ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE | WEBINAR SERIES

ESMO GUIDELINES: REAL WORLD CASES WEBINAR

BLADDER CANCER

TUMOUR TOPIC, PRESENTATION OF EPIDEMIOLOGY, MOLECULAR PATHOLOGY FROM THE ESMO CPG

Prof Yohann Loriot, MD, PhD,

Gustave Roussy, Univervité Paris-Saclay;

ESMO bladder cancer CPG

Bladder cancer

FREQUENT

lethal

Highly mutated

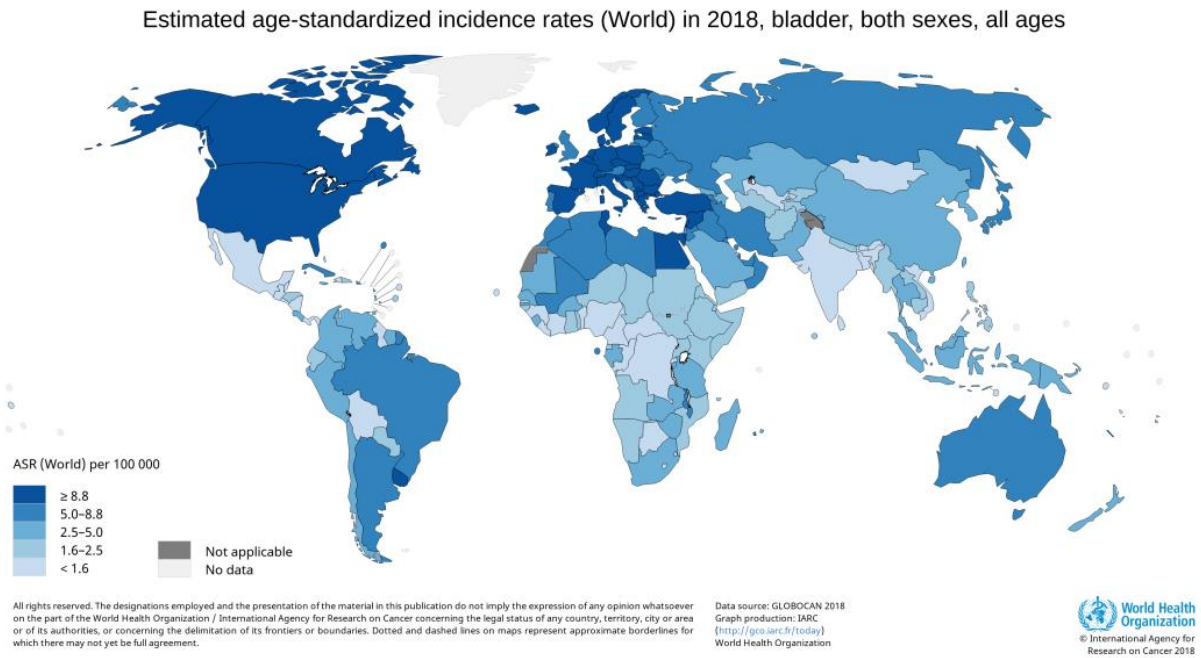
chemosensitive

radiosensitive

IO sensitive

Epidemiology

FREQUENT



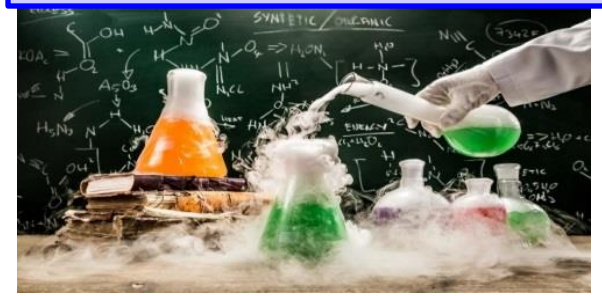
- 9th most common cancer type worldwide.
- increasing trend in both incidence and mortality has been observed
- Worldwide disease
- Mainly in male

Risk factors

FREQUENT

50%: smoking

workplace exposures (aromatic amines, polycyclic hydrocarbons, benzidines)



Infections (shistosomiasis) and chronic irritation

Other

Cyclophosphamide, Pelvic radiation - lynch syndrom (upper tract)

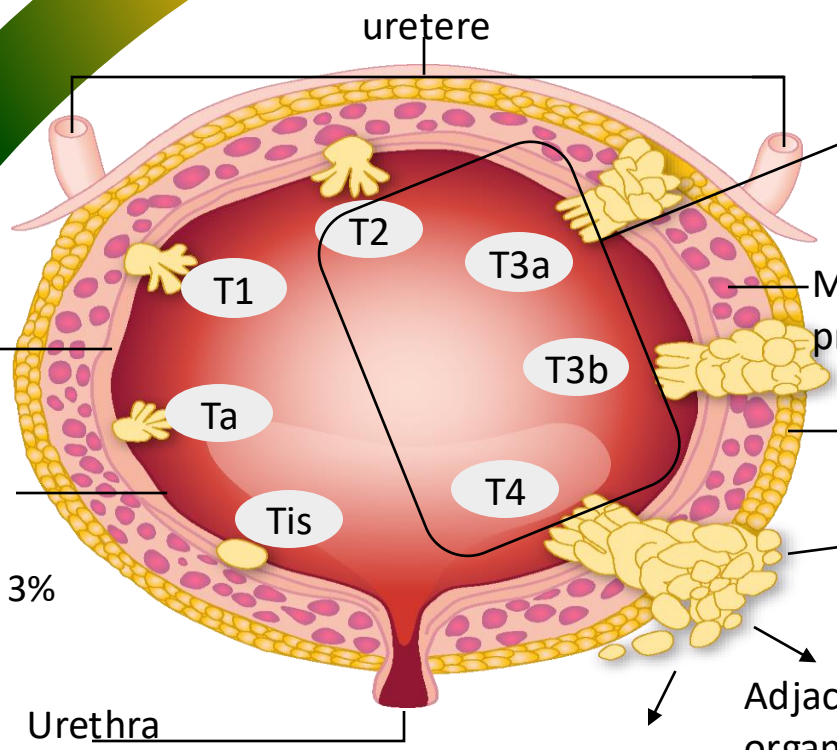
Natural disease history

NMIBC
(Tis, Ta, T1)
≈75% at diagnosis[1–4]

Low grade
or
High grade

MIBC
(T2, T3a, T3b, T4)
≈30 % des patients [1,4]

High grade



30%
Lamina propria
40%
Urothelium
3%

Locally advanced

Muscularis propria

Perivesical fat

Adjacent organs

Metastase
(N1,N2,N3, M1)
≈5-10% [1,5]

1. Howlader, et al. (eds). SEER Cancer Statistics Review 1975–2011

2. NCCN Guidelines – Bladder cancer v1.2015; 3. Sharma, et al. Am Fam Physician 2009

4. Kaufman, et al. Lancet 2009; 5. American Cancer Society 2014: Bladder Cancer

2016 WHO Classification

Invasive urothelial carcinoma	Non-invasive urothelial carcinoma

Urothelial (90%)

subtypes

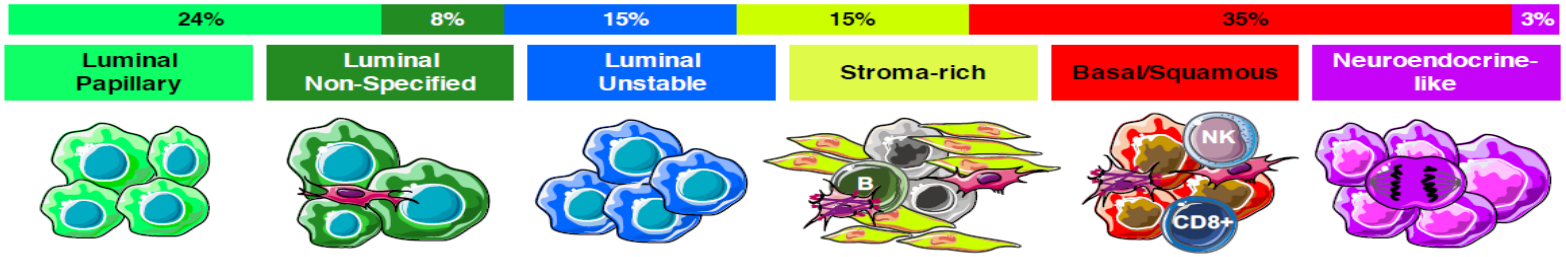
- Micropapillary
- microcystic
- Lymphoepithelioma-like
- Plasmacytod/signet ring cell/diffuse
- Sarcomatoid
- Giant cell
- Poorly diffentiated
- Lipid-rich
- Clear cell
- Large nested
- Trabecular
- nested

- Urothelial carcinoma in situ
- Papillary urothelial carcinoma, low-grade
- Papillary urothelial carcinoma, high-grade
- PUNLMP
- All histologies referred in the invasive urothelial carcinoma

If the squamous or adenocarcinoma part is > 95%, the UC should be considered as a pure squamous/adenocarcinoma.

Humphrey PA, et al, Eur Urol. 2016

Molecular classification

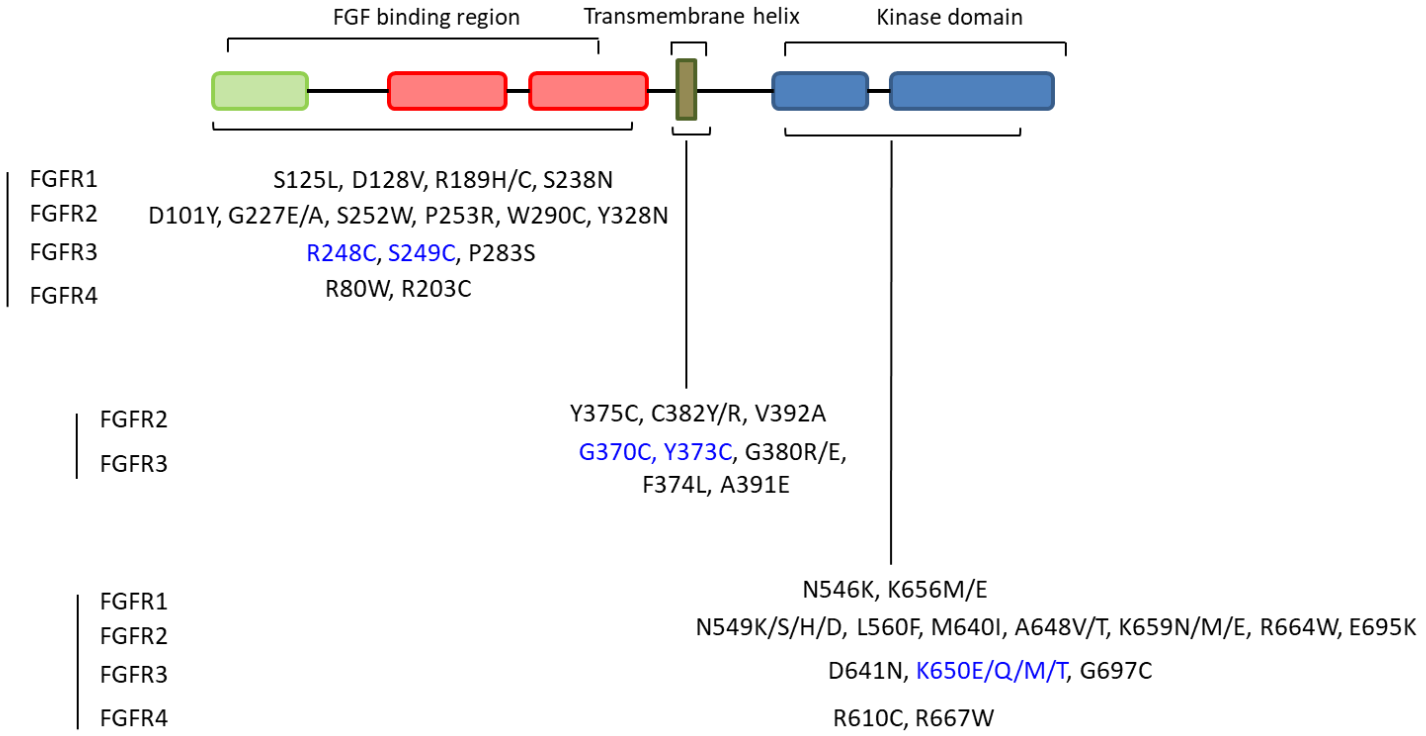


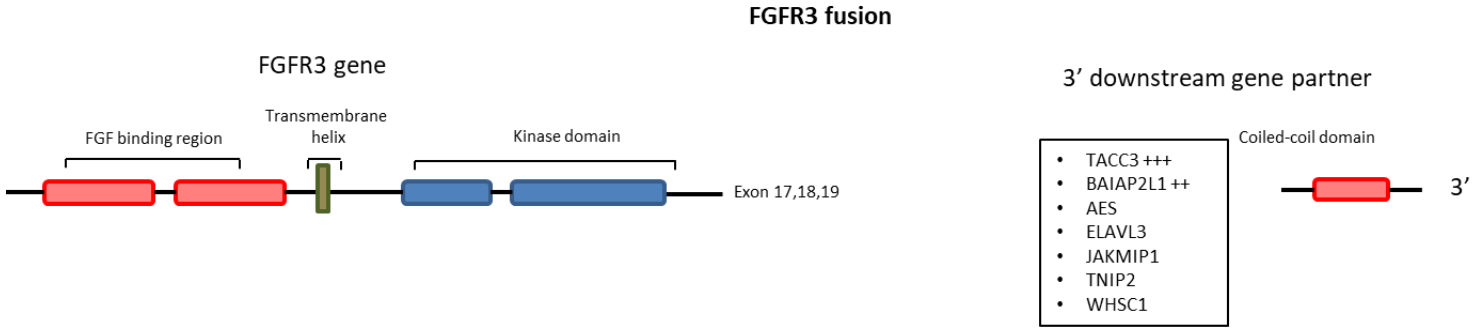
	Luminal Papillary	Luminal Non-Specified	Luminal Unstable	Stroma-rich	Basal/Squamous	Neuroendocrine-like
Differentiation	Urothelial / Luminal				Basal	Neuroendocrine
Oncogenic mechanisms	FGFR3 ++ CDKN2A -	PPAR-γ ++	PPAR-γ ++ E2F3 +, ERBB2 + Genomic instability		EGFR +	TP53 --, RB1 --, Cell cycle +
Mutations	*FGFR3* (40%), *KDM6A* (38%), *STAG2* (22%)	*ELF3* (35%)	*TP53* (76%), *ERCC2* (22%) TMB +, APOBEC +		*TP53* (61%), *RB1* (25%)	*TP53* (94%) *RB1* (39%)
Stromal infiltrate		Fibroblasts		Smooth muscle Fibroblasts Myofibroblasts	Fibroblasts Myofibroblasts	
Immune infiltrate				B cells	CD8 T cells NK cells	
Histology	Papillary morphology	Micropapillary variants			Squamous differentiation	Neuroendocrine differentiation
Clinical	T2 stage +	Older patients + (80+)			Women + T3/T4 stage +	
Median overall survival (years)	4	1.8	2.9	3.8	1.2	1

The role of further molecular diagnosis has yet to be clearly defined

Kamoun et al. Eur Urol 2019

FGFR3 alterations





- Up to 50 % in NMIBC
- ≈ 15% in MIBC
- Treatment available for FGFR3-alt metastatic UC

Molecular biology: recommendations

- Pathological diagnosis must be made according to the latest WHO classification
- In addition to stage and grade, presence and percentage of subtypes, lymphovascular invasion and presence of detrusor muscle should be reported
- Molecular diagnostics such as The Cancer Genome Atlas (TCGA) classification and PD-L1 status is not required for all tumours [IV, C].
- Genomic testing [polymerase chain reaction (PCR) or next-generation sequencing (NGS)-based] should be used for detection of *FGFR2/3* mutations and fusions

ESMO ON AIR

Real World case of Advanced Urothelial Bladder Cancer

Akhil Kapoor

Tata Memorial Centre, Varanasi, India

26th February 2025

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

Diagnosis, Staging, Risk Factors, Management, Outcomes

Clinical Presentation

64 years gentleman

Smoker 30 pack years

No known comorbidities

Presented in ER in January 2024 with hematuria

Initial work up revealed bladder mass

Referred to tertiary oncology centre for further work up and evaluation

Work Up

Imaging confirmed Bladder mass with no regional nodes or distant metastasis

Cystoscopy and TURBT, histology showed Transitional Cell Carcinoma

Staging: cT4aN0M0

DTPA GFR: 55 ml/min

Received NACT with Gemcitabine cisplatin (Split doses of Cis on D1 and D8)

Further treatment

Post 4#, scans showed good response

Underwent Robotic Radical Cystectomy in April 2024

HPR showed ypT3N0 disease

Started on Adjuvant Nivolumab (Checkmate 274)

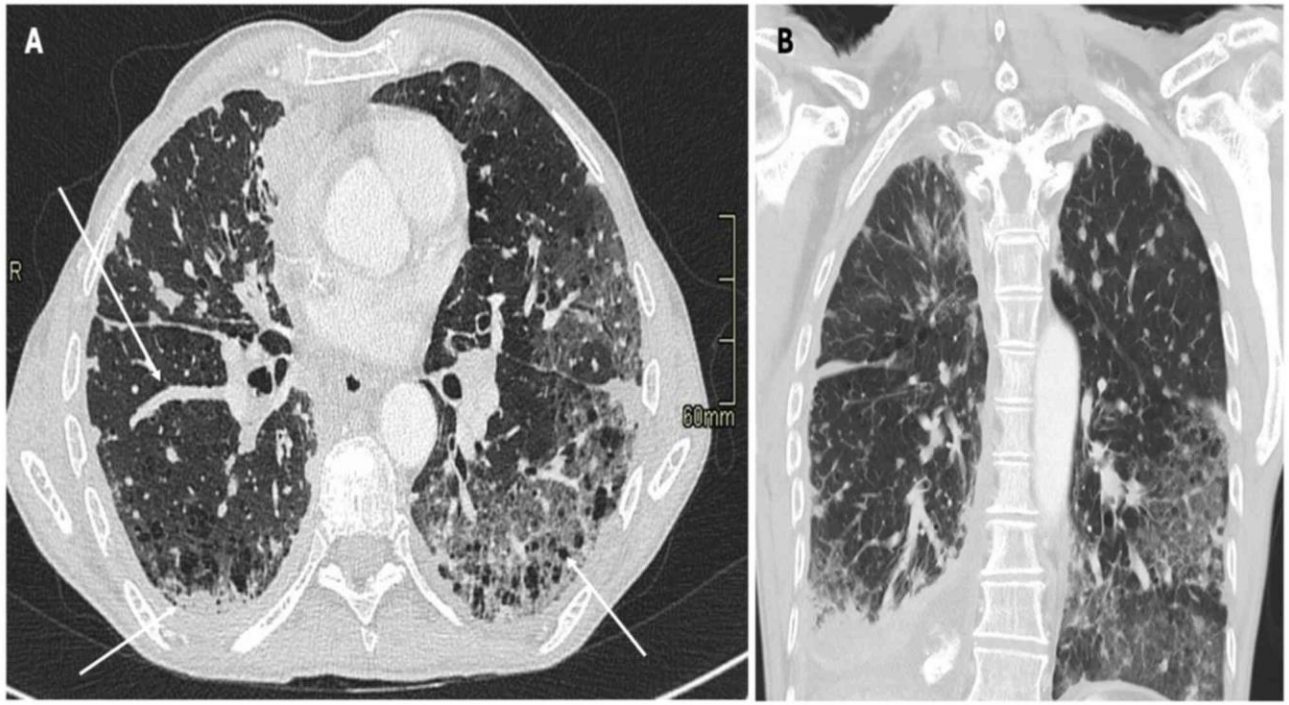
Toxicities and Follow up

Developed Grade 4 Immune mediated Pneumonitis after 3 months of Nivolumab

Required hospitalization and IV Methylpredsinolone

Symptoms resolved and patient discharged after 10 days of hospitalization

Further Nivolumab was discontinued



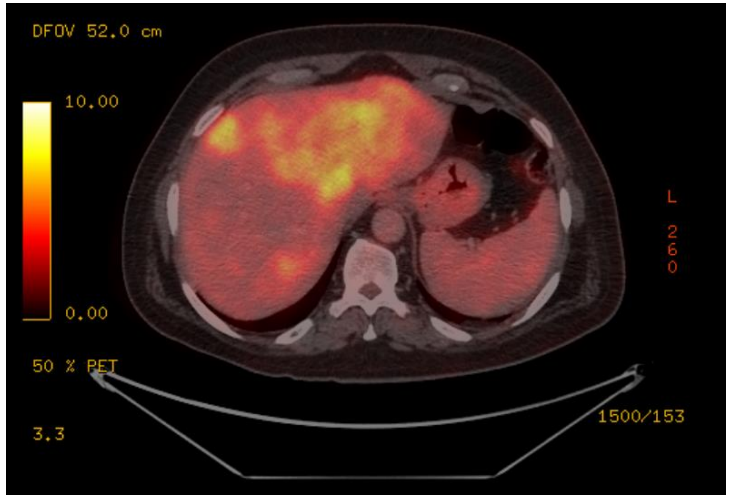
Recurrence

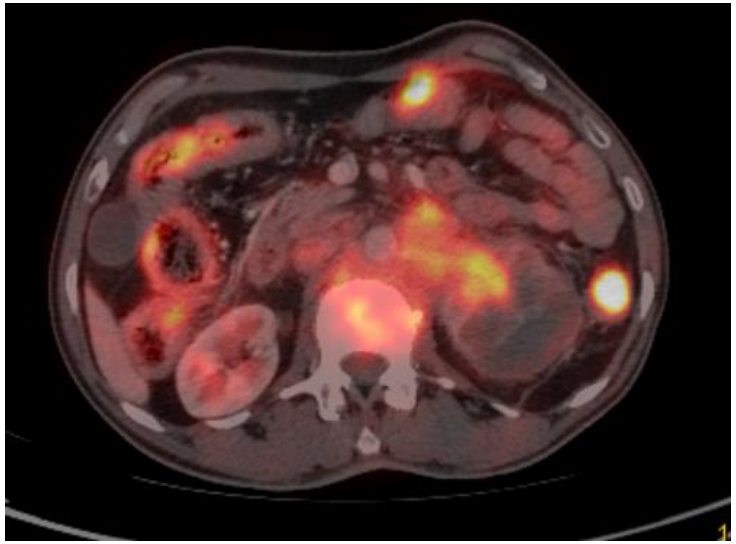
Patient presented after 3 months (October 2024) with pain and heaviness in right hypochondrium

PET CT showed multiple sites of metastasis

Sites of mets: Liver, bone, nodes, adrenal

Biopsy from Liver confirmed metastatic TCC





Further Treatment for Metastatic disease

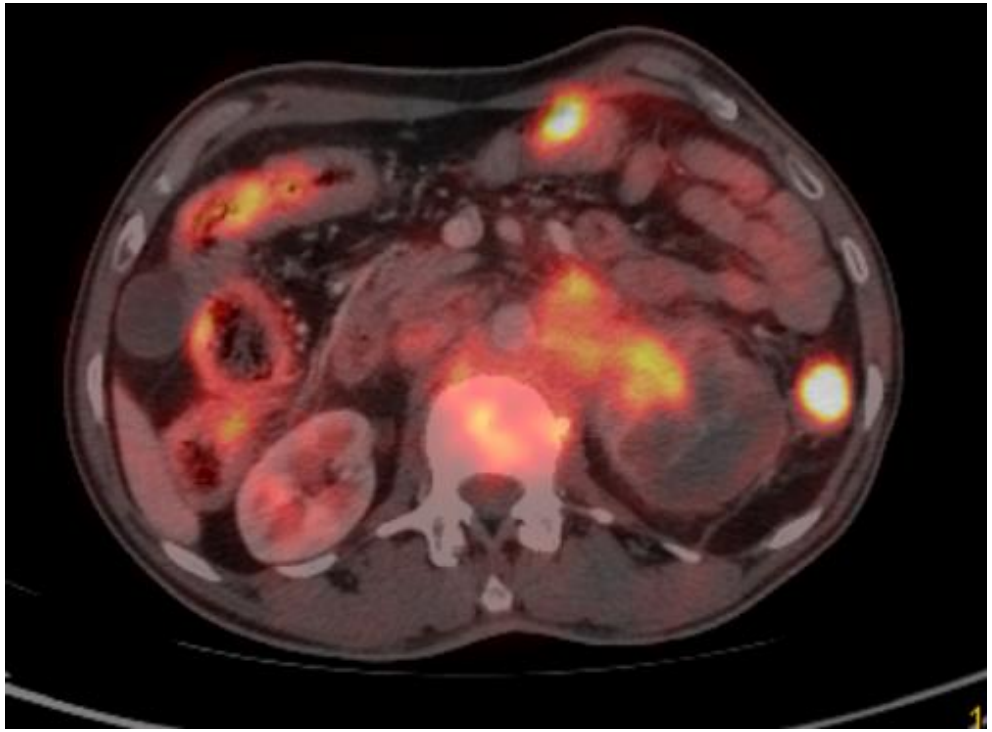
All the options discussed

Patient was extremely anxious due to prior toxicities

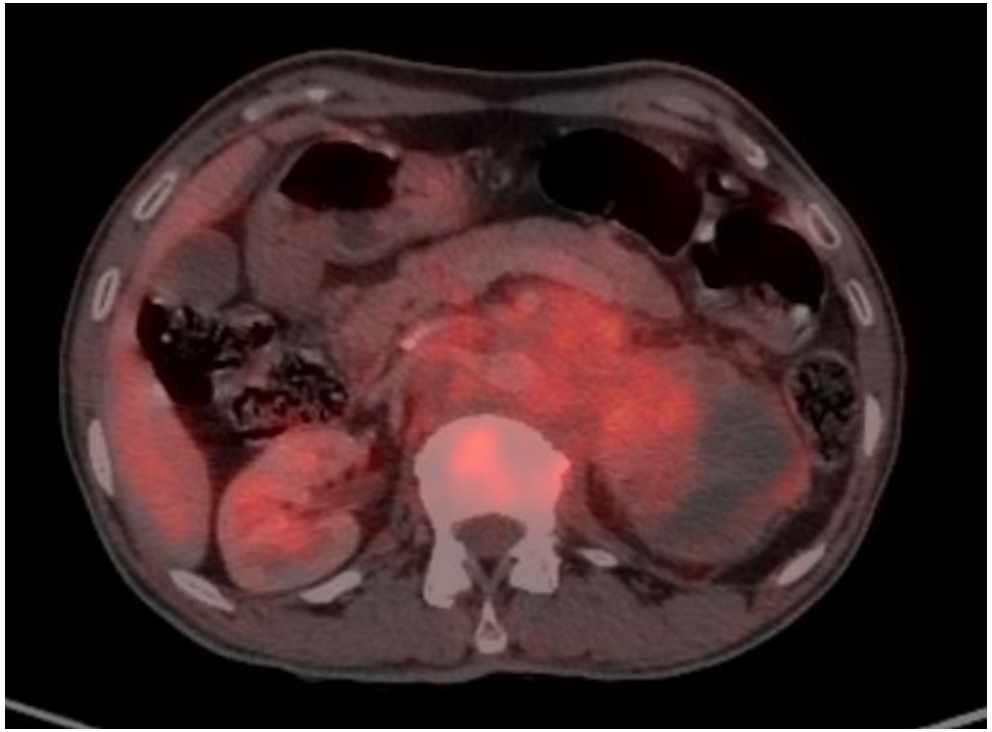
Started on Enfortumab vedotin after repeated counselling

Had significant symptomatic benefit with resolution of symptoms after 3 cycles

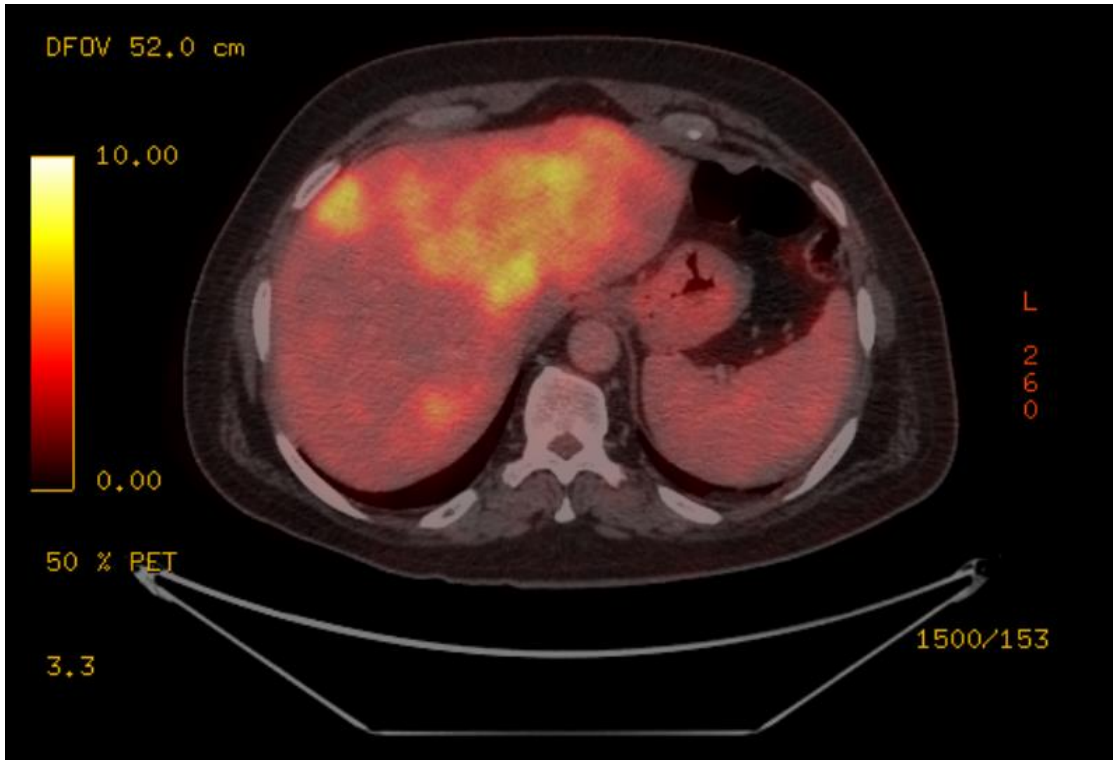
Before



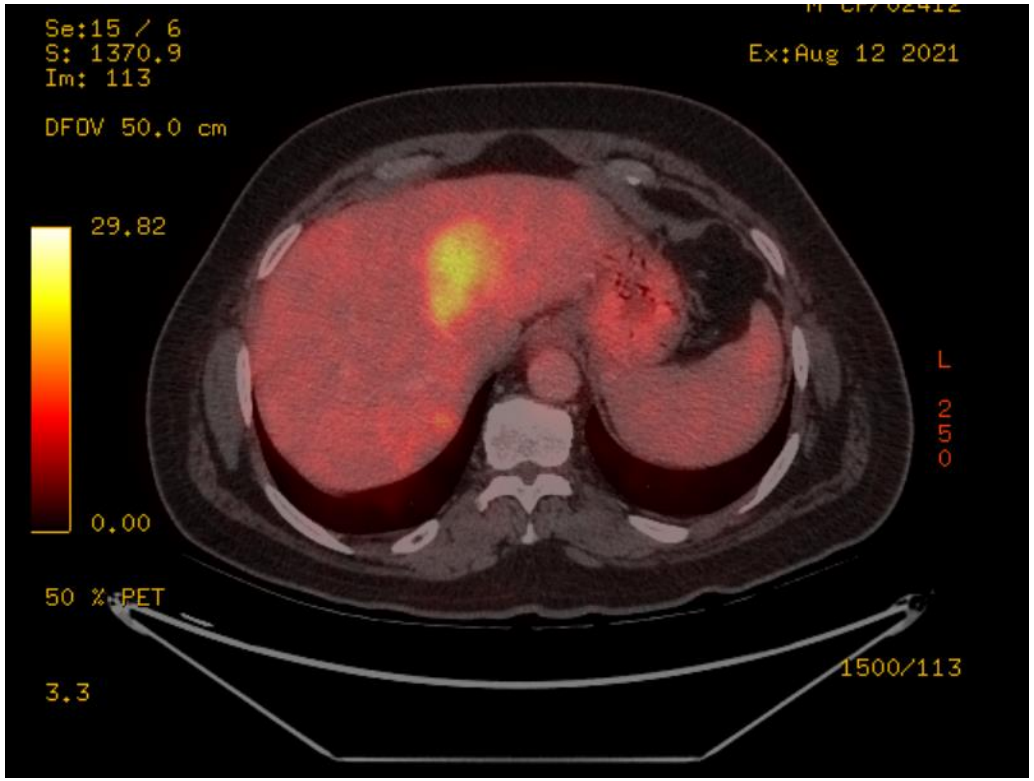
After



Before



After



Toxicities

Developed Grade 2 Peripheral Neuropathy after 5 cycles

Patient reluctant for other treatment and chose to be on follow up

Maintained Partial Response after 2 months of stopping EV.

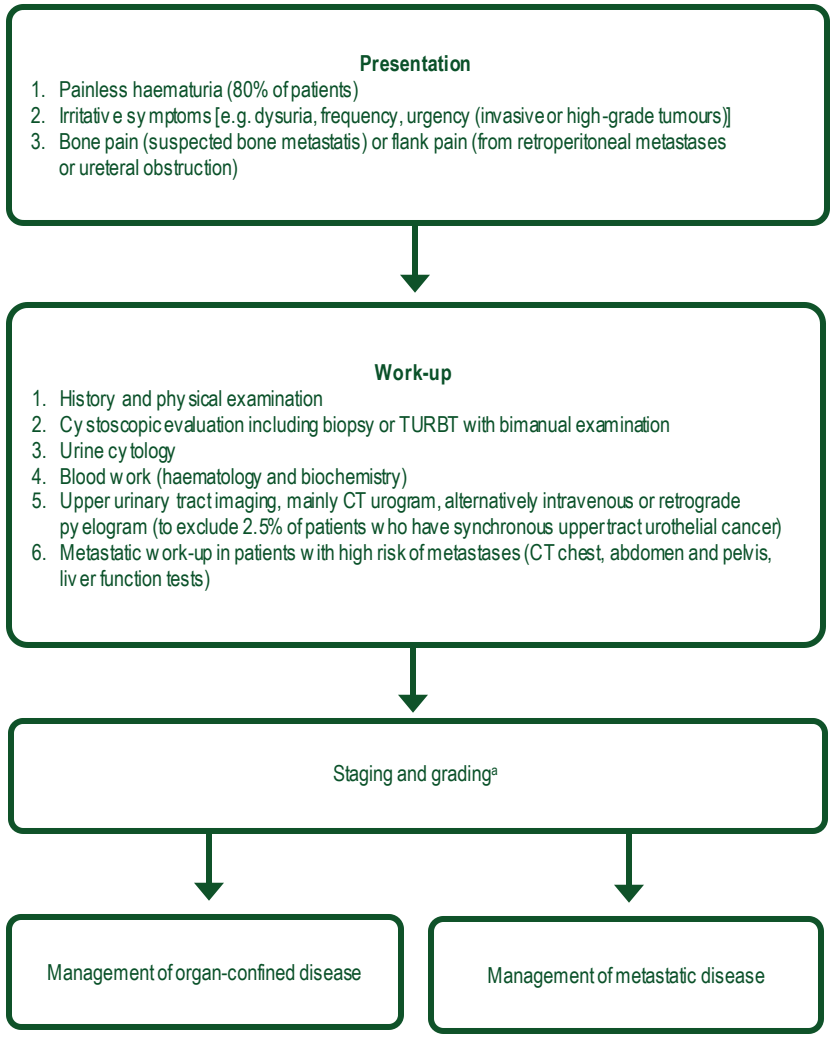
CRITICAL ANALYSIS OF THE CASE AND PARALLEL PRESENTATION OF THE ESMO CPG RECOMMENDATIONS, FLOW CHARTS, MCBS, SECTION BY SECTION

Prof Yohann Loriot, MD, PhD,

Gustave Roussy, Univervité Paris-Saclay;

ESMO bladder cancer CPG

Diagnosis and general work-up



Clinical classification UICC TNM 8th edition for urothelial carcinoma of the bladder

T - Primary tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Ta	Non-invasive papillary carcinoma	
Tis	Carcinoma in situ: ‘flat tumour'	
T1	Tumour invades subepithelial connective tissue	
T2	Tumour invades muscle	
	T2a	Tumour invades superficial muscle (inner half)
	T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue	
	T3a	Microscopically
	T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall	
	T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina
	T4b	Tumour invades pelvic wall or abdominal wall

N – Regional lymph nodes		
NX	Regional lymph nodes cannot be assessed tissue	
N0	No regional lymph node metastasis	
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in common iliac lymph node(s)	
M - Distant metastasis		
M0	No distant metastasis	
	M1a	Non-regional lymph nodes
	M1b	Other distant metastases

AJCC TNM staging system for urothelial carcinoma of the bladder

Stage 0a	**Ta**	**N0**	**M0**
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a–T2b	N0	M0
Stage IIIA	T3a–T3b, T4a	N0	M0
	T1-4a	N1	M0
Stage IIIB	T1-T4a	N2 or N3	M0
Stage IVA	T4b	N0	M0
	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

Pathological diagnosis of urothelial carcinoma of the bladder WHO classification of tumours of the urothelial tract

Invasive urothelial carcinoma	Non-invasive urothelial carcinoma
Urothelial	Urothelial carcinoma in situ
Microcystic	Papillary urothelial carcinoma, low-grade
Micropapillary	Papillary urothelial carcinoma, high-grade
Lymphoepithelioma-like	PUNLMP
Plasmacytoid/signet ring cell/diffuse	All histologies referred in the invasive urothelial carcinoma column
Sarcomatoid	
Giant cell	
Poorly differentiated	
Lipid-rich	
Clear cell	
Large nested	
Trabecular	
nested	

Personalised medicine synopsis table for bladder cancer

Biomarker	Method	Use	LoE, GoR
PD-L1 expression in metastatic setting [4-7]	IHC to identify PD-L1 expression on either immune and/or tumour cells. Trial assays are validated (SP142 and 22C3 antibody)	To select patients for atezolizumab or pembrolizumab in the advanced cisplatin-ineligible, treatment-naïve setting. The partner diagnostics for these two agents are ≥5% of immune component using SP142 antibody and CPS of ≥10% for 22C3 respectively	III, C
PDL1 expression in adjuvant setting [8]	IHC to identify PD-L1 expression on tumor cells.	To select patients for nivolumab in adjuvant setting. The positivity is defined as ≥1% of positive tumor cell membrane staining in a minimum of 100 tumor cells that could be evaluated with the use of the PD-L1 IHC 28-8 pharmDx immunohistochemical assay (Dako)	I, A
FGFR3 gene alteration [9]	DNA alterations to FGFR3 can either be detected by PCR (FGFR RT-PCR Kit), by whole exome sequencing or gene panels	FGFR-targeted therapy (erdafitinib) is recommended in patients with FGFR gene alteration in the platinum refractory setting [FGFR3 mutations, or FGFR3 fusions (FGFR RT-PCR Kit)]	I, A
HER2 expression in metastatic setting [10]	IHC to identify HER2 expression on tumor cells.	To select patients for trastuzumab deruxtecan in metastatic setting	III, B
TCGA gene expression [11]	RNA analysis	Provide novel insights into disease biology	IV, D
Minimal residual disease (MRD) [12]	Circulating tumor DNA using personalized and tumor-informed ctDNA testing (Natera Signatera assay)	To identify patients with higher risk of relapse after cystectomy and those with very low risk of relapse	III, B

NMIBC statification

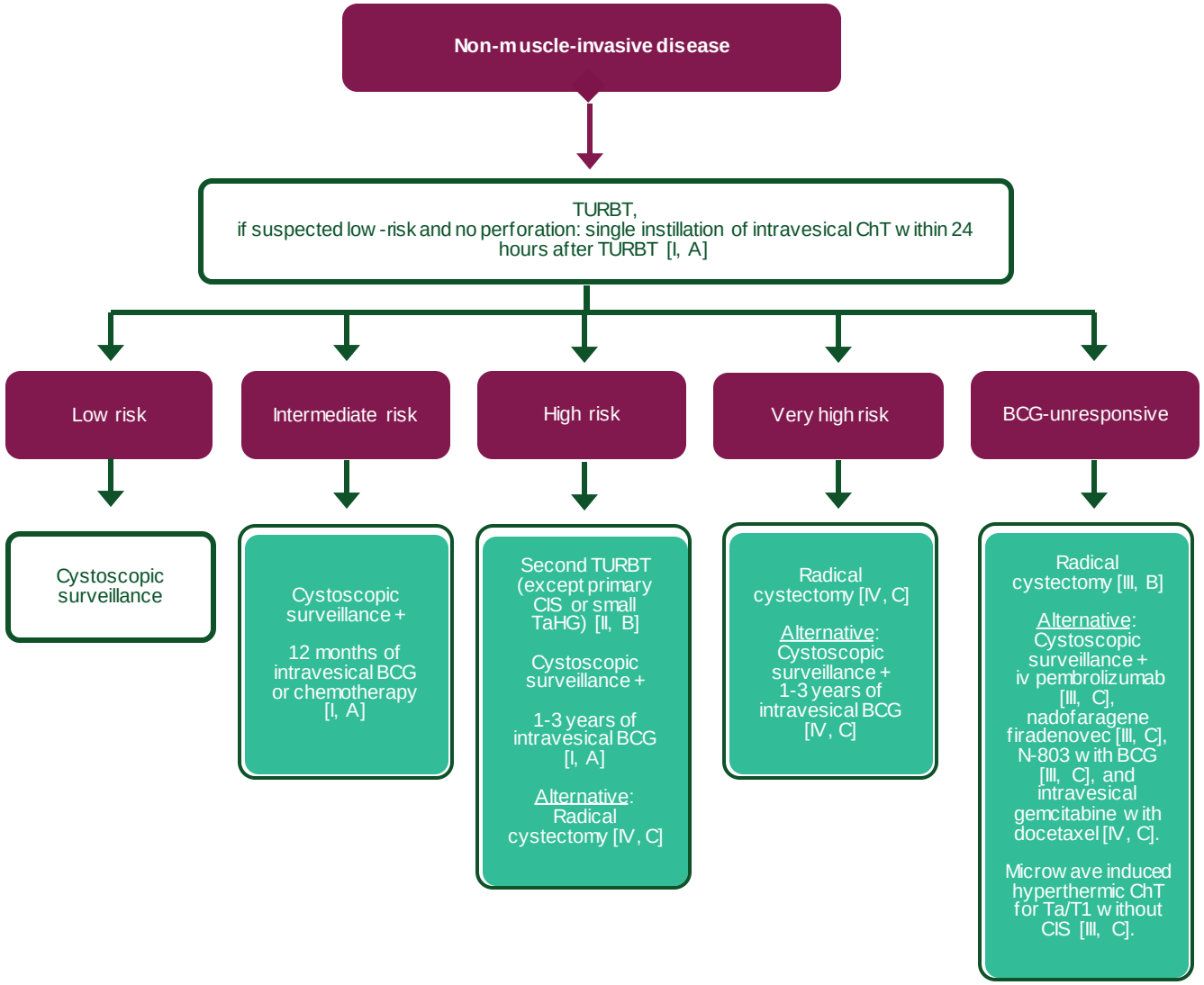
Low risk	Intermediate risk	High risk	Very hisk risk
Patiente with primary, single, TaT1 low-grade (LG) tumour <3 cm in diameter and without CIS.	Patient without CIS who do not fall into the low-, high-, or very high-risk categories. Can be further stratified based on five clinical factors: tumour size, focality, timing and frequency of recurrence, and failure of prior intravesical treatment	All patients with T1 or Ta HG tumours and/or CIS, except those included in the very high-risk group	Patients with features such as lympho-vascular invasion (LVI), CIS in the prostatic urethra, or select histological subtypes (i.e., micropapillary, sarcomatoid, nested, plasmacytoid, or neuroendocrine histological subtypes).

Staging and risk assessment

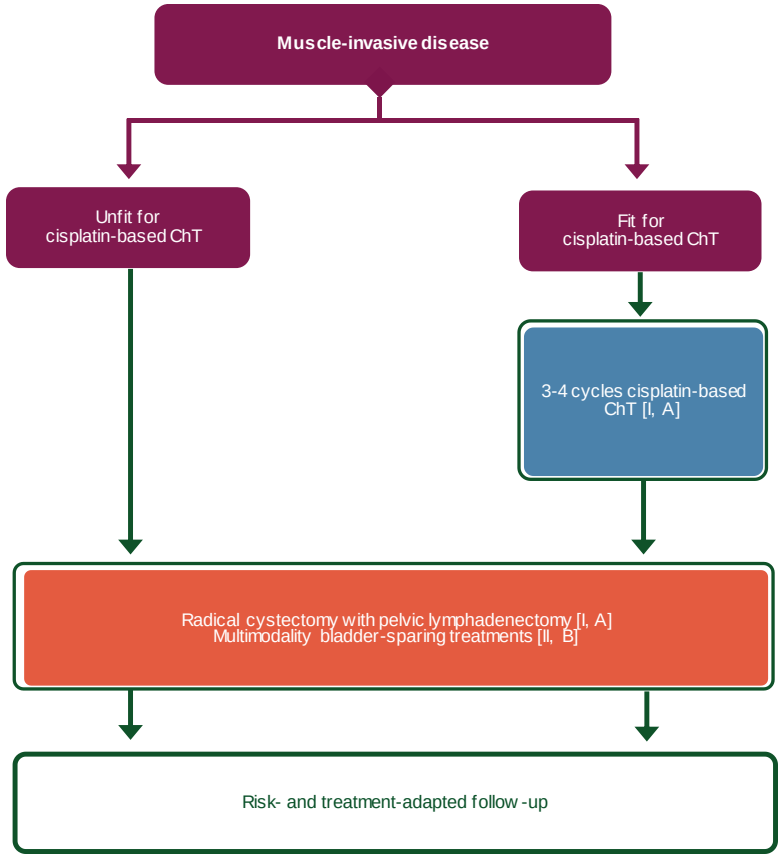
- Patients with NMIBC are classified into four risk categories based on tumour characteristics (low-risk, intermediate-risk, high-risk, very high-risk; Table 1), which constitutes the basis for treatment and follow-up recommendations [IV, B].

- In patients with invasive disease (≥T2), regional and distant staging should be carried out with further imaging studies such as contrast-enhanced CT of chest/abdomen/pelvis or MRI of abdomen/pelvis combined with chest CT [IV, B]. FDG-PET-CT may aid in the detection of LN and distant metastases [IV, C], but no clear consensus was reached.

Management of NMIBC

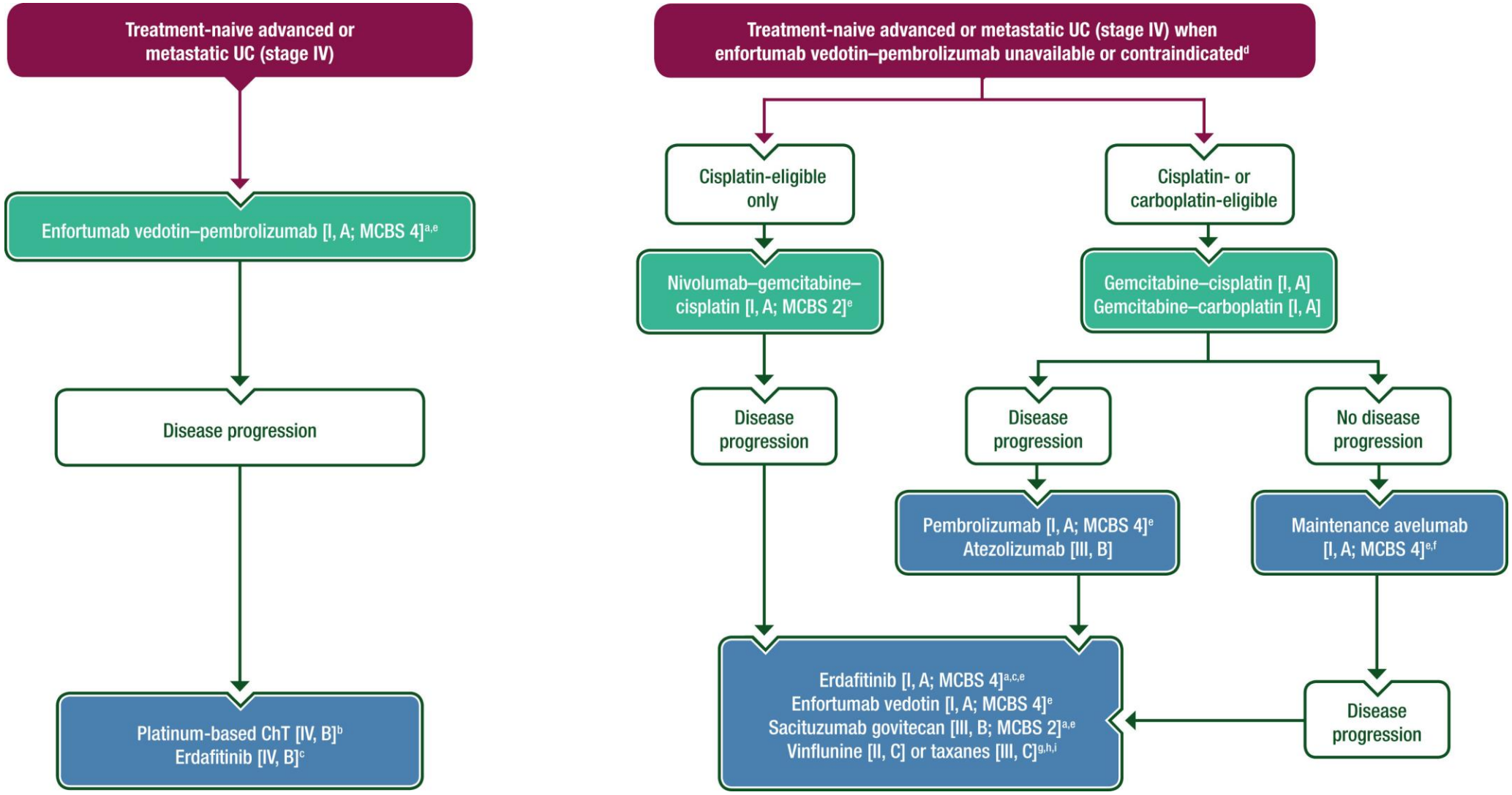


Management of MIBC



- Multidisciplinary care via tumour board discussions and/or directed consultations with a medical oncologist, radiation oncologist and urologist is recommended for the optimal management of bladder cancer
- Cisplatin-based neoadjuvant chemotherapy should be given for MIBC [I, A].
- **Durvalumab is recommended as peri-operative therapy, in addition to cisplatin-gemcitabine chemotherapy in cT2-4N0-1 MIBC** [I,A].
- There is weak evidence to support the use of adjuvant cisplatin-based ChT in patients who did not receive neoadjuvant therapy [II, B]. Neoadjuvant ChT is preferred.
- **Adjuvant nivolumab is recommended in high risk MIBC (defined as pT3, pT4a, or pN+ or ypT2 - ypT4a or ypN+ for patients who received neoadjuvant chemotherapy) [I, B]**
- **Adjuvant pembrolizumab is recommended in high risk MIBC (defined as pT3, pT4a, or pN+ or ypT2 - ypT4a or ypN+ for patients who received neoadjuvant chemotherapy) [I, B]**

Management of advanced disease



Follow-up, long-term implications, and survivorship

- Follow-up for NMIBC requires regular cystoscopic examination according to the patient's risk category [IV, A].
- Follow-up after curative therapy for MIBC requires cross-sectional imaging for 5 years. This should include 3-4 monthly imaging for the first 2 years. Bladder-sparing approaches also require regular cystoscopy [IV, B].
- Follow-up during and after systemic therapy for advanced UC should focus on regular cross-sectional imaging of the chest, abdomen and pelvis and other target lesions [IV, B].

THANK YOU

Prof Yohann Loriot, MD, PhD,

Gustave Roussy, Univervité Paris-Saclay;

ESMO bladder cancer CPG

ESMO ON AIR

Considerations related to Guideline implementation in everyday clinical practice

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DOI

Speaker/Advisor/Investigator: Astra Zeneca, MSD, BMS, Pfizer, Roche, Merck, Novartis, Lilly, Gilead, Takeda, Helsinn, Astellas, Janssen, Sanofi, Sandoz, Actavis, Amgen, Archigen, Amicus, Taiho, Infinity, Bioclin, G1 Therapeutics, MEI Pharma, Immunocore/Medison, NAPO Pharmaceuticals, Oktal, PharmaSwiss, Abbvie, MedicaLinea, MAK pharma, Agendia, Recordati, Incyte, Bicycle Thepeutics

The ESMO POWG serves to identify the practice needs of oncologists who are hospital and office-based by developing educational services, practice tools and quality indicators that will facilitate the implementation of best practice at the point of care.

The POWG members are relevant stakeholders to the ESMO Guidelines Webinars as experts who are consulting and implementing the guidelines in their daily practices

For more information about the ESMO POWG visit **esmo.org**

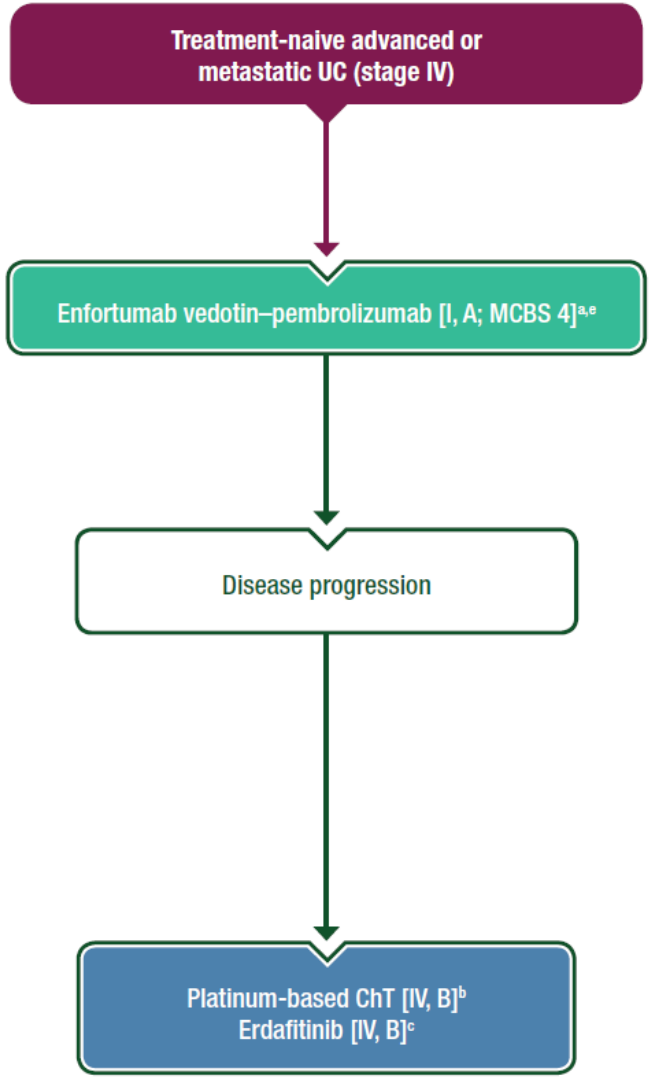
ESMO > About ESMO > Organisational Structure > Educational Committee

ESMO PRACTISING ONCOLOGISTS WORKING GROUP

Don't miss:

- The «ESMO Checklists» on OncologyPRO

ESMO Guideline: Metastatic Urothelial Cancer



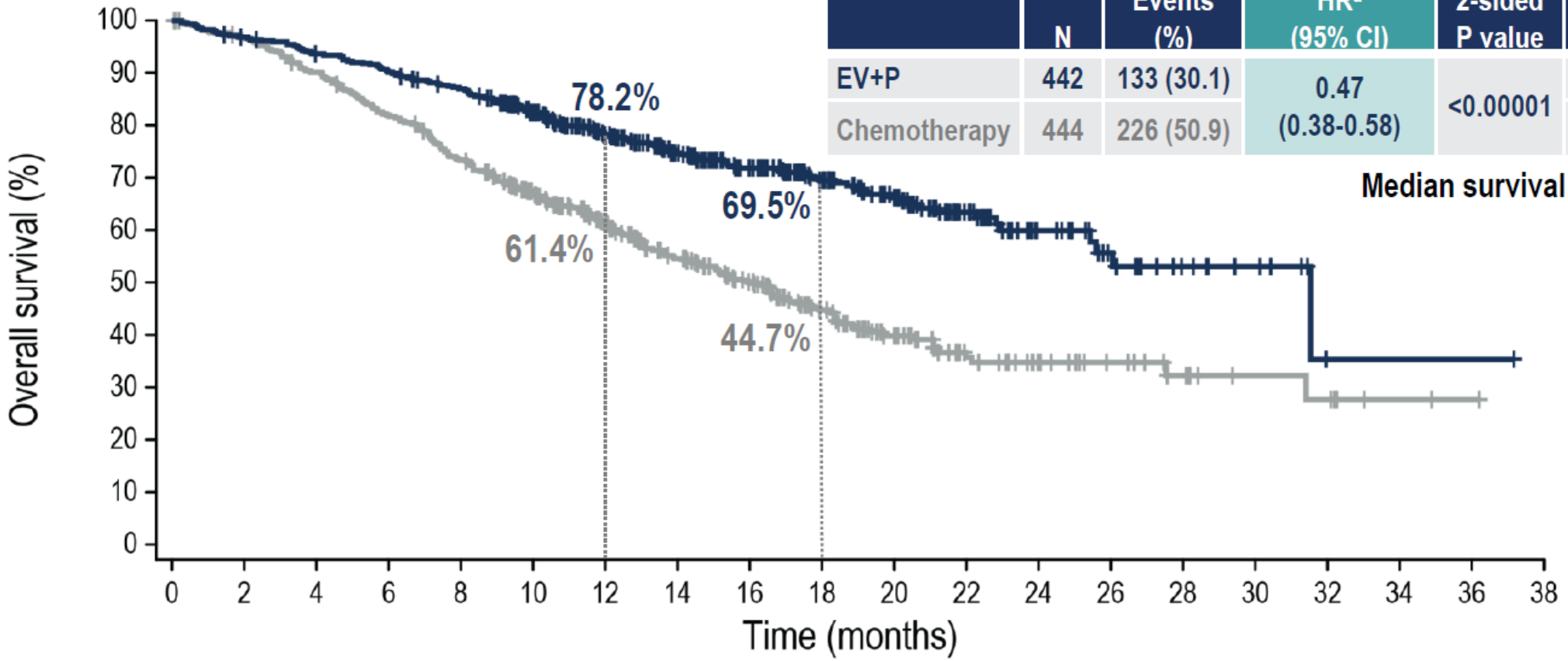
Powles Ann Oncol 2024

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

Data cutoff: 08 Aug 2023

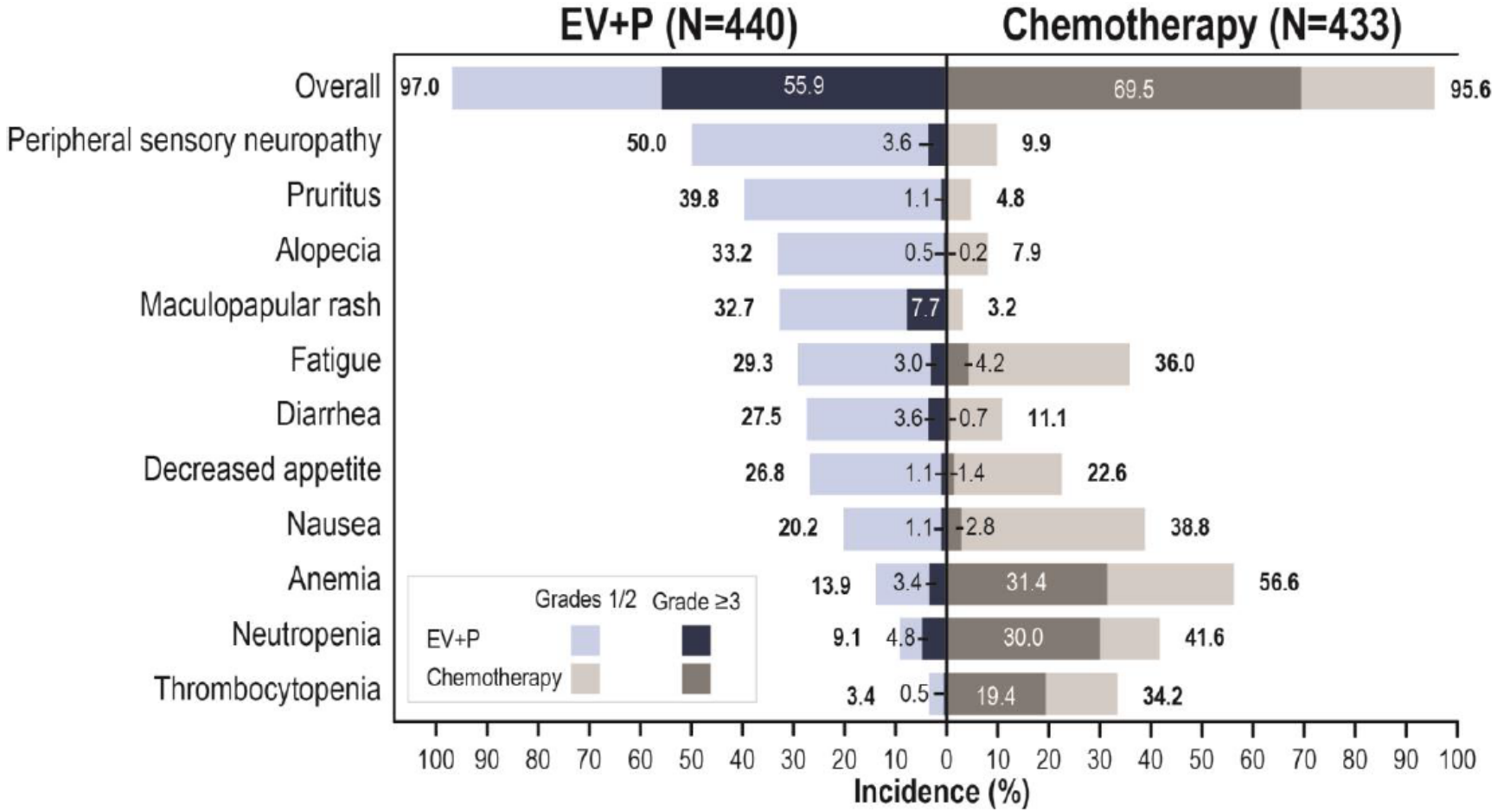
OS at 12 and 18 months was estimated using Kaplan-Meier method
mOS, median overall survival; NR, not reached
[a]Calculated using stratified Cox proportional hazards model. A hazard ratio <1 favors the EV+P arm

MADRID 2023 ESMO congress

Powles et al.

Treatment-Related Adverse Events

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



Serious TRAEs:

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

TRAEs leading to death (per investigator):

EV+P: 4 (0.9%)

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

Chemotherapy: 4 (0.9%)

- Febrile neutropenia
- Myocardial infarction
- Neutropenic sepsis
- Sepsis

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

Data cutoff: 08 Aug 2023

MADRID 2023 ESMO congress

Powles et al.

TRAEs shown in figure are any grade by preferred term in ≥20% of patients for any grade in either arm
TRAEs, treatment-related adverse events

Pembro/EV availability

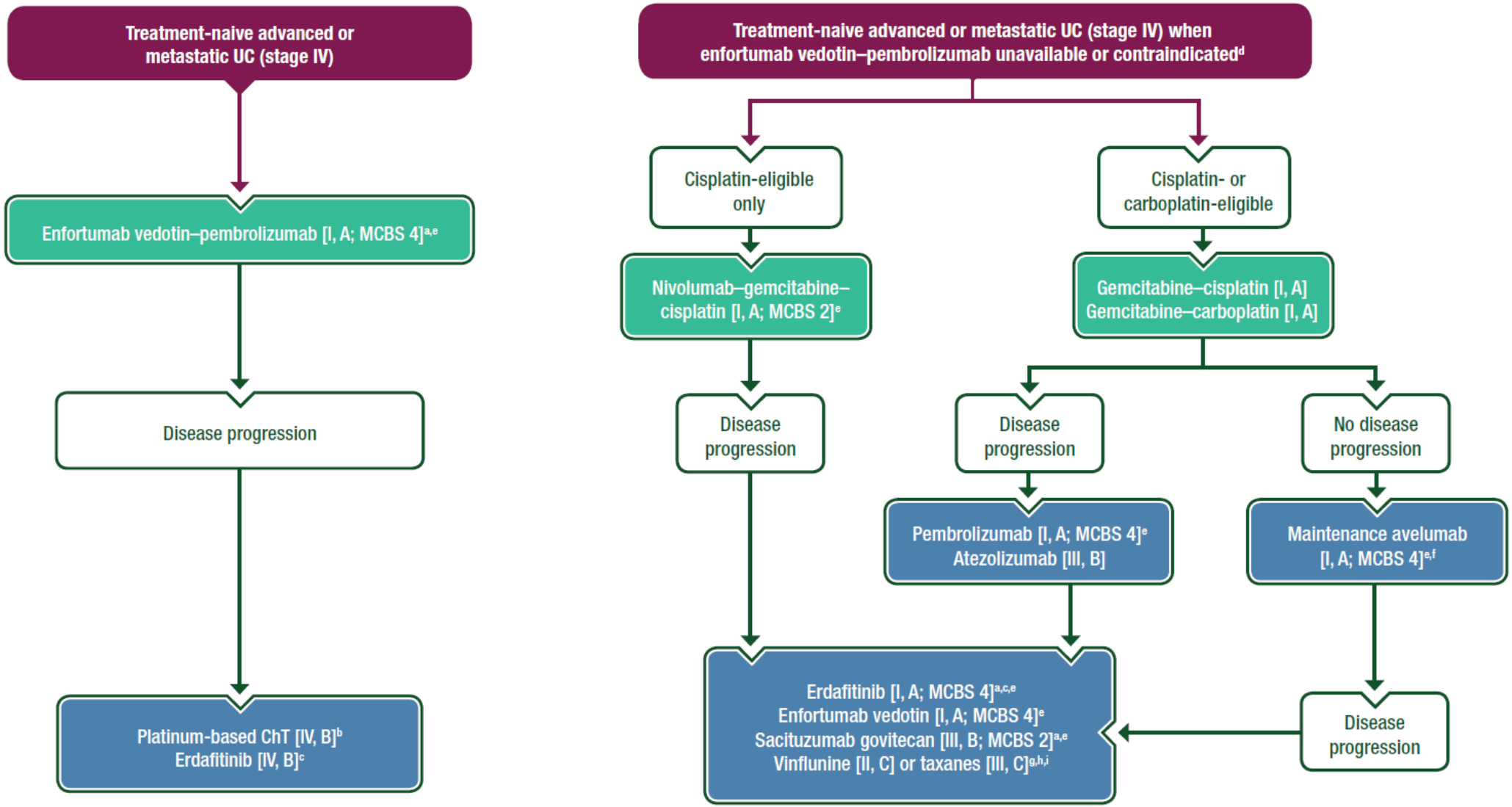
BLADDR 2024

Availability: EV/P

Country	Status
Austria	Reimbursed
Belgium	?
Bulgaria	?
Demark	?
Finnland	?
France	Reimbursed
Germany	Reimbursed
Greece	Reimbursed
Italy	Not available
Israel	?
Norway	?
Slovenia	?
Sweden	?
Switzerland	Reimbursed
Croatia, Slovakia, Lithuania, Latvia, Estonia	?

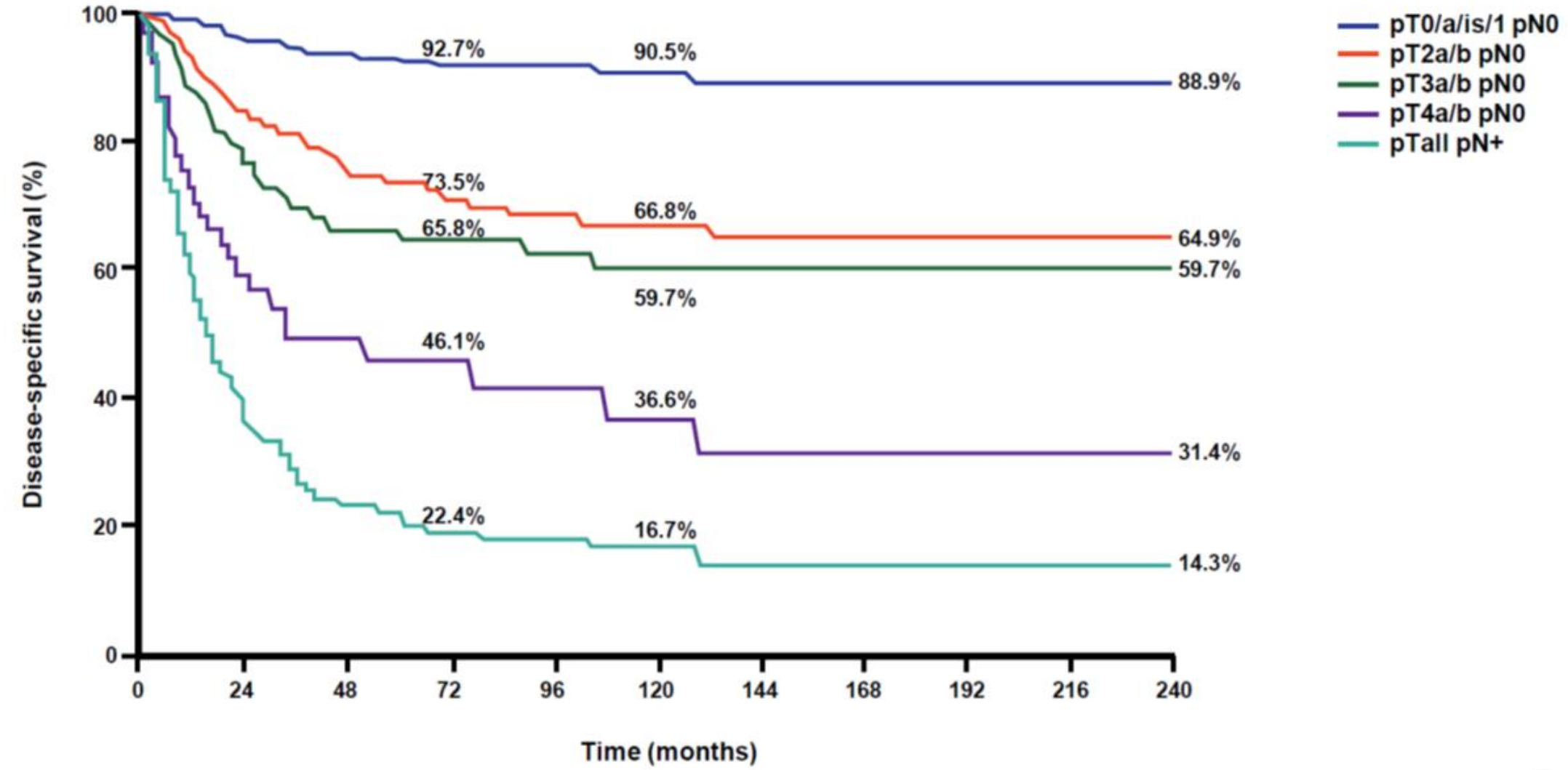
Some European countries have patient-specific reimbursement programs to bridge the gap until reimbursement of the combination is secured.

ESMO Guideline: Metastatic Urothelial Cancer

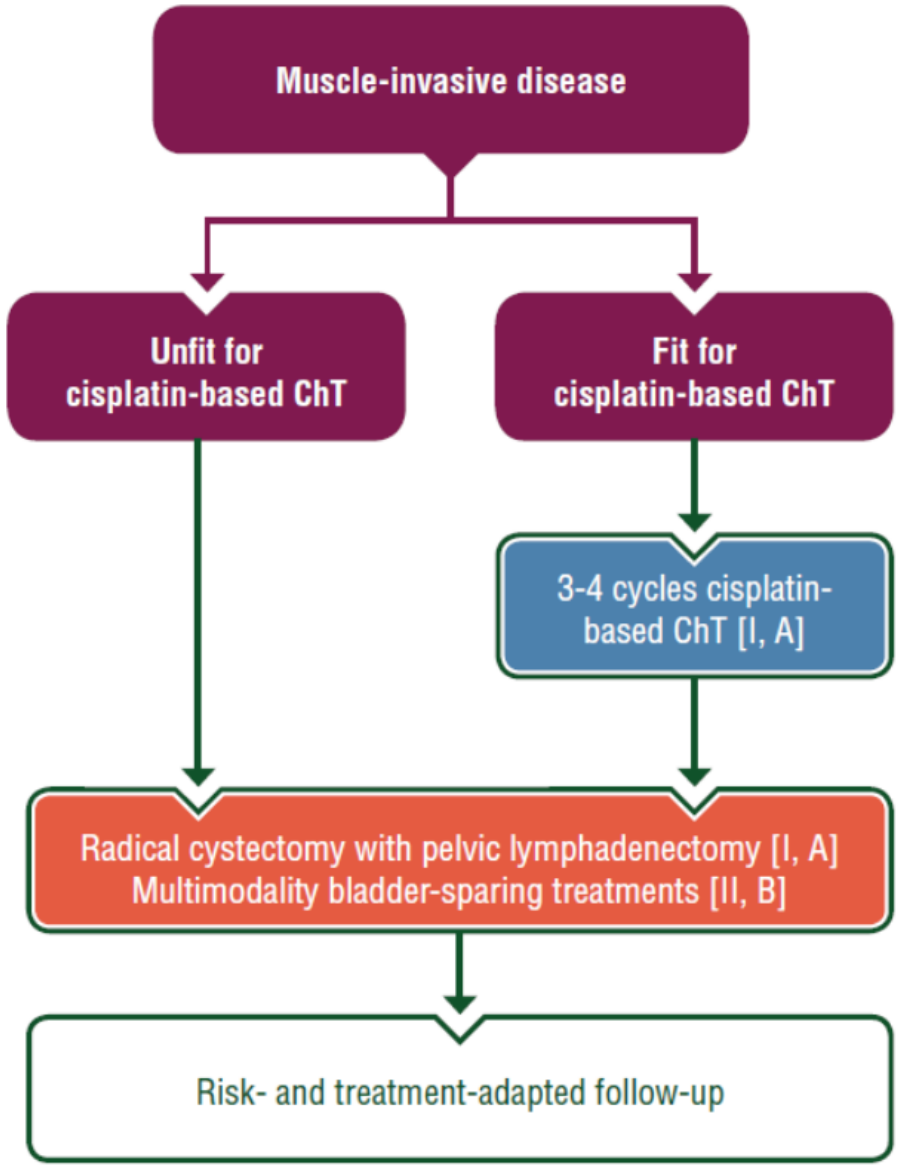


Powles Ann Oncol 2024

Survival after cystectomy without (neo)adjuvant therapy



ESMO Guideline: Muscle Invasive Bladder Cancer



Powles Ann Oncol 2021;

Cisplatin-based Neoadjuvant Chemotherapy

European Urology

European Urology 48 (2005) 202–206

Review—Bladder Cancer

Neoadjuvant Chemotherapy in Invasive Bladder Cancer: Update of a Systematic Review and Meta-Analysis of Individual Patient Data

Advanced Bladder Cancer (ABC) Meta-analysis Collaboration

Meta-analysis Group, Medical Research Council Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK

Accepted 6 April 2005

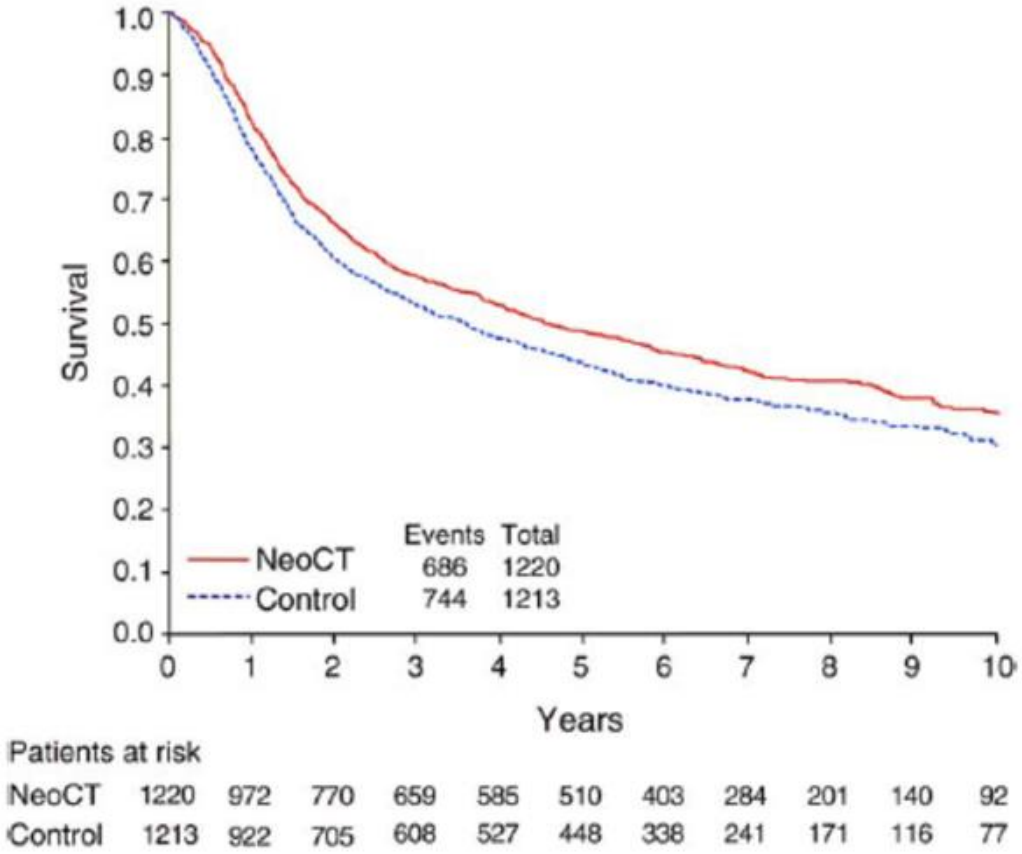
Available online 21 April 2005

11 trials, 3005 patients

mOS HR 0,86

p=0,003

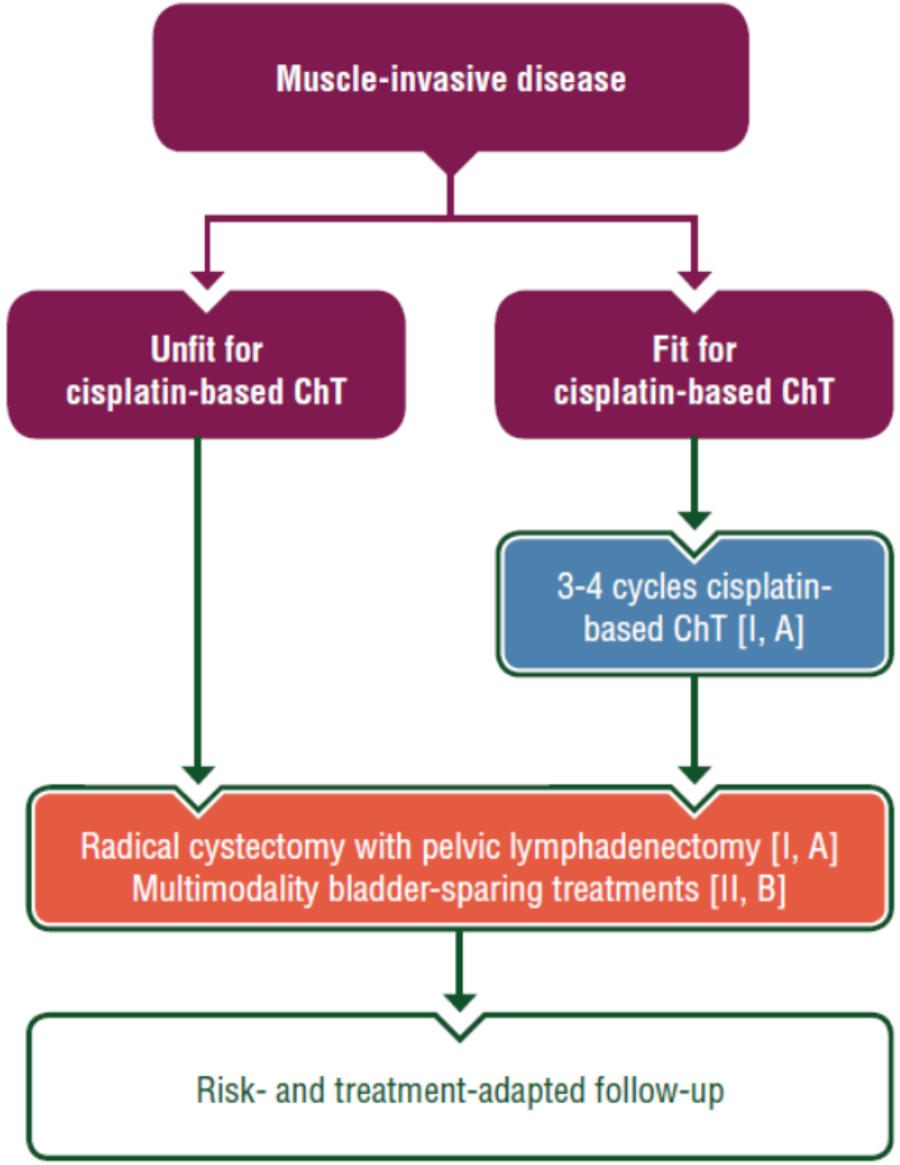
5-years absolute difference 5%



ABC-Meta analysis Colaboration, Eur Urol, 2005

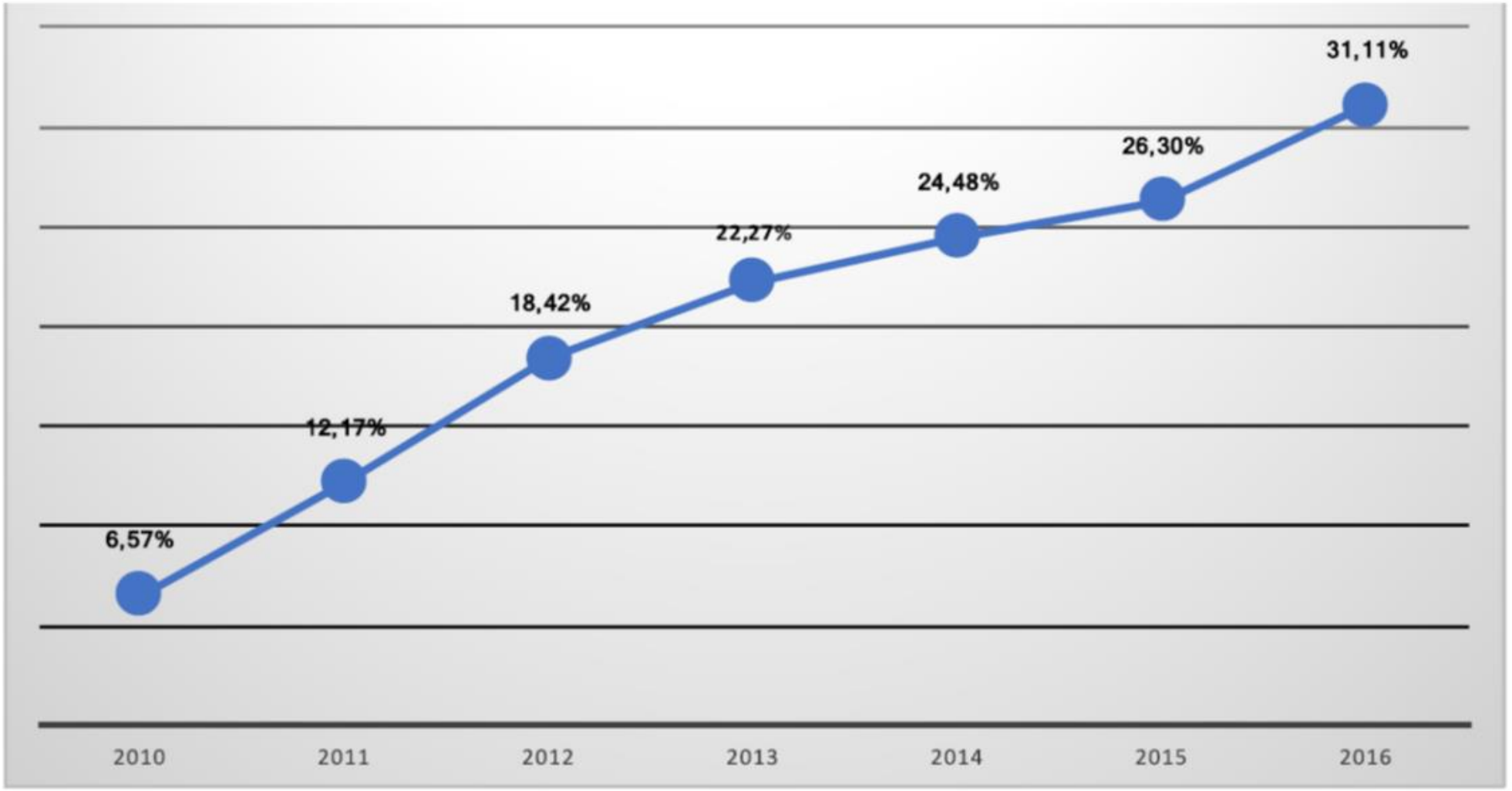
ESMO Guideline: Muscle Invasive Bladder Cancer

Only
12–13%
of MIUC patients undergoing radical cystectomy receive neoadjuvant chemotherapy, despite current guidelines[3,4]

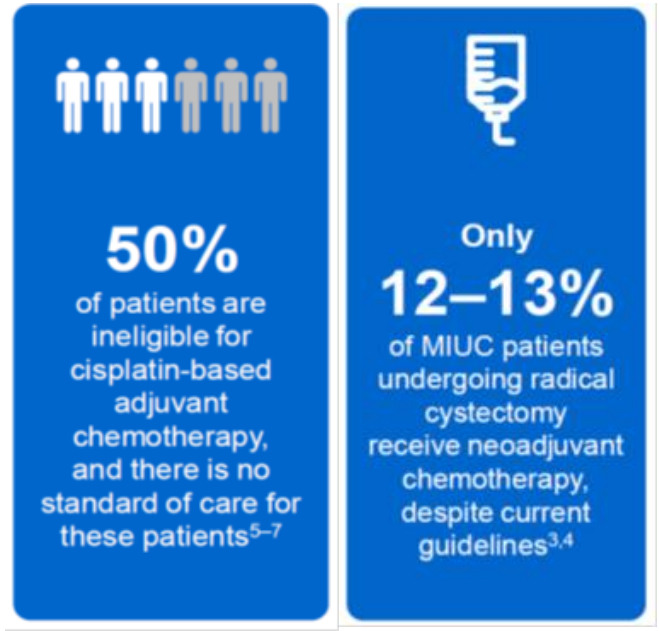


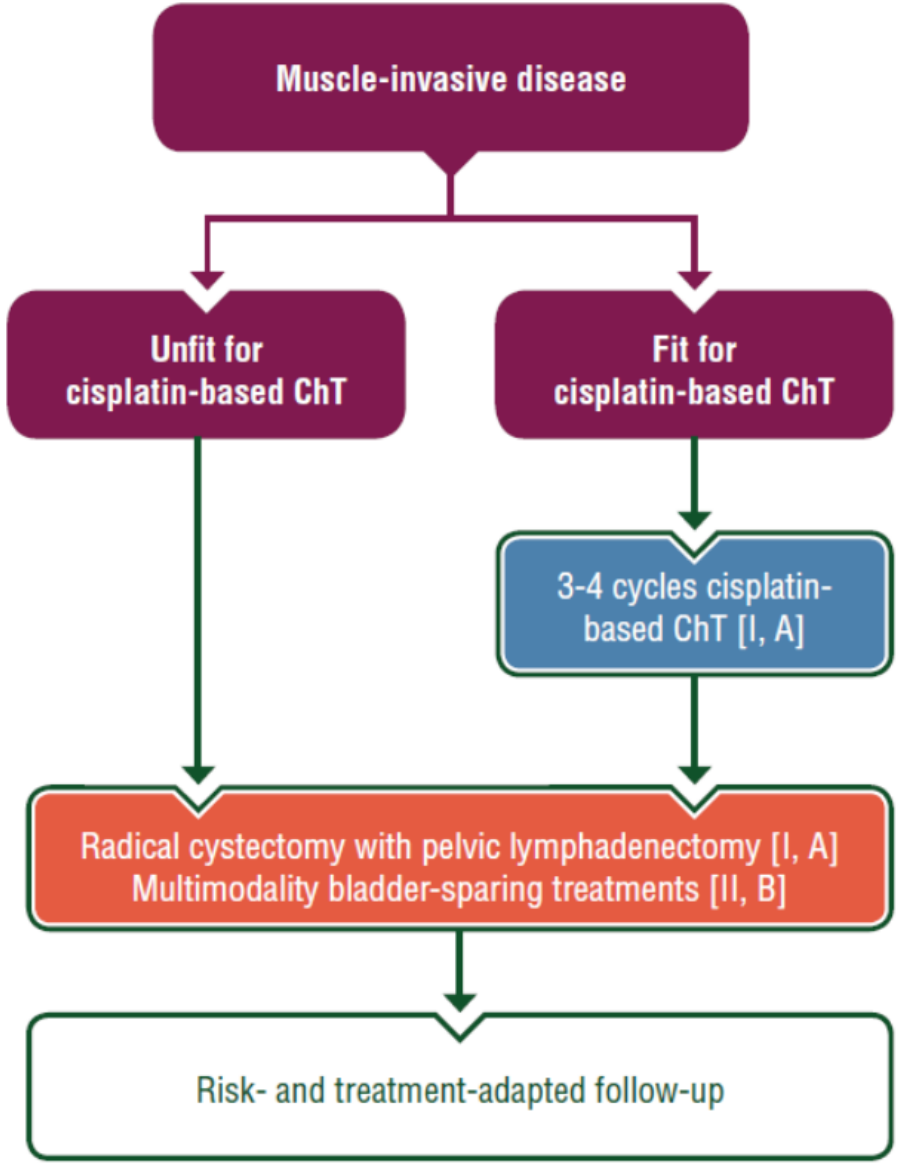
Powles Ann Oncol 2021; Burger Eur Urol 2012;
Huo Eur Urol Oncol 2019;

French Data on utility of NACT



ESMO Guideline: Muscle Invasive Bladder Cancer

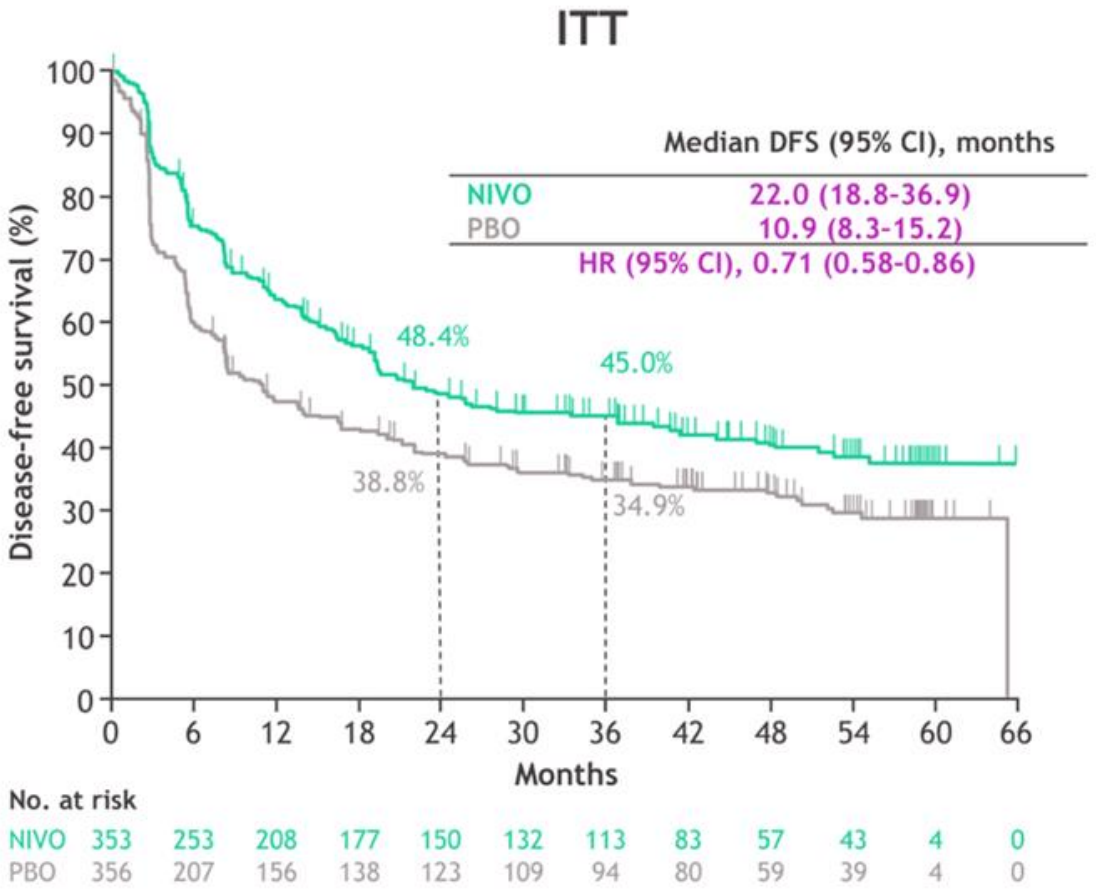


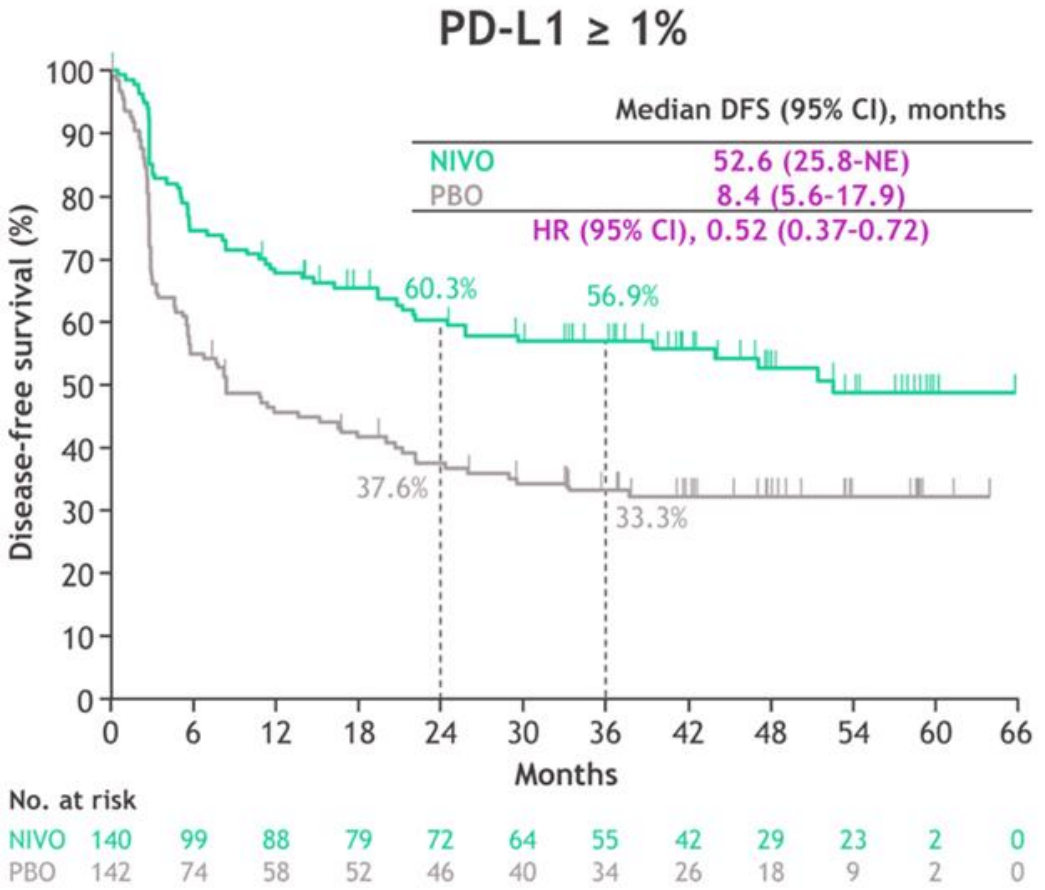


Powles Ann Oncol 2021; Burger Eur Urol 2012;
Huo Eur Urol Oncol 2019; Dash Cancer 2006;
Sonpavde J Urol 2011; Galsky JCO 2011

PD1/PDL1 Checkpoint inhibitors in adjuvant setting

Checkmate 274: Overall Survival

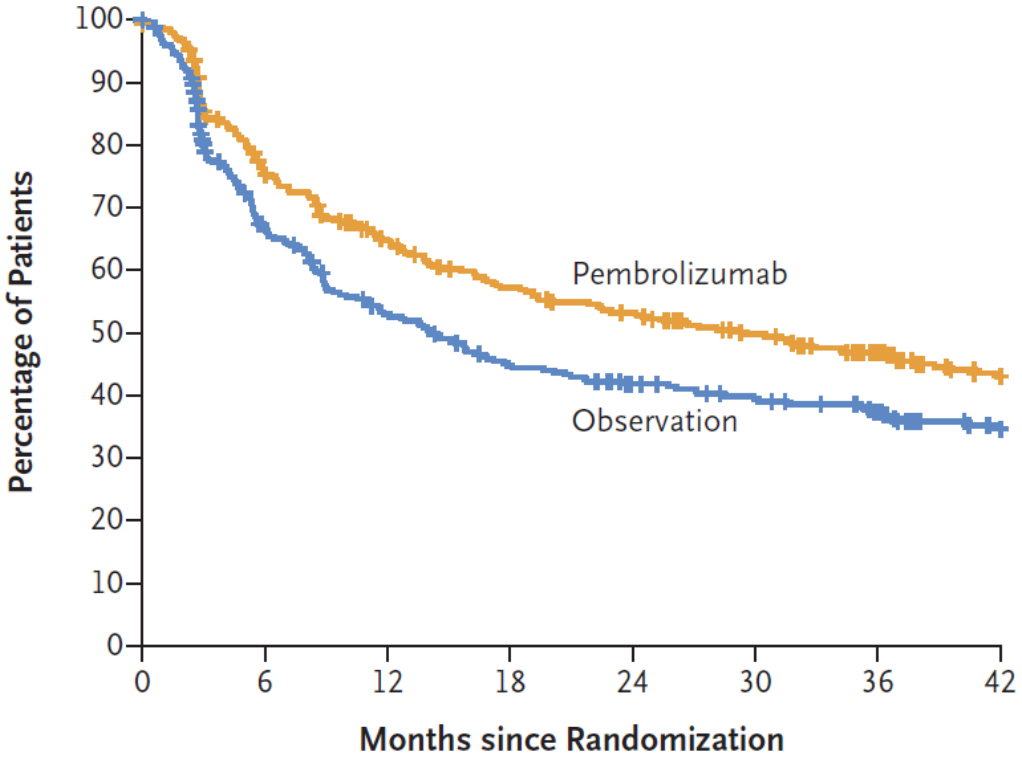




Galsky ASCO GU 2023

PD1/PDL1 Checkpoint inhibitors in adjuvant setting

AMBASSADOR Trial: Adjuvant Pembrolizumab



No. at Risk								
Pembrolizumab	354	247	202	174	159	137	114	85
Observation	348	198	150	124	107	96	81	58

	No. of Events/ Total No. of Patients	Median Disease-free Survival (95% CI)
		mo
Pembrolizumab	185/354	29.6 (20.0–40.7)
Observation	194/348	14.2 (11.0–20.2)

Hazard ratio for disease progression or death, 0.73 (95% CI, 0.59–0.90)
Stratified P=0.003 by log-rank test

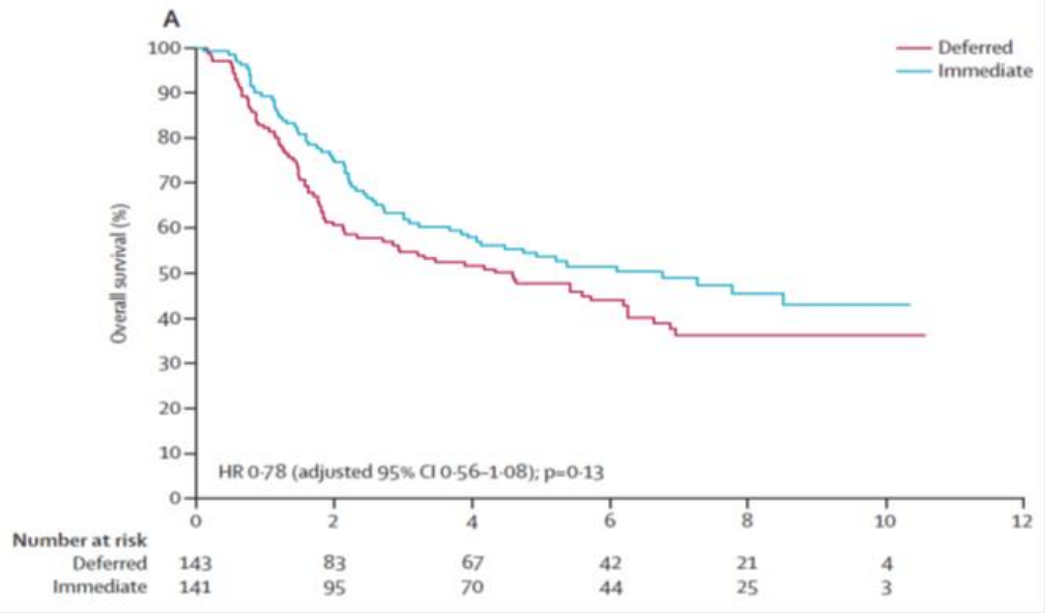
Apolo NEJM 2025

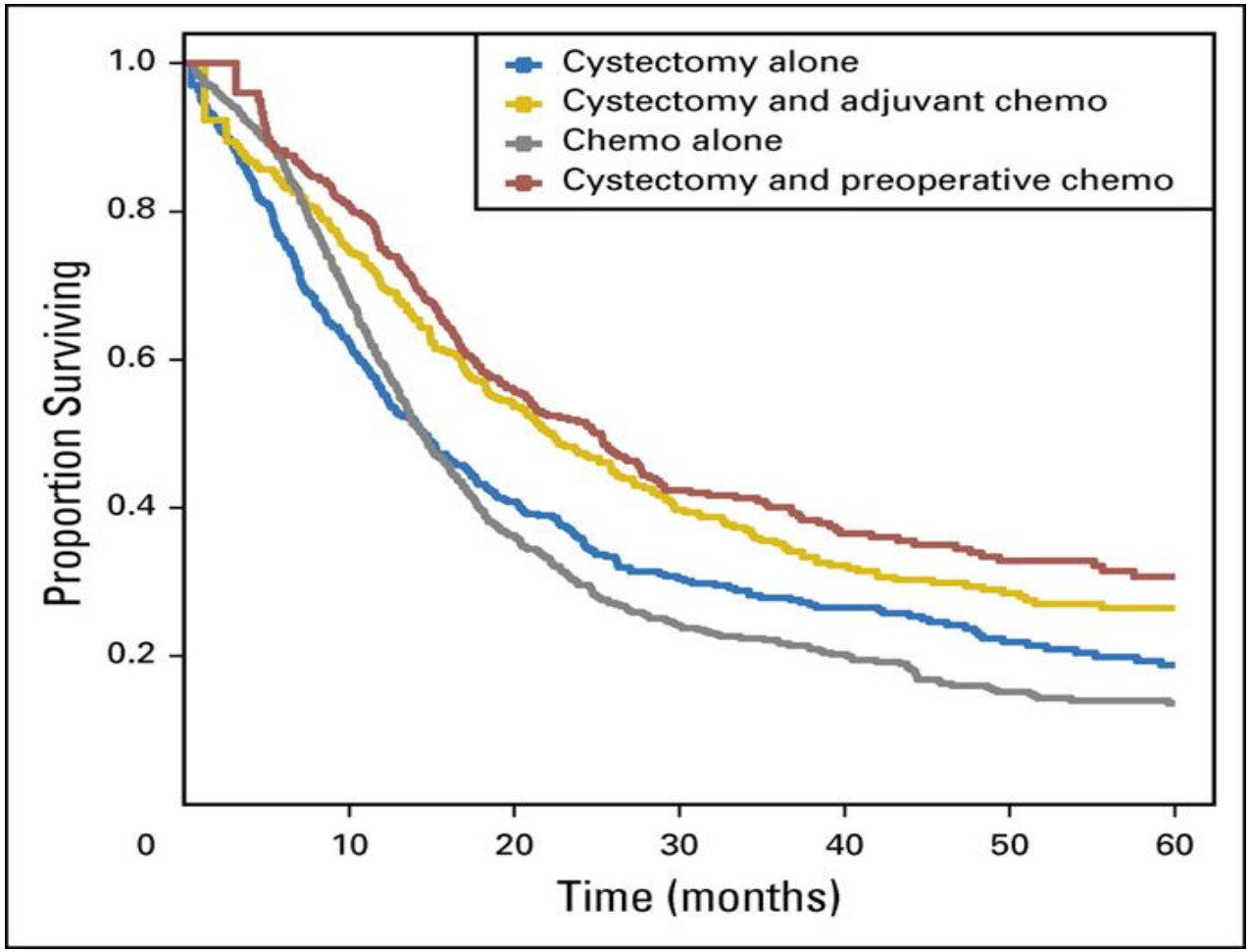
Adjuvant Chemotherapy

1,739 patients included in the analysis, (cN1, 48%; cN2, 45%; cN3, 7%), 36% received treatment with chemotherapy alone, 24% underwent cystectomy alone, 21% received preoperative chemotherapy followed by cystectomy, and 19% underwent cystectomy followed by adjuvant chemotherapy

Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3–pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial

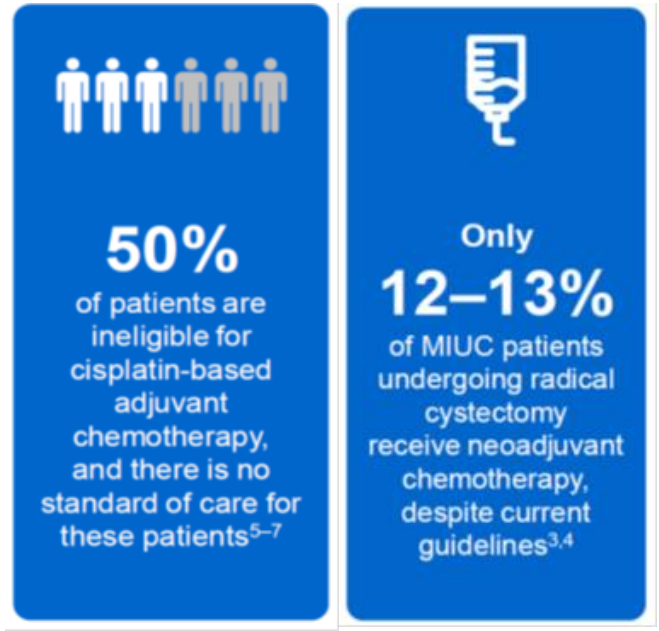
Cora N Sternberg, Iwona Skoneczna, J Martijn Kerst, Peter Albers, Sophie D Fossa, Mads Agerbaek, Herlinde Dumez, Maria de Santis, Christine Théodore, Michael G Leahy, John D Chester, Antony Verbaeys, Gedske Daugaard, Lori Wood, J Alfred Witjes, Ronald de Wit, Lionel Geoffrois, Lisa Sengelov, George Thalmann, Danielle Charpentier, Frédéric Rolland, Laurent Mignot, Santhanam Sundar, Paul Symonds, John Graham, Florence Joly, Sandrine Marreaud, Laurence Collette, Richard Sylvester, for the European Organisation for Research and Treatment of Cancer Genito-Urinary Cancers Group, Groupe d'Etude des Tumeurs Urogénitales, National Cancer Research Institute Bladder Cancer Study Group, National Cancer Institute of Canada Clinical Trials Group, and German Association of Urologic Oncology (AUO)

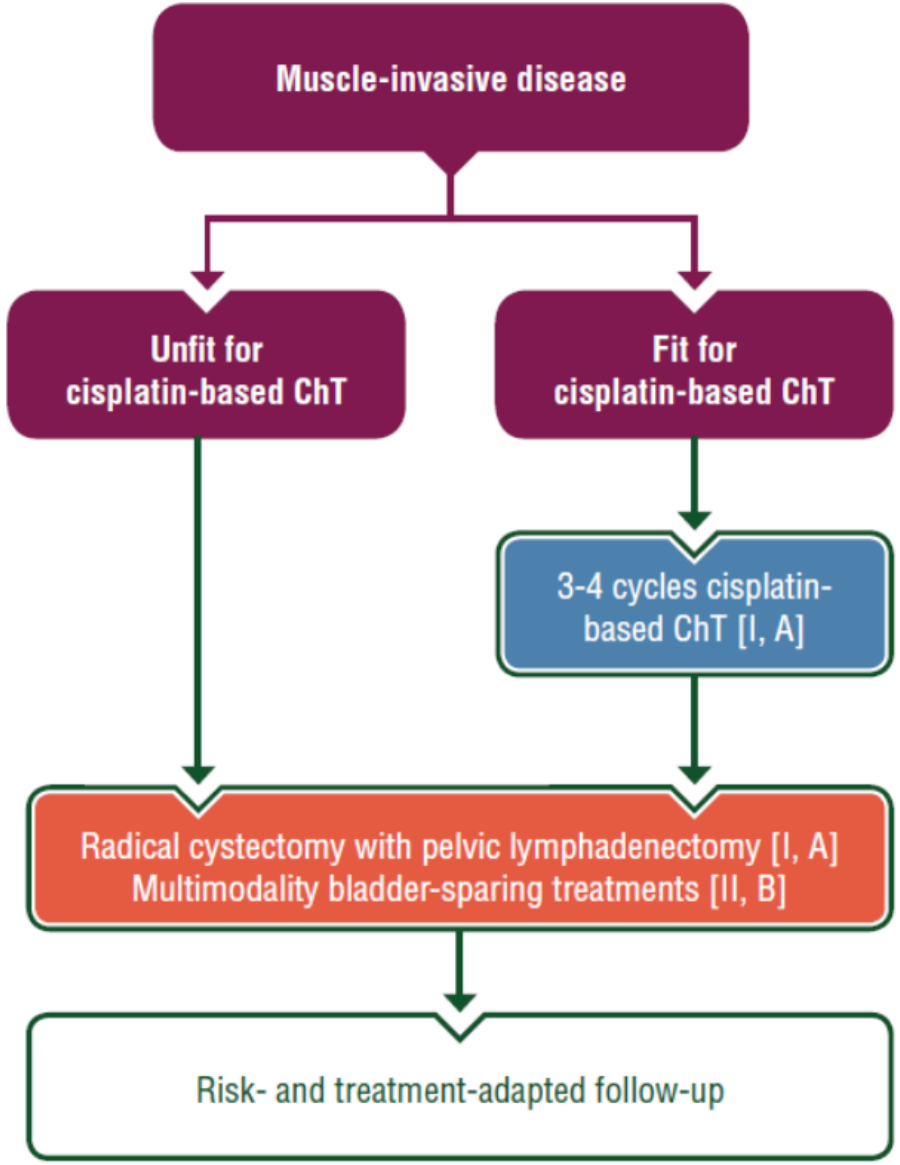




Sternberg Lancet Oncol 2015
Galsky JCO 2016

ESMO Guideline: Muscle Invasive Bladder Cancer





Powles Ann Oncol 2021; Burger Eur Urol 2012;
Huo Eur Urol Oncol 2019; Dash Cancer 2006;
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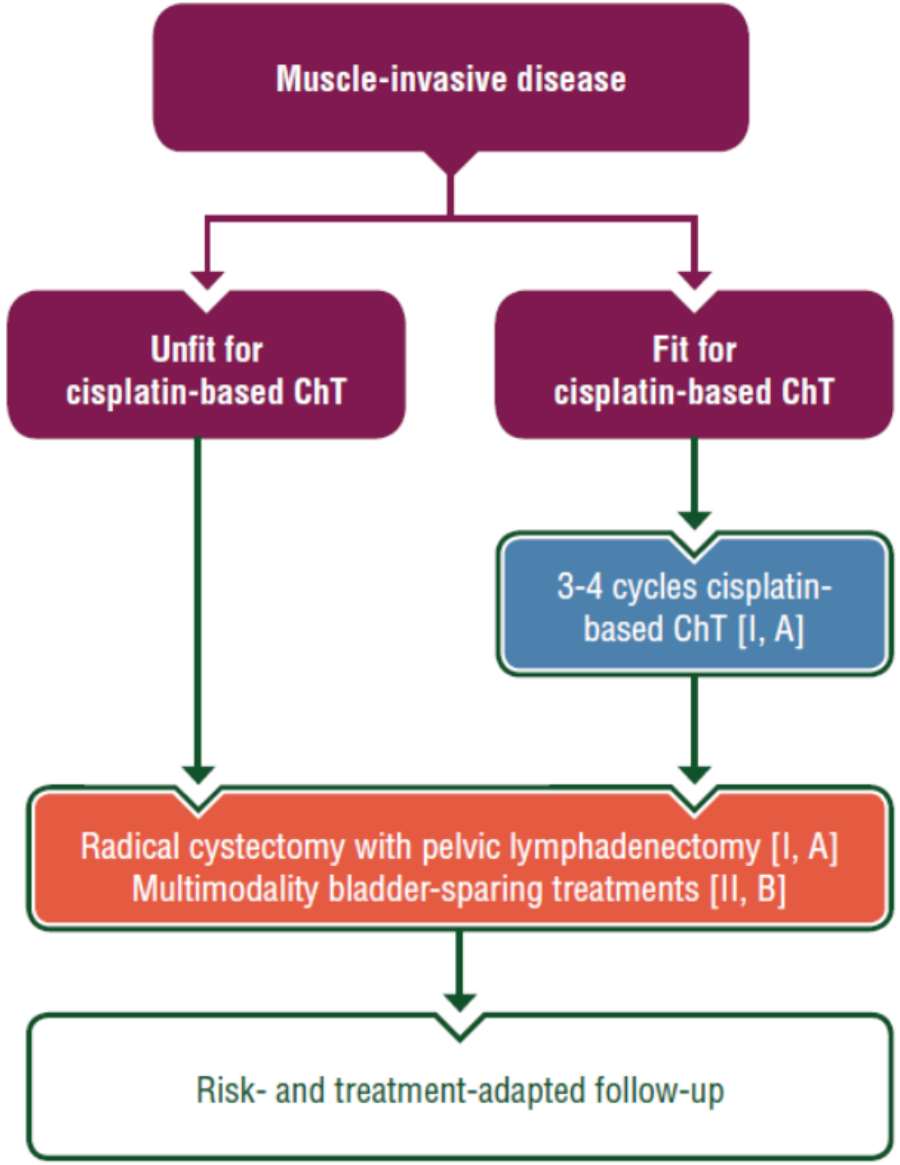
ESMO Guideline: Muscle Invasive Bladder Cancer

50%
of patients who receive neoadjuvant chemotherapy have residual high-risk disease (≥pT2) with an associated median survival of 3.4 years[5]

40–67%
of patients with pT3–T4a or lymph node-positive disease relapse after RC alone, with a poor 5-year OS (25–30%)[1,2]

50%
of patients are ineligible for cisplatin-based adjuvant chemotherapy, and there is no standard of care for these patients[5–7]

Only
12–13%
of MIUC patients undergoing radical cystectomy receive neoadjuvant chemotherapy, despite current guidelines[3,4]



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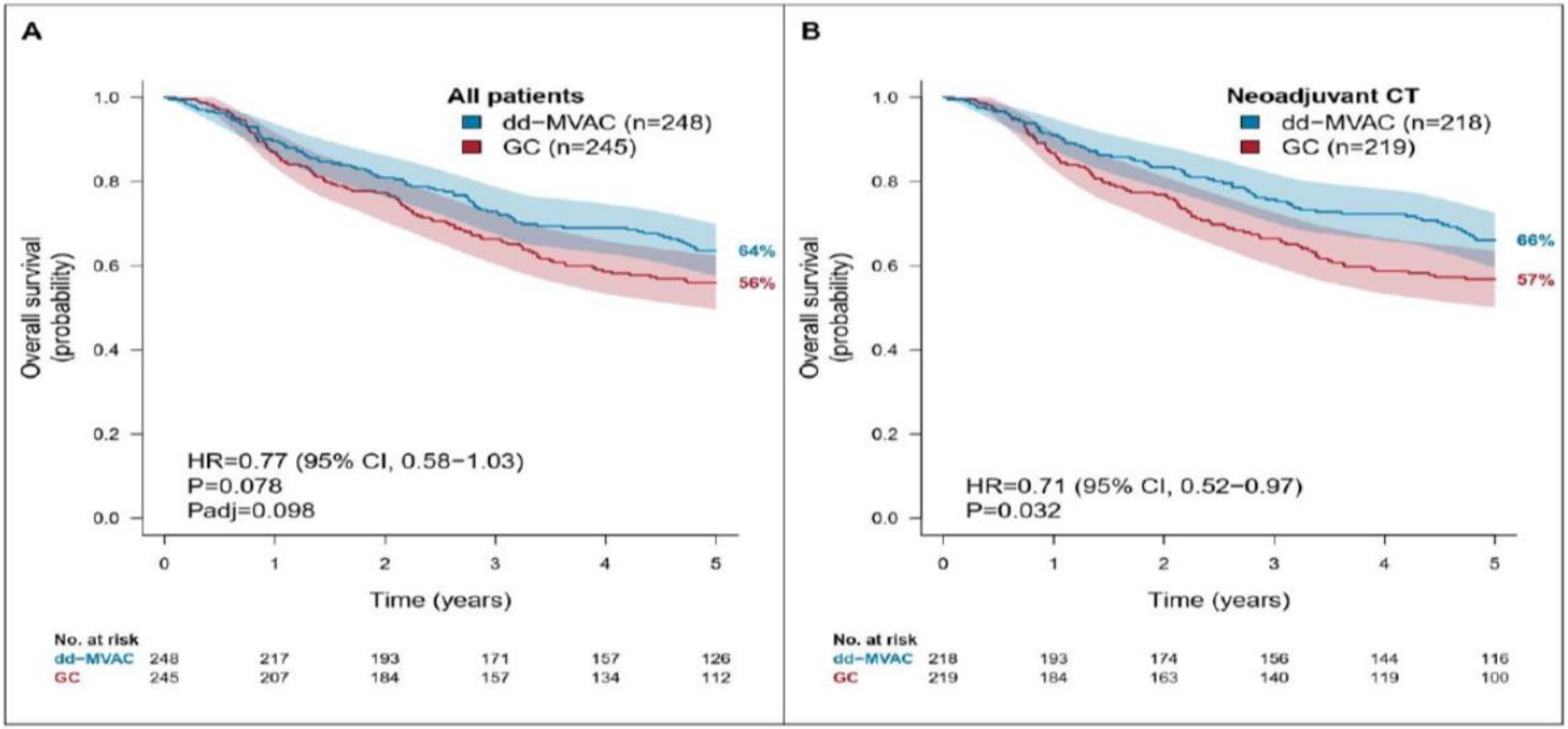
Sonpavde J Urol 2011; Galsky JCO 2011;
Gschwned Eur Urol 2002; Shariat J Urol 2006;

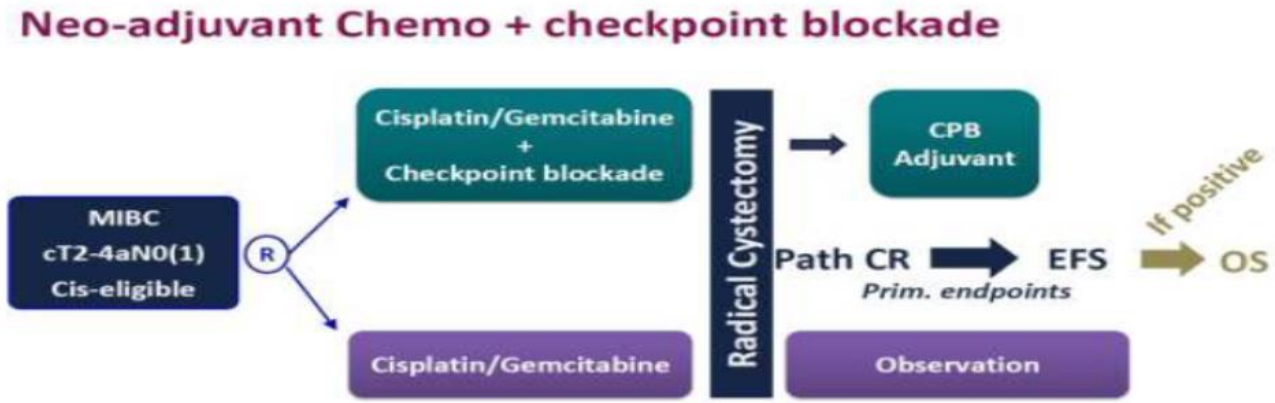
„Optimal“ Chemotherapy

VESPER Trial 5-year OS



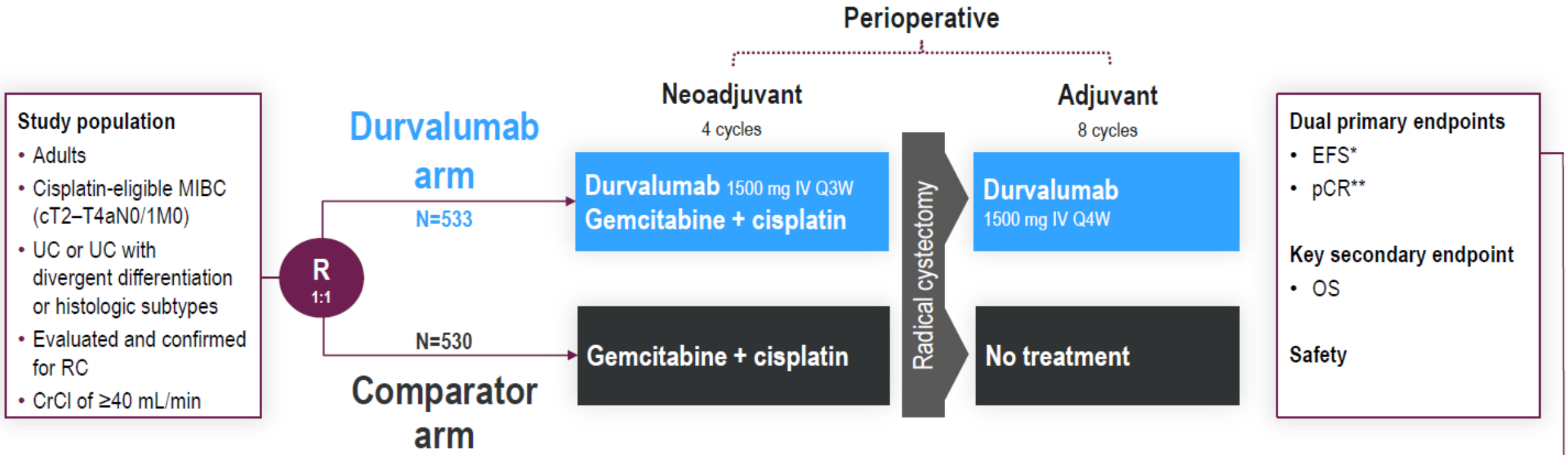
Checkpoint inhibitors in neoadjuvant setting

Cisplatin Eligible Population



KEYNOTE-866 NCT03924856	—	CDDP-GEM + pembro	Chemo	pCR, EFS	06/2025
NIAGARA NCT03732677	—	CDDP-GEM + durva	Chemo	pCR, EFS	06/2025
EV-304 NCT04700124	—	neoadj. 4x EV + pembro adj. 5x EV + P → 13x P adj.	Chemo	pCR, EFS	12/2026
ENERGYZE NCT04700124	Chemo + nivo+ linrodostat	Chemo + nivo	Chemo	pCR, EFS	12/2026

NIAGARA: Study Design



Stratification factors

Clinical tumour stage (T2N0 vs >T2N0)

Renal function (CrCl ≥60 mL/min vs ≥40–<60 mL/min)

PD-L1 status (high vs low/negative expression)

Gemcitabine/cisplatin dosing

CrCl ≥60 mL/min: Cisplatin 70 mg/m^2 + gemcitabine 1000 mg/m^2 Day 1, then gemcitabine 1000 mg/m^2 Day 8, Q3W for 4 cycles

CrCl ≥40–<60 mL/min: Split-dose cisplatin 35 mg/m^2 + gemcitabine 1000 mg/m^2 Days 1 and 8, Q3W for 4 cycles

EFS was defined as:

- Progressive disease that precluded RC
- Recurrence after RC
- Date of expected surgery in patients who did not undergo RC
- Death from any cause

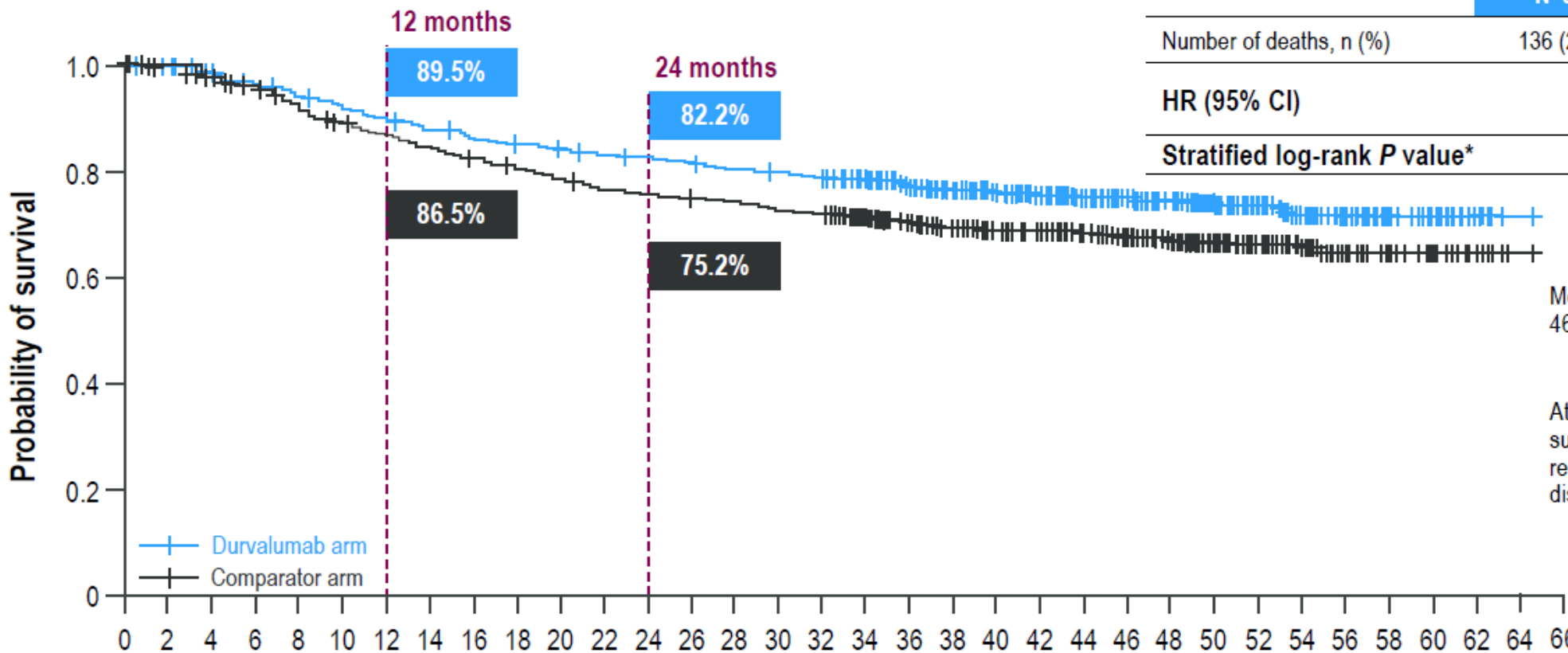
Other endpoints (not reported here): DFS, DSS, MFS, HRQoL, 5-year OS

*Evaluated by blinded independent central review or central pathology review (if a biopsy was required for a suspected new lesion). **Evaluated by blinded central pathology review.

ClinicalTrials.gov, NCT03732677; EudraCT number, 2018-001811-59. CrCl, creatinine clearance; DFS, disease-free survival; DSS, disease-specific survival; EFS, event-free survival; HRQoL, health-related quality of life; IV, intravenous; MFS, metastasis-free survival; MIBC, muscle-invasive bladder cancer; OS, overall survival; pCR, pathologic complete response; PD-L1, programmed cell death ligand-1; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomised; RC, radical cystectomy; UC, urothelial carcinoma..

NIAGARA: Overall Survival (ITT)

	Durvalumab arm N=533	Comparator arm N=530
Number of deaths, n (%)	136 (25.5)	169 (31.9)
HR (95% CI)	0.75 (0.59–0.93)	
Stratified log-rank *P* value*	0.0106	



No. of patients at risk

Durvalumab arm	533	528	517	505	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	516	507	490	467	450	438	425	413	402	392	383	378	373	368	363	358	334	311	281	259	239	215	194	174	141	113	90	60	38	21	10	2	0

Median follow-up in censored patients: 46.3 months (range, 0.03–64.7)

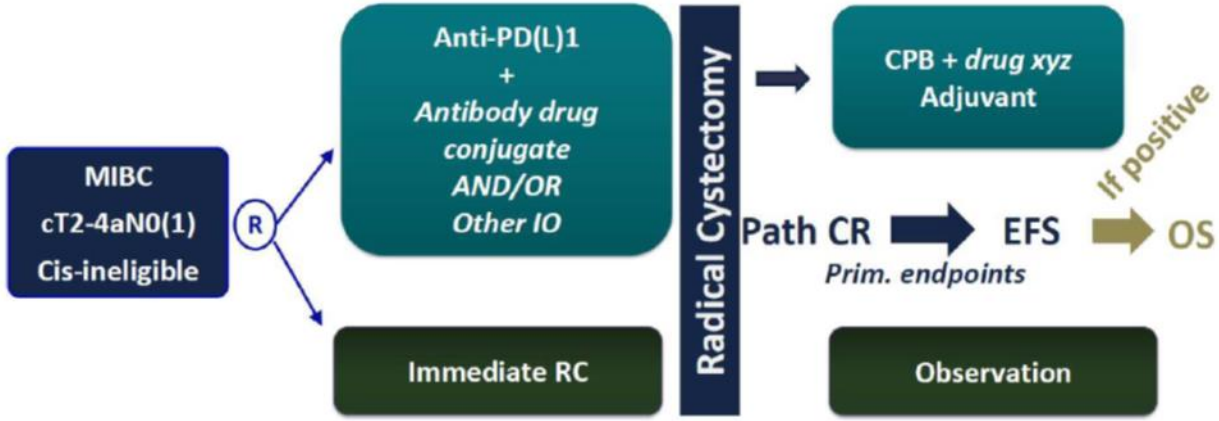
At the time of this analysis, at least 1 subsequent anti-cancer therapy was reported after treatment discontinuation for:

- 53 patients in the durvalumab arm
- 93 patients in the comparator arm

OS is the time from the date of randomisation until death due to any cause regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy. *The threshold for statistical significance was based on a Lan-DeMets alpha spending function with O'Brien-Fleming boundary – with the observed number of events, the boundary for declaring statistical significance was 0.01543 for a 4.9% overall 2-sided alpha.
Data cutoff 29 Apr 2024. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat population; OS, overall survival.

Checkpoint inhibitors in neoadjuvant setting

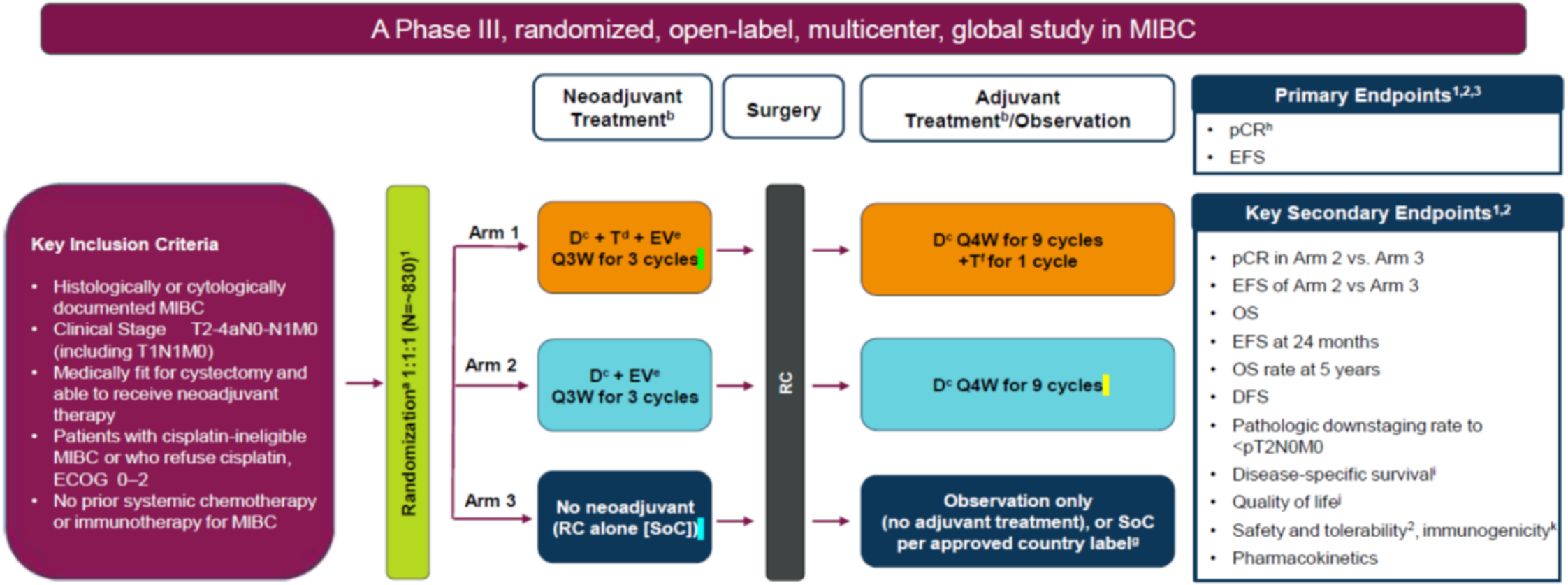
Cisplatin Ineligible Population



MK-905 NCT03924895	neoadj. 3x Pembro adj. 14x Pembro	neoadj: 3x P+ EV adj: 6x P + EV → 8x P	+	pCR, EFS	05/2027
PIVOT-IO-09 NCT04209114	neoadj + adj Nivo	neoadj + adj. Nivo + NKTR-214*	+	pCR, EFS	06/2023
VOLGA NCT04960709	neoadj and adj. Durva + EV	neoadj. and adj. Durva + Treme + EV	+ (+/- SOC adj IO)	EFS, OS, safety	07/2025

Checkpoint inhibitors in neoadjuvant setting

VOLGA Trial



NCT04960709

Conclusion

- **Enfortumab-vedotin plus pembrolizumab are SOC for 1L LA/mUC**
- Toxicity and economy issues
- Platinum based chemo with avelumab maintenance or Nivo plus cisplatinum-based chemo are valid options

- **Cisplatinum-based neoadjuvant chemo is SOC for MIBC**

- **50% of patients are unfit for cisplatin (and up to 30% of patients recieve NACT)**
- Adjuvant immunotherapy
- Neoadjuvant trials with novel agents

- **Low pCR and DFS rates for standard theapies**
- Immunotherapy and ADC incorporation in the treatment
- More intensive chemotherapy regimens

Thank you!

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