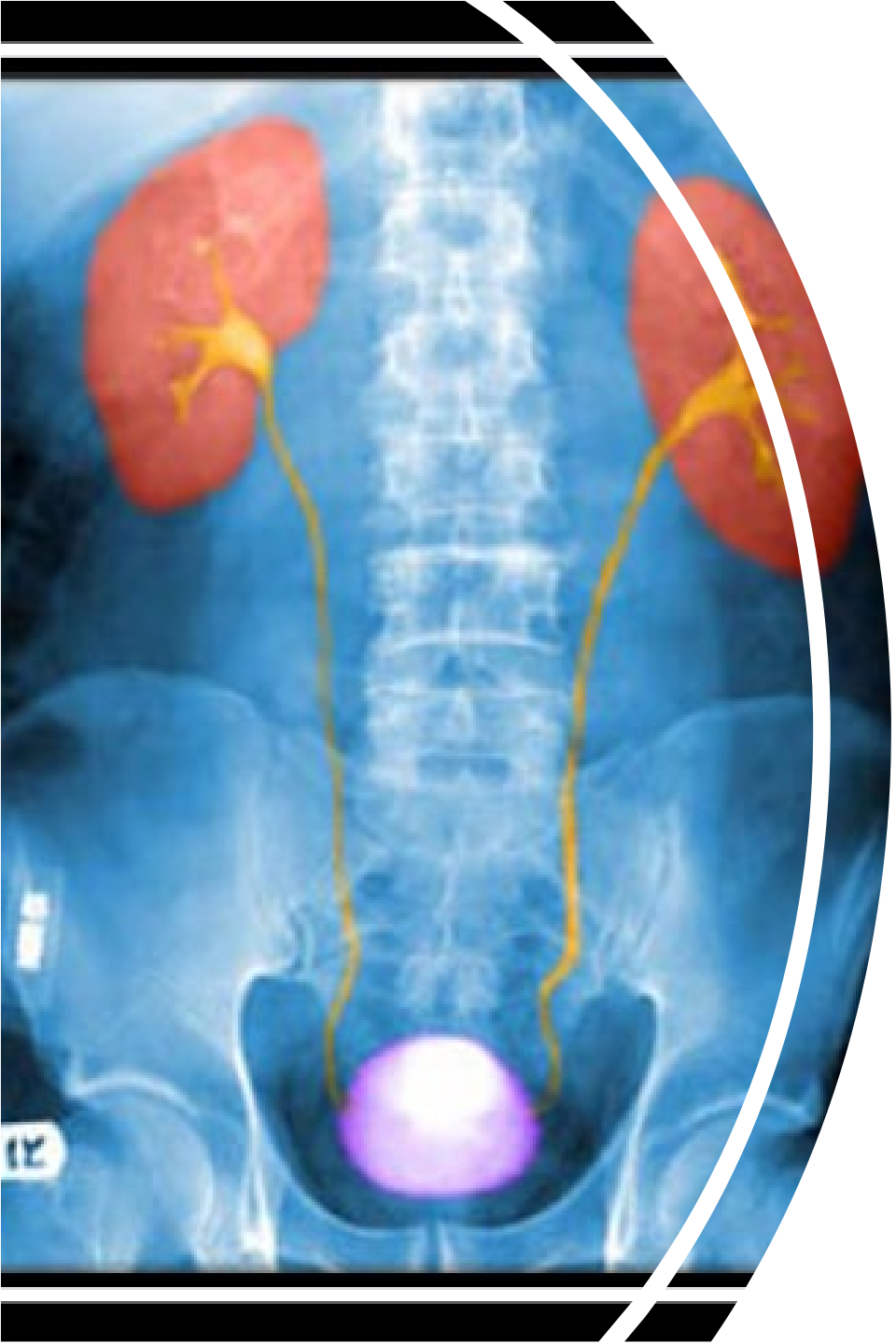


Bladder Cancer: An Update on Systemic Therapies and Precision Oncology

April 19, 2024
LOS 4th Annual Louisiana Cancer Congress

Karine Tawagi, MD

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

UI Health | UIC
UNIVERSITY OF ILLINOIS CANCER CENTER

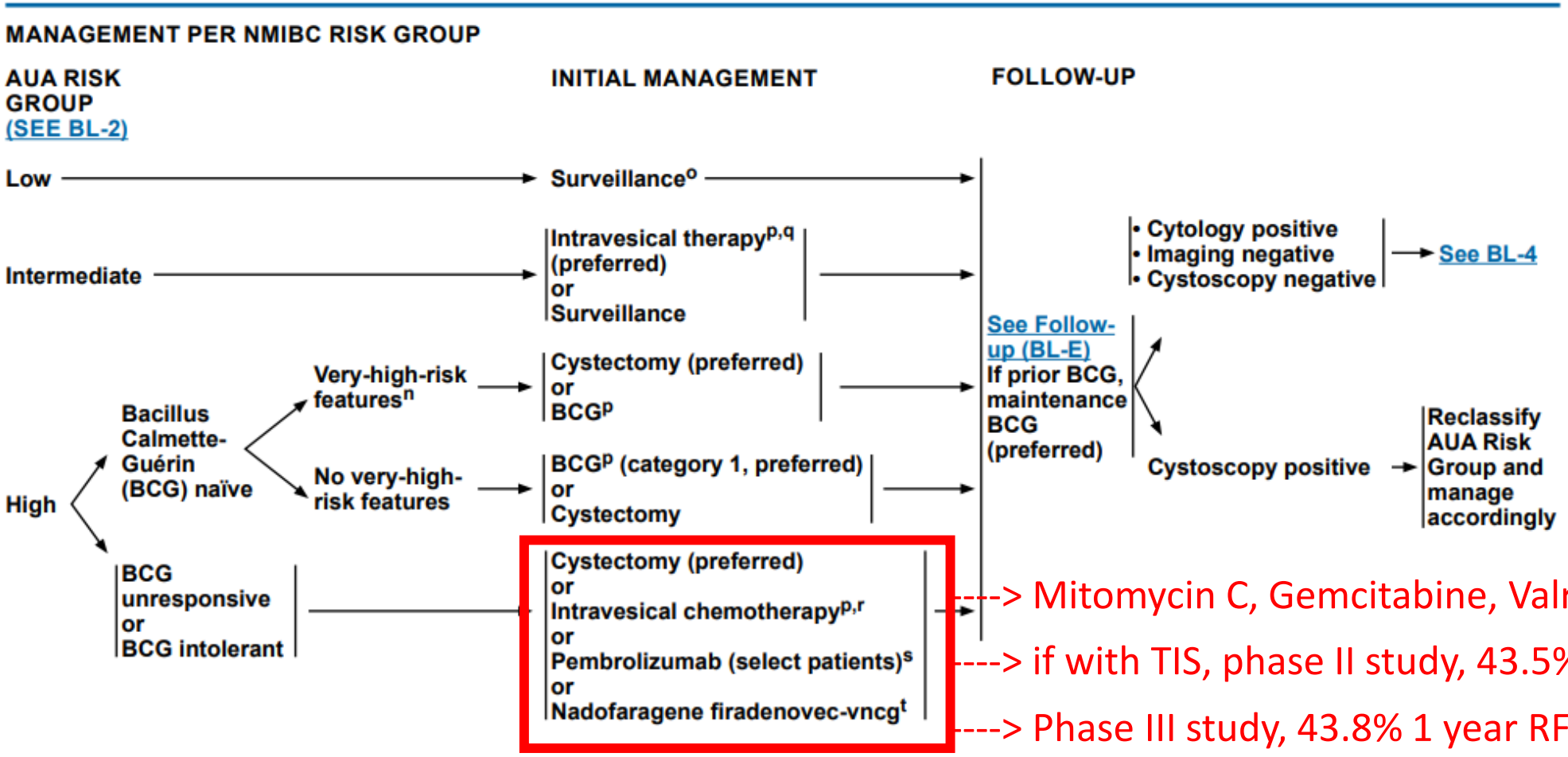
Outline

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

2. **Muscle-invasive bladder cancer (MIBC)**
    - Adjuvant immunotherapy
    - Ongoing trials & role of ctDNA

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

Non-Muscle Invasive Bladder Cancer (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

https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf

Balar et al, Lancet Oncology, 2021

Boorjan et al, Lancet Oncology, 2020

Recurrence-free survival in HR-papillary BCG unresponsive/recurrence

Agent	Pembrolizumab	Nadrofaragene Firadenovec	N-803 + BCG	GEM/DOCE	Radiofrequency hyperthermia
1yr RFS	43.5%	43.8%	57%	~70%	77.9%
2yr RFS	34.9%	N/A	48%	58%	57.5%
Setting	Phase 2 Single arm	Phase 3 Nonrandomized	Phase 2/3 Nonrandomized	Retrospective Heterogeneous	Retrospective Heterogeneous
N	132	35	77	34	134
REF	ASCO-GU 2023	Dinney 2021	ASCO 2022	Steinberg 2020	Brummelhuis 2021

KN-57: persistent or recurrent HR NMIBC ineligible or refusing cystectomy

- **IV pembrolizumab**
- IV pembrolizumab + vibostolimab (TIGIT) coformulation
- IV pembrolizumab + favezelimab (LAG-3) coformulation

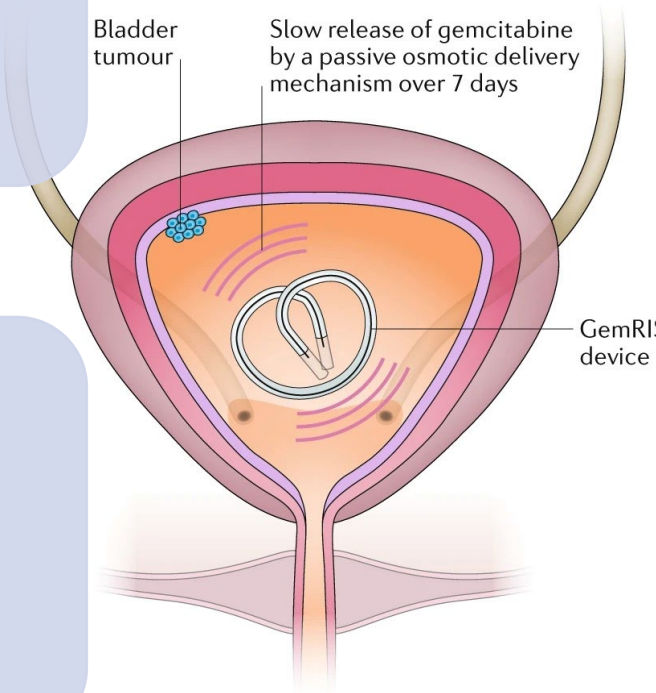
NMIBC – Ongoing Phase III Trials

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

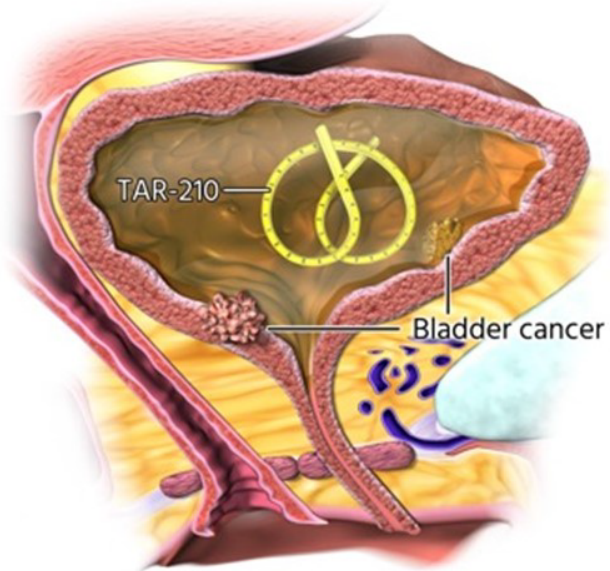


Nature Reviews Urology, 2018

TAR-210 Is a Novel Drug Delivery System Designed to Provide Local Targeted Therapy for Patients With Bladder Cancer

- Treatment options are limited for patients with recurrent NMIBC
- ***FGFR* alterations** are prevalent in ~50 to 80% of NMIBC and may function as oncogenic drivers[1-3]
- **Erdafitinib** is an oral selective pan-FGFR tyrosine kinase inhibitor approved in the US and 18 other countries to treat *FGFR*-altered advanced or mUC after progression on platinum-containing chemotherapy[4-8]
- Oral erdafitinib has shown activity in HR NMIBC and IR NMIBC populations[9-11]

TAR-210 is designed to provide local, sustained release of erdafitinib within the bladder for 3 months while limiting systemic toxicities

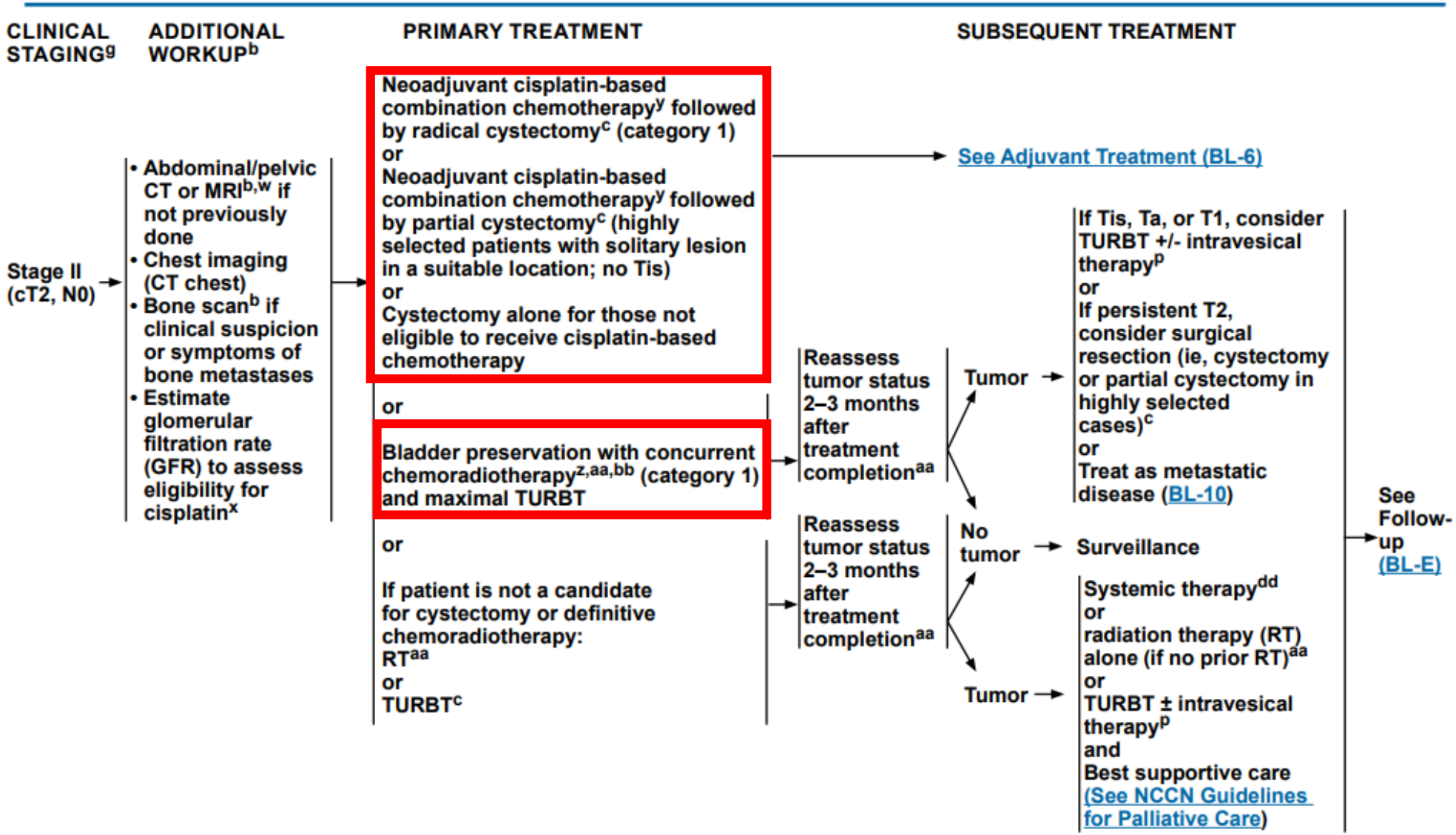


TAR-210 is inserted into the bladder through a dedicated urinary placement catheter and removed via cystoscopy.

FGFR, fibroblast growth factor receptor; HR, high risk; IR, intermediate risk; MIBC, muscle-invasive bladder cancer; mUC, metastatic urothelial carcinoma; NMIBC, non–muscle-invasive bladder cancer.

1. Hernández S, et al. *J Clin Oncol.* 2008;24:3664-3671; 2. Knowles MA, Hurst CD. *Nat Rev Cancer.* 2014;15:25-41; 3. Khalid S, et al. *Eur Urol Open Sci.* 2020;21:61-68; 4. BALVERSA® (erdafitinib) [package insert]. Horsham, PA: Janssen Products, LP; 2023; 5. Perera TPS, et al. *Mol Cancer Ther.* 2017;16:1010-1020; 6. Loriot Y, et al. *N Engl J Med.* 2019;381:338-348; 7. Siefker-Radtke AO, et al. *Lancet Oncol.* 2022;23:248-258. 8. Loriot Y, et al. *Clin Oncol.* 2023;41(Suppl 17):LBA4619; 9. Daneshmand S, et al. *J Clin Oncol.* 2023;41(6_suppl):504; 10. Catto JWF, et al. *J Clin Oncol.* 2023;41(6_suppl):503. 11. Catto JWF, et al. ESMO, 2023.

Muscle Invasive Bladder Cancer (MIBC)

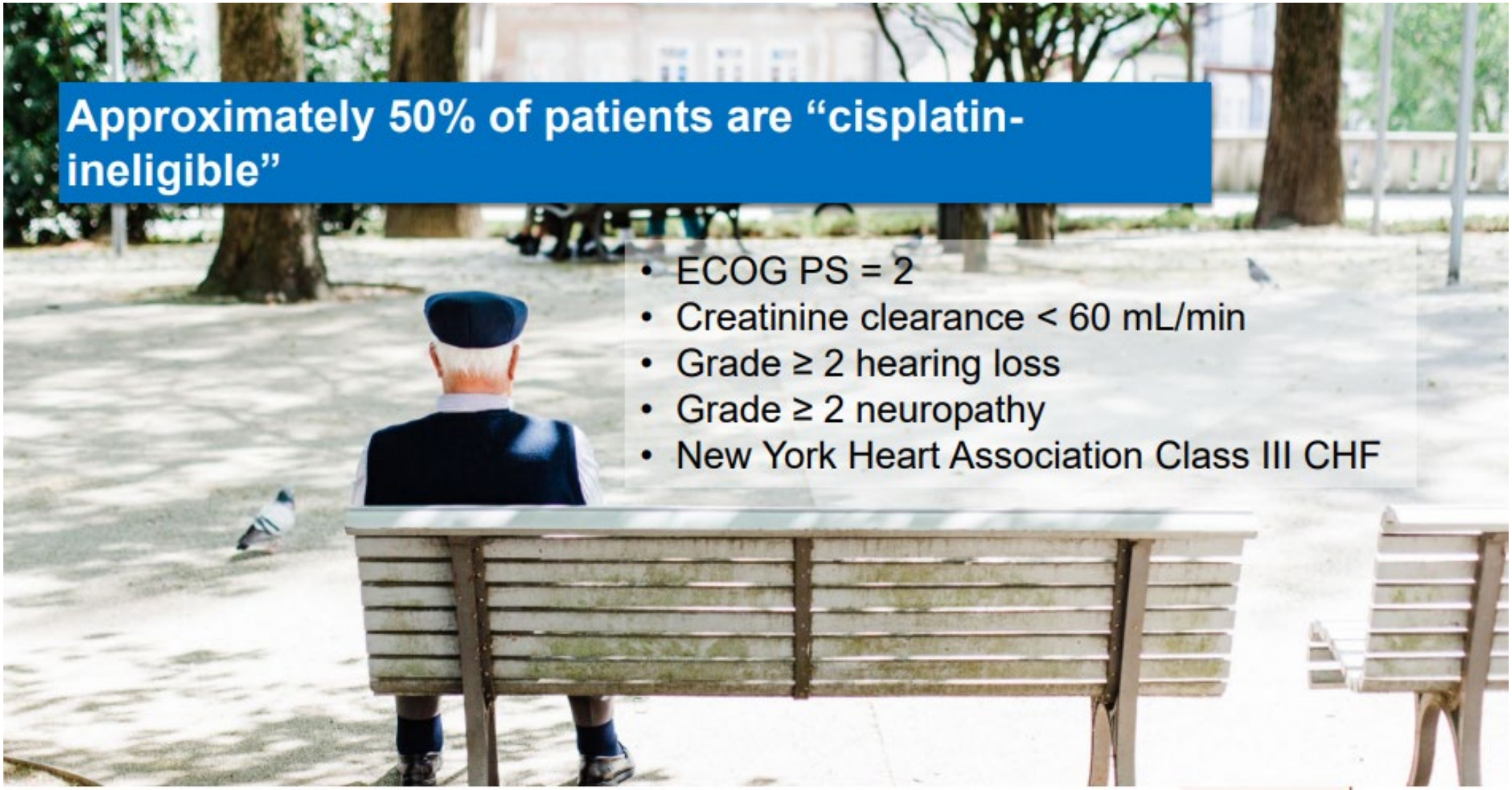


https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf

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*)

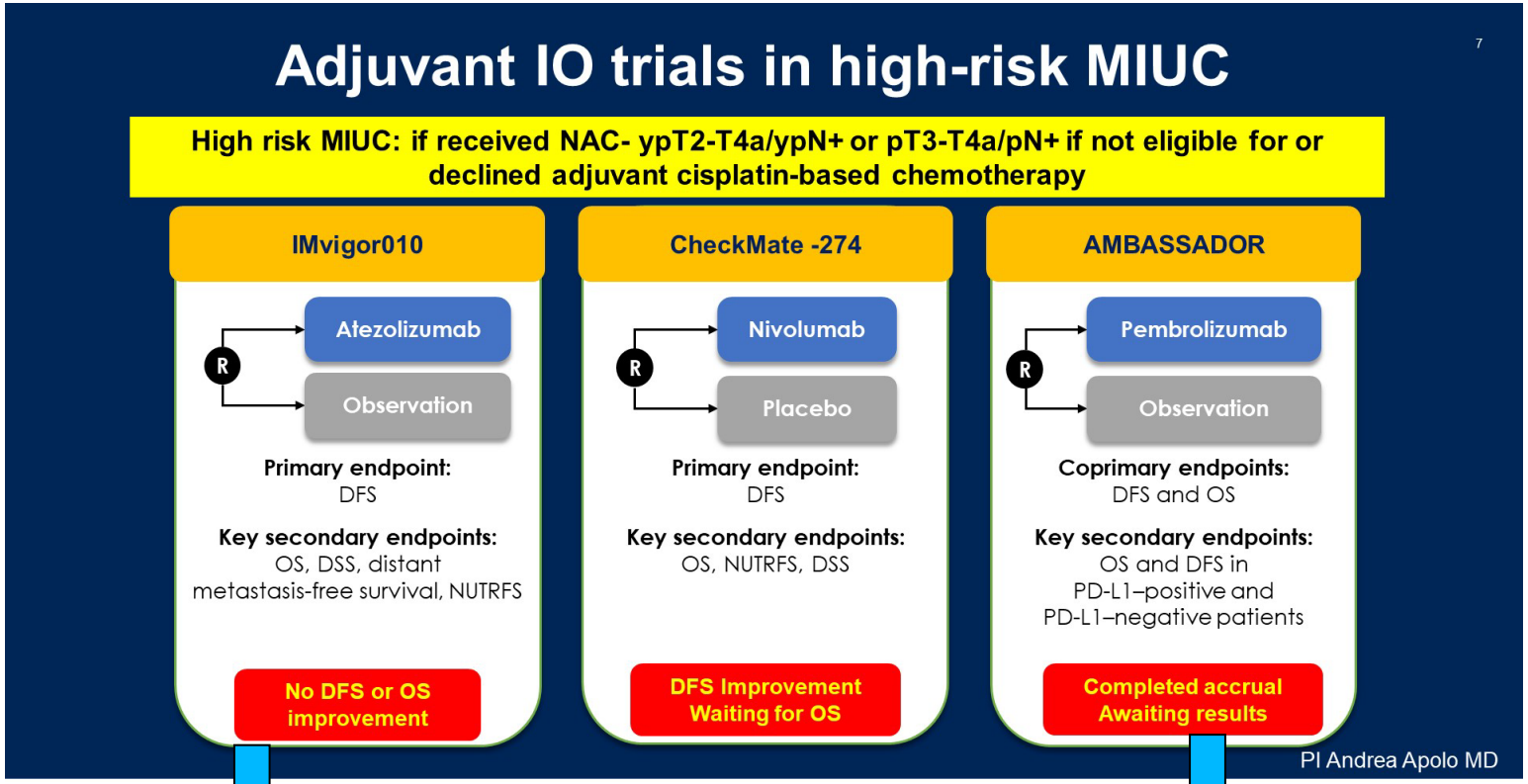


ECOG PS = Eastern Cooperative Oncology Group Performance Status; CHF = chronic heart failure.
Galsky MD, et al. *Lancet Oncol*. 2011;12(3):211-4.

Great Debates & Updates | Genitourinary Oncology

M. Galsky, Sept 2022

MIBC – Adjuvant Treatment



Difference between PDL1 and PD1?

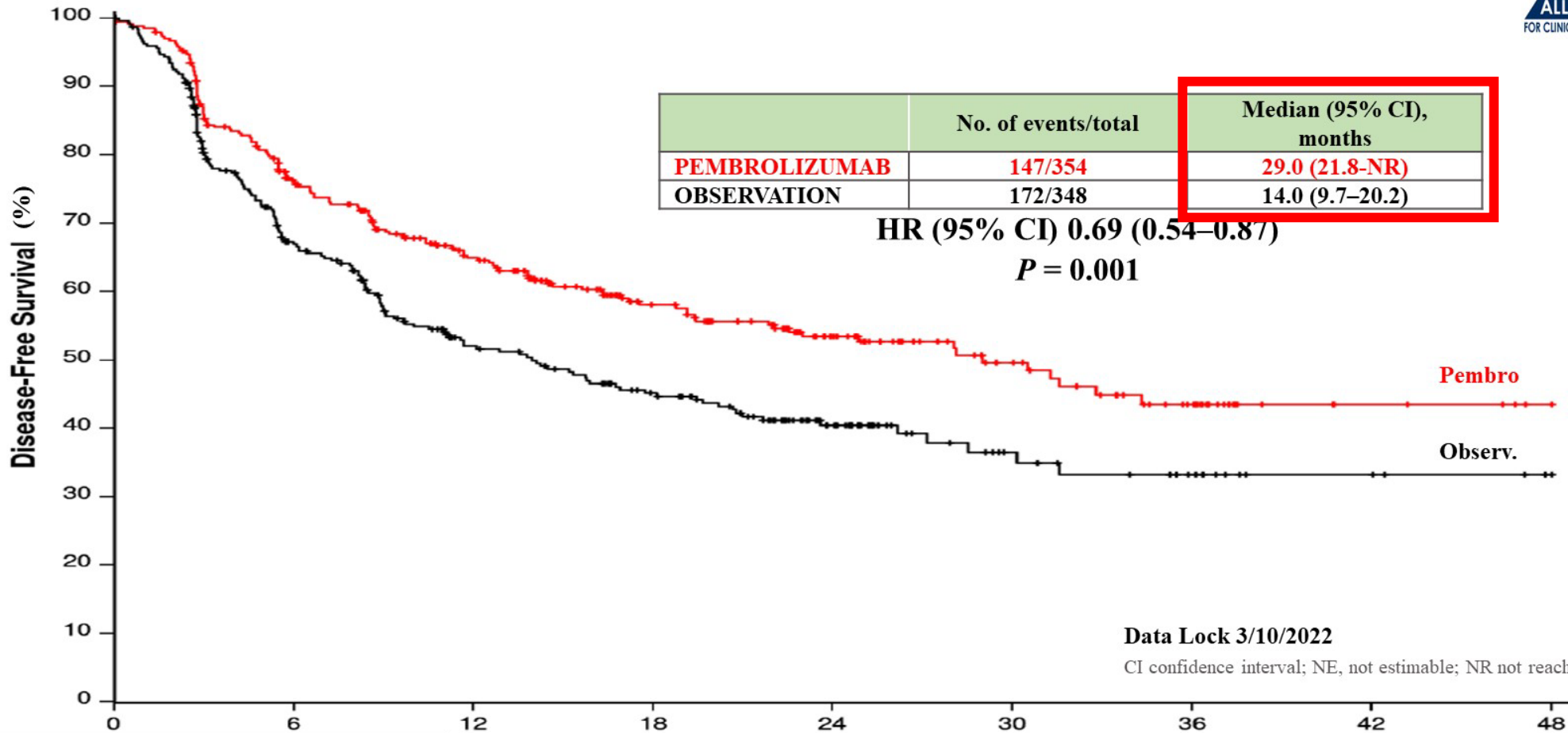
AMBASSADOR (adjuvant Pembrolizumab – resulted at ASCO GU 2024 – met DFS endpoint, regardless of PDL1 status, but did not meet interim OS endpoint)

A031501 AMBASSADOR: Disease-Free Survival (ITT)

	No. of events/total	Median (95% CI), months
PEMBROLIZUMAB	147/354	29.0 (21.8-NR)
OBSERVATION	172/348	14.0 (9.7–20.2)

HR (95% CI) 0.69 (0.54–0.87)

***P* = 0.001**



Data Lock 3/10/2022

CI confidence interval; NE, not estimable; NR not reached.

Median follow-up (range) 22.3 months (0.03-48.9)

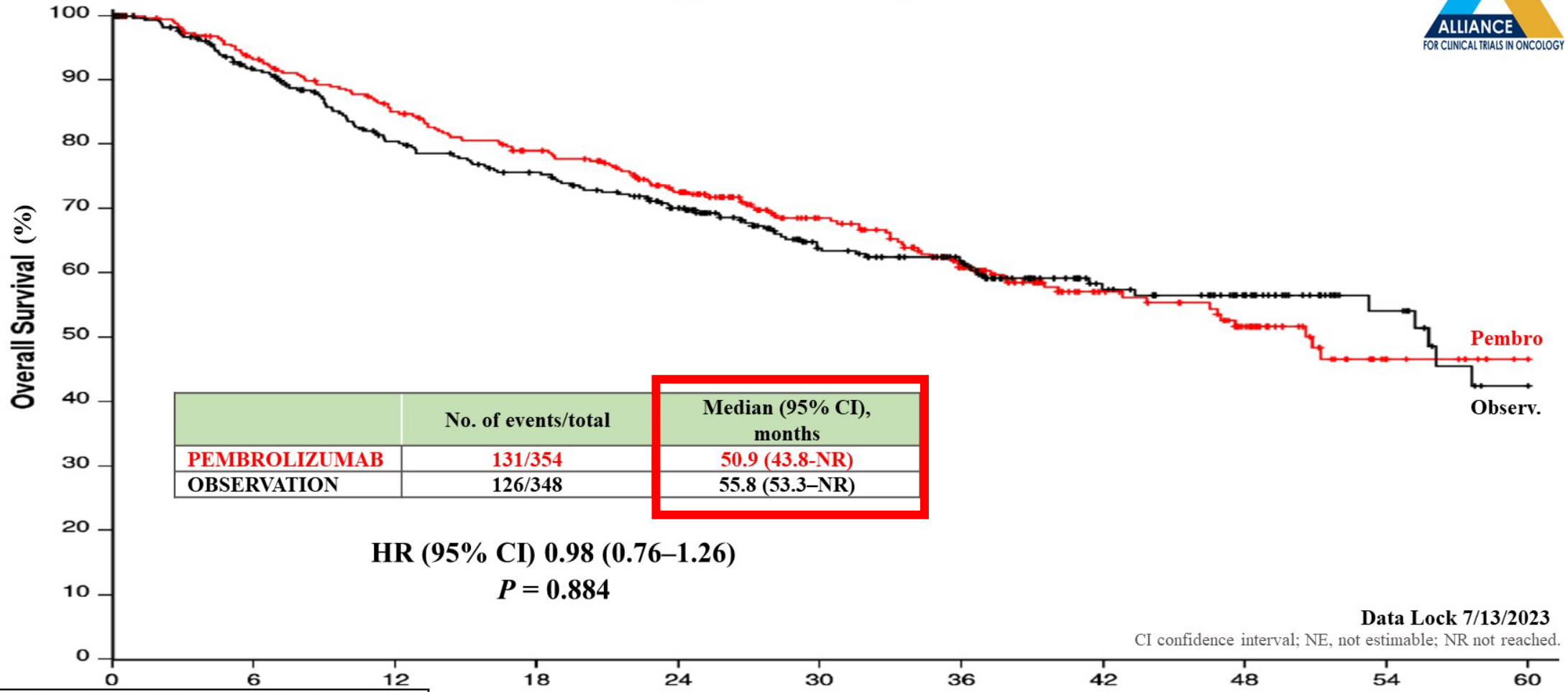
Patients-at-Risk

Pembro	354	238	178	123	80	45	26	6	2
Observ.	348	192	125	97	53	23	13	6	1

PRESENTED BY: Andrea B. Apolo, MD

@apolo_andrea

A031501 AMBASSADOR: (interim) Overall Survival



	No. of events/total	Median (95% CI), months
PEMBROLIZUMAB	131/354	50.9 (43.8-NR)
OBSERVATION	126/348	55.8 (53.3–NR)

HR (95% CI) 0.98 (0.76–1.26)
***P* = 0.884**

Data Lock 7/13/2023

CI confidence interval; NE, not estimable; NR not reached.

Median follow-up (range) 36.9 months (0-63.9)

Patients-at-Risk

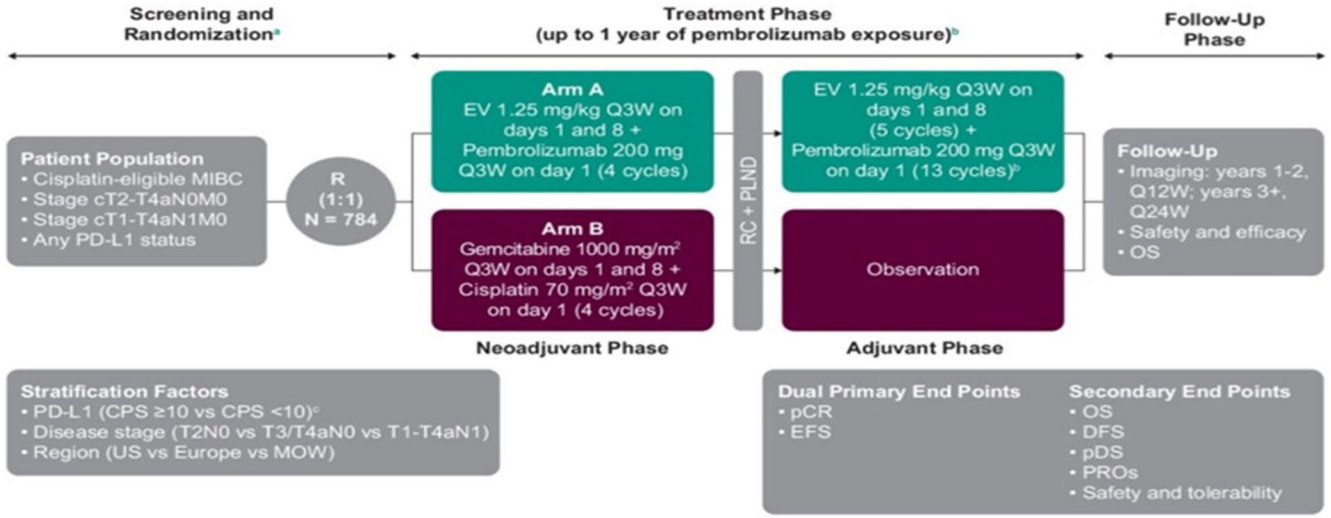
Pembro	354	313	280	253	218	152	115	69	50	17	10
Observ.	348	296	249	227	195	139	117	65	45	23	12

PRESENTED BY: Andrea B. Apolo, MD

@apolo_andrea

KEYNOTE-B15/EV-304

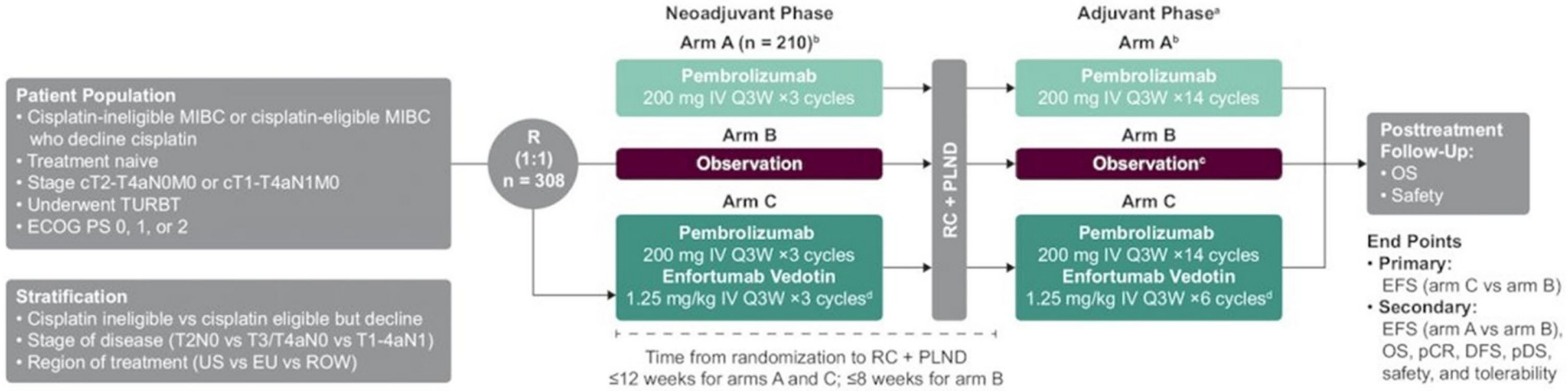
EV/P (w/ maintenance EV x 5cycles + pembro 13 cycles)
vs Gem/Cis for cisplatin-eligible x 4 cycles



KEYNOTE-905/EV-303

EV/P x 4 cycles (w/ maintenance) for cisplatin–ineligible (w/ maintenance pembro 14 cycles and EV x 6 cycles)

Study design



Presented by Necci, ASCO 2023 https://www.urotoday.com/v
Presented byHoimes, ASCO 2021 https://www.urotoday.com/

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)

https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf

One Future Cystectomy-Sparing Approach?

nature medicine HCRN 16-257 trial

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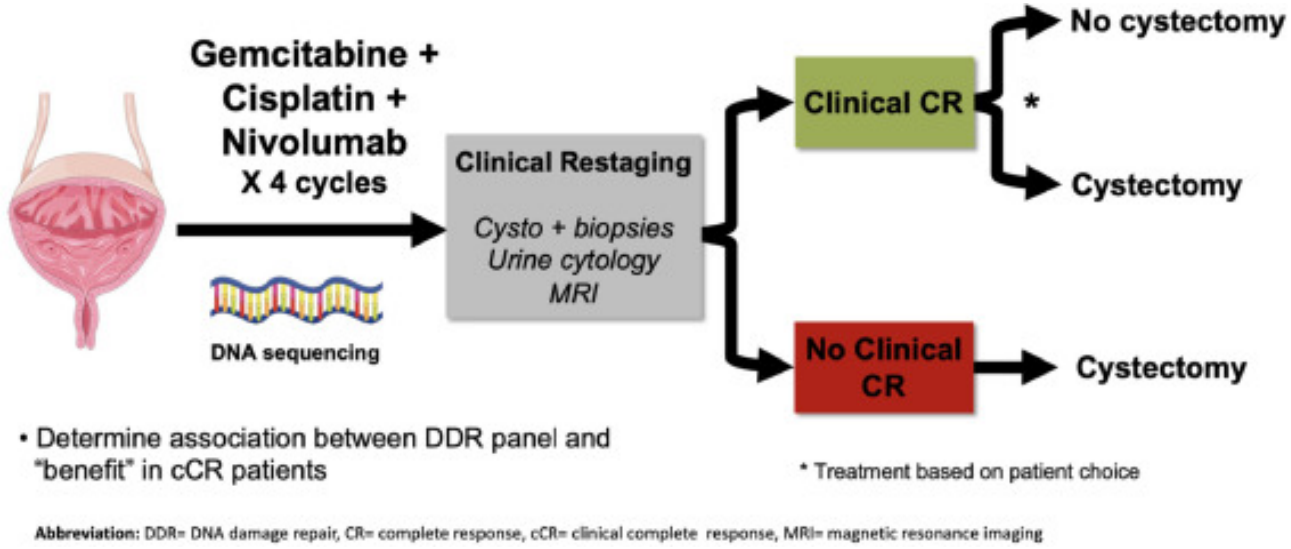
nature > nature medicine > articles > article

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

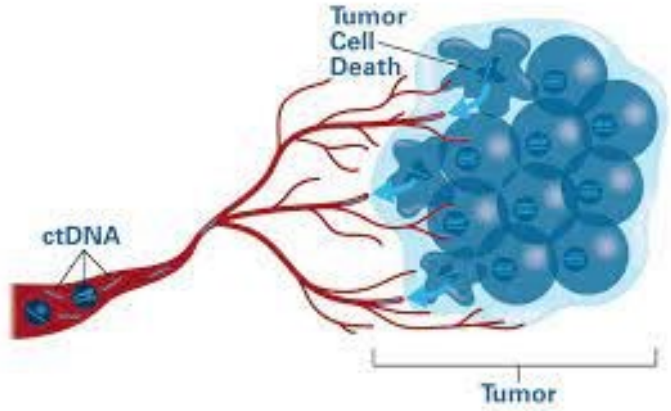
Matthew D. Galsky ✉, Siamak Daneshmand, Sudeh Izadmehr, Edgar Gonzalez-Kozlova, Kevin G. Chan, Sara Lewis, Bassam El Achkar, Tanya B. Dorff, Jeremy Paul Cetnar, Brock O. Neil, Anishka D'Souza, Ronac Mamtani, Christos Kyriakopoulos, Tomi Jun, Mahalya Gogerly-Moragoda, Rachel Brody, Hui Xie, Kai Nie, Geoffrey 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

Role of ctDNA in MIBC



- *Lindskrog et al, Clinical Cancer Research, 2023*:
  - ctDNA status is prognostic in both NAC-treated & 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

ELSEVIER

European Urology

Volume 85, Issue 2, February 2024, Pages 114-122

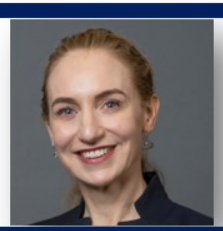
Platinum Priority – Urothelial Cancer – Editor's Choice

Editorial by Natacha Naoun, Yohann Loriot on pp. 123–124 of this issue

Updated Overall Survival by Circulating Tumor DNA Status from the Phase 3 IMvigor010 Trial: Adjuvant Atezolizumab Versus Observation in Muscle-invasive Urothelial Carcinoma

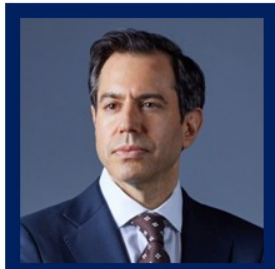
Thomas Powles [a †], Zoe June Assaf [b †], Viraj Degaonkar [b], Petros Grivas [c], Maha Hussain [d], Stephane Oudard [e], Jürgen E. Gschwend [f], Peter Albers [g], Daniel Castellano [h], Hiroyuki Nishiyama [i], Siamak Daneshmand [j], Shruti Sharma [k], Himanshu Sethi [k], Alexey Aleshin [k], Yi Shi [b], Nicole Davarpanah [b], Corey Carter [b], Joaquim Bellmunt [i ‡], Sanjeev Mariathasan [b ‡]

Melanoma



Georgina Long, AO, BSc, PhD, MBBS

- "In melanoma we have consistently shown that adding checkpoints improves the outcomes for pts, including overall survival. We saw this synergistic effect with PD1+ CTLA4, and now PD1+LAG3."

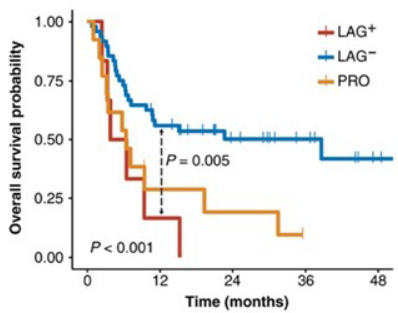


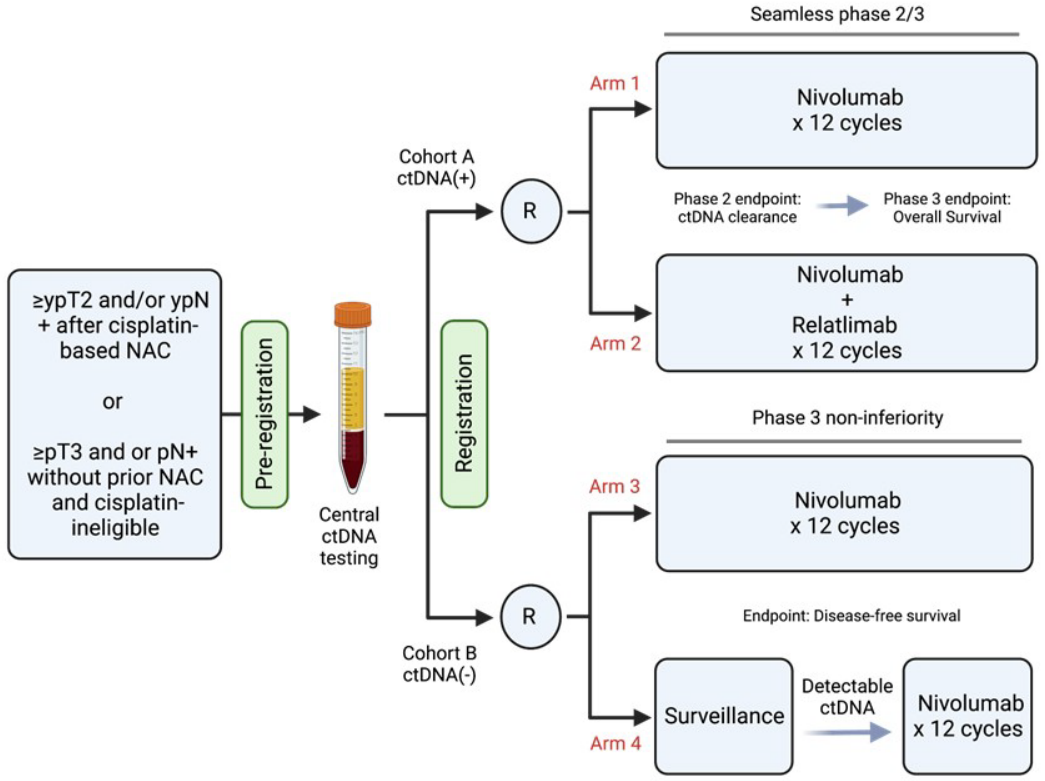
A032103 (MODERN)
PI: Matthew Galsky

Study Rationale:

- Translational data suggesting inferior outcomes in mUC with LAG3$^+$ phenotype
- A subset of CD8 T-cells in the bladder cancer microenvironment co-express PD-1 & LAG3

Immunotype	LAG$^+$	LAG$^-$	PRO
CR/PR	0%	44%	23%
Median OS (mo)	5.2	36.65	6.5





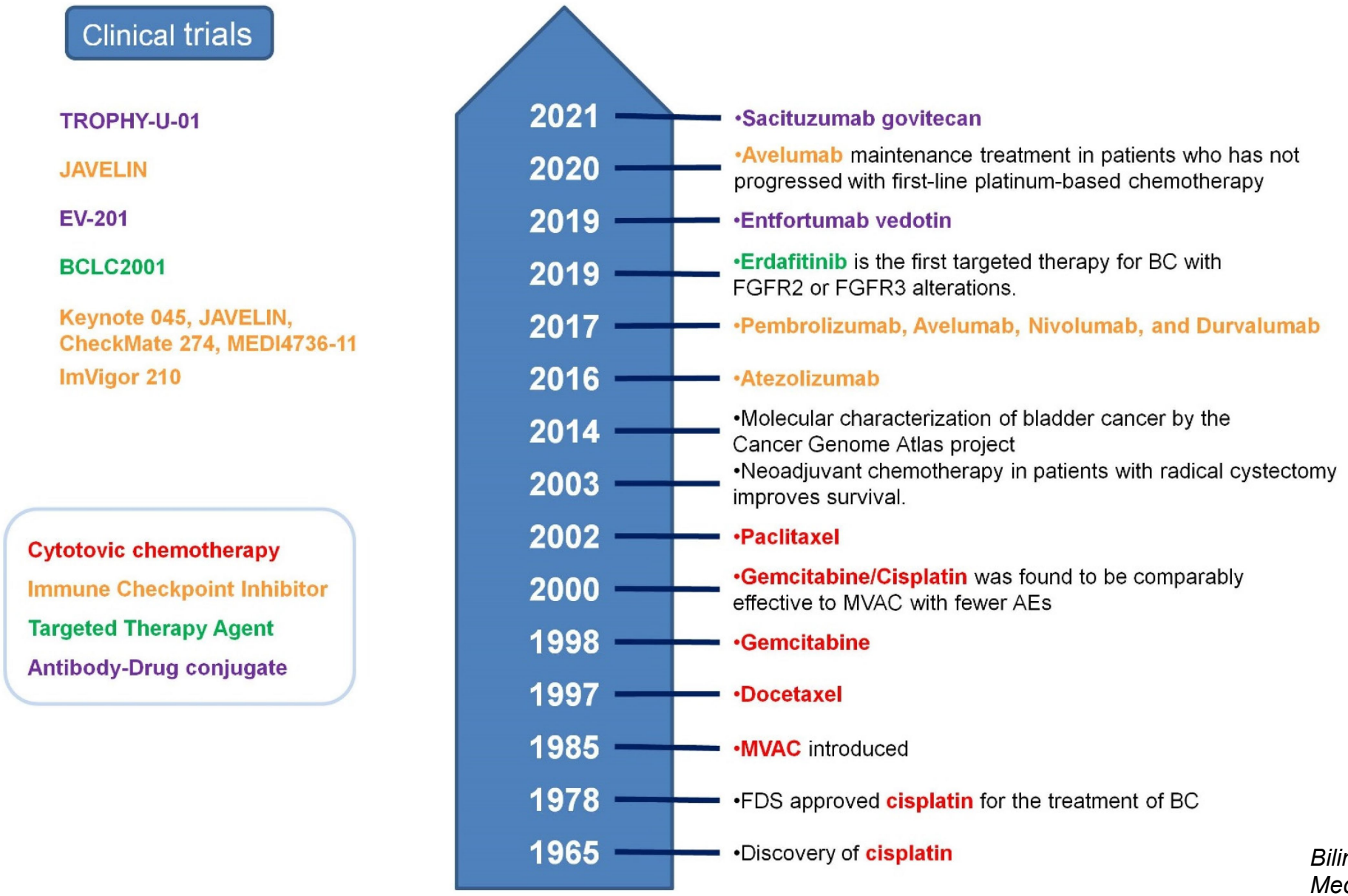
PRESENTED BY: Sumanta K. Pal, MD, FASCO

References:
1. Shen *et al* Sci Transl Med 2021
2. Wang *et al* Clin Cancer Res 2021

MIBC Unanswered Questions

- More bladder preservation options – role of systemic therapy alone option?
- Do all patients with high-risk features need adjuvant therapy? Need biomarkers.
  - Omit for ctDNA (-) post cystectomy?
  - Intensify for ctDNA (+)?
  - Role of adjuvant therapy in variant histologies? E.g. squamous
- Is 1 year of pembrolizumab (18 cycles) or nivolumab (24 cycles) necessary for all patients?
- Will EV/P continue to change the standard for MIBC as well?

Advanced Bladder Cancer Approvals



The era of precision oncology in bladder cancer is here!

Bilim et al, Journal of Personalized Medicine, 2022

1L Metastatic Urothelial Carcinoma pre-ESMO 2023

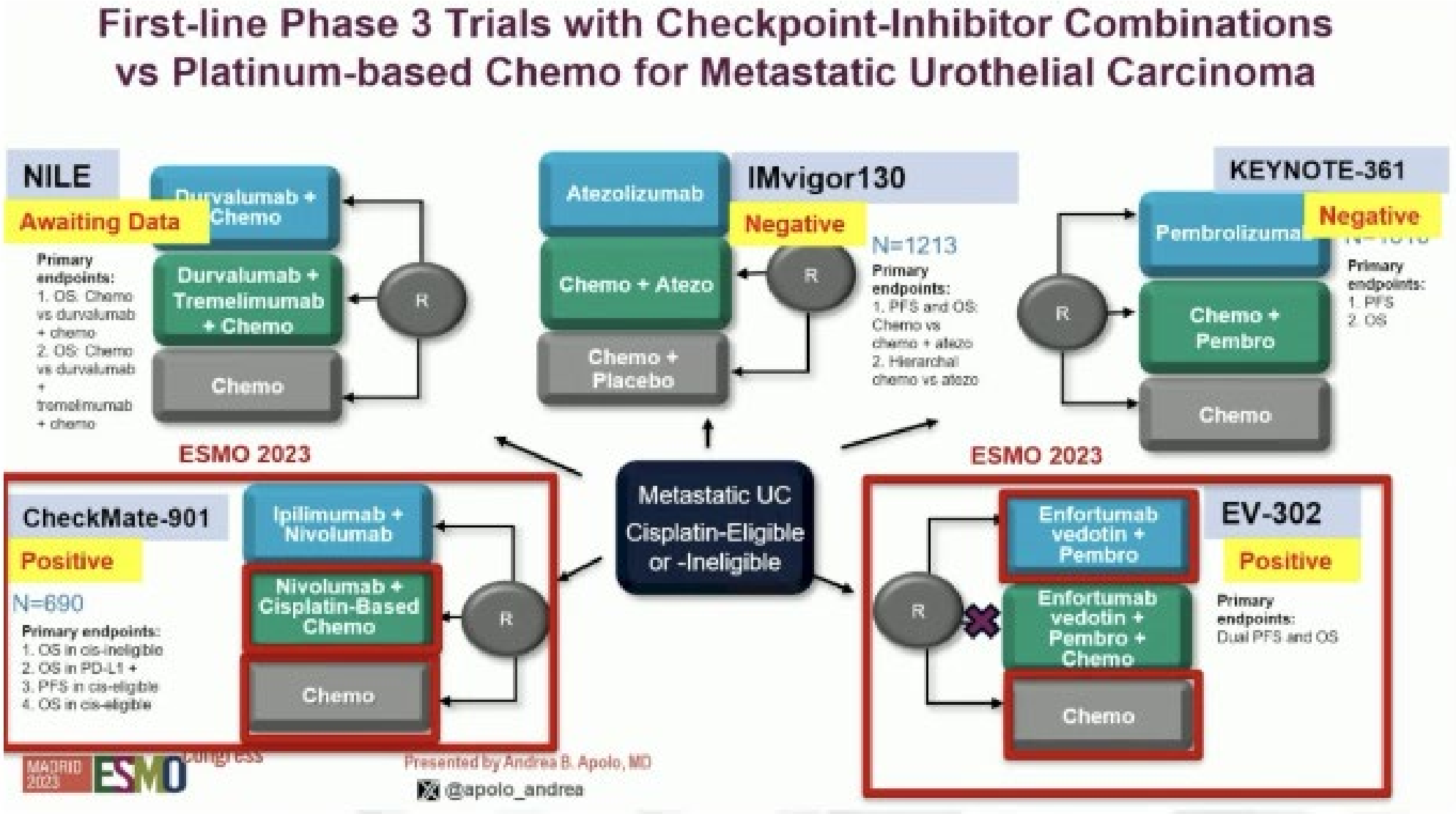
PRINCIPLES OF SYSTEMIC THERAPY

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

https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf

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



1L Metastatic Urothelial Carcinoma post-ESMO 2023

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Bladder Cancer

NCCN Guidelines Index
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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,13] • DDMVAC with growth factor support (category 1)[2,8] followed by avelumab maintenance therapy (category 1)[a,13] • Nivolumab, gemcitabine, and cisplatin followed by nivolumab maintenance therapy[14] ★ Pembrolizumab and enfortumab vedotin-ejfv[15]
Cisplatin ineligible	**Preferred regimens** • Gemcitabine and carboplatin[16] followed by avelumab maintenance therapy (category 1)[a,13] ★ Pembrolizumab and enfortumab vedotin-ejfv[17] **Other recommended regimens** • Gemcitabine[18] • Gemcitabine and paclitaxel[19] • Atezolizumab[20] (only for patients whose tumors express PD-L1[b]) (category 2B) **Useful under certain circumstances** • Ifosfamide, doxorubicin, and gemcitabine[21] (for patients with good kidney function and good performance status) • Pembrolizumab[22] (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy) • Atezolizumab[20] (only for patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 2B)

https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf

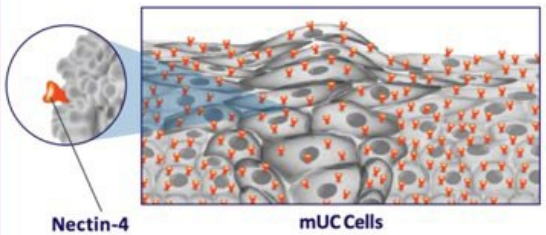
Enfortumab vedotin (EV)

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]

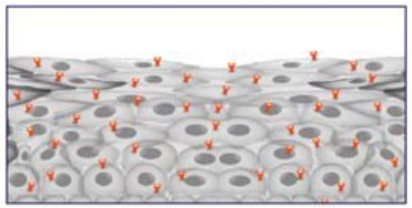
- Cell adhesion
- Migration
- Proliferation
- Differentiation
- Survival

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



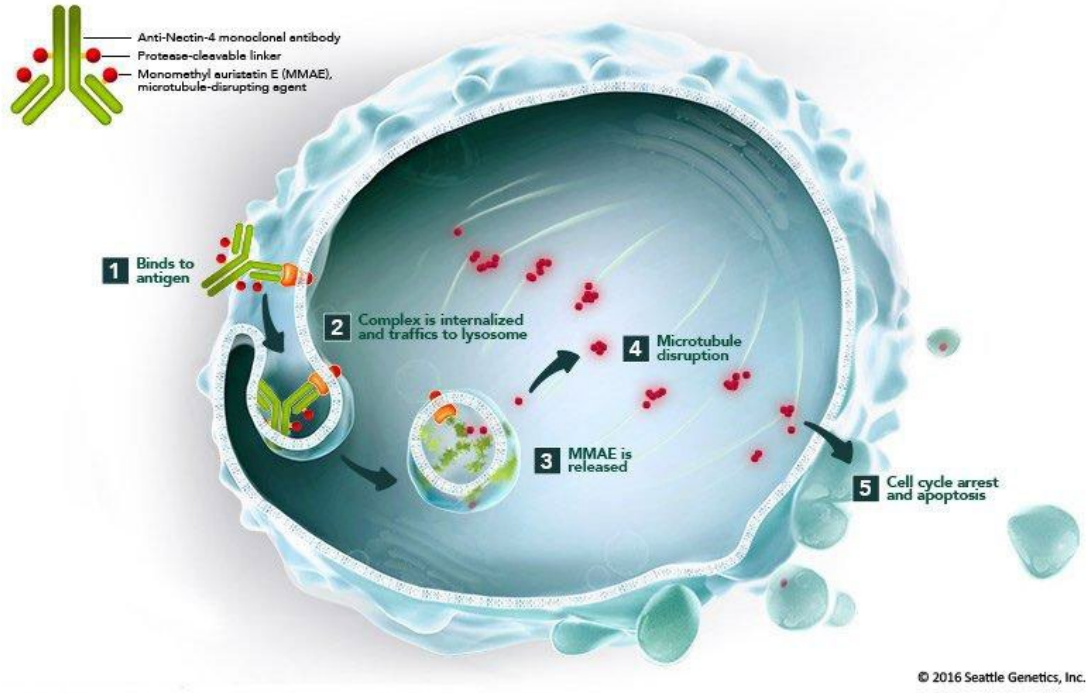
Density of Nectin-4 expression is for illustrative purposes only.

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



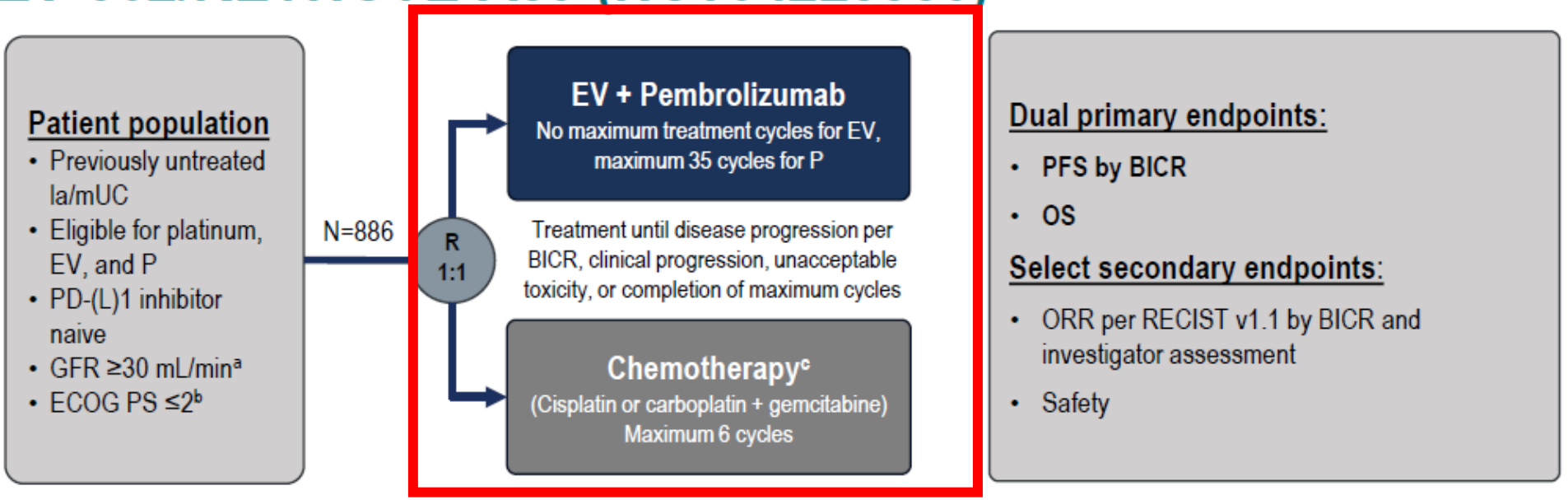
Normal tissues include, but are not limited to[6]

- 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

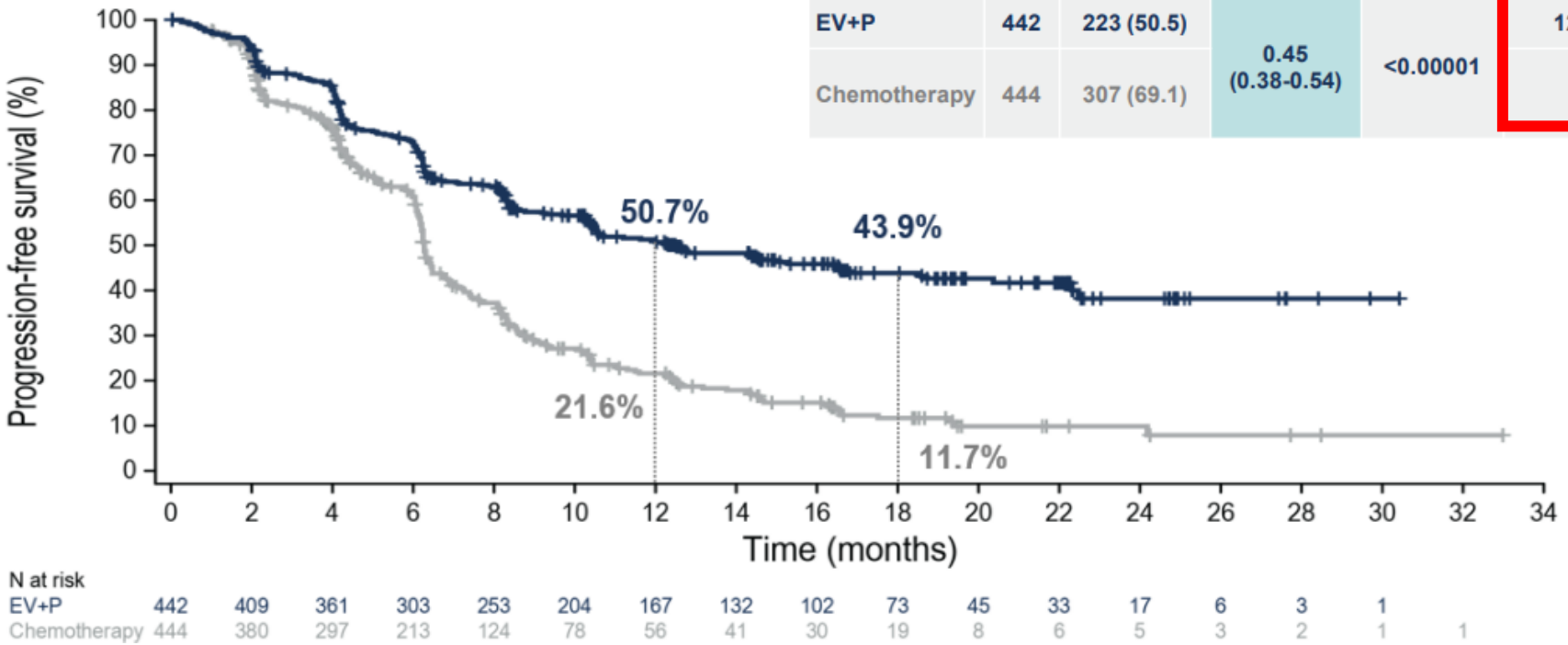
MADRID 2023 ESMO congress

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)



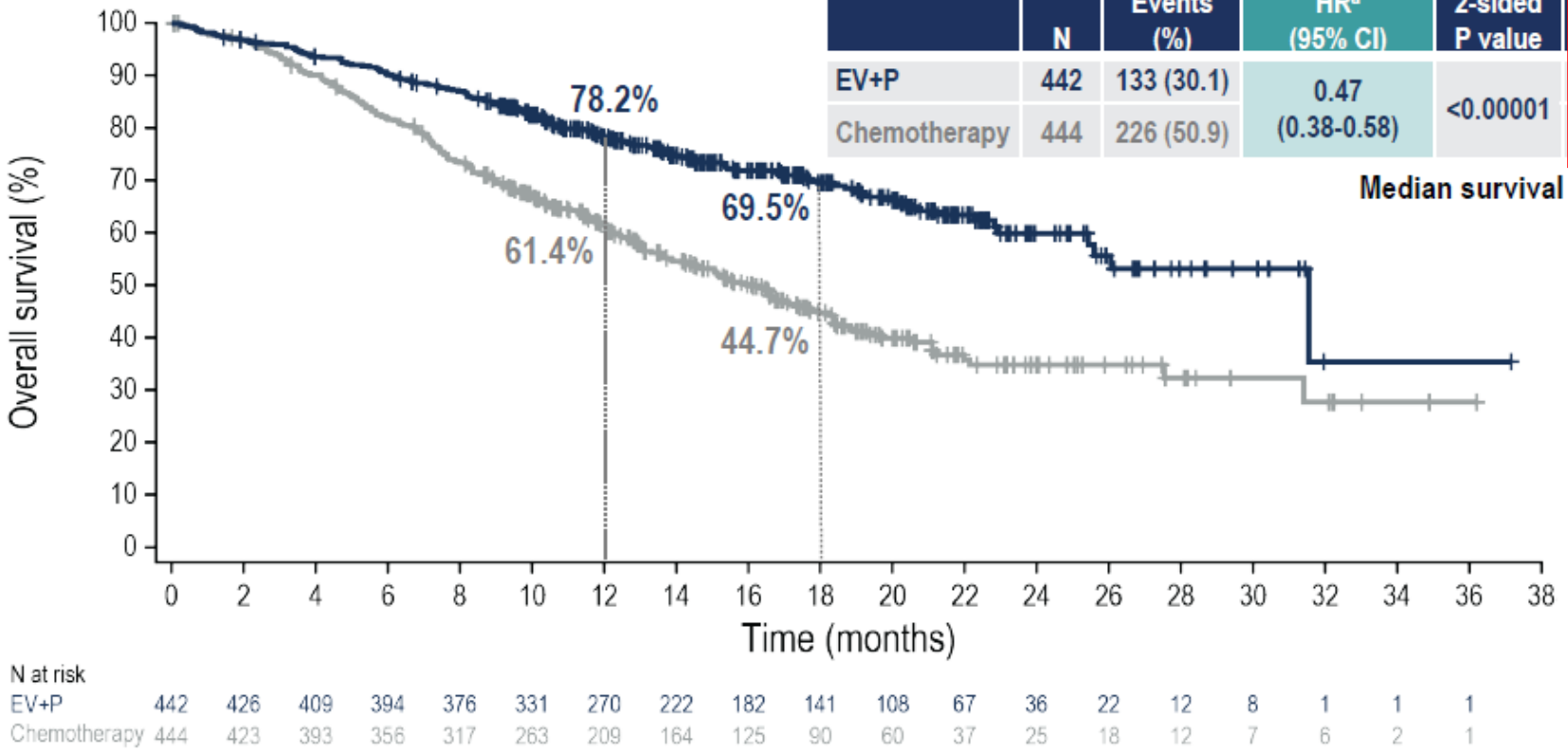
Powles, ESMO 2023

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

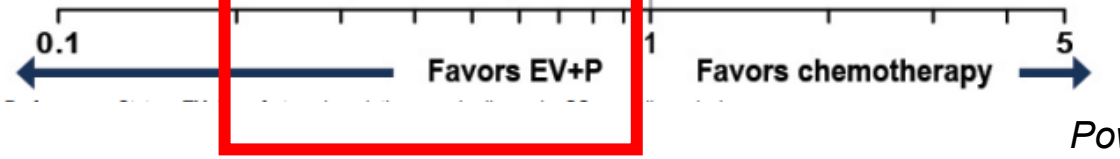
Almost doubling of PFS and OS!

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)

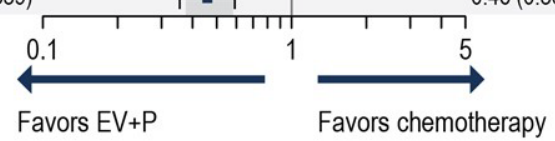


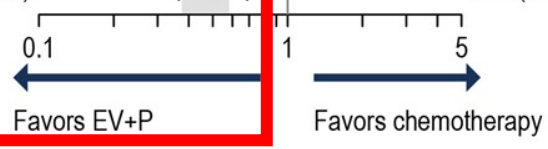
Powles, ESMO 2023

Subgroup Analysis of OS

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

Subgroup	mOS, months (Events/N) EV+P	Chemotherapy	Hazard Ratio (95% CI)
Overall	31.5 (133/442)	16.1 (226/444)	0.47 (0.38–0.58)
Age			
<65 years	NR (39/144)	19.7 (58/135)	0.46 (0.30–0.71)
≥65 years	31.5 (94/298)	14.6 (168/309)	0.48 (0.38–0.63)
Race			
White	26.1 (104/308)	15.3 (162/290)	0.47 (0.36–0.60)
Other	NR (29/134)	19.3 (64/154)	0.46 (0.29–0.72)
Region			
North America	25.6 (40/103)	21.2 (42/85)	0.71 (0.44–1.12)
Europe	NR (56/172)	13.9 (110/197)	0.40 (0.28–0.56)
Rest of world	NR (37/167)	16.4 (74/162)	0.41 (0.27–0.61)
Sex			
Female	25.4 (32/98)	14.6 (54/108)	0.51 (0.32–0.80)
Male	31.5 (101/344)	16.6 (172/336)	0.47 (0.36–0.60)
ECOG PS			
0	NR (44/223)	18.4 (94/215)	0.36 (0.25–0.53)
1-2	25.4 (89/219)	13.1 (131/227)	0.54 (0.41–0.72)
Primary disease site of origin			
Upper tract	NR (38/135)	18.4 (45/104)	0.53 (0.34–0.83)
Lower tract	31.5 (94/305)	15.6 (180/339)	0.46 (0.36–0.59)
Liver metastases			
Present	19.1 (43/100)	10.1 (67/99)	0.47 (0.32–0.71)
Absent	NR (90/342)	17.9 (159/345)	0.47 (0.36–0.61)
PD-L1 expression			
Low (CPS <10)	NR (53/184)	15.5 (99/185)	0.44 (0.31–0.61)
High (CPS ≥10)	31.5 (79/254)	16.6 (125/254)	0.49 (0.37–0.66)
Cisplatin eligibility			
Eligible	31.5 (69/244)	18.4 (106/234)	0.53 (0.39–0.72)
Ineligible	NR (64/198)	12.7 (120/210)	0.43 (0.31–0.59)
Metastatic disease site			
Visceral metastases	25.6 (108/318)	13.6 (182/318)	0.47 (0.37–0.60)
Lymph node only	NR (22/103)	27.5 (39/104)	0.46 (0.27–0.78)
Renal function[a]			
Normal	26.1 (24/84)	18.4 (44/95)	0.51 (0.30–0.86)
Mild	NR (42/165)	16.4 (78/162)	0.44 (0.30–0.65)
Moderate/Severe	31.5 (67/193)	13.3 (104/187)	0.50 (0.37–0.69)





Data cutoff: 08 August 2023

[a]Renal function categories defined as: Normal (≥90 mL/min), Mild (≥60 to <90 mL/min), Moderate/Severe (≥15 to <60 mL/min)

Summary of Subsequent Systemic Therapy

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

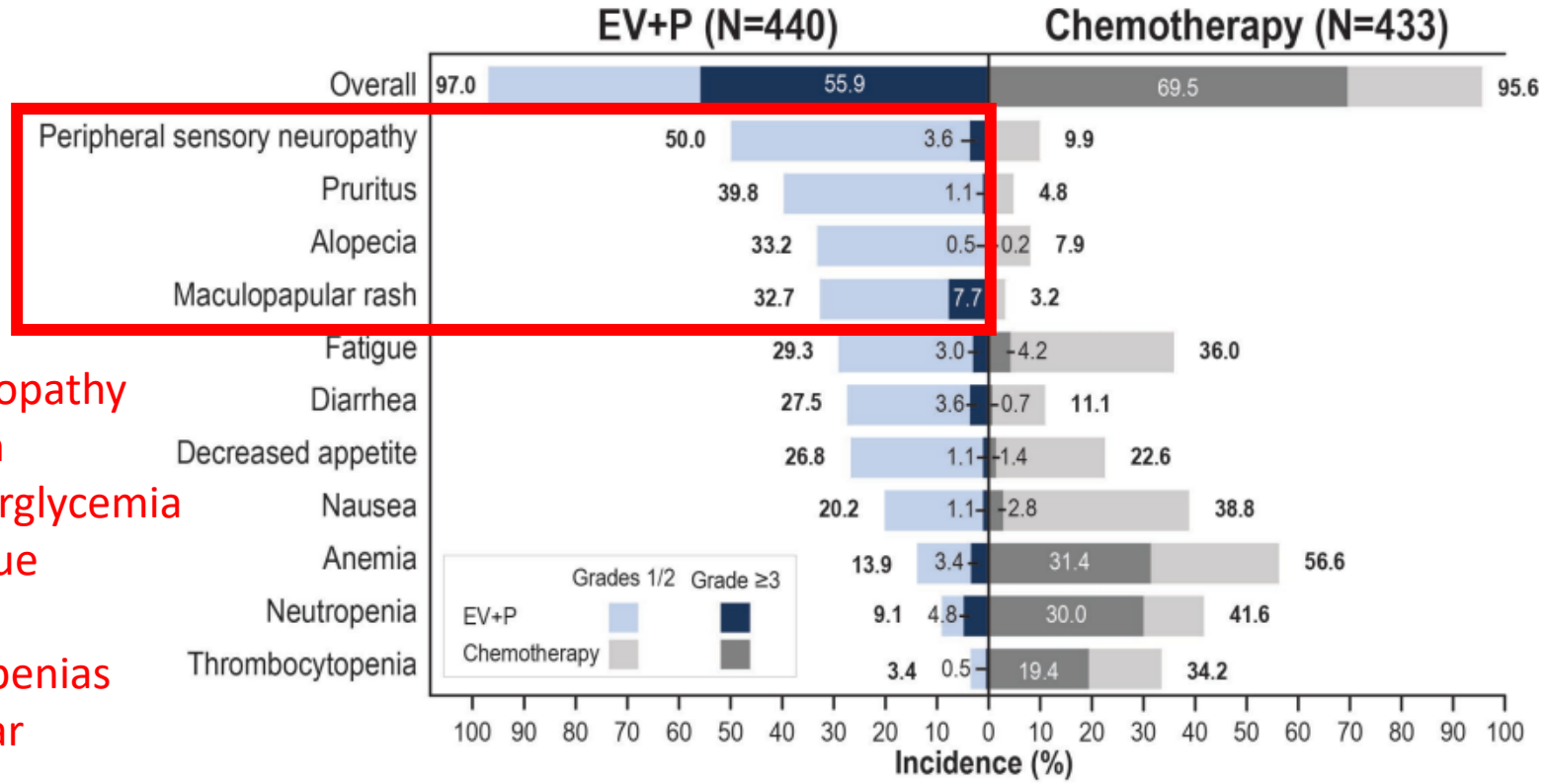
	EV+P (N=442) n (%)	Chemotherapy (N=444) n (%)
First subsequent systemic therapy[a]	128 (28.9)	294 (66.2)
Platinum-based therapy	110 (24.9)	17 (3.8)
PD-1/L1 inhibitor-containing therapy	7 (1.6)	260 (58.6)
Maintenance therapy	0	143 (32.2)
Avelumab maintenance	0	135 (30.4)
PD-1/L1 inhibitor-containing therapy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

30% of patients received maintenance avelumab

Powles, ESMO 2023

Treatment-Related Adverse Events

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



Neuropathy
Derm
Hyperglycemia
Fatigue
GI
Cytopenias
Ocular

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

New learning curve for toxicity management and early intervention

EV Treatment related Adverse Events of Special Interest

Adverse events - N (%)	EV+P (N= 440)		Chemotherapy (N= 433)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Skin reactions	294 (66.8)	68 (15.5)	60 (13.9)	1 (0.2)
Peripheral neuropathy	278 (63.2)	30 (6.8)	53 (12.2)	0 (0.0)
Sensory events	260 (59.1)	19 (4.3)	51 (11.8)	0 (0.0)
Motor events	44 (10.0)	12 (2.7)	5 (1.2)	0 (0.0)
Ocular disorders	94 (21.4)	0 (0.0)	12 (2.8)	0 (0.0)
Dry eyes	82 (18.6)	0 (0.0)	8 (1.8)	0 (0.0)
Hyperglycemia	57 (13.0)	27 (6.1)	3 (0.7)	0 (0.0)
Infusion-related reactions	9 (2.0)	0 (0.0)	9 (2.1)	0 (0.0)

Powles T. ESMO 2023

Toxicity management - Pearls

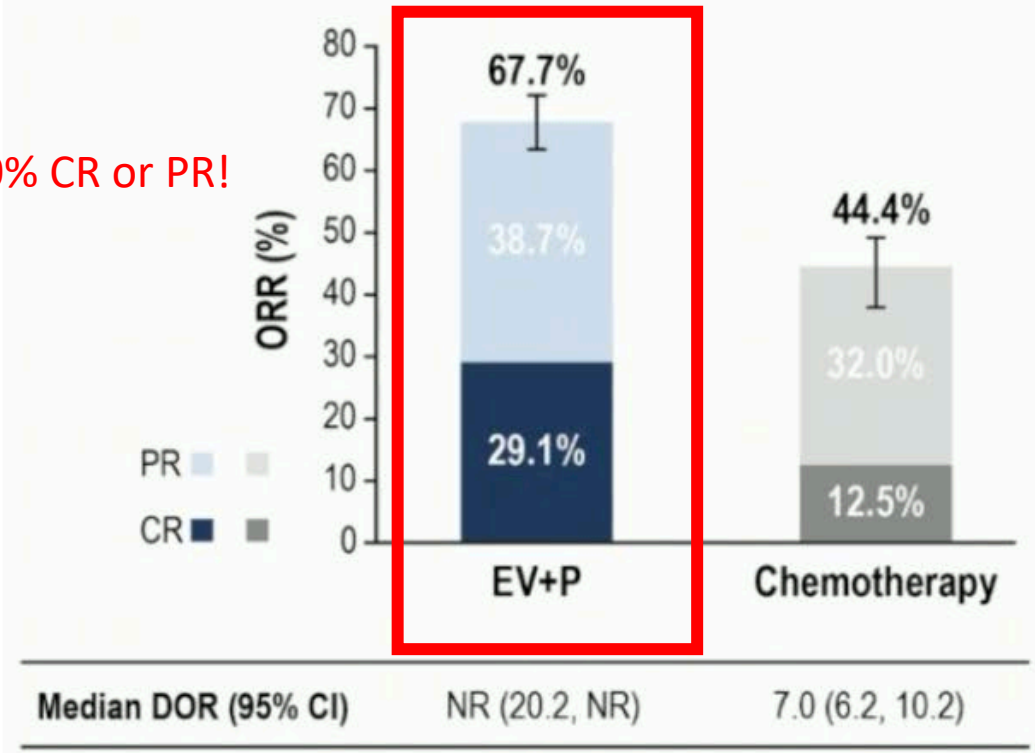
- Early dose reduction of EV for neuropathy – 1mg/kg or 0.75mg/kg
- Growth factor support for cytopenia
- Topical steroids and dose reduction for skin rash – use lotion not ointment
- Strict diabetes management
- Ocular toxicity
- And treatment interruptions in exceptional responders – need to be investigated

ORR for EV/P

Almost 70% CR or PR!

Confirmed Overall Response per BICR

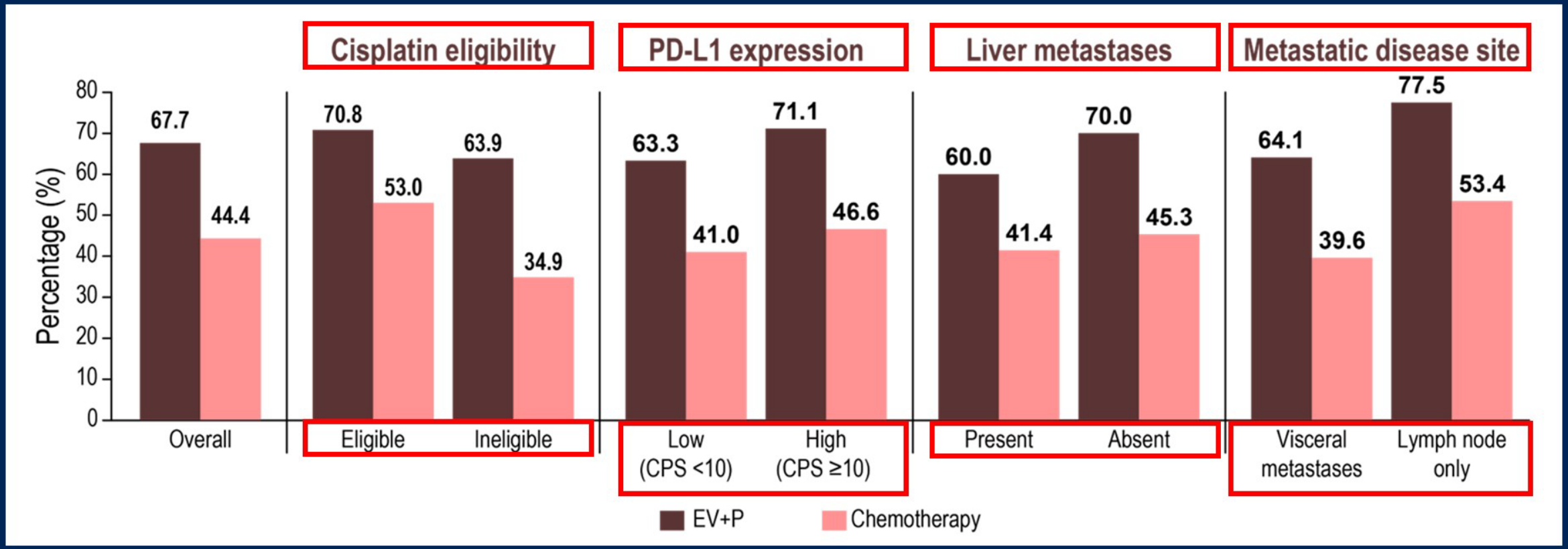
Significant improvement in objective response rate was observed with EV+P



	EV+P (N=437)	Chemotherapy (N=441)
Confirmed ORR, n (%) (95% CI)	296 (67.7) (63.1-72.1)	196 (44.4) (39.7-49.2)
2-sided P value	<0.00001	
Best overall response[a], n (%)		
Complete response	127 (29.1)	55 (12.5)
Partial response	169 (38.7)	141 (32.0)
Stable disease	82 (18.8)	149 (33.8)
Progressive disease	38 (8.7)	60 (13.6)
Not evaluable/No assessment[b]	21 (4.8)	36 (8.2)
Median DOR (95% CI)	NR (20.2, NR)	7.0 (6.2, 10.2)

Select subgroups of objective response rate by BICR

Objective response rates were ≥60% for EV+P across select subgroups



Data cutoff: 08 August 2023

van der Heijden MS. ASCO GU 2024

Checkmate 901

Many prior negative chemo-IO trials in 1L mUC

Cisplatin more immune inducing?

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

22 References 1 Citing Article

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

Key inclusion criteria

- Age ≥ 18 years
- Previously untreated unresectable or mUC involving the renal pelvis, ureter, bladder, or urethra
- Cisplatin eligible
- ECOG PS of 0-1

- Tumor PD-L1 expression (≥ 1% vs < 1%)
- Liver metastases (yes vs no)

R

Combination phase

N = 304: **NIVO** 360 mg on D1 + **Gemcitabine** 1000 mg/m² on D1/D8 + **Cisplatin** 70 mg/m² on D1 Q3W (up to 6 cycles)[b]

N = 304: **Gemcitabine** 1000 mg/m² on D1/D8 + **Cisplatin** 70 mg/m² on D1 Q3W (up to 6 cycles)[b]

3 weeks

Monotherapy phase

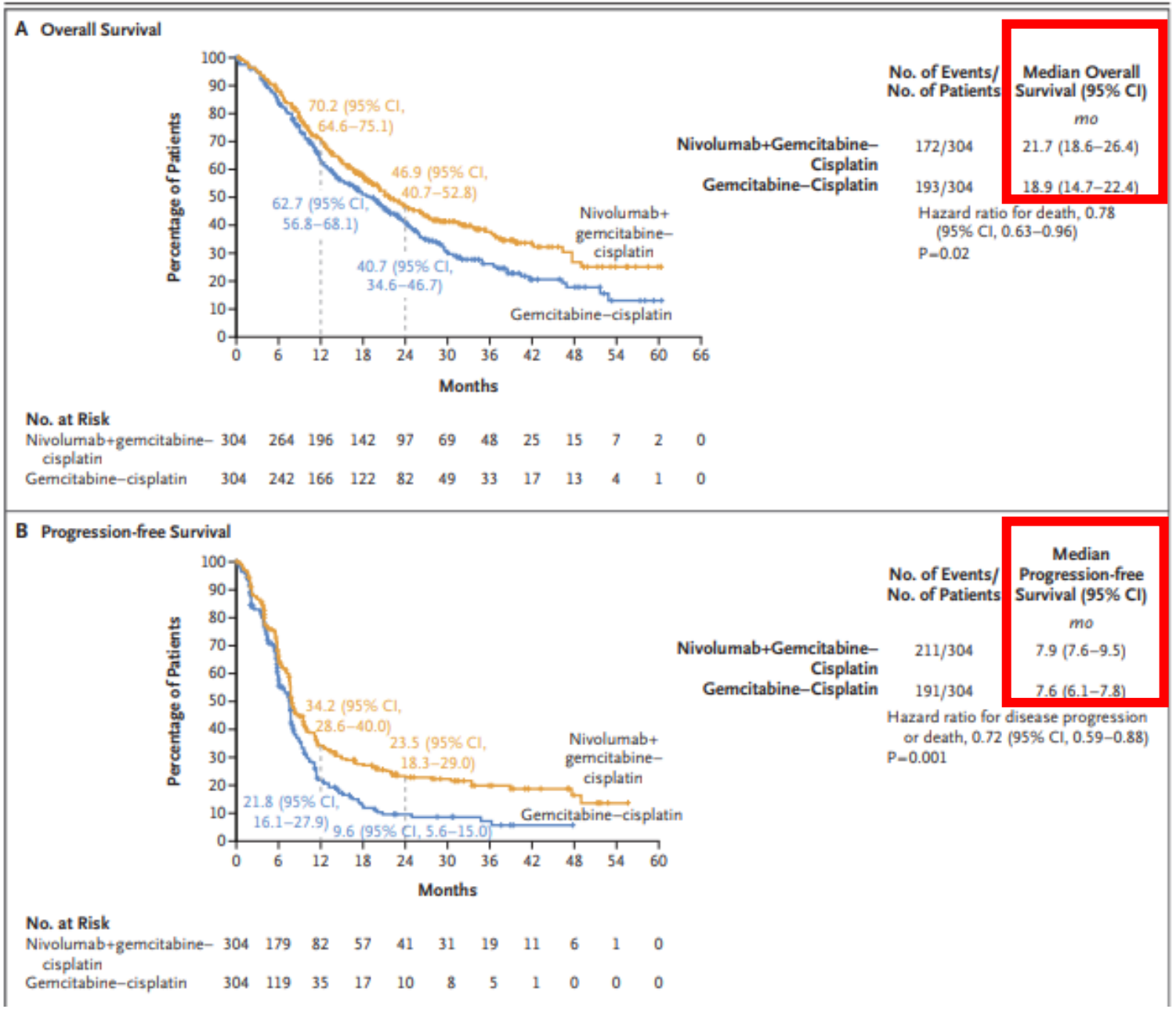
NIVO 480 mg Q4W (until progression, unacceptable toxicity, withdrawal, or up to 24 months[c])

Median (range) study follow-up, 33.6 (7.4-62.4) months

Primary endpoints: OS, PFS per BICR
Key secondary endpoints: OS and PFS by PD-L1 ≥ 1%,[d] HRQoL
Key exploratory endpoints: ORR per BICR, safety

CM-901

25% of patients in control arm received maintenance avelumab



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

Immunomodulatory effects of cisplatin >>> carboplatin

CellPress
Cell Reports Medicine

Cell Rep Med. 2024 Feb 20; 5(2): 101393. PMCID: PMC10897541
Published online 2024 Jan 26. doi: 10.1016/j.xcrm.2024.101393 PMID: 38280376

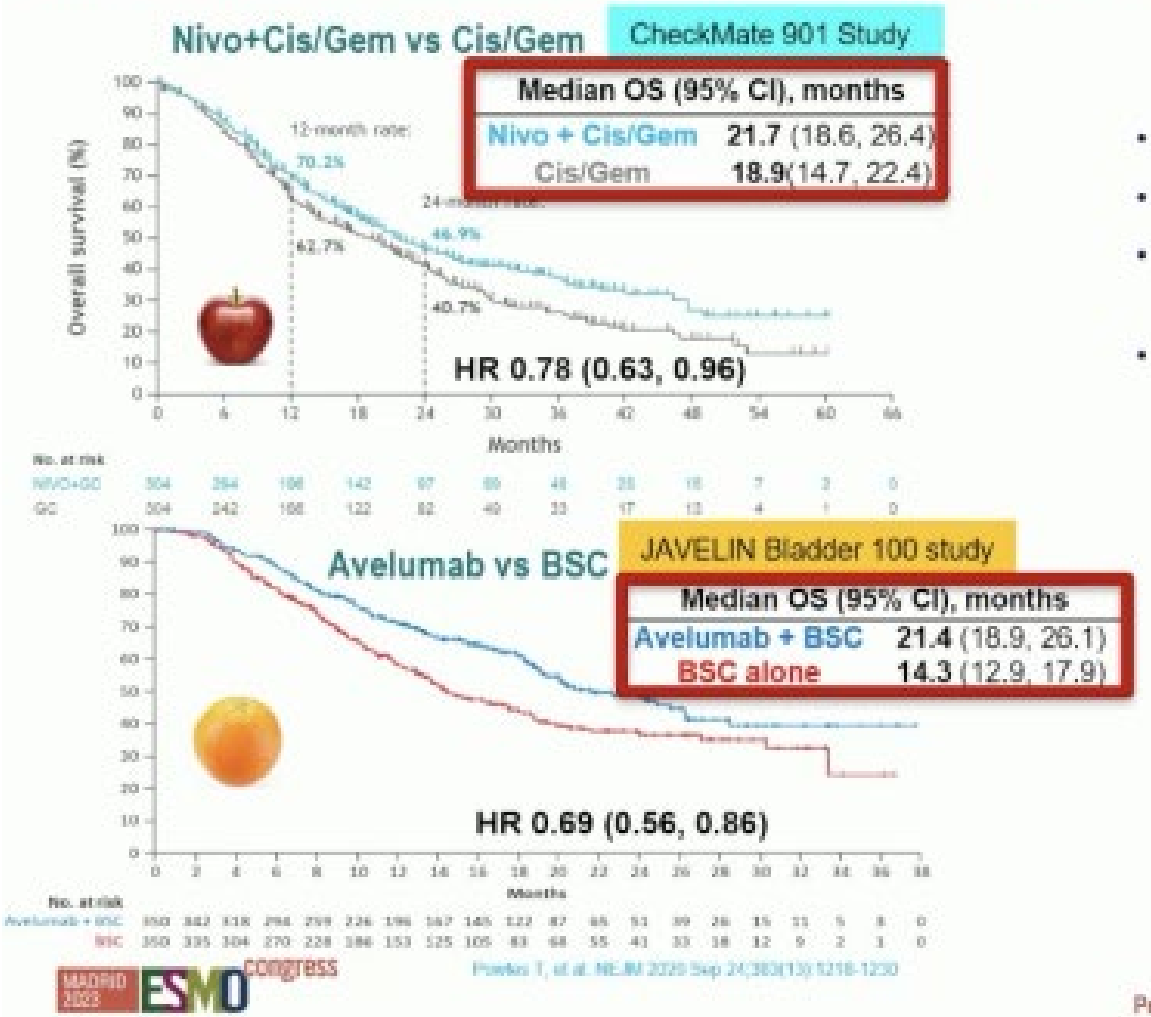
Journal Article

Immunomodulatory effects and improved outcomes with cisplatin- versus carboplatin-based chemotherapy plus atezolizumab in urothelial cancer

Matthew D. Galsky,[1,*] Xiangnan Guan,[2,16] Deepali Rishipathak,[2,16] Aaron S. Rapaport,[2,16] Hesham M. Shehata,[2,16] Romain Banchereau,[2] Kobe Yuen,[2] Eugene Varfolomeev,[2] Ruozhen Hu,[2] Chia-Jung Han,[2] Haocheng Li,[3] Yuxin Liang,[2] Domagoj Vucic,[2] Li Wang,[4,5] Jun Zhu,[4,5] Haocheng Yu,[5] Rebecca H. Herbst,[6] Emma Hajaj,[6] Evgeny Kiner,[6] Aristotelis Bamias,[7] Maria De Santis,[8,9] Ian D. Davis,[10] José Ángel Arranz,[11] Eiji Kikuchi,[12] Sandrine Bernhard,[13] Patrick Williams,[2] Chooi Lee,[13] Ira Mellman,[2] Shomyseh Sanjabi,[2] Robert Johnston,[2] Peter C. Black,[14] Enrique Grande,[15] and Sanjeev Mariathasan[2,17,**]

- GemCis versus GemCarbo ± atezolizumab:
  - Induces transcriptional changes in circulating immune cells, including upregulation of antigen presentation and T cell activation programs
  - Direct immunomodulatory effects on cancer cells, promoting dendritic cell activation and antigen-specific T cell killing
- Importance of specific chemotherapy backbones in immunotherapy combination regimens

Both sequential and combination chemo and CPI have efficacy



- 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

74% completed induction regimen in CM-901 vs 55% of induction phase in JAVELIN-100

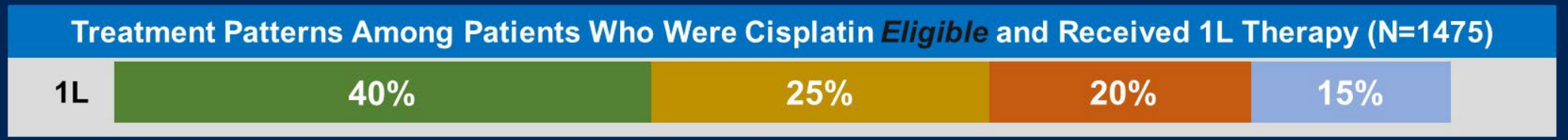
Upfront IO allows more pts to get to maintenance phase?

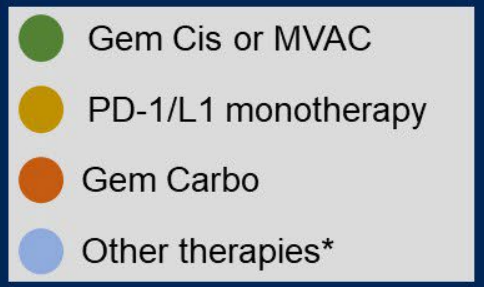
Presented by Andrea B. Apolo, MD

@apolo_andrea

First line and second line therapy in UC patients in real world – Flatiron database

~One-Quarter of Patients Did Not Receive 1L Therapy (989/4300; 23%)
~Half of Patients Did Not Receive 2L Therapy





This is likely to change dramatically with vast majority of patients in both categories getting EV + Pembro

- Patients aged ≥18 years diagnosed with Ia/mUC from May 2016 to October 2020 in the Flatiron Health database.
- Patients were followed until death or end of data availability in June 2021.
- **Other therapies* included PD-1/L1 combination therapy, monochemotherapy (taxanes, gemcitabine, cisplatin monotherapy, carboplatin monotherapy), and other off-label treatments.

Sonpavde GP, ASCO 2022

1L mUC Takeaways

- EV + Pembro is **practice changing** for cisplatin eligible & ineligible patients
  - Up to ECOG 2
  - Good response in those with even visceral metastases
  - No need for PDL-1 stratification
  - No need for NGS results to determine eligibility
- Understand new toxicities of ADCs & establishing guidelines & dose adjustments is important
  - Pts who can't qualify? Pre-existing neuropathy, uncontrolled DM, cirrhosis, autoimmune disease
- Think of access: cost **$39k** per 1 cycle of EV + P!!

Unanswered Questions

- Role of cystectomy in those with CR on EV/P?
- De-escalation of therapy for responders?
- Role in those who progress on adjuvant IO or maintenance IO
- Role of CM-901 data for those who may be predicted to have CR, like LN+ only metastatic disease?
- 2L regimen?
- Role if EV/P moved to NAC setting?
- Optimal treatment for variant histologies? AdenoCA, squamous predominant, plasmacytoid...

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

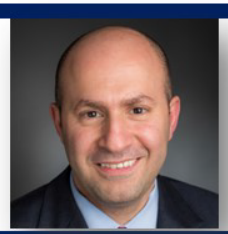
- Erdafitinib (if tumor + FGFR 2/3 genetic alterations)
- Sacituzumab govitecan
- Clinical trial
- Paclitaxel, docetaxel, or vinflunine

Disitamab vedotin for her-2+?

Can we use radiation to control oligo-progression?

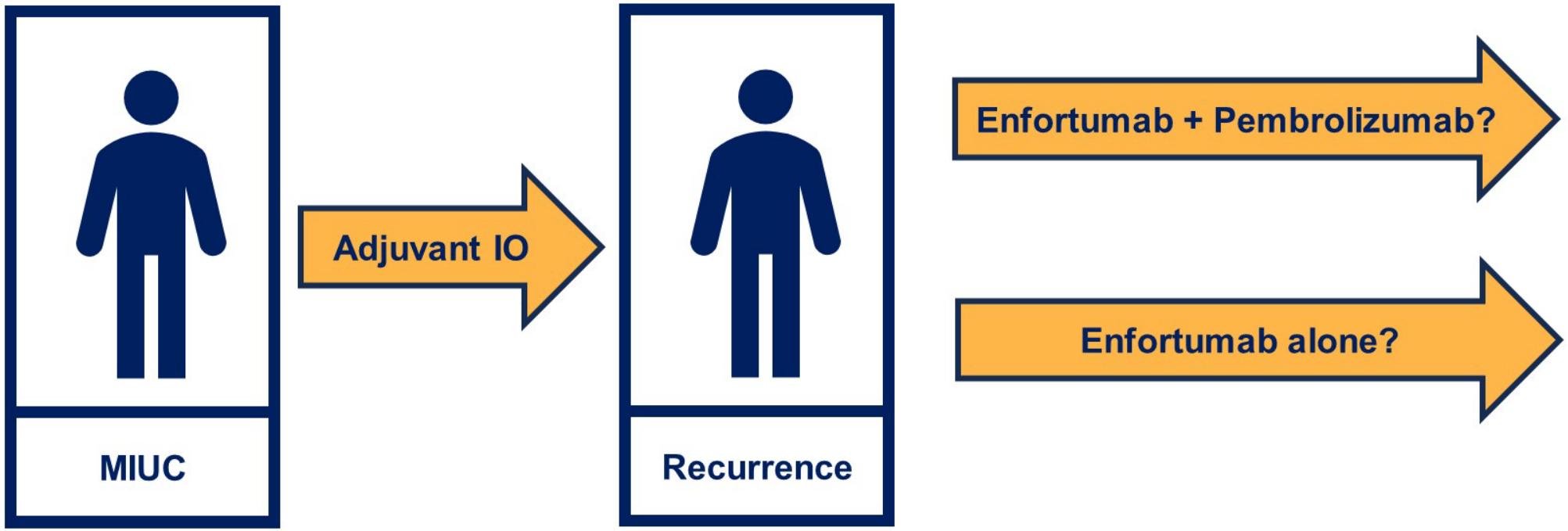
A. Apolo, ESMO, Oct 2023

Kidney Cancer



Toni Choueiri, MD, FASCO

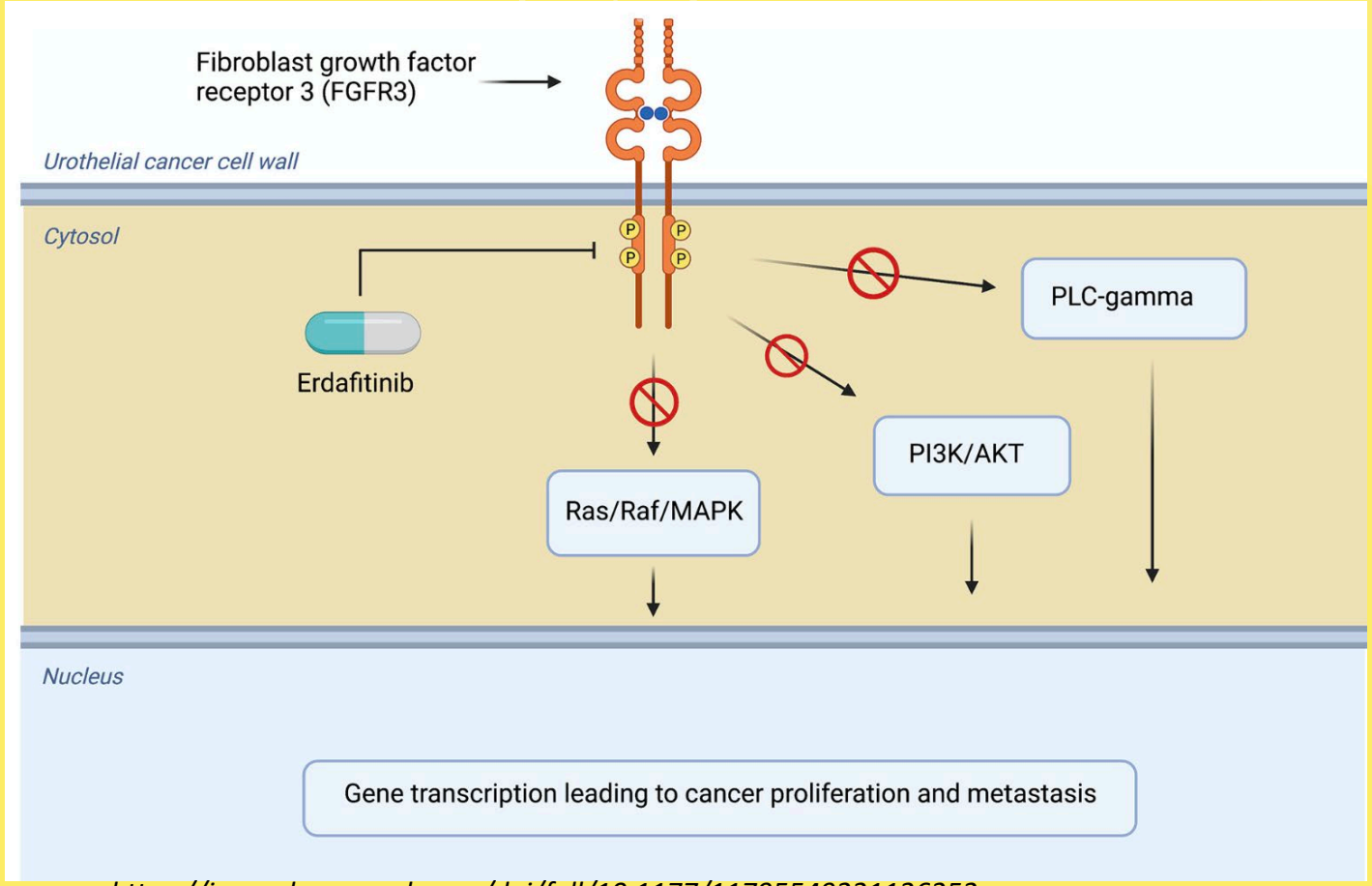
- "CONTACT-03 highlights the importance of randomized, prospective assessment of rechallenge with checkpoint inhibitors in renal cell carcinoma and potentially in other tumor types."



References:
1. Choueiri *et al* ASCO 2023
2. Pal *et al* Lancet 2023

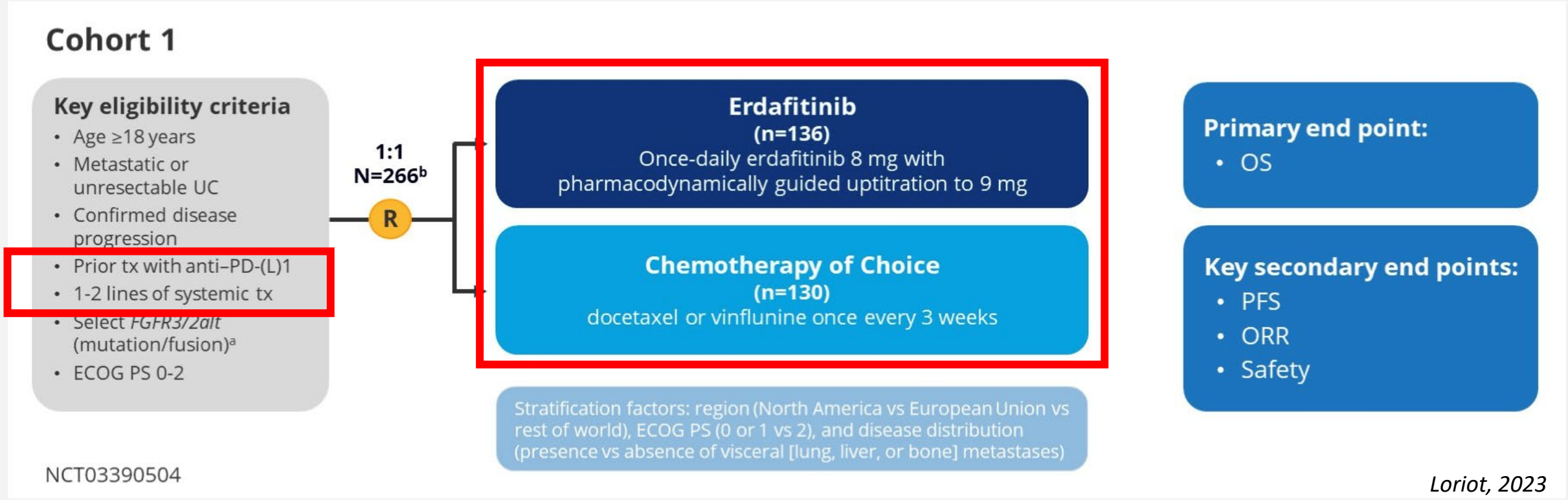
FGFR Pathway in mUC

- 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.

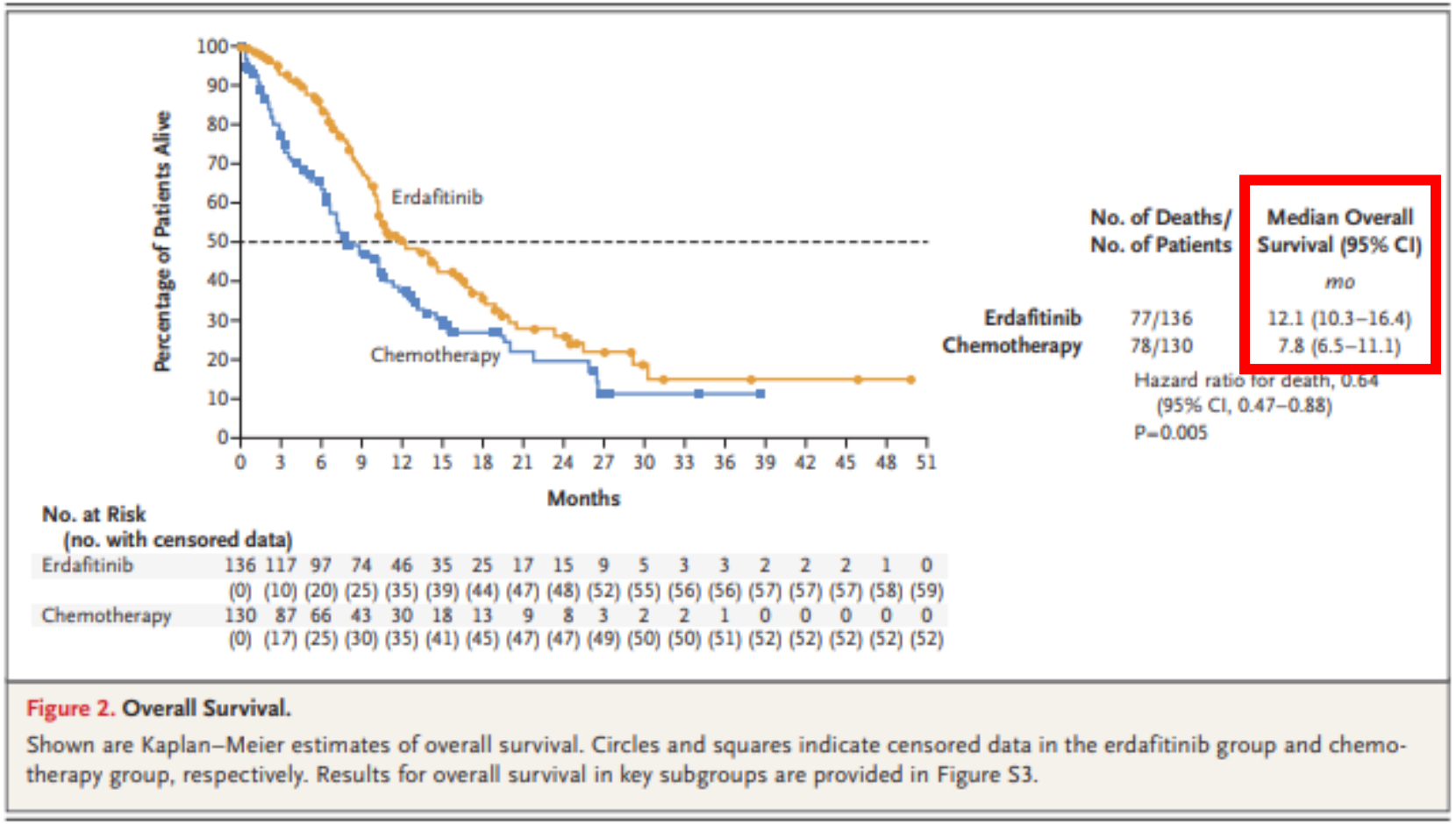


Figure 2. Overall Survival.

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.

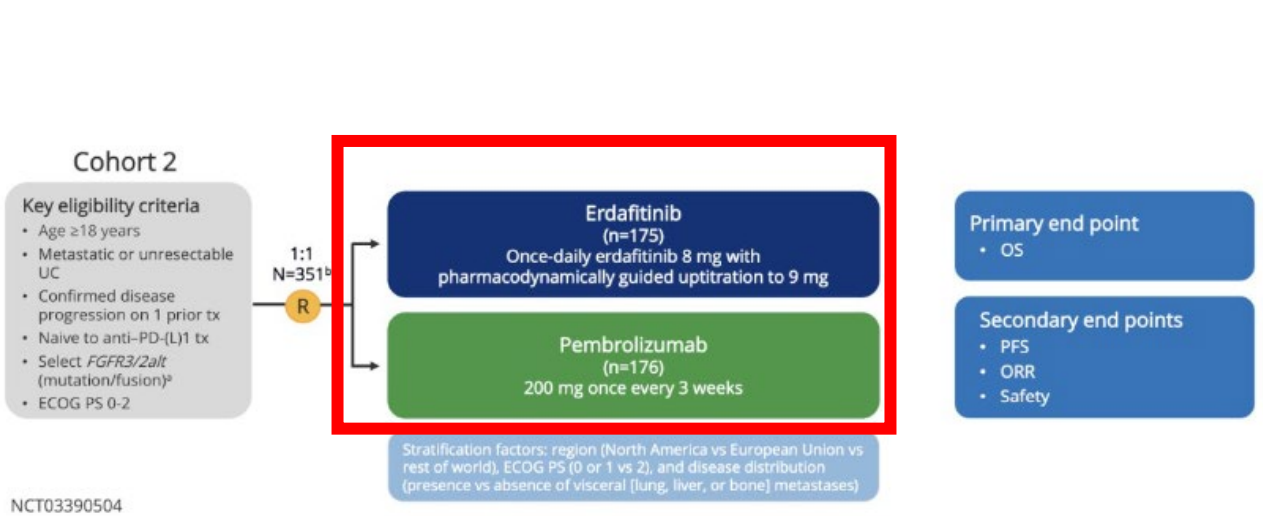
2L or 3L post IO and for many post chemo

- **OS:** 12.1 mo vs 7.8 mo
- **PFS:** 5.6 vs 2.7 mo
- **ORR:** 45.6% vs 11.5%

Loriot, NEJM, 2023

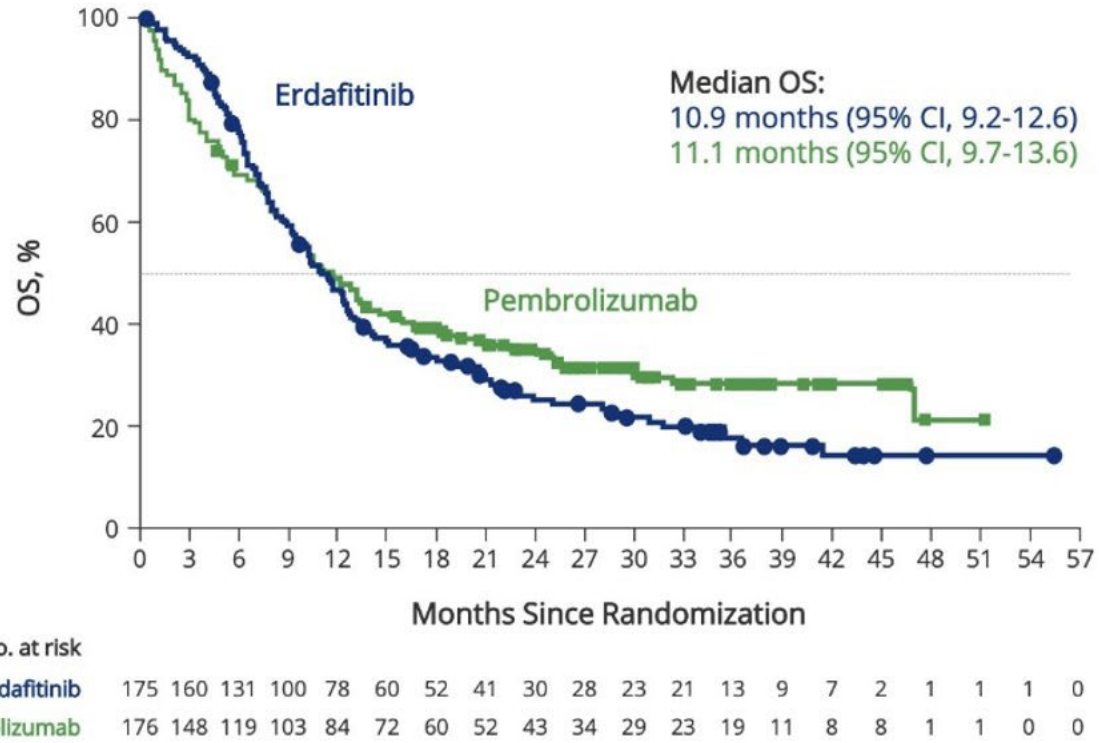
THOR Cohort 2 – 2L Erdafitinib vs IO

No difference in OS



Primary end point
- OS

Secondary end points
- PFS
- ORR
- Safety



Siefker-Radtke, ESMO 2023

NORSE Trial –

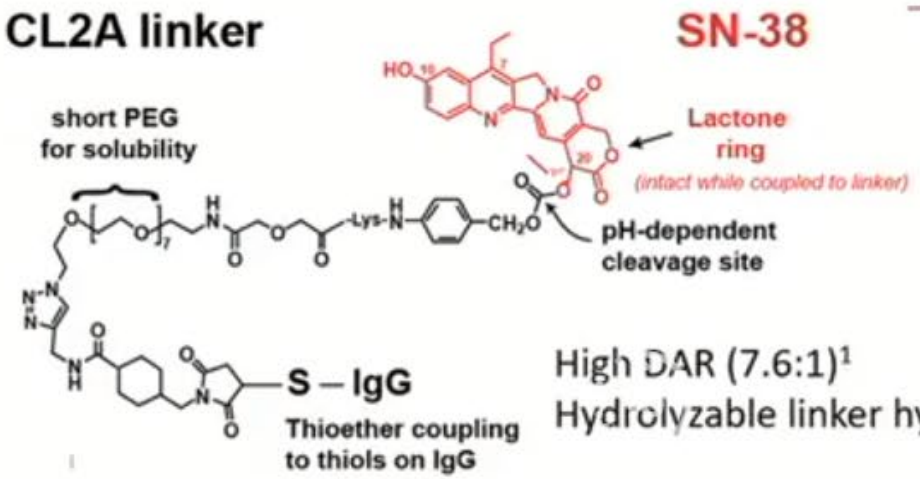
1L erdafitinib vs erdafitinib + IO in cisplatin ineligible

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.

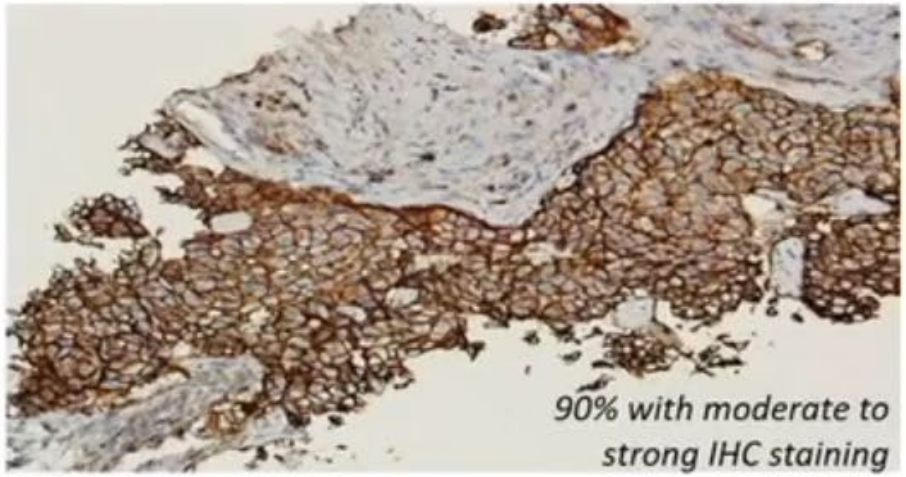
	ERDA+CET (n=44)	ERDA (n=43)
ORR, % (95% CI)	54.5 (38.8, 69.6)	44.2 (29.1, 60.1)
Confirmed CR, n (%)	6 (13.6)	1 (2.3)
DCR, % (95% CI)	79.5 (64.7, 90.2)	88.4 (74.9, 96.1)
Median DOR (95% CI), mo	11.10 (8.77, NE)	9.72 (4.60, NE)
Median PFS (95% CI), mo	10.97 (5.45, 13.63)	5.62 (4.34, 7.36)

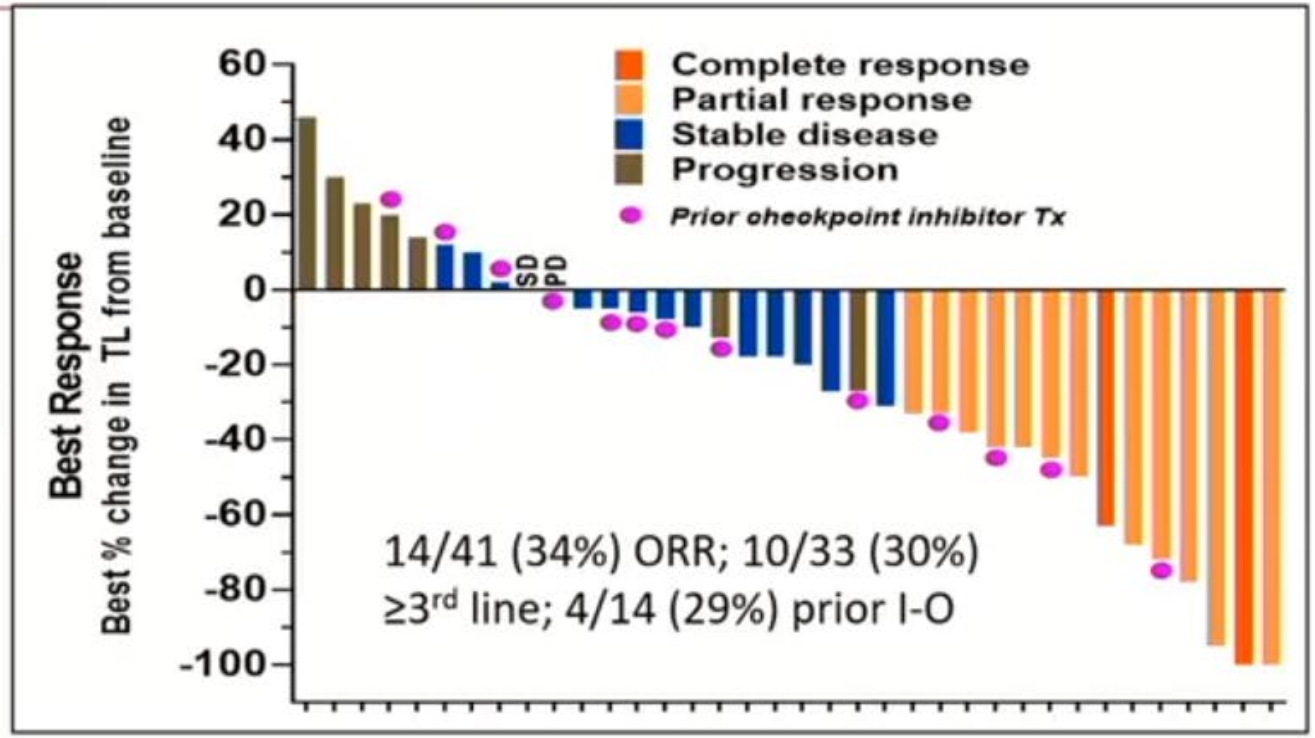
Siefker-Radtke, ESMO 2023

Sacituzumab govitecan



High DAR (7.6:1)[1]
Hydrolyzable linker hydrolysis[2]





- Final 14/45 (31%) ORR
- Median PFS 7.3 months
- Median OS 18.9 months

1. Cardillo TM, et al. Bioconjug Chem 2015; 26:919-31
2. Govindan SV, et al. Mol Cancer Ther 2013; 12:968-78

Tagawa S, et al. Ann Oncol (2017) 28 (suppl_5):v295-v329
Tagawa S, et al. J Clin Oncol 37, no. 7_suppl (March 1, 2019) 354-354

TROPHY-U-01 Is a Registrational, Open-Label, Multicohort Phase 2 Trial in Patients With mUC

TROPHY U-01

Grivas, Scripps Clinical Hematology Oncology 2024

Cohort 1* (~100 patients): patients with mUC who progressed after prior platinum-based and CPI-based therapies — SG 10 mg/kg Days 1 and 8, every 21 days

Cohort 2 (~40 patients): patients with mUC ineligible for platinum-based therapy and who progressed after prior CPI-based therapies — SG 10 mg/kg Days 1 and 8, every 21 days

Cohort 3[a] (up to 61 patients): mUC CPI naïve patients who progressed after prior platinum-based therapies — SG 10 mg/kg Days 1 and 8, every 21 days; Pembrolizumab 200 mg day 1 every 21 days

Cohort 4 (up to 60 patients): mUC platinum-naïve patients — SG Days 1 and 8, every 21 days; Cisplatin[b]

Cohort 5 (up to 60 patients): mUC platinum-naïve patients — SG Days 1 and 8, every 21 days; Cisplatin[c] Avelumab 800 mg every 2 weeks

Cohort 1: ORR 31%

Continue treatment in the absence of unacceptable toxicity or disease progression

Continue until a maximum of 6 cycles has been completed,[d] disease progression, lack of clinical benefit, toxicity, or withdrawal of consent → Maintenance avelumab (800 mg every 2 weeks) with SG (Days 1 and 8 every 21 days) for those without disease progression

Primary Endpoint:
Objective response rate per RECIST 1.1 criteria

Key Secondary Endpoints:
Safety/tolerability, DOR, PFS, OS

Key Inclusion Criteria: Age ≥18 years, ECOG of 0/1, creatinine clearance (CrCl) ≥30 mL/min,[b,c] adequate hepatic function
Key Exclusion Criteria: Immunodeficiency, active Hepatitis B or C, active secondary malignancy, or active brain metastases

***Accelerated FDA approval for treatment of patients with locally advanced or mUC who previously received platinum-containing chemotherapy and PD-1/L1 inhibitor[1]**

[a]Exclusions for Cohort 3 only: active autoimmune disease or history of interstitial lung disease. [b]In patients with CrCl ≥60 mL/min; [c]In patients with creatinine clearance 50–60 mL/min. [d]For patients who have not progressed, maintenance therapy will begin with infusions of avelumab (800 mg every 2 weeks beginning cycle 1, day 1 and every 2 weeks thereafter) followed by SG on days 1 and 8 every 21 days.
CBR, clinical benefit rate; CPI, checkpoint inhibitor; CrCl, creatinine clearance; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mUC, metastatic urothelial cancer; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan.

1. TRODELVY™ (sacituzumab govitecan-hziy). Prescribing Information. Immunomedics, Inc.; April 2021; EudraCT Number: 2018-001167-23; ClinicalTrials.gov Number: NCT03547973. IMMU-132-06 study.

TROPiCS-04 Design

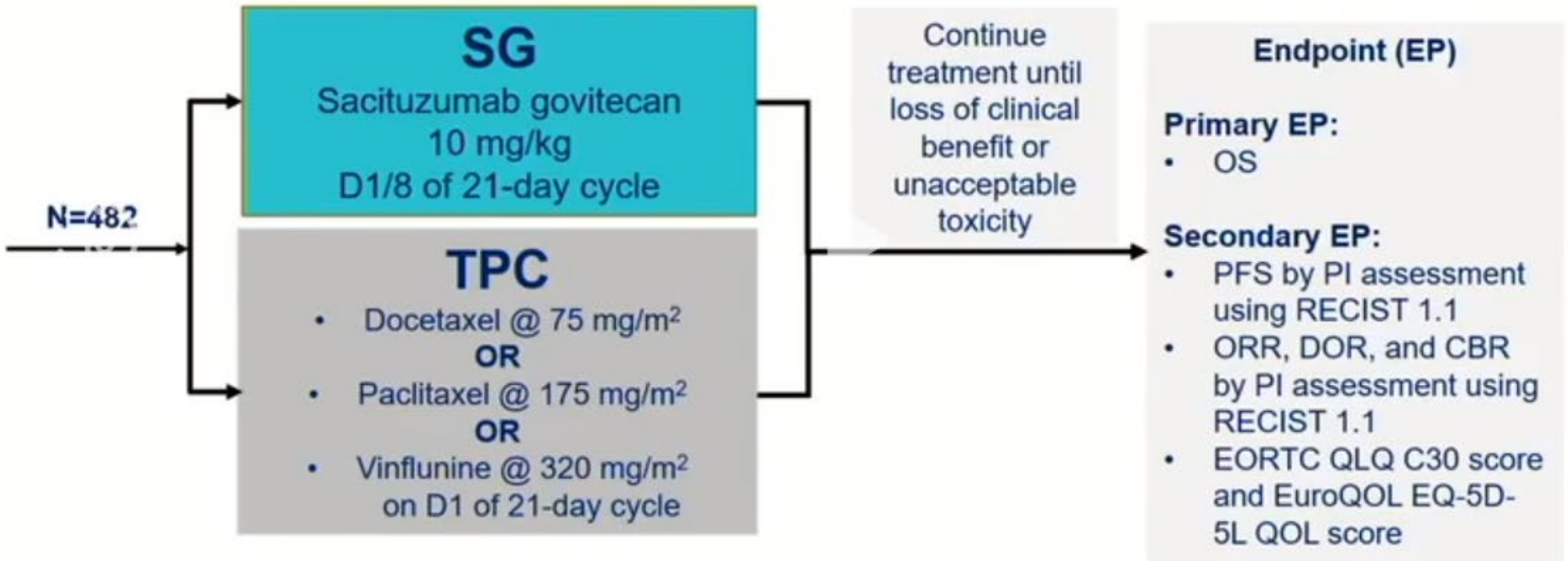
Grivas, Scripps
Clinical Hematology Oncology
2024

Study Population

- Locally advanced unresectable or mUC
- Upper/lower tract tumors
- Mixed histologic types are allowed if urothelial is predominant
- Progression after platinum-based **and** anti–PD-1/PD-L1 therapy

OR

- Platinum in neo/adj setting if progression within 12 months and subsequent CPI

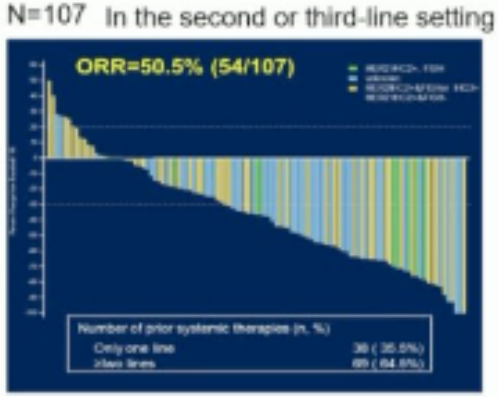


Grivas et al. 10.1200/JCO.2021.39.6_suppl.TPS498 *JCO* 39, no. 6_suppl

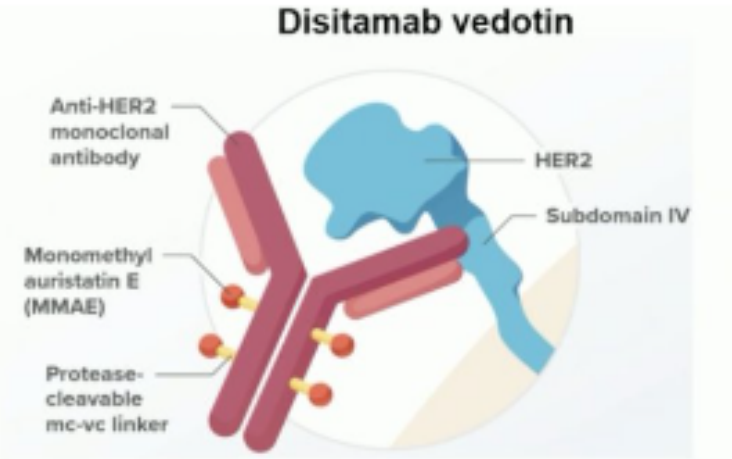
Her-2 in mUC

- 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.



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

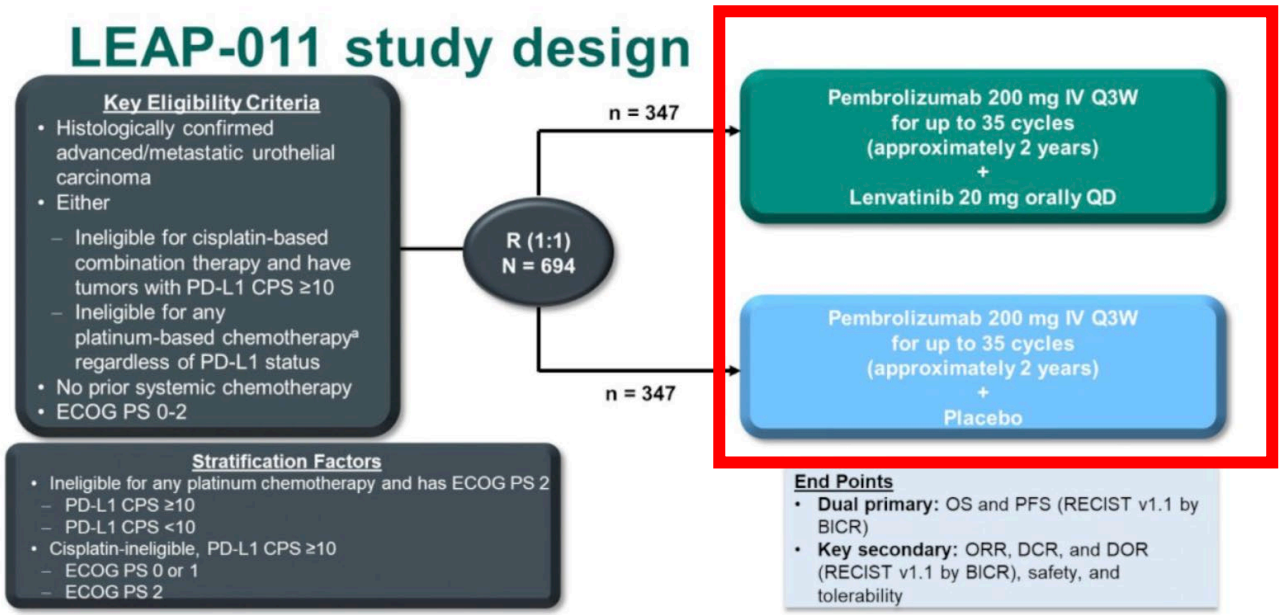


Similar to EV + pembrolizumab, it appears that the combination of disitamab vedotin + toripalimab (anti-PD-1) is associated with promising efficacy outcomes in HER2+ metastatic urothelial carcinoma patients.

Phase III study (NCT04264936) ongoing

A. Apolo, Oct 2023

TKI in mUC – ASCO GU 2024

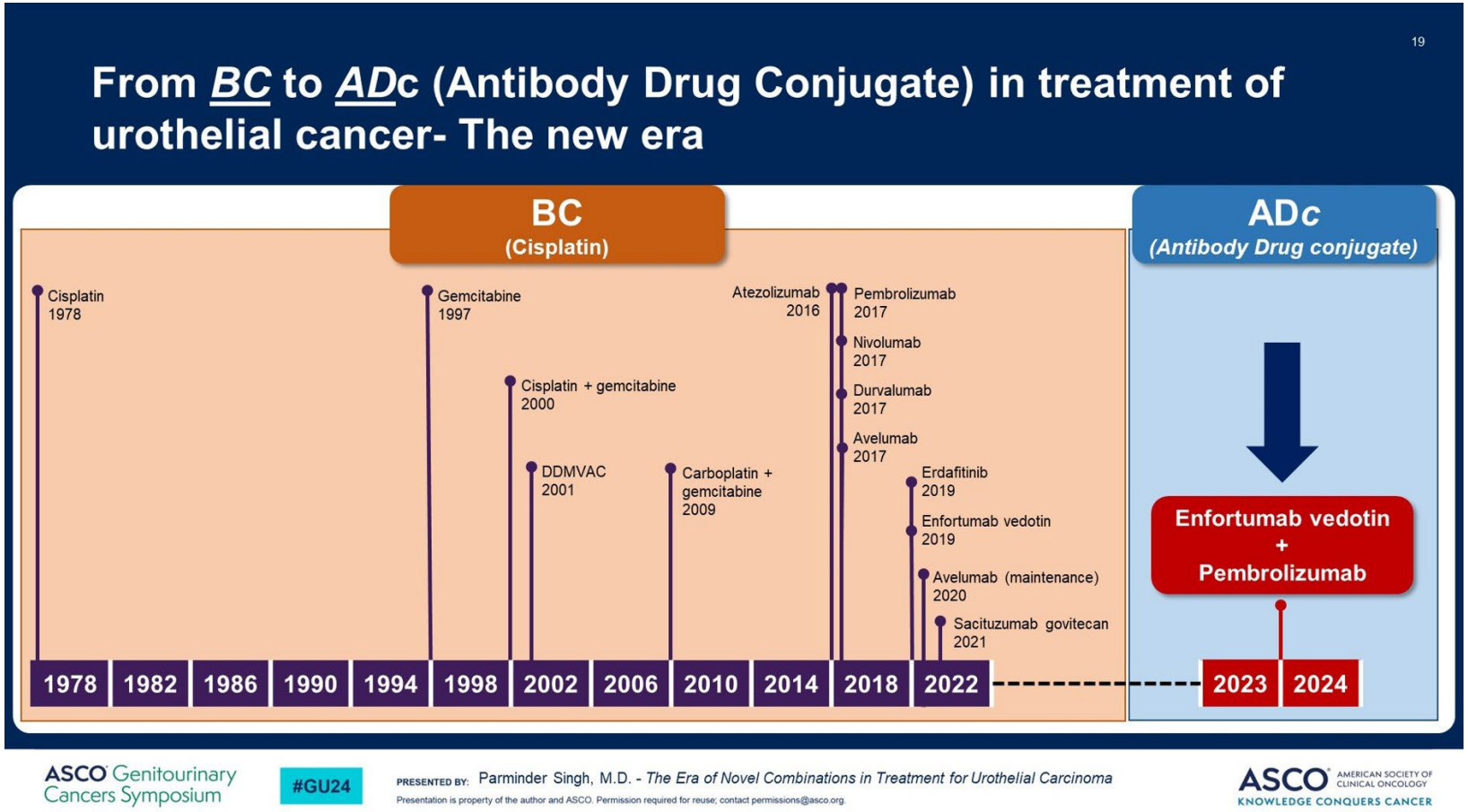


- Some encouraging efficacy (ORR 45%) but did not improve outcomes
- Modest responses of other TKI trials in mUC
- Future directions:
  - Zanzalitinib (XL-092) - similar to cabozantinib with better tolerability/therapeutic index
  - IO/TKI to re-invigorate IO response?
  - TKI as salvage monotherapy if can find right biomarker?
  - Add to pembro for EV/pembro responders and drop EV to prevent cumulative neuropathy?

Dr. R. Jain, ASCO GU 2024

Conclusions

- The new era of precision oncology & novel treatments in bladder cancer is here!
  - NGS testing important in metastatic setting
  - Landscape will continue to change in years to come
  - Role of ctDNA evolving



Thank You.

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