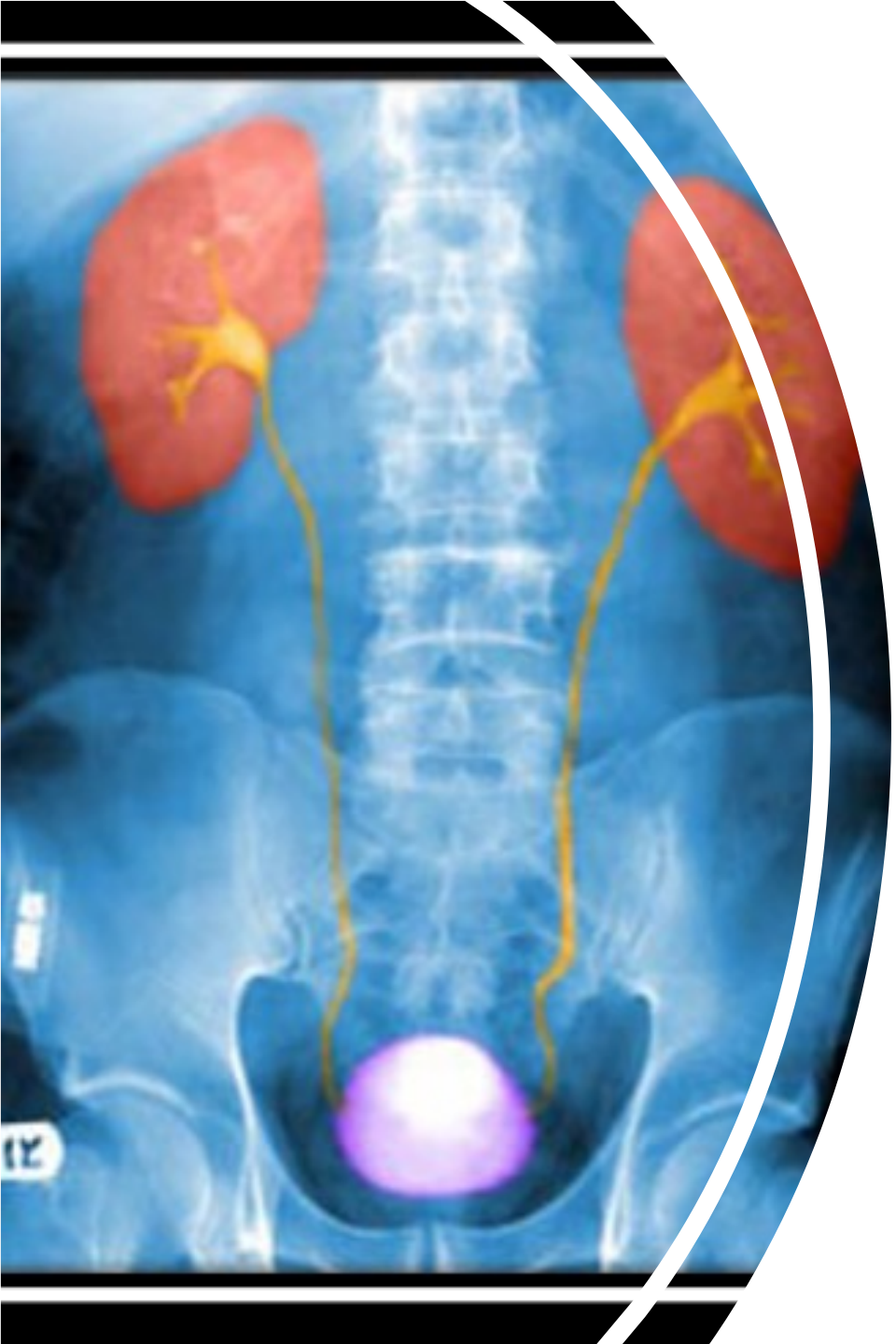


Updates in Kidney and Bladder Cancers: Where are we with immunotherapy and precision medicine?

December 1, 2023
Updates in Cancer Therapies: A Review of the 2023 ASCO & ESMO Annual Meetings

Karine Tawagi, MD

Assistant Professor of Medicine, Division of Hematology/Oncology, Genitourinary Oncology | UIC
Program Director, Division of Hematology/Oncology | UIC

UI Health | UIC
UNIVERSITY OF ILLINOIS CANCER CENTER

Bladder Updates Outline

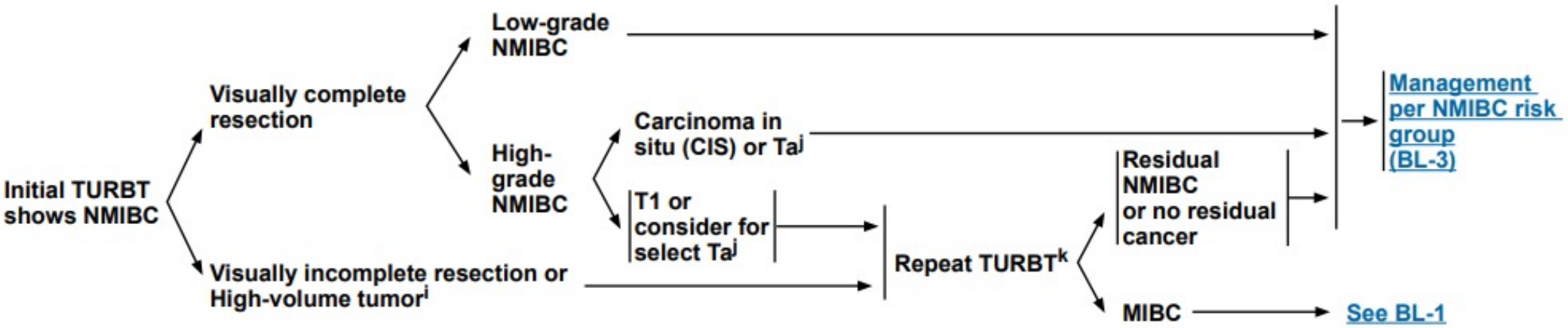
1. **Non-muscle invasive bladder cancer (NMIBC)**
   - Systemic therapy & novel intravesical therapy

2. **Muscle-invasive bladder cancer (MIBC)**
   - Adjuvant immunotherapy
   - Ongoing trials

3. **Metastatic urothelial carcinoma (mUC)**
   - New practice changing 1L regimen
   - Role of precision oncology: FGFR, her-2

NMIBC

RISK STRATIFICATION OF NMIBC



AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer*

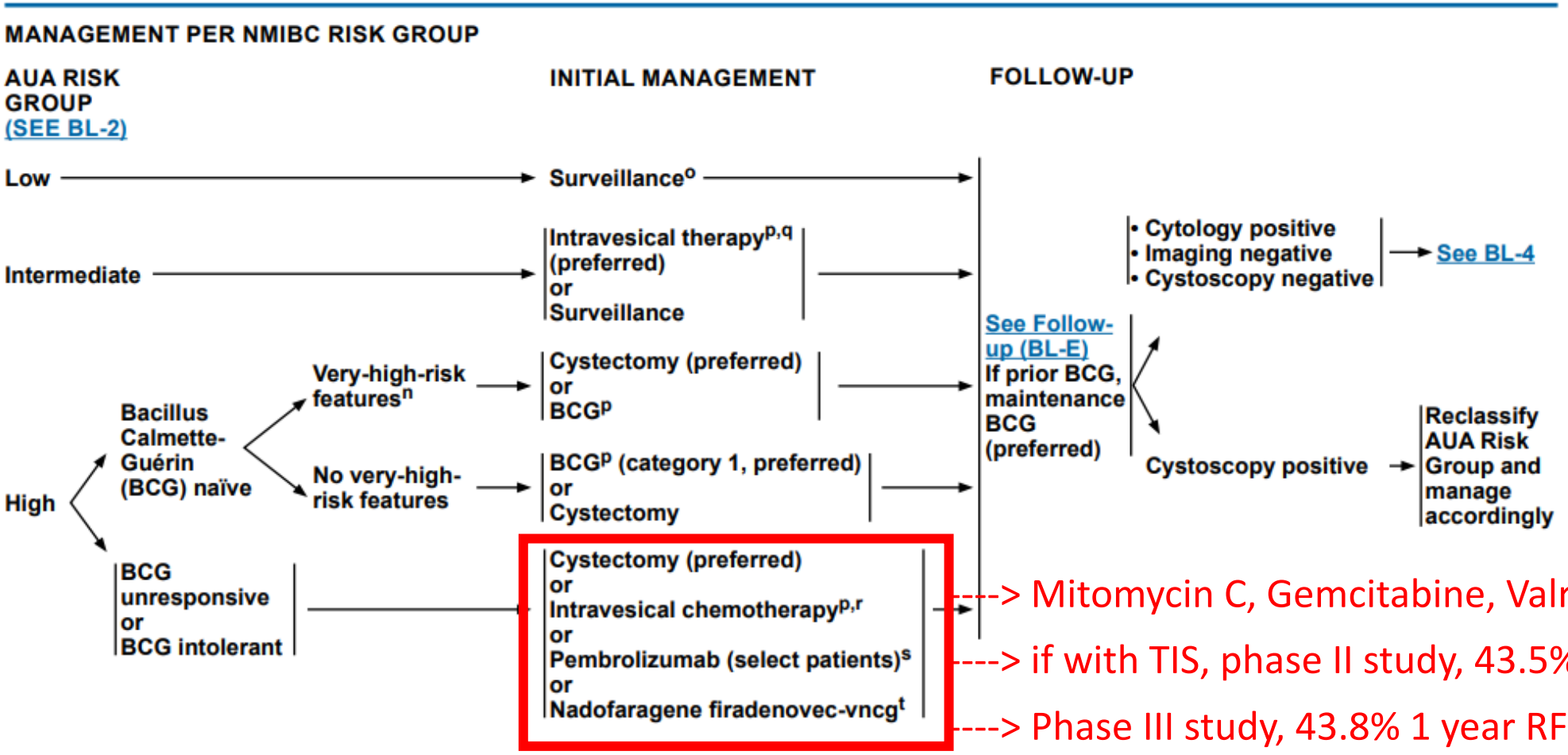
Low Risk	Intermediate Risk	High Risk
• Papillary urothelial neoplasm of low malignant potential • Low grade urothelial carcinoma ▸ Ta and ▸ ≤3 cm and ▸ Solitary	• Low grade urothelial carcinoma ▸ T1 or ▸ >3 cm or ▸ Multifocal or ▸ Recurrence within 1 year • High grade urothelial carcinoma ▸ Ta and ▸ ≤3 cm and ▸ Solitary	• High grade urothelial carcinoma ▸ CIS or ▸ T1 or ▸ >3 cm or ▸ Multifocal • Very high risk features (any): ▸ BCG unresponsive[l] ▸ Variant histologies[m] ▸ Lymphovascular invasion ▸ Prostatic urethral invasion

Reproduced with permission from Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol 2016;196:1021.
*Within each of these risk strata an individual patient may have more or fewer concerning features that can influence care.

--> higher risk of progression to invasive disease

--> CIS can metastasize without clinical invasion

NMIBC



----> Mitomycin C, Gemcitabine, Valrubicin, Gem/Doce

----> if with TIS, phase II study, 43.5% 1 year RFS, for 2 yrs

----> Phase III study, 43.8% 1 year RFS

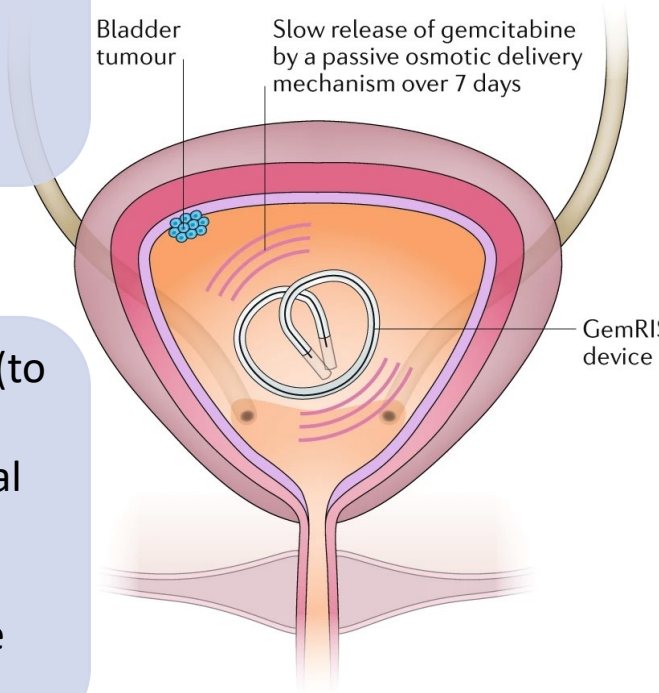
NMIBC – Ongoing Phase III Trials

KN-676: persistent or recurrent HR NMIBC after adequate BCG induction

- **IV pembrolizumab** (for 2 years) **+ BCG** vs **BCG monotherapy**
- Similar trials for other IO agents – POTOMAC (Durvalumab), CM-7G8 (Nivolumab), ALBAN (Atezolizumab)

SunRISe-2: HR NMIBC CIS (with or without papillary disease) unresponsive to BCG

- **TAR-200 + cetrelimab** vs **TAR-200 alone** vs **cetrelimab alone** (to 78 weeks)
- **TAR-200** is a novel drug delivery system for the sustained local release of gemcitabine in the bladder, relying on an osmotic system
- **TAR-210** - phase I trial looking at erdafitinib delivery via same route

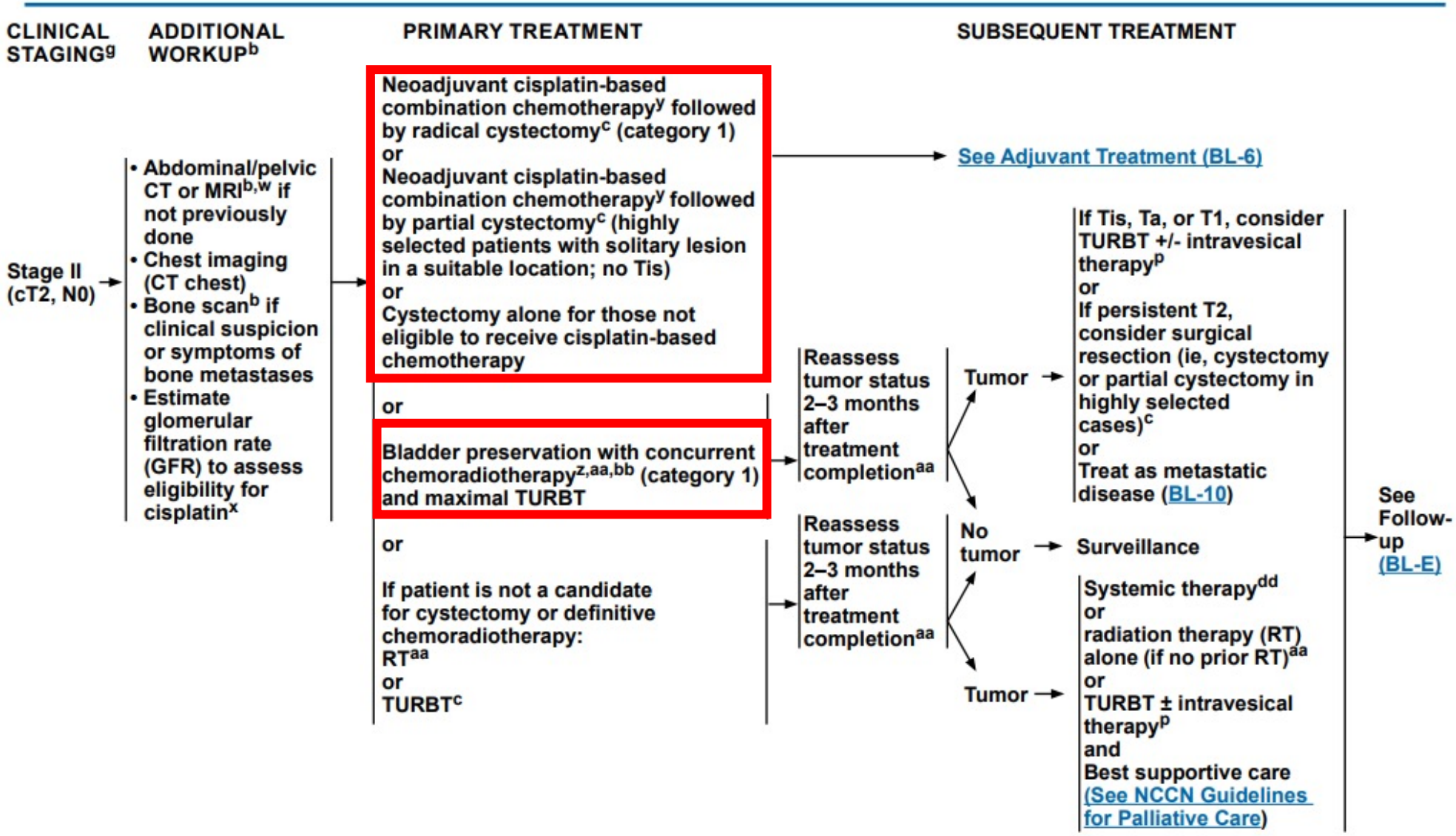


Nature Reviews Urology, 2018

MIBC

- Gold standard treatment is neoadjuvant chemo (NAC) followed by cystectomy
  - NAC: Gemcitabine/Cisplatin vs dose-dense MVAC
- Consider chemo-XRT / trimodal therapy
- If no neoadjuvant given, consider adjuvant chemo (cisplatin only, not carboplatin)
    - Lack of NAC option for cisplatin-ineligible patients

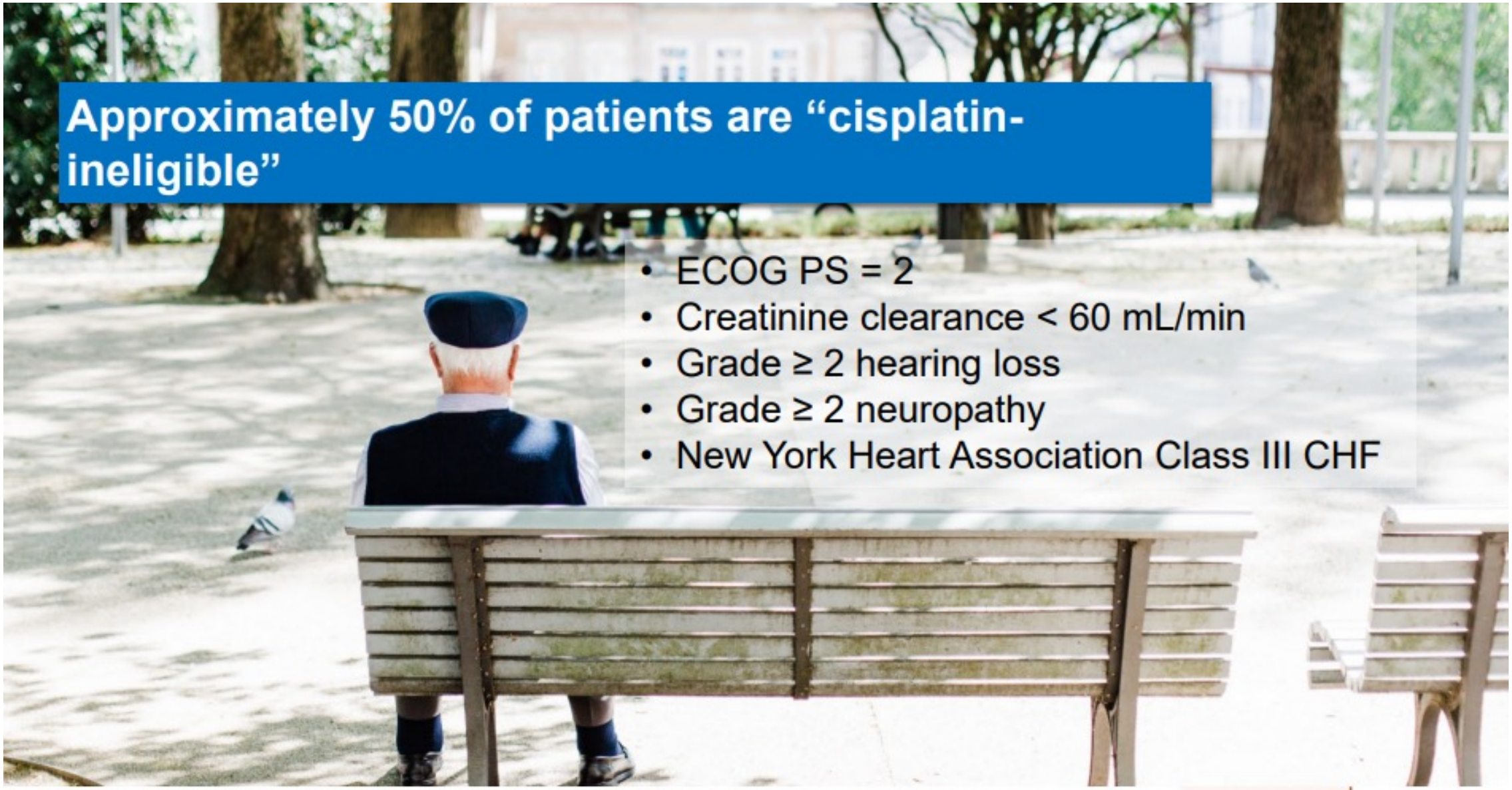
MIBC


CLINICAL STAGING[g]
ADDITIONAL WORKUP[b]
PRIMARY TREATMENT
SUBSEQUENT TREATMENT
Stage II (cT2, N0)
• Abdominal/pelvic CT or MRI[b,w] if not previously done
• Chest imaging (CT chest)
• Bone scan[b] if clinical suspicion or symptoms of bone metastases
• Estimate glomerular filtration rate (GFR) to assess eligibility for cisplatin[x]
Neoadjuvant cisplatin-based combination chemotherapy[y] followed by radical cystectomy[c] (category 1)
or
Neoadjuvant cisplatin-based combination chemotherapy[y] followed by partial cystectomy[c] (highly selected patients with solitary lesion in a suitable location; no Tis)
or
Cystectomy alone for those not eligible to receive cisplatin-based chemotherapy
See Adjuvant Treatment (BL-6)
or
Bladder preservation with concurrent chemoradiotherapy[z,aa,bb] (category 1) and maximal TURBT
Reassess tumor status 2–3 months after treatment completion[aa]
Tumor
If Tis, Ta, or T1, consider TURBT +/- intravesical therapy[p]
or
If persistent T2, consider surgical resection (ie, cystectomy or partial cystectomy in highly selected cases)[c]
or
Treat as metastatic disease (BL-10)
No tumor
Surveillance
or
If patient is not a candidate for cystectomy or definitive chemoradiotherapy:
RT[aa]
or
TURBT[c]
Reassess tumor status 2–3 months after treatment completion[aa]
Tumor
Systemic therapy[dd]
or
radiation therapy (RT) alone (if no prior RT)[aa]
or
TURBT ± intravesical therapy[p]
and
Best supportive care
(See NCCN Guidelines for Palliative Care)
See Follow-up (BL-E)

MIBC

Post cystectomy, there are high rates of distant recurrence in up to 50% of patients (*Donat et al, World Journal of Urology, 2006*)

Meta-analyses shows an absolute 5-year OS improvement of 5% with NAC (*Vale et al, European urology, 2005*)

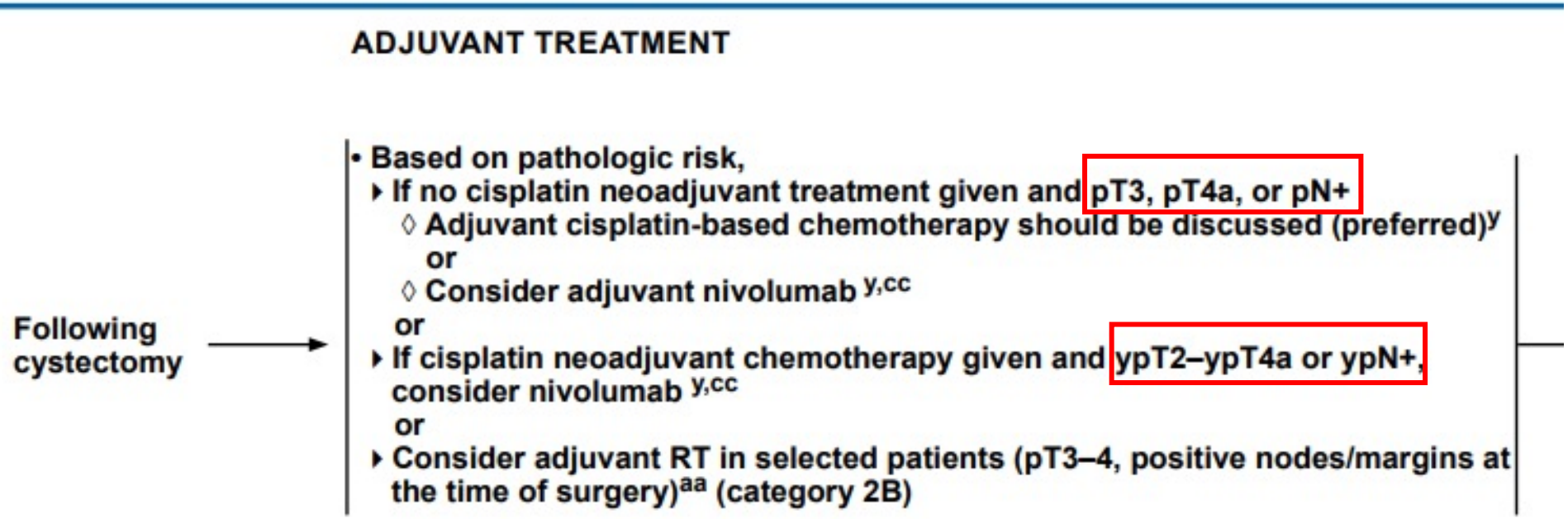


ECOG PS = Eastern Cooperative Oncology Group Performance Status; CHF = chronic heart failure.
Galsky MD, et al. *Lancet Oncol*. 2011;12(3):211-4.

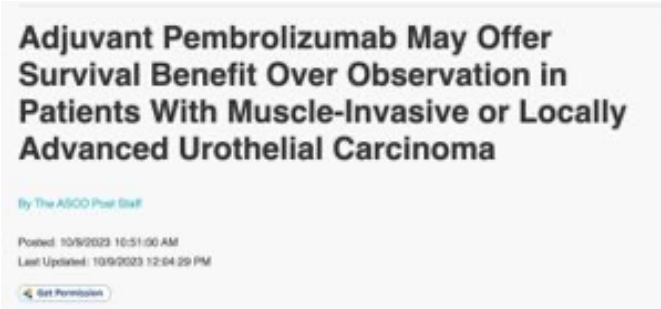
Great Debates & Updates | Genitourinary Oncology

M. Galsky, Sept 2022

MIBC – Adjuvant Treatment



- Based on **CM-274**: Nivolumab x 1 year improved DFS, await OS
  - **IMvigor010** (adjuvant Atezolizumab) was a negative trial, difference between PDL1 and PD1?
  - **AMBASSADOR** (adjuvant Pembrolizumab with recent press release
- Unclear role of adjuvant IO in some variant histologies e.g. squamous
- OS needed for PDL-1 negative group, and patients without NAC


Adjuvant Pembrolizumab May Offer Survival Benefit Over Observation in Patients With Muscle-Invasive or Locally Advanced Urothelial Carcinoma

MIBC – Definitive Systemic Therapy

- A subset of patients with MIBC will achieve a **pCR with NAC** (26%–38%) (*Griffiths, JCO 2011; Plimack, JCO 2014*)
  - Goal to avoid local treatment and its complications
  - Post-operative QOL may improve, but urinary and sexual dysfunction remains inferior to the general population (*Yang et al, Surg Oncol, 2016*)
- Need reliable biomarkers that can predict favorable outcomes for NAC
- Several potential DNA-based genetic alterations seem to correlate with pathologic response to NAC (*Girardi et al, Urologic Oncology, 2023*)
  - Many ongoing risk-adapted trials in patients with select deleterious DDR gene alterations – RETAIN (ddMVAC), RETAIN-2 (ddMVAC + nivolumab), A031701

One Future Cystectomy-Sparing Approach?

nature medicine HCRN 16-257 trial

Explore content ∨ About the journal ∨ Publish with us ∨

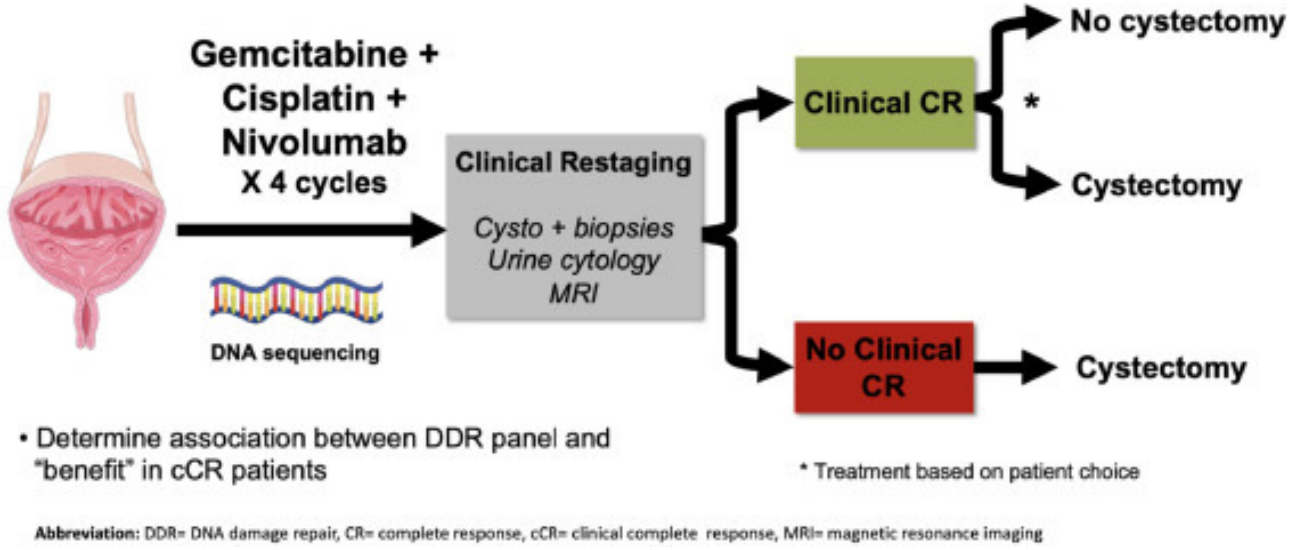
nature > nature medicine > articles > article

Article | Open access | Published: 02 October 2023

Gemcitabine and cisplatin plus nivolumab as organ-sparing treatment for muscle-invasive bladder cancer: a phase 2 trial

Matthew D. Galsky ✉, Siamak Daneshmand, Sudeh Izadmehr, Edgar Gonzalez-Kozlova, Kevin G. Chan, Sara Lewis, Bassam El Achkar, Tanya B. Dorff, Jeremy Paul Cetnar, Brock O. Neil, Anishka D'Souza, Ronac Mamtani, Christos Kyriakopoulos, Tomi Jun, Mahalya Gogerly-Moragoda, Rachel Brody, Hui Xie, Kai Nie, Geoffrey Kelly, Amir Horwitz, Yayoi Kinoshita, Ethan Ellis, Yohei Nose, Giorgio Ioannou, … Sumanta K. Pal + Show authors

Nature Medicine (2023) | Cite this article



- 76 patients were enrolled; of these, 33 achieved a cCR (43%, 95% CI: 32%-55%), and 32 of 33 who achieved a cCR opted to forgo immediate cystectomy
  - Somatic alterations in pre-specified genes (*ATM*, *RB1*, *FANCC* and *ERCC2*) or increased tumor mutational burden did not improve the positive predictive value of cCR

Neodjuvant/Adjuvant - what is approved

PRINCIPLES OF SYSTEMIC THERAPY

Neoadjuvant Chemotherapy (preferred for bladder)
Preferred regimen • DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3–6 cycles[1,2] **Other recommended regimens** • Gemcitabine and cisplatin for 4 cycles[3,4]

Adjuvant Therapy	
No previous platinum-based neoadjuvant therapy (pT3, pT4a, pN+)	**Preferred regimen** • DDMVAC with growth factor support for 3–6 cycles[1,2] **Other recommended regimens** • Gemcitabine and cisplatin for 4 cycles[3,4] • Nivolumab[5] Soon also Pembrolizumab?
Previous platinum-based neoadjuvant therapy (ypT2–ypT4a or ypN+)	**Other recommended regimen** • Nivolumab[5]

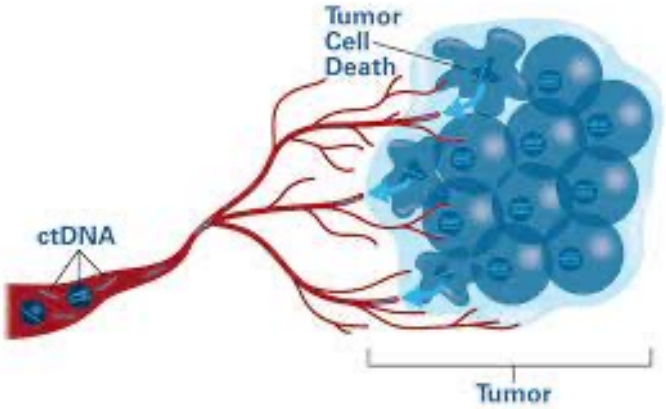
TMT/chemo-RT - what is approved

- Two phase III trials are looking at IO + TMT given radiation may be immunostimulatory and have synergistic effects with IO:
  - CRT +/- Pembrolizumab (MK-3475/KN-992)
  - CRT +/- Atezolizumab (SWOG/MRG 1806)

PRINCIPLES OF SYSTEMIC THERAPY

Radiosensitizing Chemotherapy Regimens[i]
Preferred regimens • Cisplatin[h] alone[35,39] • Low-dose gemcitabine[32,36,37] • 5-FU and mitomycin[34]
Other recommended regimen • Cisplatin and 5-FU[31,32] • Cisplatin and paclitaxel[31,33]
Useful in certain circumstances (not generally used for curative-intent chemoradiotherapy for organ preservation) • Taxane (docetaxel or paclitaxel) (category 2B) • 5-FU (category 2B) • Capecitabine (category 3)

Role of ctDNA in MIBC



- *Lindskrog et al, Clinical Cancer Research, 2023*:
  - ctDNA status is prognostic in NAC-treated and NAC-naïve patients and outperforms pathological downstaging in predicting treatment efficacy

- *Powles et al, European Urology, 2023:*
  - Updated OS from the **IMvigor 010** trial, showing those patients who were ctDNA positive post-surgery benefited from adjuvant atezolizumab with improved DFS and OS.
  - **IMvigor 011** should result next year, which is a randomized phase III study assessing the efficacy of atezolizumab vs placebo in patients with high-risk muscle-invasive bladder cancer who are ctDNA positive post-cystectomy

- **ALLIANCE A032103 (MODERN)** is a trial that will have a risk-adaptive approach based on ctDNA in the peri-operative space

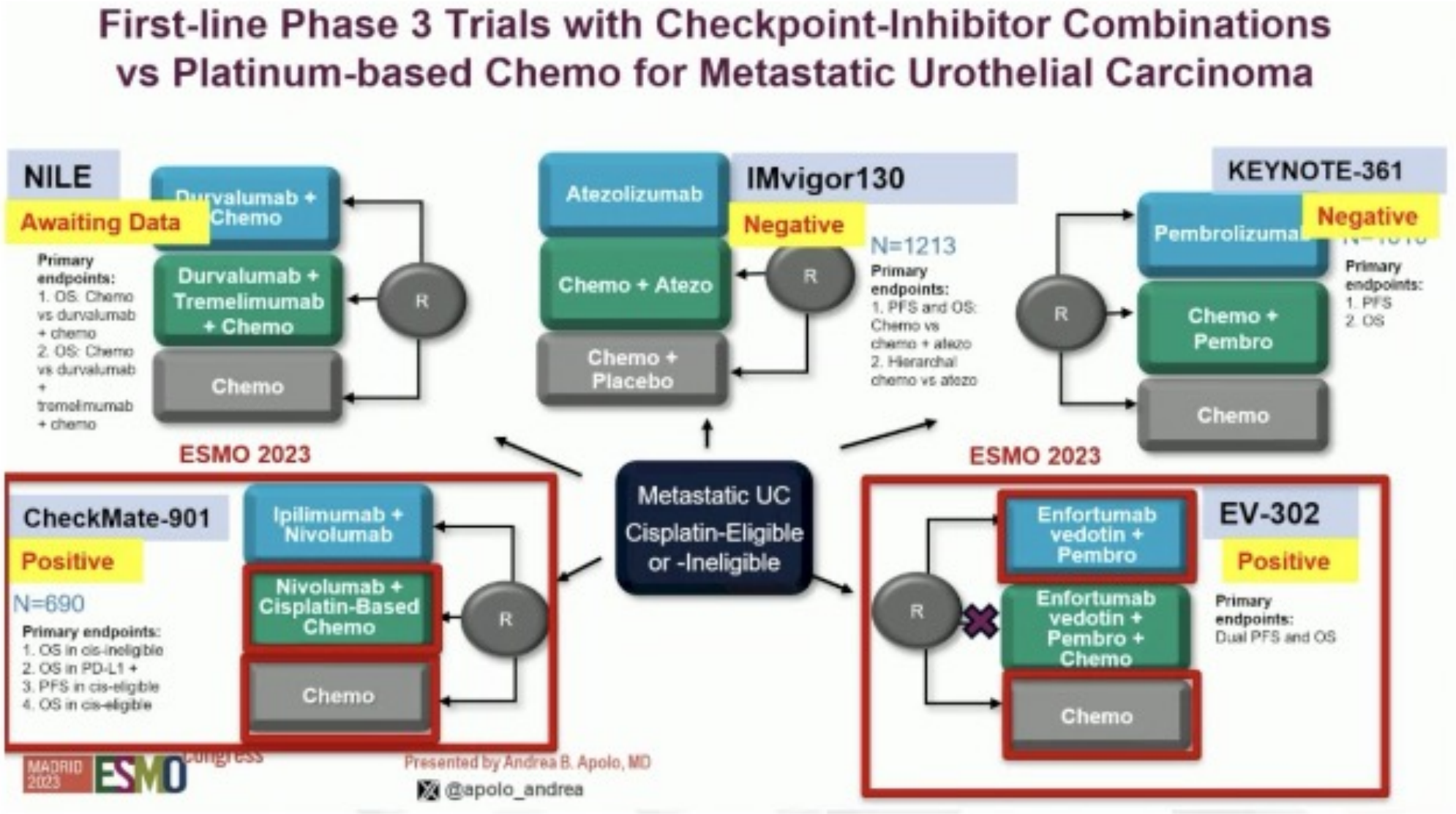
1L mUC pre-ESMO 2023

PRINCIPLES OF SYSTEMIC THERAPY

First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)	
Cisplatin eligible	**Preferred regimens** • Gemcitabine and cisplatin[4] (category 1) followed by avelumab maintenance therapy (category 1)[a,11] • DDMVAC with growth factor support (category 1)[2,8] followed by avelumab maintenance therapy (category 1)[a,11]
Cisplatin ineligible	**Preferred regimens** • Gemcitabine and carboplatin[12] followed by avelumab maintenance therapy (category 1)[a,11] • Pembrolizumab[14] (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy) • Pembrolizumab and enfortumab vedotin-ejfv[17] **Other recommended regimens** • Gemcitabine[15] • Gemcitabine and paclitaxel[16] • Atezolizumab[13] (only for patients whose tumors express PD-L1[b]) (category 2B) **Useful under certain circumstances** • Ifosfamide, doxorubicin, and gemcitabine[18] (for patients with good kidney function and good performance status) • Atezolizumab[13] (only for patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 3)

--> accelerated FDA approval in April 2023 based on Cohort K of EV-103

First-line Phase 3 Trials with Checkpoint-Inhibitor Combinations vs Platinum-based Chemo for Metastatic Urothelial Carcinoma



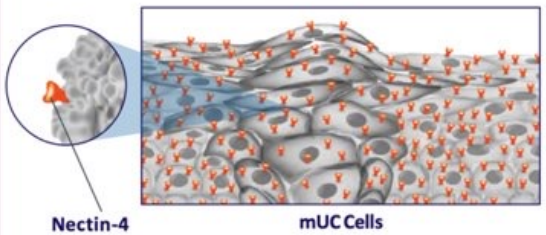
Enfortumab vedotin (EV)

Nectin-4 Is an Adhesion Protein Located On The Surface of Cells[1]

Nectin-4 is a cell adhesion molecule involved in multiple cellular processes known to be associated with oncogenesis, including[2-6]

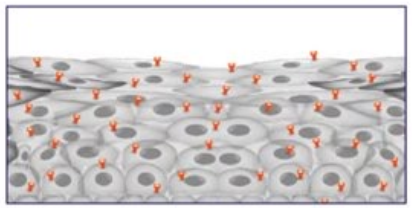
- Cell adhesion
- Migration
- Proliferation
- Differentiation
- Survival

Nectin-4 has been found to be over-expressed in **mUC cells**[1,6]



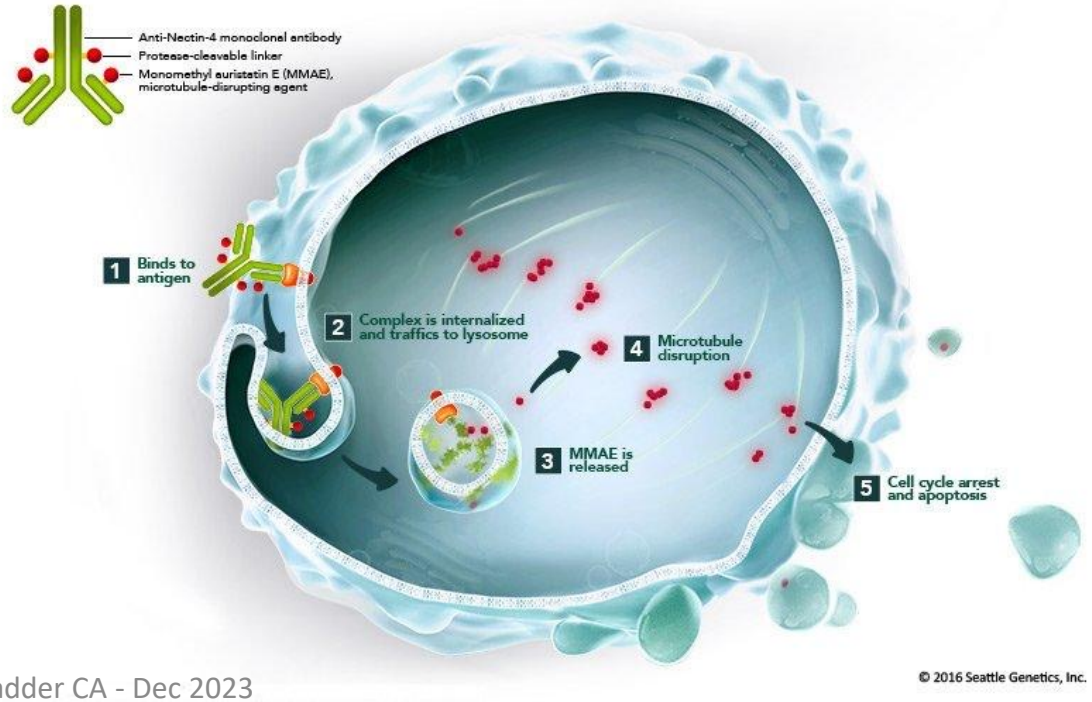
Density of Nectin-4 expression is for illustrative purposes only.

Nectin-4 was shown to be expressed to a lesser degree in **normal tissues**[6]



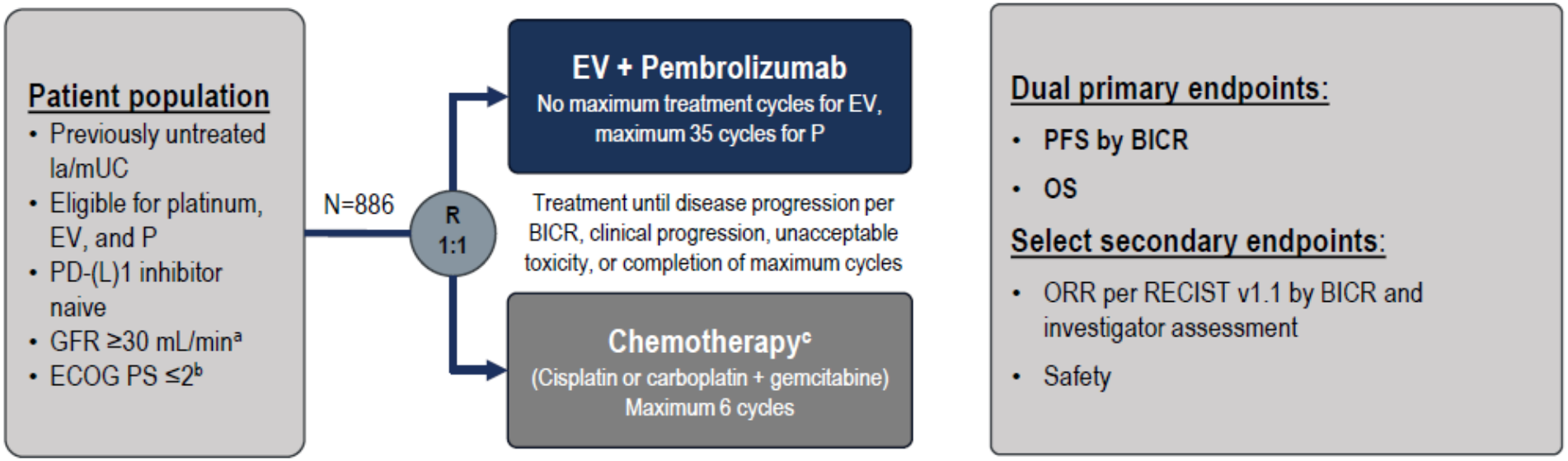
Normal tissues include, but are not limited to[6]

- Epithelium of the bladder
- Skin
- Salivary gland ducts
- Gastrointestinal tract
- Breast ducts



NCI Staff, Jan 2020

EV-302/KEYNOTE-A39 (NCT04223856)



Stratification factors: cisplatin eligibility (eligible/ineligible), PD-L1 expression (high/low), liver metastases (present/absent)

Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol-defined; patients received 3-week cycles of EV (1.25 mg/kg; IV) on Days 1 and 8 and P (200 mg; IV) on Day 1

Statistical plan for analysis: the first planned analysis was performed after approximately 526 PFS (final) and 356 OS events (interim); if OS was positive at interim, the OS interim analysis was considered final

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; ORR, overall response rate; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors
[a]Measured by the Cockcroft-Gault formula, Modification of Diet in Renal Disease, or 24-hour urine
[b]Patients with ECOG PS of 2 were required to also meet the additional criteria: hemoglobin ≥10 g/dL, GFR ≥50mL/min, may not have NYHA class III heart failure
[c]Maintenance therapy could be used following completion and/or discontinuation of platinum-containing therapy

Data cutoff: 08 Aug 2023; FPI: 7 Apr 2020, LPI: 09 Nov 2022

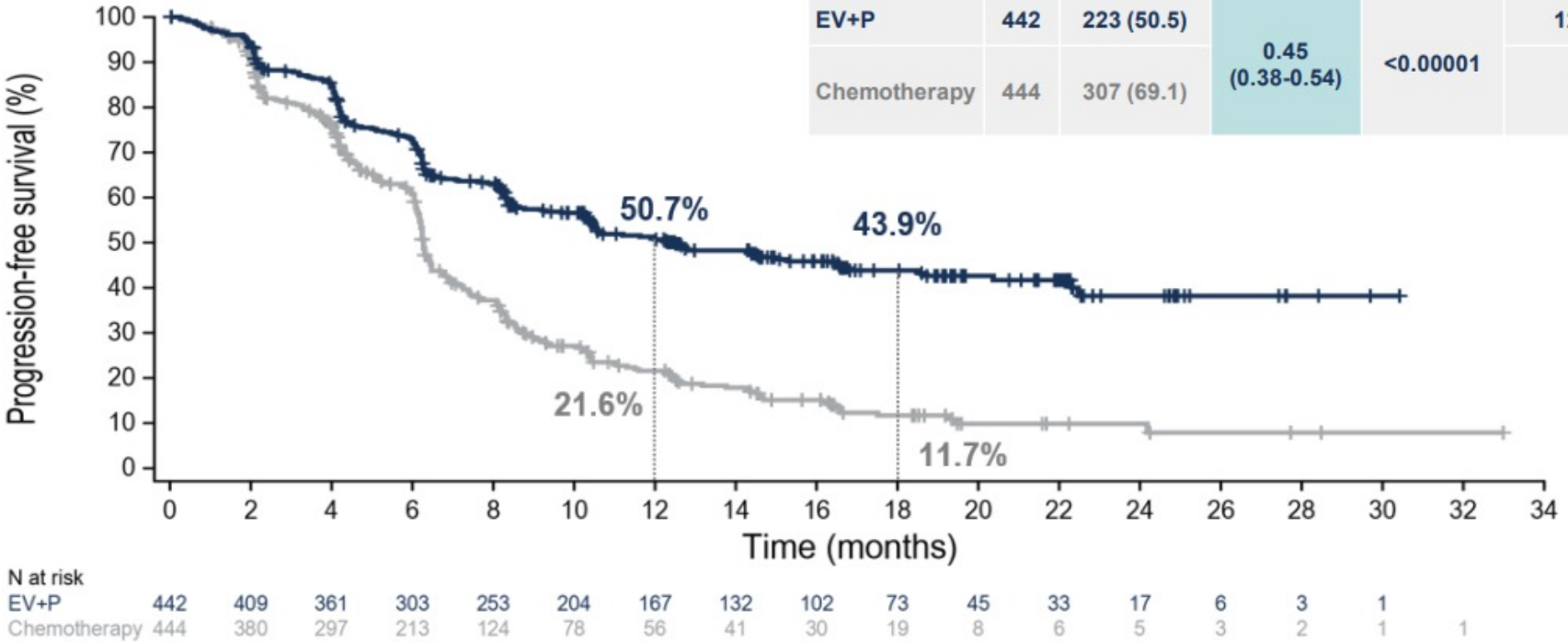
MADRID 2023 ESMO congress

Powles et al.

Progression-Free Survival per BICR

Risk of progression or death was reduced by 55% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mPFS (95% CI), months
EV+P	442	223 (50.5)	0.45 (0.38-0.54)	<0.00001	12.5 (10.4-16.6)
Chemotherapy	444	307 (69.1)			6.3 (6.2-6.5)



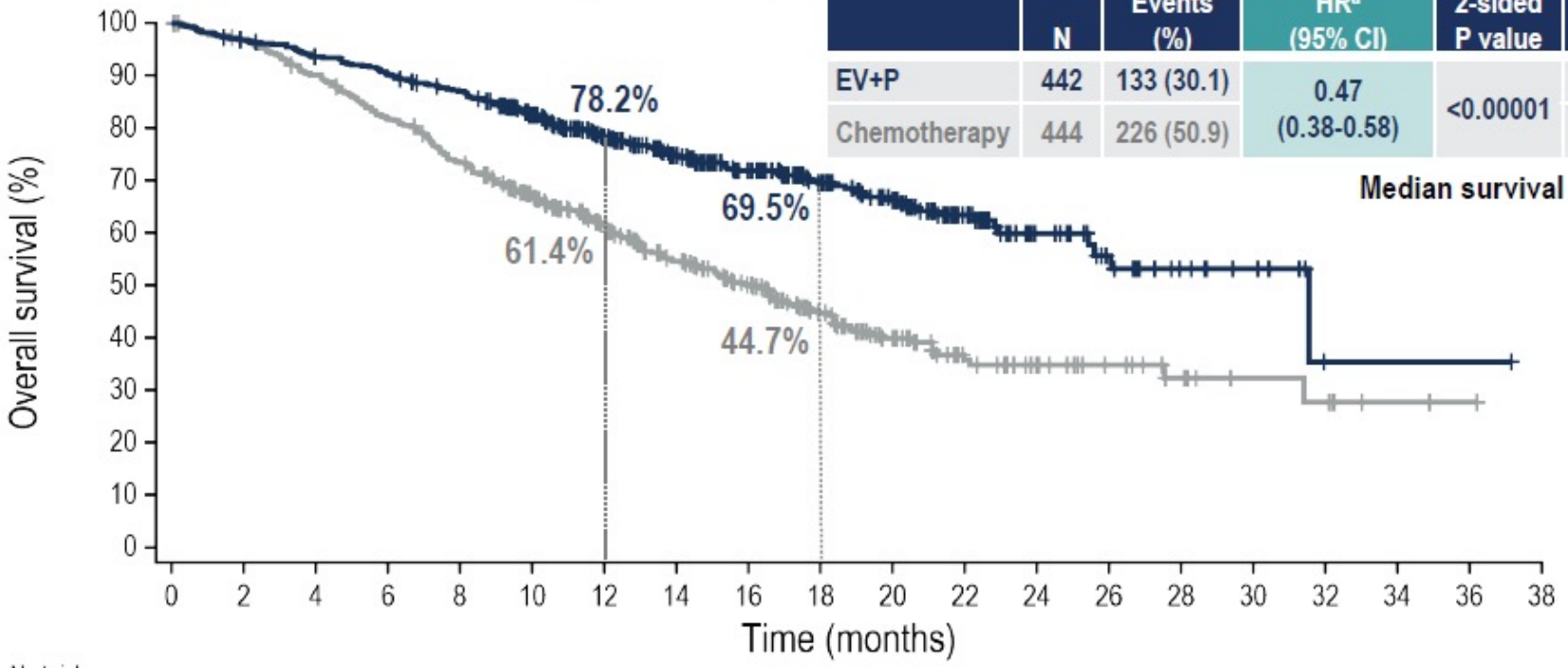
Powles, ESMO 2023

Overall Survival

Risk of death was reduced by 53% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mOS (95% CI), months
EV+P	442	133 (30.1)	0.47 (0.38-0.58)	<0.00001	31.5 (25.4-NR)
Chemotherapy	444	226 (50.9)			16.1 (13.9-18.3)

Median survival follow-up: 17.2 months



N at risk

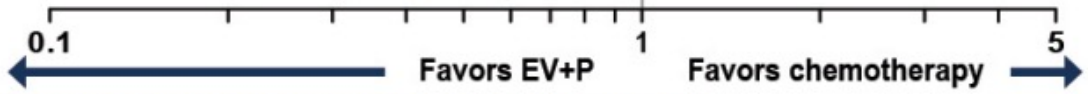
EV+P	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

Powles, ESMO 2023

Subgroup Analysis of OS

OS benefit in select pre-specified subgroups was consistent with results in overall population

Subgroup	Events/N EV+P	Events/N Chemotherapy	Hazard Ratio (95% CI)
Overall	133/442	226/444	0.47 (0.38-0.58)
Age			
<65 years	39/144	58/135	0.46 (0.30-0.71)
≥65 years	94/298	168/309	0.48 (0.38-0.63)
Sex			
Female	32/98	54/108	0.51 (0.32-0.80)
Male	101/344	172/336	0.47 (0.36-0.60)
ECOG PS			
0	44/223	94/215	0.36 (0.25-0.53)
1-2	89/219	131/227	0.54 (0.41-0.72)
Primary disease site of origin			
Upper tract	38/135	45/104	0.53 (0.34-0.83)
Lower tract	94/305	180/339	0.46 (0.36-0.59)
Liver metastases			
Present	43/100	67/99	0.47 (0.32-0.71)
Absent	90/342	159/345	0.47 (0.36-0.61)
PD-L1 expression			
Low (CPS <10)	53/184	99/185	0.44 (0.31-0.61)
High (CPS ≥10)	79/254	125/254	0.49 (0.37-0.66)
Cisplatin eligibility			
Eligible	69/244	106/234	0.53 (0.39-0.72)
Ineligible	64/198	120/210	0.43 (0.31-0.59)



Powles, ESMO 2023

Summary of Subsequent Systemic Therapy

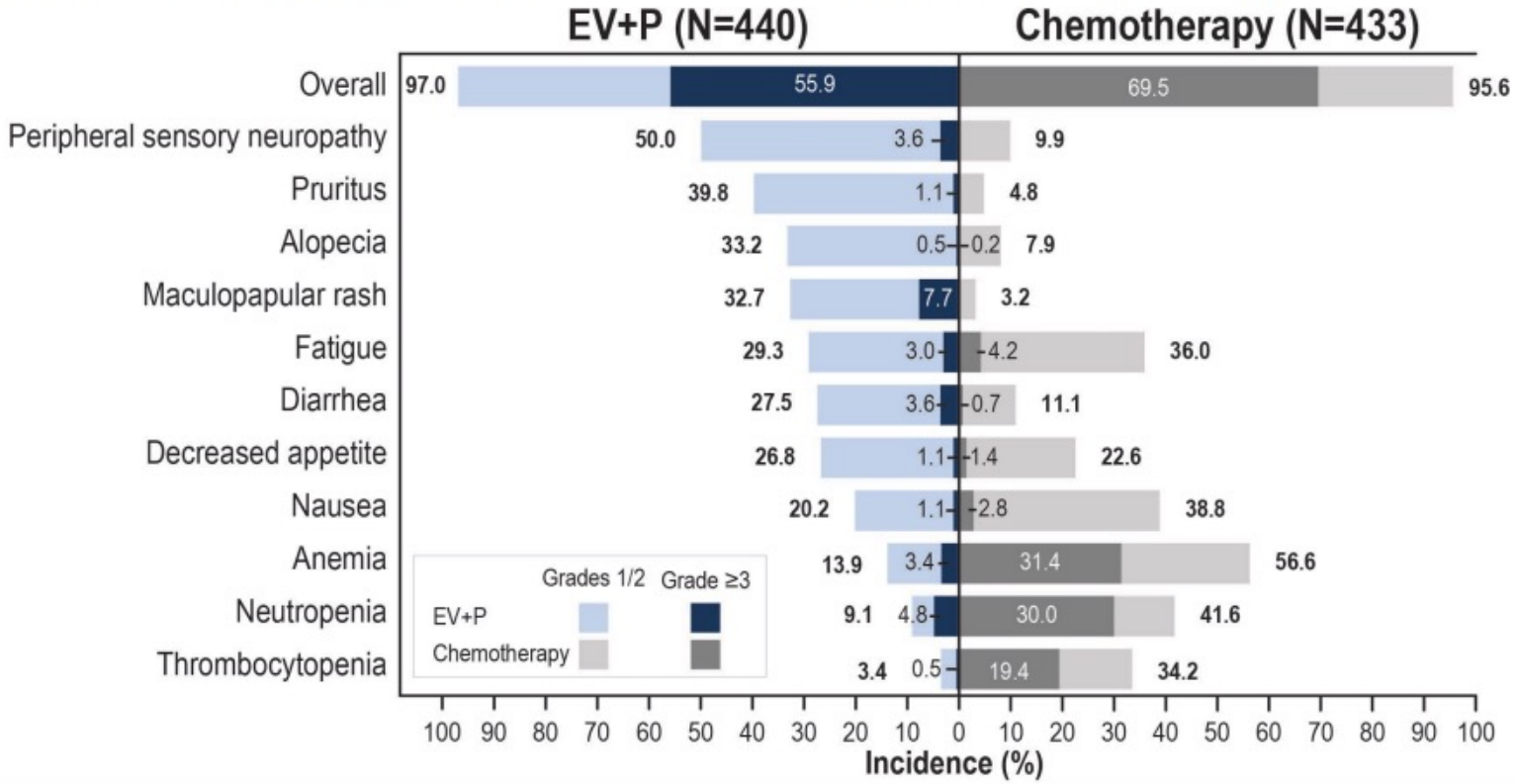
59% of patients in chemotherapy arm received subsequent PD-1/L1 inhibitors

	EV+P (N=442) n (%)	Chemotherapy (N=444) n (%)
First subsequent systemic therapy[a]	128 (28.9)	294 (66.2)
Platinum-based therapy	110 (24.9)	17 (3.8)
PD-1/L1 inhibitor-containing therapy	7 (1.6)	260 (58.6)
Maintenance therapy	0	143 (32.2)
Avelumab maintenance	0	135 (30.4)
PD-1/L1 inhibitor-containing therapy following progression	7 (1.6)	117 (26.4)
Other	11 (2.5)	17 (3.8)

Powles, ESMO 2023

Treatment-Related Adverse Events

Grade ≥3 events were 56% in EV+P and 70% in chemotherapy



Serious TRAEs:

- 122 (27.7%) EV+P
- 85 (19.6%) chemotherapy

TRAEs leading to death (per investigator):

EV+P: 4 (0.9%)

- Asthenia
- Diarrhea
- Immune-mediated lung disease
- Multiple organ dysfunction syndrome

Chemotherapy: 4 (0.9%)

- Febrile neutropenia
- Myocardial infarction
- Neutropenic sepsis
- Sepsis

Median number of cycles (range): 12.0 (1,46) for EV+P; 6.0 (1,6) for chemotherapy

Powles, ESMO 2023

CM-901

ORIGINAL ARTICLE

Nivolumab plus Gemcitabine–Cisplatin in Advanced Urothelial Carcinoma

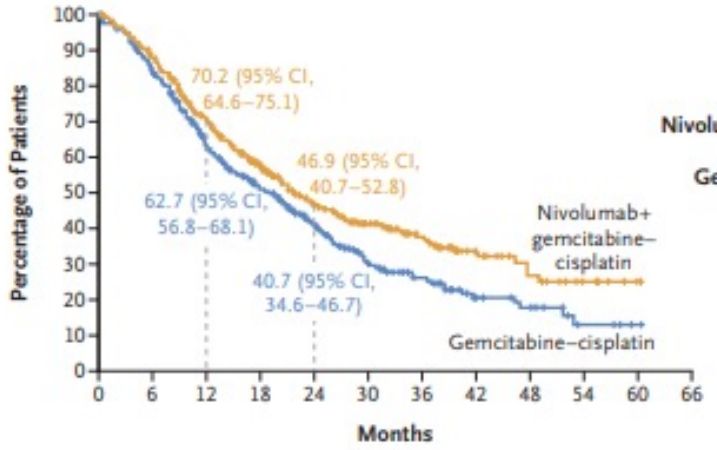
Michiel S. van der Heijden, M.D., Ph.D., Guru Sonpavde, M.D., Thomas Powles, M.D., Andrea Necchi, M.D., Mauricio Burotto, M.D., Michael Schenker, M.D., Ph.D., Juan Pablo Sade, M.D., Aristotelis Bamias, M.D., Ph.D., Philippe Beuzeboc, M.D., Jens Bedke, M.D., Jan Oldenburg, M.D., Ph.D., Gurkamal Chatta, M.D., et al., for the CheckMate 901 Trial Investigators*

Article Figures/Media Metrics

November 9, 2023
N Engl J Med 2023; 389:1778-1789
DOI: 10.1056/NEJMoa2309863

22 References 1 Citing Article

A Overall Survival



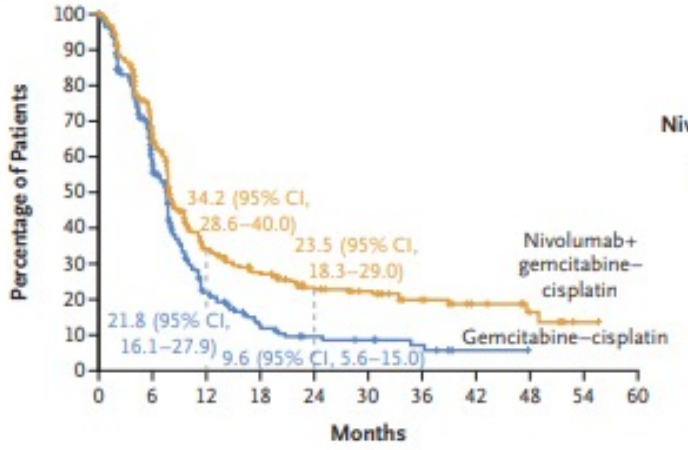
	No. of Events/ No. of Patients	Median Overall Survival (95% CI)
		mo
Nivolumab+Gemcitabine–Cisplatin	172/304	21.7 (18.6–26.4)
Gemcitabine–Cisplatin	193/304	18.9 (14.7–22.4)

Hazard ratio for death, 0.78 (95% CI, 0.63–0.96)
P=0.02

No. at Risk

Nivolumab+gemcitabine–cisplatin	304	264	196	142	97	69	48	25	15	7	2	0
Gemcitabine–cisplatin	304	242	166	122	82	49	33	17	13	4	1	0

B Progression-free Survival



	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)
		mo
Nivolumab+Gemcitabine–Cisplatin	211/304	7.9 (7.6–9.5)
Gemcitabine–Cisplatin	191/304	7.6 (6.1–7.8)

Hazard ratio for disease progression or death, 0.72 (95% CI, 0.59–0.88)
P=0.001

No. at Risk

Nivolumab+gemcitabine–cisplatin	304	179	82	57	41	31	19	11	6	1	0	
Gemcitabine–cisplatin	304	119	35	17	10	8	5	1	0	0	0	

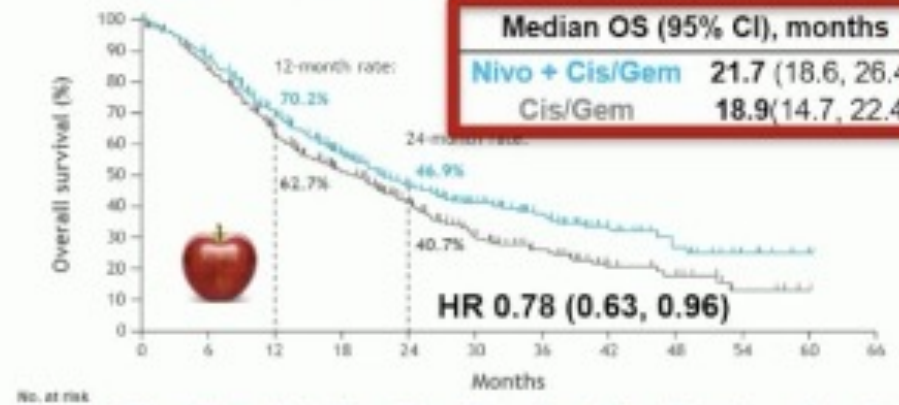
https://www.nejm.org/doi/pdf/10.1056/NEJMoa2309863

Both sequential and combination chemo and CPI have efficacy

Nivo+Cis/Gem vs Cis/Gem

CheckMate 901 Study

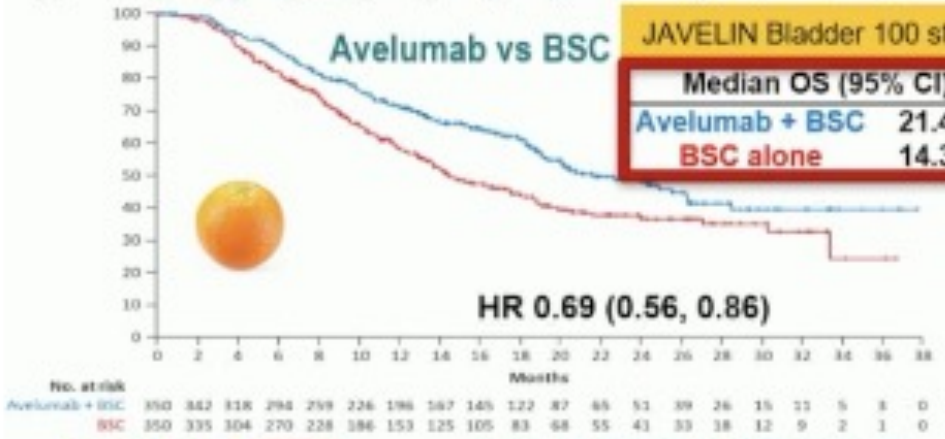
Median OS (95% CI), months	
Nivo + Cis/Gem	**21.7** (18.6, 26.4)
Cis/Gem	**18.9** (14.7, 22.4)



Avelumab vs BSC

JAVELIN Bladder 100 study

Median OS (95% CI), months	
Avelumab + BSC	**21.4** (18.9, 26.1)
BSC alone	**14.3** (12.9, 17.9)



MADRID 2023 ESMO congress

Powles T, et al. NEJM 2020 Sep 24;383(13):1218-1230

- We cannot directly compare these studies
- Different patient populations
- Avelumab maintenance study included only responders to 1L chemo
- Length of maintenance CPI therapy was similar: ~6 months for both

Presented by Andrea B. Apolo, MD

@apolo_andrea

What would be the best 2nd line therapy?

First-Line

- Enfortumab vedotin + Pembrolizumab

Second-Line?

Cisplatin-eligible

- Cisplatin + gemcitabine
- Dose-dense methotrexate + vinblastine + doxorubicin + cisplatin (ddMVAC)

Cisplatin-ineligible

- Carboplatin + gemcitabine

Beyond-Second -Line

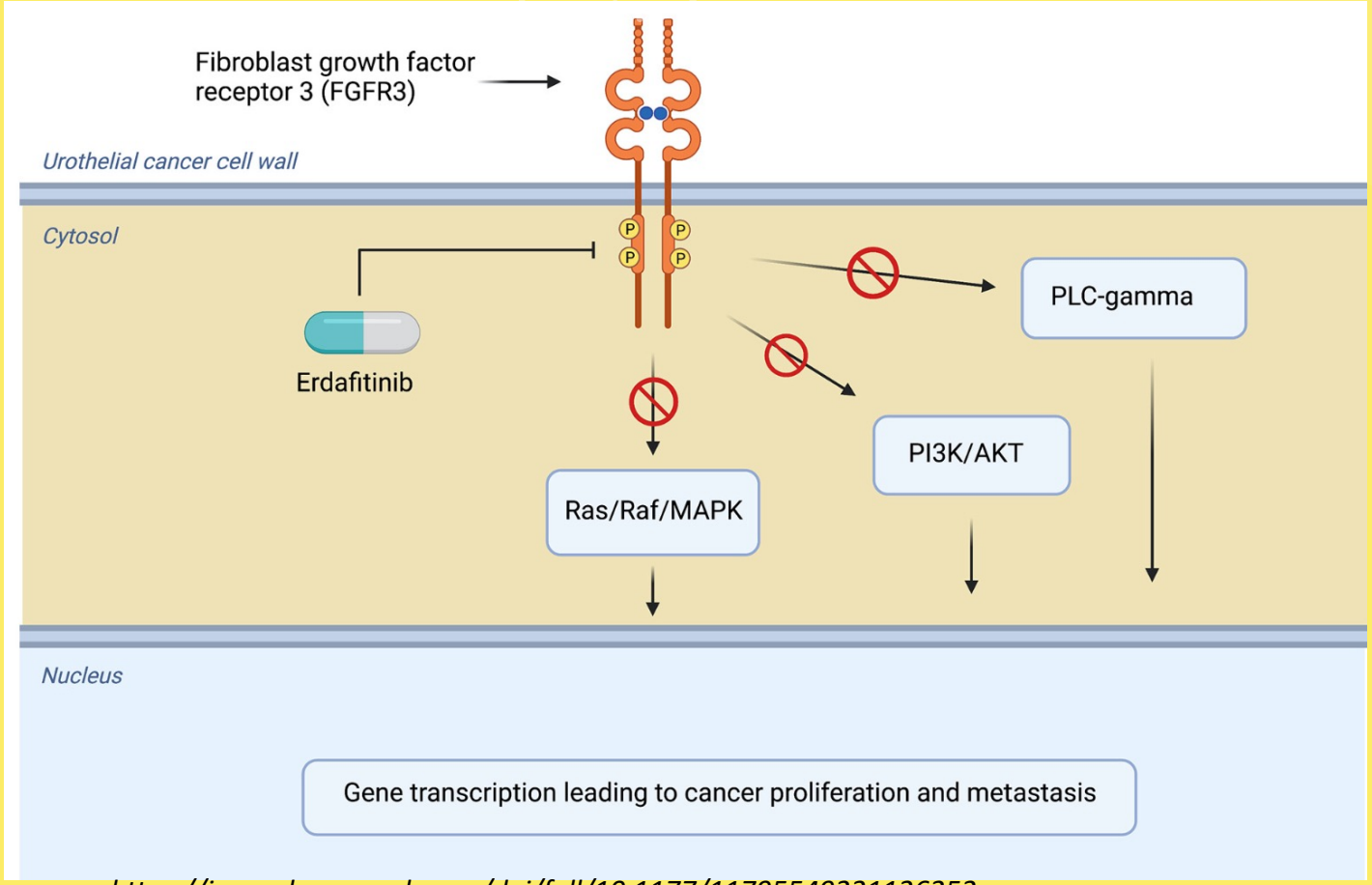
- Erdafitinib (if tumor + FGFR 2/3 genetic alterations)
- Sacituzumab govitecan
- Clinical trial
- Paclitaxel, docetaxel, or vinflunine

Disitamab vedotin for her-2+?

A. Apolo, ESMO, Oct 2023

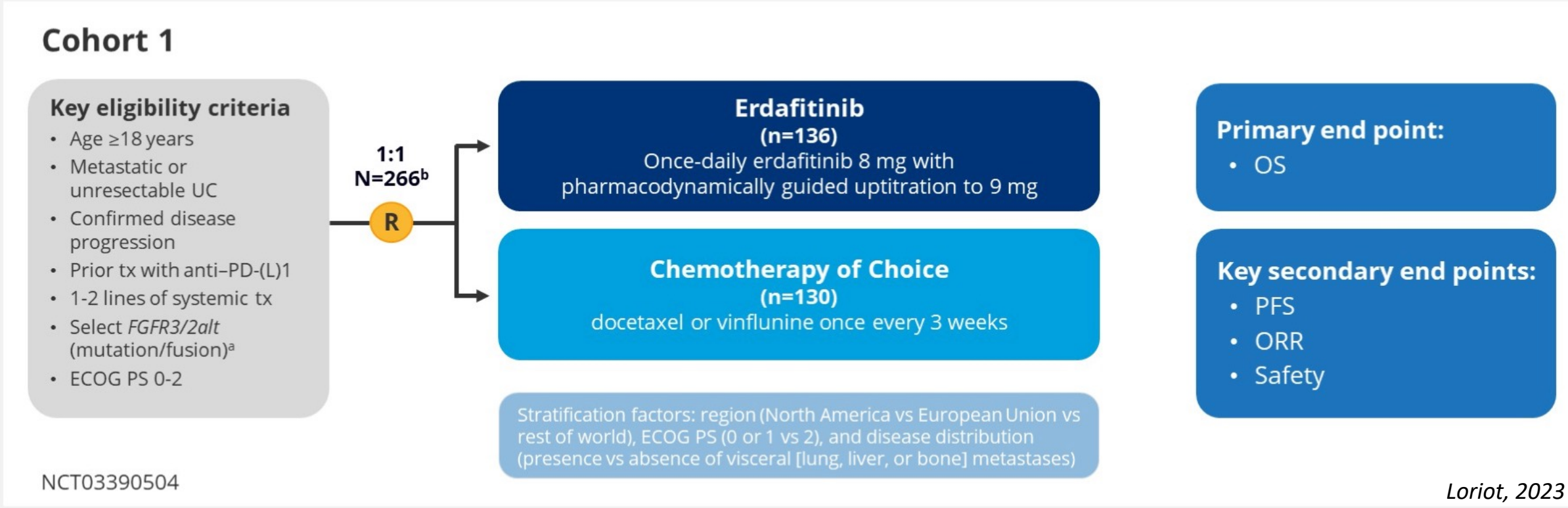
FGFR Pathway in mUC

- All patients should be tested for FGFR 2/3 alterations - **seen in 20% of all mUC and 30% of UTUC**:
  - NGS testing of DNA and RNA
  - FGFR3 mutations (R248C, S249C, G370C, or Y373C)
  - Fusions (translocations): FGFR2–BICC1, FGFR2–CASP7, FGFR3–TACC3_V1, FGFR3–TACC3_V3, or FGFR3–BAIAP2L1



https://journals.sagepub.com/doi/full/10.1177/11795549221126252

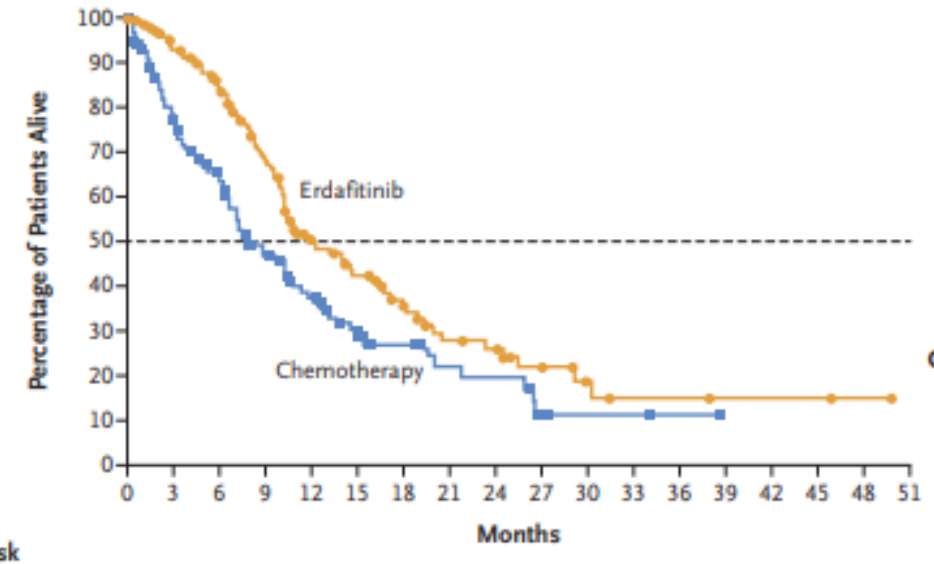
Phase 3 THOR Study: Erdafitinib Versus Chemotherapy of Choice in Patients With Advanced Urothelial Cancer and Selected FGFR Aberrations



Loriot, 2023

- Demonstrated superior OS, PFS and ORR of Erdafitinib compared to single agent chemotherapy in patients with FGFR 3/2 alterations

[a]Molecular eligibility can be confirmed using either central or local historical *FGFR* test results (Qiagen assay). If a patient was enrolled based on local historical testing, a tissue sample must still be submitted at the time of enrollment for retrospective confirmation (by central lab) of *FGFR* status. Tumors must have ≥1 of the following translocations: *FGFR2-BICC1*, *FGFR2-CASP7*, *FGFR3-TACC3_V1*, *FGFR3-TACC3_V3*, *FGFR3-BAIAP2L1*; or 1 of the following *FGFR3* gene mutations: R248C, S249C, G370C, Y373C.
[b]Number of patients randomized at the time of the interim analysis (data cutoff January 15, 2023).
ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; *FGFR3/2alt*, *FGFR3/2* alterations; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Q3W, every 3 weeks; tx, treatment; UC, urothelial cancer.



	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI)
		mo
Erdafitinib	77/136	12.1 (10.3–16.4)
Chemotherapy	78/130	7.8 (6.5–11.1)

Hazard ratio for death, 0.64 (95% CI, 0.47–0.88)
P=0.005

No. at Risk (no. with censored data)

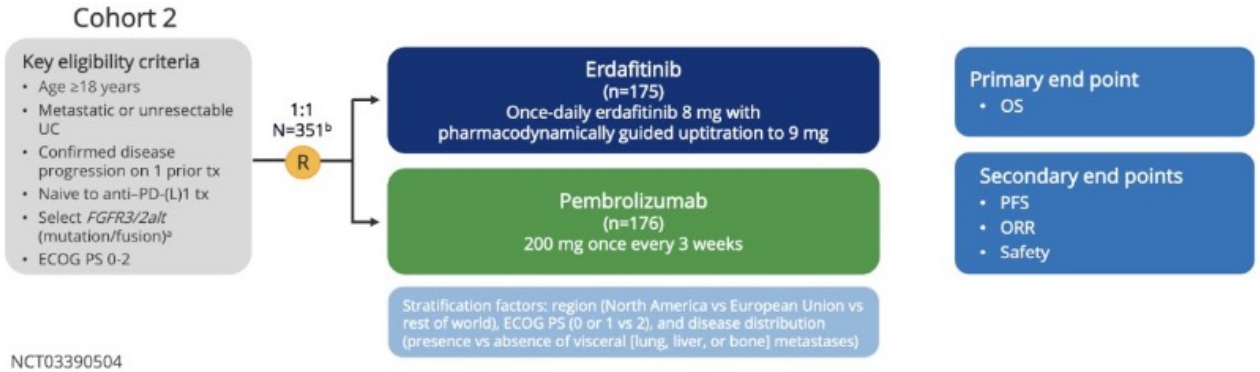
Erdafitinib	136	117	97	74	46	35	25	17	15	9	5	3	3	2	2	2	1	0
	(0)	(10)	(20)	(25)	(35)	(39)	(44)	(47)	(48)	(52)	(55)	(56)	(56)	(57)	(57)	(57)	(58)	(59)
Chemotherapy	130	87	66	43	30	18	13	9	8	3	2	2	1	0	0	0	0	0
	(0)	(17)	(25)	(30)	(35)	(41)	(45)	(47)	(47)	(49)	(50)	(50)	(51)	(52)	(52)	(52)	(52)	(52)

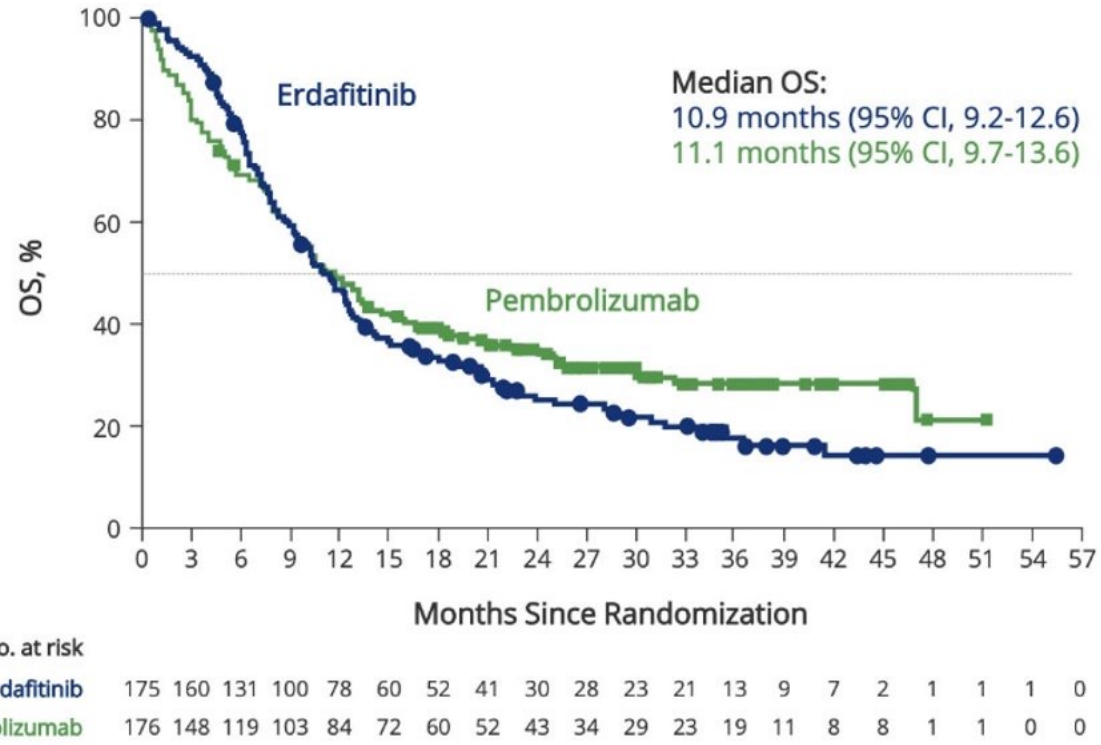
Figure 2. Overall Survival.

Shown are Kaplan–Meier estimates of overall survival. Circles and squares indicate censored data in the erdafitinib group and chemotherapy group, respectively. Results for overall survival in key subgroups are provided in Figure S3.

Loriot, NEJM, 2023

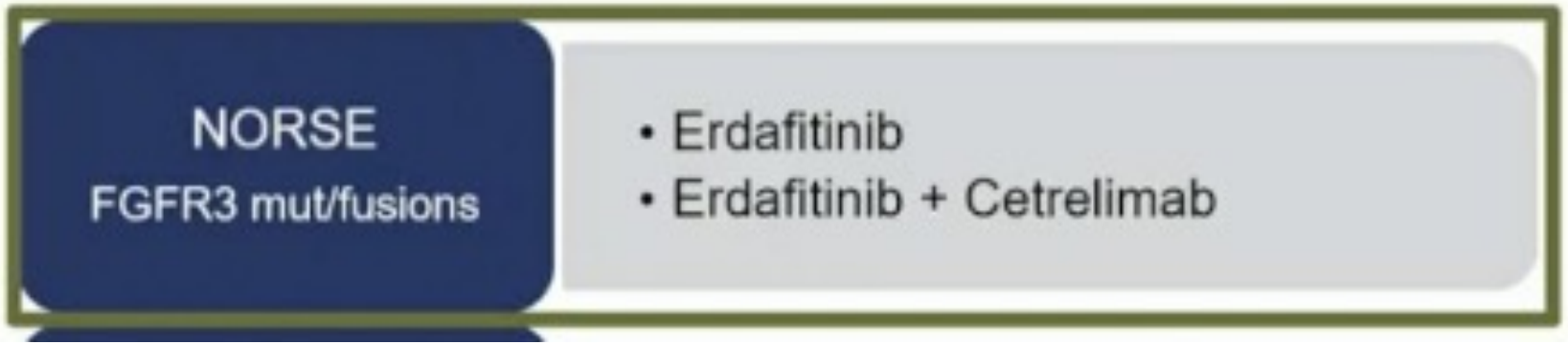
THOR Cohort 2





Siefker-Radtke, ESMO 2023

NORSE Trial –



Conclusions: Combination ERDA+CET demonstrated clinically meaningful activity and was well tolerated. These results, in 1L cis-ineligible pts, support previously described activity of ERDA monotherapy in FGFRa mUC. The safety profile was consistent with the known profile for ERDA and CET with no additive toxicity for the combination. Clinical trial information: NCT03473743.

	ERDA+CET (n=44)	ERDA (n=43)
ORR, % (95% CI)	54.5 (38.8, 69.6)	44.2 (29.1, 60.1)
Confirmed CR, n (%)	6 (13.6)	1 (2.3)
DCR, % (95% CI)	79.5 (64.7, 90.2)	88.4 (74.9, 96.1)
Median DOR (95% CI), mo	11.10 (8.77, NE)	9.72 (4.60, NE)
Median PFS (95% CI), mo	10.97 (5.45, 13.63)	5.62 (4.34, 7.36)

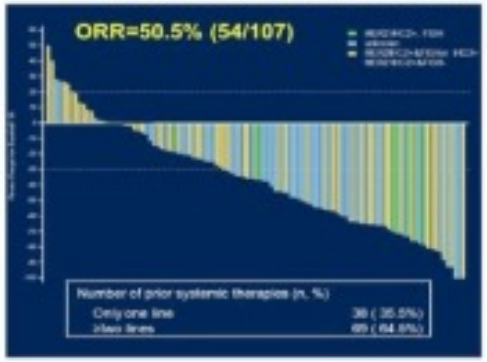
Siefker-Radtke, ESMO 2023

Her-2 in mUC

- Expression level of HER2 in UC : 48% with overexpression and approximately 20% with low expression *(Fleischmann et al., 2011; Yorozu et al., 2020)*

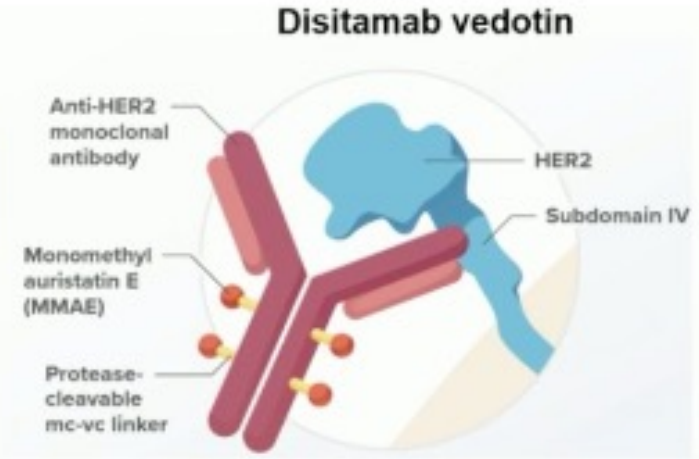
Another antibody drug conjugate with an MMAE payload is disitamab vedotin, which targets HER2. In September 2020, this drug was granted US FDA breakthrough therapy designation for urothelial carcinoma in the 2nd or 3rd line settings.

N=107 In the second or third-line setting



Sheng, et al. ASCO 2022 abstract 4518

Sept 2020 USA FDA granted Breakthrough Therapy designation to disitamab vedotin in UC



Similar to EV + pembrolizumab, it appears that the combination of disitamab vedotin + toripalimab (anti-PD-1) is associated with promising efficacy outcomes in HER2+ metastatic urothelial carcinoma patients.

Phase III study (NCT04264936) ongoing

A. Apolo, Oct 2023

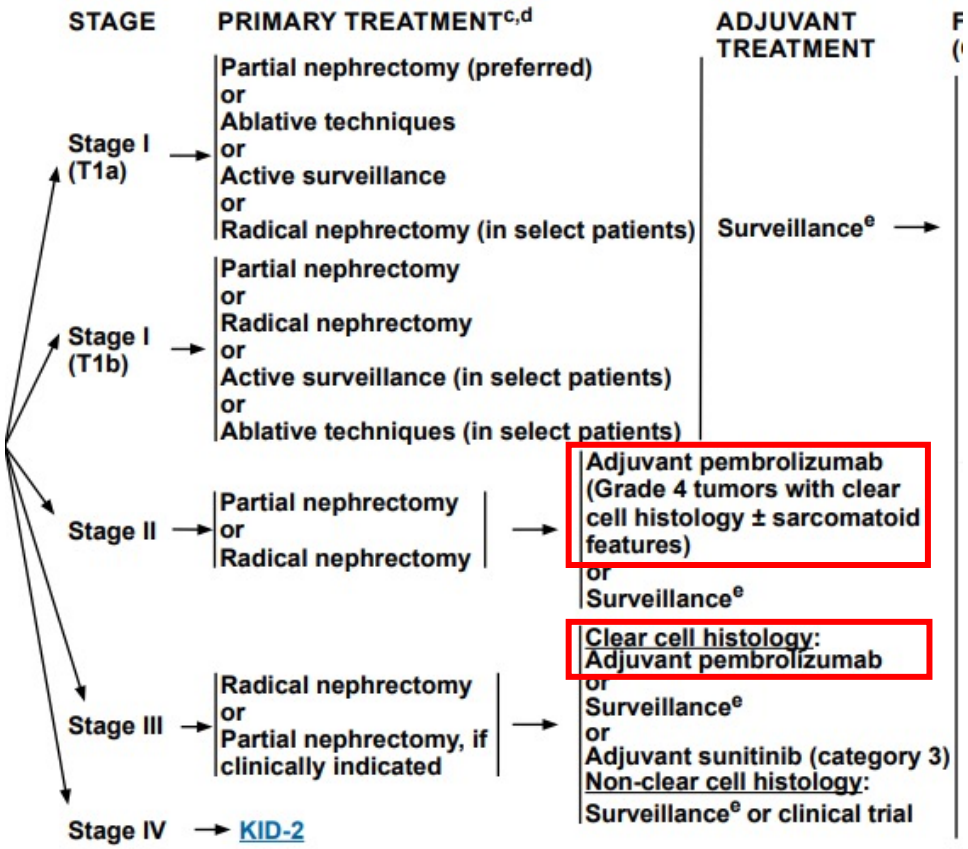
RCC Updates Outline

1. **Adjuvant RCC**
   - Survival data for KN-564

2. **Metastatic RCC 1L**
   - Updates on CLEAR (pembro/lenva) and KN-426 (axi/pembro)
   - The future including HI2-alpha

3. **Metastatic RCC 2L+**
   - CONTACT03: no role for rechallenge with IO
   - HIF2-alpha

Adjuvant Therapy for RCC



Phase 3 KEYNOTE-564 Meets it Secondary Endpoint in RCC

November 5, 2023
Chris Ryan

News *Article*

Adjuvant pembrolizumab improved overall survival vs placebo in patients with renal cell carcinoma at intermediate-high or high risk of recurrence.

Merck has announced that adjuvant pembrolizumab (Keytruda) has met its key secondary end point of the phase 3 KEYNOTE-564 trial (NCT03142334), improving overall survival (OS) over placebo in patients with renal cell carcinoma (RCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

1L Systemic Therapies for RCC

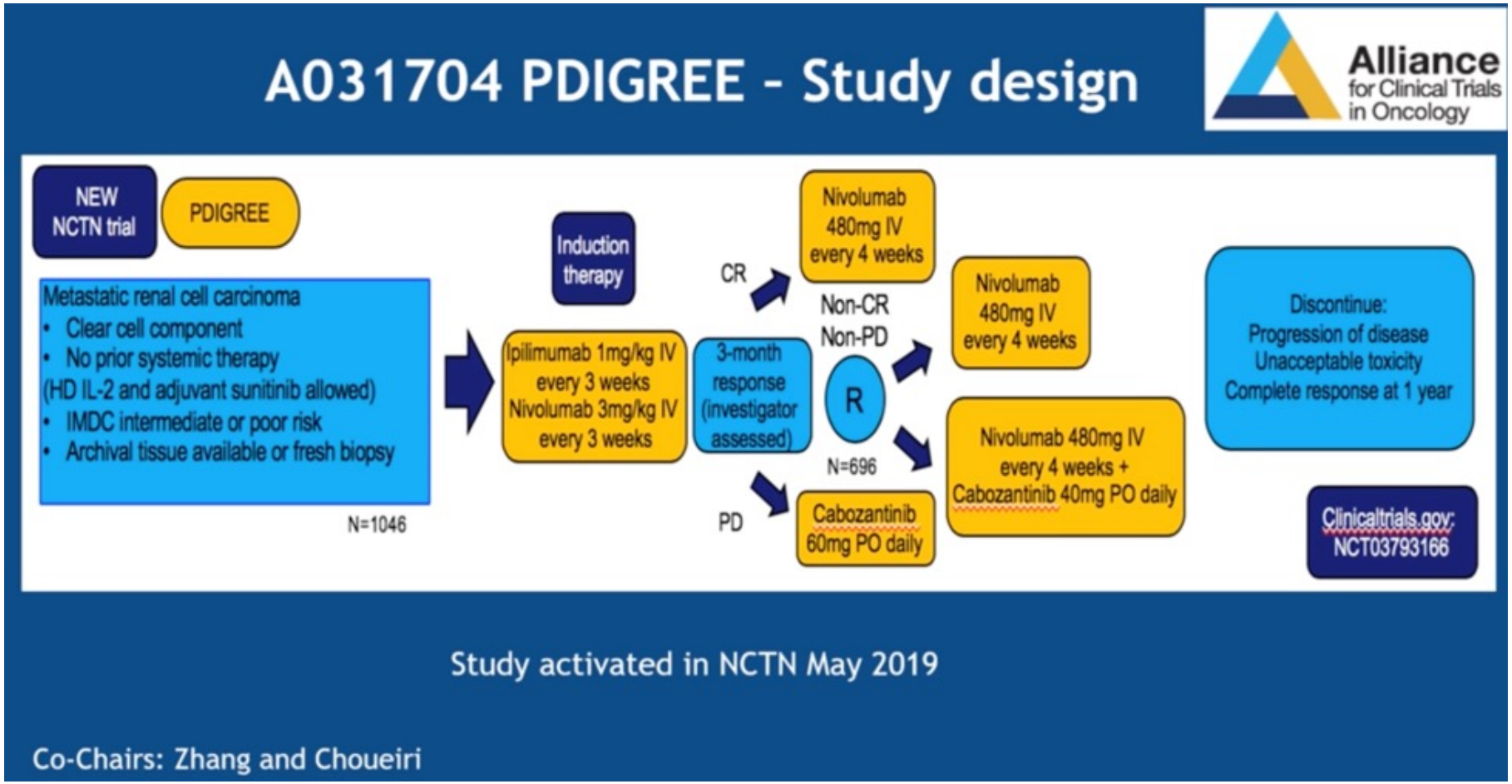
FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY	
Risk	**Preferred Regimens**
Favorable[a]	• **Axitinib + pembrolizumab**[b] **(category 1)** • **Cabozantinib + nivolumab**[b] **(category 1)** • **Lenvatinib + pembrolizumab**[b] **(category 1)**
Poor/ intermediate[a]	• **Axitinib + pembrolizumab**[b] **(category 1)** • **Cabozantinib + nivolumab**[b] **(category 1)** • **Ipilimumab + nivolumab**[b] **(category 1)** • **Lenvatinib + pembrolizumab**[b] **(category 1)** • **Cabozantinib**

- ASCO 2023: updates on CLEAR (pembro/lenva) and KN-426 (axi/pembro) reaffirm its use, but IO/TKI do not lead to durable responses or cure for most patients, but best option if require a **rapid response**

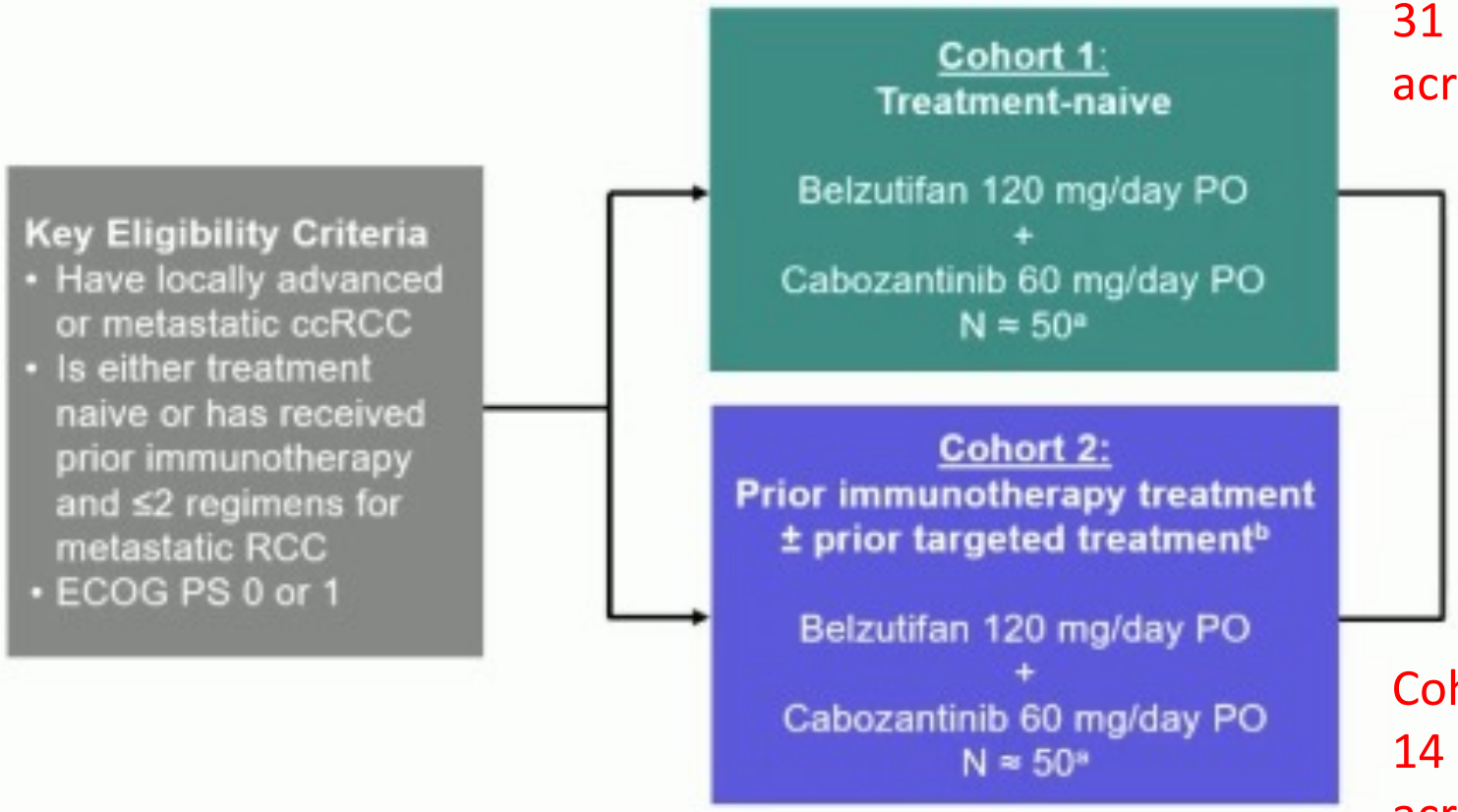
- For **sarcomatoid** features or aim for **durable response** -> favor ipi/nivo

(Braun, ASCO 2023)

The future of 1L Systemic Therapies for RCC – PDIGREE – An Adaptive Phase III Trial



Study Design of LITESPARK-003 (NCT03634540)



Tumor Assessments

- Week 9, then Q8W for 12 months and Q12W thereafter

End Points

- Primary: ORR per RECIST v1.1 by investigator
- Secondary: PFS, DOR, and TTR per RECIST v1.1 by investigator, OS, safety/tolerability

Cohort 1: ORR=70% (4 complete and 31 partial responses); consistent across IMDC risk categories

Cohort 2: ORR=31% (2 complete and 14 partial responses); consistent across IMDC risk categories and prior anti-cancer therapy

(Choeuiri, ESMO 2023)

2L+ Systemic Therapies for RCC

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY (IN ALPHABETICAL ORDER BY CATEGORY)			
Immuno-oncology (IO) Therapy History Status	**Preferred Regimens**	**Other Recommended Regimens**	**Useful in Certain Circumstances**
IO Therapy Naïve	• None	• Axitinib + pembrolizumab[b] • Cabozantinib • Cabozantinib + nivolumab[b] • Ipilimumab + nivolumab[b] • Lenvatinib + everolimus • Lenvatinib + pembrolizumab[b] • Nivolumab[b]	• Axitinib • Everolimus • Pazopanib • Sunitinib • Tivozanib[f] • Belzutifan (category 2B) • Bevacizumab[g] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B) • Axitinib + avelumab[b] (category 3)
Prior IO Therapy	• None	• Axitinib • Cabozantinib • Lenvatinib + everolimus • Tivozanib[f]	• Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Everolimus • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Belzutifan (category 2B) • Bevacizumab[g] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Temsirolimus[e] (category 2B) • Axitinib + avelumab[b] (category 3)

- **CONTACT-03** (ASCO 2023): no role of re-challenge with ICI+TKI in patients who have received previous ICI – addition of atezolizumab to cabozantinib did NOT improved response or PFS vs cabozantinib alone

(Choueiri, ASCO 2023)

Trials in 2L+ mRCC

LITESPARK-005 Study (NCT04195750)

Key Eligibility Criteria

- Unresectable, locally advanced or metastatic clear cell RCC
- Disease progression after 1-3 prior systemic regimens, including ≥1 anti–PD-(L)1 mAb and ≥1 VEGFR-TKI
- Karnofsky Performance Status score ≥70%

R 1:1

N = 374 → **Belzutifan** 120 mg orally daily

N = 372 → **Everolimus** 10 mg orally daily

Stratification Factors

- IMDC prognostic score[a]: 0 vs 1-2 vs 3-6
- Prior VEGF/VEGFR-targeted therapies: 1 vs 2-3

Dual Primary Endpoints:

- PFS per RECIST 1.1 by BICR
- OS

Key Secondary Endpoint:

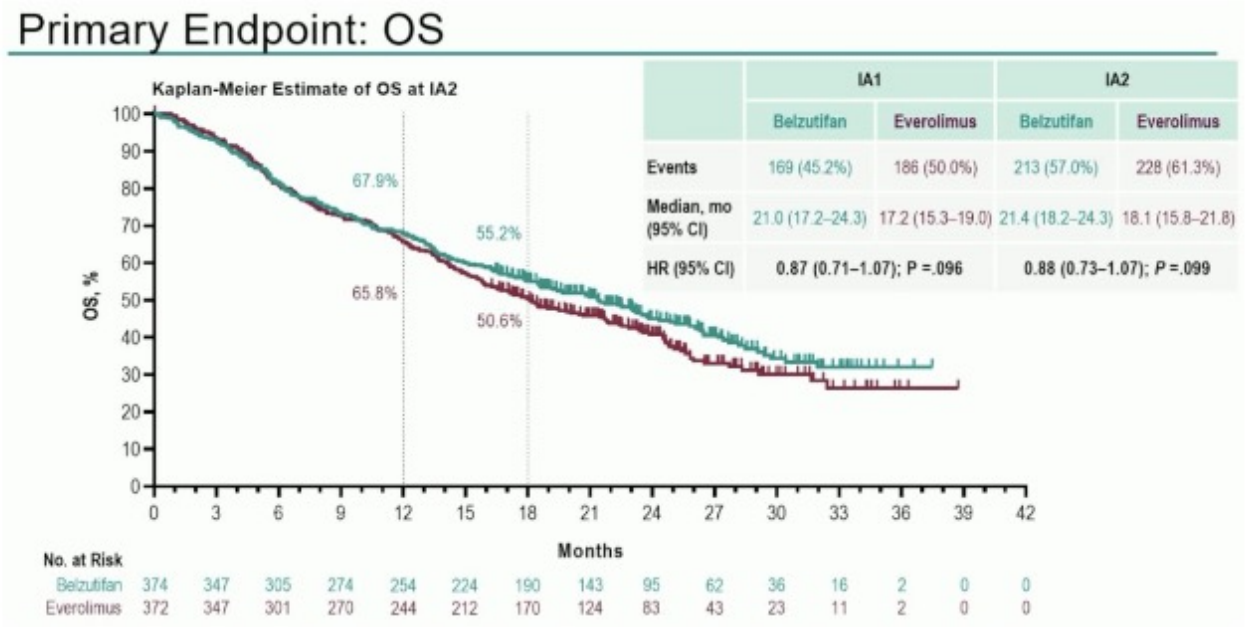
- ORR per RECIST 1.1 by BICR

Other Secondary Endpoints Include:

- DOR per RECIST 1.1 by BICR
- Safety
- Time to deterioration in FKSI-DRS and EORTC QLQ-C30 GHS/QoL

(Albiges, ESMO 2023)

LITESPARK-005



	IA1		IA2	
	Belzutifan	Everolimus	Belzutifan	Everolimus
Events	169 (45.2%)	186 (50.0%)	213 (57.0%)	228 (61.3%)
Median, mo (95% CI)	21.0 (17.2–24.3)	17.2 (15.3–19.0)	21.4 (18.2–24.3)	18.1 (15.8–21.8)
HR (95% CI)	0.87 (0.71–1.07); P =.096		0.88 (0.73–1.07); *P* =.099	

- Belzutifan with significant improvement in progression-free survival and objective response rate versus everolimus
  - Overall survival difference has *not reached* statistical significance; final analysis is pending
- Well tolerated - Quality of life as assessed by FKSI-DRS and QLQ30
  GHS/QoL favored belzutifan
- Established role of HIF-2a in advanced RCC, ongoing phase 3 studies in adjuvant, 1L and 2L setting

(Albiges, ESMO 2023)

Thank You.

Karine Tawagi - ktawagi@uic.edu @*drkarinetawagi*