IO based combos plus radiotherapy: is this the way to go in bladder preservation?

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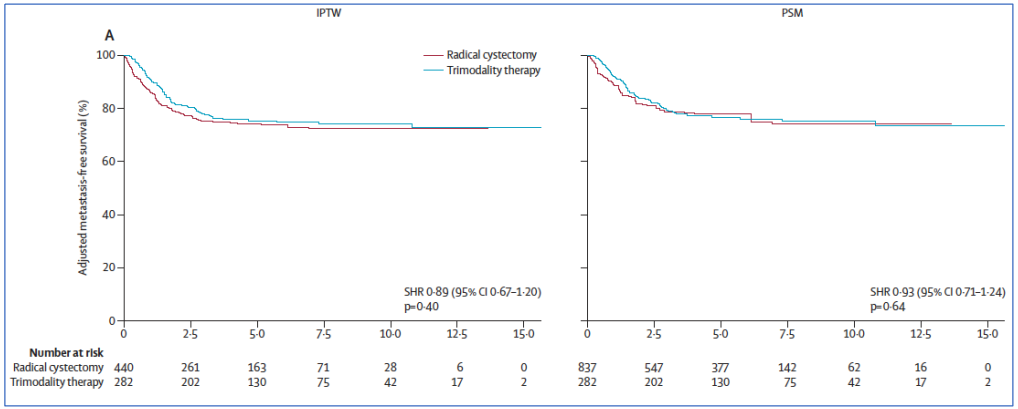
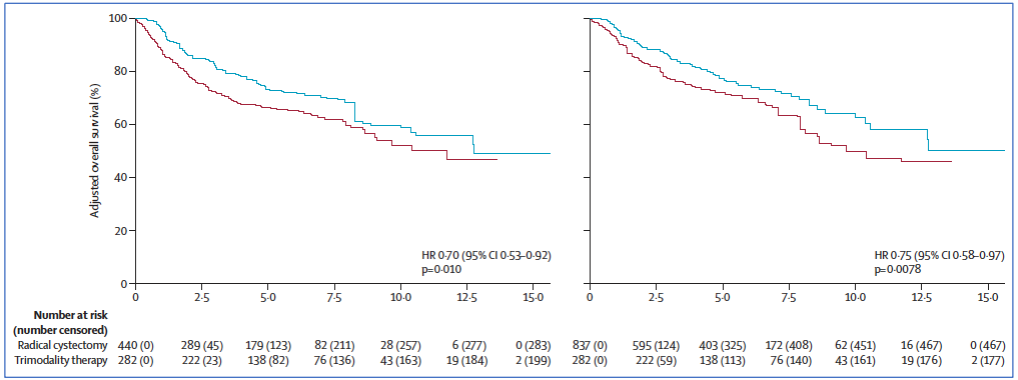
Radical cystectomy versus trimodality therapy for muscle-invasive bladder cancer: a multi-institutional propensity score matched and weighted analysis

Material and Methods

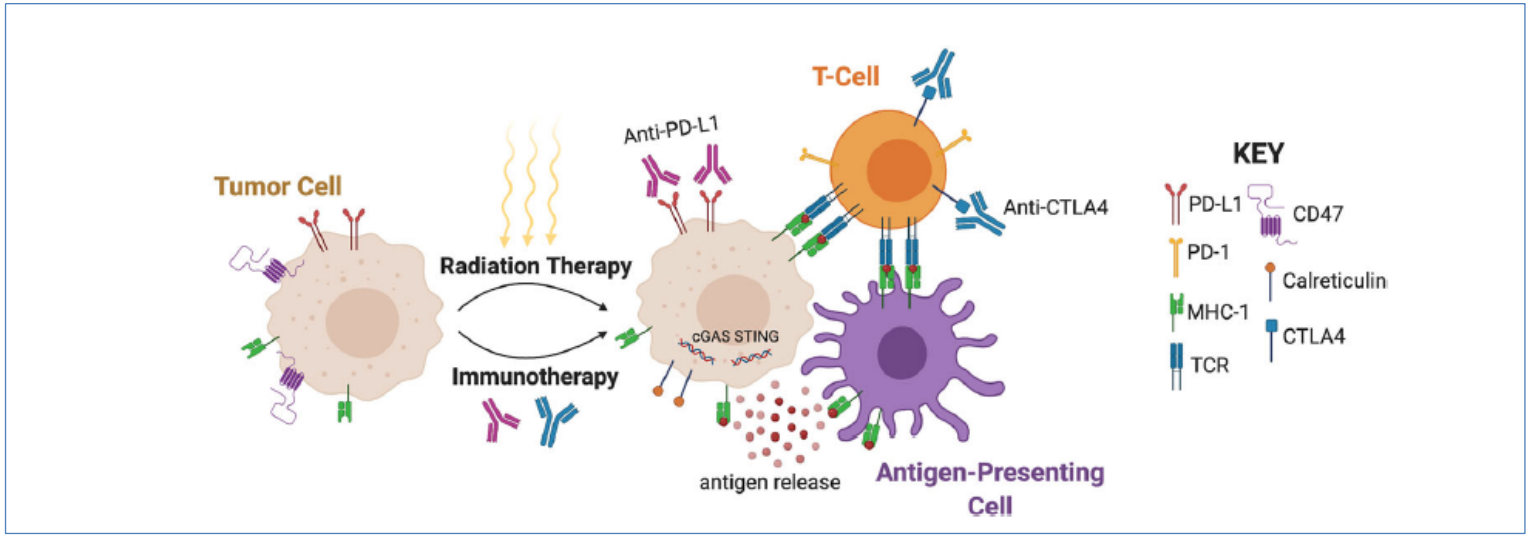
- Retrospective analysis
- 703 patients with MIBC clinical stage T2-T3/4aN0M0 MIBC (urothelial), 421 RC and 282 TMT who would have been eligible for both TMT or RC, treated at the Massachusetts General Hospital, Boston; PMCC, Toronto; and University of Southern California, Los Angeles between 2005-2017.
- In order to compare homogenous cohorts, all patients included in this analysis had:
  1. Solitary tumors <7 cm
  2. No or unilateral hydronephrosis
  3. No extensive carcinoma in situ.
- Primary endpoint of interest: metastasis-free survival.





Ziotta AR et al. Lancet Oncol 2023

Potential mechanisms of synergy of radiotherapy and immunotherapy



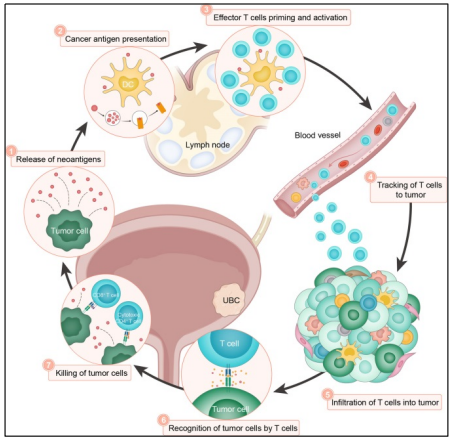
- RT promotes the ability of APC to present tumor antigens to naive T cells through antigen release, stimulation of calreticulin, and downregulation of CD47.
- MHC-1 expression and the subsequent antigen presentation leads to interaction with TCR.
- RT activate a type I interferon response through the sensing of cytoplasmic DNA via cGAS-STING.
- RT can upregulate PD-L1 and CTLA-4, and augment radiation efficacy by targeting these pathways

Ukleja J et al. Front Oncol 2021

INCORPORATION OF IMMUNOTHERAPY TO THE MULTIMODAL BLADDER SPARING THERAPY: DIFERENT APPROACHES

- **Incorporation of Immunotherapy to the multimodal therapy**
  - *ICI in combination with radiotherapy instead of chemotherapy*
  - *Chemotherapy, ICI and radiotherapy combinations*

- **Approaches lacking radiotherapy**
  - *Chemotherapy and ICI, without radiation*
  - *Selection based on biomarkers and response*



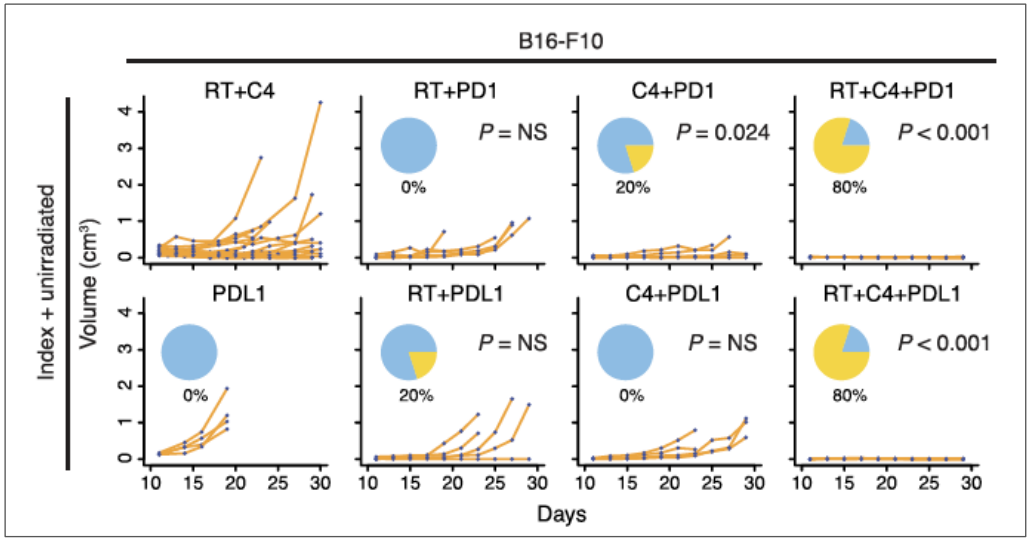
Dual immune checkpoint inhibition in combination with radiotherapy

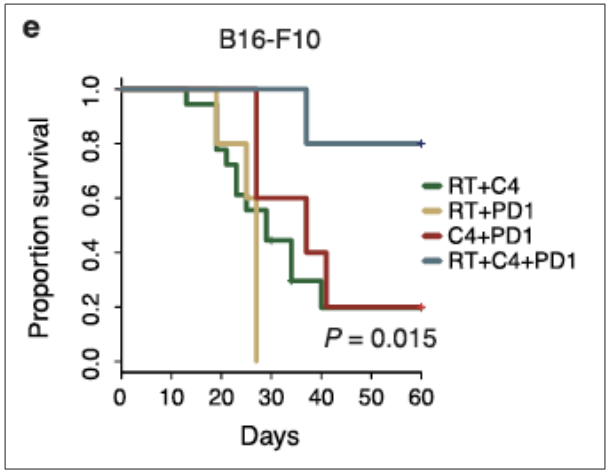
LETTER

doi:10.1038/nature14292

Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer

Christina Twyman-Saint Victor[1,2]*, Andrew J. Rech[2]*, Amit Maity[3,4], Ramesh Rengan[3,4]†, Kristen E. Pauken[5,6], Erietta Stelekati[5,6], Joseph L. Benci[2,3], Bihui Xu[2,3], Hannah Dada[2,3], Pamela M. Odorizzi[5,6], Ramin S. Herati[1,6], Kathleen D. Mansfield[5,6], Dana Patsch[3], Ravi K. Amaravadi[1,4], Lynn M. Schuchter[1,4], Hemant Ishwaran[7], Rosemarie Mick[4,8], Daniel A. Pryma[4,9], Xiaowei Xu[4,10], Michael D. Feldman[4,10], Tara C. Gangadhar[1,4], Stephen M. Hahn[3,4]†, E. John Wherry[4,5,6]§, Robert H. Vonderheide[1,2,4,6]§ & Andy J. Minn[2,3,4,6]§





- Combination of radiation and dual checkpoint blockade appears to activate non-redundant immune mechanisms, potentiating antitumor activity

Twyman-Saint Victor C et al. Nature 2015;520:373-7

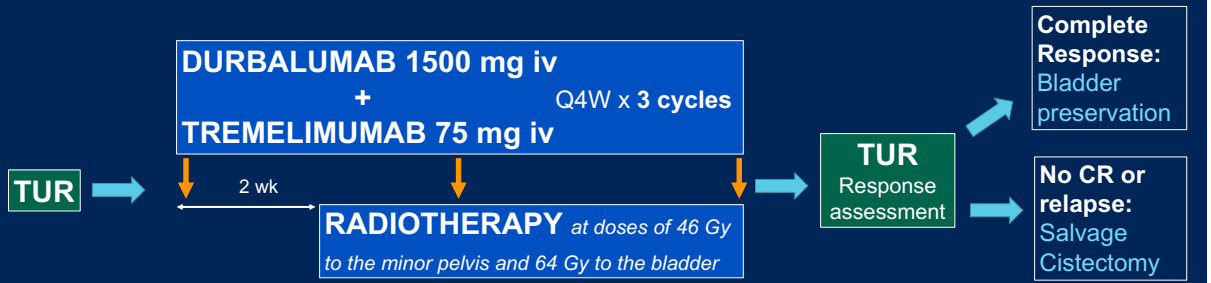
CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

Clin Cancer Res 2025;31:659–66

Bladder Preservation with Durvalumab plus Tremelimumab and Concurrent Radiotherapy in Patients with Localized Muscle-Invasive Bladder Cancer (IMMUNOPRESERVE): A Phase II Spanish Oncology GenitoUrinary Group Trial

Xavier Garcia-del-Muro[1], Begoña P. Valderrama[2], Ana Medina-Colmenero[3], Olatz Etxaniz[4], Regina Gironés Sarrió[5], María José Juan-Fita[6], Marcel Costa-García[7], Rafael Moreno[7], Isabel Miras Rodríguez[2], Irene Ortiz[1], Andrés Cuéllar[1], Ferran Ferrer[8], Francesc Vigués[9], Roberto de Haro Piedra[10], Arturo Candal Gomez[11], Salvador Villà[12], José Luis Pontones[13], Yasmina Murria[14], Guillermo Lendínez-Cano[15], and Ramon Alemany[7]

IMMUNOPRESERVE: Trial Design



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

Translational Study:

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

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

Safety

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)**	

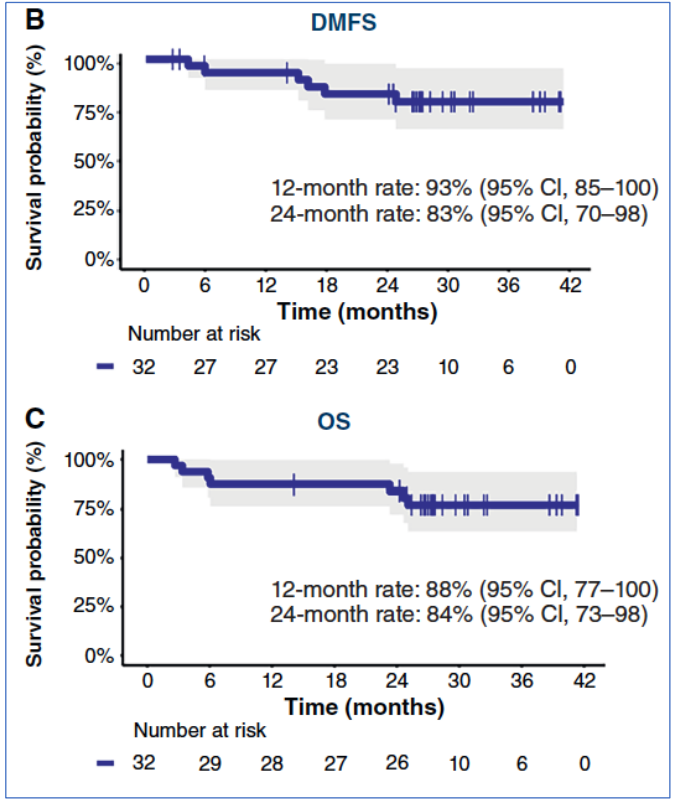
Grade 5 AE was observed in one patient: peritonitis

Garcia del Muro X et al. Clin Cancer Res 2025

IMMUNOPRESERVE: Results

Between 1/2019 and 8/2020, 32 pts were included at 6 centers with a median follow-up: 12.7 months (5.3 -24.5 m.)

Response at the post-treatment TUR	*N*	*%*	95% CI
Complete Response (≤T1)	**26**	**81 %**	**(95% CI, 63.5-93)**
- T0 response	*25*	*78 %*	
- NMIBC (T1, Ta, Tis)	*1*	*3 %*	
Non-response (MIBC)	**2**	**6 %**	**(95% CI, 0.7-21)**
Not evaluated	**4**	**12.5%**	
- Rejection			
- Clinical impairment			
- Death from COVID 19			
- Toxic death from peritonitis			

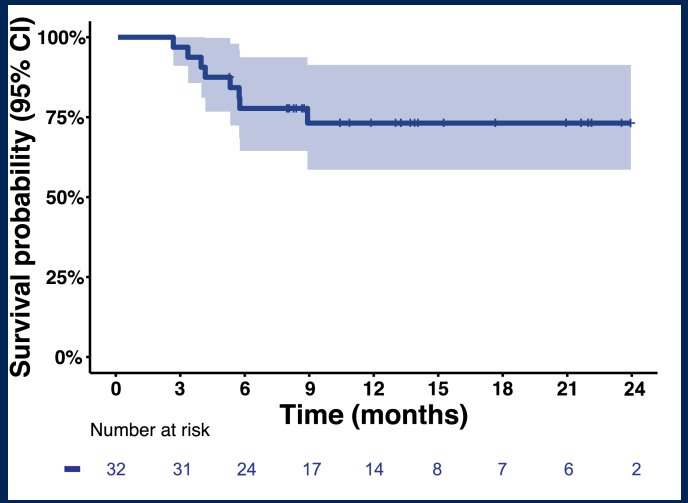


Garcia del Muro X et al. Clin Cancer Res 2025

Bladder preservation

- Median follow-up: 27 months (14 -4 1 months)
- Salvage cystectomy: 2
  - *Immediate 0*
  - *Late 2*
- 12 m NMIBC local failure: 3% (95%IC, 0.2-14)
- 12 m MIBC local failure: 19% (95%IC, 7.5-35)
- 12 m Distant metastases: 13.6% (95%IC, 4-29)

BLADDER INTACT DISEASE FREE SURVIVAL



24 m Bladder Intact DFS rate: 65% (95%CI, 50%-84%)

Garcia del Muro X et al. Clin Cancer Res 2025

Concurrent durvalumab and radiation therapy (DUART) followed by adjuvant durvalumab in patients with localized UBC: a phase II study, BTCRC-GU15- 023

T2-4 N0-2 M0 pure or mixed urothelial cancer of bladder; unresectable/unfit for surgery or cisplatin ineligible

(T2-3N0 must be cis-ineligible)

ECOG 0-2; GFR >30; max TUBRT attempt

↓

DurvaRT:

Durvalumab 1500 mg q 4 weekly (X 2 doses) + XRT to gross disease (64.8 Gy in 36 fractions over 7 weeks)

Durvalumab to start on Day 1

↓

Response evaluation by imaging and cystoscopy, biopsy

2 – 3 weeks post completion of DurvaRT

↓

CR, PR, SD

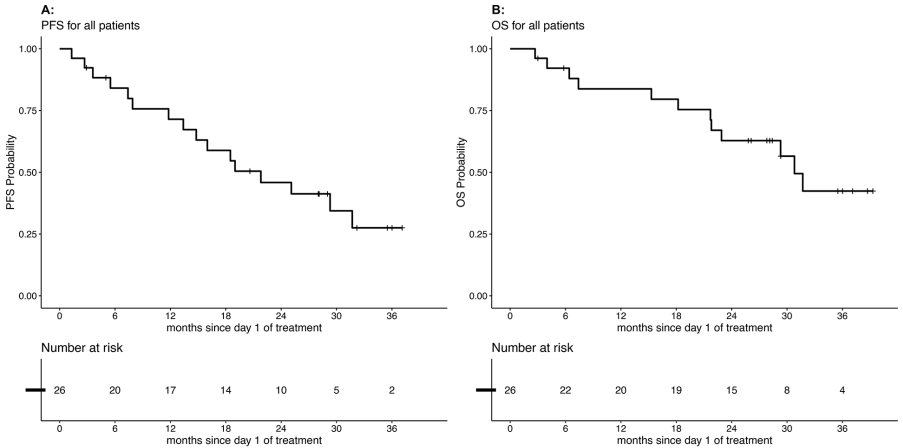
↓

Adjuvant Durvalumab Monotherapy

Durvalumab maintenance q4 weekly (up to 12 months; 13 doses)

Durvalumab to start 4 weeks (±7 d) post completion of DurvaRT

- PFS was 71.5%, median PFS was 21.8 months.
- 1-year OS was 83.8%, median OS was 30.8 months.
- CR at 8 weeks post durvaRT was 62.5%.



Joshi M, et al. J Immunother Cancer 2023

EUROPEAN UROLOGY ONCOLOGY 7 (2024) 469–477

available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com

European Association of Urology

Pembrolizumab with Chemoradiation as Treatment for Muscle-invasive Bladder Cancer: Analysis of Safety and Efficacy of the PCR-MIB Phase 2 Clinical Trial (ANZUP 1502)

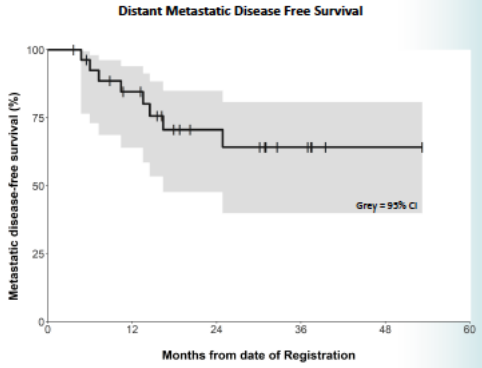
Andrew Weickhardt[a,*], *Farshad Foroudi*[a], *Nathan Lawrentschuk*[b], *Jing Xie*[c], *Mark Sidhom*[d],

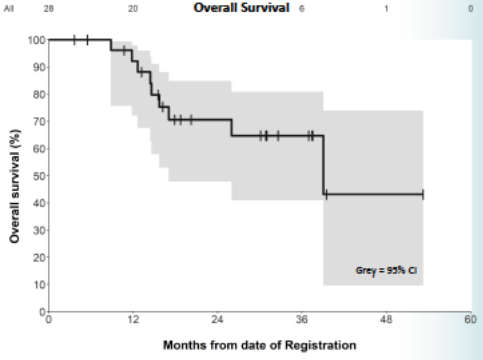
28 patients treated at 6 Australian centres between July 2017- Nov 2021

TURBT (Maximal)	Within 6 weeks
Chemoradiotherapy + Pembrolizumab	Weekly cisplatin 35mg/m² x 6 doses - Dose reduction to 30mg/m² if CrCl 40-50ml/min Week 1, 4 pembrolizumab IV 200mg
Pembrolizumab	Week 7, 10, 13, 16, 19 pembrolizumab IV 200mg
Restaging Cystoscopy/CT CAP	Week 19 - 12 weeks post ChemoRTx
End of Treatment	
Post Treatment Review Restaging Cystoscopy/CT CAP	Week 31 - 24 weeks post ChemoRTx
Survival Follow Up 3 monthly for 12 months 6 monthly for 18 months 12 monthly for 24 months (minimum follow up 5 years)	CT CAP and Cystoscopy at each visit

Best Response at Cystoscopy	Week 31 (6m)
Complete Response	23 (88% [70, 98])
Progression	3 (12% [2, 30])

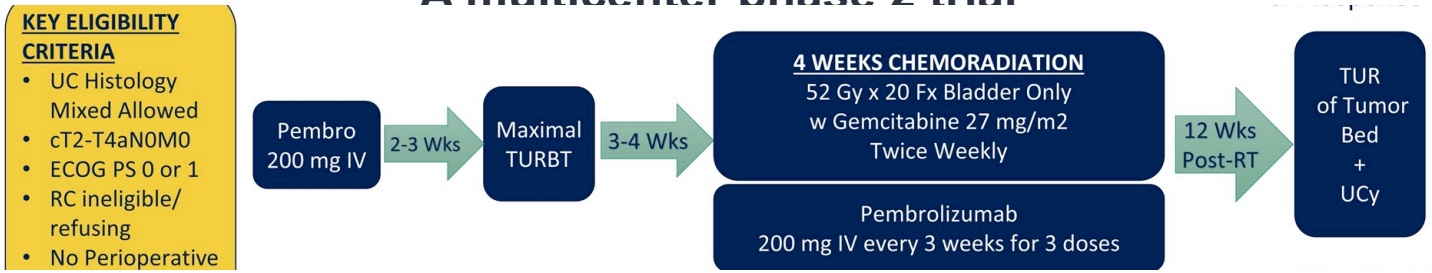
2 non assessable patients: One patient withdrew consent; another ceased treatment due to severe COPD





DMFS at 2 yr is 78% (95%CI 54–90%)
LRPFS at 2 yr of 87% (95% CI 64–96%)
median OS of 39

Long-term outcomes of pembrolizumab in combination with gemcitabine and concurrent hypofractionated radiation therapy as bladder sparing treatment for MIUC:
A multicenter phase 2 trial



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

12 Weeks Post-RT Response – Per Protocol

12 weeks post RT Response	N=6	N=48	N=54
CR	5 (83%)	27(56%)	32 (59%)
PR	0	4 (8.3%)	4 (7.4%)
NR	0	0	0
Progression	0	1 (2.4%)	1 (1.8%)
Not-evaluable[2]	1(17%)	10 (21%)	11 (20%)
Missed	0	3	3
Off-Study	0	3	3

Balar AV et al. ASCO 2021
Economides M. ASCO 2023

RESULTS SAFETY-cont'd

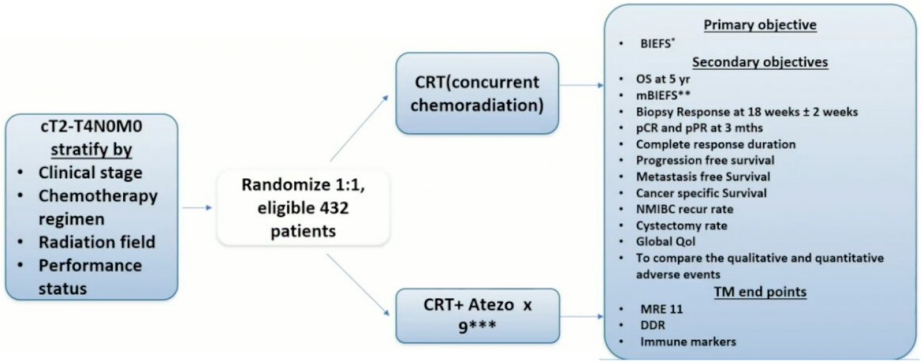
- The most common adverse events were fatigue (20; 42%), nausea (17;35%) and diarrhea (16;33%).
- Thirteen patients (24%) experienced 17 AEs that were Grade 3 or greater.
- The Grade 3 and 4 AEs are shown in Table 3.
- Grade 3 or greater immune-related AEs includes 2 patients (4%) with colitis, 1 patient with polyneuropathy and 1 patient with grade 4 colonic perforation (initially treated but subsequently developed multiple complications and patient died due to fungemia/sepsis).

Table 3. Grade 3 and 4 AEs

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

Balar AV et al. ASCO 2021
Economides M. ASCO 2023

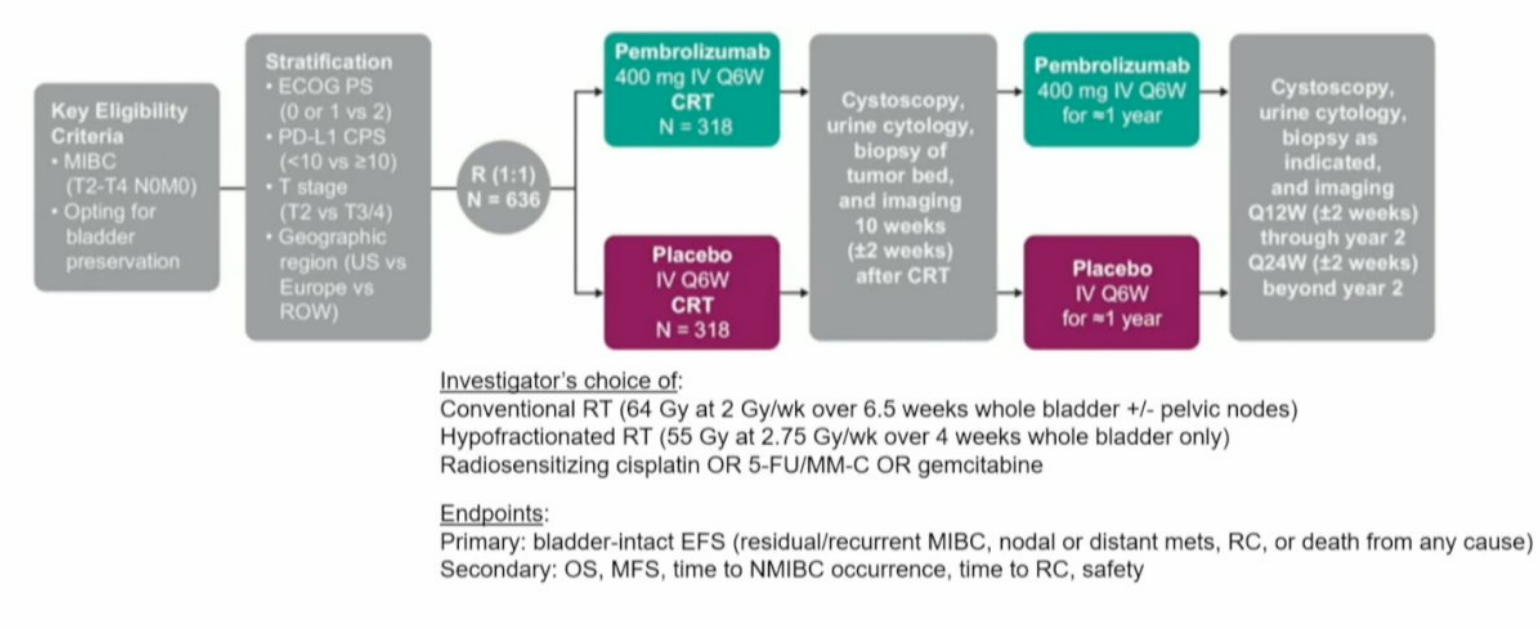
INTACT (S/N1806): Phase III Randomized Trial of Concurrent Chemoradiotherapy with or without Atezolizumab in Localized Muscle Invasive Bladder Cancer Toxicity Update on First 213 Patients



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%)

P. Singh et al ASTRO 2022

KEYNOTE-992: Randomized Phase III trial of Pembrolizumab versus Placebo in patients with muscle-invasive bladder cancer receiving concurrent chemoradiotherapy



Investigator's choice of:
Conventional RT (64 Gy at 2 Gy/wk over 6.5 weeks whole bladder +/- pelvic nodes)
Hypofractionated RT (55 Gy at 2.75 Gy/wk over 4 weeks whole bladder only)
Radiosensitizing cisplatin OR 5-FU/MM-C OR gemcitabine

Endpoints:
Primary: bladder-intact EFS (residual/recurrent MIBC, nodal or distant mets, RC, or death from any cause)
Secondary: OS, MFS, time to NMIBC occurrence, time to RC, safety

Lyer G. et al ASTRO 2024

Bladder Cancer 10 (2024) 199–213
DOI 10.3233/BLC-240036
IOS Press

Position Paper

Eligibility and Endpoints for Clinical Trials in Trimodality Therapy for Bladder Cancer

Parminder Singh[a,*], Leslie Ballas[b], Guru P. Sonpavde[c], Ronald C. Chen[d], Rick Bangs[e], Brian C. Bauman[f], Himanshu Nagar[g], Scott E. Delacroix[h], Seth P. Lerner[i] and Jason A. Efstathiou[j]

Endpoint definitions

Endpoint	Definition
Bladder Intact Event Free Survival (BIEFS)	Time to local muscle invasive recurrence, LN recurrence, systemic recurrence, radical cystectomy from any cause, death from any cause
Bladder Intact Disease Specific Survival (BIDSS)	Surviving protocol treatment and bladder cancer with no evidence of distant metastases, nodal recurrence, or nonsalvageable local recurrence with intact native bladder
Bladder Intact Disease-Free Survival (BIDFS)	Time to the earliest of muscle-invasive local recurrence in the bladder, regional pelvic recurrence, DM, bladder cancer–related death, or cystectomy
Disease Specific Survival (DSS)	Surviving protocol treatment and bladder cancer with no evidence of distant metastases, nodal recurrence, or nonsalvageable local recurrence.
Distant Metastasis Free Survival at 3 years (DMFS3)	Time to development of distant metastasis outside pelvis after TMT at 3 years.
Bladder Intact Distant Metastasis Free Survival 3 years (BIDMFS3)	Time to development of distant metastases, undergoing cystectomy, or death from any cause at 3 years
Overall Survival (OS)	Time from registration to death from any cause.
Progression Free Survival (PFS)	Time to local or systemic progression or death.
Regional Failure Free Survival (RFFS)	Local or nodal recurrence within pelvis
Disease Free Survival (DFS)	Regional and distant failure and cancer specific mortality.
Cancer Specific Survival (CSS)	Time to cancer specific mortality
Bladder Intact Survival (BIS)	Time from randomization to cystectomy or death

Recommended eligibility criteria for future clinical trials evaluating systemic therapy combination with trimodality therapy

Endpoint	Definition
Stage	Clinical stage T2-T4, N0, M0 based on cross sectional imaging preferred MRI, TURBT and examination under anesthesia. N1 patient can be included in clinical trial evaluating neoadjuvant therapy with suitable comparator arm.
Hydronephrosis	Patients with tumor associated unilateral hydronephrosis which is treated should be allowed to enroll.
Neoadjuvant/Adjuvant chemotherapy	Can be allowed if this is a predefined stratification factor
Maximal TURBT	Patients must have maximal TURBT within 70 days of randomization.
Carcinoma in Situ	Patients with diffuse CIS should be excluded. Tumor associated focal CIS is a common occurrence and should not be an exclusion
Kidney function (GFR limits)	Patients with GFR limit >25 ml/min should be eligible
Performance status	ECOG performance status of <2 should be allowed for enrollment.
Histology	Patients with mixed urothelial with squamous/adenocarcinoma/ sarcomatoid/plasmacytoid histology should be allowed. Small cell carcinoma should be excluded.

FINAL REMARKS

- Combined-modality bladder-preserving approaches including immunotherapy are feasible and safe, showing high efficacy in terms of response and eliciting bladder preservation in a large number of pts

- Different approaches are being explored, all them with promising preliminary results. Nevertheless, longer follow-up is still needed, focusing especially on long-term bladder preservation and survival

- However, agreement regarding assessment of response and efficacy endpoints in bladder preservation studies is needed

- Further research on these approaches as an alternative to radical cystectomy in selected patients with localized MIBC is warranted

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