Advances In Urothelial Cancer: 2022

EMORY WINSHIP CANCER INSTITUTE
A Cancer Center Designated by the National Cancer Institute

Debates and Didactics in Hematology and Oncology

July 21, 2022

Sea Island, GA

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Disclosures

- Consultant:
  - Eisai
  - Bristol Myers-Squibb
  - Gilead

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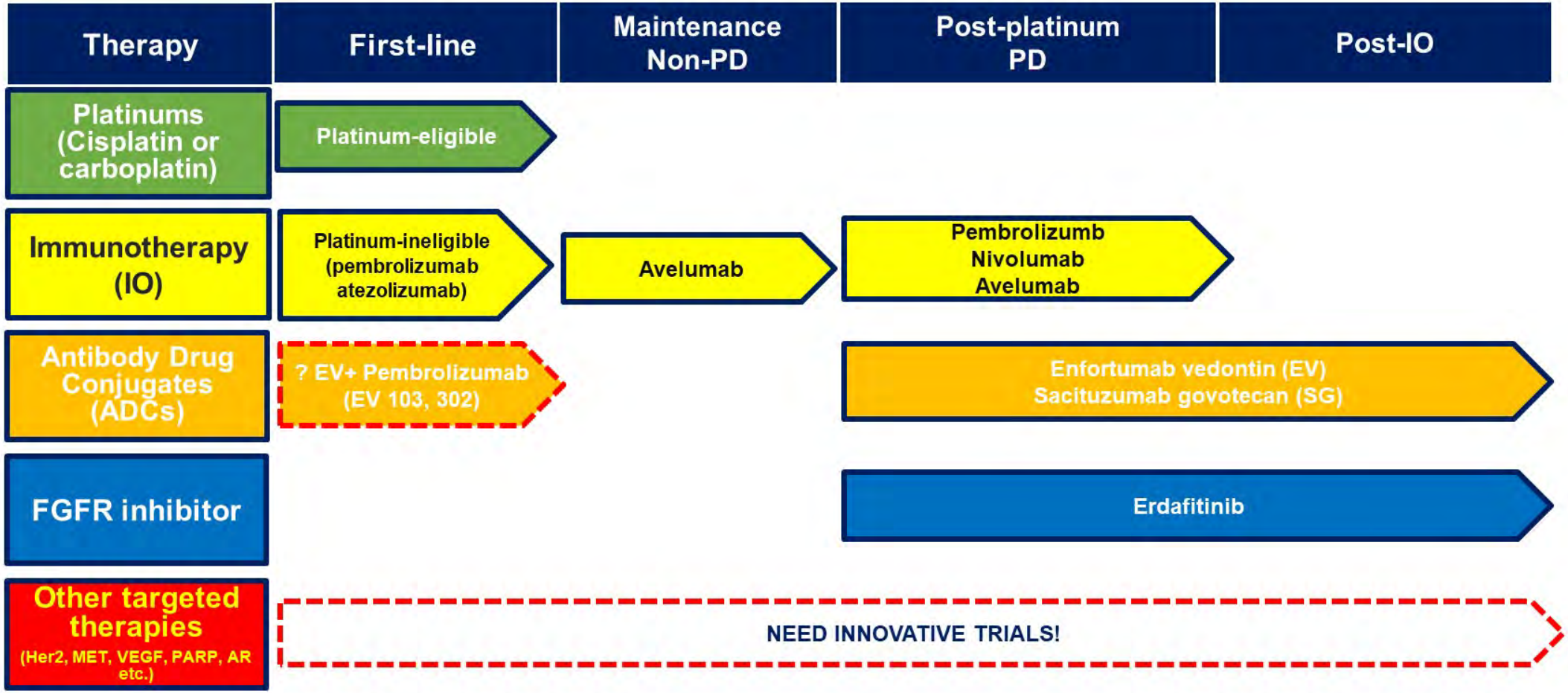
  - Bristol Myers-Squibb
  - Immunomedics
  - AstraZeneca
  - Alkermes

Objectives

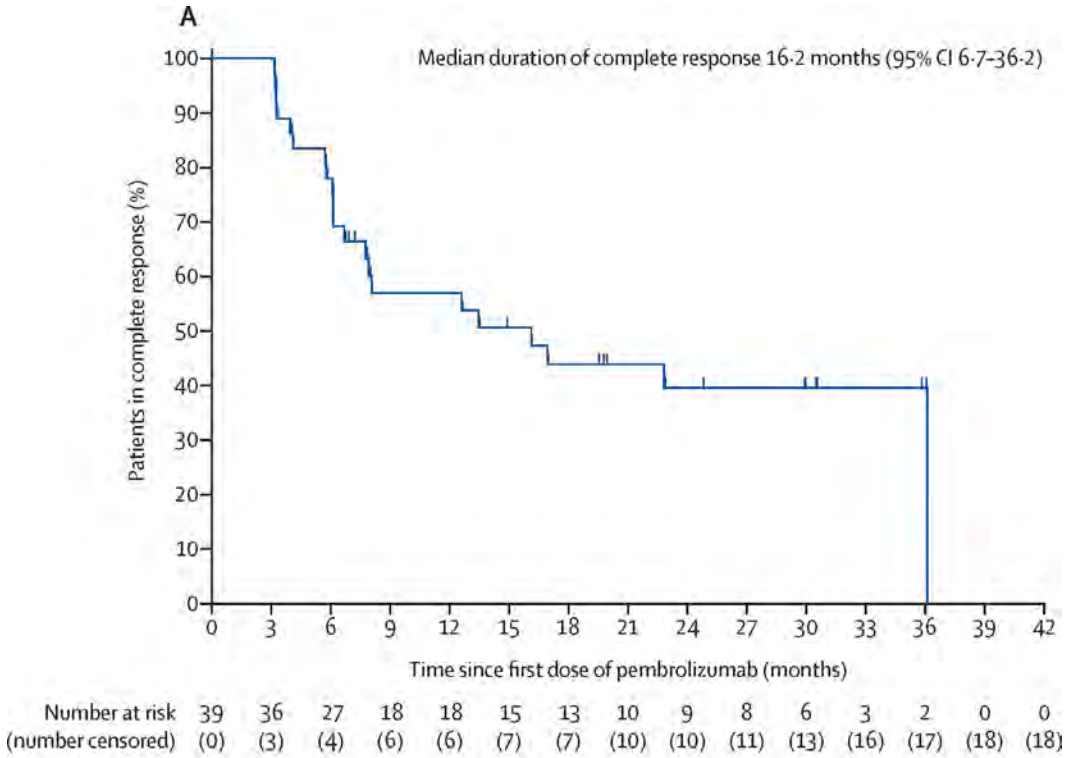
- Review of Treatment Landscape 2022 (NMIBC/MIBC)
- Review of Novel Perioperative Approaches
- Review of Bladder Sparing Approaches
- Current Recommendations for Metastatic Setting
- Promising Agents In Advanced Urothelial Cancer

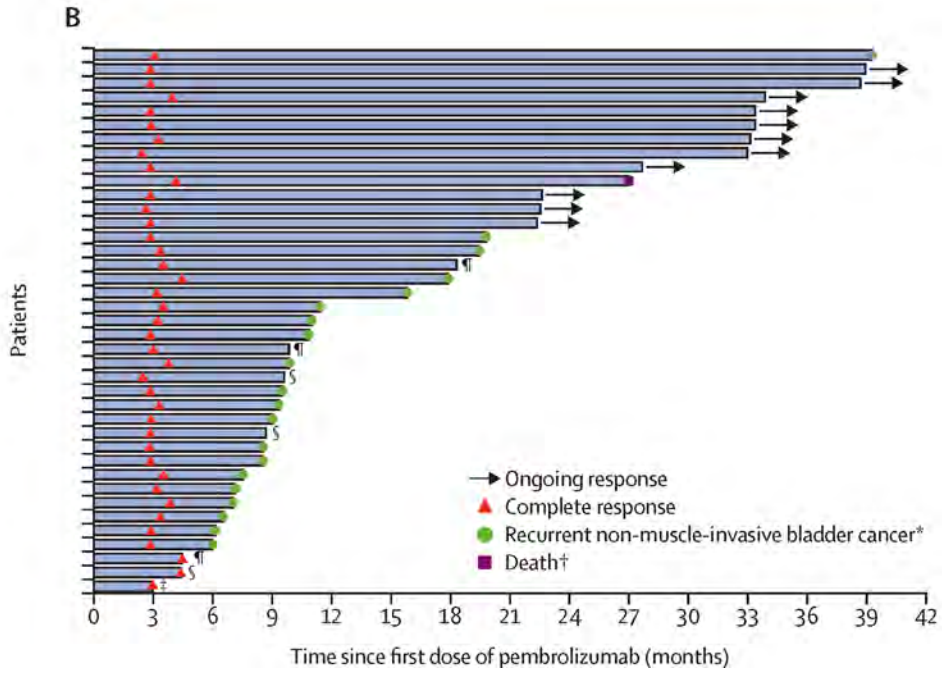
Current Treatment Options for Metastatic Urotheial Cancer (mUC) June 2022



Shupta, G. ASCO 2022

Pembrolizumab for Treatment of Patient with BCG Unresponsive High Risk NIMBC: Over 2 Years' Follow-Up of KEYNOTE-057

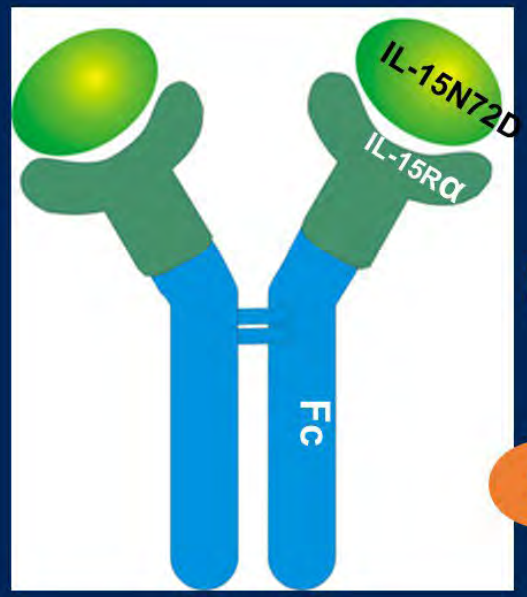




Balar AV, et al. Lancet Oncol. 2021 Jul;22(7):919-930.

Non – Muscle Invasive Bladder Cancer

N-803: First-in-Class IgG1-Fc IL-15 Cytokine Agonist



N-803

Unique Mechanisms of Action

1. **IL-15N72D**
   IL-15 N72D mutation enhances binding to IL-2Rβ, driving proliferation and activation of NK and T cells
2. **IL-15Rα**
   Allows transpresentation selectively to only IL-2Rβγ chain of NK and CD8+ T cells without binding to Tregs
3. **IgG1 Fc**
   Increases half-life and lymphoid recycling and homing
   Specific binding to NK, CD8+ T cells, dendritic cells and macrophages

Chang, S. et al. GU ASCO 2022

Non – Muscle Invasive Bladder Cancer

Efficacy Results Cohort B (Papillary)

	Overall Intent to Treat Population	QUILT-3.032
Number Enrolled	Total Number of Patients	77
Disease Free Survival	Median Disease Free Survival	23.6 months
	DFS rate at 12 months	57% (95% CI: 44%, 68%)
	DFS rate at 18 months	53% (95% CI: 40%, 65%)
	DFS rate at 24 months	48% (CI 95%: 34%, 60%)
Cystectomy Avoidance	Cystectomy Avoidance Rate	95% (73/77)
Disease Specific Overall Survival	Bladder Cancer Specific Overall Survival	99%
Duration of Follow Up	Median Duration of Follow Up	20.7 months

Chang, S. et al. GU ASCO 2022

Non – Muscle Invasive Bladder Ca

Clinically Meaningful Efficacy Results Cohort A (CIS)

	Overall Intent to Treat Population Efficacy	QUILT 3032
Complete Response	Complete Response (n)	58 / 82
	CR Rate	71% (95% CI: 59.6, 80.3)
Median DoR	Median Duration of Response in Months	26.6 Months (95% CI: 9.9, Not Reached)
Duration of Response	Duration of Response ≥12 Months per KM	61.6% (95% CI: 47.3, 73.1)
	Duration of Response ≥18 Months per KM	56.3% (95% CI: 41.5, 68.8)
	Duration of Response ≥24 Months per KM	53.2% (95% CI: 38.0, 66.2)

Chamie, K. et al. ASCO 2022

Rationale For Perioperative Chemotherapy For Muscle Invasive Bladder Cancer

- Poor overall survival in general
- Few long-term survivors after metastasis
- Perioperative chemo provides an opportunity to treat occult micrometastases
- Improved survival

Perioperative Trials in Urothelial Cancer

Study Name	NCT Identifier	No. Of Patients*	Population	Experimental Interventions	Control
AMBASSADOR[59]	NCT03244384	739	Muscle-invasive UC or LN+	**Adjuvant pembrolizumab**	Observation
CA017-078[86]	NCT03661320	976	MIBC, cisplatin eligible	**Pre-linrodostat + nivolumab + gemcitabine/cisplatin followed by pastcystectomy BMS-986205 +nivolumab OR pre-op linrodostat/placebo + nivolumab + gemcitabine/cisplatin followed by postcystectomy BMS-986205 placebo + nivolumab**	Neoadjuvant gemcitabine/cisplatin
CA045-009[87]	NCT04209114	540	MIBC, cisplatin ineligible		Radical Cystectomy alone
IMvigor011[58]	NCT04660344	495	MIBC with ctDNA+, postcystectomy	**Adjuvant atezolizumab**	Placebo
KEYNOTE-866[88]	NCT03924856	870	MIBC, cisplatin eligible	**Pre-op pembrolizumab + gemcitabine/cisplatin followe d by postcystecomy pembrolizumab**	Pre- op placebo + gem/cis followed by postcystectomy placebo
KEYNOTE-905/ EV-303[89]	NCT03924895	836	MIBC, cisplatin ineligible	**Pre-op pembrolizumab followed by postcystecomy, pembrolizumab OR peri-op enfortuman vedotin + pembrolizumab followed by postcystectomy, enfortumab vedotin +pembrolizumab, followed by pembrolizumab alone**	Radical Cystectomy alone
KEYNOTE-B15/ EV-304[90,91]	NCT04700124	784	MIBC, cisplatin eligible	**Pre-op enfortumab vedotin +pembrolizumab followed by postcystectomy, enfortumab vedotin + pembrolizumab**	Neoadjuvant gemcitabine/cisplatin
NIAGARA[92]	NCT03732677	988	MIBC, cisplatin eligible	**Neoadjuvant gemcitabine/cisplatin + durvalumab**	Neoadjuvant gemcitabine/cisplatin
PROOF302[93]	NCT04197986	218	Invasive UC with susceptible FGFR3 alterations	**Adjuvant infigratinib**	Placebo

Apolo, A. et al. American Society of Clinical Oncology Educational Book **42 (May 24, 2022) 1-16.**

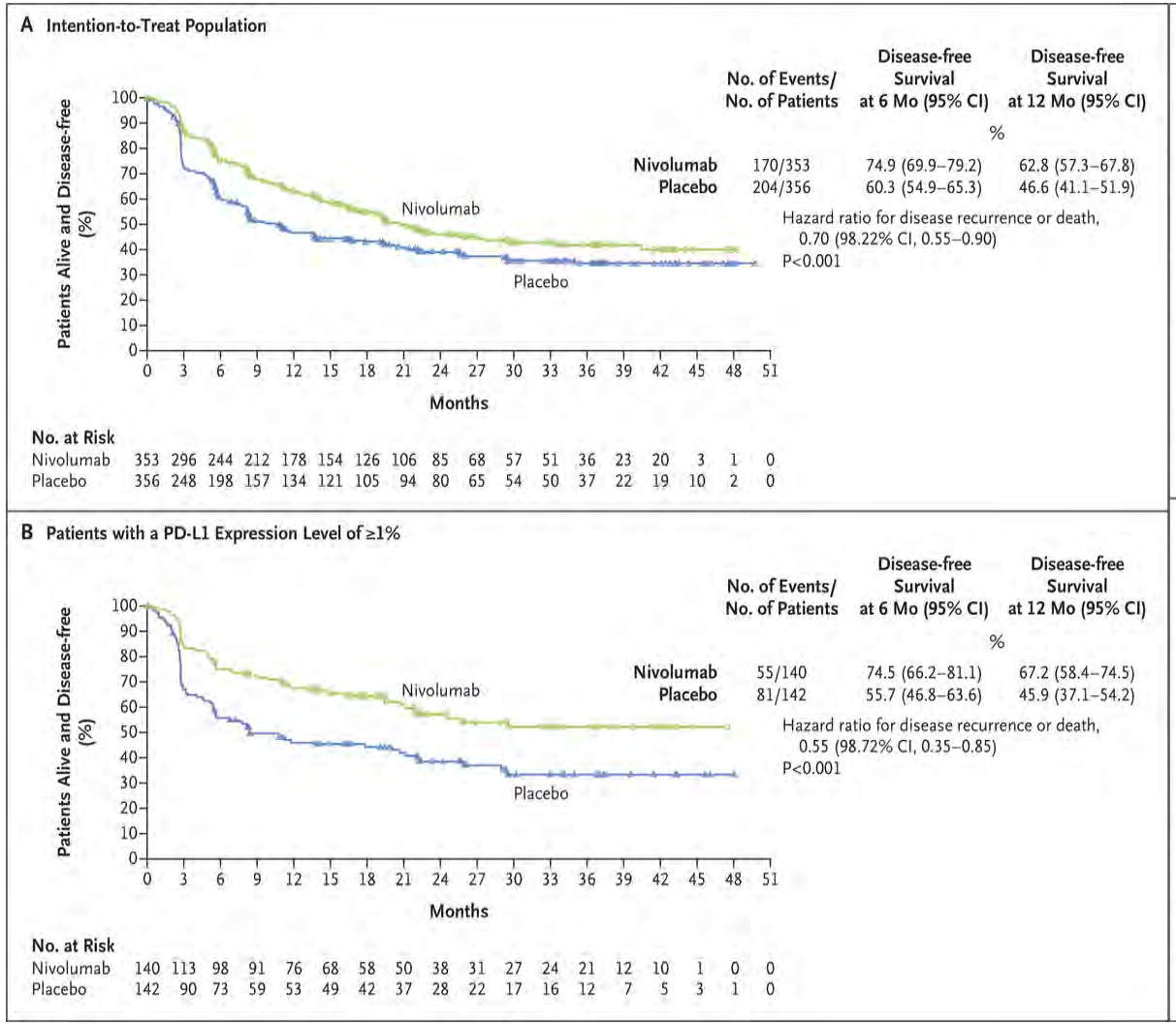
Phase III Randomized Adjuvant Trials in Urothelial CA

Study	Population	Stage	No. Of Patients	Experimental Interventions	Control	Follow-Up	Outcomes
Stadler et al (2011)[44]	MIBC, radical cystectomy	p53+ and T1 and T2, pN	114	MVAC	Observation	5.4 years	5-year recurrence rate 20% (both arms); p=.62; HR, 0.78; 5-year OS, 85% (both arms)
Cognetti et al (2012)[45]	MIBC, radical cystectomy	pT2G3, N0-2; pT3-4, N0-2; or pN1-2, any T	194	Gem/cis	Observation	35 months	DFS, 42.3% VS 37.2%; P=.70; HR, 1.08; 5-year OS, 48.5% (both arms); p=.24; HR, 1.29
Sternberg et al (2015)[3]	MIBC, radical cystectomy	pT3-4 and/or pN+	284	Gem/cis, MVAC or dd-MVAC	Observation	7 years	PFS, 31.8% vs. 47.6% p≤ .001; HR, 0.54; median OS, 6.7 vs. 4.6 years; 5-year OS, 53.6% vs.47.7%; p=.13; HR, 0.78
POUT [38,47]	UTUC following nephro-ureterectomy	pT2-T4 pN0-N3 M0 or pT any N1-3 M0	261	Gem/cis or Gem/carbo	Observation	48.1 months	Nonsignificant 28% reduction in relative risk of death (HR, 0.72; 95% CI, 0.47-1.08; p= .11; adjusted HR, 0.79; 95% CI. 0.52-1.19; p=.26)
Imvigor 010[46]	MIBC, UTUC radical surgery +/- NAC	pT3-4a or pN+ or ypT2-4a or ypN+	809	Atezolizumab	Observation	21 months	Median DFS, 20.8 vs. 10.8 months; HR for distant recurrence or death, 0.72; 95% CI, 0.59-0.89
CheckMate-274[55]	MIBC, UTUC following radical surgery +/- NAC	PT3-4a or pN+ or ypT2-4a or ypN+	709	Nivolumab	Placebo	21.9 months	Median DFs, 19.4 VS. 16.6 months; HR for recurrence or death, 0.89; 95% CI 0.74-1.08

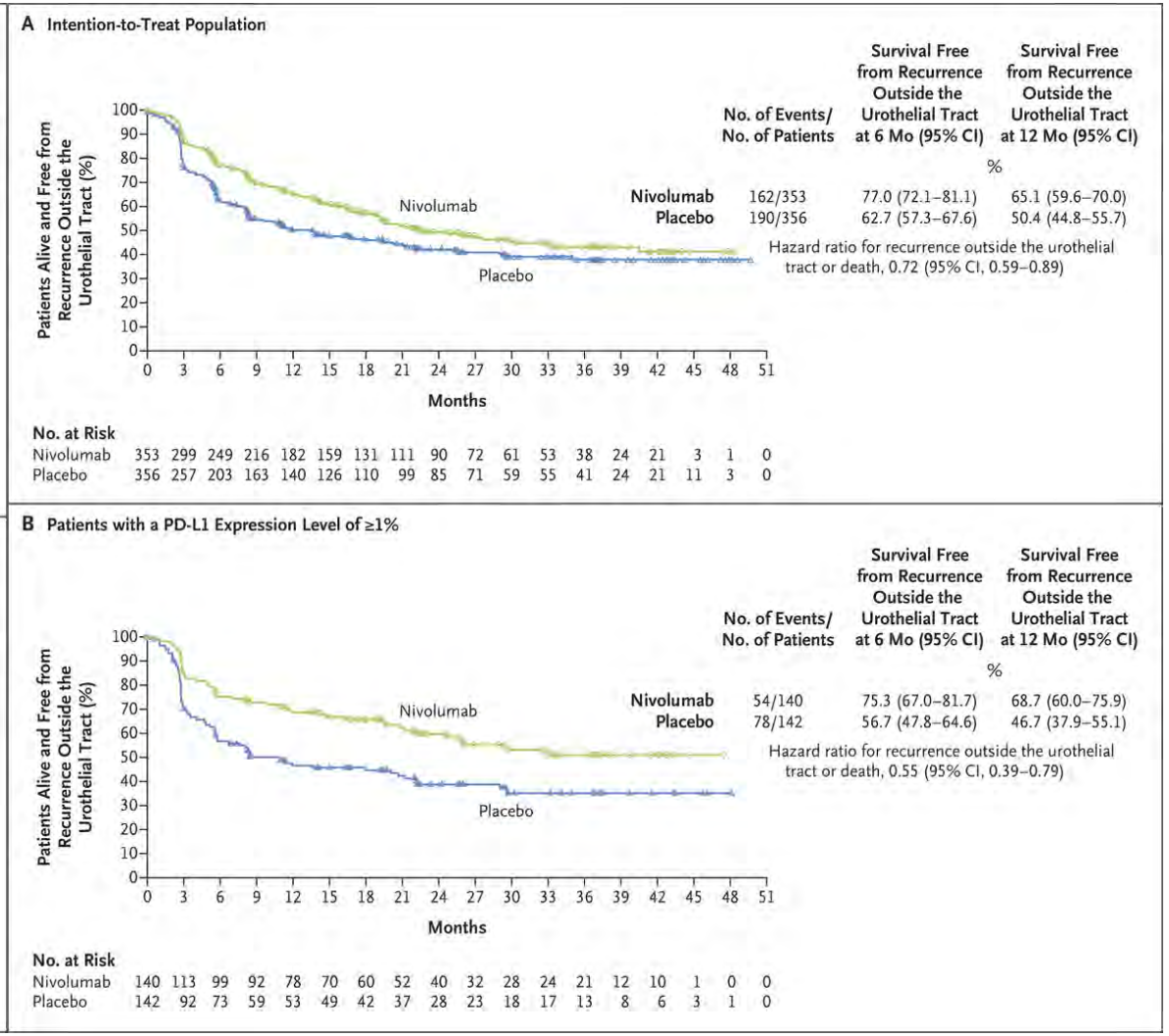
Apolo, A. et al. American Society of Clinical 203-824-7207 *Oncology Educational Book 42* (May 24, 2022) 203-824-7207 *1-16.*

CheckMate 274 Adjuvant Nivolumab in MIBC

Disease-free Survival



Metastasis Free Survival



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

Perioperative Therapy in MIBC

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Bladder Cancer

NCCN Guidelines Index
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Discussion

PRINCIPLES OF SYSTEMIC THERAPY

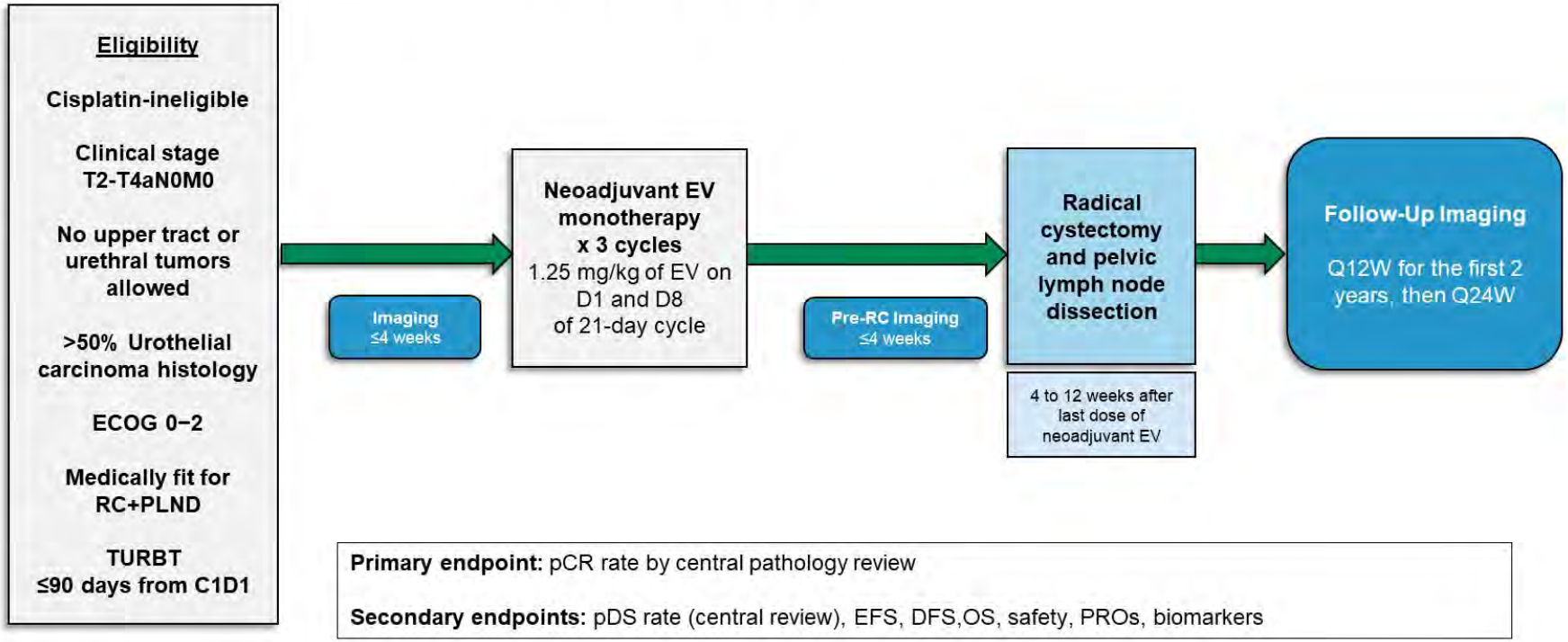
Neoadjuvant Chemotherapy [preferred for bladder]
Preferred regimen • DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor support for 3–6 cycles[1,2] Other recommended regimens • Gemcitabine and cisplatin for 4 cycles[3,4]

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]
Previous platinum-based neoadjuvant therapy (ypT2-ypT4a or ypN+)	Other recommended regimen • Nivolumab[5]

NCCN, Bladder Cancer 2022.

Study EV-103 Cohort H: Neoadjuvant EV in cisplatin-ineligible MIBC Patients

EV-103 Cohort H Study Design



DFS: Disease-free survival; ECOG: Eastern Cooperative Oncology Group; EFS: Event-free survival; EV: Enfortumab vedotin; OS: Overall survival; pCR: pathological Complete Response rate; pDS: pathological Downstaging; RC+PLND: radical cystectomy + pelvic lymph node dissection; PROs: Patient-reported outcomes; TURBT: transurethral resection of bladder tumor

Petrylak et al, GU ASCO 20222

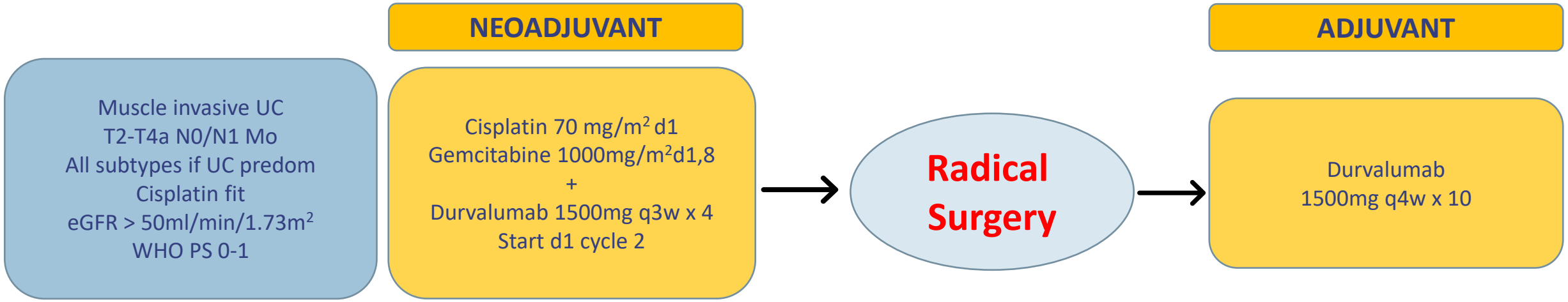
Study EV-103 Cohort H: Neoadjuvant EV in Cisplatin-Ineligible MIBC Patients

Pathological Response	Central Pathology Results (N=22) n (%) [95% Confidence Interval]
Pathological Complete Response Rate (defined as absence of any viable tumor tissue: ypT0 and N0)	**8 (36.4%)** [17.2–59.3]
Pathological Downstaging Rate (defined as presence of ypT0, ypTis, ypTa, ypT1, and N0)	**11 (50.0%)** [28.2–71.8]

Petrylak et al. GU 2022

Perioperative Chemo-Immunotherapy with Durvalumab for MIUC

METHODS



Primary endpoint:
Event-free survival (EFSS) at 2 years
(event defined as: PD during neoadjuvant treatment,
Locoregional or metastatic recurrence or death)

Secondary endpoints: pCR (ypT0), pathological response rate (PaR, ≤ypT1N0M0), EFS, RFS, OS, pattern of recurrence
Feasibility, adverse events (AEs), quality or resection

Cathoma et al. ASCO 2022

Perioperative Chemo-Immunotherapy with Durvalumab for MIUC

Figure 3 . Kaplan-Meier plot for EFS

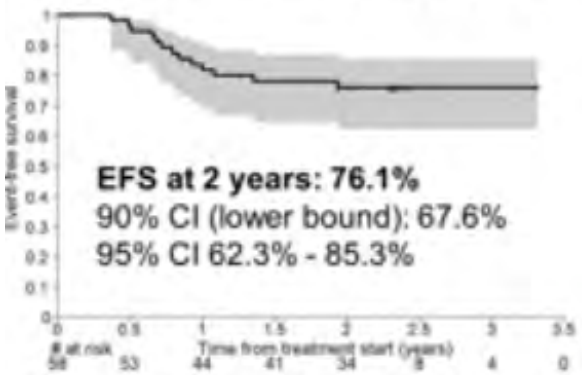


Figure 4 . Kaplan-Meier plot for OS

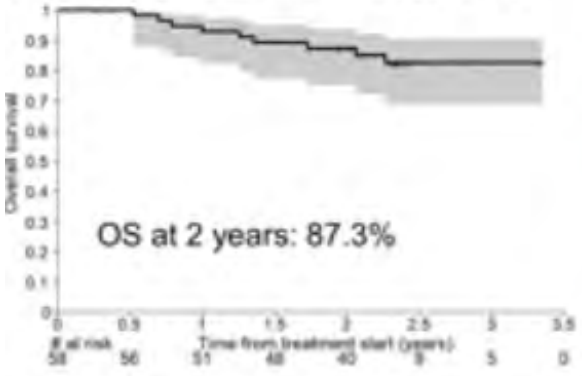


Figure 5 . EFS according to ypT stage

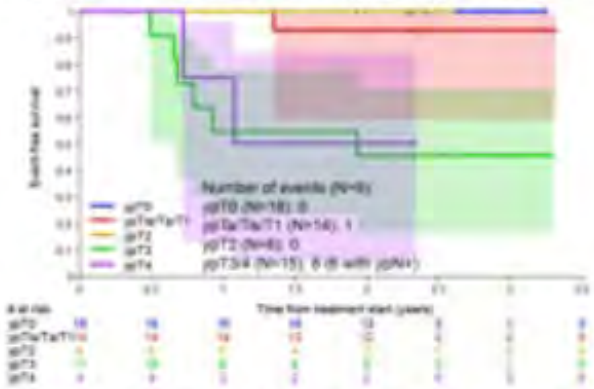


Figure 6 . EFS according to ypN stage

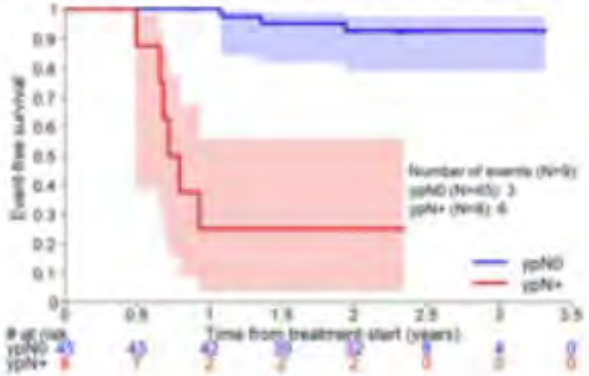


Figure 7 . EFS according to PD-L1 expression

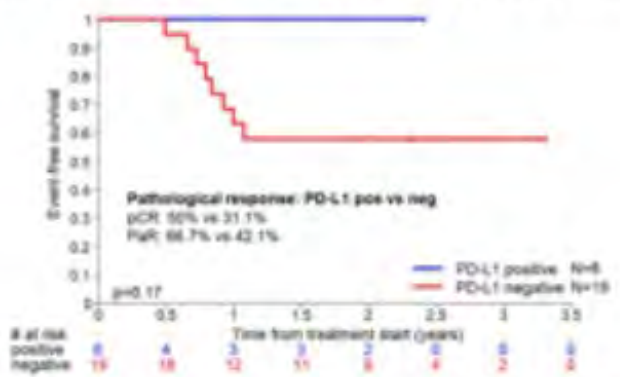
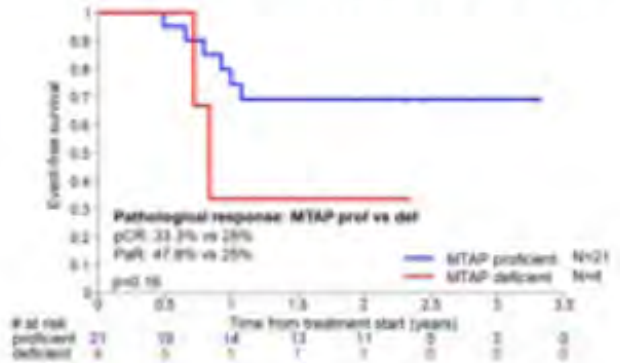


Figure 8 . EFS according to MTAP expression



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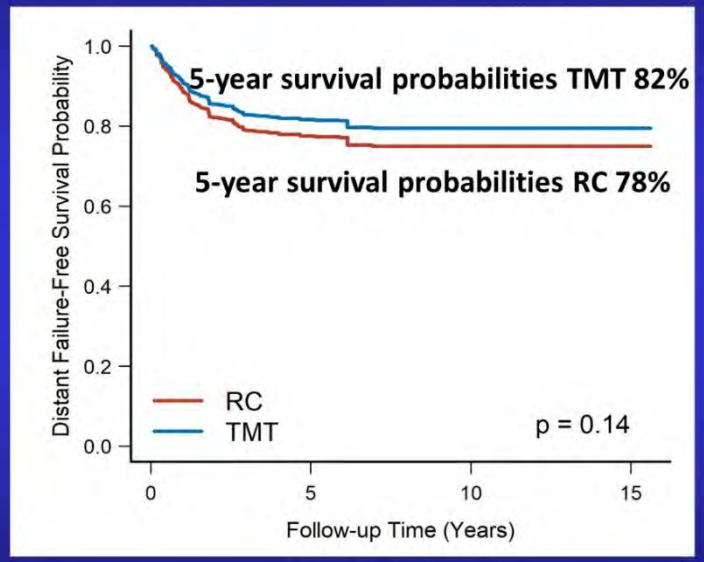
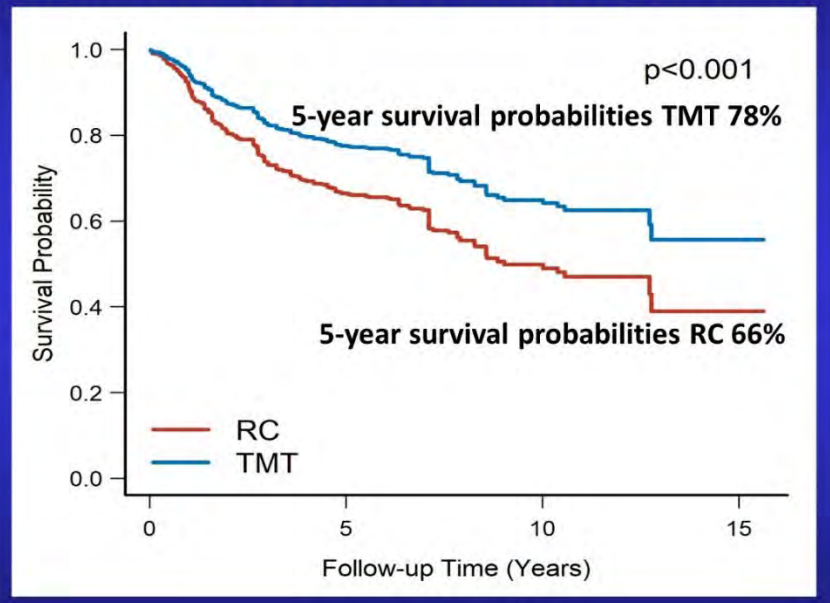
Multi-institutional matched comparison of radical cystectomy to trimodality therapy for muscle invasive bladder cancer

Distant failure-free survival
matched RC (834) vs TMT (282) patients



Death without distant failure considered a competing risk

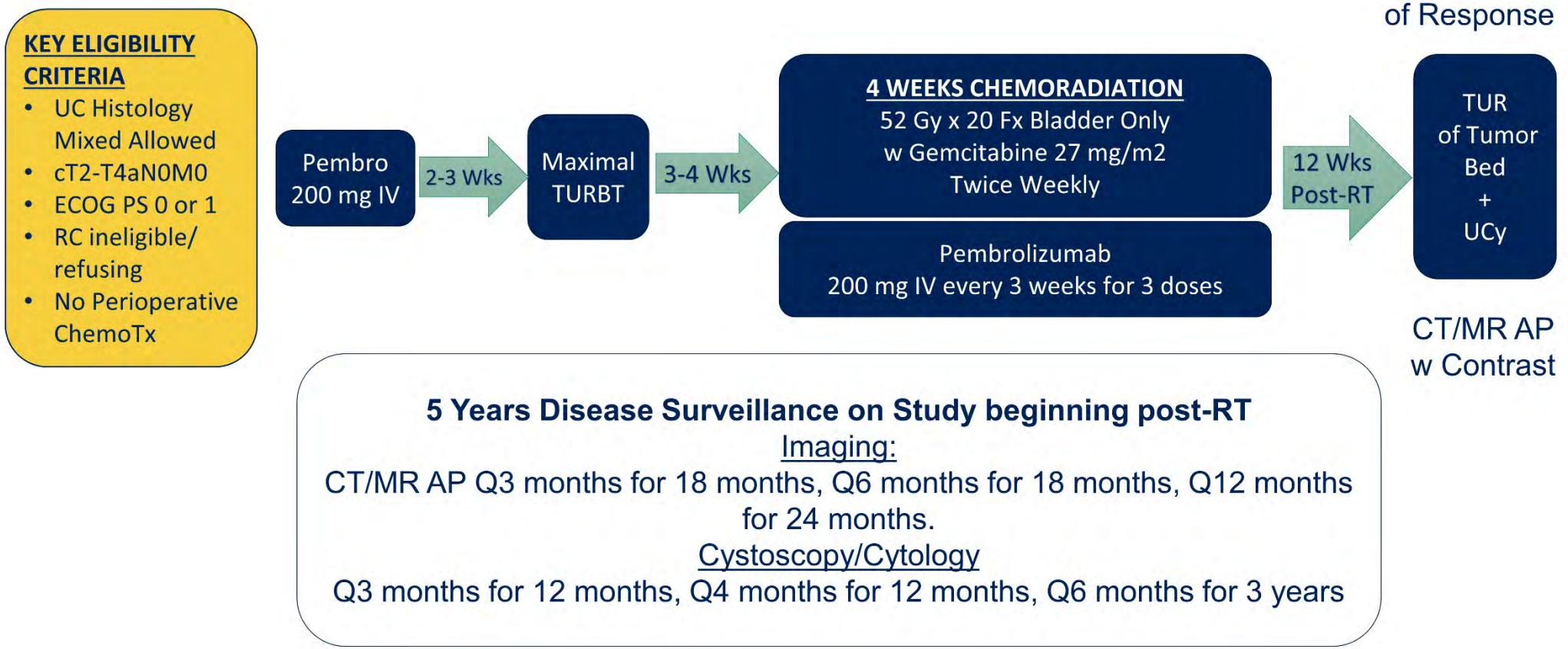
Overall survival
matched RC (834) vs TMT (282) patients



Zlotta et al. GU ASCO 2022

A Phase II Trial of Pembrolizumab + Gemcitabine Chemoradiation in Bladder Sparing Treatment of Bladder Cancer:

TREATMENT SCHEMA

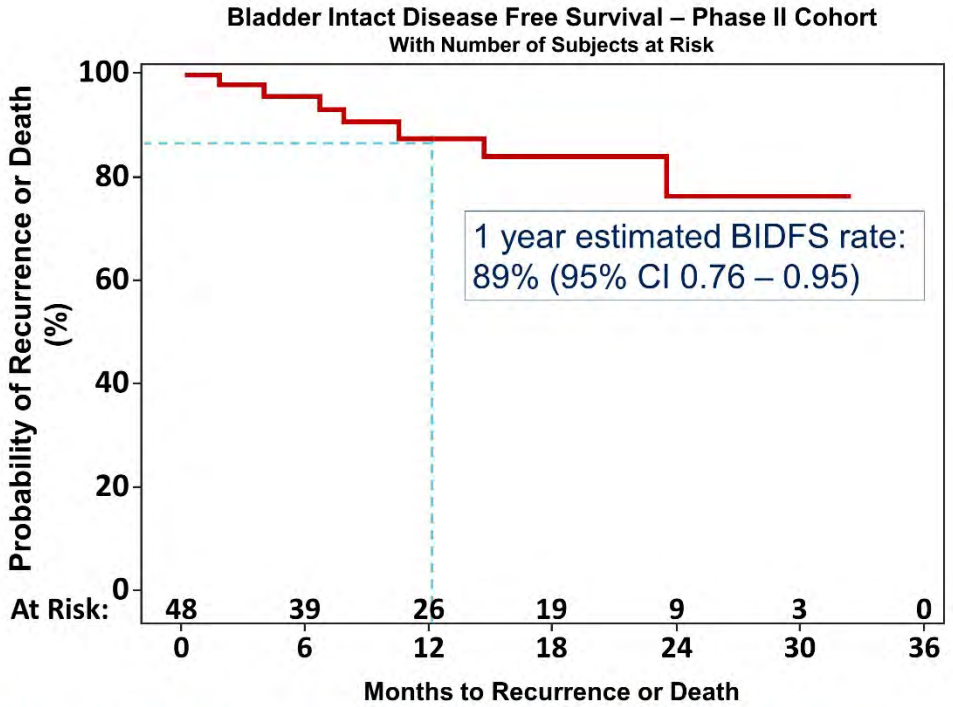


Balar, A. et al. ASCO 2021

A Phase II Trial of Pembrolizumab + Gemcitabine Chemoradiation in Bladder Sparing Treatment of Bladder Cancer:

NYU Langone Health

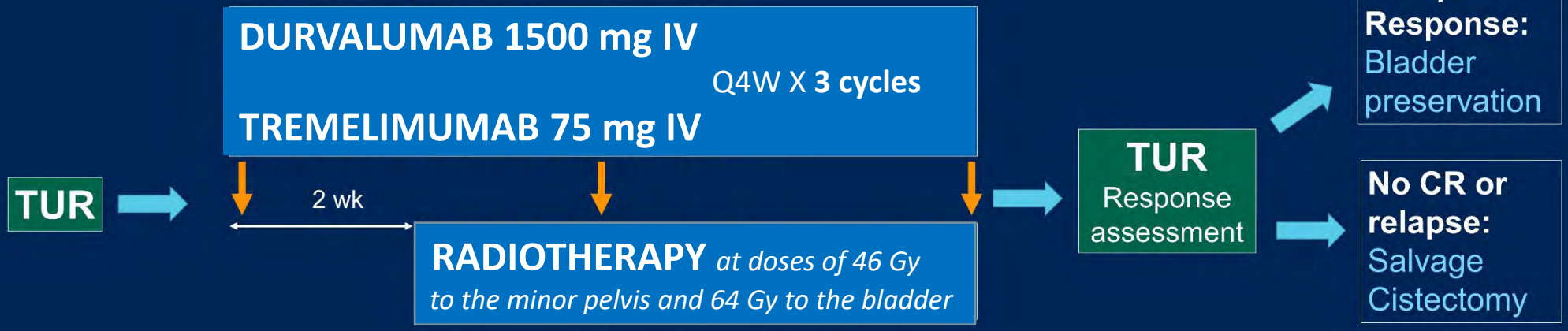
Bladder-Intact Disease-Free Survival
All Patients (N=54)



Median Follow up All Patients: 15.5 months (1.6 months – 56.5 months)

Balar, A. et al. ASCO 2021

IMMUNOPRESERVE: Trial Design



A safety run-in cohort was performed in the first 5 patients included to assess potential dose limiting toxicities

Translational Study:

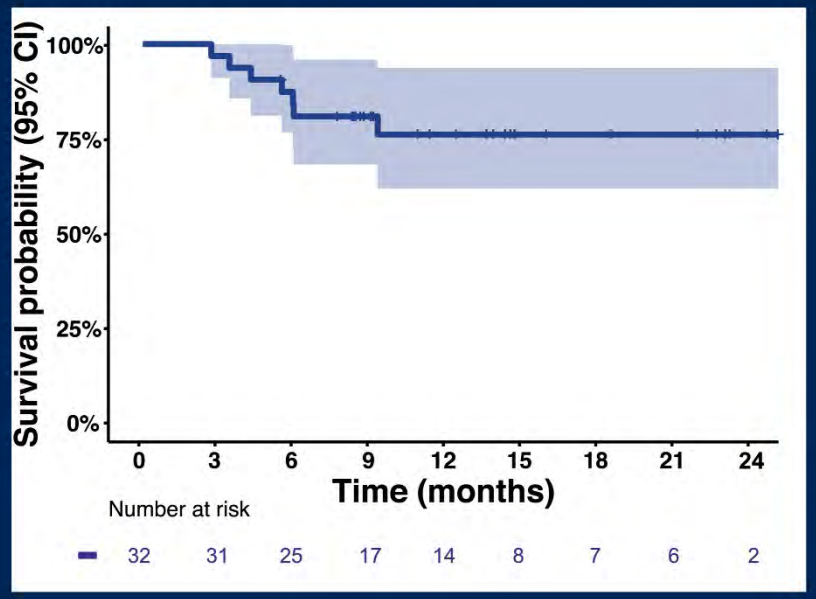
Biomarker analyses on peripheral blood, at different time points, and pre-and post-therapy tumor samples

- ***Peripheral blood:*** **peripheral lymphocytes immune profiling and cytokine multiplex**
- ***Tumor biopsy*****: PD-L1 testing, TCR-β chain clonality, immunoscore and inflammatory stroma analysis**

Del Muro, XG, et al. ASCO 2021

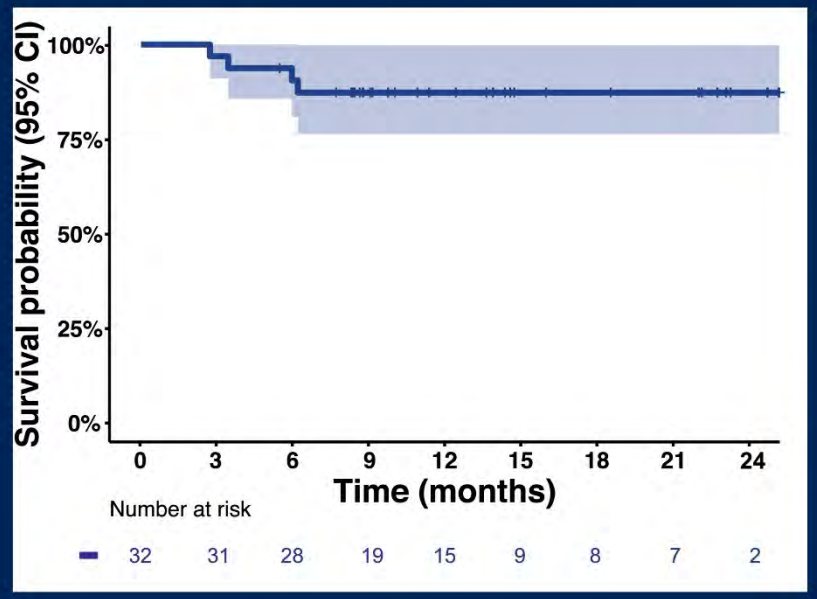
Survival Analysis

DISEASE FREE SURVIVAL



12 m DFS rate :
76% (95%CI, 62%-94%)

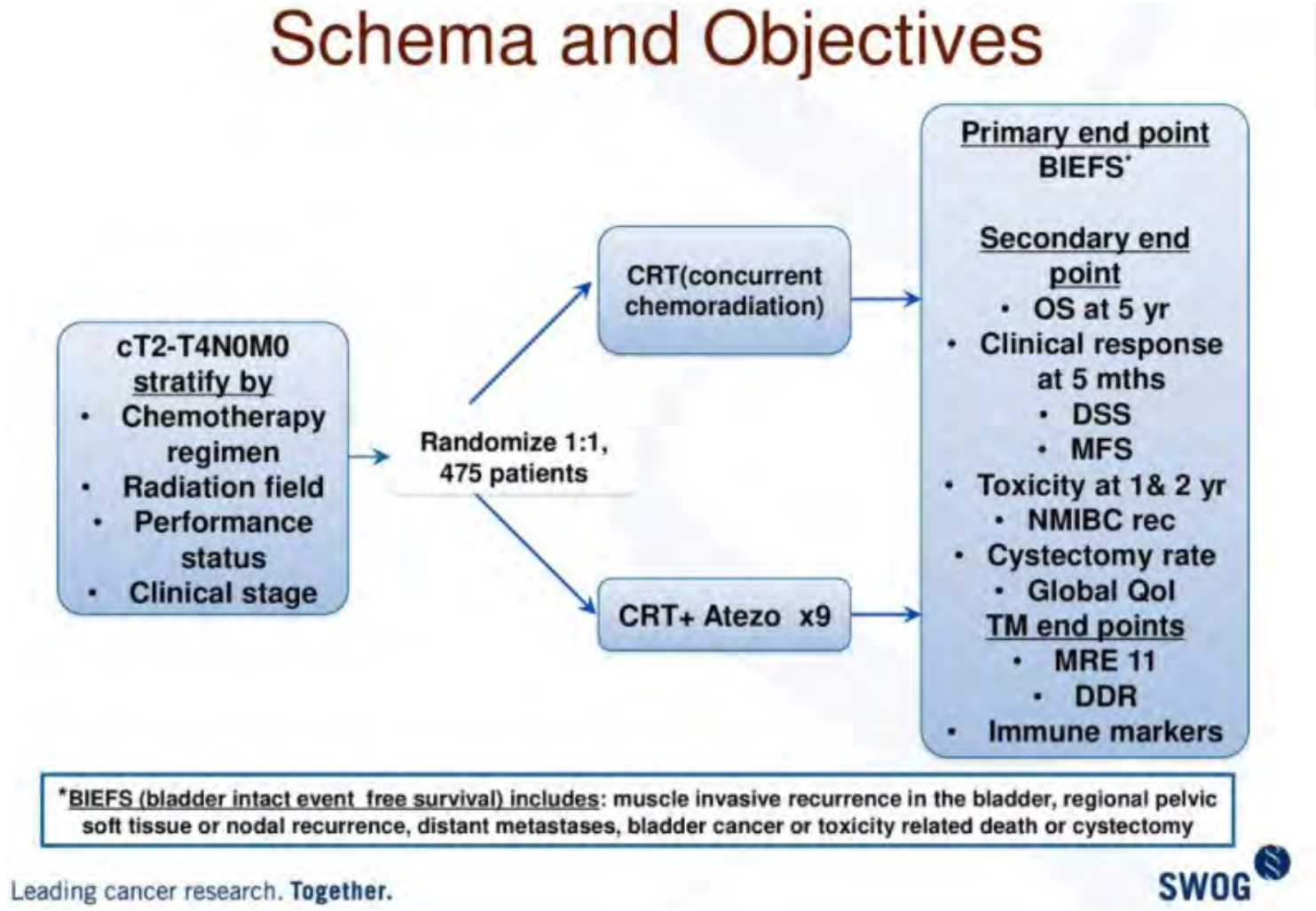
OVERALL SURVIVAL



12 m OS rate:
87% (95%CI, 76%-100%)

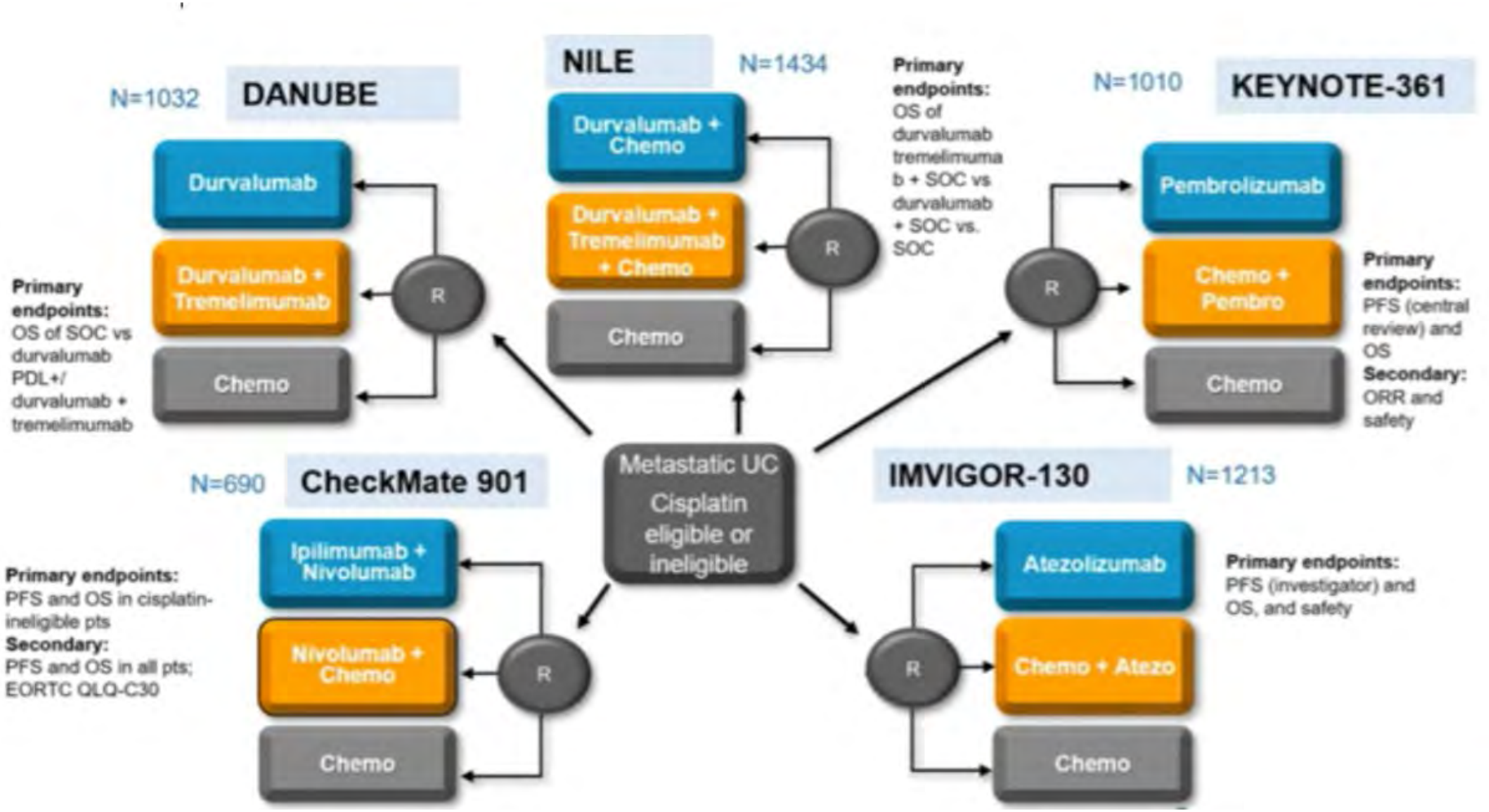
Del Muro, XG, et al. ASCO 2021

S1806: Phase III Randomized Trial of Concurrent Chemoradiotherapy with or without Atezolizumab in Localized Muscle Invasive Bladder Cancer



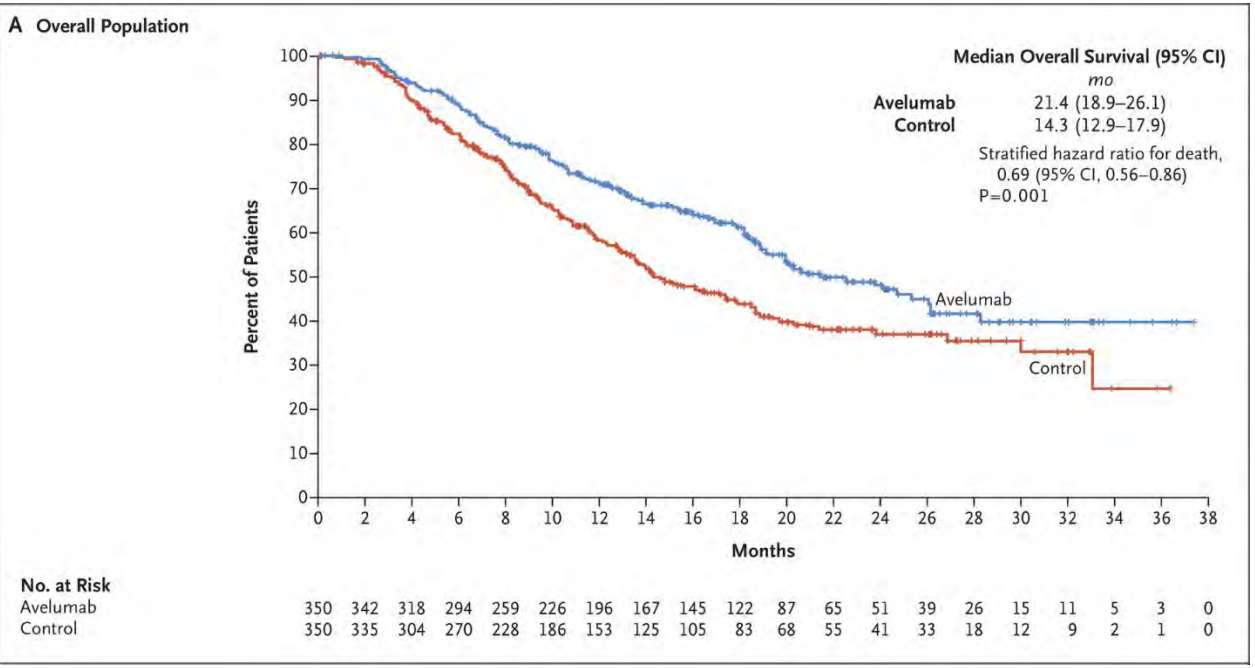
National PI: Dr. Ashesh Jani, Winship Cancer Institute

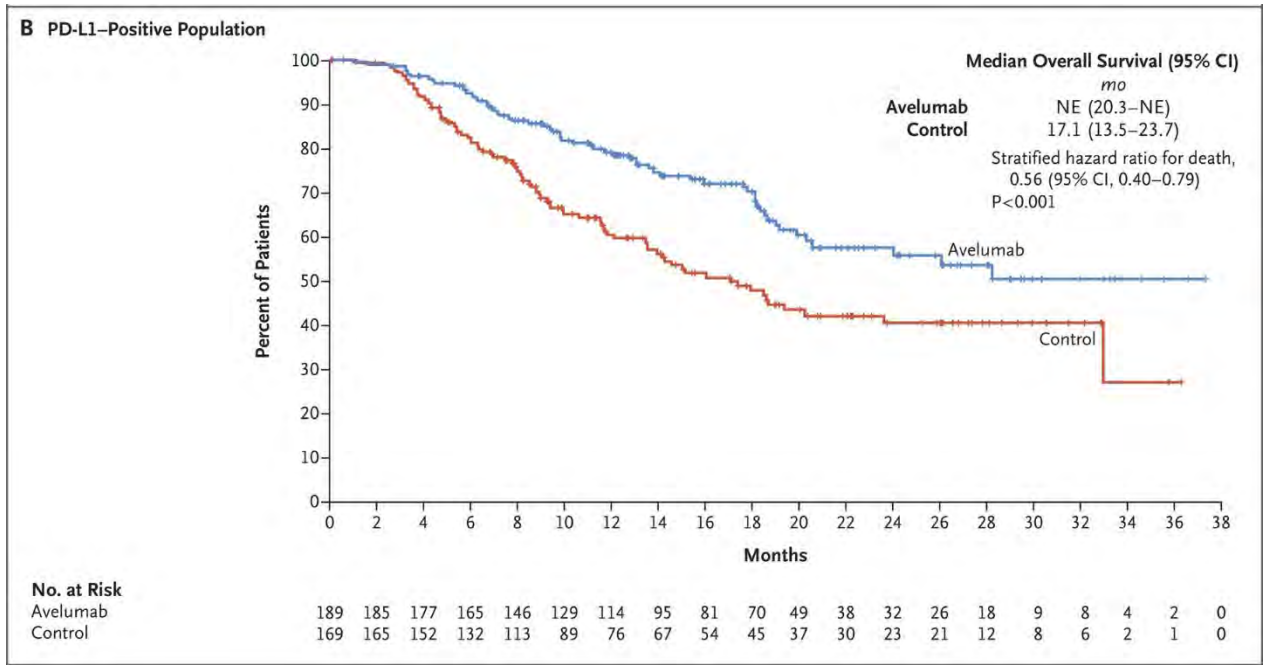
Chemotherapy vs. IO+/- Chemo in Front Line Setting



Apolo, A. GU ASCO 2021

Maintenance Avelumab after Platinum Based Chemotherapy Enhances Overall Survival: Javelin Bladder 100





Overall Population

PD-L1 Positive Population

Powles, T, et al. N Engl J Med 2020; 383:1218-1230

1st Line Systemic Therapy

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Bladder Cancer

NCCN Guidelines Index
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Discussion

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] • Atezolizumab[13] (only for patients whose tumors express PD-L1[b] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) • Pembrolizumab[14] (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy) Other recommended regimens • Gemcitabine[15] • Gemcitabine and paclitaxel[16] Useful under certain circumstances • Ifosfamide, doxorubicin, and gemcitabine[17] (for patients with good kidney function and good PS)

NCCN, Bladder Cancer 2022.

Metastatic Subsequent Systemic Therapy

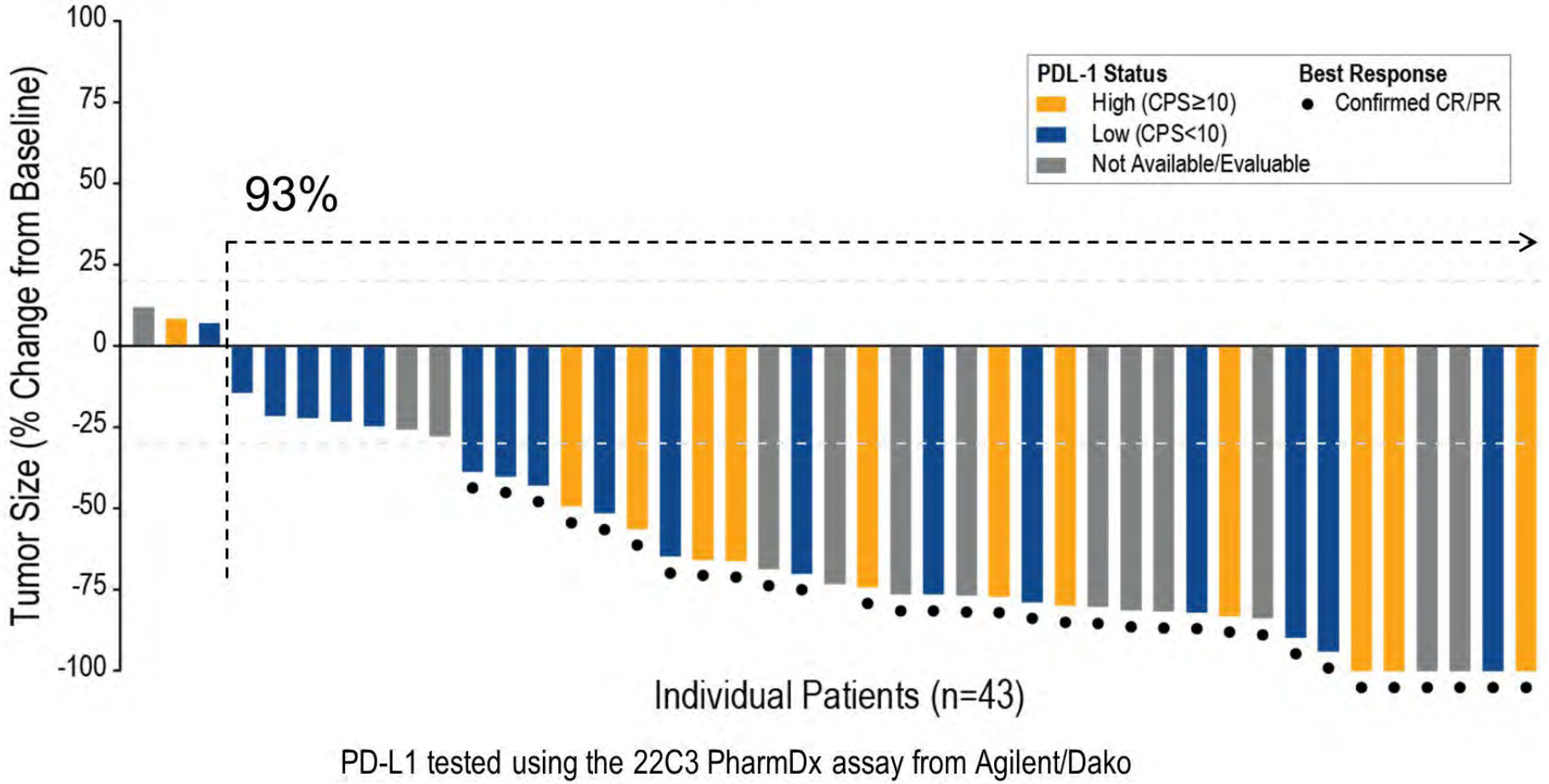
Second-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV) (post-platinum or other chemotherapy)[c] Participation in clinical trials of new agents is recommended.	
Preferred regimen • Pembrolizumab (category 1 post-platinum)[19]	Other recommended regimens • Paclitaxel[25] or docetaxel[26] • Gemcitabine[15]
Alternative preferred regimens • Immune checkpoint inhibitor ‣ Nivolumab[20] ‣ Avelumab[21,22] • Erdafitinib[d,23] • Enfortumab vedotin-ejfv[e,24]	Useful in certain circumstances based on prior medical therapy • Ifosfamide, doxorubicin, and gemcitabine[17] • Gemcitabine and paclitaxel[16] • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]

Second-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV) (post-checkpoint inhibitor) Participation in clinical trials of new agents is recommended.	
Preferred regimens for cisplatin ineligible, chemotherapy naïve • Enfortumab vedotin-ejfv[24] • Gemcitabine/carboplatin	Other recommended regimens • Erdafitinib[d,23] • Paclitaxel or docetaxel[26] • Gemcitabine[15]
Preferred regimens for cisplatin eligible, chemotherapy naïve • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]	Useful in certain circumstances based on prior medical therapy • Ifosfamide, doxorubicin, and gemcitabine[17] • Gemcitabine and paclitaxel[16]

Subsequent-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)[f,g] Participation in clinical trials of new agents is recommended.	
Preferred regimens • Enfortumab vedotin-ejfv (category 1)[27,28] • Erdafitinib[d]	Other recommended regimens • Sacituzumab govitecan-hziy[29] • Gemcitabine[15] • Paclitaxel[25] or docetaxel[26] • Ifosfamide, doxorubicin, and gemcitabine[17] • Gemcitabine and paclitaxel[16] • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]

NCCN, Bladder Cancer 2022.

PEMBROLIZUMAB + ENFORTUMAB VEDOTIN IN FIRST LINE PLATINUM INELIGIBLE DISEASE



PD-L1 tested using the 22C3 PharmDx assay from Agilent/Dako

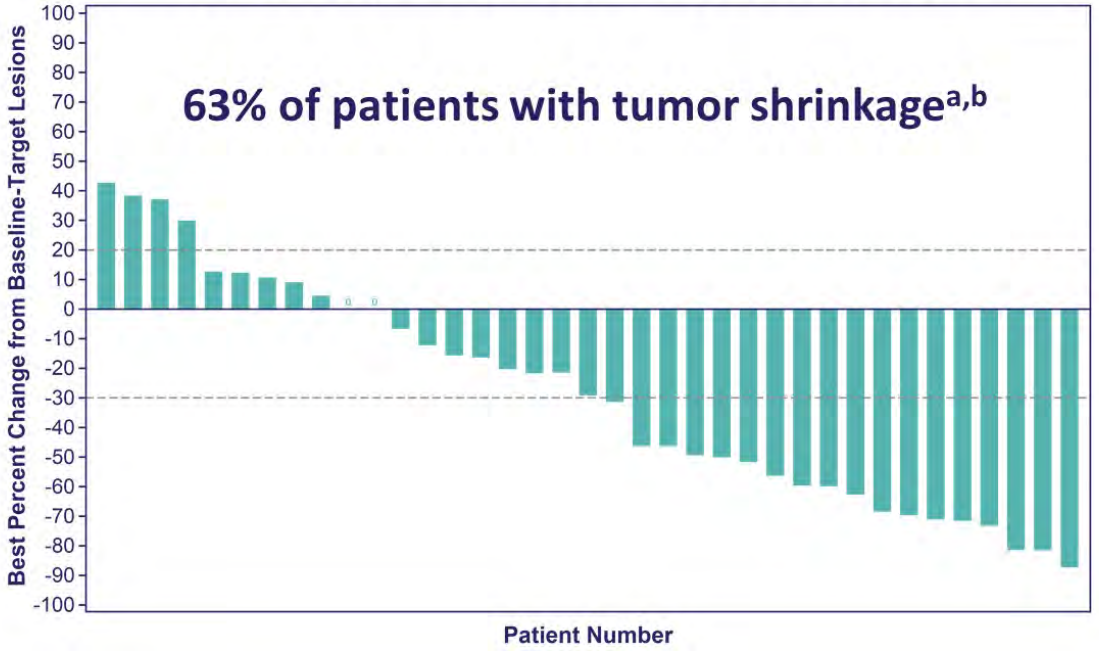
ORR: 73.3%
CR: 17.8%
ORR Liver Mets: 57.1%

Friedlander et al, ASCO 2021.

Trophy-U-01: Sacituzumab Govitecan Plus Pembrolizumab in mUC Patients After Platinum Regimens

Overall Response and Best % Change From Baseline in Tumor Size

- Median follow-up: 5.8 months (data cutoff date: 2021-09-24)
- Median time to response: 2 months (1.3–2.8; n=14)
- Median DOR not yet reached: N/A (2.80-N/A)
- Median PFS (95% CI), 5.5 months (1.7–NR); median OS, not reached

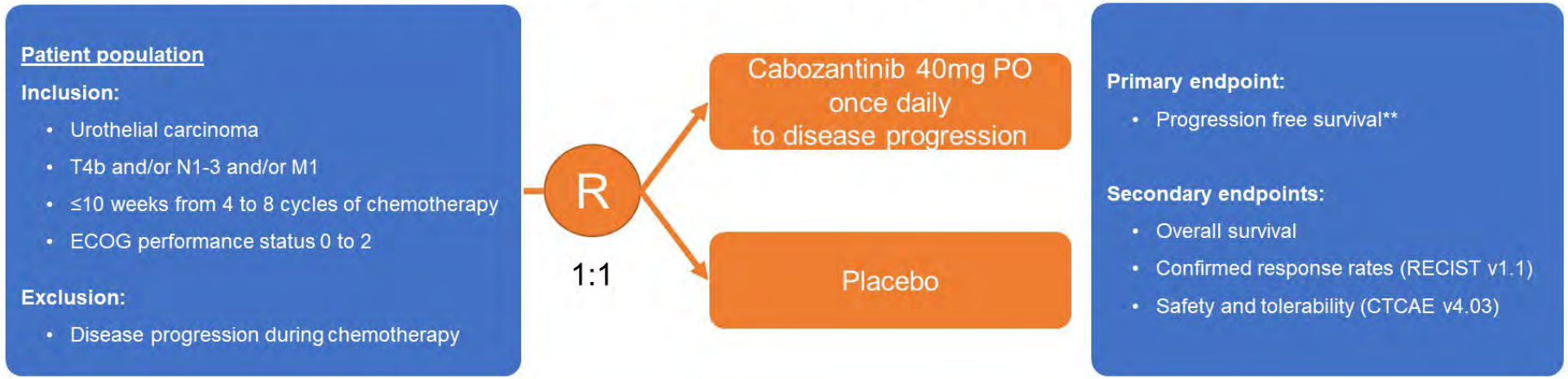


	Cohort 3[a] (N=41)
Objective response rate (CR + PR), n (%) [95%CI]	**14 (34) [20.1-50.6]**
Objective response rate (CR + PR), evaluable patients, n (%)	14 (38)
Best overall response, n (%)	
CR	1 (2)
PR	13 (32)
SD	11 (27)
SD ≥ 6 months	*4 (10)*
PD	12 (29)
Not assessed	4 (10)
Clinical Benefit Rate (CR + PR + SD), n (%) [95%CI]	25 (61) [44.5-75.8]

Grivas, P. et al. GU ASCO 2022

Cabozantinib Maintenance After Chemo in UC

Cabozantinib comparison arm trial design[1]



Population was enriched for patients who were excluded from other comparisons which required the following molecular characteristics:

- ≥10% genome-wide loss of heterozygosity
- Somatic alteration in any of: *ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L*
- Androgen receptor positive by immunohistochemistry

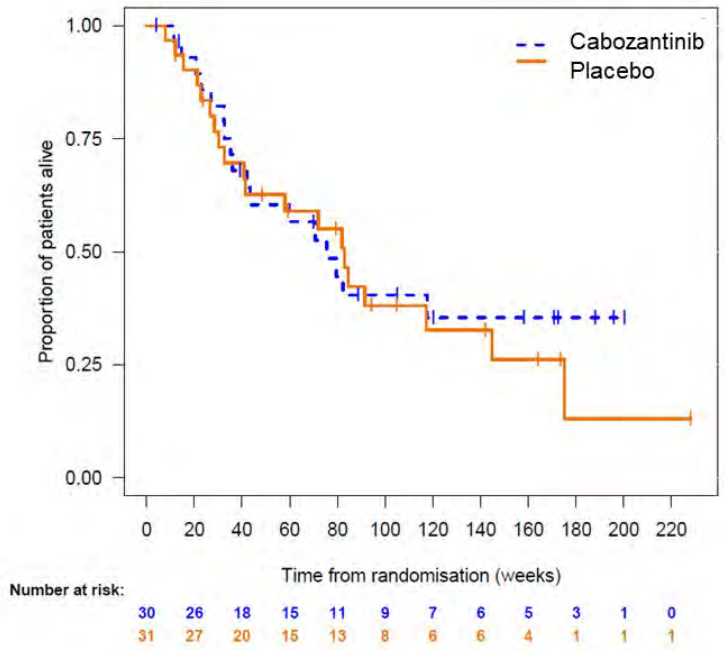
Recruitment period Feb 2017 – March 2021

[1]Fulton et al, Trials. 2020 Apr 19;21(1):344. **Progression free survival, as assessed by investigator, was defined as time from randomisation until progressive disease (RECIST v1.1) or death from any cause

Jones, R. ASCO 2022

Cabozantinib Maintenance After Chemo in UC

Overall survival (secondary endpoint)

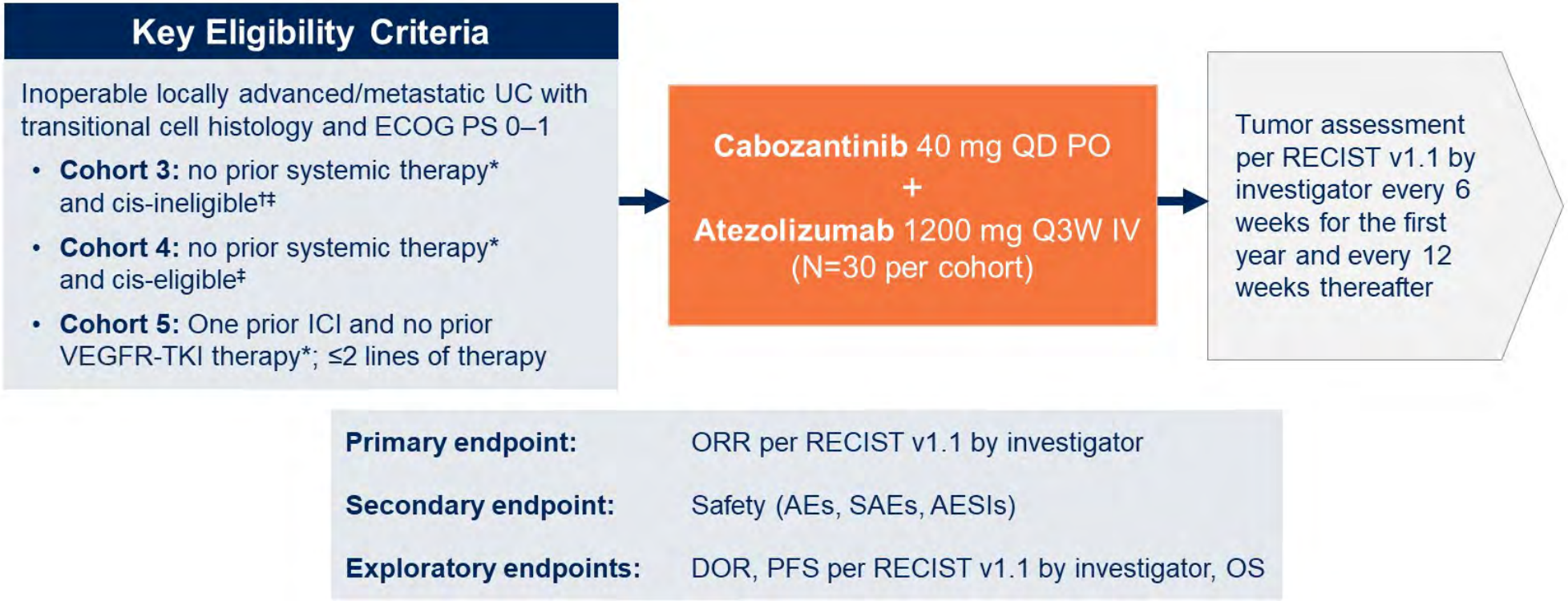


	Cabozantinib	Placebo	p
OS events	17 (57%)	20 (65%)	
Median OS, weeks	75.5 (80% CI 43.4, 117.6)	82.9 (80% CI 58.0, 117.1)	
Hazard ratio*	0.80 (80% CI 0.52, 1.30)		0.25

*adjusted for minimization factors

Jones, R. ASCO 2022

COSMIC-021 Study Design for UC Cohorts 3, 4, and 5



*For inoperable locally advanced/metastatic disease. †Defined as impaired renal function (glomerular filtration rate <60 mL/min/1.73 m^2), hearing loss ≥25 dB at two contiguous frequencies, or grade ≥2 peripheral neuropathy per NCI CTCAE v4. ‡Prior neoadjuvant or adjuvant platinum-based chemotherapy allowed if disease recurrence >12 months from end of last therapy.
AESI, AE of special interest; SAE, serious AE

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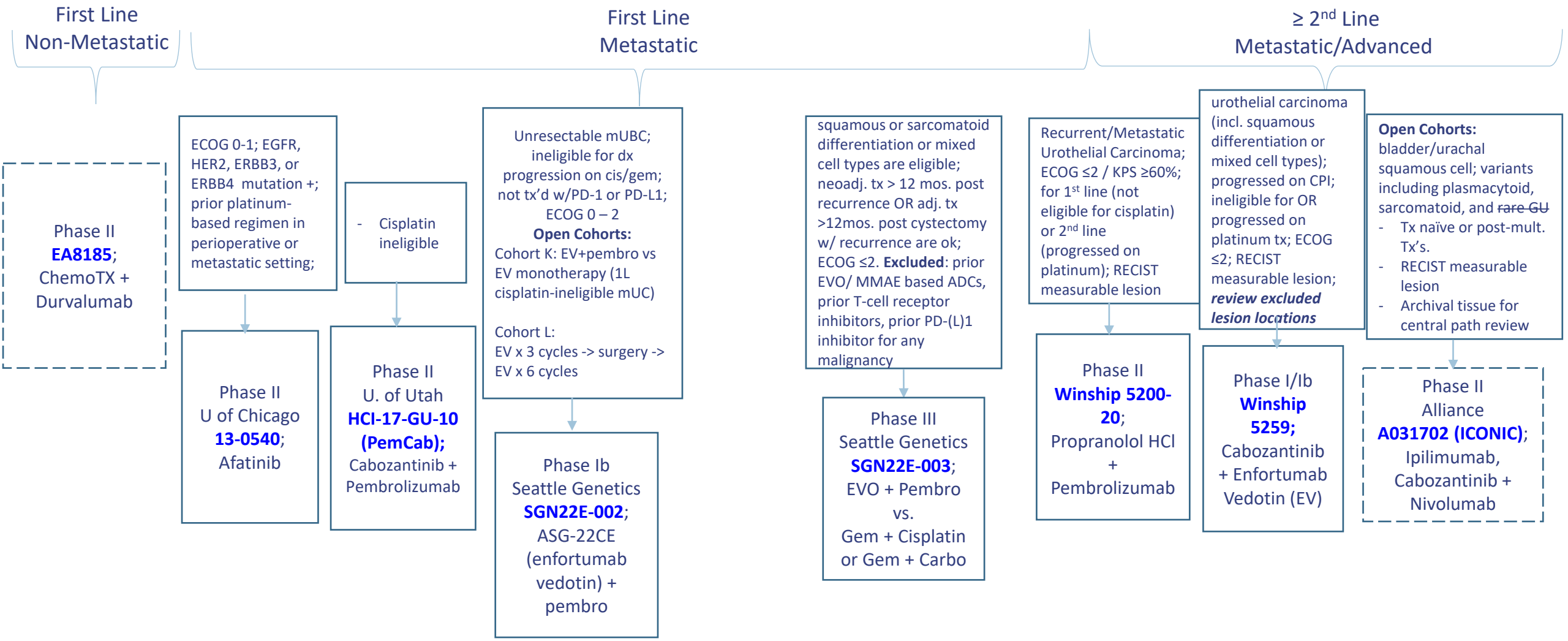
Tumor Response per Investigator by RECIST v1.1

	Cohort 3 Cis-ineligible (N=30)	Cohort 4 Cis-eligible (N=30)	Cohort 5 Received prior ICI (N=31)
ORR, % (95% CI)	**20 (8–39)**	**30 (15–49)**	**10 (2–26)**
Best overall response, n (%)			
Complete response	1 (3)	2 (7)	0
Partial response	5 (17)	7 (23)	3 (10)
Stable disease	18 (60)	10 (33)	16 (52)
Progressive disease	3 (10)	7 (23)	8 (26)
Missing / not evaluable	3 (10)	4 (13)	4 (13)
Disease control rate, % (95% CI)	**80 (61–92)**	**63 (44–80)**	**61 (42–78)**

Objective response rate = complete response + partial response.
Disease control rate = complete response + partial response + stable disease.

Pal, S. et al. ASCO 2022

Winship Advanced Urothelial Cancer Trials



Conclusions

- Continued Advances in BCG Unresponsive Disease
- Multiple Novel Perioperative Approaches in Urothelial Cancer
- Promising Options and Data for MIBC Patients Utilizing Chemoradiation
- Systemic Therapy with Maintenance IO after Platinum Remains 1st Line SOC
- Aggressive Efforts for Novel Combinations with Some Success (IO/EV/SG)
- Refer For Clinical Trials For Urothelial Cancer Patients

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  - Urology and Radiation Oncology Colleagues

- Participating Patients and Clinician Researchers

Patient Case

A 62-year-old male with hx of HTN and pre-diabetes presents with hematuria. He has a cystoscopy and is diagnosed with high grade muscle invasive urothelial cell carcinoma of the bladder. Imaging shows no obvious metastases, but suspicious left pelvic lymph nodes and perivesicular thickening. Creatinine was normal. The patient was started on Gemcitabine/Cisplatin neoadjuvant therapy and completed 6 cycles. He subsequently underwent cystectomy that showed pT3N1 disease. Repeat imaging showed no metastases.

He presents for f/u 2 months following the cystectomy. He recovered well and PS remained at 1. The next best step for this patient would be:

a. Additional 2 cycles of Gemcitabine/Cisplatin
b. Adjuvant Nivolumab
c. Surveillance scans q 6 months
d. Enfortumab Vedotin
e. Adjuvant Avelumab

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