ASCO Genitourinary Cancers Symposium

Safety and Efficacy of Durvalumab (MEDI 4736) in combination with neoadjuvant chemotherapy (Gemcitabine / Cisplatin or Carboplatin) in patients with operable high-risk upper tract urothelial carcinoma

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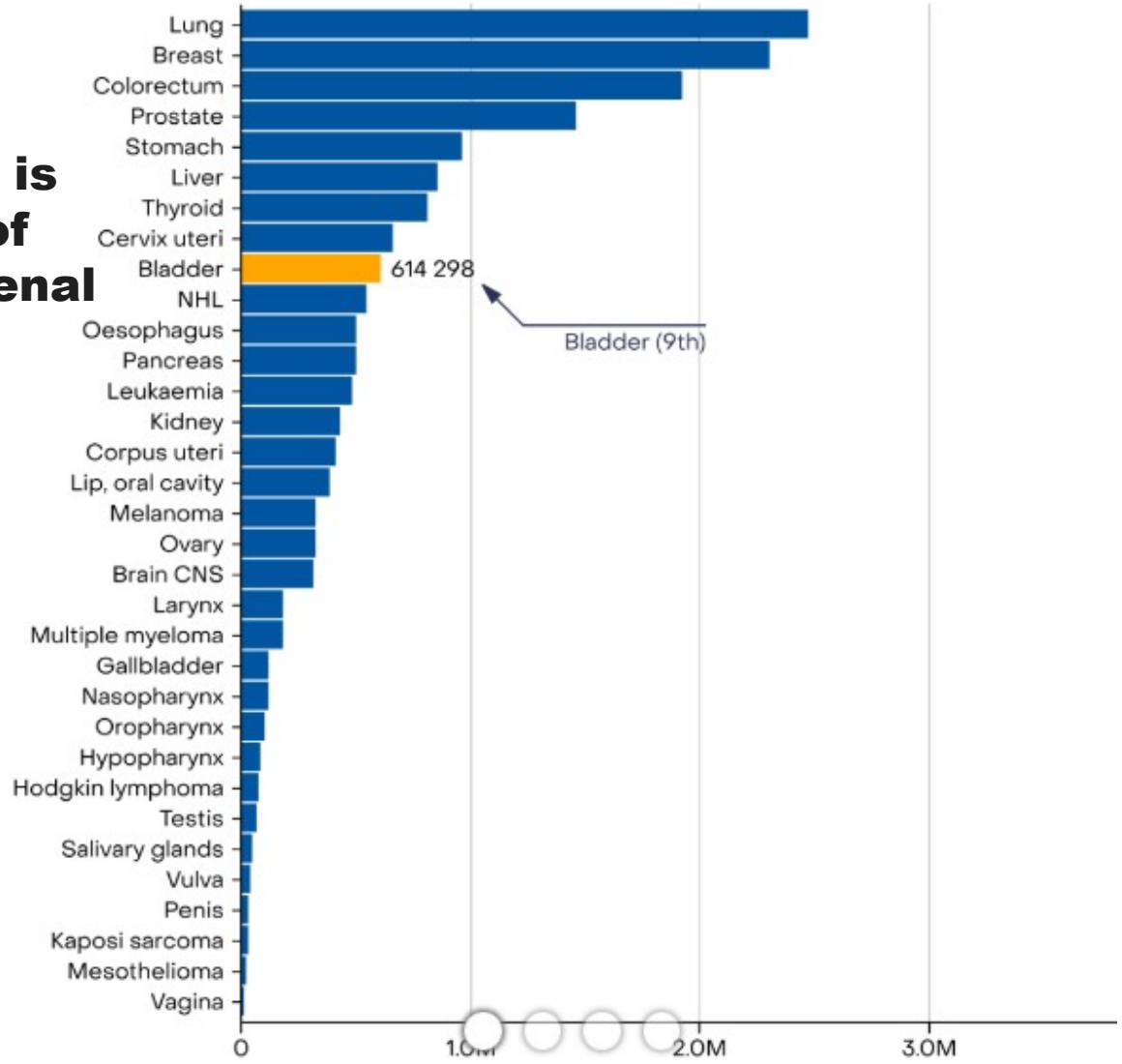
EPIDEMIOLOGY

Upper Tract Urothelial Carcinoma (UTUC) is relatively uncommon, accounting for 5% of urothelial cancers and less than 10% of renal tumours.



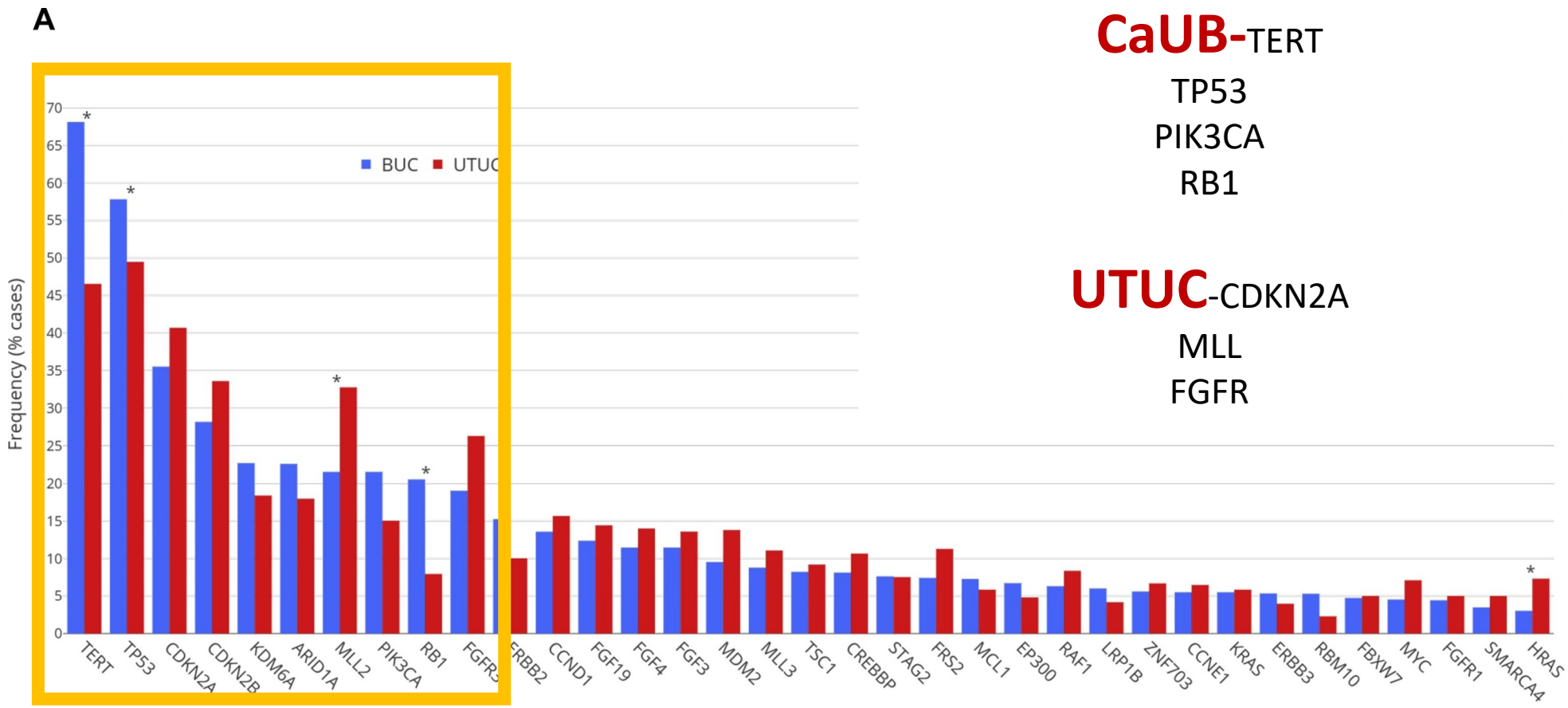
A. Masson-Lecomte, P. Gontero (Chair), A. Birtle, E.M. Compérat, J.L. Dominguez-Escrig, F. Liedberg, P. Mariappan, B.W.G. van Rhijn, T. Seisen, S.F. Shariat, J. Teoh, E.N. Xylinas Guidelines Associates: O. Capoun, M. Moschini, B. Pradere, B.P. Rai, F. Soria, V. Soukup Patient Advocates: L. Makaroff, R. Wood Guidelines Office: E.J. Smith

BACKGROUND-

UTUC and Ca UB : disparate twins-

- There is increasing evidence to show that UTUC is a distinct disease entity from UCB based on phenotypical and genotypical differences.
- This may account for why the natural history of UTUC is different from that of Ca UB, with >60% of UTUCs and only 15%–25% of UCB presenting with invasion at diagnosis.
- Management of UTUC is thus different from Ca UB in a variety of ways, ranging from surgical management, and medical management (Neoadjuvant and adjuvant chemotherapy).

- **Ca bladder & UTUC:**
  Different genomic landscapes



CaUB-TERT
TP53
PIK3CA
RB1

UTUC-CDKN2A
MLL
FGFR

- Necchi A et al. Comprehensive Genomic Profiling of Upper-tract and Bladder Urothelial Carcinoma. Eur Urol Focus. 2021 Nov; 7(6):1339–1346

BACKGROUND-

- High-risk upper tract urothelial carcinoma (UTUC) has a poor 5-year survival rate
  - less than 50% for pT2/pT3 and under 10% for pT4 tumors without perioperative treatment[1].

- Radical nephroureterectomy (RNU) with bladder cuff excision is the current standard
  - but it leads to loss of kidney function, limiting post-surgery treatment options like cisplatin-based chemotherapy.

- The POUT **only** phase III trial showed improved disease-free survival (62% vs 45%) with adjuvant chemotherapy over surveillance[2].

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Rationale for Neoadjuvant therapy

- **Poor prognosis**
  - 5-year survival ~69% (recurrence-free), 73% (cancer-specific)
  - Renal function decline post-RNU limits adjuvant cisplatin use
- **Benefits of Neoadjuvant Approach**
  - Treats systemic disease early
  - Improves pathologic response rate
  - Enhances tolerability before kidney loss
- **Combination Advantage**
  - Synergy of immunotherapy and chemotherapy

WHY immunotherapy-

- Data in urothelial carcinoma of the bladder (BCa): NIAGARA trial[1] EFS NR vs 46 MONTHS HR-0.68 and for OS HR 0.75

- PURE-01—pT0 rate was 37% and the pT ≤ 1 rate was 55%
- Data in UTUC: PURE-02[2]: 10 patients treated with pembrolizumab, 1yPT0
  - Although small size,no promising signals of activity from single agent pembrolizumab

1.Powles T et al. Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer. NEJM 2024 Nov 14; 391(19):1773–1786.
2.Necchi A et al. A feasibility study of preoperative pembrolizumab before radical nephroureterectomy in patients with high-risk, upper tract urothelial carcinoma: PURE-02. Urol Oncol 2022 Jan; 40(1):10.e1–10

iNDUCT-

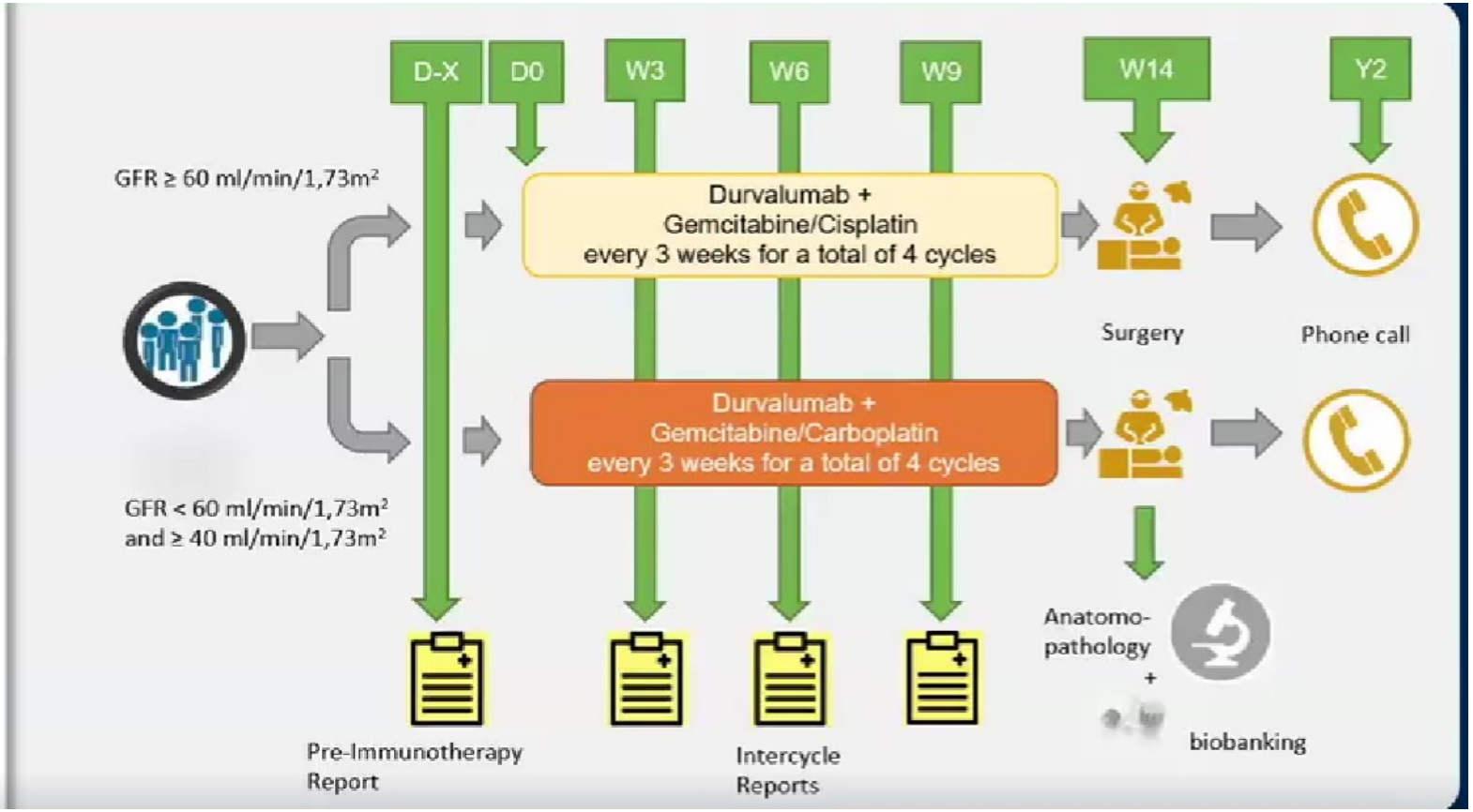
iNDUCT --Phase 2 trial

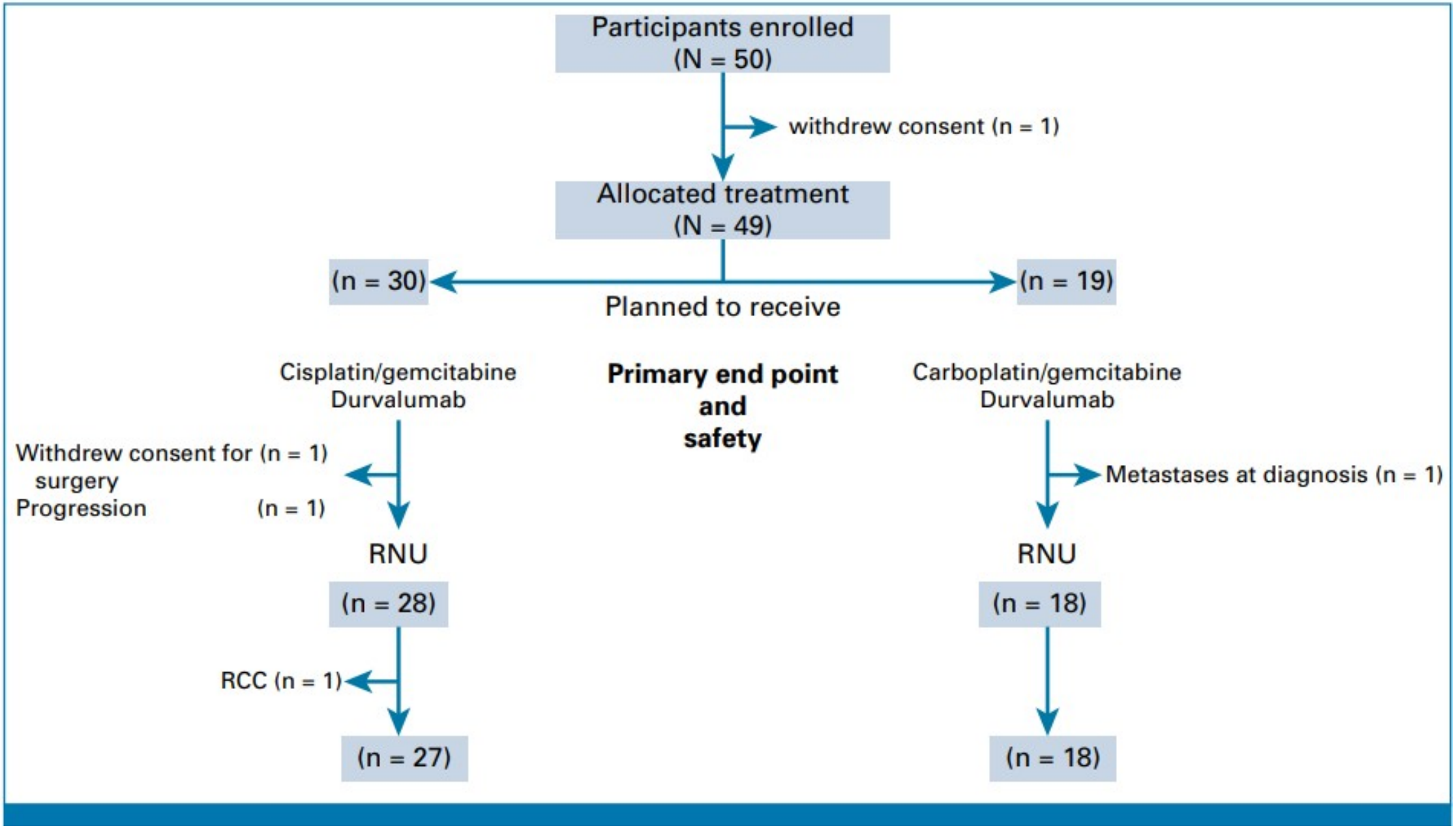
Inclusions criteria:

- ECOG status ≤1
- Presence of either:
  - o High-grade disease on tumor biopsy or High-grade disease on urine cytology AND /OR
  - o Infiltrative aspect of renal pelvis/ureteral wall on imaging with negative cystoscopy.
- cTNM: ≤T3, ≤N1
- M0

Primary endpoint:

- Rate of ypT0





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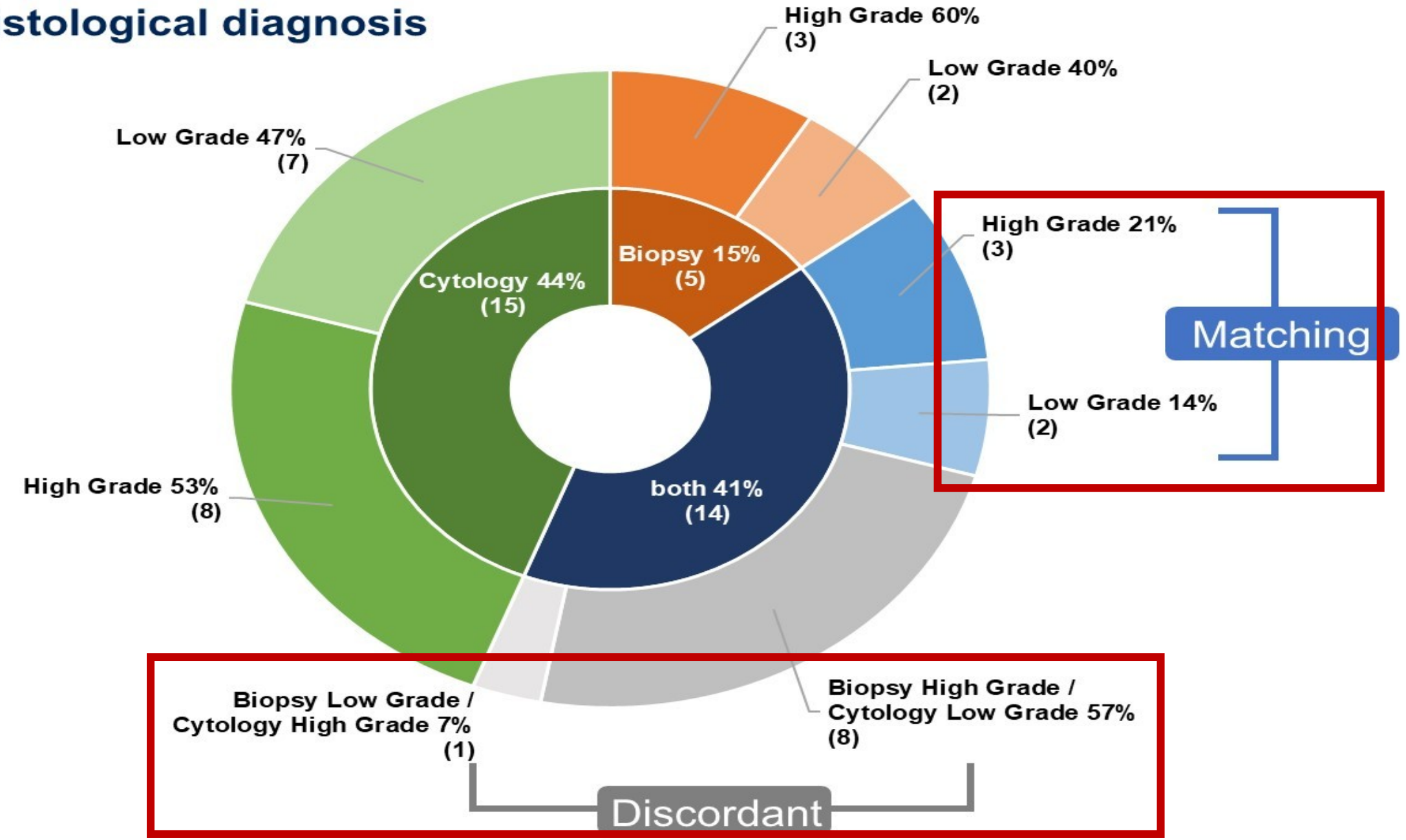
Results

- Study population

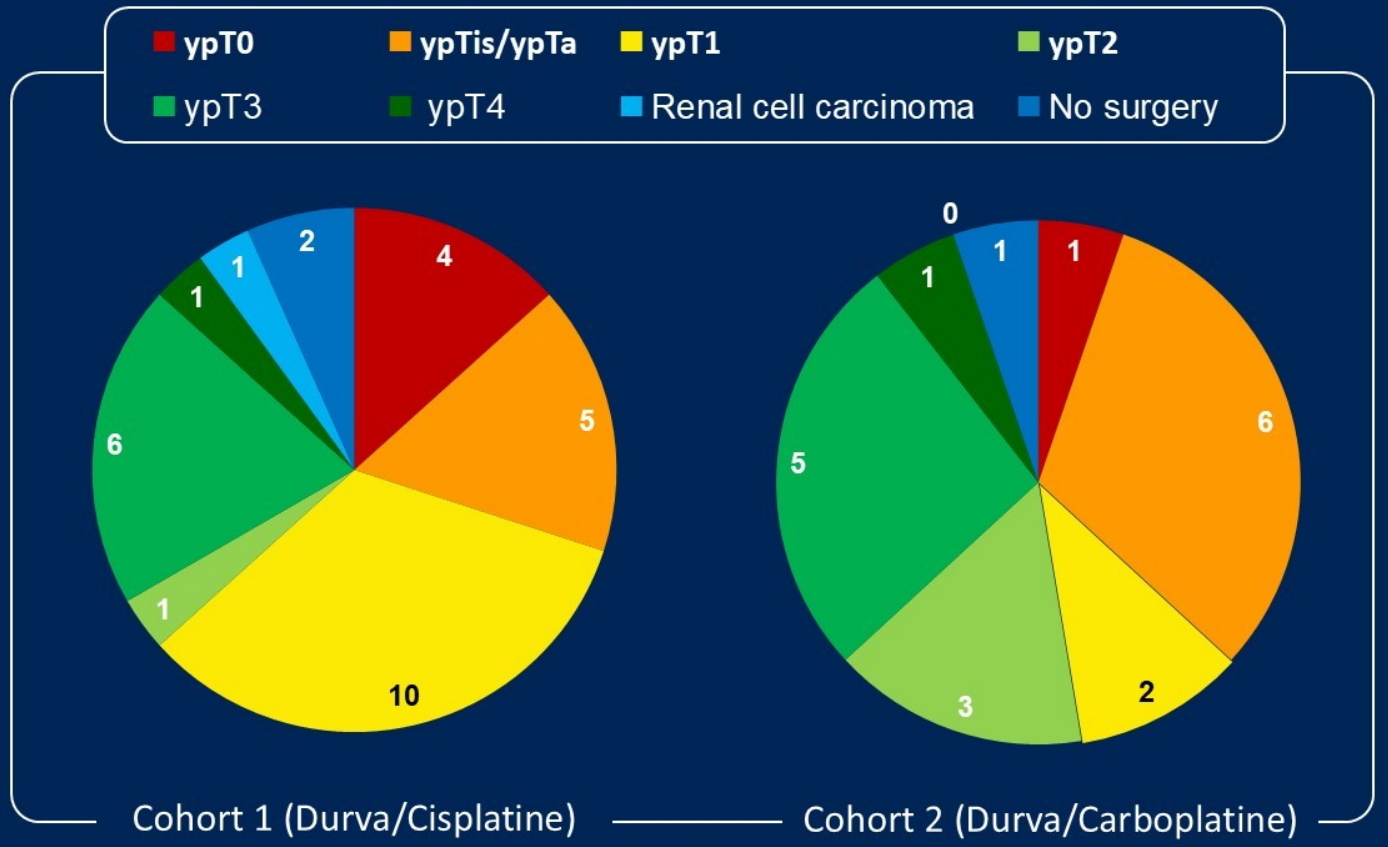
	Patients (n=49)	Cohort 1 (Durva /Cisplatine) (30)	Cohort 2 (Durva /Carboplatine) (19)
Age (years), median (range)	68 (38 - 79)	64.5 (38 -78)	71 (64 -79)
Sex (female), No (%)	20 (41%)	14 (47%)	6 (32%)
Smoker status, No (%)			
• Current or former smoker	27 (55%)	25 (83%)	7 (37%)
• Never smoked	22 (5%)	5 (17%)	12 (63%)
ECOG Performance-status score, No. (%)			
• 0	32 (65%)	21 (70%)	11 (58%)
• 1	17 (35%)	9 (30%)	8 (42%)
Tumor size mm, median (range)	38.2 (11-140)	33.4 (11-80)	49.6 (2–140)
Missing data	1	0	1
Tumor localization No (%)			
• Pelvic	6 (12%)	5 (17%)	1 (5%)
• Lumbar or iliac	11 (23%)	7 (23%)	4 (21%)
• Pyelocaliceal	31 (63%)	18 (60%)	13 (69%)
• Missing	1 (2%)		1 (5%)
GFR, No. (%)			
• ≥ 60 ml/min/1.73m2	30 (61%)	27 (90%)	3 (16%)
• <60 and ≥ 40 ml/min/1.73m^2	13 (27%)	2 (7%)	11 (58%)
• < 40 ml/min/1.73m2	2 (4%)	0	2 (10%)
• Missing data	4 (8%)	1 (3%)	3 (16%)
Tumor stage, No. (%)			
• Tis/Ta	3 (6%)	2 (7%)	1 (5%)
• T1	5 (10%)	3 (10%)	2 (11%)
• T2	18 (37%)	12 (40%)	6 (32%)
• T3	16 (33%)	11 (36%)	5 (26%)
• Missing	7 (14%)	2 (7%)	5 (26%)
Nodal involvement, No. (%)			
• N0	39 (80%)	25 (83%)	14 (74%)
• N1	3 (6%)	3 (10%)	0
• Missing	7 (14%)	2 (7%)	5 (26%)
Biopsy done, No. (%)	19 (39%)	13 (40%)	6 (32%)
Among them :			
• High grade	13/19 (68%)	10/13 (77%)	4/6 (66%)
Cytology done, No. (%)	29 (59%)	16 (55%)	13 (68%)
Among them :			
• High grade	12/29 (41%)	7/16 (43%)	5/13 (38%)

Histological diagnosis



Results

- Pathological response



	Cohort 1 (Durva /Cisplatine) (30)	Cohort 2 (Durva /Carboplatine) (19)
Pathological tumor stage at surgery No. (%)		
ypT0	**4 (13%) [95 CI 5%-30%]**	**1 (5%) [95 CI 1%-25%]**
ypTis/ypTa	5 (17%)	6 (31%)
ypT1	10 (34%)	2 (12%)
ypT2	1 (3%)	3 (16%)
ypT3	6 (20%)	5 (26%)
ypT4	1 (3%)	1 (5%)
Renal cell carcinoma	1(3%)	0
No surgery	2 (7%)	1 (5%)
Nodal status at surgery No. (%)		
Nx	8 (30%)	7 (39%)
N0	18 (67%)	9 (50%)
N1	0	2 (11%)
N2	1 (3%)	0 (%)

Secondary end point

TABLE 3. Most Frequent TRAEs, Including Grade 3 and 4 Adverse Events

Toxicity	Any Grade, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)
Adverse events of any cause			
Hematologic TRAEs	67		
Anemia	22 (45)	4 (8)	0
Neutropenia	10 (20)	4 (8)	1 (2)
Thrombopenia	5 (10)	1 (2)	1 (2)
Asthenia	29 (59)	2 (4)	0
Creatinine increase	23 (47)	2 (4)	0
Nausea	26 (53)	2 (4)	0
Diarrhea	8 (16)	1 (2)	0
Tinnitus	6 (12)	0	0
Mucositis	6 (12)	1 (2)	0
Urinary infection	5 (10)	0	0
Transaminase increase	4 (8)	0	0
Neuropathy	3 (6)	0	0
Infection	3 (6)	1 (2)	0
Lipase increase	2 (4)	1 (2)	0
Myocardial infarction	2 (4)	2 (4)	0
Unstable angina	1 (2)	1 (2)	0
Immuno-related adverse events			
Pruritus	3 (6)	0	0
Decrease cortisol level	1 (2)	0	
Rash	1 (2)	0	

Results

- Kidney function at baseline and cycle 4

Kidney function at baseline (clairance creatinine cockroft)	Arm 1 (n=30)	Arm 2 (n=19)
> 60 ml/min	26 (87%)	9 (47%)
40-60 ml/min	4 (13%)	8 (69%)
<40 ml/min	0 (0%)	2 (13%)
Missing data	0	0
Kidney function at cycle 4	**Arm 1**	**Arm 2**
> 60 ml/min	24 (80%)	6 (32%)
40-60 ml/min	4 (13%)	9 (47%)
<40 ml/min	1 (3%)	1 (5%)
Missing data	1	3

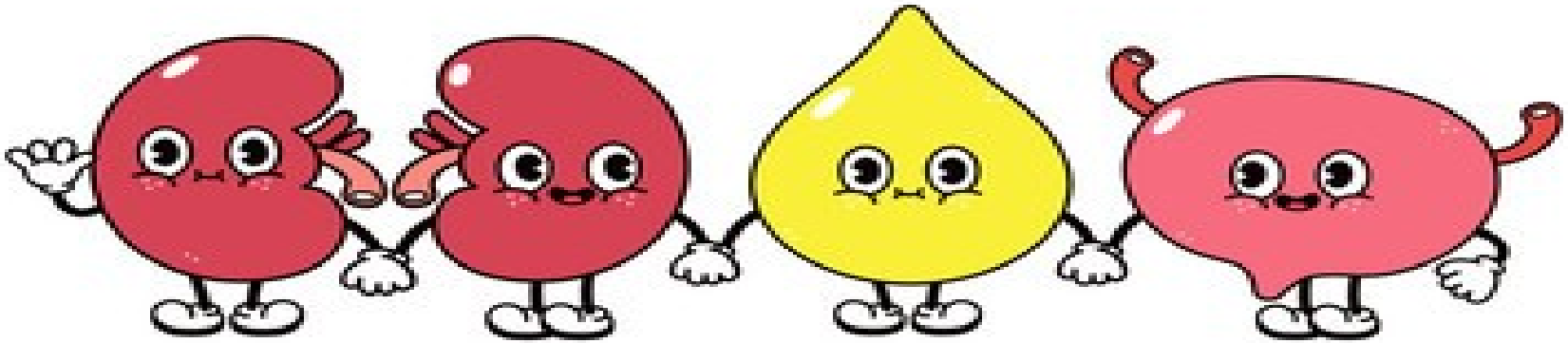
LIMITATIONS-

- Biopsy (not mandatory) for only 50% of the patients
- No control arm with platinum-based chemotherapy alone
- Absence of adjuvant IO
- Preliminary results, waiting for 2 years DFS (Disease-Free Survival)

Key Points-

This is the **first completed phase 2 neoadjuvant clinical trial** in **UTUC** that combines **immunotherapy with platinum-based chemotherapy**.

- The combination therapy has been shown to be **safe** and **does not negatively impact surgical outcomes**.
- The study demonstrated **promising results in reducing residual disease**, particularly with **cisplatin-based chemotherapy**.
- A **phase 3 trial** is planned to compare **chemotherapy alone** versus **chemotherapy plus immunotherapy**:
  → **INDUCT-3 trial**



THANK YOU