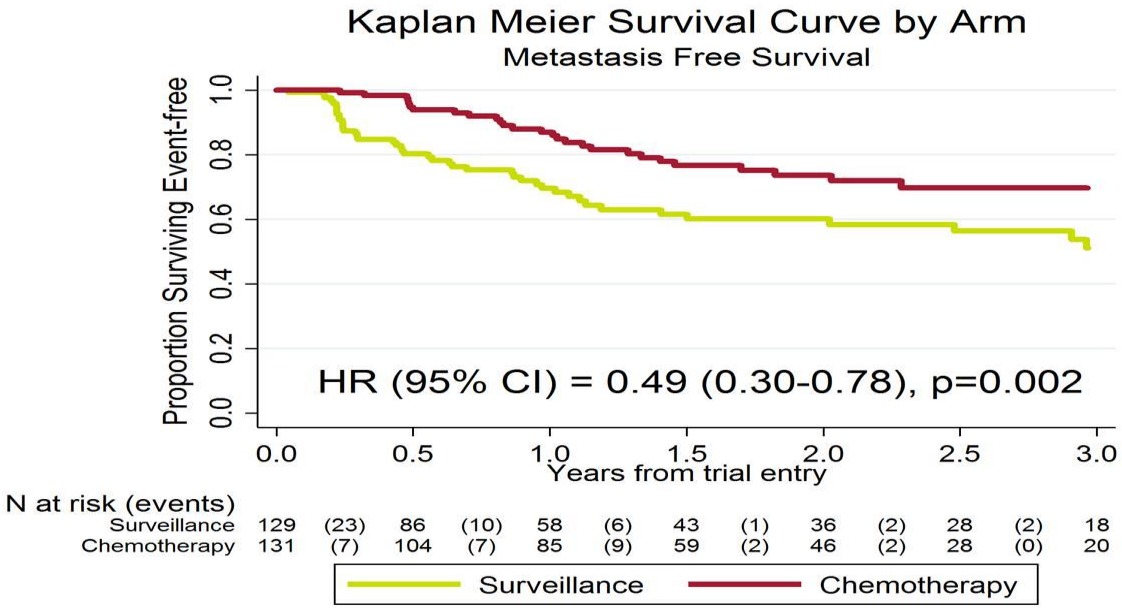
Secondary endpoint: MFS



MFS defined as time from randomisation to first distant recurrence or death from any cause

Proportion event free at 2 years:

Chemotherapy: 0.74 (95% CI: 0.63, 0.81)

Surveillance: 0.60 (95% CI: 0.49, 0.69)

After adjustment for nodal involvement, microscopic margin status and planned chemotherapy type:

HR (95% CI) = 0.47 (0.30-0.76); p=0.002

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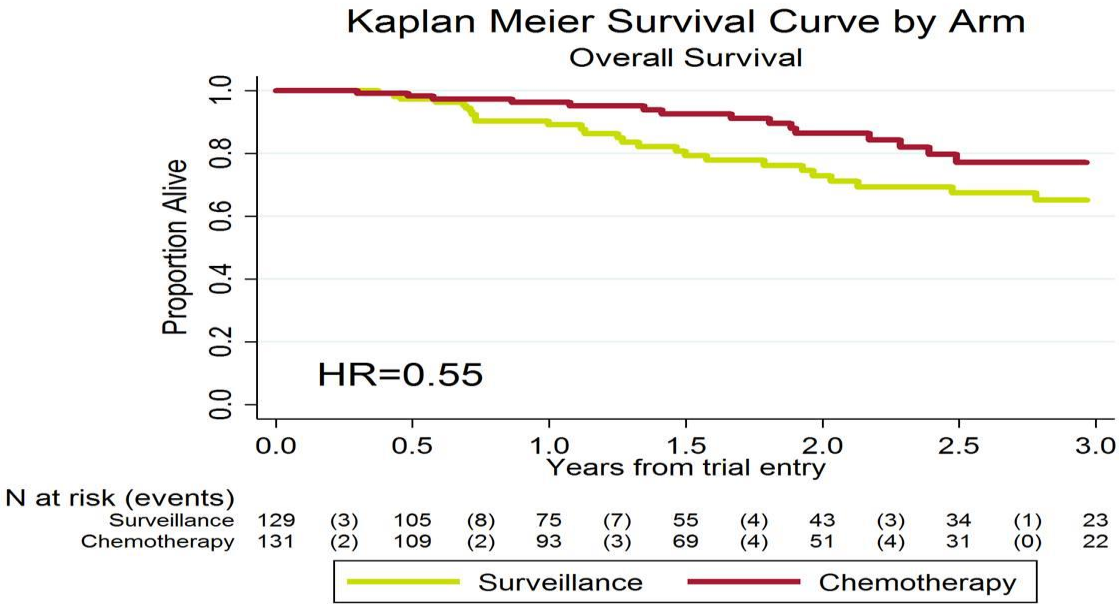
Secondary endpoint: OS



OS defined as time from randomisation to death from any cause

Overall survival data are currently immature and will be formally analysed after either:

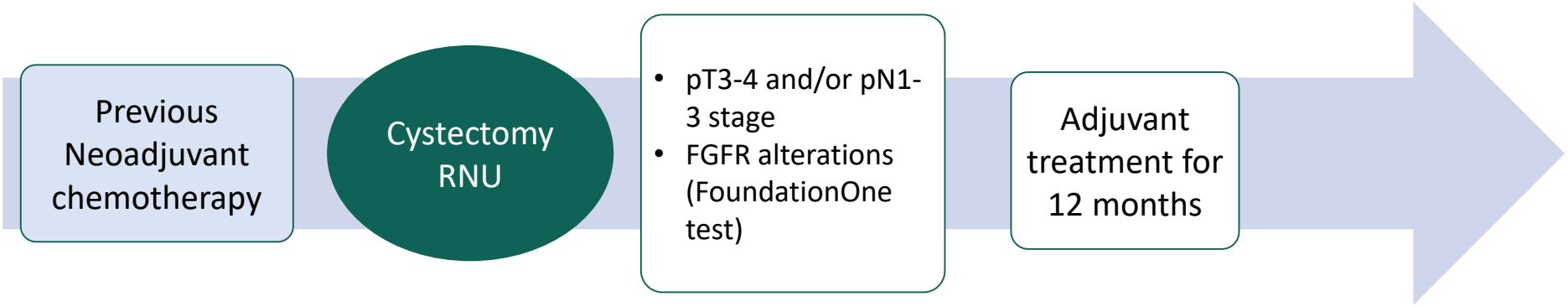
- 88 deaths have occurred
- Median follow-up in patients alive has passed two years

Ph3 Adjuvant/ Registrational Studies in MIBC

IO Therapy/Study	Phase/N	Study Arms	Primary Endpoints	**Secondary Endpoints**	Estimated Primary Completion Date
Nivolumab[1] CheckMate 274 (NCT02632409)	Phase 3 N=640	• Nivolumab (adjuvant) • Placebo	• Disease-free survival	• Non-urothelial track recurrence-free survival • Disease-specific survival • OS	April 2020
Pembrolizumab[2] AMBASSADOR (NCT03244384)	Phase 3 N=739	• Pembrolizumab (adjuvant) • Observation	• Disease-free survival • OS (up to 5 years)	• Disease-free survival and OS in PD-L1^{+} and **PD-L1**$^{-}$ patients	February 2019
Atezolizumab[3] IMvigor010 (NCT02450331)	Phase 3 N=700	• Atezolizumab (adjuvant) • Observation	• Disease-free survival	• Disease-specific survival • OS • Distant metastasis-free survival • Non-urinary tract recurrence-free survival • Safety, QoL • PK, immunogenicity	October 2019

1. Study NCT02632409. ClinicalTrials.gov website. Accessed July 24, 2017. 2. Study NCT03244384. ClinicalTrials.gov website. Accessed July 24, 2017 3. Study NCT02450331. ClinicalTrials.gov website. Accessed July 24, 2017.

Open-label, single-arm, Phase II study, evaluating safety and efficacy of INCB054828 as adjuvant therapy for molecularly-selected, high-risk patients with urothelial carcinoma who have received neoadjuvant chemotherapy and surgery



Primary Endpoint: Relapse-free survival; N=56
(100 pts screened)

Study sponsor: EAU-RF

Power: 0.90; Alpha: 0.10; H0: 2-year RFS: 30%; H1: 2-year RFS: 45%
Follow-up duration: 2 years

SIU UPDATES

ASCO GU

ASCO GENITOURINARY CANCER SYMPOSIUM

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