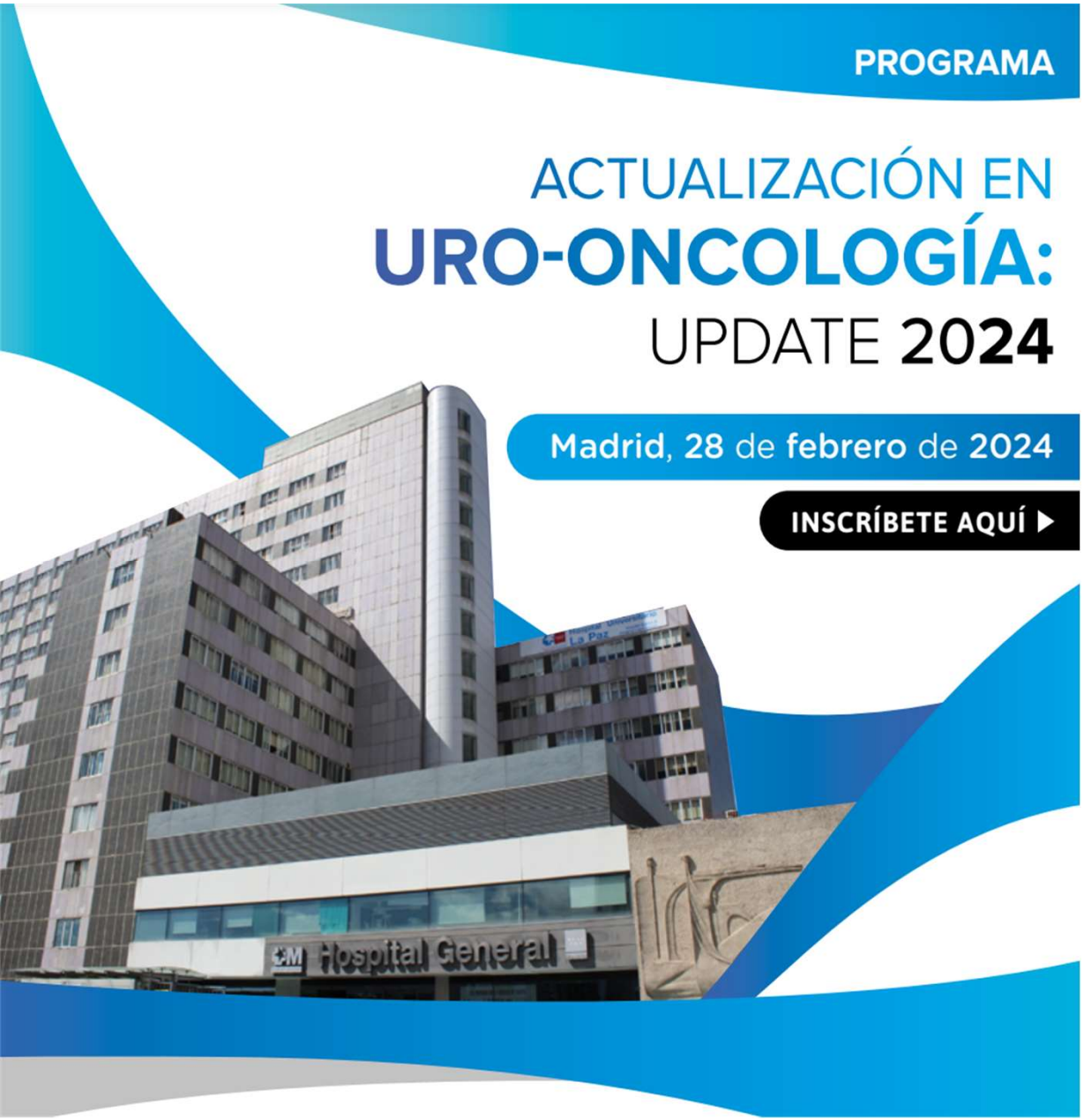
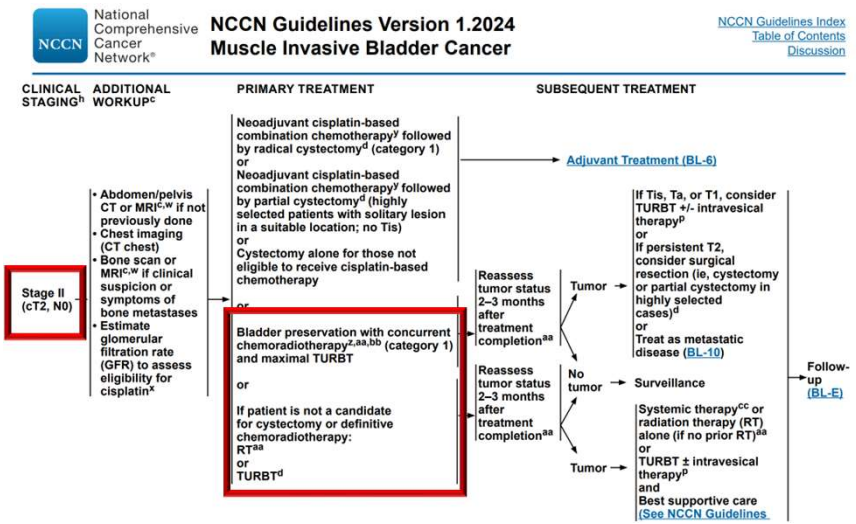
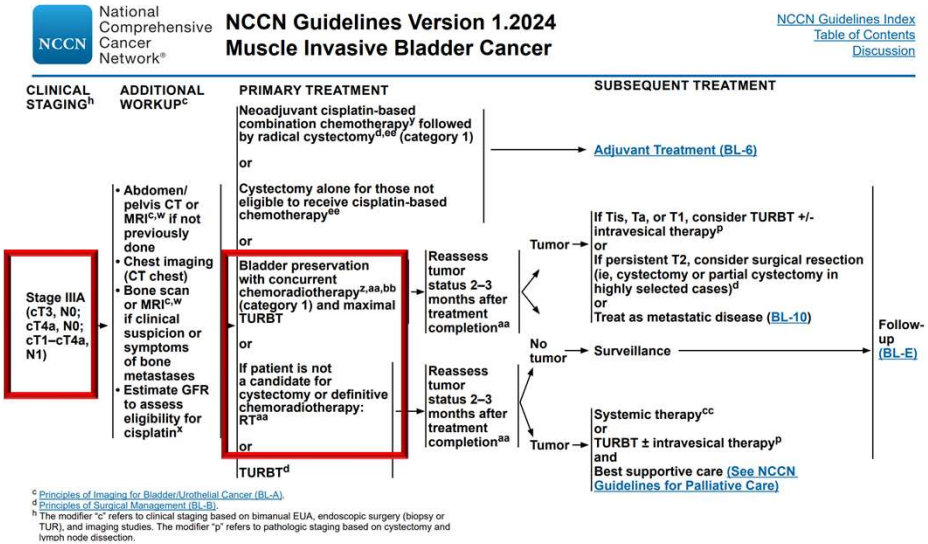


¿Pueden las nuevas terapias reforzar el papel del tratamiento de preservación vesical en cáncer de vejiga músculo-invasivo?

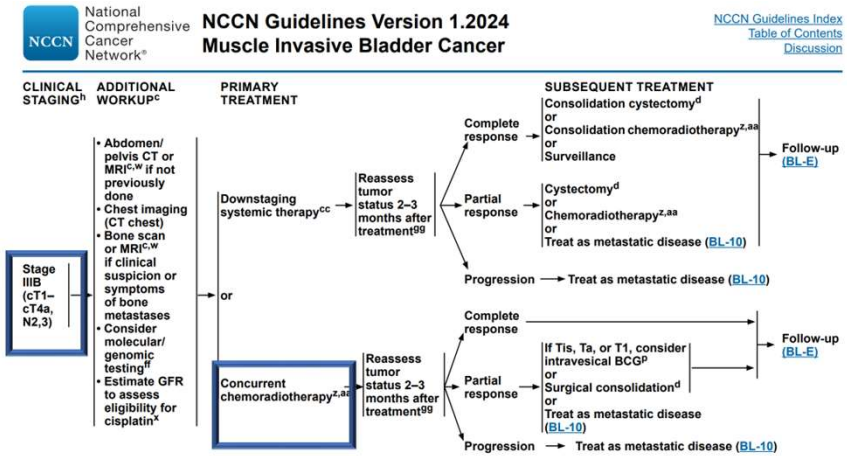
Felipe Couñago PhD
Director Médico Nacional GenesisCare
Universidad Europea de Madrid
Universidad Alfonso X El Sabio

Indications for Bladder Preservation (TMT)





[c] Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[d] Principles of Surgical Management (BL-B).
[h] The modifier "c" refers to clinical staging based on bimanual EUA, endoscopic surgery (biopsy or TUR), and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.



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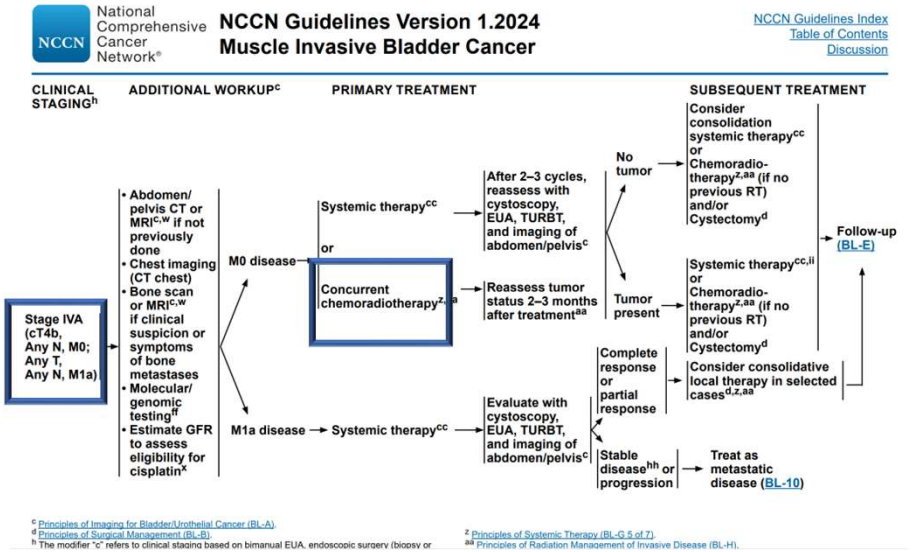
[z] Principles of Systemic Therapy (BL-G 5 of 7).
[aa] Principles of Radiation Management of Invasive Disease (BL-H).
[cc] Principles of Systemic Therapy (BL-G 2 of 7).



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[z] Principles of Systemic Therapy (BL-G 5 of 7).
[aa] Principles of Radiation Management of Invasive Disease (BL-H).

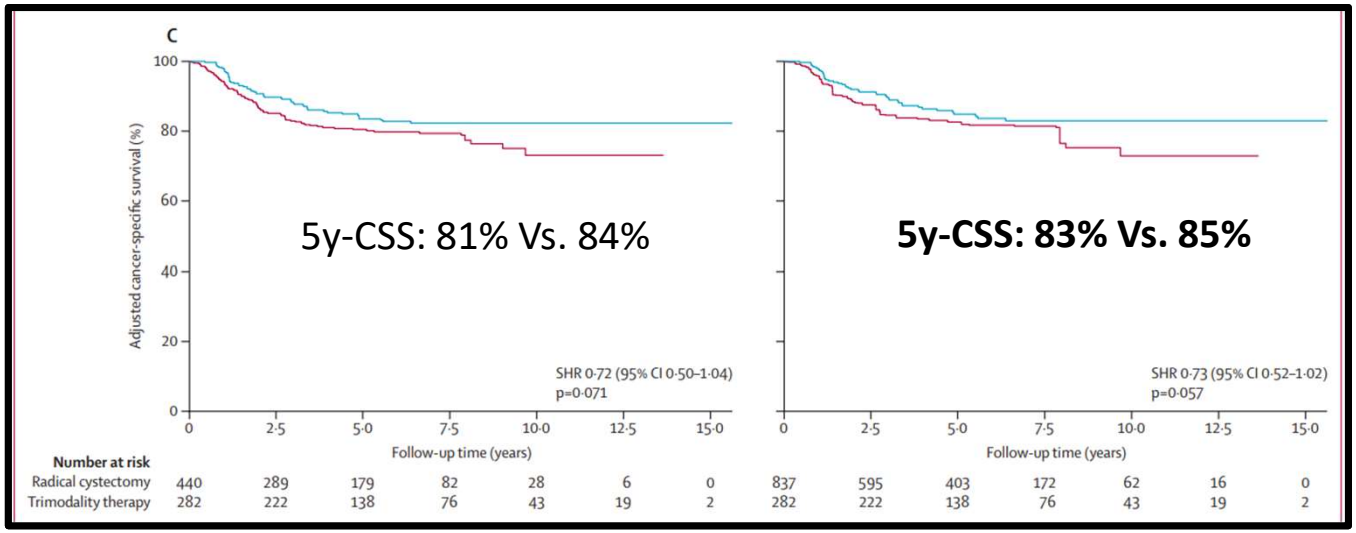
Radical cystectomy versus trimodality therapy for muscle invasive bladder cancer: a multi-institutional propensity score matched and weighted analysis

	Before matching			After 3:1 matching		
	Radical cystectomy (n=440)	Trimodality therapy (n=282)*	p value	Radical cystectomy (n=837)†	Trimodality therapy (n=282)*	p value
Age, years	71·2 (63·7–77·2)	71·6 (64·0–78·9)	0·22	71·4 (66·0–77·1)	71·6 (64·0–78·9)	0·76
Sex	..	..	0·31	..	..	0·65
Female	92 (21%)	68 (24%)	..	213 (25%)	68 (24%)	..
Male	348 (79%)	214 (76%)	..	624 (75%)	214 (76%)	..
Carcinoma in situ	..	..	0·096	..	..	0·51
No	324 (74%)	223 (79%)	..	646 (77%)	223 (79%)	..
Yes	116 (26%)	59 (21%)	..	191 (23%)	59 (21%)	..
Clinical T-stage	..	..	0·0024	..	..	0·91
T2	362 (82%)	255 (90%)	..	755 (90%)	255 (90%)	..
T3–4	78 (18%)	27 (10%)	..	82 (10%)	27 (10%)	..
BMI	..	..	0·014	..	..	0·40
<30 kg/m²	340 (77%)	192 (69%)	..	600 (72%)	192 (69%)	..
≥30 kg/m²	100 (23%)	86 (31%)	..	237 (28%)	86 (31%)	..
Missing	0	4	..	0	4	..
Hydronephrosis	..	..	<0·0001	..	..	0·35
No	339 (77%)	255 (90%)	..	740 (88%)	255 (90%)	..
Yes	101 (23%)	27 (10%)	..	97 (12%)	27 (10%)	..
Neoadjuvant or adjuvant chemotherapy	..	..	<0·0001	..	..	0·42
No	259 (60%)	123 (44%)	..	340 (41%)	123 (44%)	..
Yes	176 (40%)	159 (56%)	..	492 (59%)	159 (56%)	..
Missing	5	0		5	0	
Smoking history	..	..	0·57	..	..	0·91
Never smoked	115 (26%)	69 (24%)	..	201 (24%)	69 (24%)	..
Current or former smoker	321 (74%)	213 (76%)	..	632 (76%)	213 (76%)	..
Missing	4	0	..	4	0	..
ECOG status	..	..	0·59	..	..	0·57
0	189 (75%)	218 (77%)	..	392 (76%)	218 (77%)	..
1 or 2	62 (25%)	64 (23%)	..	127 (24%)	64 (23%)	..
Missing	189	0	..	318	0	..

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. *All patients in the trimodality therapy cohort received concurrent radiosensitising chemotherapy. †Of the 282 trimodality therapy patients, with 3:1 matching, nine could only be matched to two radical cystectomy patients, therefore resulting in a total of 837 matched radical cystectomy patients, instead of 846.

Table: Baseline characteristics before and after matching

N=1119



- **This multi-institutional study provides the best evidence to date showing similar oncological outcomes between radical cystectomy and trimodality therapy for select patients with muscle-invasive bladder cancer.**

Zlotta AR. Lancet Oncol. 2023

TMT: Radiotherapy

Choudhury A. Lancet Oncol 2021

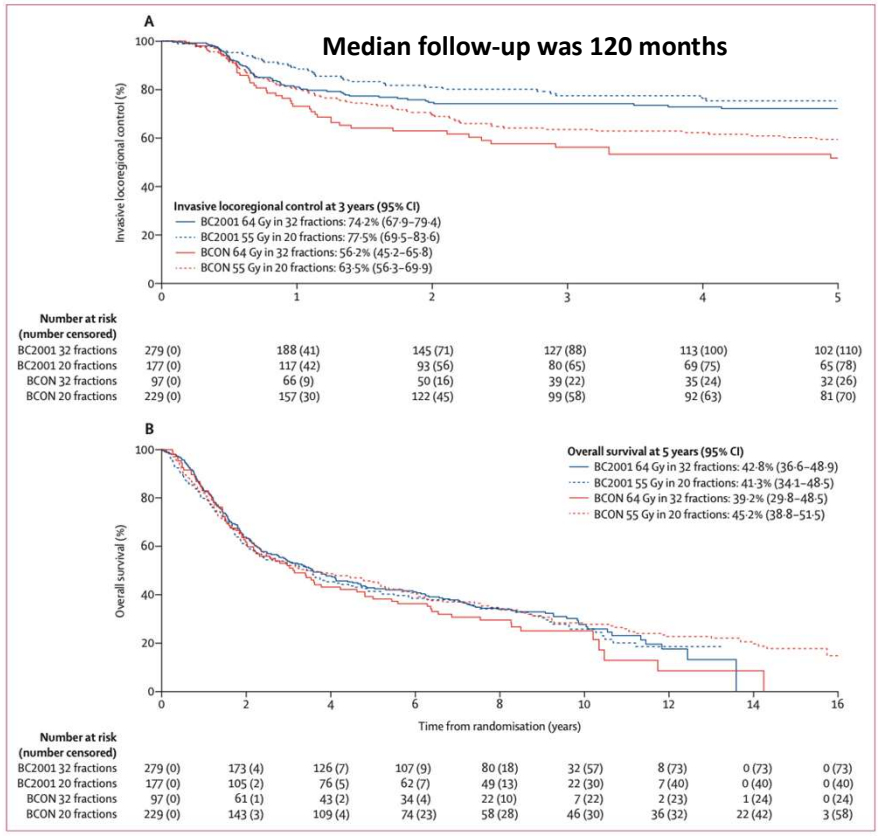


Figure 2: Kaplan-Meier estimates of observed invasive locoregional control (A) and observed overall survival (B) by trial and fractionation group

Hypofractionated radiotherapy in locally advanced bladder cancer: an individual patient data meta-analysis of the BC2001 and BCON trials

Ananya Choudhury, Nuria Porta*, Emma Hall, Yee Pei Song, Ruth Owen, Ranald MacKay, Catharine M L West, Rebecca Lewis, Syed A Hussain, Nicholas D James†, Robert Huddart†, Peter Hoskin†, on behalf of the BC2001 and BCON investigators*

	64 Gy in 32 fractions (n=278)	55 Gy in 20 fractions (n=295)
2-year late toxicity		
Rectum	7 (3%)	17 (6%)
Bladder	66 (24%)	74 (25%)
Rectum or bladder	69 (25%)*	82 (28%)†
5-year late toxicity		
Rectum	8 (3%)	21 (7%)
Bladder	86 (31%)	88 (30%)
Rectum or bladder	89 (32%)‡	97 (33%)§

LENT-SOMA urinary and rectal dysfunction subscales were recorded up to 5 years after radiotherapy in the BC2001 and BCON trials. LENT-SOMA=Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic. *Four patients with both. †Nine patients with both. ‡Five patients with both. §12 patients with both.

Table 2: **LENT-SOMA grade 3–4 bladder or rectum toxicity after the end of treatment by fractionation groups**

55 Gy in 20 fractions should be adopted as a standard of care for bladder preservation in patients with locally advanced bladder cancer

TMT: Concomitant Chemotherapy

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Bladder Cancer

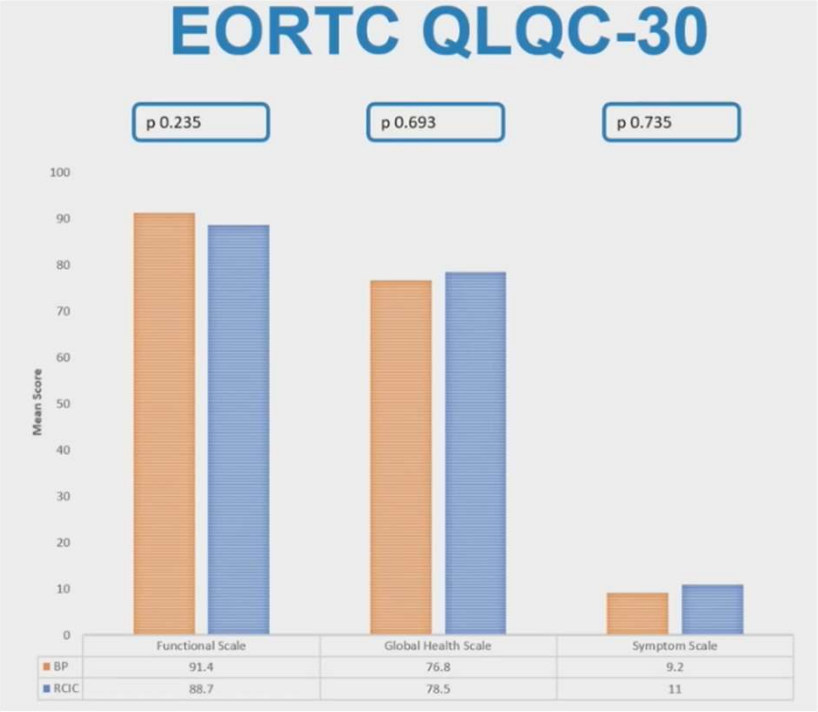
NCCN Guidelines Index
Table of Contents
Discussion

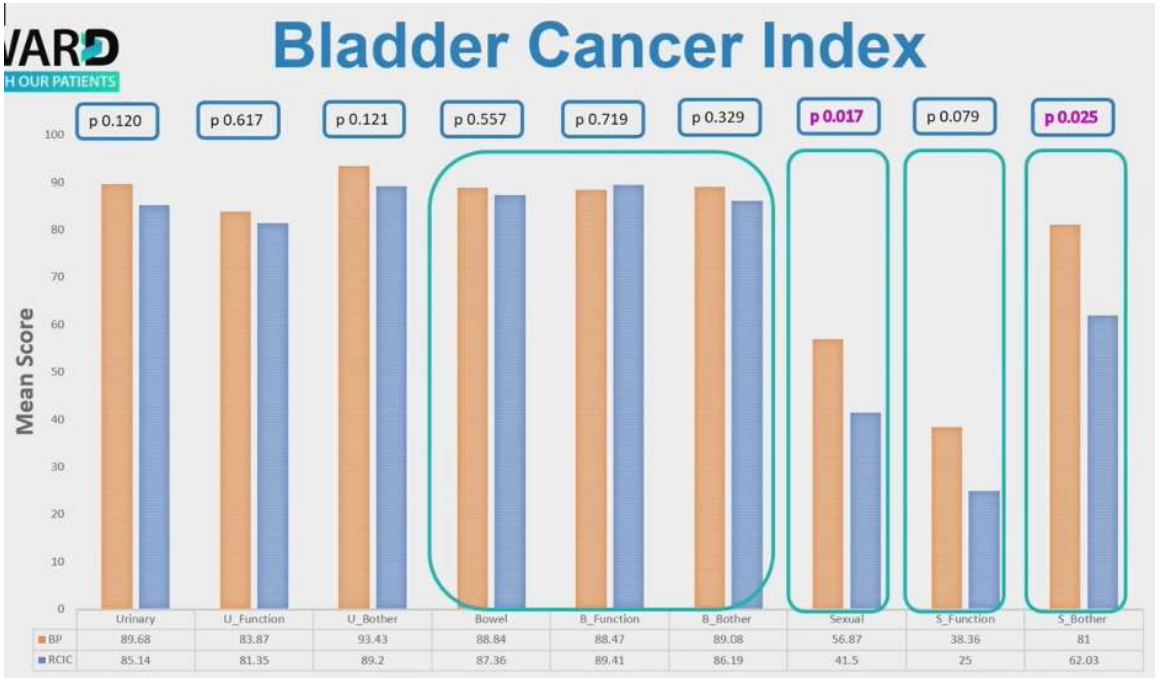
PRINCIPLES OF SYSTEMIC THERAPY

Radiosensitizing Chemotherapy Regimens[i]
Preferred regimens • Cisplatin[h] alone[35,36] • Low-dose gemcitabine[37-39] • 5-FU and mitomycin[40]
Other recommended regimen • Cisplatin and 5-FU[37,41] • Cisplatin and paclitaxel[37,42]
Useful in certain circumstances (not generally used for curative-intent chemoradiotherapy for organ preservation) • Taxane (docetaxel or paclitaxel) (category 2B) • 5-FU (category 2B) • Capecitabine (category 3)

*RTOG 02-33; RTOG 95-06; RTOG 99-06; RTOG 09-26; BC2011; RTOG 0712; BCON

Prospective Comparative Study of Quality of Life in Bladder Cancer Patients Undergoing Cystectomy or Bladder Preservation





- Overall, bladder cancer survivors have good quality-of-life outcomes. There are no differences in urinary and bowel domains with radiotherapy and surgery
- Sexual bother scores are better with radiotherapy compared to radical cystectomy
- Quality-of-life should be central to the decision-making process

Murthy V. ASTRO 2023

Quality of life after radical treatment for muscle invasive bladder cancer: A systematic review and meta-analysis

Methods: A systematic review was carried out including all prospective and retrospective studies enrolling patients treated with radical intent for non-metastatic MIBC from 1999 to 2021 (either RC or TMT). All studies included specifically reported QoL for one of the main treatment approaches explored (RC followed by ileal conduit urinary diversion-ICUD, ONB or TMT). Review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Results: Fifty studies were included in the final analysis, assessing QoL after RC followed by ICUD or ONB in 6 and 15 cases, respectively. Six studies addressed QoL after TMT. ICUD vs ONB and TMT vs ICUD/ONB comparisons were carried out in 21 and 1 studies, respectively. Pooled analysis for EORTC QLQ- C30 and BLM-30 questionnaires showed that ONB yielded a significant advantage if compared to ICUD only for Physical Functioning (pooled mean standardized difference -0.73 SD, p-value 0.019, I 2 =93%) and for Emotional Functioning (pooled mean standardized difference -0.16 SD, p-value 0.029, I 2 =0%). A trend in favour of higher mean reported values after TMT for Global Health Score, Physical Functioning and Role Functioning was found, if compared to both RC approaches

In most cases, CR entails the need to an external urinary diversion and urostomy, unless orthotopic reconstruction can be performed. This has an impact on sexual function and can cause psychological and emotional problems, worsening the quality of life.

Francolini G. ASCO 2023

Clinical Studies of TMT in MIBC

Estudio	Esquema de tratamiento	Medida de resultado primaria	Estado
ARTIA-Vesica NCT05295992	Radioterapia adaptativa diaria	Toxicidad	Reclutamiento
HIRACOM NCT5453682	CT (cisplatino) + hypo-IMRT (64 Gy en 32 fx) CT (cisplatino) + hypo-IMRT (56-64 Gy en 20 fx vol. riesgo alto) y 40-44 Gy vol. riesgo bajo	PFS a 2 años	Reclutamiento
HyBla_RCT NCT05397262	Hipertermia 1-2/semanas en 10 sesiones + RT (50,4 Gy en 28 fx + *boost* 5,4 Gy (R0) o 9 Gy (R1/2) + CT (cisplatino + 5 FU)	OS	Reclutamiento
ARTIA-Bladder NCT05700227	Radioterapia diaria adaptativa + CT	Toxicidad	Reclutamiento
RAIDER NCT02447549	WBRT; SART; DART	Toxicidad	Activo, no reclutando
NCT01104350	RT + Gemcitabina RT dosis: 23.4 Gy/1,8 Gy × 13 fx (total 68,4 Gy) 27 Gy/1,8 Gy × 15 fx (total 72 Gy) 30,6 Gy/1,8 Gy × 17 fx (total 75,6 Gy)	Dosis máxima tolerada	Activo, no reclutando
GETUGV04 NCT01495676	RT (45 Gy pelvis y 63 Gy vejiga a 1,8 Gy/fx) + Cisplatino Cisplatino + gemcitabina	PFS	Activo, no reclutando

These trials include adaptive radiation techniques, dose escalation, hypofractionation and different sensitizing agents

Lopez Valcarcel M. Actas Urol Esp. 2024.

Stereotactic Ablative Radiotherapy Boost to Bladder Tumor for Bladder Preservation

General Treatment Schema

Maximal TURBT

↓

SABR (18 Gy/ 3frs) delivered to the tumor or tumor bed in the filling bladder

↓

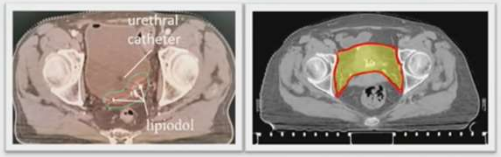
CFRT to the pelvic lymph nodes and emtpy bladder of 45 Gy/ 25 frs, and receive concomitant weekly Gemcitabine

↓

Cystoscopic response evaluation → (No CR) Salvage Radical Cystectomy

↓ CR

Frequent cystoscopy → Invasive recurrence



18 Gy/ 3 frs to tumor bed

45 Gy/ 25 frs to the empty bladder and pelvie LNs

Characteristics of all patients		
Characteristics	No.	%
Age at diagnosis	Median 76 yr, IQR 35-90	
Sex		
Male	49	81%
Female	11	19%
Clinical T stage		
T2	31	51%
T3	20	34%
T4	9	15%
Hydronephrosis		
Present	9	15%
Absent	51	85%

Characteristics of all patients		
Characteristics	No.	%
TURBT		
Visibly complete	26	42%
Visibly incomplete	34	58%
Pelvic RT		
Yes	34	56%
No	26	44%
Concurrent chemotherapy		
Yes	38	63%
No	22	37%

T3-4 : 49%

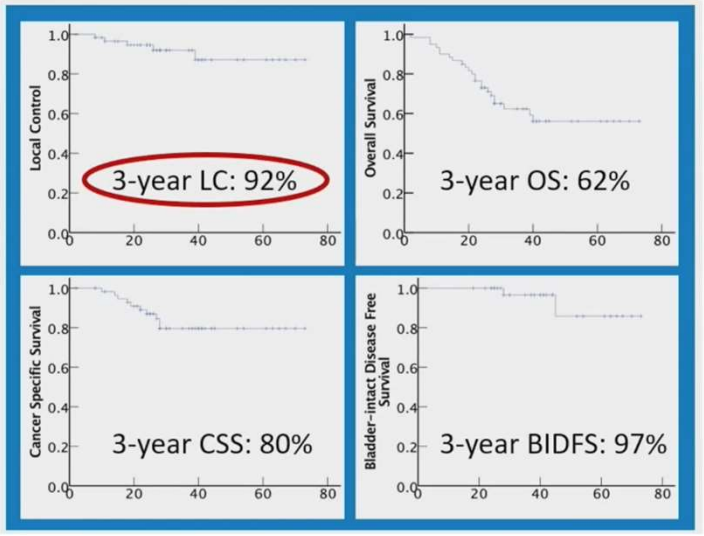


Table 2. Acute and late toxicity after TMT

	G1	G2	G3	G4
Acute GI	81.6% (49/60)	15.0% (9/60)	1.6% (1/60)	0
Acute GU	73.3% (44/60)	23.3% (14/60)	1.6% (1/60)	0
Late GI	8.3% (5/60)	0	0	0
Late GU	33.3% (20/60)	11.7% (7/60)	5.0% (3/60)	0

Shang-Bin Qin. ASTRO 2023

- **SABR boost followed by chemoradiation to the pelvis achieved an adequate local control rate at 3 years (92%) and was well-tolerated**
- **Given that distant metastasis was a 'critical mode of failure', this suggests that patients receiving trimodal therapy may benefit from adjuvant systemic therapy, such as immunotherapy.**

Ongoing studies of TMT with immune checkpoint inhibitors

Estudio	Esquema de tratamiento	1.er *End-point*	Estado
	Quimiorradioterapia + inmunoterapia		
ANZUP 1502 NCT02662062	RT (64 Gy en 32 fx) + cisplatino (35 mg/m^2) + pembrolizumab (200 mg	Seguridad	Activo, no reclutando
MK3475 NCT02621151	**Pembrolizumab**	e BIDFS a 2 años	Activo, no reclutando
	pembrolizumab (200 mg cada 3 semanas × 3 ciclos)		
KEYNOTE 992 NCT04241185	Brazo A: RT (64 Gy o 55 Gy) + CT (cisplatino 35 mg/m^2 o 5 FU 500 mg/m^2 + MMC 12 mg/m^2 Brazo B: gemcitabina 27 mg/m^2) ± pembrolizumab (400 mg cada 6 semanas)	BIDFS	Reclutamiento
SWOG/NRG 1806 NCT03775265	**Atezolizumab**		Reclutamiento
	6 semanas por 6 meses)		
CRIMI NCT03844256	**Nivolumab+Ipi**		Reclutamiento
	ipilimumab + nivolumab		
ML-39576 NCT03620435	RT (50 Gy) + atezolizumab	Seguridad	Completado
BladderSpar	**Atezolizumab**		Reclutamiento
	1200 mg / 3 semanas por 12 meses		
INSPIRE NCT04216290	RT + CT + durvalumab (3 ciclos)	Respuesta clínica completa	Reclutamiento
SunRISe-2 NCT04658862	**Durva+Cetrelimab+TAR**		Reclutamiento
	partir de la semana 24/12 semanas durante 3 años Brazo B: CTRT (cisplatino o gemcitabina) + RT (64 Gy o 55 Gy solo vejiga)		
RADIOTERAPIA + IMMUNOTERAPIA NUTRA NCT03421652	**Nivolumab**	es	Activo, no reclutando
	nivolumab (240 mg cada 2 semanas)		
IMMUNOPRESERVE NCT03702179	**Durva+Tremilumumab**		Activo, no reclutando
	4 semanas)		
ATEZOBLADDER PRESERVE NCT04186013	**Atezolizumab**	ógica	Activo, no reclutando

Lopez Valcarcel M. Actas Urol Esp. 2024.

Long-Term Outcomes of Pembrolizumab in Combination with Gemcitabine and Concurrent Hypofractionated Radiation Therapy as Bladder Sparing Treatment for Muscle-Invasive Urothelial Cancer of the Bladder: A Multicenter Phase 2 Trial

Economides M. ASCO 2023

Adverse Event	N (%)
Cytopenias	7 (13%)
Colitis/colonic perforation	5 (9%)
Cystitis	2 (4%)
Polyneuropathy	1 (2%)
Fatigue	1 (2%)
Hypokalemia	1 (2%)

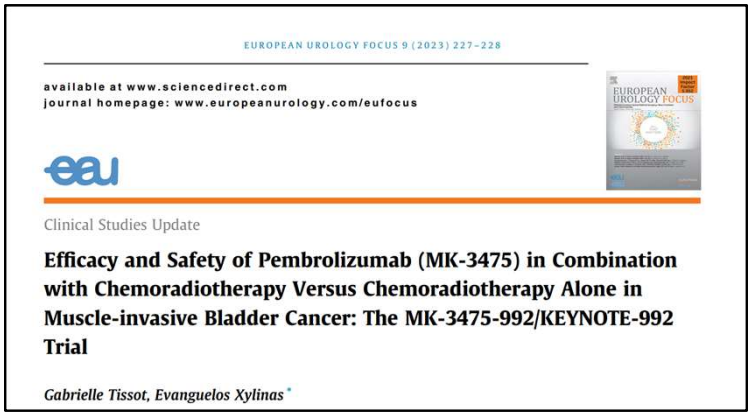
Efficacy (n=54)	2-year % (95%CI)	Median in months (range)
BIDFS	71% (69%-91%)	47.4 (33.2-not reached)
MFS	78% (64%-87%)	47.4 (47.4-not reached)
OS	83% (69%-91%)	Not reached
12-week CR rate	80%	NA

- ✓ **Trimodality therapy combined with pembrolizumab was well tolerated and continues to show promising early outcomes data**
- ✓ **A large phase 3 trial is underway to further explore this treatment**

Pembrolizumab and TMT: KEYNOTE-992

Rationale. Previous phase 2 study :

- An estimated 1-yr bladder-intact disease-free survival rate of 88%. in the efficacy cohort (n = 48), with acceptable toxicity (35% experienced grade 3 treatment-related adverse events).
- The 12-wk complete response rate was 83%, while the 1-yr metastasis-free survival rate (secondary endpoint) was 85%.

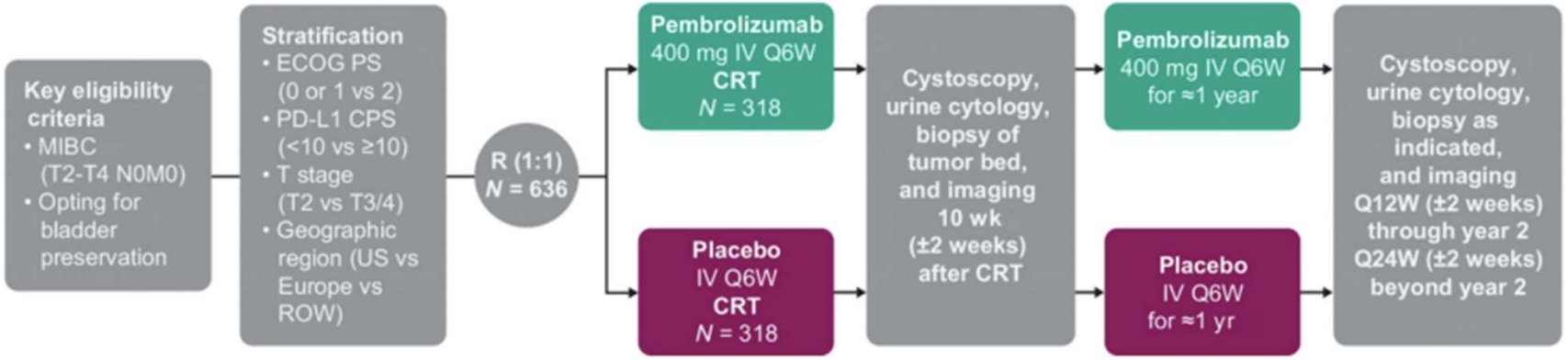

EUROPEAN UROLOGY FOCUS 9 (2023) 227–228

available at www.sciencedirect.com
journal homepage: www.europeanurology.com/eufocus

Clinical Studies Update

Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Chemoradiotherapy Versus Chemoradiotherapy Alone in Muscle-invasive Bladder Cancer: The MK-3475-992/KEYNOTE-992 Trial

Gabrielle Tissot, Evanguelos Xylinas *



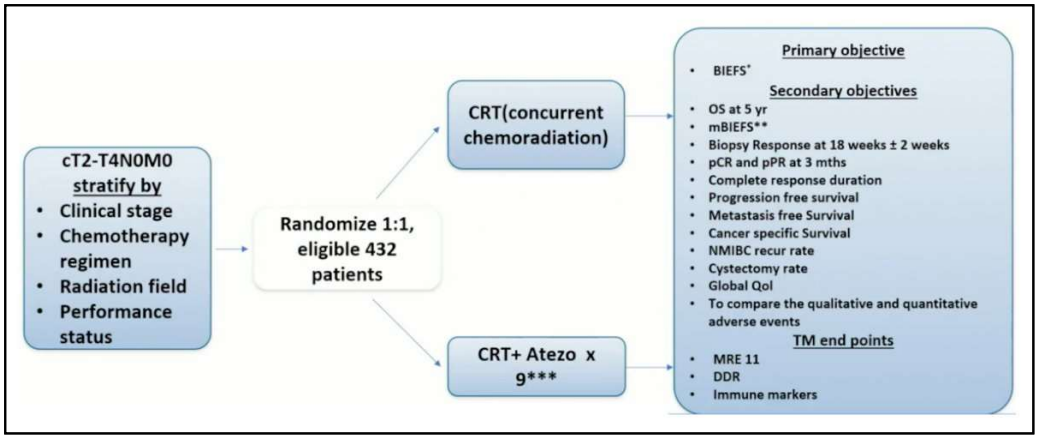
Endpoints

- **Primary:** bladder-intact EFS
- **Key secondary:** OS
- **Other secondary:** MFS, time to occurrence of NMIBC, time to cystectomy, safety and tolerability

Tissot G. Eur Urol Focus. 2023

Atezolizumab and TMT: INTACT

Jhavar SG. ASTRO 2022.



	CRT + A (n=113)	CRT alone (n=100)
Median Age (yrs)	75	72
T2 (N, %)	93 (82%)	81 (81%)
Chemotherapy regimen (N, %)		
Cisplatin	54 (48%)	50 (50%)
MMC + 5FU	17 (15 %)	13 (13%)
Gemcitabine	42 (37%)	37 (37%)
Radiation field (N, %)		
Small pelvis	64 (57%)	58 (58%)
Bladder only	49 (43%)	42 (42%)
Performance status 0-1 (N, %)	109 (96%)	95 (95%)

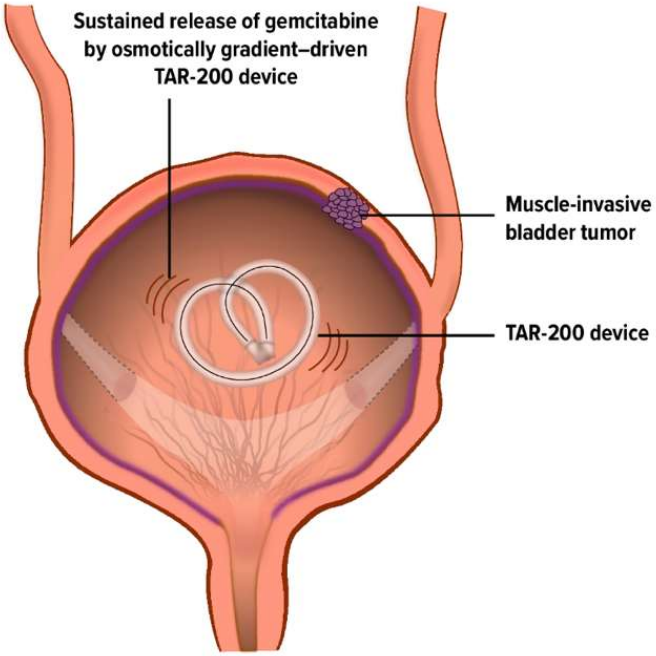
Toxicity Update on First 213 Patients

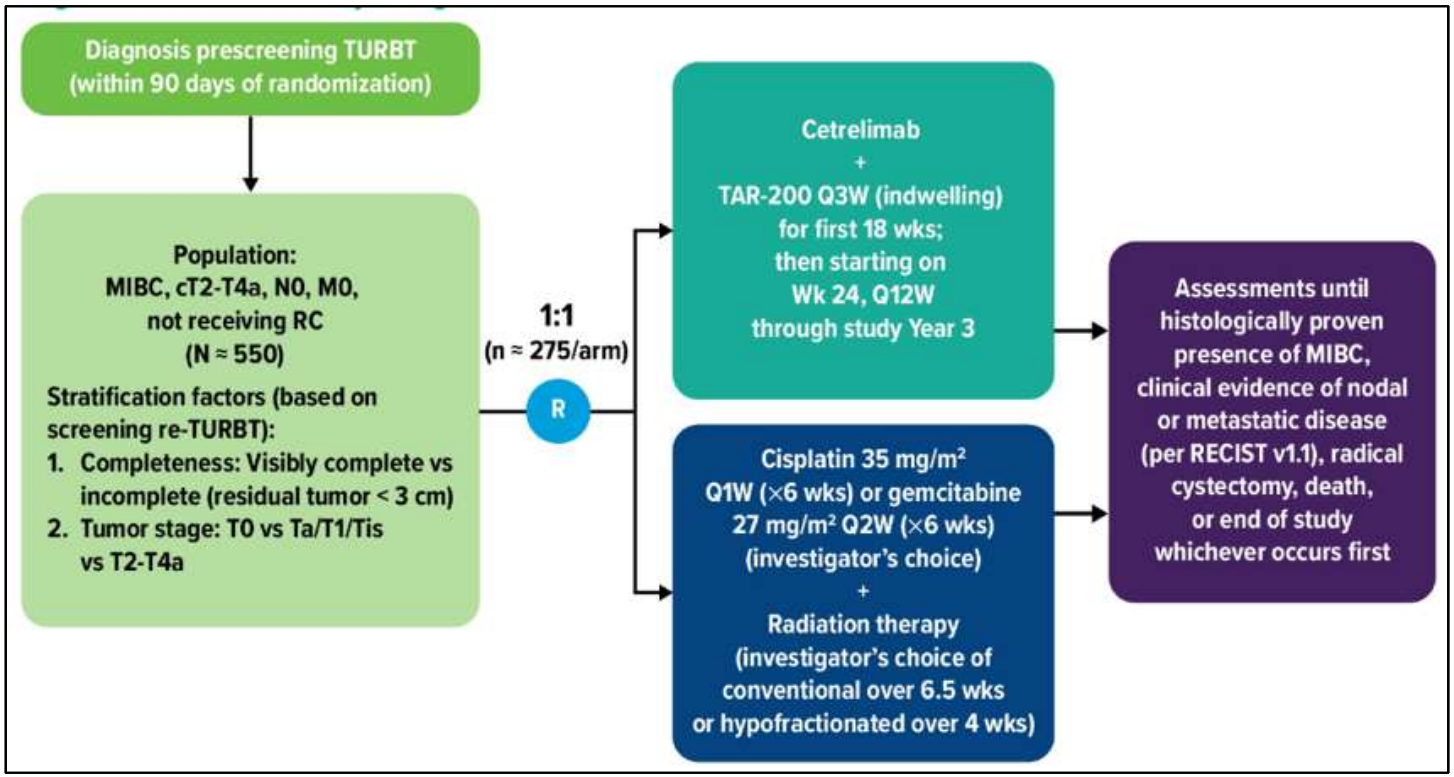
Toxicity Grade ≥ 3	Number of patients = 213	
	CRT + A =113	CRT=100
Any toxicity	65 (58%)	44 (44%)
Hematological (non-immune related)	49 (43%)	36 (36%)
Non -Heme toxicity	31 (27%)	15 (15%)
Colitis	2 (1.7%)	2 (2%)
Cystitis	2 (1.7%)	1 (1%)

✓ **The trial is expected to finish accrual in next two years and this update demonstrates no safety concerns.**

TAR-200 IN COMBINATION WITH CETRELIMAB Vs. TMT: SUNRISE-2

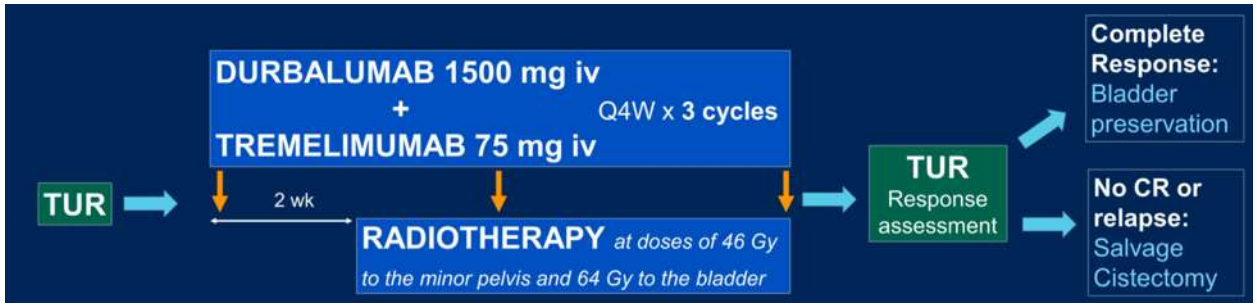
TAR-200 Device





Williams S. J Clin Oncol. 2021

Durvalumab Plus Tremelimumab and Radiotherapy: IMMUNOPRESERVE



- ✓ Complete Response: 85%
- ✓ 1y-DFS: 76%
- ✓ 1y-OS: 87%
- ✓ 12-month bladder-intact disease-free survival: 73%.

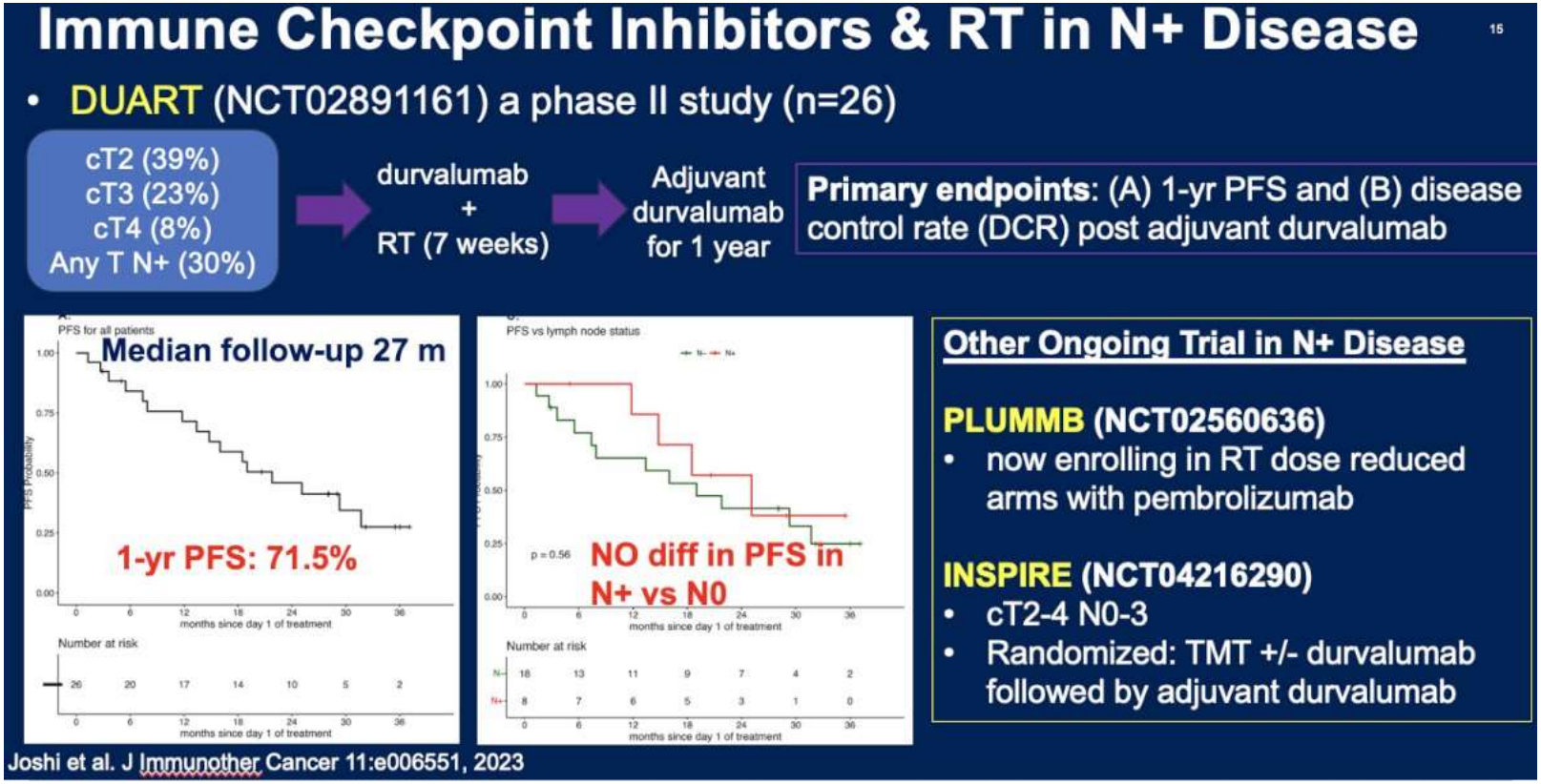
Treatment-Related Adverse Events

Toxicity	Any grade (%)	Grade 3-4 (%)
Any event	**31 (97)**	**10 (31)**
Diarrhea	13 (41)	4 (12)
Urinary disorders	12 (37)	1 (3)
Hyperthyroidism	8 (25)	-
Asthenia	8 (19)	1 (3)
Pruritus	7 (22)	-
Skin rash	5 (16)	1 (3)
Hypothyroidism	4 (12)	-
Acute kidney injury	2 (6)	2 (6)
Hepatitis	2 (6)	2 (6)
Peritonitis	1 (3)	1 (3)
Panhypopituitarism	1 (3)	1 (3)
Thrombocytopenia	1 (3)	1 (3)
AE leading to discontinuation	**7 (22)**	

Combined modality bladder-preserving with combined immunotherapy (durvalumab and tremelimumab) and concurrent radiotherapy if feasible, safe, and has a high-rate of clinical response and bladder preservation at least at 12-month follow-up.

Garcia del Muro X. ASCO 2021

Durvalumab and RT: DUART

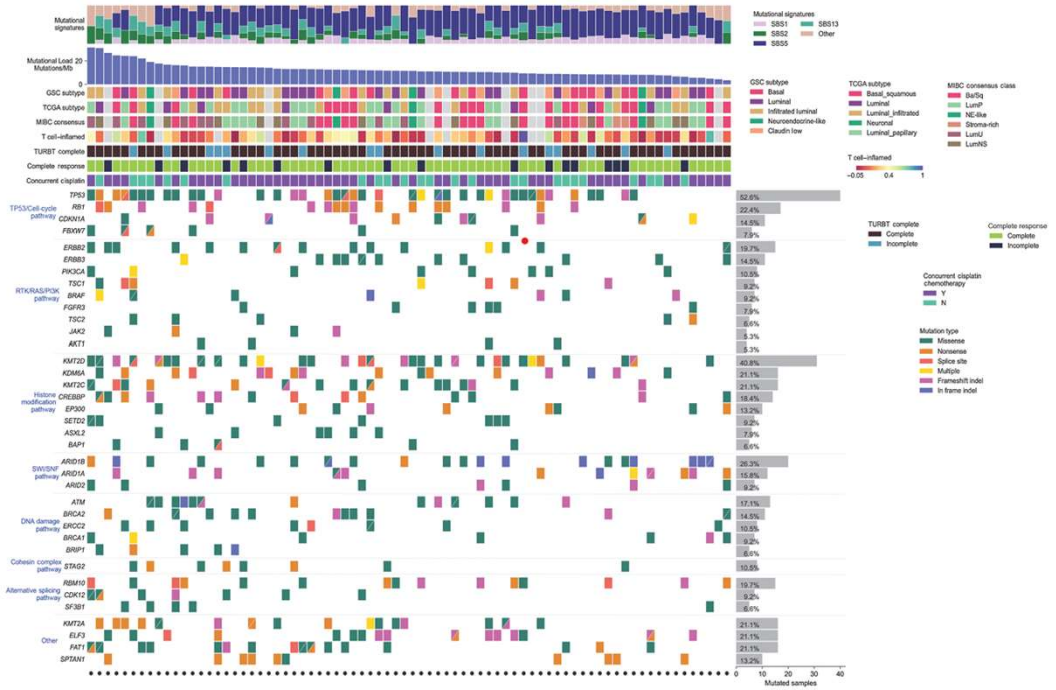


Durva with RT followed by adjuvant durva was safe with promising efficacy in localized BC patients with comorbidities, including N+ patients. Larger randomized studies, like S1806 and EA8185, are needed to evaluate the efficacy of combining immunotherapy and RT in BC.

Joshi M. Journal for ImmunoTherapy of Cancer 2023

Molecular Biomarkers of Response to Trimodal Therapy in Bladder Cancer

- ✓ **Bax/Bcl-2**
- ✓ **Sobreexpresión EGFR**
- ✓ **MRE-11**
- ✓ **Infiltración por Linfocitos T CD8**
- ✓ **IFN-Gamma**
- ✓ **Sobreexpresión de HER-2**
- ✓ **Valor Neutrófilo/Linfocito≥4**
- ✓ **Mutaciones ERCC2**
- ✓ **Modificadores de la hipoxia con firmas de expresión génica elevadas para hipoxia (HIF-1$^{\alpha}$, CAIX y GLUT1)**



Currently, there are possible predictive biomarkers of response to TMT related to apoptosis, cell proliferation, response to DNA damage or hypoxia, but none have been validated.

Lopez Valcarcel M. Actas Urol Esp. 2024.

ASCO GU 2024: A New Era in the Perioperative Management of Muscle Invasive Bladder Cancer

Current MIBC Perioperative Paradigm

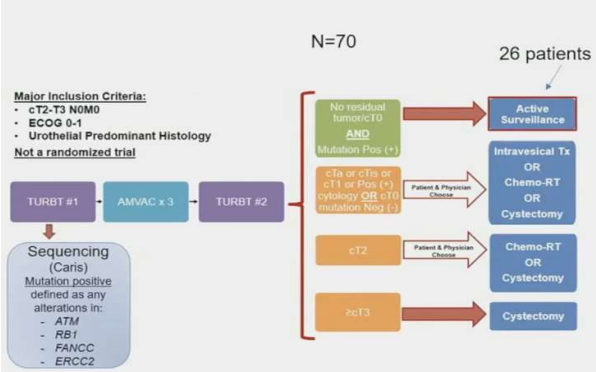
"If this is true, What does it imply" – Don Coffey

Disrupter #1: AI derived Biomarker to predict response to neoadjuvant therapy
Implication: Widespread bladder preservation for CR

Disrupter #2: 2ND Adjuvant immune checkpoint inhibitor shown to improve DFS
Implication: Multimodal, multidisciplinary approach for patients with locally advanced bladder cancer

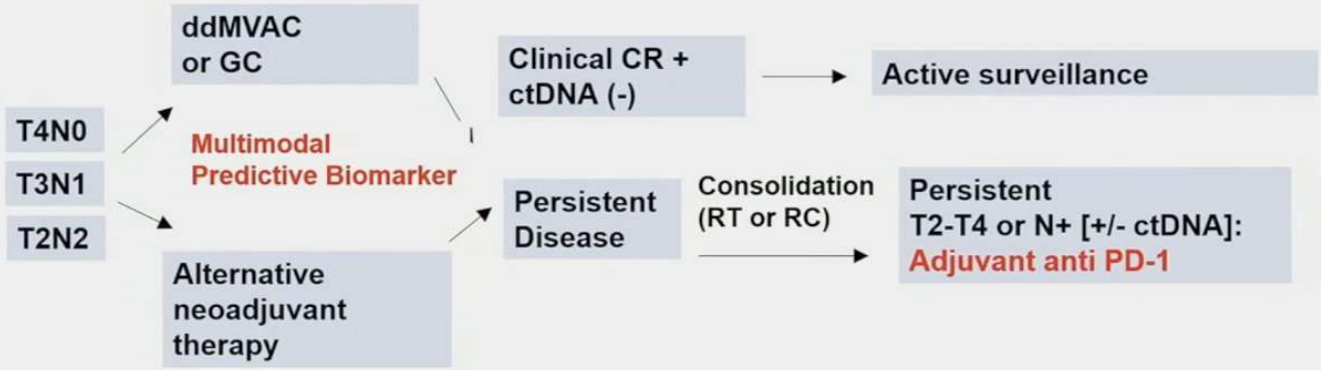
T2-4N0 → Cis-eligible NAC → Persistent T2-T4 or N+: Adjuvant Nivolumab

RETAIN: Neoadjuvant AMVAC Followed by Observation Among Those with CR



- Of the 26 patients with CR on AS:
  - 18 (69%) had UC recurrence
  - 8 had a cystectomy
    - pTa, pT2, pT2, pT3N0, pT0N2, pT3aN1, pT3bN3, pT4bN3
- 12 (46%) are metastasis-free with an intact bladder and no radiation to the bladder

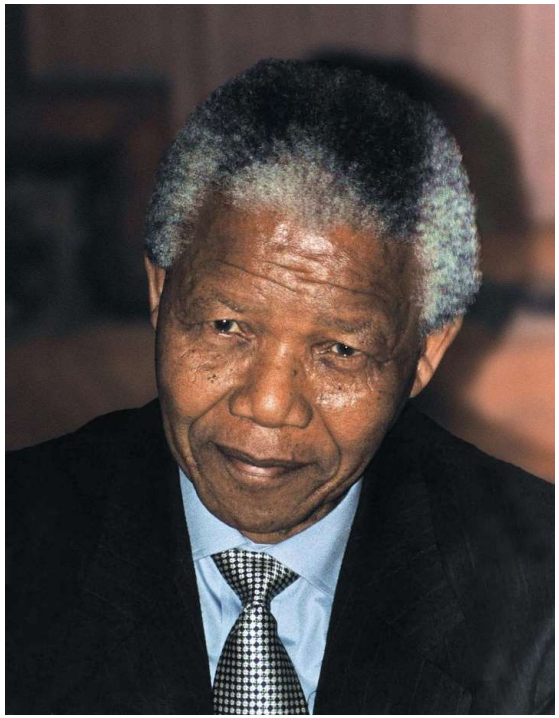
Future Paradigms in cis-eligible MIBC



Kates MR. ASCO GU 2024

CONCLUSIONS

- ✓ **Bladder preservation with Trimodality Therapy is an alternative strategy to radical cystectomy for selected patients with muscle invasive bladder cancer.**
- ✓ **Hypofractionation as a standard.**
- ✓ **TMT could improve sexual, psychological and emotional quality of life**
- ✓ **Inmunotherapy and TMT is feasible, safe, and has a high-rate of clinical response and bladder preservation.**
- ✓ **Larger randomized studies are needed to evaluate the efficacy of combining immunotherapy and TMT in BC.**
- ✓ **Be aware of molecular classification.**



" Siempre parece imposible hasta que se hace"