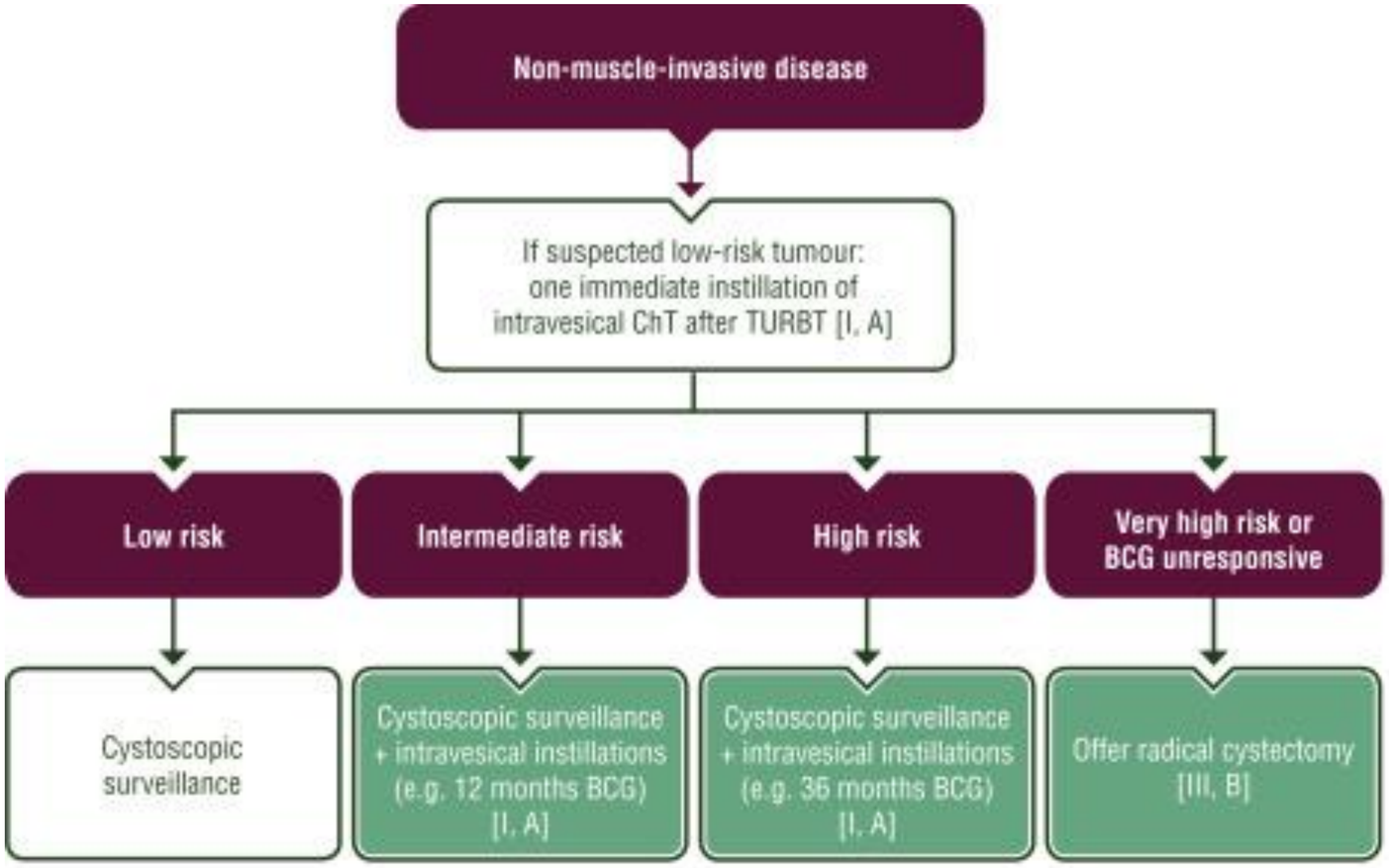
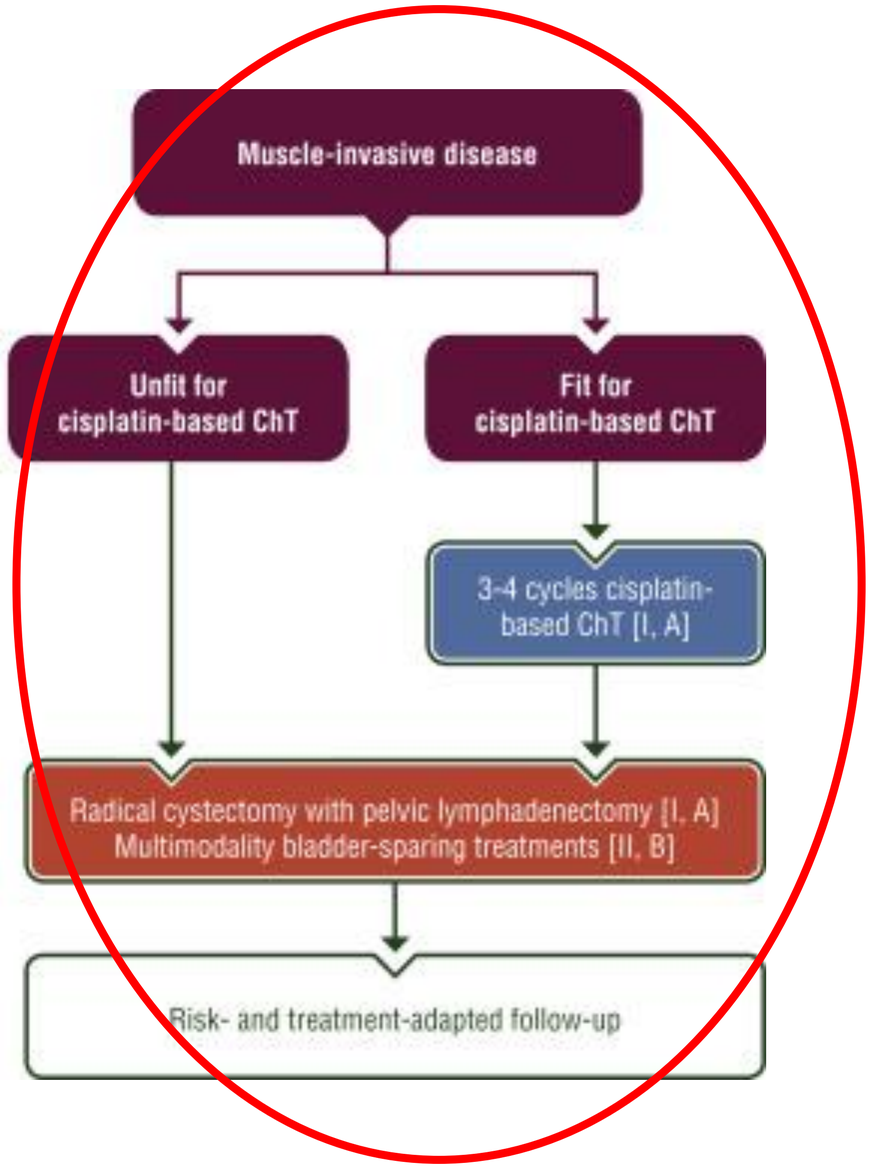
Nuevos estándares en el tratamiento sistémico perioperatoriodel cáncer de vejiga músculo-invasivo

Dr. Guillermo de Velasco

Servicio de Oncología Médica,

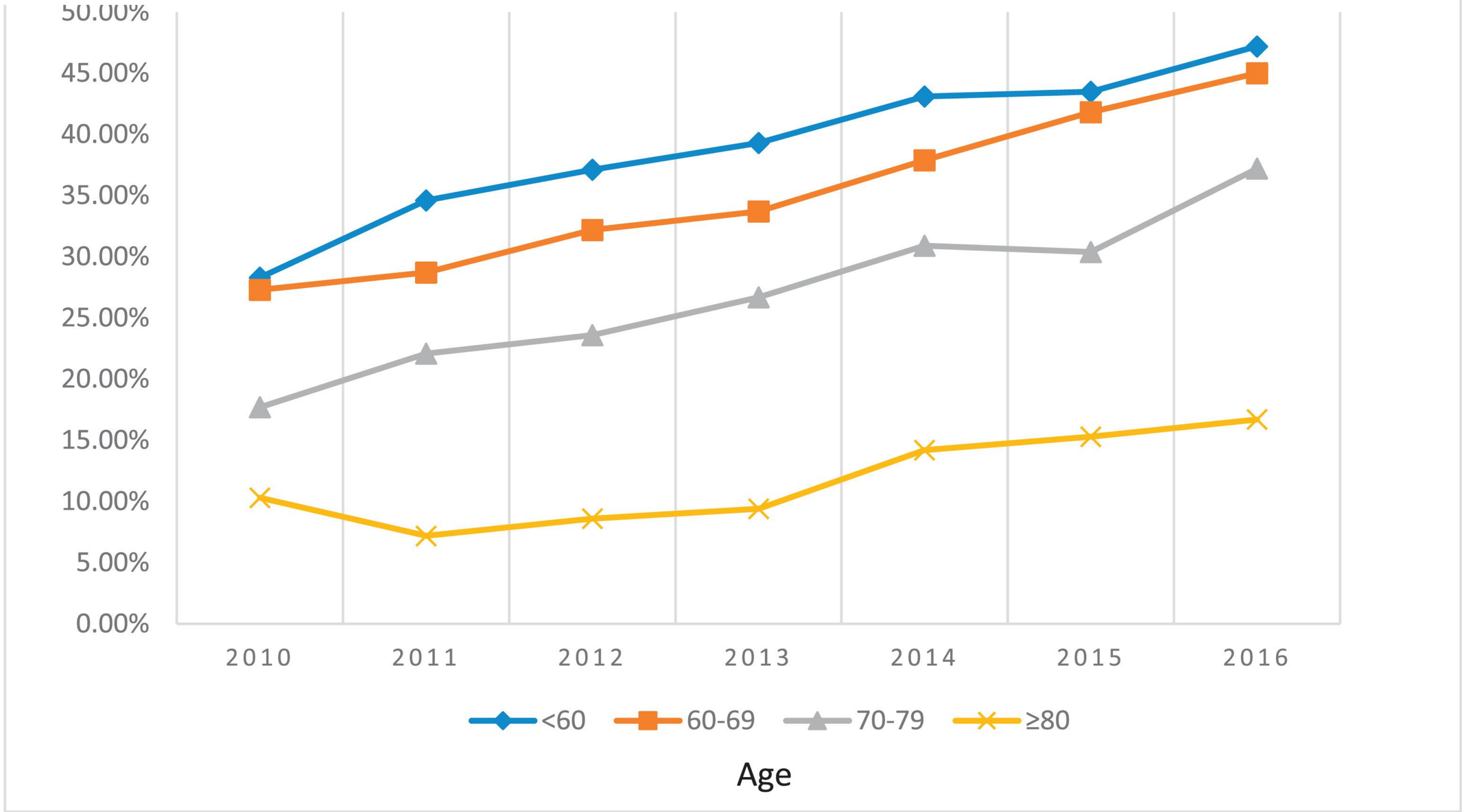
Hospital Universitario 12 de Octubre,





ESMO Guidelines 2023

UTILIZATION RATES OF NAC



Abigail Kohut-Jackson et al. Urology Onocology 2024

Conceptos sin cambios respecto a la quimio

- **Pacientes no candidatos a cisplatino**: No hay evidencia que avale quimioterapia perioperatoria. POUT?
-
-

Conceptos sin cambios respecto a la quimio

- **Pacientes no candidatos a cisplatino**: No hay evidencia que avale quimioterapia perioperatoria.
- **Quimioterapia neoadyuvante basada en cisplatino (3-4 ciclos)**: Los ensayos aleatorizados y metanálisis muestran un beneficio en supervivencia en MIBC (carcinoma urotelial músculo-invasivo).
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Conceptos sin cambios respecto a la quimio

- **Pacientes no candidatos a cisplatino**: No hay evidencia que avale quimioterapia perioperatoria.
- **Quimioterapia neoadyuvante basada en cisplatino (3-4 ciclos)**: Los ensayos aleatorizados y metanálisis muestran un beneficio en supervivencia en MIBC (carcinoma urotelial músculo-invasivo).
- **Quimioterapia adyuvante**: Si no se administró neoadyuvancia y el paciente presenta pT3/4 o N+ tras cistectomía, se recomienda gemcitabina-cisplatino. Menor evidencia.

Recommendations	Strength rating
If eligible for cisplatin-based chemotherapy, offer neoadjuvant cisplatin-based combination chemotherapy to patients with muscle-invasive bladder cancer (T2-T4a, cN0 M0).	Strong
Do not offer NAC to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong
Only offer neoadjuvant immunotherapy to patients within a clinical trial setting.	Strong

Adyuvancia

Study design: CheckMate 274

- Phase 3, randomized, double-blind, multicenter study of adjuvant NIVO vs PBO for high-risk MIUC[a]

N = 709

Key inclusion criteria

- Patients with ypT2-ypT4a or ypN+ MIUC who had NAC chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior NAC chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of randomization

Stratification factors

- Tumor PD-L1 status (≥ 1% vs < 1% or indeterminate)[b]
- Prior NAC-based chemotherapy
- Nodal status

Treat for up to 1 year of adjuvant therapy

Primary endpoints:
DFS in all randomized patients (ITT population) and DFS in all randomized patients with tumor PD-L1 ≥ 1%

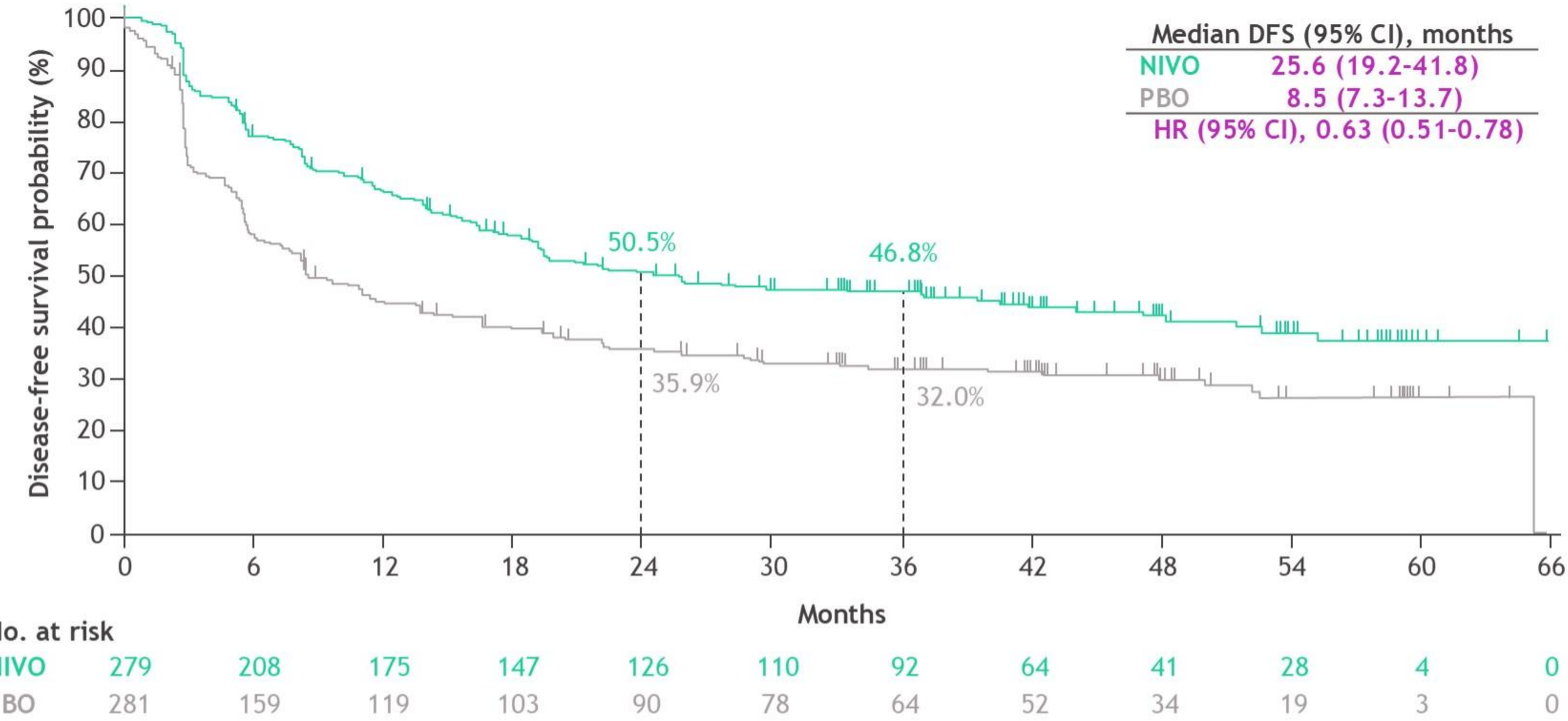
Post hoc analysis endpoints reported here:

- DFS in all randomized patients with MIBC, and in patients with MIBC according to prior NAC
- OS in all randomized patients with MIBC, patients with MIBC and tumor PD-L1 ≥ 1%, and MIBC according to prior NAC

[a]NCT02632409. [b]Defined by the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells using the validated Dako PD-L1 IHC 28-8 pharmDx assay. [c]OS is being tested using a hierarchical procedure in each population (ITT and PD-L1 ≥ 1%), per the statistical analysis plan. OS data are from preplanned interim analyses for the ITT and PD-L1 ≥ 1% populations. OS follow-up is ongoing, as the prespecified statistical boundary for significance was not met at the time of these analyses.

Bajorin D, et al. *N Engl J Med* 2021;384:2102-2114.

DFS: all randomized patients with MIBC

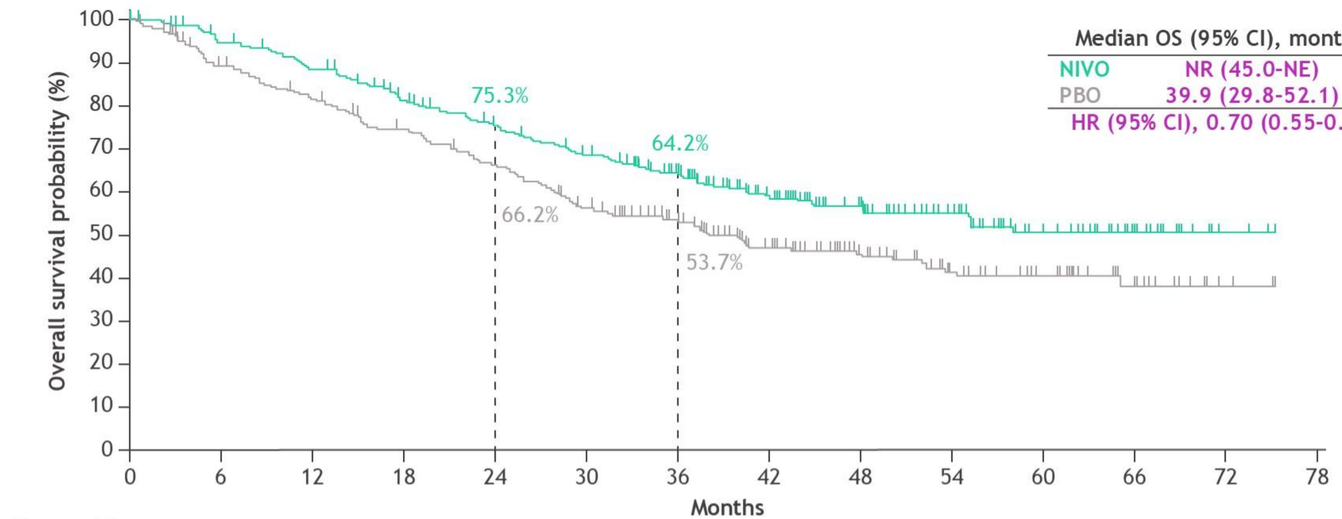


edian follow-up of 36.1 months in the ITT population and 34.5 months in the MIBC population.
alski MS, et al. *J Clin Oncol* 2023;43:4515-21.

OS: all randomized patients with MIBC

CheckMate 274

OS[a]: all randomized patients with MIBC



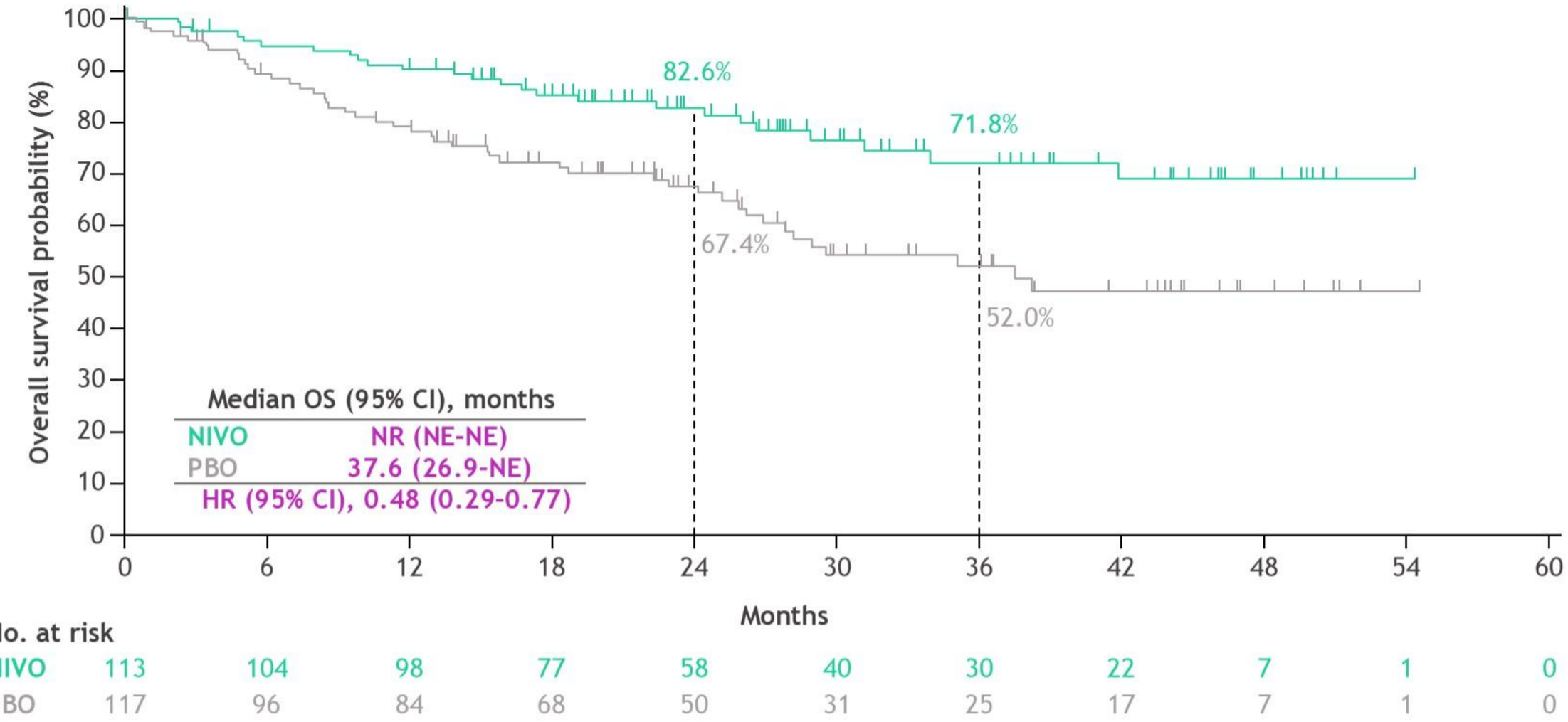
No. at risk

NIVO	279	258	239	213	193	172	145	107	81	56	34	20	3	0
PBO	281	240	218	195	172	143	119	89	65	43	31	17	6	0

[a]Interim OS analysis.
Median follow-up of 36.1 months in the ITT population and 34.5 months in the MIBC population.
Galsky MD, et al. *J Clin Oncol* 2025;43:15-21.

Milowsky et al. ASCO GU 2025

OS[a]: all randomized patients with MIBC and tumor PD-L1 ≥ 1%



[a]Interim OS analysis.
Median follow-up of 36.1 months in the ITT population and 36.7 months in the MIBC and PD-L1 ≥ 1% population.

Milowsky et al. ASCO GU 2025

Summary

- With extended follow-up in CheckMate 274, adjuvant NIVO continued to show DFS benefits vs PBO in patients with MIBC, regardless of prior treatment with NAC[1,2]
- OS data from interim analyses favored adjuvant NIVO over PBO in the MIBC population, regardless of prior NAC, as well as in patients with MIBC and tumor PD-L1 expression ≥1%[2]
- No new safety signals were identified[1,2]
- The improveme…itional support for adjuvant NIVO as a stand…adical surgery and regardless of prior NAC
- Subcutaneous N…standard IV dosing and may provide an alternative for patients across various tumors[3-5]

El estudio CheckMate 274 ha redefinido la adyuvancia en cáncer urotelial músculo-invasivo, con nivolumab mostrando beneficio en supervivencia libre de enfermedad, pero aún sin madurez en OS.

1. Bajorin D, et al. *N Engl J Med* 2021;384:2102-2114. 2. Galsky MD, et al. *J Clin Oncol* 2025;43:15-21. 3. Albigès L, et al. *Ann Oncol* 2025;36:99-107. 4. Lonardi S, et al. Poster presentation at the ASCO 2021 Annual Meeting; June 4-8, 2021; Virtual. Poster 2575. 5. Zhao Y, et al. Poster presentation at the SITC 2024 Annual Meeting; November 6-10, 2024; Houston, TX & Online. Poster 524.

Milowsky et al. ASCO GU 2025

Estudios en adyuvancia

Estudio	Intervención	Comparador	Supervivencia libre de enfermedad (SLE)	PD-L1+ SLE	PD-L1- SLE	Referencia
CheckMate 274	Nivolumab 240 mg cada 2 semanas por 1 año	Placebo	Mediana: 20.8 meses vs. 10.8 meses (HR: 0.70; p<0.001)	74.5% vs. 55.7% (HR: 0.55)	57.7% vs. 43.6% (HR: 0.77)	Bajorin et al., 2021 (NCT02632409)
AMBASSADOR (A031501)	Pembrolizumab 200 mg cada 3 semanas por 1 año	Observación	Mediana: 29.6 meses vs. 14.2 meses (HR: 0.73; p=0.0027)	32.8 meses vs. 20.7 meses (HR: 0.77; p=0.091)	22.1 meses vs. 9.1 meses (HR: 0.61; p=0.002)	Apolo et al., 2025 (NCT03244384)
IMvigor010	Atezolizumab 1200 mg cada 3 semanas por 1 año	Observación	Mediana: 19.4 meses vs. 16.6 meses (HR: 0.89; p=0.24) (no significativo)	IC2/3: NE vs. 49.5 meses (HR: 0.57; IC 0.29-1.15)	IC0: NE vs. 52.9 meses (HR: 1.09; IC 0.77-1.53)	Bellmunt et al., 2021 (NCT02450331)

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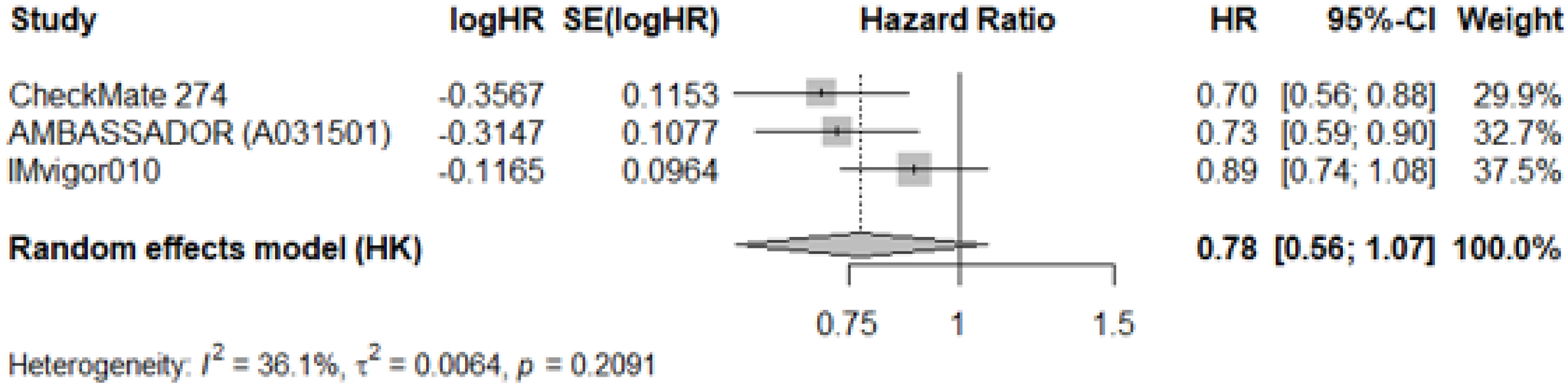
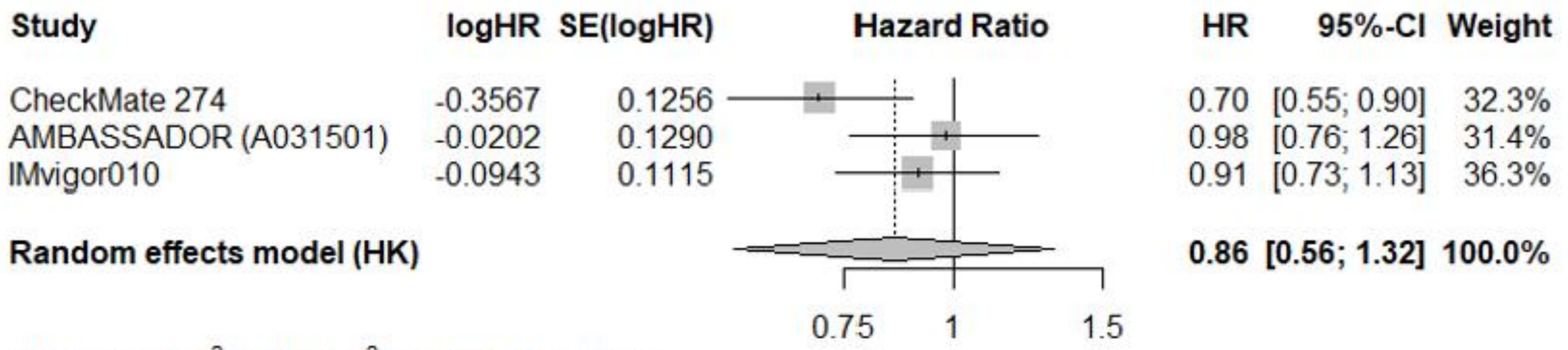
Supervivencia libre de enfermedad (DFS): metaanálisis de ensayos clínicos aleatorizados

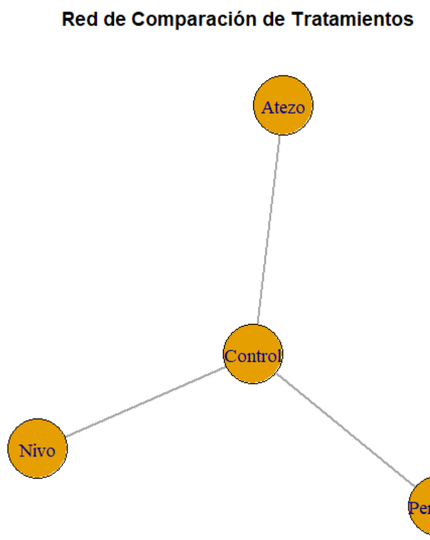


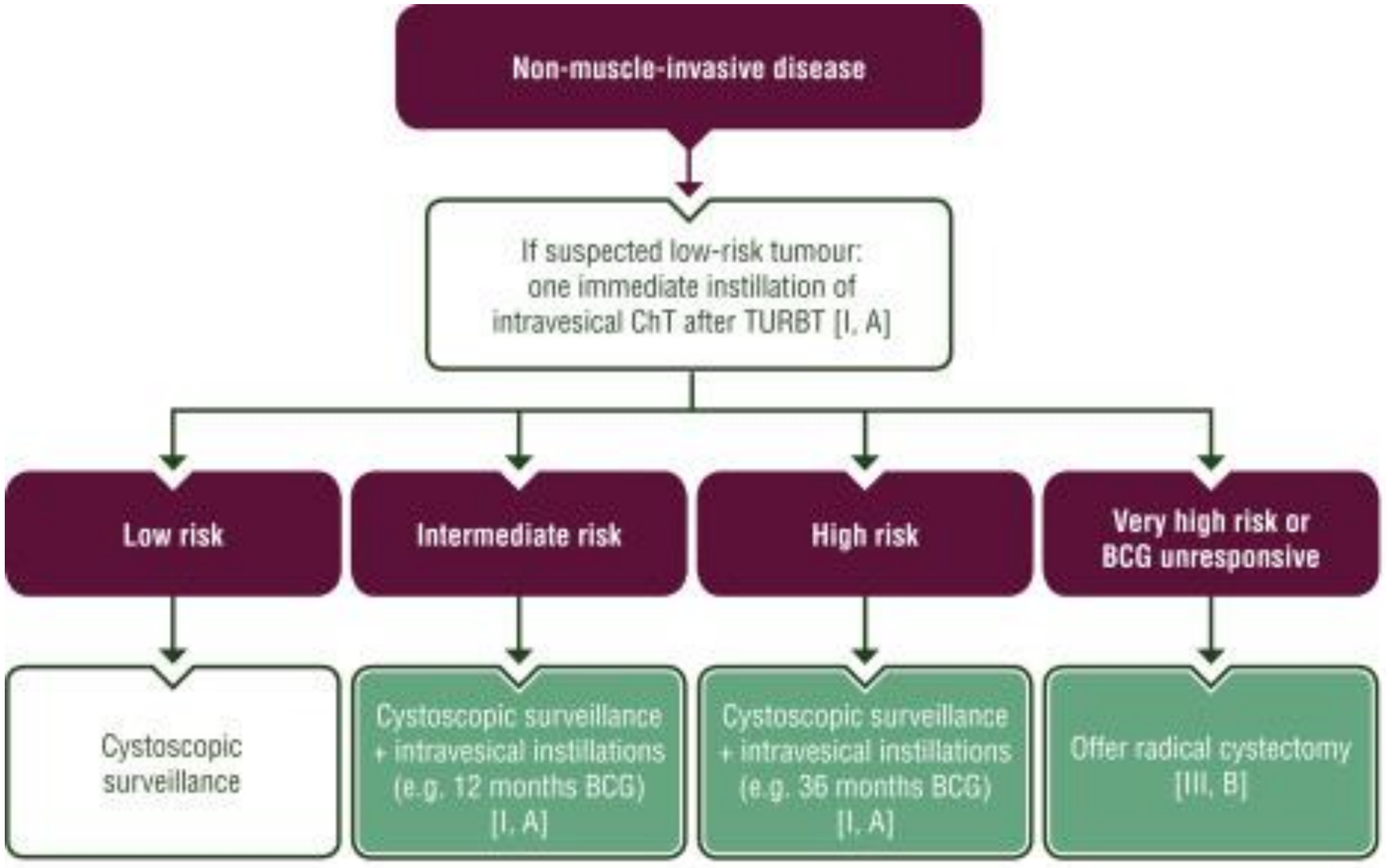
OS. Metaanálisis de ensayos clínicos aleatorizados

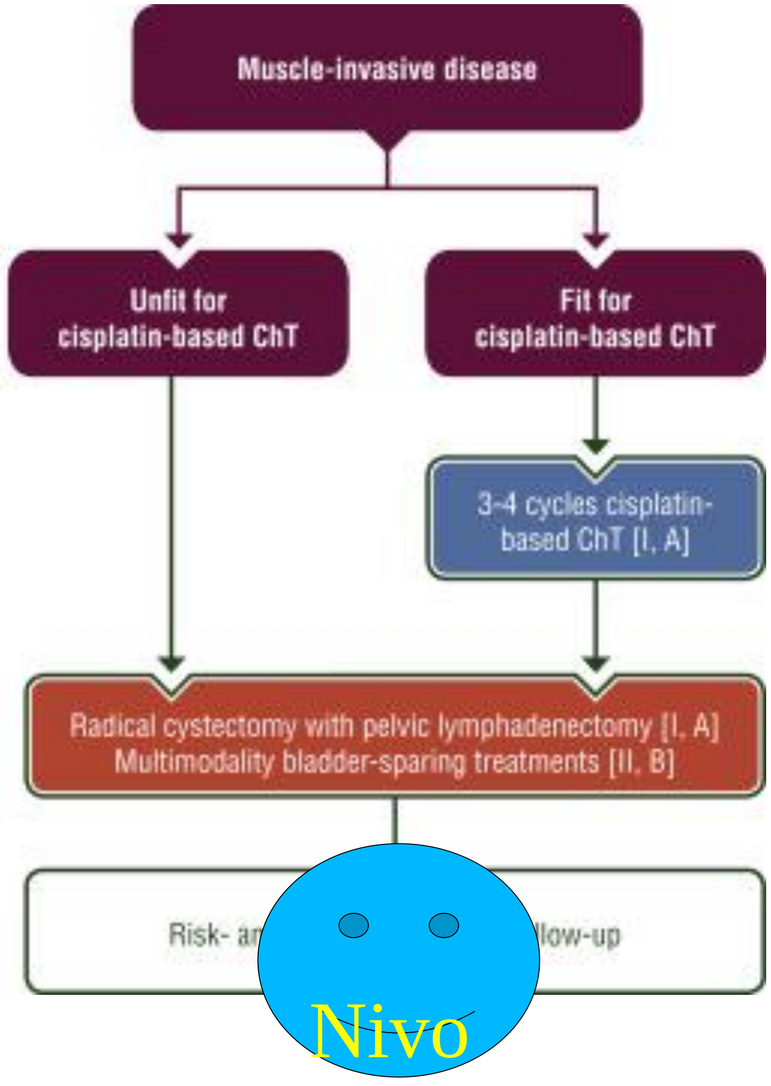


Network meta-análisis

- Treatment Best Second Worst
- Nivo 85% 10% 5%
- Pembro 10% 50% 40%
- Atezo 5% 40% 55%







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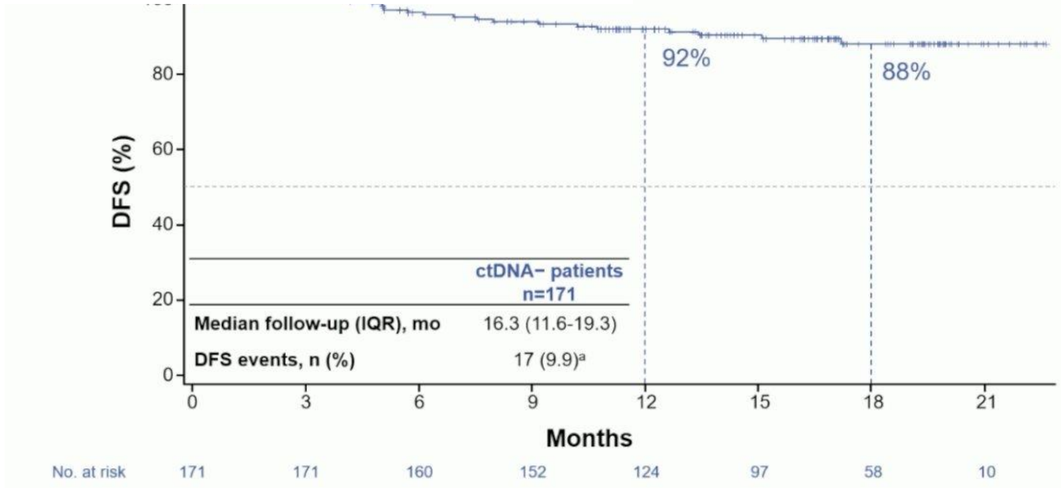
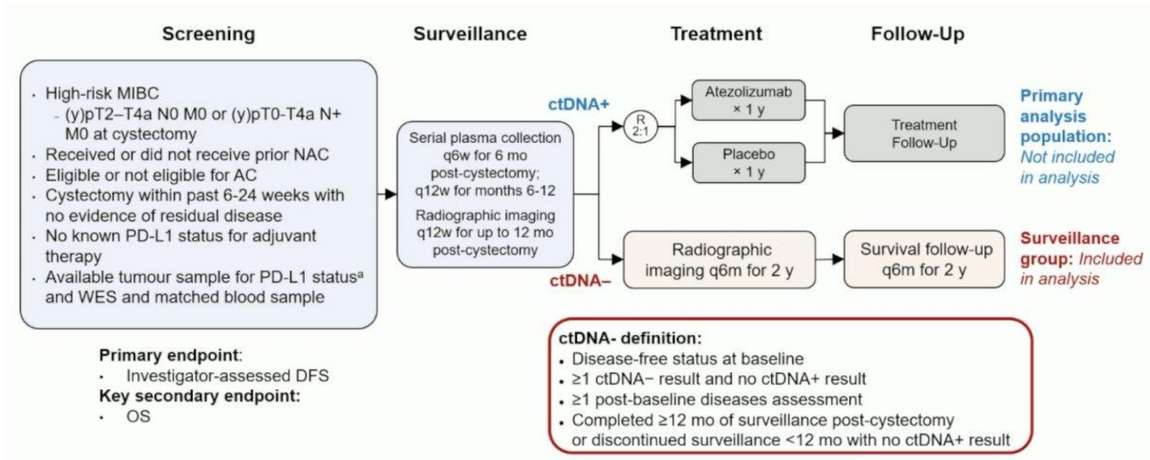
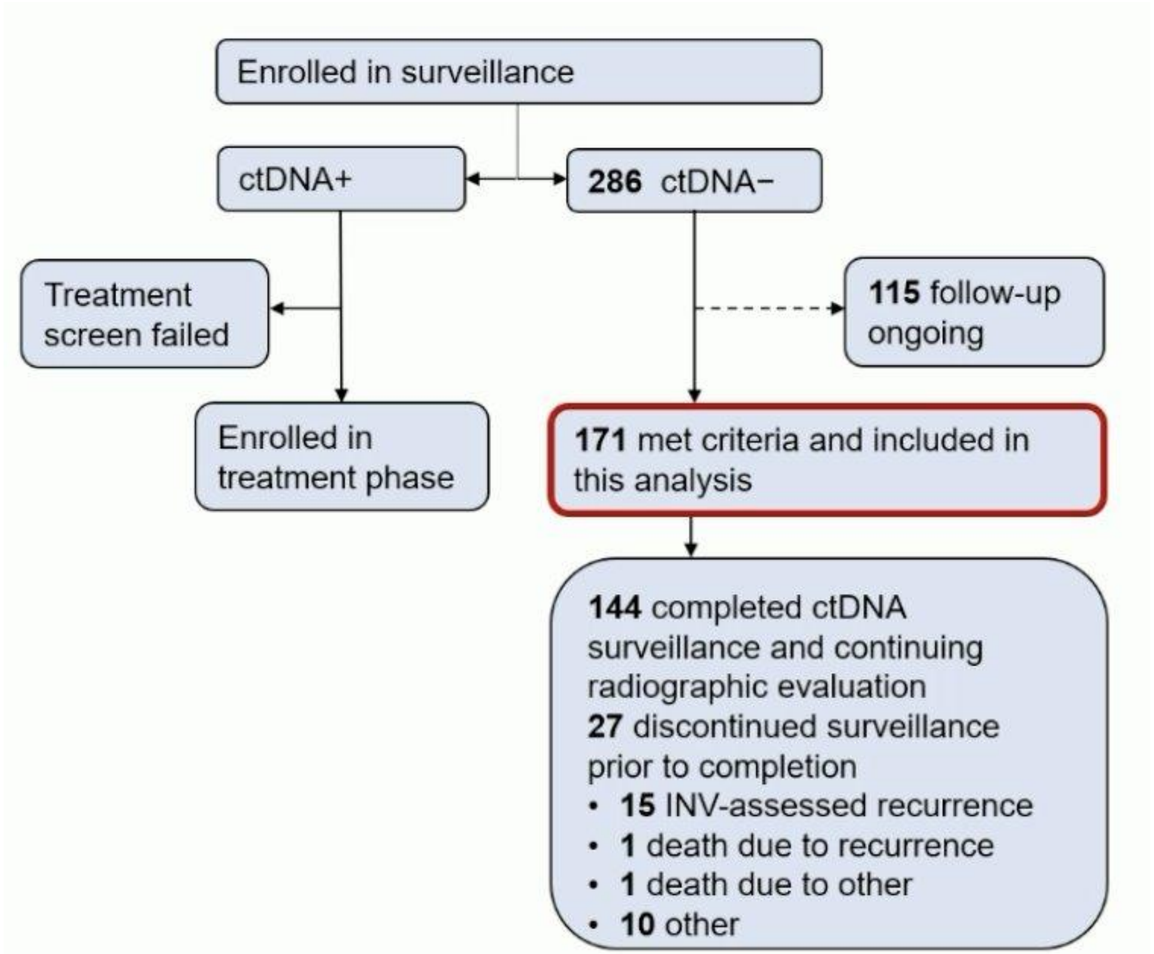
ctDNA


DFS (%)
80
60
40
20
0
92%
88%
ctDNA− patients
n=171
Median follow-up (IQR), mo
16.3 (11.6-19.3)
DFS events, n (%)
17 (9.9)a
0
3
6
9
12
15
18
21
Months
No. at risk
171
171
160
152
124
97
58
10

IMVIGOR 011

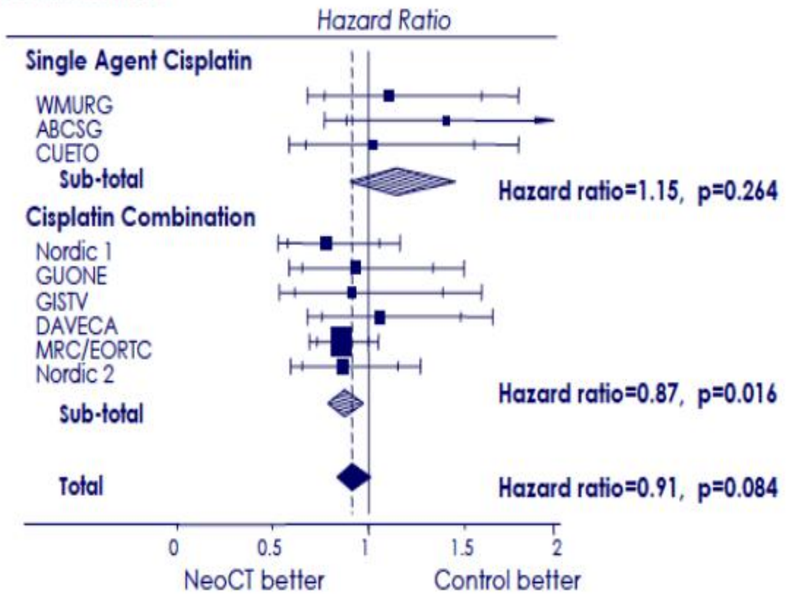

Screening
Surveillance
Treatment
Follow-Up
High-risk MIBC
(y)pT2–T4a N0 M0 or (y)pT0-T4a N+ M0 at cystectomy
Received or did not receive prior NAC
Eligible or not eligible for AC
Cystectomy within past 6-24 weeks with no evidence of residual disease
No known PD-L1 status for adjuvant therapy
Available tumour sample for PD-L1 statusa and WES and matched blood sample
Serial plasma collection q6w for 6 mo post-cystectomy; q12w for months 6-12
Radiographic imaging q12w for up to 12 mo post-cystectomy
ctDNA+
ctDNA−
R 2:1
Atezolizumab × 1 y
Placebo × 1 y
Treatment Follow-Up
Radiographic imaging q6m for 2 y
Survival follow-up q6m for 2 y
Primary analysis population: Not included in analysis
Surveillance group: Included in analysis
Primary endpoint:
Investigator-assessed DFS
Key secondary endpoint:
OS
ctDNA- definition:
Disease-free status at baseline
≥1 ctDNA− result and no ctDNA+ result
≥1 post-baseline diseases assessment
Completed ≥12 mo of surveillance post-cystectomy or discontinued surveillance <12 mo with no ctDNA+ result


Enrolled in surveillance
ctDNA+
286 ctDNA−
Treatment screen failed
115 follow-up ongoing
Enrolled in treatment phase
171 met criteria and included in this analysis
144 completed ctDNA surveillance and continuing radiographic evaluation
27 discontinued surveillance prior to completion
15 INV-assessed recurrence
1 death due to recurrence
1 death due to other
10 other

Neoadyuvancia

ABC (Advanced Bladder Cancer) Meta-analysis Collaboration

Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data from *10 randomised trials*



Test for interaction: χ^2=4.034, p=0.045
Test for heterogeneity: χ^2=7.132, p=0.522

Cisplatin-containing combinations:
Absolute OS benefit of 5%

Cisplatin combination sig. better than cisplatin alone p=0.044

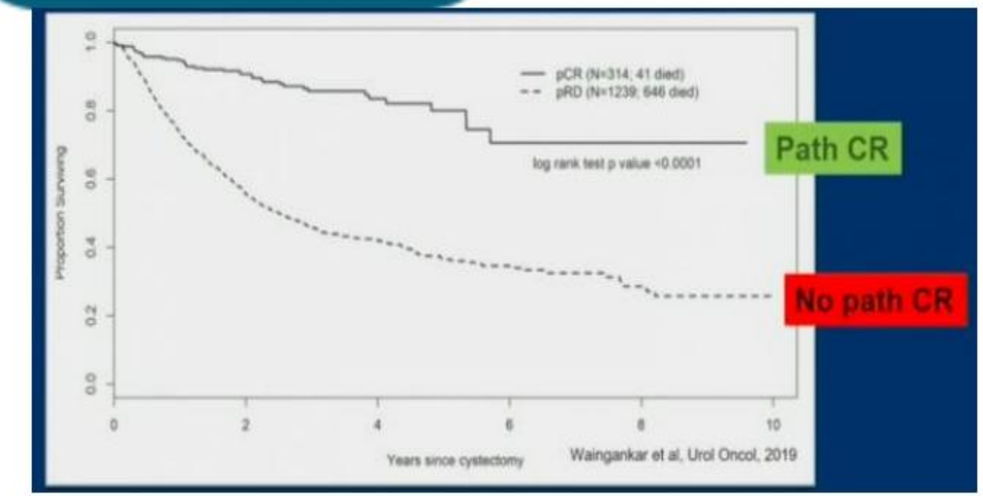
Eur Urol 2005

EORTC/MRC[11]	CMV/RT or cystectomy	RT or cystectomy	976	5.5% difference in favor of CMV	SG 7 años
SWOG Intergroup[20]	M-VAC/cystectomy	Cystectomy	298	Benefit with M-VAC (P = 0.06)	SG 5 años

pT0 Rates With CT:

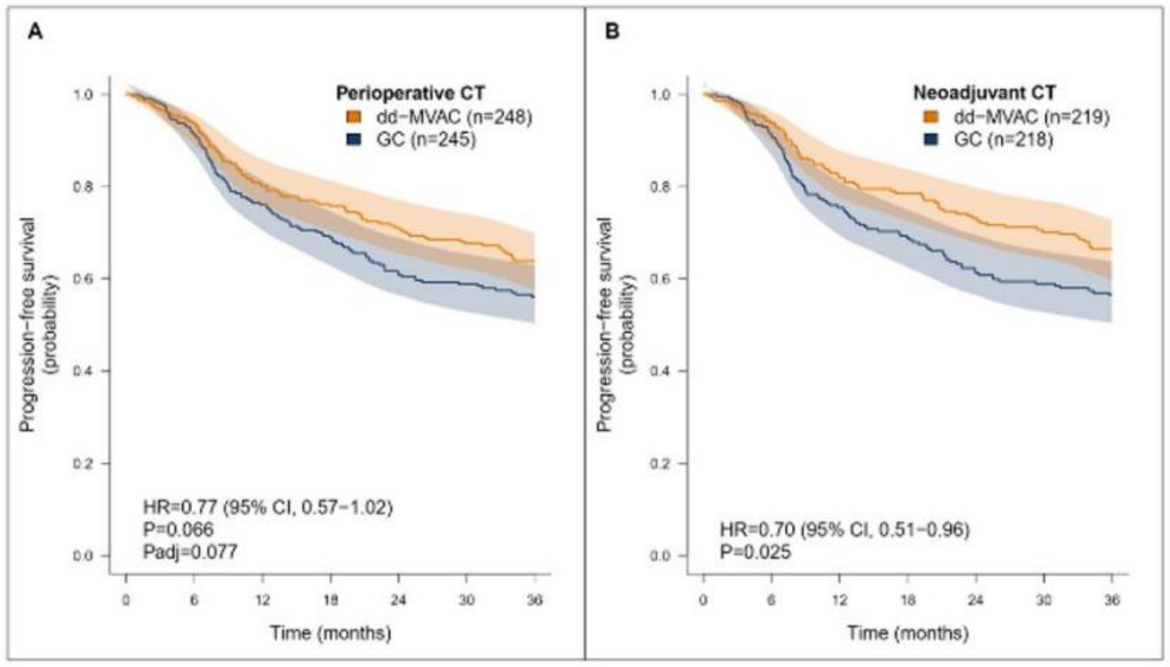
Gem/Cis, 15% to 32%

DD MVAC, 26% to 43%

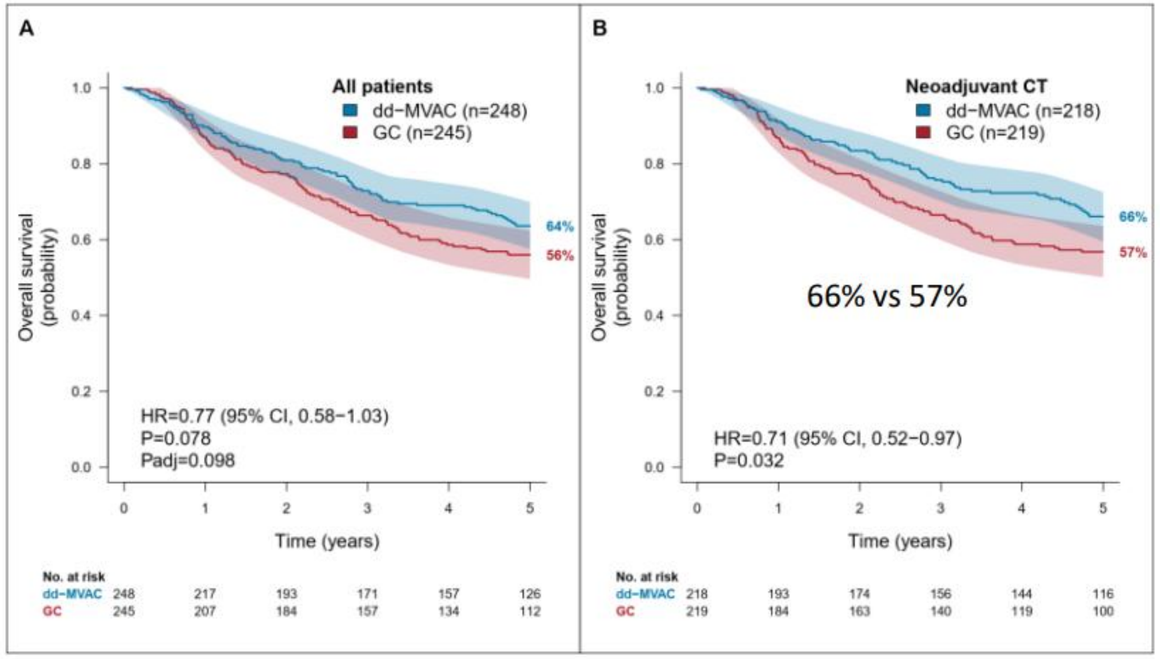


HB, et al. N Engl J Med 2003;Herr HW, et al. J Clin Oncol 2004;

VESPER trial (88% neoadjuvant)



5y OS



Pfister C, et al. ASCO2023

Statistical design:
To demonstrate dd-MVAC improves PFS compared to GC with a **HR 0.74 and α risk of 5% and a power of 80%.**

Primary endpoint: 3y-PFS.

For all patients: 64% vs 56%; HR 0.77 (95%CI, 0.57-1.02); **p=0.066**

ddMVAC associated with longer time to progression: 3y rate:69% vs 58%,HR 0.68,**p=0.014**

In the neoadjuvant group:

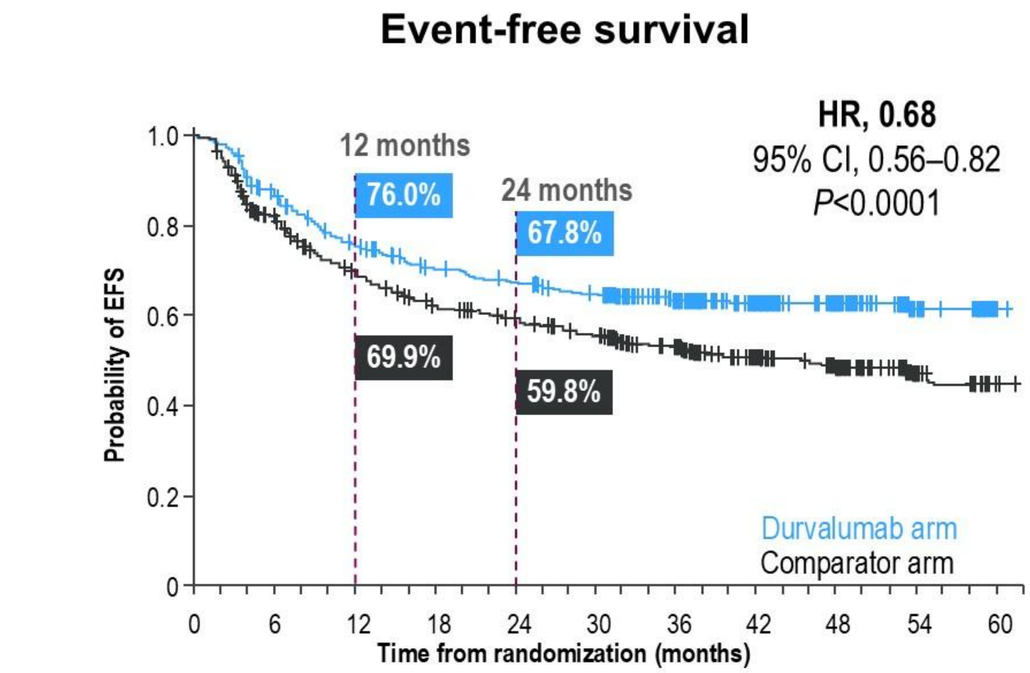
3yPFS was s.s higher with ddMVAC: 66% vs 56%, HR 0.70 (95%CI 0.51-0.96), **p=0.025**

ypT0N0
36% (GC) vs 42% (dd-MVAC)
p=0.20

Cambio de SOC?

Background

- In NIAGARA, the addition of perioperative durvalumab to NAC demonstrated[1]:
  - Statistically significant and clinically meaningful improvement in
    - EFS: HR, 0.68 (95% CI, 0.56–0.82), *P*<0.0001
    - OS: HR, 0.75 (95% CI, 0.59–0.93), *P*=0.0106
  - 10% improvement in pathological complete response (pCR) rate
  - No delay to surgery and no impact on patients' ability to undergo/complete surgery
- Here, we report additional efficacy and safety results from NIAGARA



Median EFS follow-up in censored patients: 42.3 months (range, 0.03–61.3)

1. Powles T, et al. *N Engl J Med*. 2024;391:1773–1786.
EFS, event-free survival; HR, hazard ratio; MIBC, muscle-invasive bladder cancer; NAC, neoadjuvant chemotherapy; OS, overall survival.

From *N Engl J Med*, Powles T, Catto JWF, Galsky MD, et al. Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer, 391:1773–86. Copyright © (2024) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

NIAGARA: Study Design

Study population
- Adults
- Cisplatin-eligible MIBC (cT2–T4aN0/1M0)
- UC or UC with divergent differentiation or histologic subtypes
- Evaluated and confirmed for RC
- CrCl of ≥40 mL/min

R 1:1

Perioperative

Neoadjuvant
Q3W, 4 cycles

Adjuvant
Q4W, 8 cycles

Durvalumab arm
N=533
Durvalumab 1500 mg IV
Gemcitabine + cisplatin

Comparator arm
N=530
Gemcitabine + cisplatin

Radical cystectomy

Durvalumab 1500 mg IV

No treatment

Primary endpoints
- EFS
- pCR

Key secondary endpoint
- OS

Secondary endpoints
- Metastasis-free survival
- Disease-specific survival

Safety
- Immune-mediated AEs

Exploratory post-hoc analysis
- EFS by pCR
- OS by pCR

Full study design details are available in Powles T, et al. *N Engl J Med*. 2024;391:1773–1786.

ClinicalTrials.gov, NCT03732677; EudraCT number, 2018-001811-59.

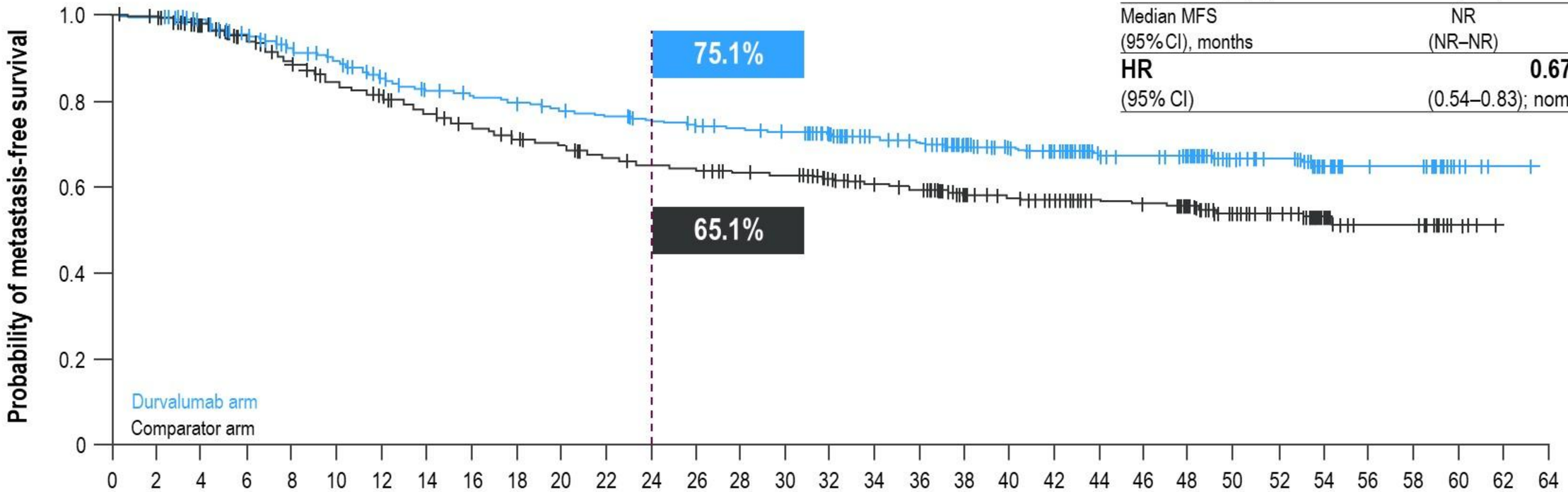
AE, adverse event; CrCl, creatinine clearance; EFS, event-free survival; IV, intravenous; MIBC, muscle-invasive bladder cancer; OS, overall survival; pCR, pathological complete response; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomized; RC, radical cystectomy; UC, urothelial carcinoma.

PRESENTED BY: Prof Matthew D. Galsky

NIAGARA: Metastasis-free Survival (ITT)

Perioperative D + NAC reduced the risk of distant metastases or death by 33%

	Durvalumab arm N=533	Comparator arm N=530
No. of events, n (%)	152 (28.5)	201 (37.9)
Median MFS (95% CI), months	NR (NR–NR)	NR (48.0–NR)
HR (95% CI)	**0.67** (0.54–0.83); nominal *P*<0.001	



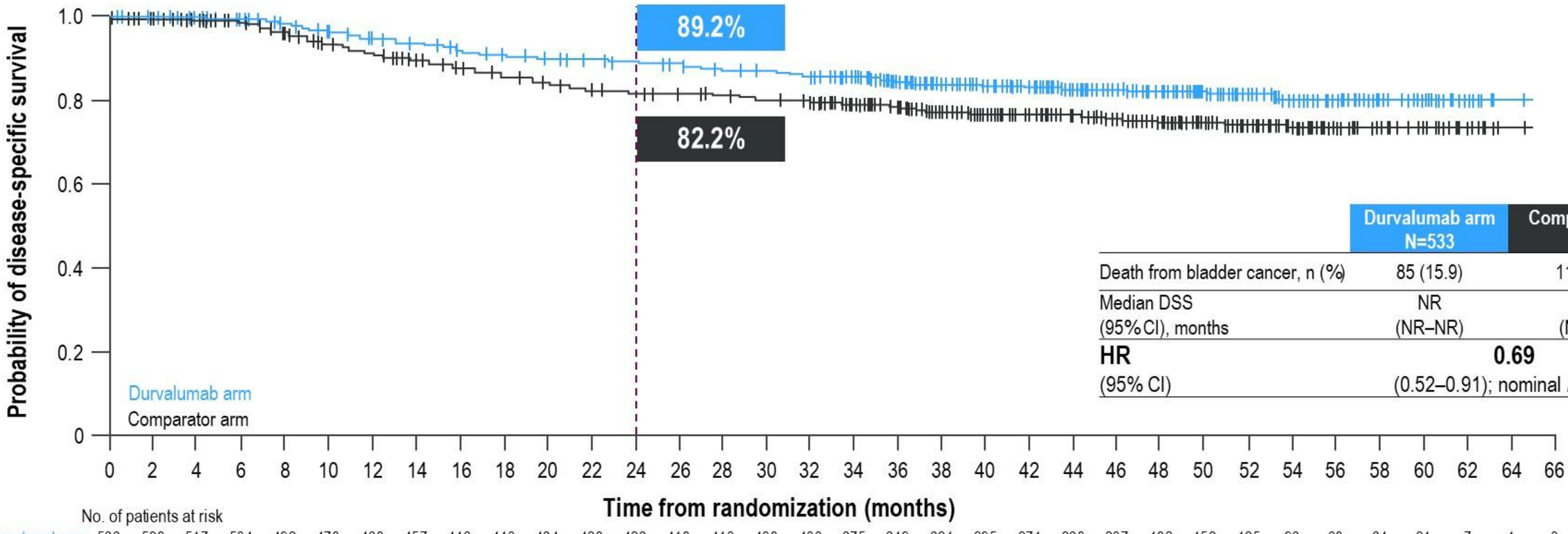
No. of patients at risk

Durvalumab arm	533	522	492	470	442	422	397	382	372	365	355	349	340	331	327	322	291	278	265	225	212	189	147	146	121	90	85	33	22	22	3	1	0
Comparator arm	530	498	473	443	409	384	365	350	332	315	309	293	286	279	274	271	240	231	224	184	178	163	136	134	99	72	64	27	21	19	3	0	0

Data cutoff Apr 29, 2024. Metastasis-free survival is defined as the time from date of randomization until the first recognition of distant metastases or death, whichever occurs first. Tick marks indicate patients with censored data. CI, confidence interval; D, durvalumab; HR, hazard ratio; ITT, intent-to-treat population; MFS, metastasis-free survival; NAC, neoadjuvant chemotherapy; NR, not reached.

NIAGARA: Disease-specific Survival (ITT)

Perioperative D + NAC reduced the risk of death from bladder cancer by 31%



	Durvalumab arm N=533	Comparator arm N=530
Death from bladder cancer, n (%)	85 (15.9)	114 (21.5)
Median DSS (95% CI), months	NR (NR–NR)	NR (NR–NR)
HR (95% CI)	**0.69** (0.52–0.91); nominal *P*=0.008	

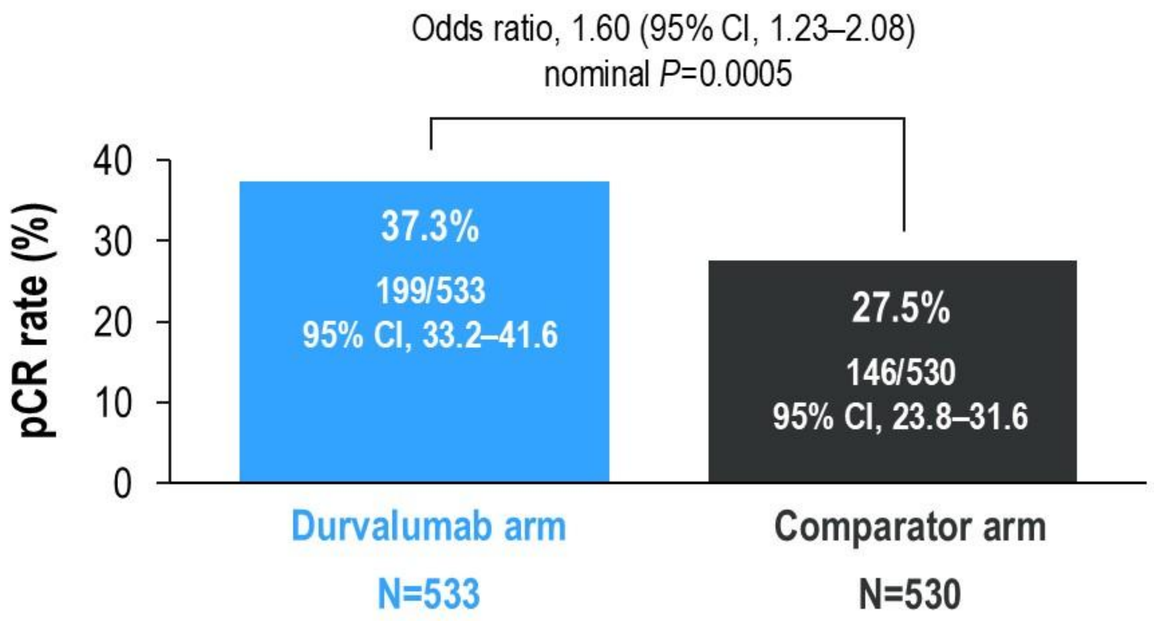
No. of patients at risk

Durvalumab arm	533	528	517	504	492	478	468	457	446	440	434	428	423	418	410	408	400	375	349	321	295	271	238	207	182	152	125	96	68	34	21	7	1	0
Comparator arm	530	515	506	489	466	449	437	424	412	401	391	382	377	372	368	363	358	333	310	280	258	238	214	193	173	141	113	90	60	38	21	10	2	0

Data cutoff Apr 29, 2024. Disease-specific survival is defined as the time from the date of randomization until death due to bladder cancer. Tick marks indicate patients with censored data. CI, confidence interval; D, durvalumab; DSS, disease-specific survival; HR, hazard ratio; ITT, intent-to-treat population; NAC, neoadjuvant chemotherapy; NR, not reached.

NIAGARA: Pathological Complete Response (ITT)

10% improvement in pathological complete response rate in favor of the durvalumab arm



From *N Engl J Med*, Powles T, Catto JWF, Galsky MD, et al. Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer, 391:1773–86. Copyright © (2024) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Further details are available in Powles T, et al. *N Engl J Med*. 2024;391:1773–1786.
Data cutoff Apr 29, 2024. Odds ratio, corresponding CI, and *P* value are obtained using logistic regression adjusted for the stratification factors (renal function, tumor stage, and PD-L1 status). Pathological staging of samples taken during RC was performed centrally; pCR was the proportion of patients with stage T0N0M0 at RC (American Joint Committee on Cancer 8th edition classification). CI, confidence interval; ITT, intent-to-treat population; pCR, pathological complete response; RC, radical cystectomy.

Conclusions

- NIAGARA demonstrated statistically significant and clinically meaningful improvement in EFS (HR, 0.68; 95% CI, 0.56–0.82) and OS (HR, 0.75; 95% CI, 0.59–0.93), with a 10% improvement in pCR rate[1]
- In the durvalumab arm, the risk of an MFS event was reduced by 22%, and the risk of a DSS event w
- Perioperative du and non-pCR groups in an exploratory post-hoc analysis
- imAEs were mostly low grade and consistent with the known profile of durvalumab

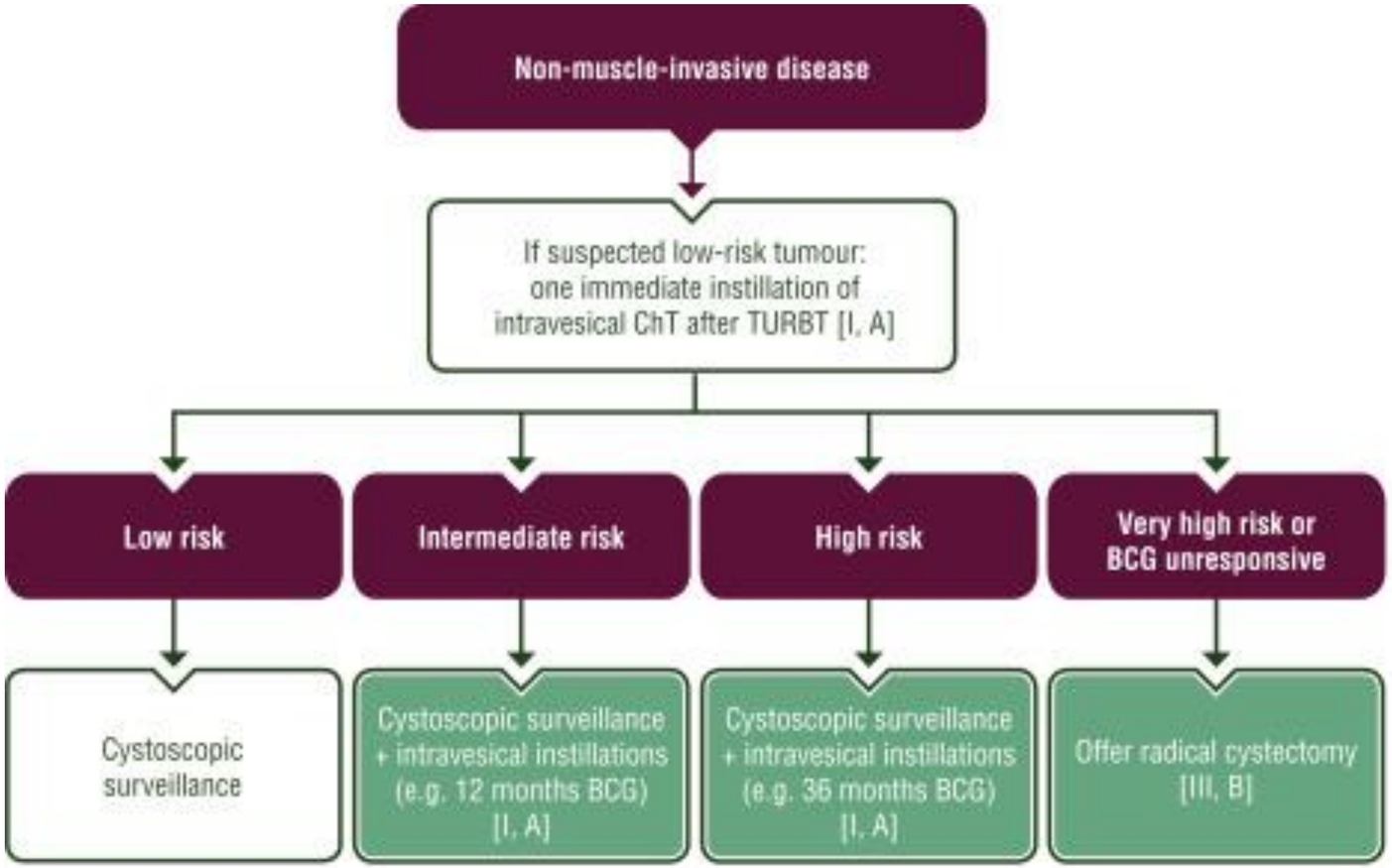
NIAGARA universaliza la neoadyuvancia

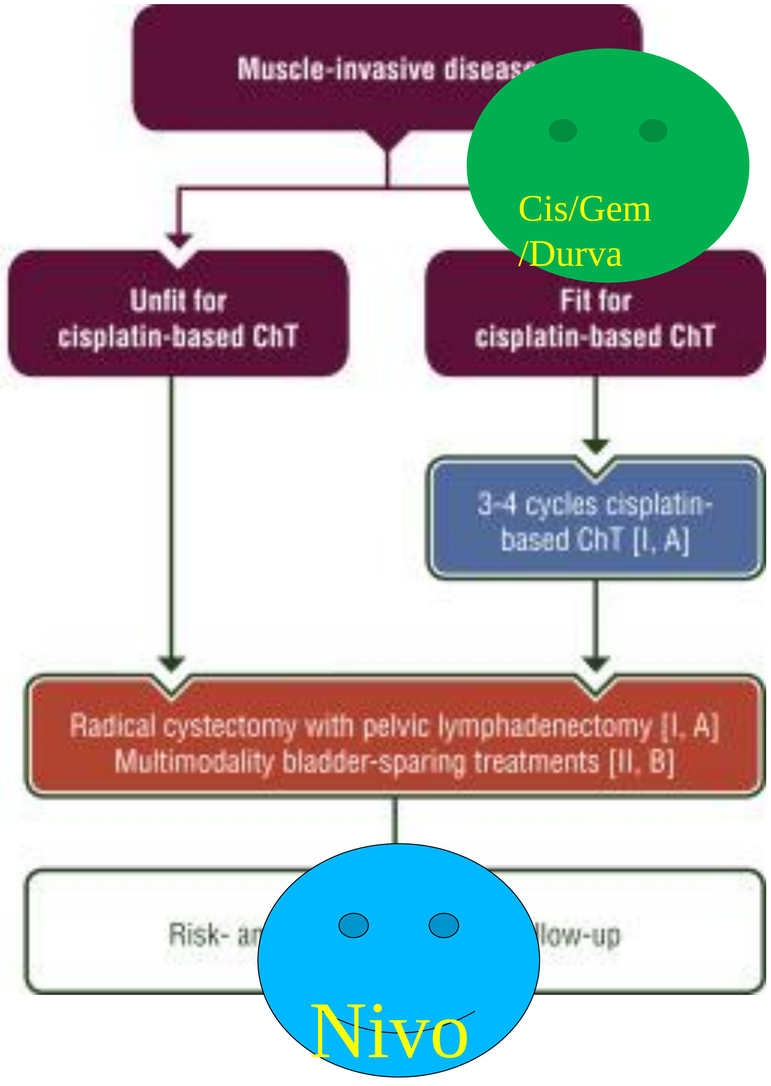
This additional NIAGARA data further supports perioperative durvalumab with NAC as a potential new treatment for patients with cisplatin-eligible MIBC

1. Powles T, et al. *N Engl J Med*. 2024;391:1773–1786. CI, confidence interval; DSS, disease-specific survival; EFS, event-free survival; HR, hazard ratio; imAE, immune-mediated adverse event; MFS, metastasis-free survival; MIBC, muscle-invasive bladder cancer; NAC, neoadjuvant chemotherapy; OS, overall survival; pCR, pathological complete response.

Scan the QR code to access:

- Slide presentation
- Plain language summary





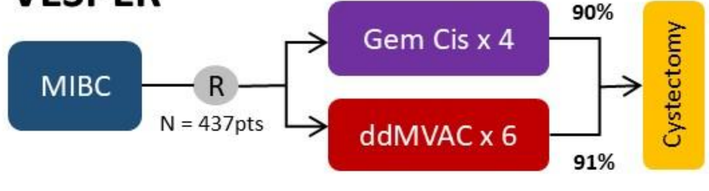
ESMO Guidelines 2023

NIAGARA in the context of currently available treatment options

NIAGARA

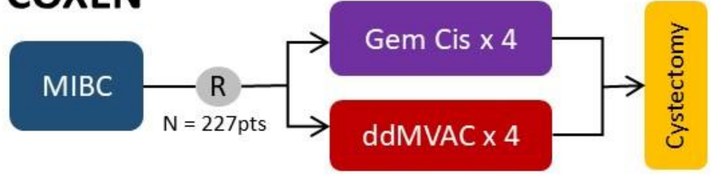
DGC “sandwich” vs GC
EFS benefit at 2 yrs: 8%
OS benefit at 2 yrs: 7%

VESPER

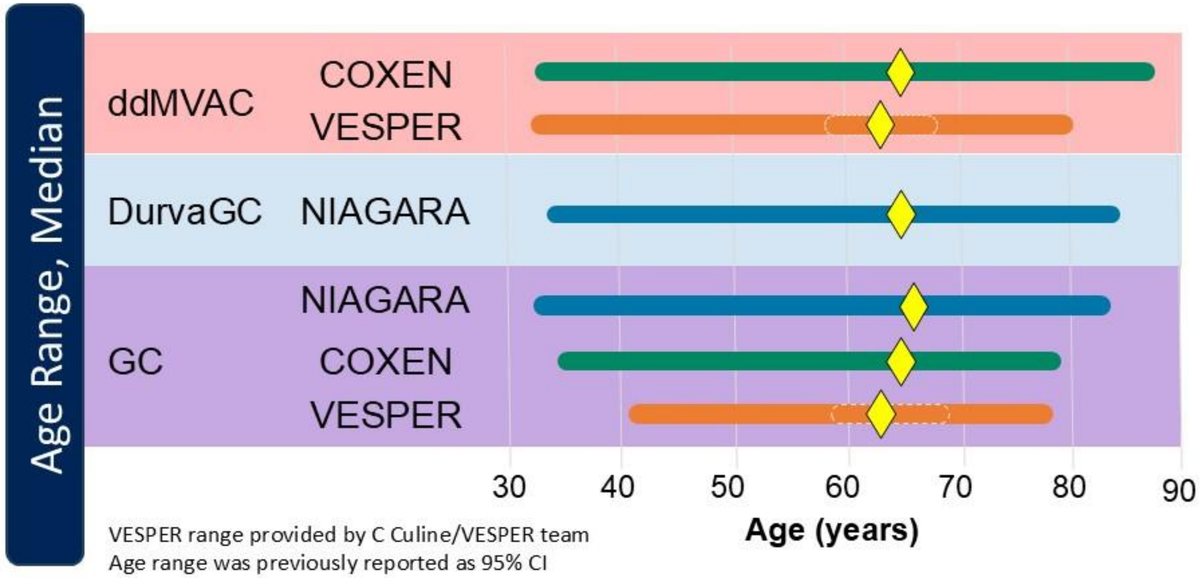


ddMVAC vs GC
EFS benefit at 5 yrs: 9%
OS benefit at 5 yrs: 9%

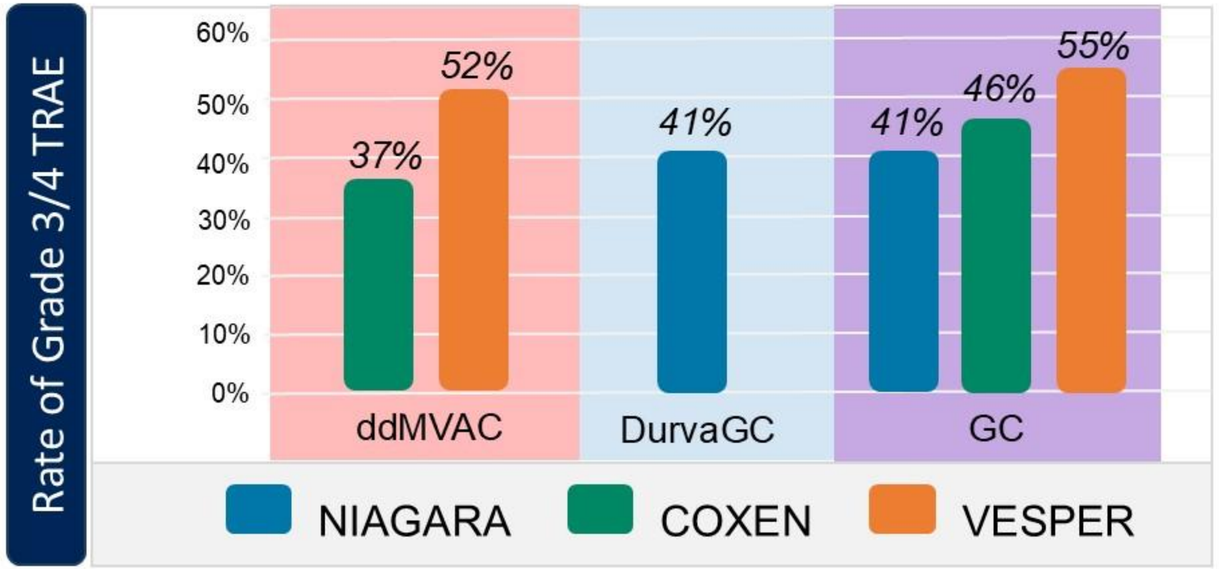
COXEN



ddMVAC vs GC
EFS benefit at 5 yrs: 4%
OS benefit at 5 yrs: 7%
Differences were not statistically significant



VESPER range provided by C Culine/VESPER team
Age range was previously reported as 95% CI



PRESENTED BY: Elizabeth Plimack, MD MS FASCO

NIAGARA Galsky et al. ASCO GU 2025
Pfister et al. The Lancet Onc 25, 255-264 (2024).
Flaig et al. Eur Urol 84, 341-347 (2023).

Take Home: 2 options for clinic on Monday

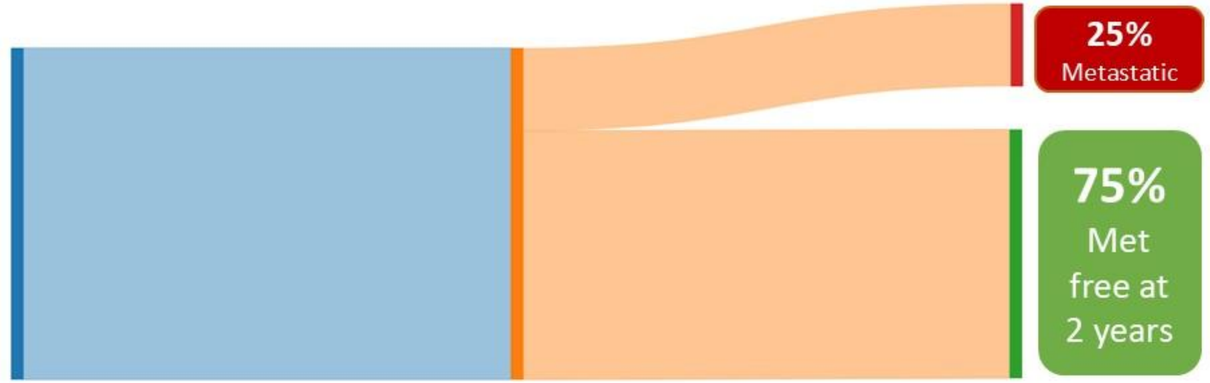
Neoadjuvant ddMVAC

Neoadj ddMVAC **Observation**

Benefits of risk adapted approach using ddMVAC

- **≥ypT2 35%** patients would qualify for and may gain additional benefit from adjuvant nivolumab or the MODERN trial
- Avoids overtreatment and IO toxicity for **<ypT2 65%**
- Cost and time saving

"Sandwich" Approach with GC Durva



Neoadj Gem Cis + Durva **Durvalumab x 8**

Benefits of a "sandwich" approach

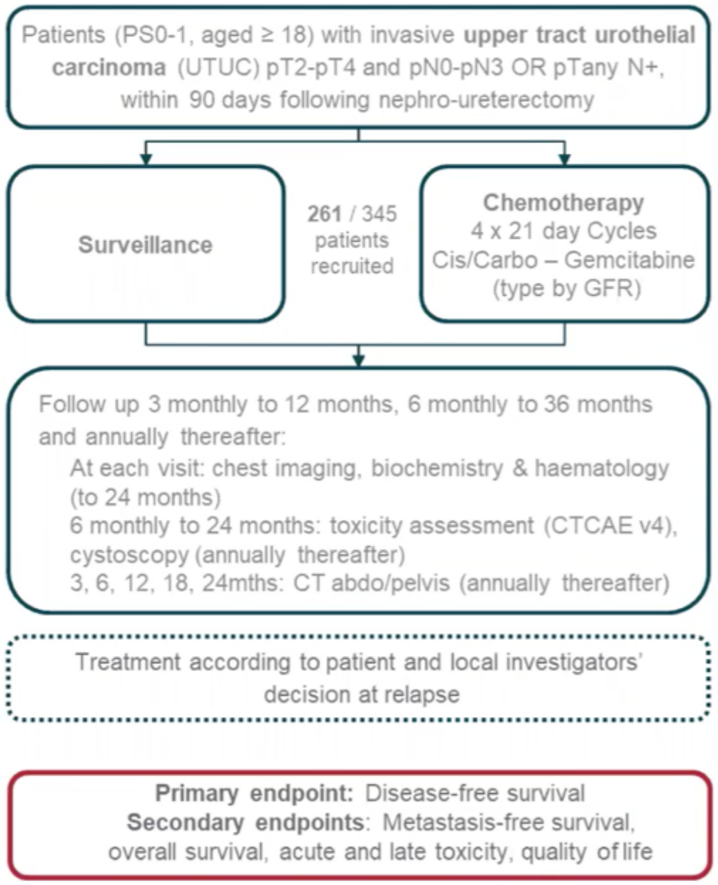
- If using Gem Cis, adding durvalumab pre and post adds benefit in direct and cross trial comparison
- Adjuvant durvalumab may benefit some of the ~10% of <ypT2 who develop metastases but would not have qualified for adjuvant nivolumab

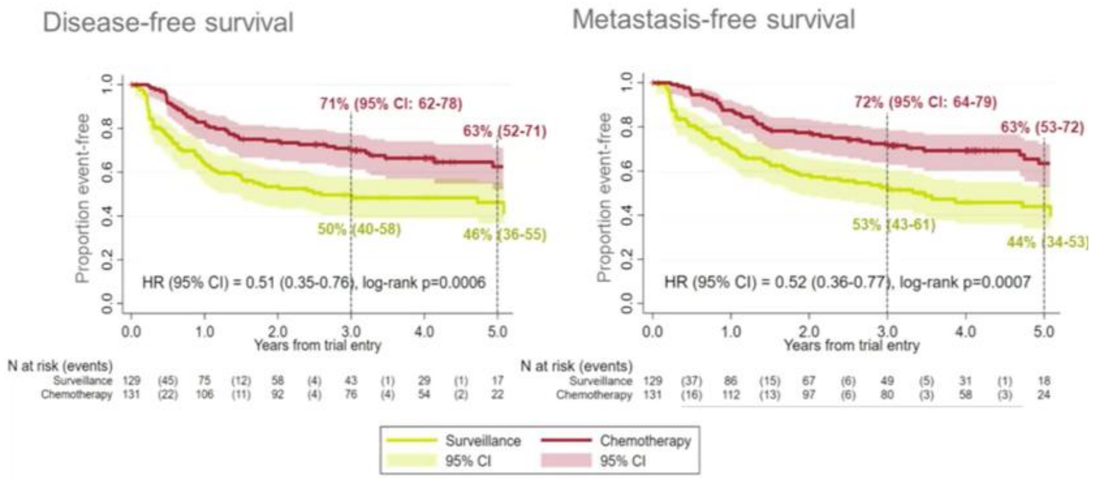
PRESENTED BY: Elizabeth Plimack, MD MS FASCO

NIAGARA Galsky et al. ASCO GU 2025
VESPER Pfister et al. LBA4507, ASCO 2023
S Culine and VESPER team personal communication

Datos de UTUC?

gemcitabine-carboplatin if GFR 30-49ml/min





Birtle et al. Lancet 2020

ASCO Genitourinary Cancers Symposium

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

Nadine HOUEDE[1,2], Thierry CHEVALLIER[3,4,], Loïc JAFFRELOT[5], Constance THIBAULT[6], Yann NEUZILLET[7], Christine ABRAHAM[8], Alexandra MASSON-LECOMTE[9], Gwenaelle GRAVIS[10], Géraldine PIGNOT[11], Sophie TARTAS[12], Damien POUESSEL[13], Brigitte LAGUERRE[14], François AUDENET[6], Evanguelos XYLINAS[15], Guillaume LUQUIENS[3], Morgan ROUPRET[16]

[1]Department of Oncology, CHU Nîmes, Univ. Montpellier, Nîmes, France; [2]INSERM U1194, Université de Montpellier CHU Nîmes, [3]Department of Biostatistics, Epidemiology, Public Health and Innovation in Methodology30029 Nîmes, France; Univ. Montpellier, [4]NSERM, UMR 1302, Institute Desbrest of Epidemiology and Public Health, Montpellier, France; [5]AP-HP, Oncology, Pitie-Salpetriere Hospital, F-75013 PARIS, France; [6]Department of medical oncology, Hôpital Européen Georges Pompidou, AP-HP, University Paris Cité, Paris, France, Institut du Cancer Paris CARPEM, AP-HP Centre, Université Paris Cité, Paris; [7]Foch Hospital, Department of Urology, University of Paris-Saclay – UVSQ, Suresnes, France; [8]Foch Hospital, Department of Oncology, Suresnes, France; [9]Service d'Urologie Hôpital Saint Louis, Université Paris Cité, Service de Recherche en Hémato-Immunologie CEA - INSERM U976 HIPI; [10]Institut Paoli-Calmettes, Department of Medical Oncology, Aix Marseille Univ, INSERM, CNRS, CRCM, Immunity and Cancer Team, Marseille, France; [11]Department of Surgical Oncology, Paoli-Calmettes Institute, Marseille, France.[12]Department of Medical Oncology, IMMUCARE, Centre Hospitalier Lyon Sud, Institut de Cancérologie des Hospices de Lyon (IC-HCL), Pierre-Bénite, France; [13]Department of Medical Oncology, Institut Universitaire du Cancer -Toulouse- Oncopole, Toulouse, France; [14]Department of Medical Oncology, Centre Eugene - Marquis, Rennes, France; [15]Department of Urology, Bichat-Claude Bernard Hospital, APHP, Paris University; [16]Sorbonne University, GRC 5 Predictive Onco-Uro, AP-HP, Urology, Pitie-Salpetriere Hospital, F-75013 PARIS, France

PRESENTED BY: Houede N. MD PhD

Methods

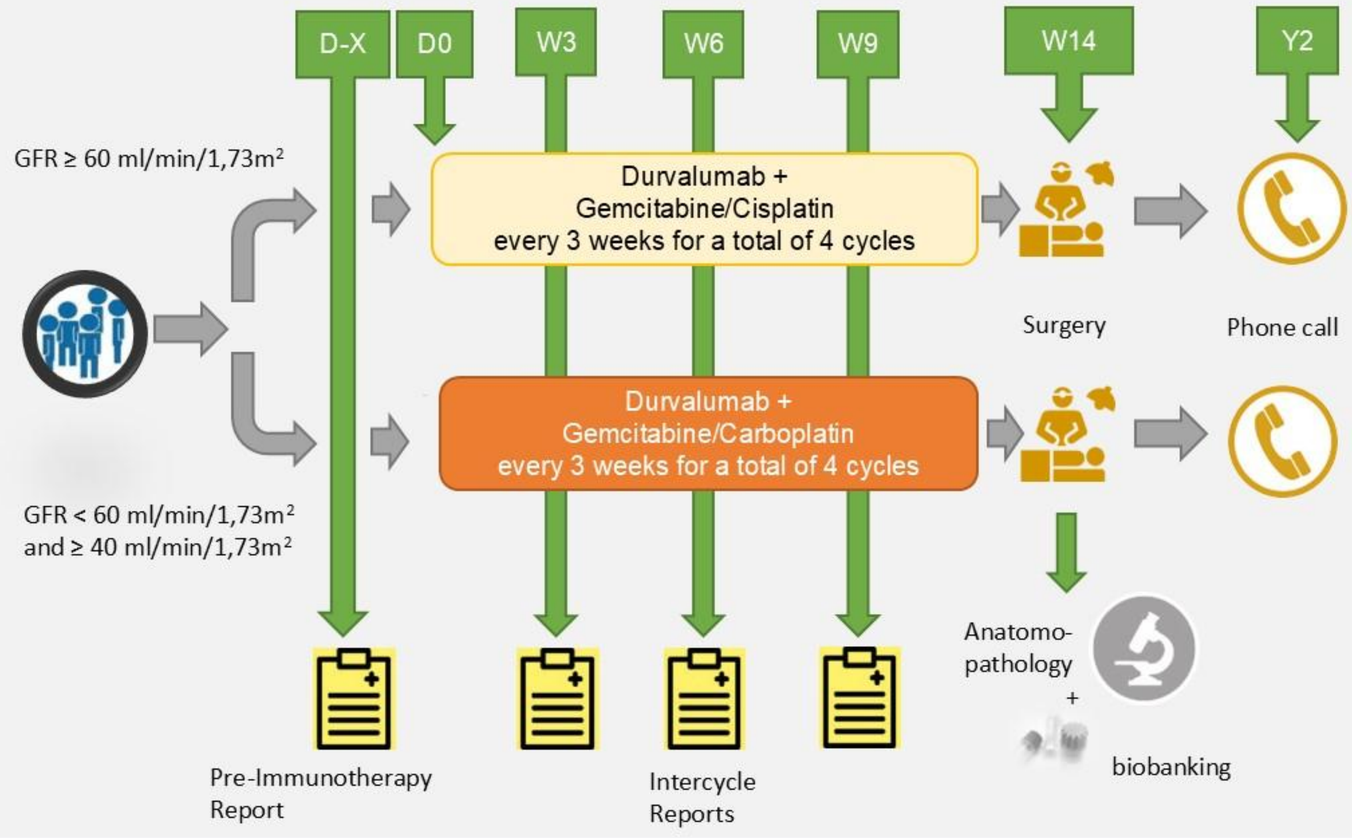
- iNDUCT – GETUG V 08 phase 2 clinical trial

Inclusions criteria:

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

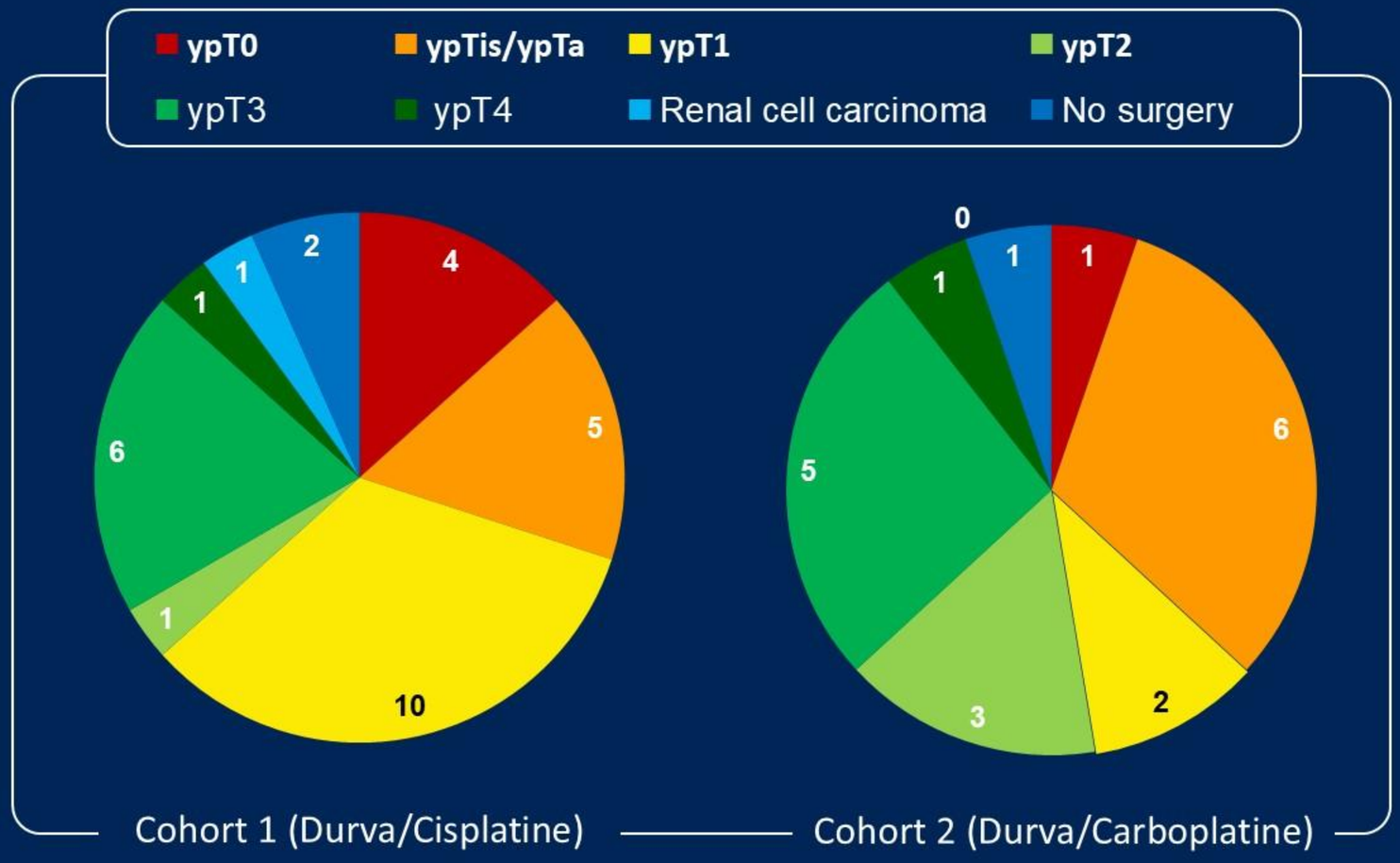
Primary endpoint:

- Rate of ypT0



Results

- Pathological response



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

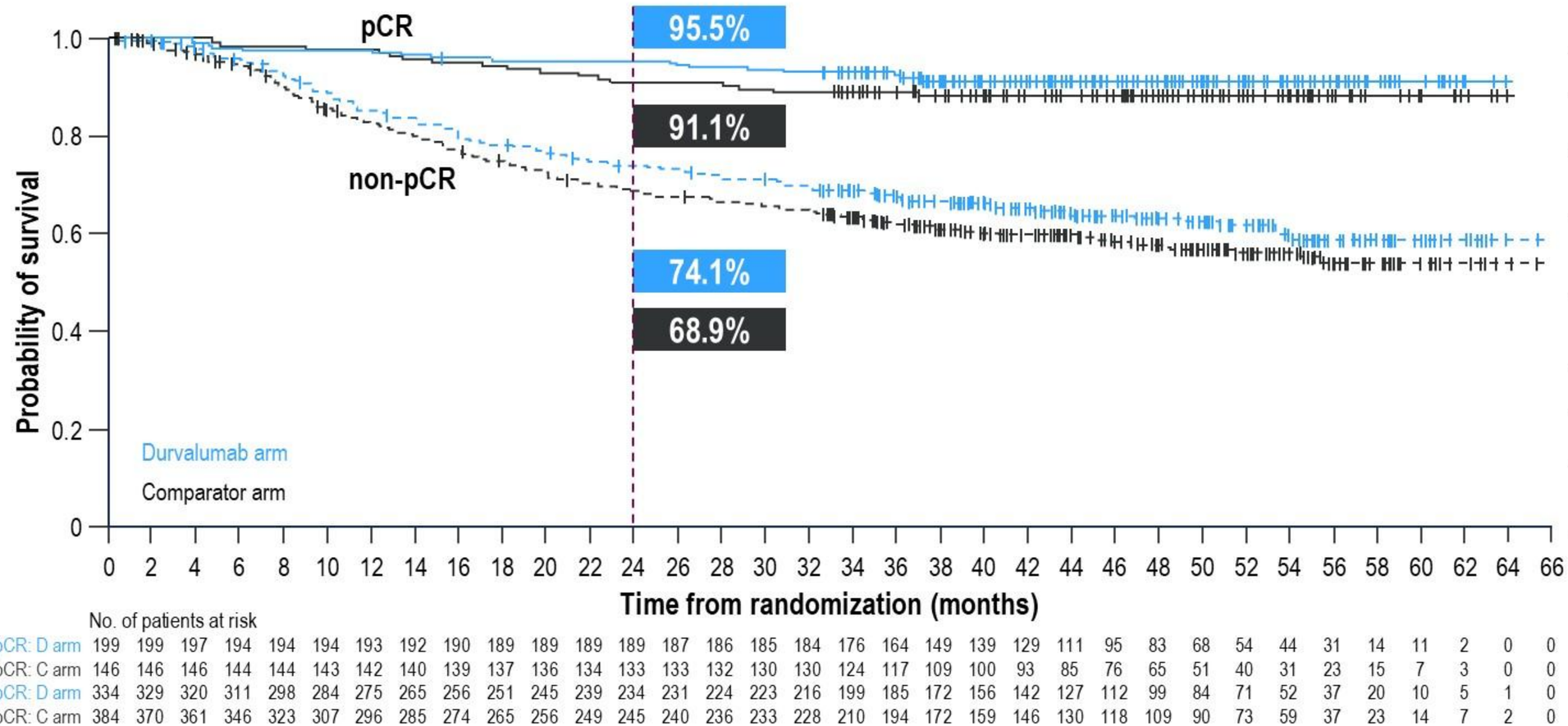
Key Points

- First completed neoadjuvant phase 2 clinical trial in UTUC combining immunotherapy and platinum-based chemotherapy
- This combination is safe and do not impact negatively surgery
- Encouraging results in terms of residual disease, mainly when cisplatin-based chemotherapy is used
- Will follow a phase 3 comparing chemotherapy alone vs chemotherapy + immunotherapy: **iNDUCT-3** *(grant PHRC-K 2024 & MERCK sponsor)*

¿Qué hacemos con los pacientes que hacen pCR?

NIAGARA: Overall Survival in pCR and Non-pCR Groups

Perioperative D + NAC improved OS in both groups



No. of patients at risk

pCR: D arm	199	199	197	194	194	194	193	192	190	189	189	189	189	187	186	185	184	176	164	149	139	129	111	95	83	68	54	44	31	14	11	2	0	0
pCR: C arm	146	146	146	144	144	143	142	140	139	137	136	134	133	133	132	130	130	124	117	109	100	93	85	76	65	51	40	31	23	15	7	3	0	0
non-pCR: D arm	334	329	320	311	298	284	275	265	256	251	245	239	234	231	224	223	216	199	185	172	156	142	127	112	99	84	71	52	37	20	10	5	1	0
non-pCR: C arm	384	370	361	346	323	307	296	285	274	265	256	249	245	240	236	233	228	210	194	172	159	146	130	118	109	90	73	59	37	23	14	7	2	0

pCR

	Durvalumab N=199	Comparator N=146
No. deaths, n (%)	17 (9)	17 (12)
Median OS (95% CI), months	NR (NR–NR)	NR (NR–NR)
OS HR (95% CI)	**0.72** (0.367–1.426)	

non-pCR

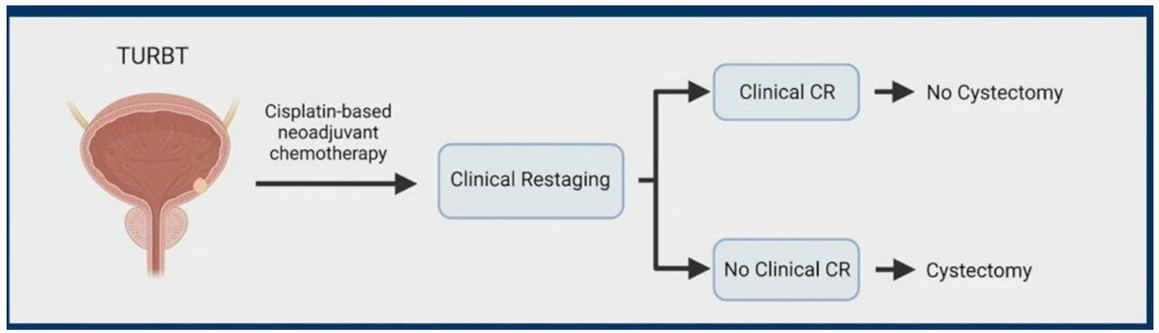
	Durvalumab N=334	Comparator N=384
No. deaths, n (%)	119 (36)	152 (40)
Median OS (95% CI), months	NR (NR–NR)	NR (53.9–NR)
OS HR (95% CI)	**0.84** (0.660–1.068)	

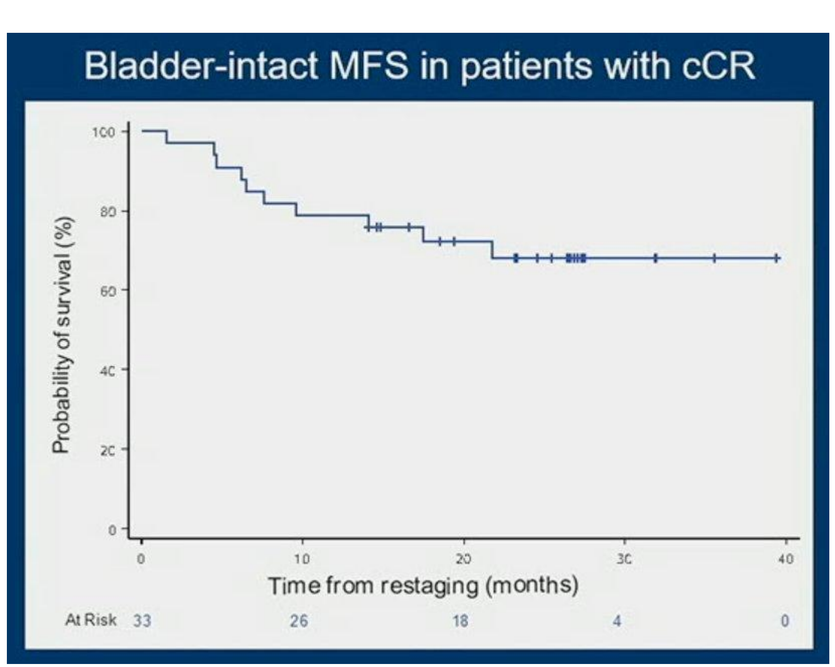
ITT

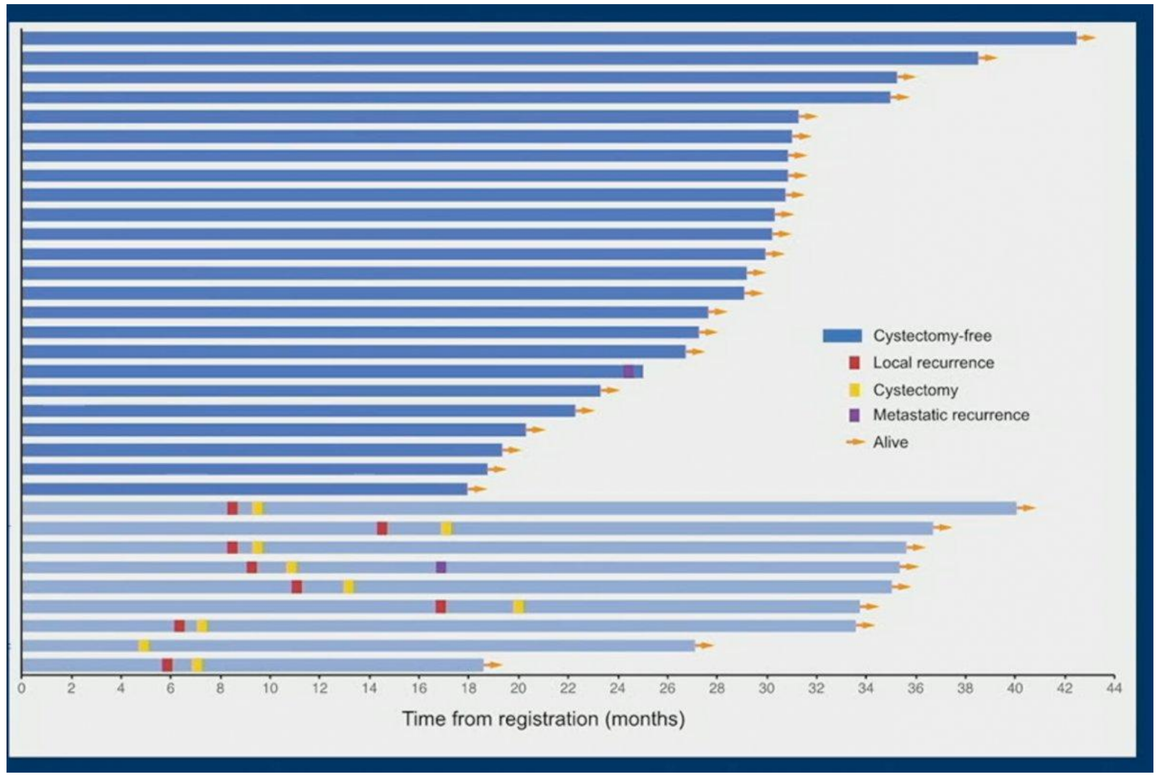
OS HR (95% CI)	**0.75** (0.59–0.93)

Data cutoff Apr 29, 2024. Exploratory post-hoc analysis. Tick marks indicate patients with censored data. C, comparator; D, durvalumab; HR, hazard ratio; ITT, intent-to treat; NAC, neoadjuvant chemotherapy; pCR, pathological complete response; OS, overall survival.

PRESENTED BY: Prof Matthew D. Galsky







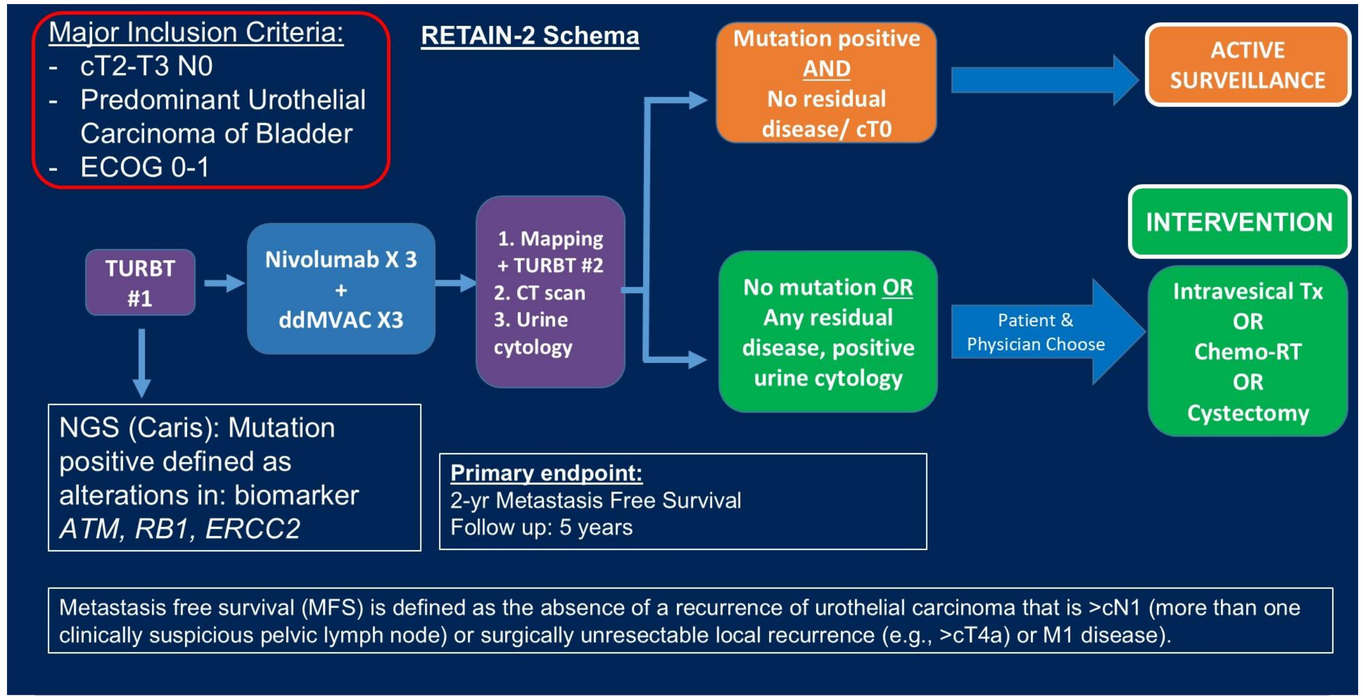
Galsky et al. JCO 2023

ASCO Genitourinary Cancers Symposium

A phase 2 trial of risk enabled therapy after neoadjuvant chemo-immunotherapy for muscle-invasive bladder cancer: RETAIN-2 Interim results

Pooja Ghatalia[1], Eric Ross[1], Matthew R. Zibelman[1], Fern Anari[1], Philip Abbosh[1], William J Tester[2], Patrick Mille[2], Tracy Rose[3], Suzanne Cole[4], James R. Mark[2], Rosalia Viterbo[1], Erika Jerome[1], Eric M. Horwitz[1], Mark Hallman[1], Andres Correa[1], Marc C. Smaldone[1], Robert Uzzo[1], David Chen[1], Alexander Kutikov[1], Elizabeth R. Plimack[1], Daniel M. Geynisman[1]

[1]*Fox Chase Cancer Center*
[2]*Thomas Jefferson University Hospital*
[3]*University of North Carolina- Chapel Hill*
[4]*UT Southwestern Medical Center*



ASCO Genitourinary Cancers Symposium #GU25 PRESENTED BY: Pooja Ghatalia, MD
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ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Results: Baseline Characteristics

Characteristic	N = 71	(%)
Age		
Median	69	
Range	68-86	
Gender		
Male	55	77%
Female	16	23%
ECOG PS		
0	57	80%
1	14	20%
Histology		
Pure UC	48	68%
UC/Variant histology	23	32%
Clinical Stage		
cT2	41	58%
cT3	30	42%
Mutation		
positive	31	44%
negative	40	56.3%

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Mutation		
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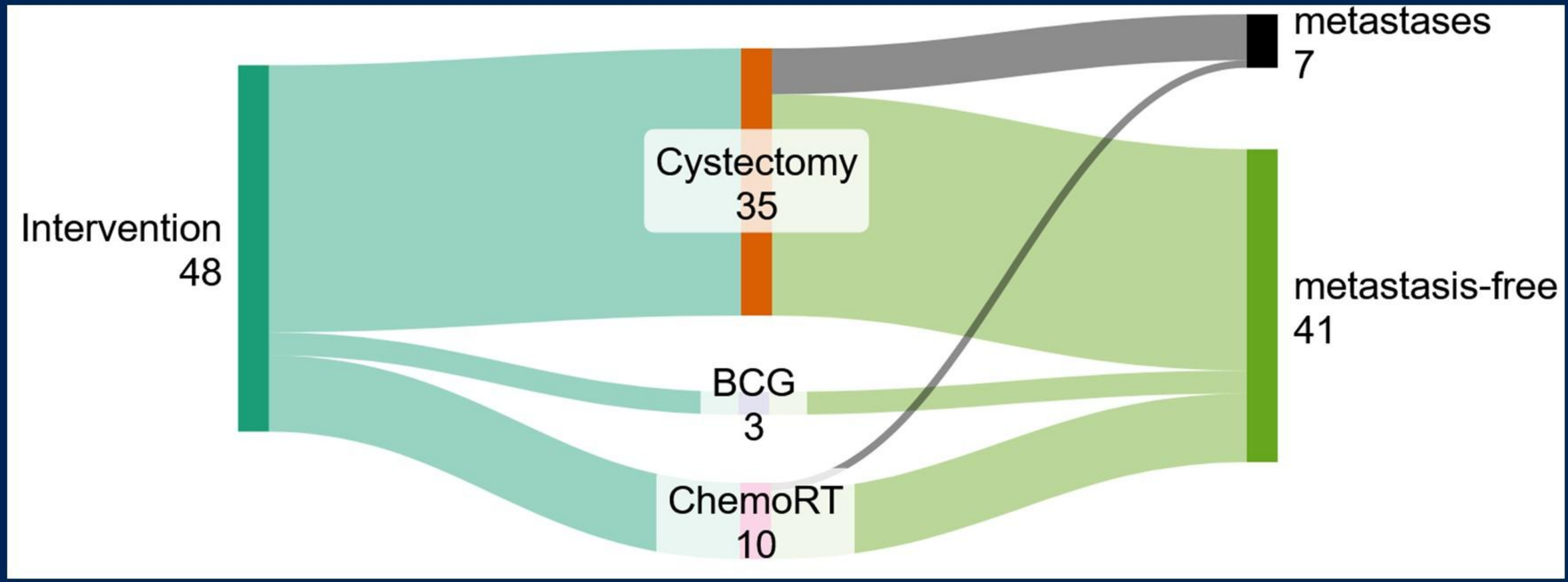
negative	40	56.3%

Safety

- Grade 3/4 TRAE in 19% patients
- 2 deaths with ddMVAC/nivolumab after completing 3 cycles
  - Multi-organ failure
  - AKI
- 1 death in chemoRT patient likely related to pneumonitis
  - Pneumonitis within 1-2 months of starting chemoRT (with 5FU/mitomycin)

Results: Intervention

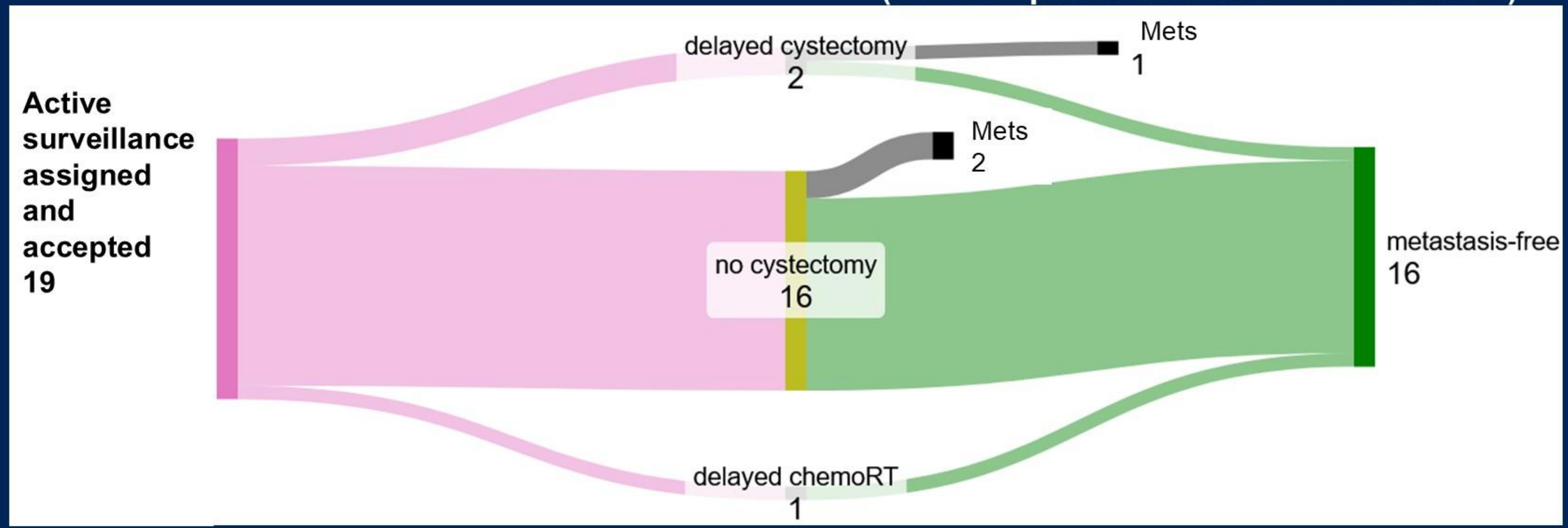
Median follow-up: 21.7 months
(25th-75th percentile: 13.6 – 30.3 months)



- **Among cystectomy pts, 40% are ypT0; 63% are ≤ ypT1**
- **Among intervention accepted pts, 85% are metastasis-free**

Results: Active Surveillance

Median follow-up: 21.7 months
(25th-75th percentile: 13.6 – 30.3 months)



Results: Active Surveillance

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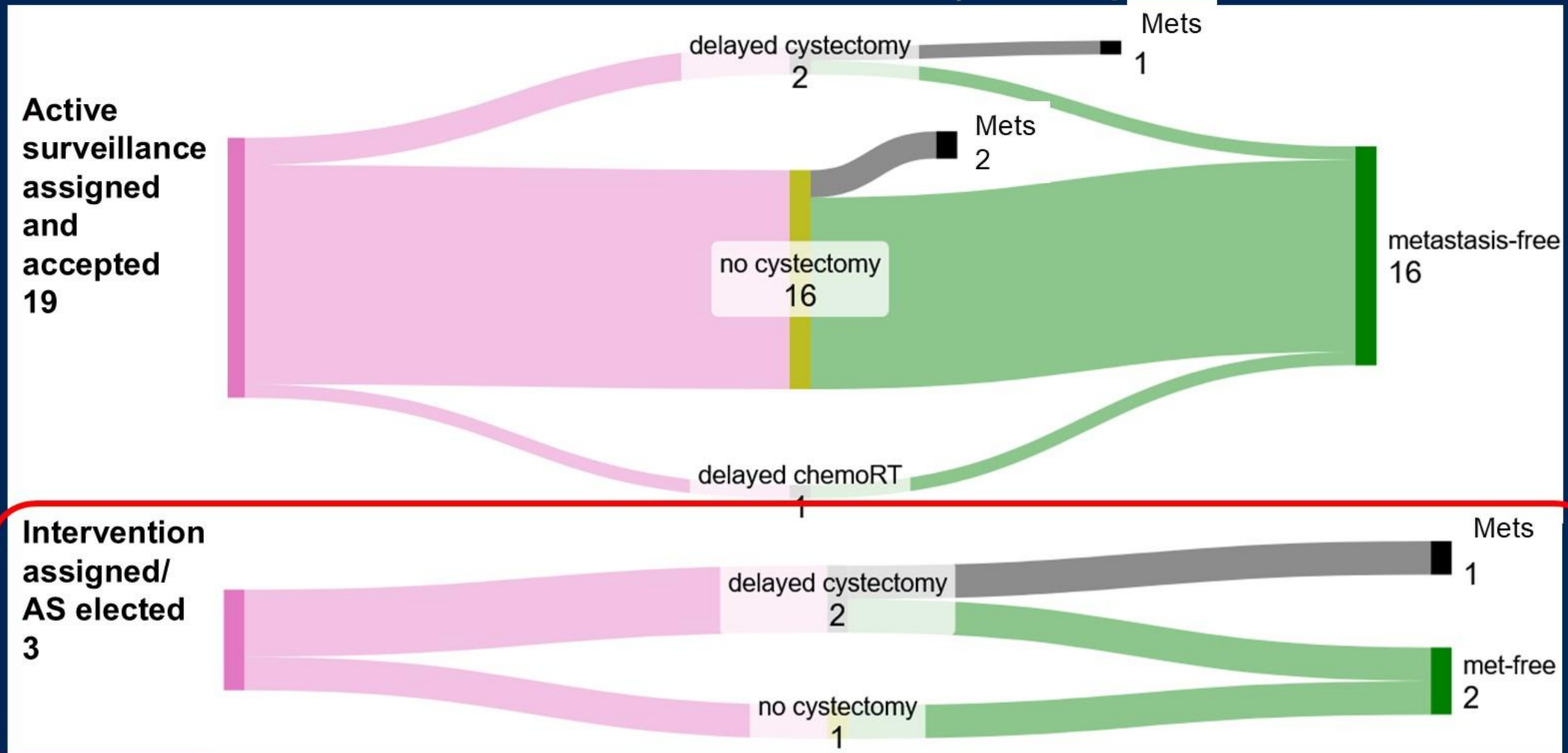
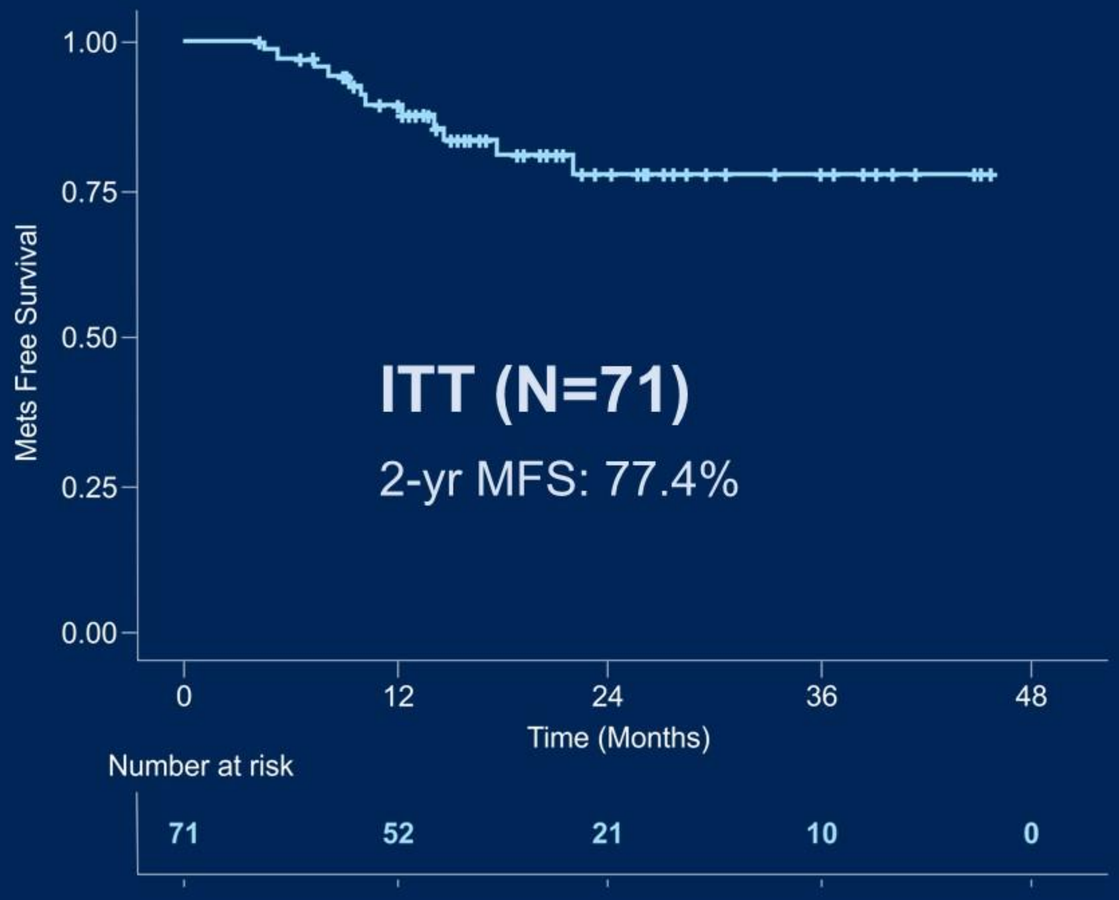


Among AS pts, 82% are metastases-free, 60% metastases-free and with an intact un-radiated bladder

Outcomes of patients on Active Surveillance

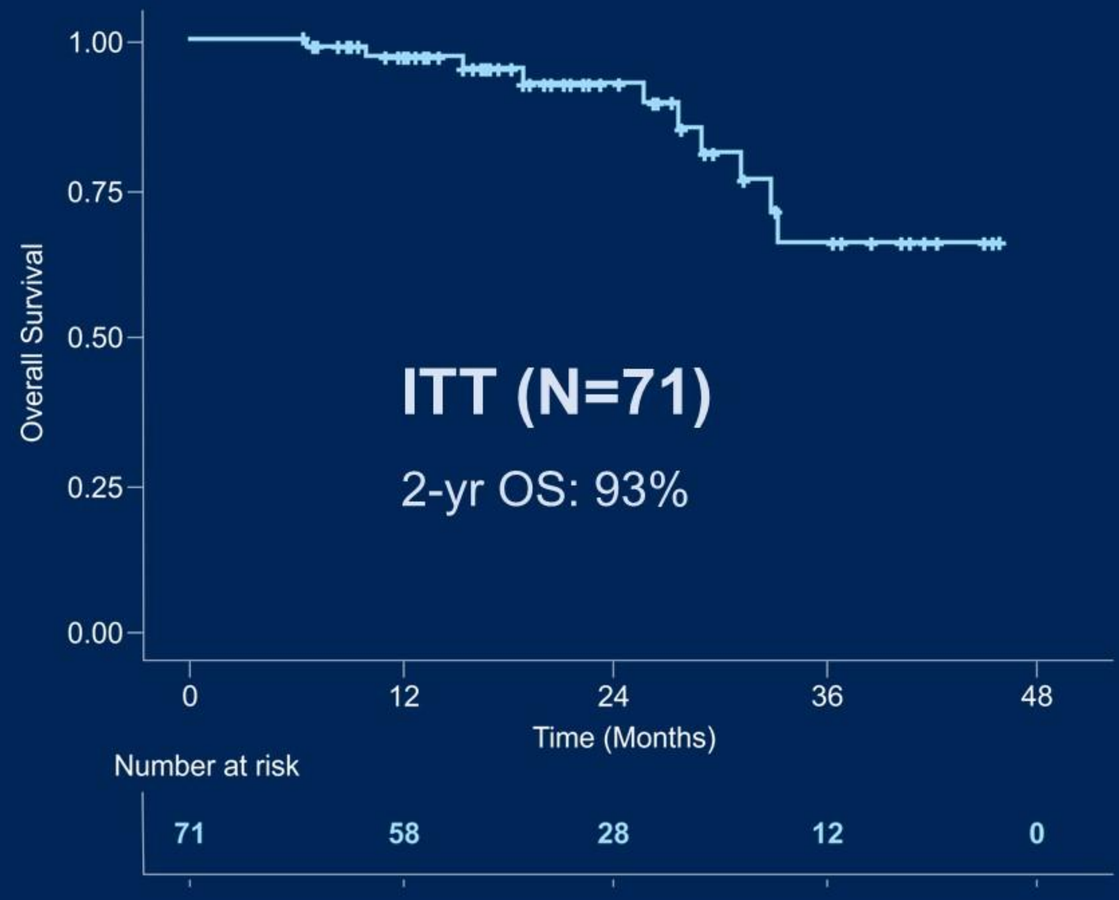
Median follow-up: 21.7 months (25th-75th percentile: 13.6 – 30.3 mo)

Interim Results: OS and MFS in ITT



ITT (N=71)

2-yr MFS: 77.4%



ITT (N=71)

2-yr OS: 93%

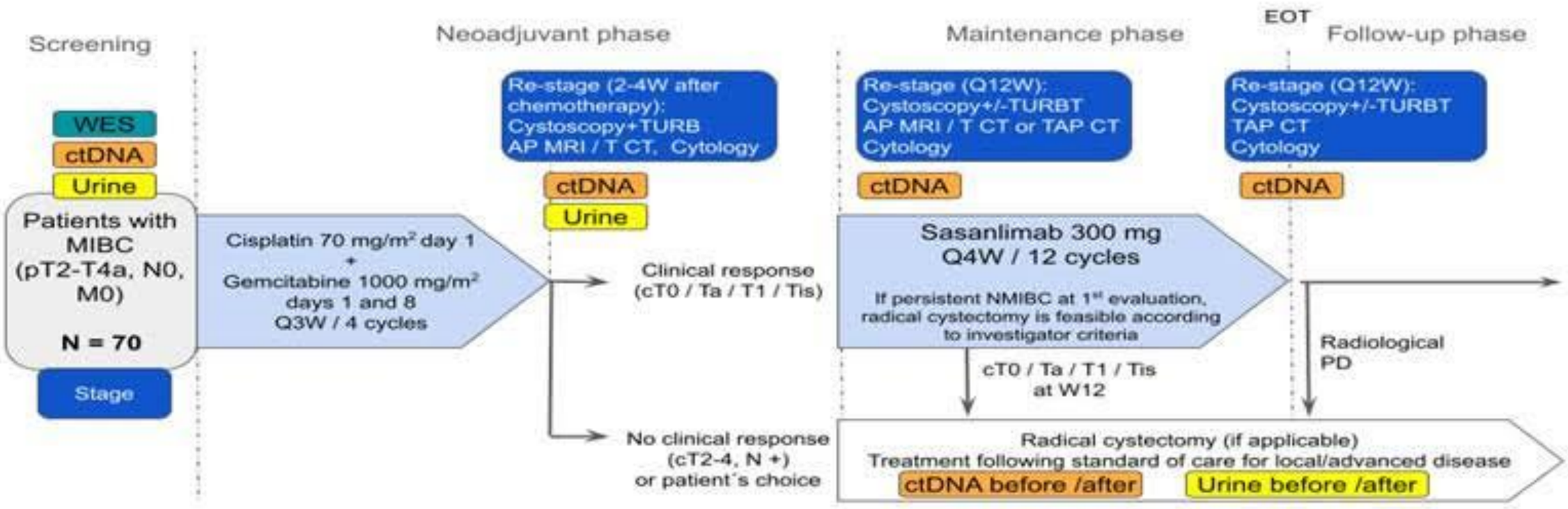
Median follow-up: 21.7 months (25th-75th percentile: 13.6 – 30.3 months)

Comparison of RETAIN-1 vs RETAIN-2 results

	RETAIN-1 (ddMVAC)	RETAIN-2 (ddMVAC + nivolumab)
Mutation pos	47%	44%
% active surveillance	36%	31.4%
Median duration of f/u	40 mo	22 mo
In AS – mets free	64%	82%
In cystectomy – ypT0	15%	40%
In ITT – ypT0 + cCR	27%	54%
In AS – no local recurrence	38%	68%
In AS – metastases-free with intact unradiated bladder	48%	60%

- At the time of interim analysis, ddMVAC/ nivolumab was associated with metastases-free rate of **84.2%** in ITT and **82%** in the AS arm
- **60%** AS pts are metastases-free and with an intact un-radiated bladder
- Compared to RETAIN-1 the ypT0 rate was higher at **40%** and rate of ypT0 + cCR of **54%** in RETAIN-2 suggesting additive benefit of adding nivolumab to ddMVAC

SASAN-SPARING



PI: Elena Sevillano & Guillermo de Velasco

Nuevos combos

ASCO Genitourinary Cancers Symposium

Abstract number: 665

Neoadjuvant treatment with disitamab vedotin plus perioperative toripalimab in patients with muscle-invasive bladder cancer (MIBC) with HER2 expression: updated efficacy and safety results from the phase II RC48-C017 trial

Xinan Sheng[1*], Cuijian Zhang[2], Peng Du[3], Kaiwei Yang[2], Yongpeng Ji[3], Li Zhou[1], Benkui Zou[4], Hang Huang[5], Yonghua Wang[6], Xue Bai[7], Dan Feng[7], Yong Yang[3], Jiasheng Bian[4], Zhixian Yu[5], Haitao Niu[6], Jianmin Fang[8], Zhisong He[2], **Jun Guo[1**]**

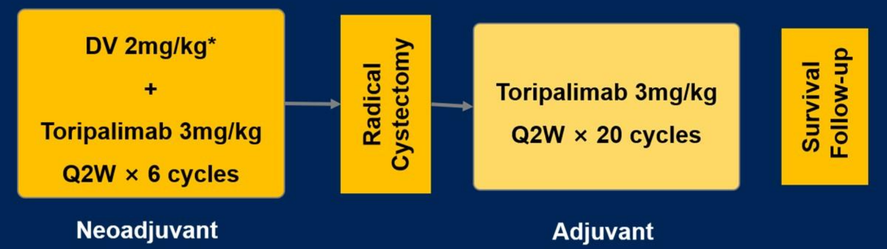
*presenting author **corresponding author

[1] Department of Genitourinary Oncology, Peking University Cancer Hospital & Institute, Beijing, China. [2] Department of Urology, Peking University First Hospital, Beijing, China. [3] Department of Urology, Peking University Cancer Hospital, Beijing, China. [4] Shandong Cancer Hospital and Institute, Beijing, China. [5] The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China. [6] The Affiliated Hospital of Qingdao University, Qingdao, China. [7] RemeGen Co., Ltd., Yantai, China. [8] School of Life Science and Technology, Tongji University, Shanghai, China.

Study design

Key Eligible Criteria:

- Histologically confirmed urothelial carcinoma;
- MIBC at stage of cT2-T4a, N0-1, and M0;
- Eligible for radical cystectomy (RC) + pelvic lymph node dissection (PLND);
- HER2 expression: IHC 1+, 2+, or 3+.



- **Primary endpoint:** Pathologic complete response (pCR, defined as ypT0N0) rate.
- **Secondary endpoints:** Pathological response rate (defined as ≤ypT1N0M0)[#]; event-free survival (EFS); overall survival (OS)^; adverse events.

The preliminary results of this trial showed promising efficacy and acceptable safety.[1] Herein, we present updated results including the pathological response, event-free survival, safety, and other outcomes with a longer follow-up (data cutoff: Dec 3, 2024).

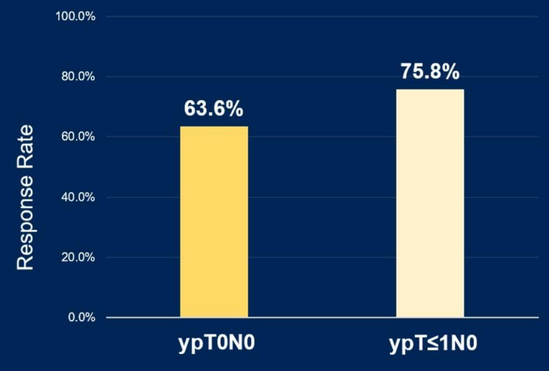
Pathological tumour response was assessed by the local pathologists and investigators based on the postoperative pathology. Radiological assessment was performed by the investigators per RECIST v1.1
*Equivalent to dose of 1.5 mg/kg using DV-based extinction coefficient outside of China. #Including complete or partial pathological response. ^OS data was not mature and not reported here. 1. Sheng, et al. J Clin Oncol. 2024, 42(16_suppl):4568.
Abbreviations: IHC=immunohistochemistry, Q2W=every two weeks, RECIST=Response Evaluation Criteria in Solid Tumors.

Pathological response

- Median time from end of neoadjuvant treatment to RC: 5.0 weeks (range: 2.6-13.1)

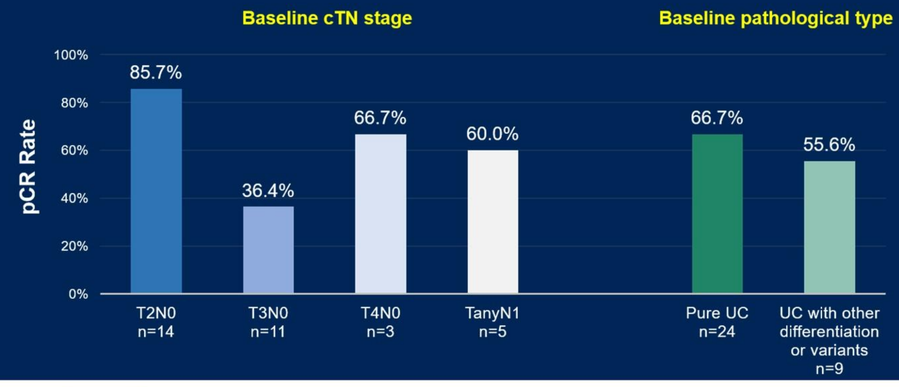
	Patients Received RC N=33
Pathological response	
pCR (ypT0N0), n (%)	**21 (63.6)**
95% CI	45.1-79.6
Pathological response (≤ypT1N0M0), n (%)	**25 (75.8)**
95% CI	57.7-88.9
Pathological staging, n (%)	
ypT0N0	21 (63.6)
ypT≤1N0	4 (12.1)
ypTisNx*	1 (3.0)
ypT2N0	4 (12.1)
ypT3N0	3 (9.1)
ypT4 or ypTanyN+	0

Pathological tumor response was assessed by the local pathologists based on the postoperative pathology.
*Pelvic lymph-node dissection was not performed.



Subgroup analysis

- The pCR rate for the T2N0 patients appeared higher than those for the other subgroups.
- The pCR rates were generally consistent between patients with pure UC and patients with UC with other differentiation or variants.



What is the efficacy of EV+CPI as Neoadjuvant or Adjuvant Therapy for MIBC?

Cisplatin-Eligible Muscle-Invasive Bladder Cancer

Cisplatin-Ineligible Muscle-Invasive Bladder Cancer

EV-304/ KEYNOTE-B15

N=784

R

5 EV cycles
13 Pembro cycle

- Enfortumab Vedotin + Pembrolizumab
- Cis/Gem

EV+P 4 cycles

- Enfortumab Vedotin + Pembrolizumab
- Observation

Radical cystectomy

Endpoint: EFS

VOLGA

N=830

R

EV+DT 3 cycles

- Enfortumab Vedotin + Durvalumab Tremelimumab

Durva+Treme 1 cycle
Durva 9 cycles

- Durvalumab + Tremelimumab

EV+D 3 cycles

- Enfortumab Vedotin + Durvalumab

Durva 9 cycles

- Durvalumab +

- No Therapy
- Observation

Radical cystectomy

Endpoint: pCR and EFS

EV-303/ KEYNOTE 905

N=847

R

EV+P 3 cycles

- Enfortumab Vedotin + Pembrolizumab

EV+P 6 cycles
Pembro 8 cycles

- Enfortumab Vedotin + Pembrolizumab

Pembro 3 cycles

- Pembrolizumab

Pembro 14 cycles

- Pembrolizumab

- No Therapy
- Observation

Radical cystectomy

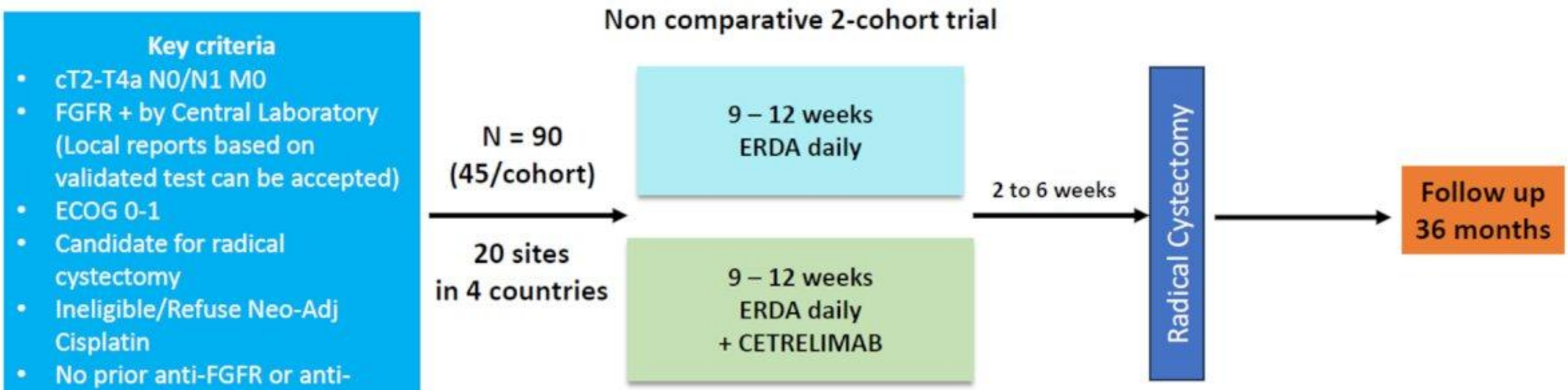
Endpoint: EFS

Presented by Andrea B. Apolo, MD
@apolo_andrea

5 preguntas para la discusión

- Conoceis vuestras metricas de neoadyuvancia?
- Neoadyuvancia con cisplatino/gemcitabina/durvalumab nuevo SOC xa todos? MVAC?
- ¿pCR es suficiente como endpoint? ¿Podemos evitar cistectomías?
- Personalización?

Neowin



Total Study Duration: 63 months from FPI to LPO
Estimated accrual: 24 months

Co-primary endpoints:
- pCR & Downstaging Rate (<ypT2)

Secondary endpoints:
- Any downstaging rate
- Event-free survival (EFS)
- Overall Survival (OS)
- Objective Response Rate (ORR) according to RECIST v1.1, after neo-adj. treatment
- Safety
- Rate of delay to surgery

Exploratory endpoint:
- Tumor response via PET-MRI
- Quality of Live (QoL)
- Biomarkers of response
- Changes in Biomarkers expression
- Genomic data in plasma, urine and feces