6th Genitourinary Cancer
Best of 2024
Panel Discussion

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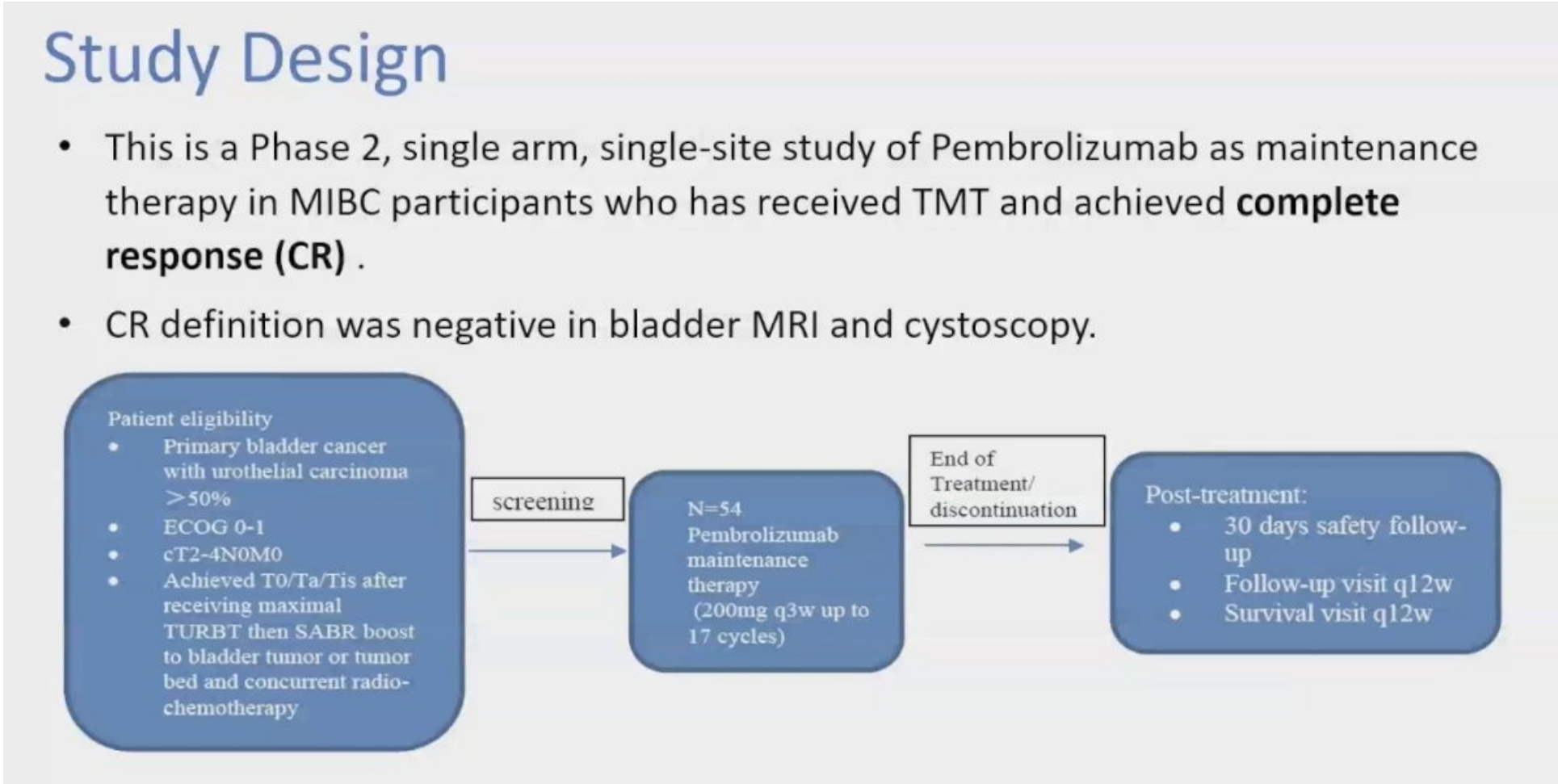
Pembrolizumab Monotherapy Following Tri-Modality Treatment for Selected Patients with Muscle-Invasive Bladder Cancer.ASTRO 2024. 220Volume 120, Issue 2, Supplement S74October 01, 2024 https://www.redjournal.org/issue/S0360-3016(24)X0011-5
Efficacy of neoadjuvant/induction (NAC) chemotherapy in nonmetastatic muscleinvasive bladder cancer treated with chemoradiotherapy (CRT): A systematic review and meta-analysis.
Long-term outcomes of neoadjuvant chemotherapy (NAC) before bladder-sparing chemoradiotherapy (CRT) for patients with nonmetastatic muscle-invasive bladder cancer (MIBC). Meghan Elizabeth Mahoney, N
ASCO GU25 Safety and efficacy of neoadjuvant immunotherapy with durvalumab (MEDI 4736) in combination with neoadjuvant chemotherapy (gemcitabine/cisplatin or carboplatin) in patients with operable high-risk upper tract urothelial carcinoma.
Improved Disease-Free Survival With Adjuvant Chemotherapy After Nephroureterectomy for Upper Tract Urothelial Cancer: Final Results of the POUT Trial. https://doi.org/10.1200/JCO.23.01659
Identification of bladder cancer patients that could benefit from early post-cystectomy immunotherapy based on serial circulating tumour DNA (ctDNA) testing: Preliminary results from the TOMBOLA trial
Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer
EV-302: Exploratory analysis of nectin-4 expression and response to 1L enfortumab vedotin (EV) + pembrolizumab (P) in previously untreated locally advanced or metastatic urothelial cancer (la/mUC)

Panelists

- Dr. M V Chandrakanth
- Dr. Shantanu Pendse
- Dr. Sumit Basu
- Dr. Vasanthapriya S
- Dr. Srigadha Vivek Kumar
- Dr. Arnav Tongaonkar

1. Pembrolizumab Monotherapy Following Tri-Modality Treatment for Selected Patients with Muscle-Invasive Bladder Cancer.ASTRO 2024. 220Volume 120, Issue 2, Supplement S74October 01, 2024



Results – Baseline Characteristics

- At cutoff date of 7th Mar, 2024, 46 out of 54 patients with MIBC were enrolled.

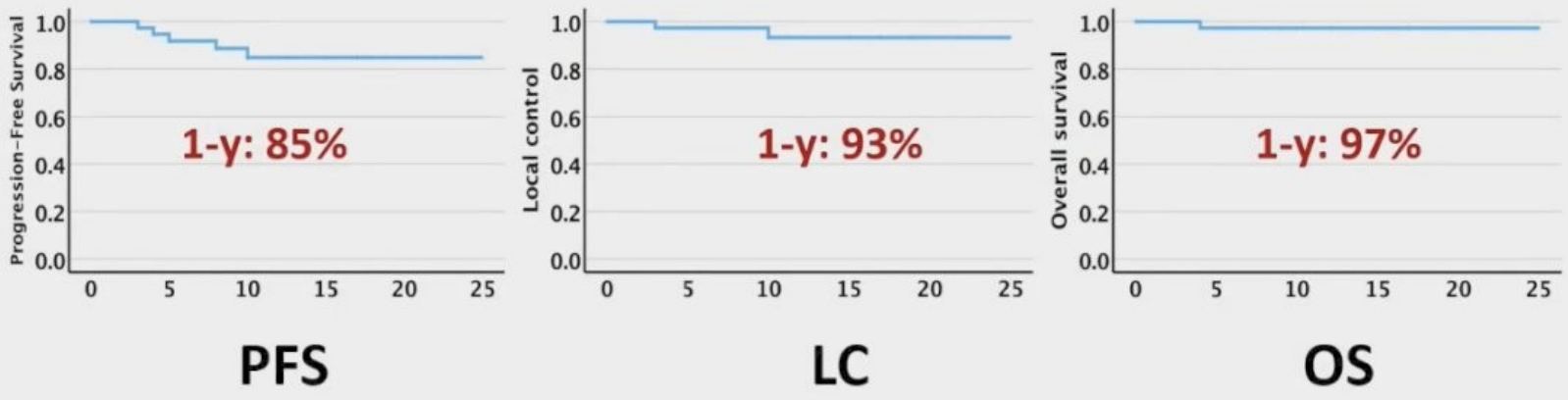
Characteristic, n (%)	No. of patients (%)
Age, median (range)	69 years, (34, 86)
Gender	
Male	36 (78%)
Female	10 (22%)
Clinical T staging	
T2	39 (85%)
T3	7 (15%)
T4	0
TURBT	
Complete	18 (39%)
Incomplete	28 (61%)

Characteristic, n (%)	No. of patients (%)
Concurrent chemotherapy	
Yes	44 (96%)
No	2 (4%)
Neo-adjuvant chemotherapy	
Yes	9 (20%)
No	37 (80%)
Hydronephrosis	
Yes	2 (4%)
No	44 (96%)

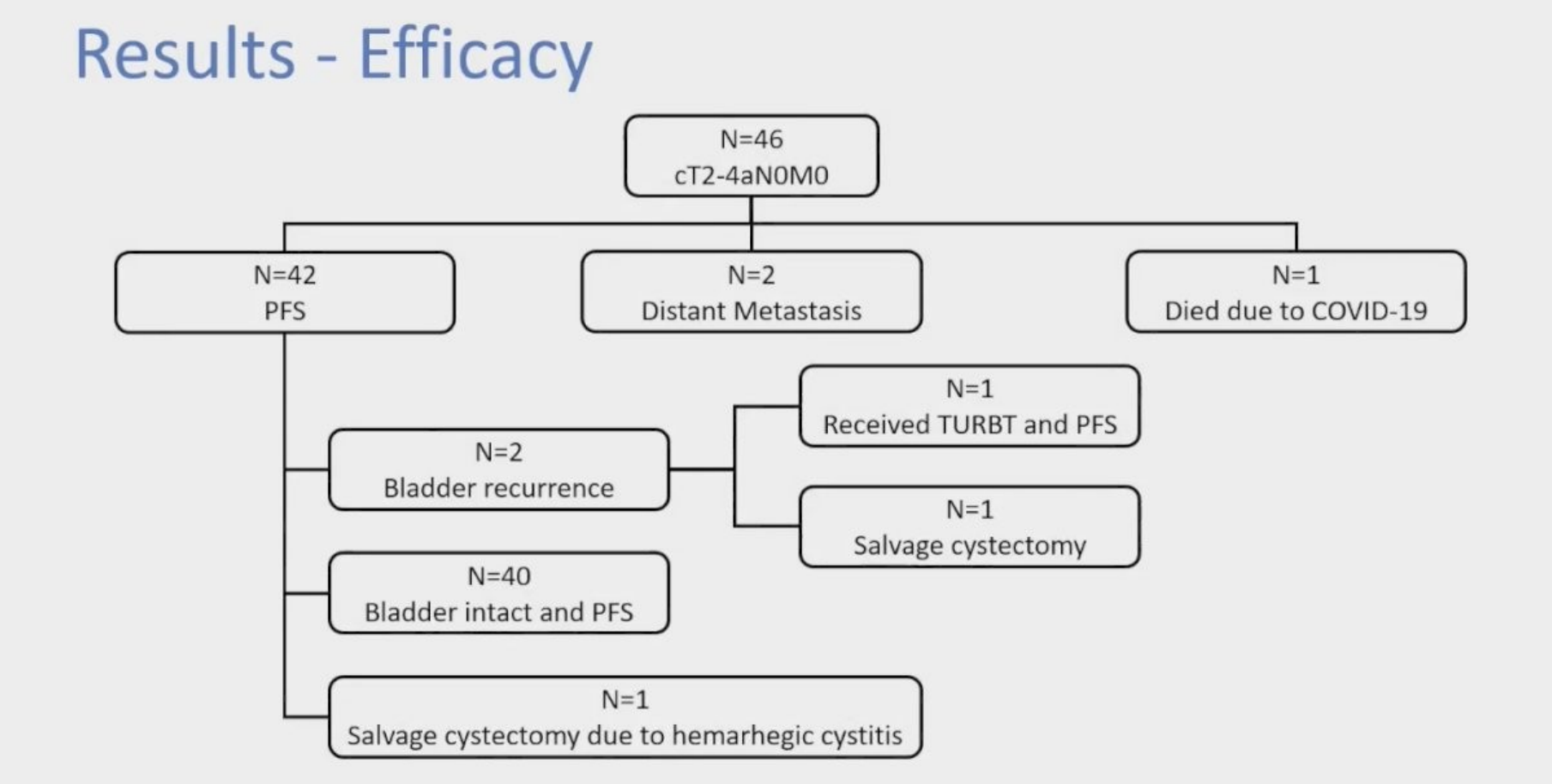
The estimated 1-year PFS, overall survival and local control rate was 85%, 97% and 93

Results - Efficacy

- The median follow-up was 10 months
- Ten participants completed Pembrolizumab for 17 cycles.
- The estimated 1-year Progression-free survival, local control and overall survival was 85%, 93% and 97%, respectively.



Results


Results - Efficacy
N=46
cT2-4aN0M0
N=42
PFS
N=2
Distant Metastasis
N=1
Died due to COVID-19
N=2
Bladder recurrence
N=1
Received TURBT and PFS
N=1
Salvage cystectomy
N=40
Bladder intact and PFS
N=1
Salvage cystectomy due to hemarhegic cystitis

Efficacy of Neoadjuvant/Induction (NAC) Chemotherapy in Nonmetastatic Muscle-Invasive Bladder Cancer Treated with Chemoradiotherapy (CRT): A Systematic Review and Meta-Analysis

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Background

- Neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) is the established standard of care for nonmetastatic muscle-invasive bladder cancer (MIBC).
- Chemoradiotherapy (CRT) is an acceptable treatment alternative for MIBC.
- While NAC has proven beneficial before RC, its value prior to CRT remains uncertain.
- **This systematic review and meta-analysis aimed to evaluate the impact of NAC on outcomes of patients undergoing CRT for bladder preservation.**

Methods

- PROSPERO registration (CRD42024590258).
- Systematic search of PubMed, Embase and Cochrane databases.
- **Inclusion criteria: (i) studies comparing NAC plus CRT versus CRT alone in MIBC; (ii) both randomized controlled trials (RCTs) and observational studies.**
- Exclusion criteria: Studies with overlapping populations or non-English publications.
- Statistical analyses were performed using random-effects models in Review Manager 5.4.1.
- Heterogeneity was assessed with I^2 statistics.

Conclusion

Our analysis found no survival benefit from adding NAC to CRT in patients with MIBC. However, the quality of the evidence is very low, largely due to the retrospective nature of the data. Further randomized clinical trials are needed to clarify the role of NAC in bladder preservation strategies.

Results

- **3.354 patients from 4 observational studies.**
- 656 (19.5%) patients received NAC with platinum-based chemotherapy.
- Follow-up time ranged from 15.9 to 74.4 months.
- **No significant difference in overall survival (OS) (HR = 0.99, 95% CI 0.87–1.12, p = 0.87, I^2 = 0%). Figure 1.**
- **No difference for disease-free survival (DFS) (HR = 1.10, 95% CI 0.76–1.60, p = 0.61, I^2 = 0%). Figure 2.**
- **High risk of bias by ROBINS-I tool.**
- **Very low certainty of the evidence by GRADE.**

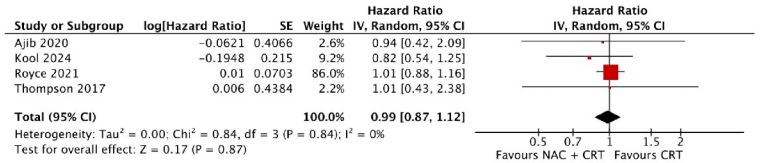


Figure 1: Forest plot for OS

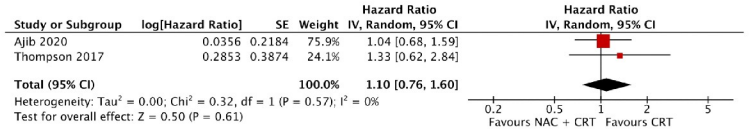


Figure 2: Forest plot for DFS

2. Efficacy of neoadjuvant/induction (NAC) chemotherapy in nonmetastatic muscleinvasive bladder cancer treated with chemoradiotherapy (CRT): A systematic review and meta-analysis.

Background: Neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) is the established standard for nonmetastatic muscle-invasive bladder cancer (MIBC). However, bladder-sparing approaches using chemoradiotherapy (CRT) offer comparable outcomes. While NAC has proven beneficial before RC, its value prior to CRT remains uncertain. This systematic review and meta-analysis aimed to evaluate the impact of NAC on outcomes in patients undergoing CRT for bladder preservation. Methods: A comprehensive search of PubMed, Embase, and Cochrane databases was conducted to identify studies comparing NAC plus CRT versus CRT alone in MIBC. Both randomized controlled trials (RCTs) and observational studies were eligible. Studies with overlapping populations or non-English publications were excluded. Heterogeneity was assessed with I2 statistics, and all analyses

were performed using random-effects models in Review Manager 5.4.1. The study was registered in PROSPERO (CRD42024590258). Results: Four observational studies, encompassing

Results Critic

3,354 patients, were included as no RCTs met the inclusion criteria. NAC was administered to 656 patients (19.5%). Median follow-up ranged from 15.9 to 74.4 months. All patients in the NAC group received platinum-based chemotherapy (MVAC, ddMVAC, GC, or CMV). Concurrent CRT regimens included cisplatin, gemcitabine, or mitomycin with radiotherapy. No significant difference in overall survival was observed between NAC + CRT and CRT alone (HR = 0.99, 95% CI 0.87–1.13, p = 0.89, I2 = 0%). Disease-free survival data were available from two studies, showing no significant difference (HR = 1.07, 95% CI 0.57–2.01, p = 0.82, I2 = 39%). **All included studies had a serious risk of bias, mainly due to confounding and selection bias, as assessed by the ROBINS-I tool**. The overall certainty of the evidence was rated as very low using the GRADE framework. Conclusions: Our analysis found no survival benefit from adding NAC to CRT in patients with MIBC. However, **the quality of the evidence is very low, largely due to the retrospective nature of the data**. Further randomized clinical trials are needed to clarify the role of NAC in bladder preservation strategies. Research Sponsor: None

Abs#819

Long-term Outcomes of Neoadjuvant Chemotherapy (NAC) before Bladder-Sparing Chemoradiotherapy (CRT) for Patients with Nonmetastatic, Muscle-invasive Bladder Cancer (MIBC)

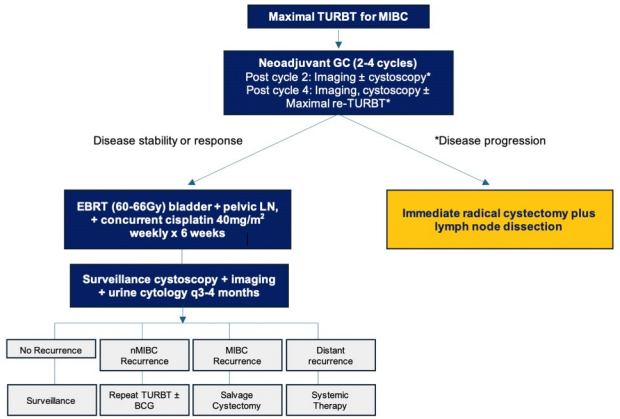
Meghan E. Mahoney[1], Nely Díaz-Mejía[1], Eshetu Atenafu[2], Peter Chung[3], Alexandre Zlotta[4], Nimira Alimohamed[5], Neil Fleshner[4], Gregory Lo[6], Pawel Zalewski[6], Girish Kulkarni[4], Alejandro Berlin[3], Robert Bristow[3], Di Maria Jiang[1], Srikala S. Sridhar[1]
Division of Medical Oncology[1], Department of Biostatistics[2], Division of Radiation Oncology[3], Division of Urology[4],Princess Margaret Cancer Center, Toronto, ON; Arthur Child Cancer Centre, Calgary, AB[5], Durham Regional Cancer Centre, Oshawa, ON[6]

Background

- Neoadjuvant, cisplatin-based combination chemotherapy followed by concurrent chemoradiation is an emerging approach in carefully selected MIBC patients who opt for bladder-sparing.
- Long-term data on its efficacy & tolerability is lacking.
- We evaluated long-term outcomes in patients with MIBC treated with this approach.

Methods

- A retrospective chart review was performed on 56 patients treated with NAC+CRT, 2008-2017 at the Princess Margaret and Durham Regional Cancer Centers.
- Primary outcomes: 5-year disease free survival (DFS), bladder intact disease-free survival (BI-DFS) & overall survival (OS).



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NAC + Concurrent Chemoradiotherapy is a safe & effective bladder-sparing approach with encouraging long-term outcomes in carefully selected patients with MIBC

Patient & Treatment Characteristics

Table 1 - Demographics	
Age (years)	72 [45-87]
Male	44 (79)
Smoking	
Never smoker	14 (25)
Current smoker	11 (20)
Ex smoker	31 (55)
ECOG PS	
0	35 (66)
1	17 (32)
2	1 (2)
CrCl (mL/min)	59 [18-137]
Hydronephrosis	14 (25)
Tumor size (cm)	4.1 [1.2-12]
Clinical Stage	
II	33 (59)
III	19 (34)
IV	4 (7)
Histology	
Pure Urothelial Carcinoma (UC)	35 (63)
UC with squamous	13 (23)
UC with plasmacytoid variant	7 (13)
UC with micropapillary variant	1 (2)
Carcinoma-in-Situ	17 (30)
LVI	10 (18)

Table 2 - Treatment	
TURBT	
Initial Max TURBT	38 (68)
NAC	
NAC Regimen	
GC q 21 days	19 (34)
GC split q 21 days	32 (57)
Other	5 (9)
No. of NAC cycles	
2	3 (5)
3	18 (32)
4	35 (63)
Completed planned NAC	53 (95)
NAC Grade 3/4 Toxicity	12 (21)
Neutropenia	6 (11)
Thrombocytopenia	2 (4)
Infection	2 (4)
Anemia	1 (2)
Other	1 (2)
NAC Dose Reduction	31 (55)
Median dose ↓ (%)	25 [15- 50]
NAC Dose Delay	22 (39)
Concurrent Chemoradiation	
Reason for TMT	
Patient preference	33 (59)
Comorbidities RC	20 (36)
Both	2 (4)
Planned RT Dose	
< 60 Gy	5 (9)
>= 60 Gy	51 (91)
Completed Planned RT	56 (100)
Completed ≥ 60% planned concurrent chemotherapy	49 (86)

Table 3: Recurrences	
Total Recurrences	23 (41)
Local recurrence	11 (20)
Required Cystectomy	8 (14)
Distant recurrence	12 (21)

Abbreviations: GC=gemcitabine + cisplatin, TURBT = transurethral resection of bladder tumor, TMT= trimodality therapy

Results

- Median follow up was 96 months (10-149).
- Median DFS was 56.6 months & 5-year DFS was 49.2%.
- Median BI-DFS was 45.6 months & 5-year BI-DFS was 47.6%.
- Median OS was 105.0 months with a 5-year OS rate of 62.2%.

Figure 1- KM Curve for DFS

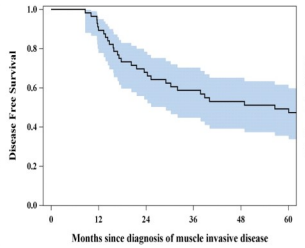


Figure 2 - KM Curve for BI- DFS

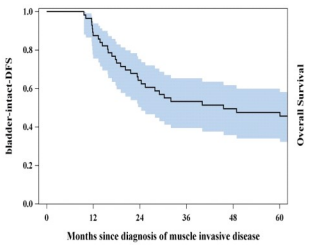
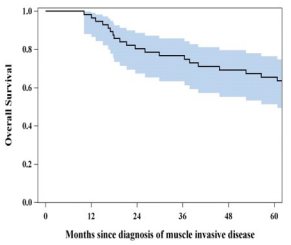


Figure 3 - KM Curve for OS



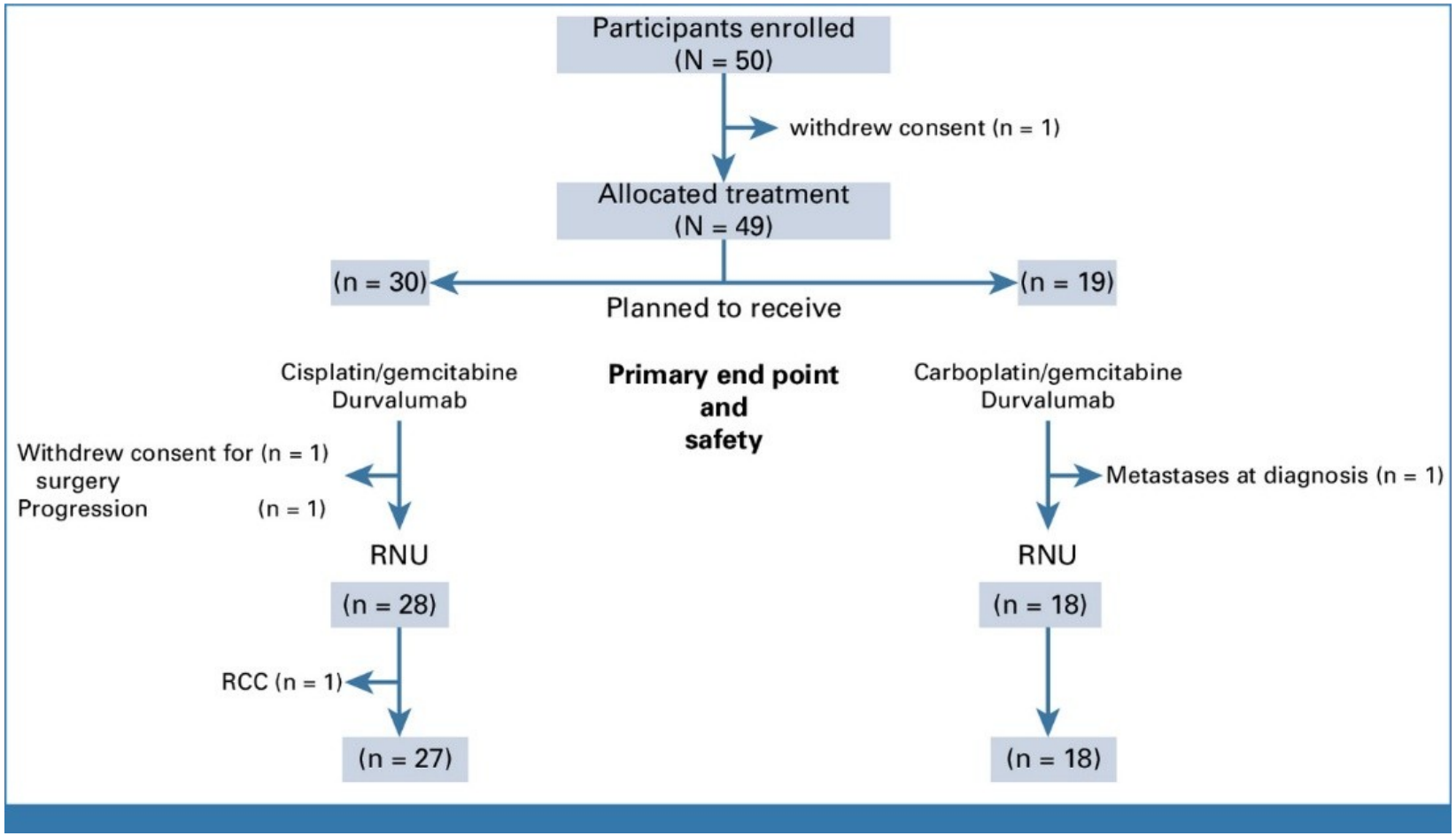
Abbreviations: KM= + Kaplan Meier

Acknowledgements

Preliminary Publication: *Jiang, D.M, Clinical Genitourinary Cancer 2019*

UHN Princess Margaret Cancer Centre · University of Toronto · ASCO Genitourinary Cancers Symposium · #GU25

4. ASCO GU25 Safety and efficacy of neoadjuvant immunotherapy with durvalumab (MEDI 4736) in combination with neoadjuvant chemotherapy (gemcitabine/cisplatin or carboplatin) in patients with operable high-risk upper tract urothelial carcinoma. Nadine Houede et al



	Any grade	Grade 3	Grade 4
Adverse events of any cause			
Hematologic TRAEs • Anemia • Neutropenia • Thrombopenia	67 • 22 (45%) • 10 (20%) • 5 (10%)	 • 4 (8%) • 4 (8%) • 1 (2%)	 • 0 • 1 (2%) • 1 (2%)
Asthenia	29 (59%)	2 (4%)	0
Creatinine increase	23 (47%)	2 (4%)	0
Nausea	26 (53%)	2 (4%)	0
Diarrhea	8 (16%)	1 (2%)	0
Tinnitus	6 (12%)	0	0
Mucositis	6 (12%)	1 (2%)	0
Urinary infection	5 (10%)	0	0
Transaminase increase	4 (8%)	0	0
Neuropathy	3 (6%)	0	0
Infection	3 (6%)	1 (2%)	0
Lipase increase	2 (4%)	1 (2%)	0
Myocardial infarction	2 (4%)	2 (4%)	0
Unstable angina	1 (2%)	1 (2%)	0
Immuno-related adverse events			
Pruritus	3 (6%)	0	0
Decrease cortisol level	1 (2%)	0	
Rash	1 (2%)	0	

4. Safety and efficacy of neoadjuvant immunotherapy with durvalumab (MEDI 4736) in combination with neoadjuvant chemotherapy (gemcitabine/cisplatin or carboplatin) in patients with operable high-risk upper tract urothelial carcinoma Nadine, Houede et al

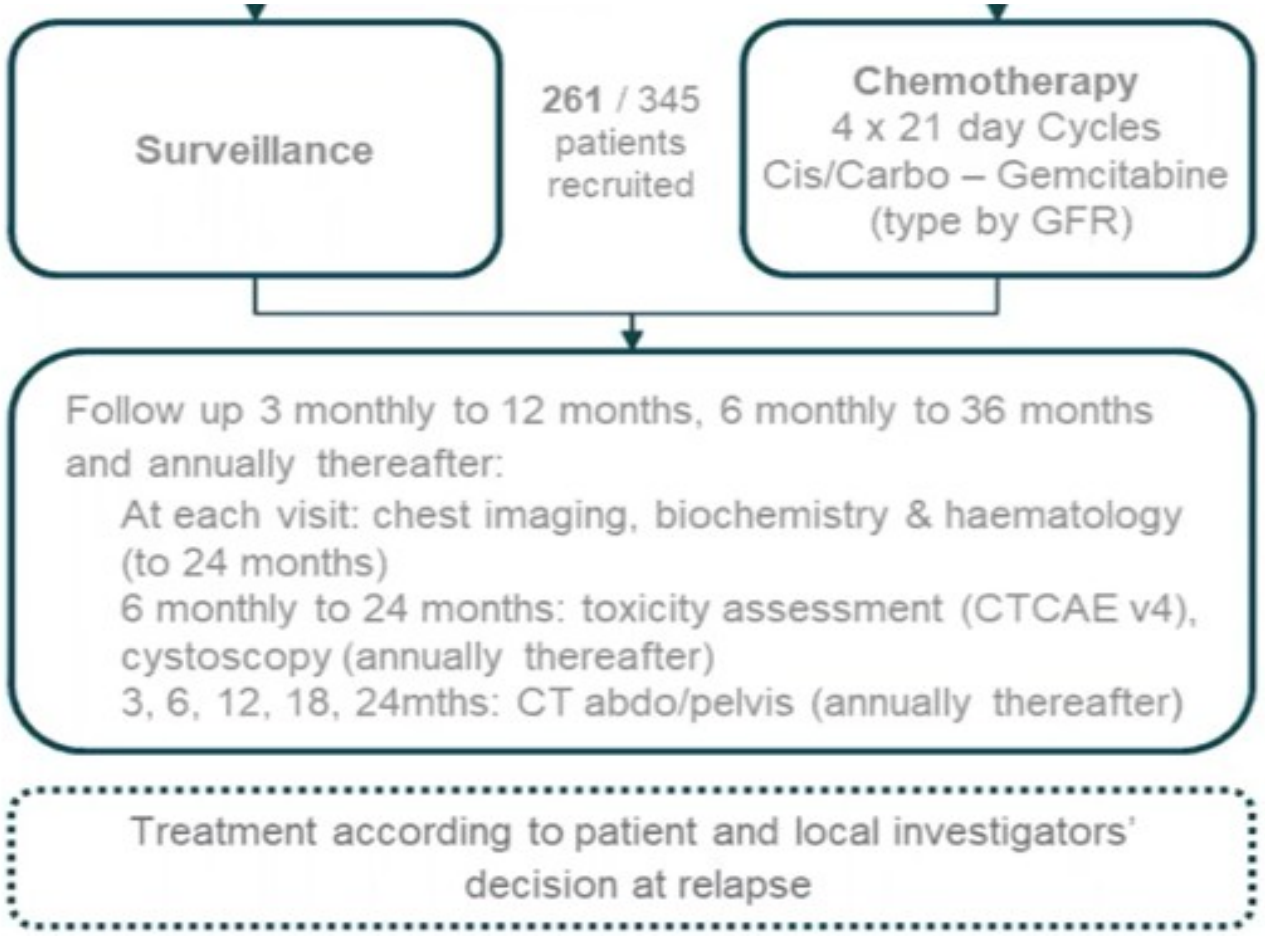
- **20/31 (65%)** patients with non infiltrative residual tumor
- In cohort 2 : **9/19 (42%)** patients
- Secondary endpoint was safety, no immunotherapy-mediated AE was observed, 2 patients had Grade 3 neutropenia, 1 grade 4, 1 patient had grade 3 thrombopenia and 1 grade 3 anemia.
- Conclusions: Combination of durvalumab with platin-based chemotherapy, especially cisplatin, showed promising activity n UTUC,
- With the occurrence of complete responses and a high rate of non-infiltrative residual tumor. Safety profile was secure without increasing surgical risk.

POUT trial
Alison Jane Birtle et al

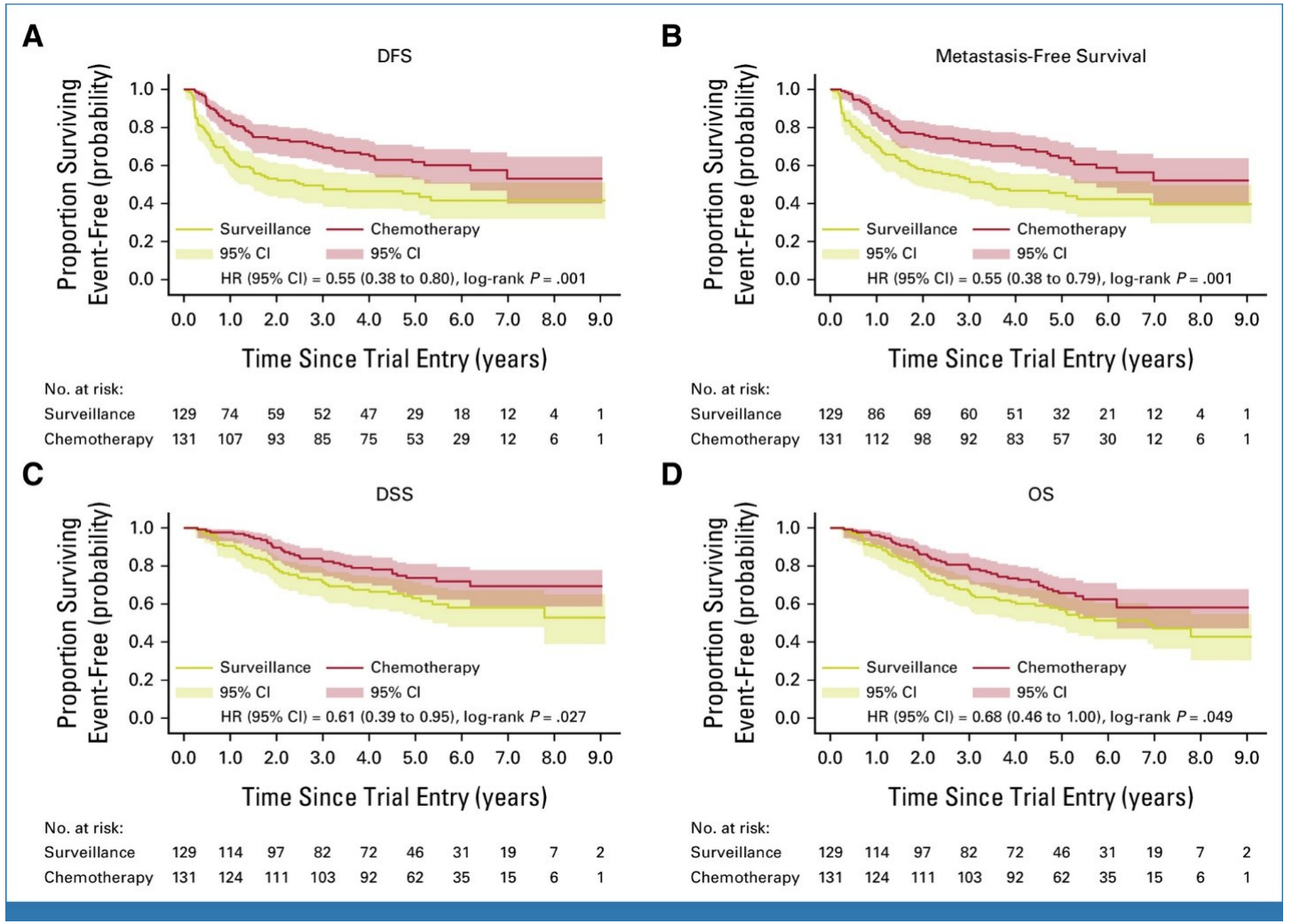
phase III, randomized, open-label trial,

including 261 patients with muscle-invasive orlymph node–positive, nonmetastatic upper tract urothelial cancer (UTUC) randomly assigned after radical nephroureterectomy

to platinum-based chemotherapy (132) or surveillance (129).



5. Improved Disease-Free Survival With Adjuvant Chemotherapy After Nephroureterectomy for Upper Tract Urothelial Cancer: Final Results of the POUT Trial



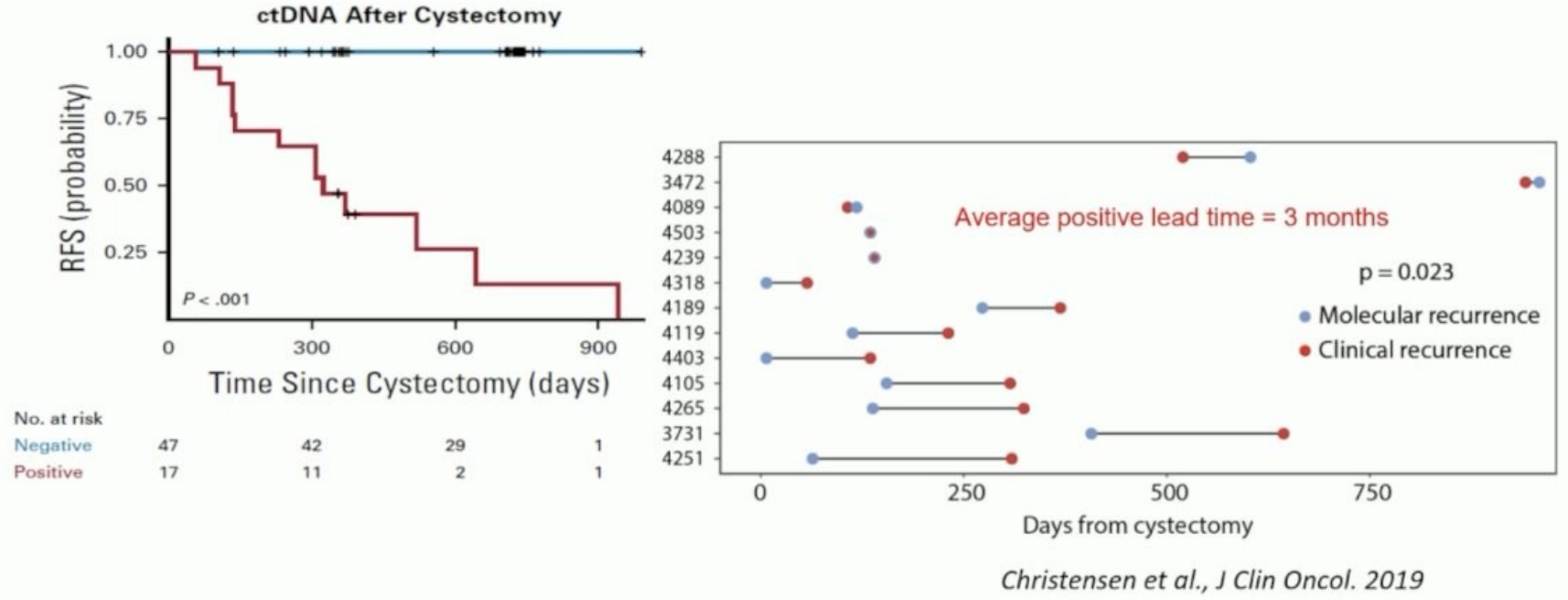
6. Identification of bladder cancer patients that could benefit from early post-cystectomy immunotherapy based on serial circulating tumour DNA (ctDNA) testing: Preliminary results from the TOMBOLA trial

- TOMBOLA was a national, non-randomized ctDNA-based intervention study conducted at 5 centers in Denmark.
- Eligible patients- cT2-4aN0-1M0, cisplatin, and immunotherapy-eligible MIBC who underwent NAC followed by radical cystectomy.
- Patients underwent serial ctDNA testing post-operatively. Upon ctDNA detection, patients were recommended for one year of atezolizumab therapy.

6. Identification of bladder cancer patients that could benefit from early post-cystectomy immunotherapy based on serial circulating tumour DNA (ctDNA) testing: Preliminary results from the TOMBOLA trial

ctDNA is prognostic in MIBC

Previous observational study – tumour informed ctDNA analyses



Christensen et al., J Clin Oncol. 2019

Tambola

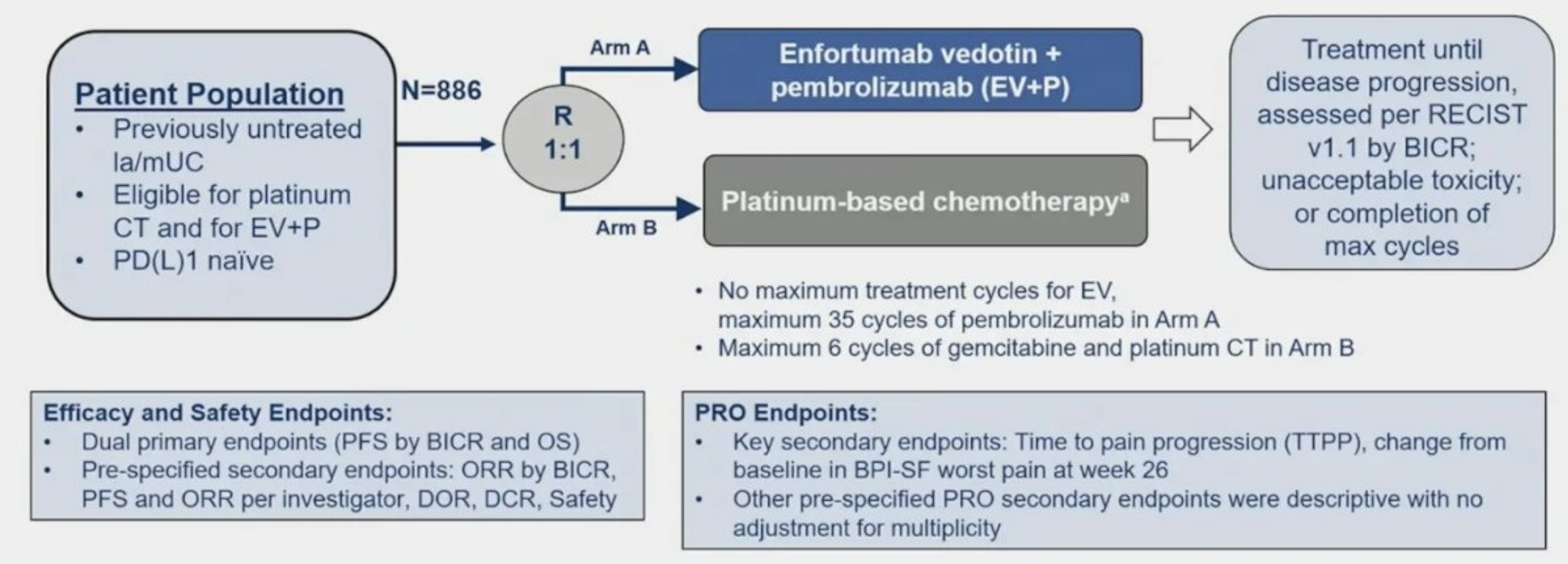
•Patients continue immunotherapy **if metastases appear**, irrespective of conventional risk

- First **153 patients** analyzed.
- **87 patients (57%)** were ctDNA-positive after RC.
  - **75%** of these detected **within 4 months** post-surgery.
- **Median lead time** from ctDNA detection to CT-confirmed metastases (in 17 patients):
  43 days (range: –13 to 501 days).
- Only **2 of the ctDNA-negative patients (3%)** developed metastases on follow-up imaging.

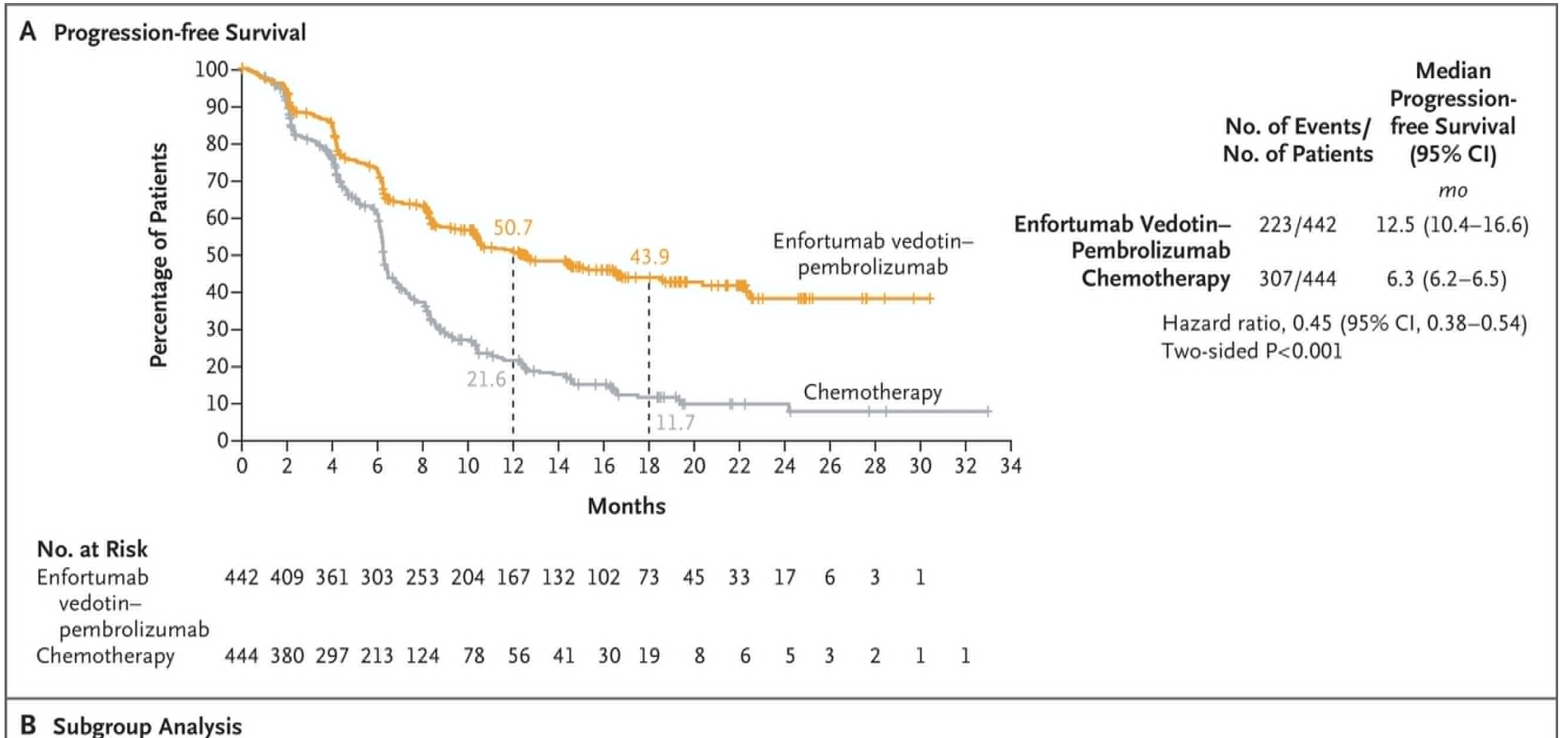
Tambola

- **Conclusions:**
- **Serial ctDNA testing** post-NAC and RC is **highly specific** for identifying early relapse.
- Enables **early initiation of immunotherapy** during minimal residual disease.
- **First trial** to report real-world use of **serial ctDNA-guided immunotherapy** in this setting.
- Interim efficacy data (from ~100 patients) expected by **August 2024**

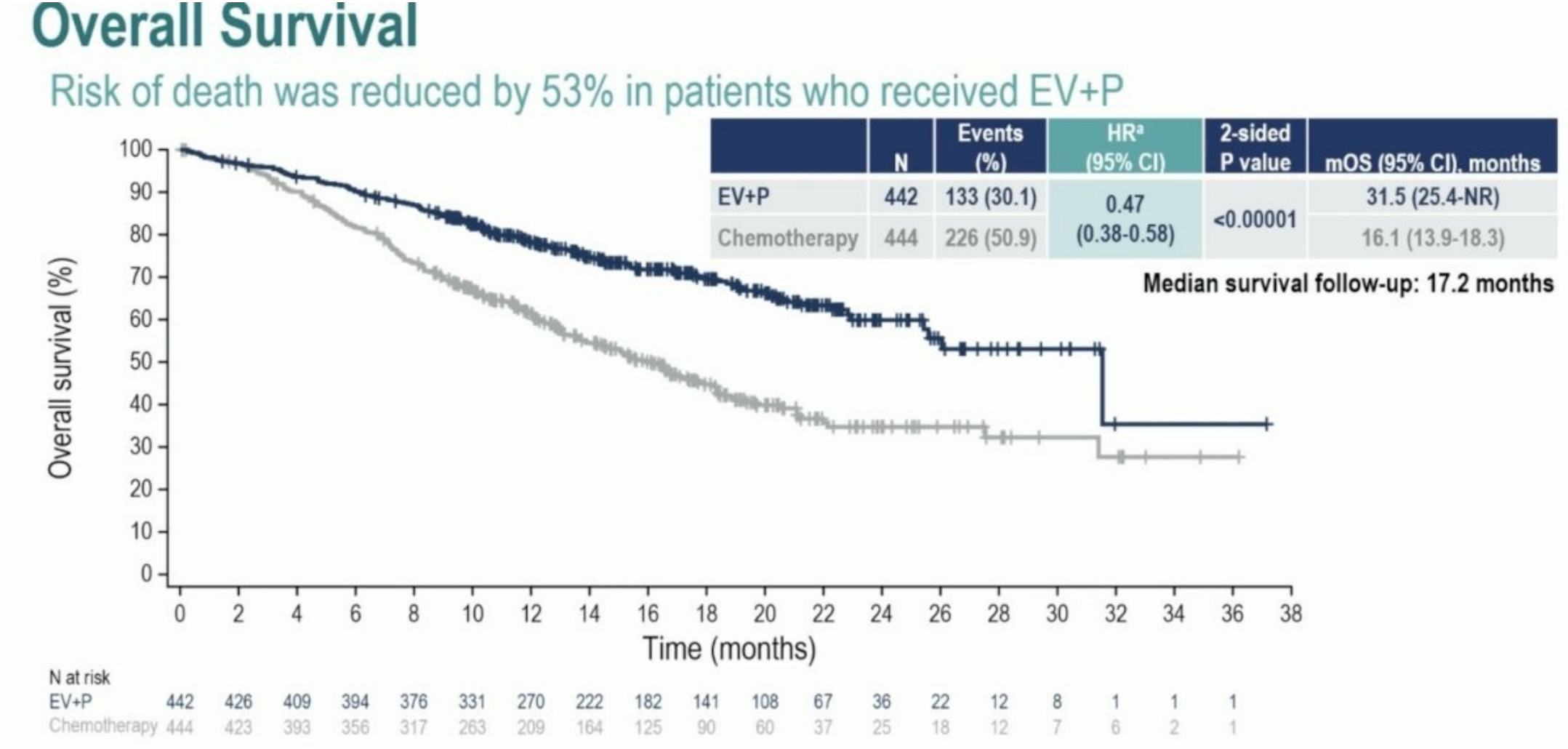
6. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer



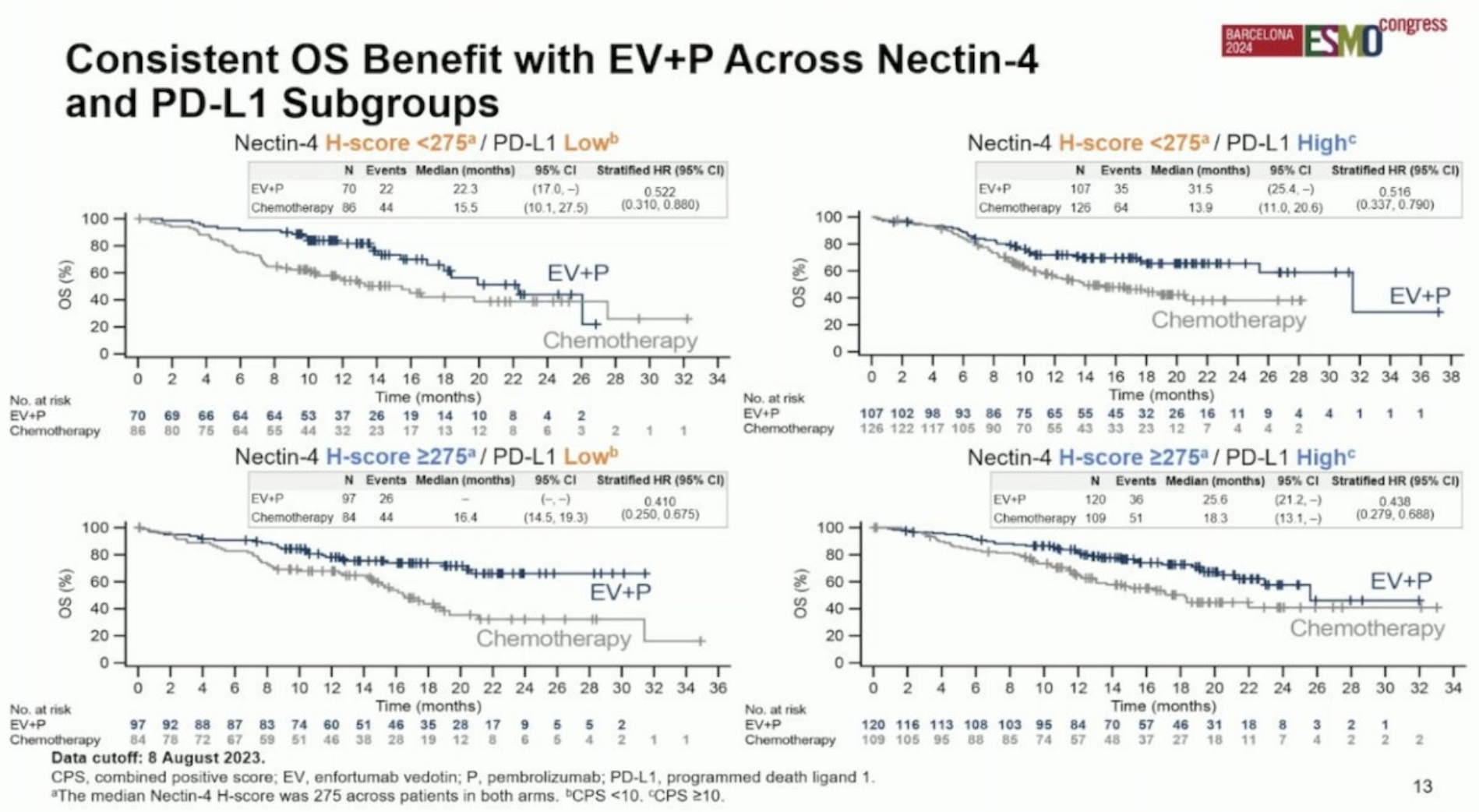
Outcome EV + P- PFS



EV302 OS


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
Overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38
Time (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

Nectin 4 and PDL1



Final Comments !

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