The role of systemic therapy for bladder preservation strategies in MIBC

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Conflicts of interest

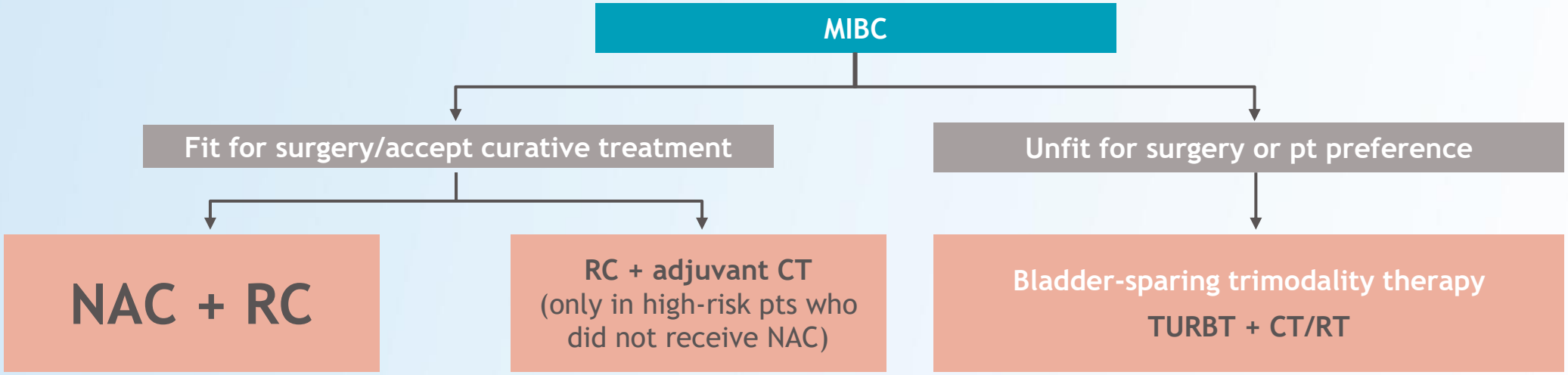
Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports	Astra Zeneca, BMS, Pfizer, Ipsen
Receipt of honoraria or consultation fees	BMS, Merck, Astellas, MSD, Ipsen

Outline

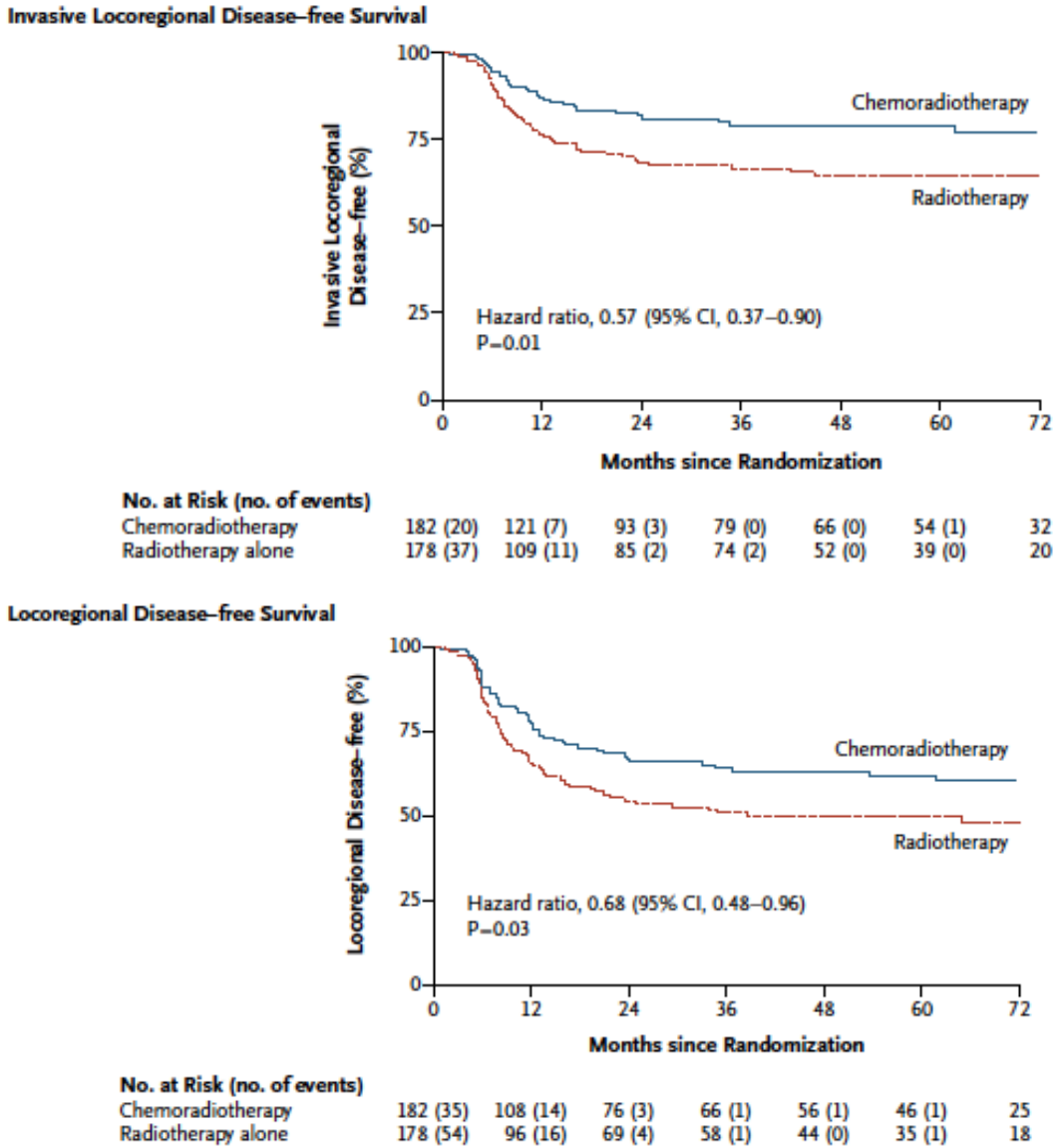
- Introduction
- Do we need systemic therapy in combination with radiotherapy + TURB-T?
- Type and timing of systemic therapy in the context of trimodality therapy
- Future perspectives

Treatment of MIBC: EAU, ESMO guidelines

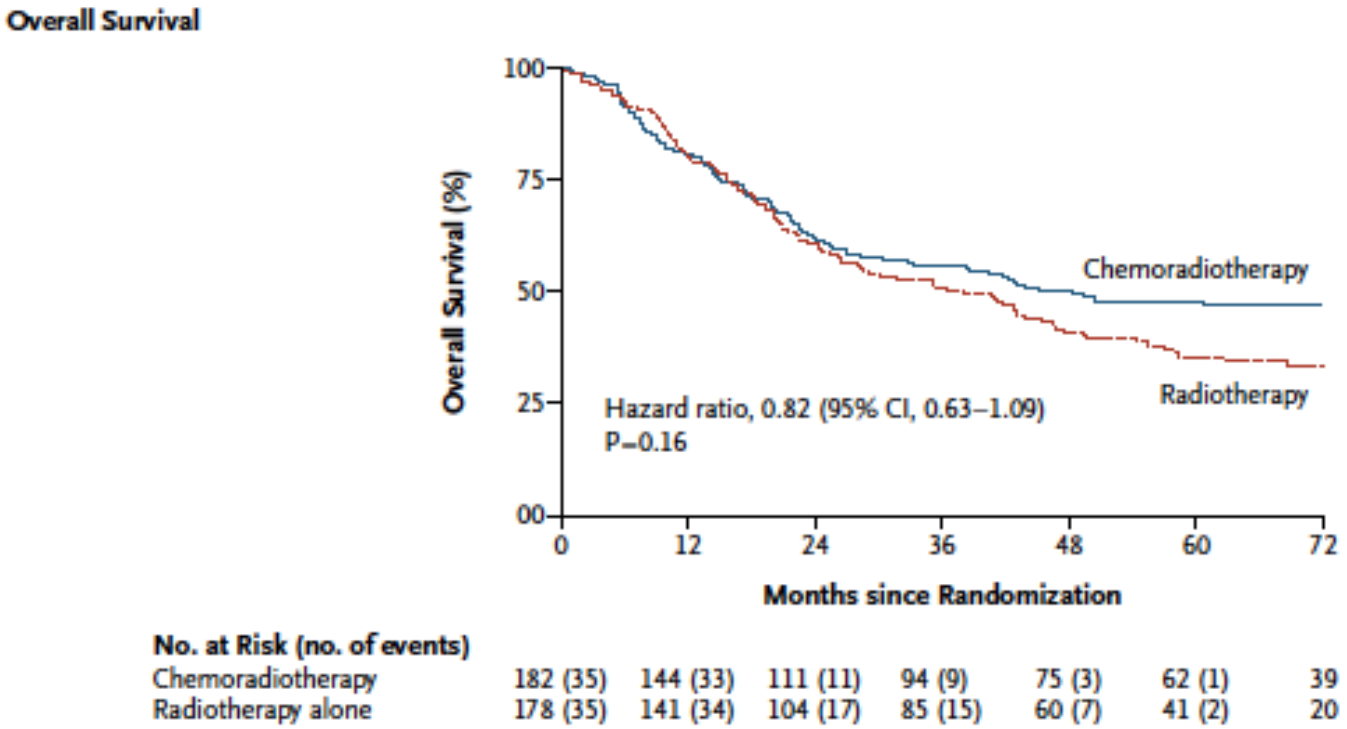
- EAU, ESMO, NCCN guidelines recommend
  - **Neoadjuvant CT + RC** for patients fit for surgery
  - **Trimodal bladder-sparing treatment** for patients unfit for surgery or who refuse surgery



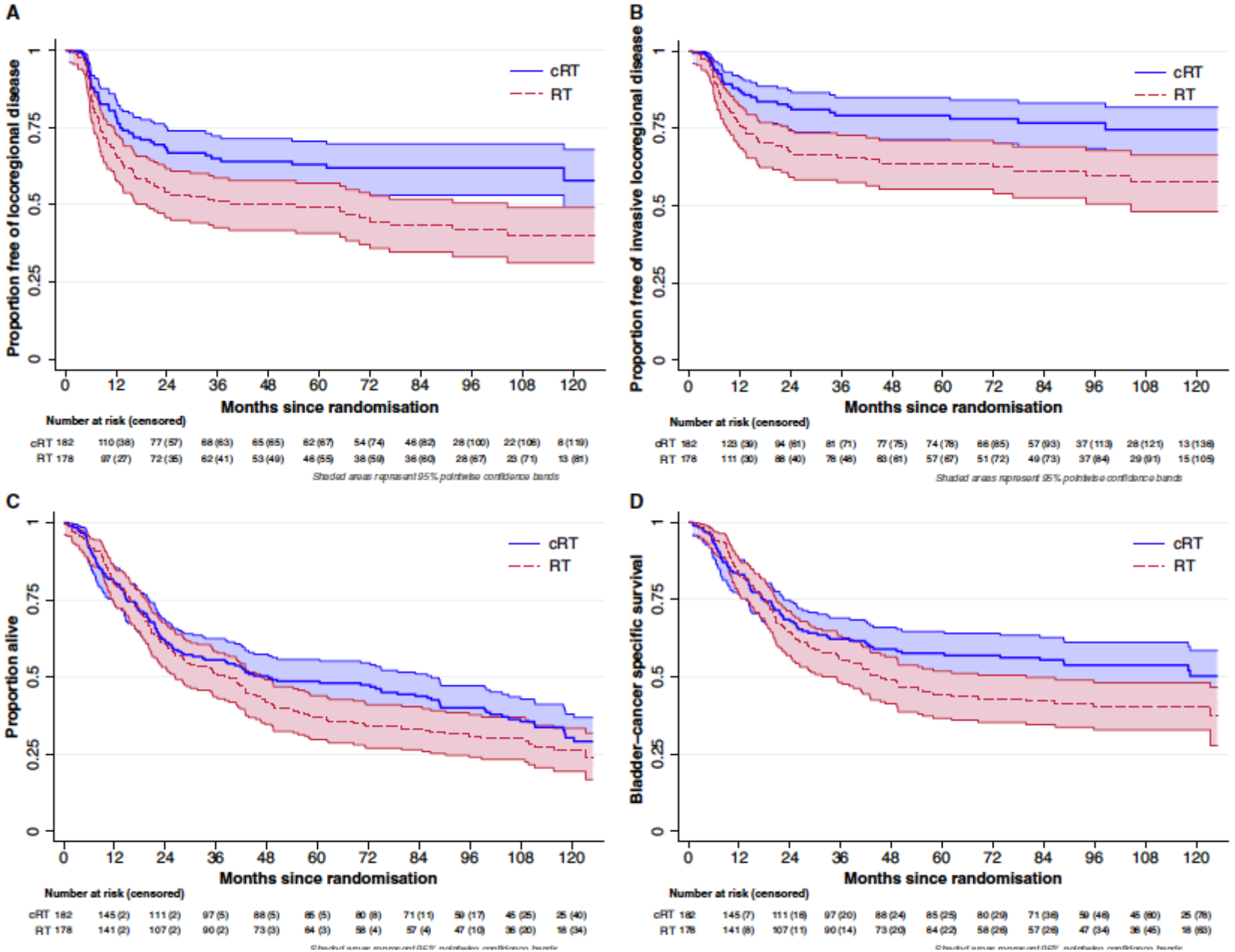
BC2001 trial- LCR DFS



BC2001 trial- OS



BC2001-
10year fup



Type and timing of systemic therapy in the context of trimodality therapy

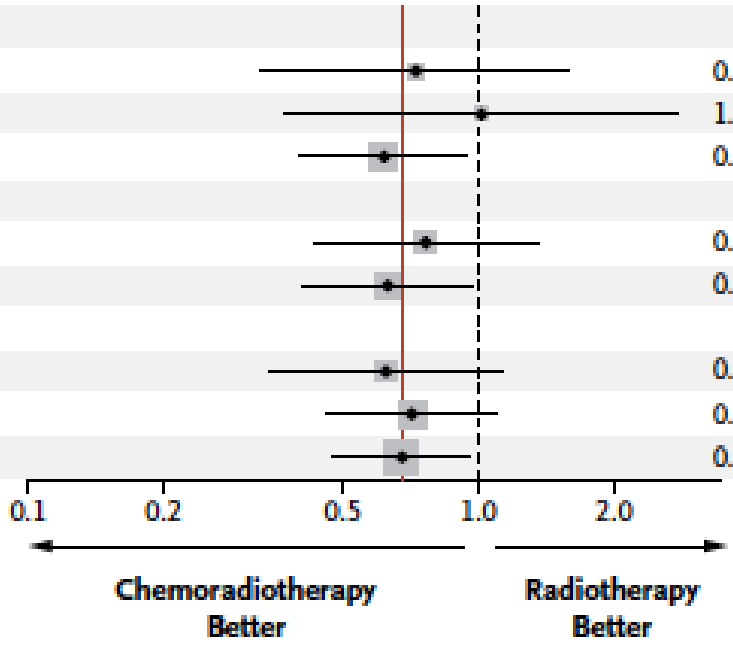
Neoadjuvant, concurrent, adjuvant?

Which drug/regime?

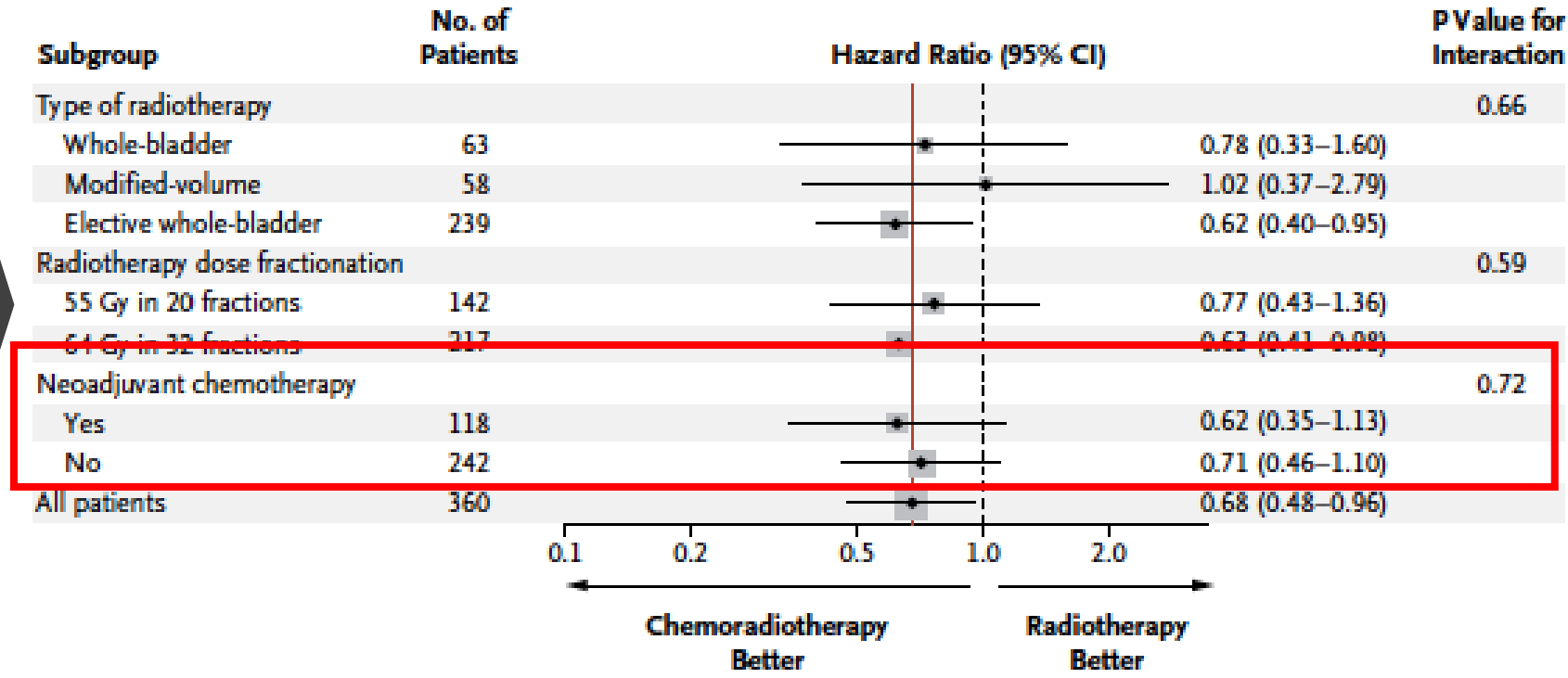
CONCURRENT is the STANDARD

BC2001 Subgroups

Subgroup	No. of Patients	Hazard Ratio (95% CI)	P Value for Interaction
Type of radiotherapy			0.66
Whole-bladder	63	0.78 (0.33–1.60)	
Modified-volume	58	1.02 (0.37–2.79)	
Elective whole-bladder	239	0.62 (0.40–0.95)	
Radiotherapy dose fractionation			0.59
55 Gy in 20 fractions	142	0.77 (0.43–1.36)	
64 Gy in 32 fractions	217	0.63 (0.41–0.98)	
Neoadjuvant chemotherapy			0.72
Yes	118	0.62 (0.35–1.13)	
No	242	0.71 (0.46–1.10)	
All patients	360	0.68 (0.48–0.96)	

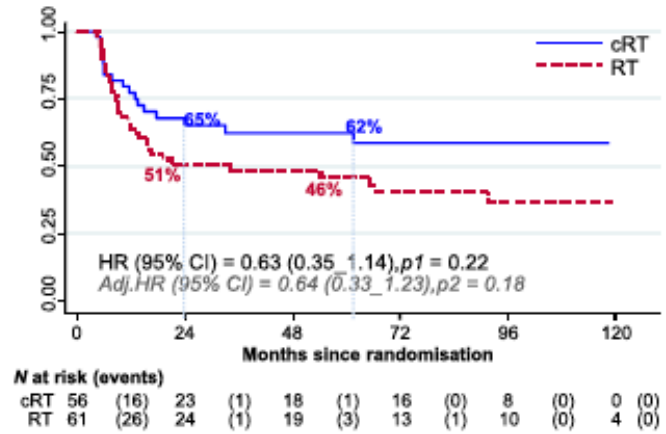


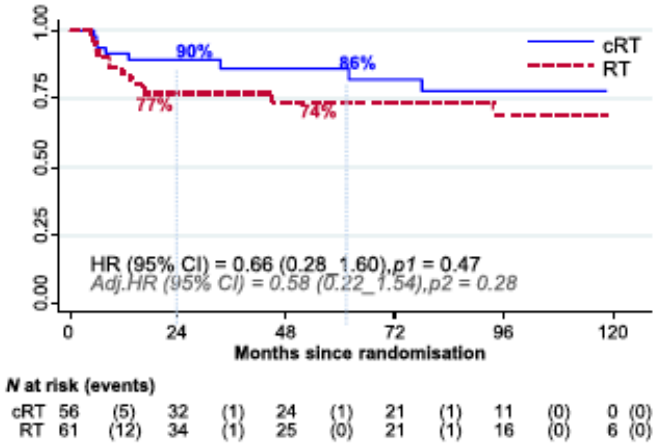
BC2001 Subgroups



BC2001- Neoadjuvant cohort

A





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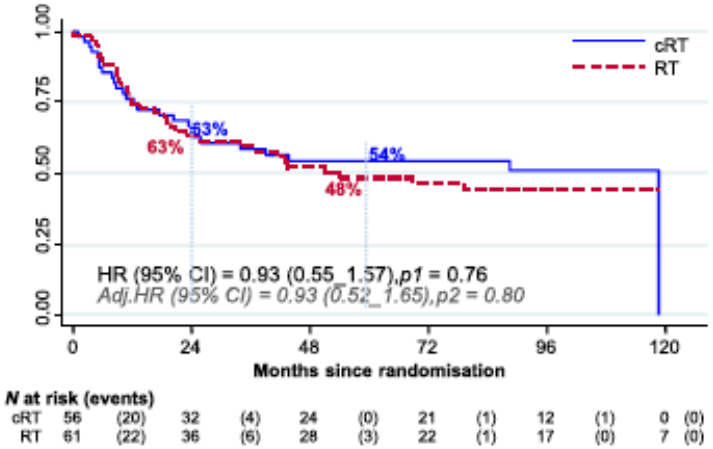

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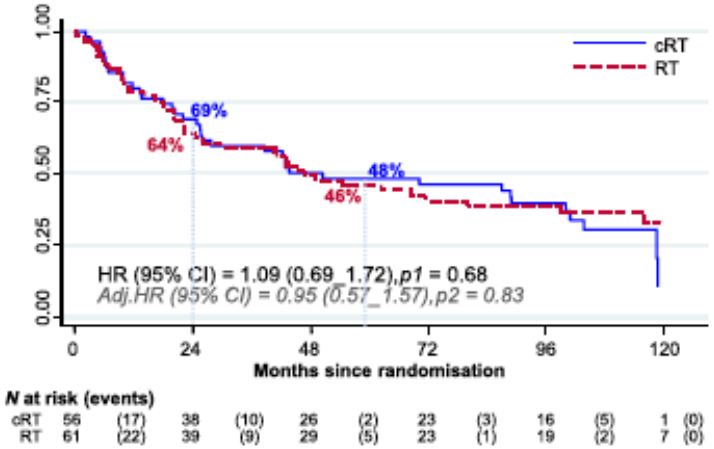


MGH series

Time period	1986–1995	1996–2004	2005–2013	*p* value
Neoadjuvant chemotherapy, *n* (%)				<0.001
Yes	103 (50)	15 (10)	0 (0)	
No	105 (50)	143 (90)	109 (100)	
Adjuvant chemotherapy, *n* (%)				<0.001
Yes	20 (10)	115 (73)	80 (73)	
No	188 (90)	43 (27)	29 (27)	

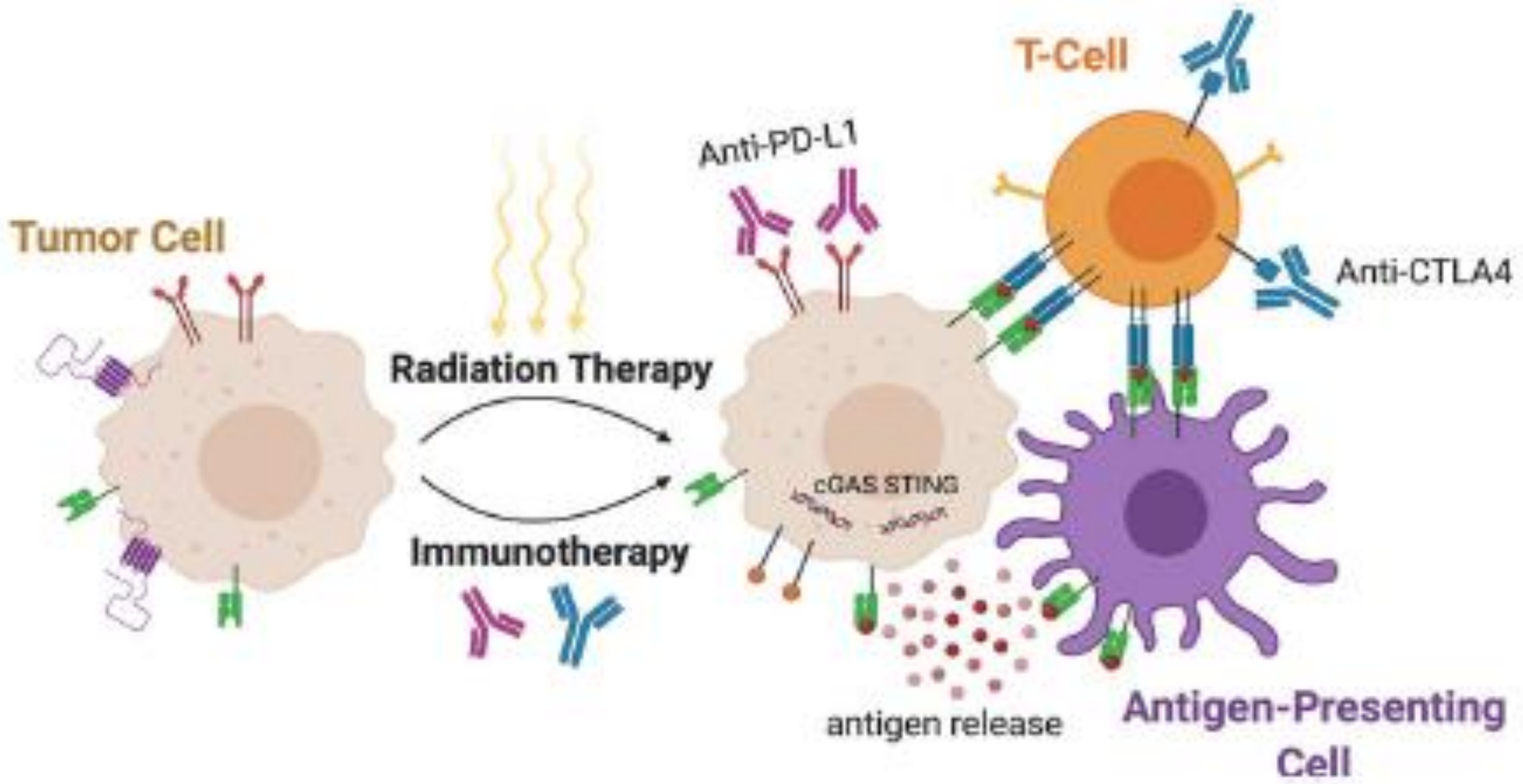
MGH series

Protocol	Neoadjuvant chemotherapy	Induction	Response	Consolidation or cystectomy	Maximum RT dose to tumor (Gy)	Adjuvant chemotherapy	Pts., *n* (%)
MGH 180	MCV 2 cycles	CP + QD RT	CR	CP + RT	64.8	None	52 (11)
MGH 880, RTOG 8903 Arm 1	MCV 2 cycles	CP + QD RT	IR CR	Cystectomy CP + RT	64.8	None	56 (12)
MGH 880, RTOG 8903 Arm 2	None	CP + QD RT	IR CR	Cystectomy CP + RT	64.8	None	50 (11)
MGH 930A	None	CP + 5-FU + BID RT	IR CR	Cystectomy CP + 5-FU + BID RT	64.8	MCV 3 cycles	21 (4.4)
RTOG 9506	None	CP + 5-FU + BID RT	IR CR	Cystectomy CP + 5-FU + BID RT	44	None	15 (3.2)
RTOG 9706	None	CP + BID RT	IR CR	Cystectomy CP + BID RT	64.8	MCV 3 cycles	23 (4.8)
RTOG 9906	None	CP + pacl + BID RT	IR CR	Cystectomy CP + Pacl + BID RT	64.3	CP + gem 4 cycles	44 (9.3)
RTOG 0233 Arm 1	None	CP + 5-FU + BID RT	IR CR	Cystectomy CP + 5-FU + BID RT	64.3	CP + Pacl + gem 4 cycles	28 (5.9)
RTOG 0233 Arm 2	None	CP + Pacl + BID RT	IR CR	Cystectomy CP + Pacl + BID RT	64.3	CP + Pacl + gem 4 cycles	33 (6.9)
RTOG 0524 Group 2	None	Pacl + QD RT	CR	CP + RT	64.8	None	3 (0.6)
RTOG 0712 Arm 1	None	CP + 5-FU + BID RT	IR CR	Cystectomy CP + 5-FU + BID RT	64.3	CP + gem 4 cycles	18 (3.8)
RTOG 0712 Arm 2	None	Gem + QD RT	IR CR	Cystectomy Gem + RT	64	CP + gem 4 cycles	14 (2.9)
Per protocol	Varied[a]	Varied[b]	IR CR	Cystectomy Varied[b]	64–66	Varied[c]	118 (25)

MGH series

Protocol	Neoadjuvant chemotherapy	Induction	Response	Consolidation or cystectomy	Maximum RT dose to tumor (Gy)	Adjuvant chemotherapy	Pts., *n* (%)
MGH 180	MCV 2 cycles	Cisplatin			64.8	None	52 (11)
MGH 880, RTOG 8903 Arm 1	MCV 2 cycles				64.8	None	56 (12)
MGH 880, RTOG 8903 Arm 2	None	Cisplatin+5-FU			64.8	None	50 (11)
MGH 930A	None				64.8	MCV 3 cycles	21 (4.4)
RTOG 9506	None	Cisplatin+Paclitaxel			44	None	15 (3.2)
RTOG 9706	None				64.8	MCV 3 cycles	23 (4.8)
RTOG 9906	None	Gemcitabine			64.3	CP + gem 4 cycles	44 (9.3)
RTOG 0233 Arm 1	None				64.3	CP + Pacl + gem 4 cycles	28 (5.9)
RTOG 0233 Arm 2	None	5-FU+MMC			64.3	CP + Pacl + gem 4 cycles	33 (6.9)
RTOG 0524 Group 2	None				64.8	None	3 (0.6)
RTOG 0712 Arm 1	None	Cisplatin+Gemcitabine			64.3	CP + gem 4 cycles	18 (3.8)
RTOG 0712 Arm 2	None				64	CP + gem 4 cycles	14 (2.9)
Per protocol	Varied[a]	Carboplatin			64–66	Varied[c]	118 (25)

The future

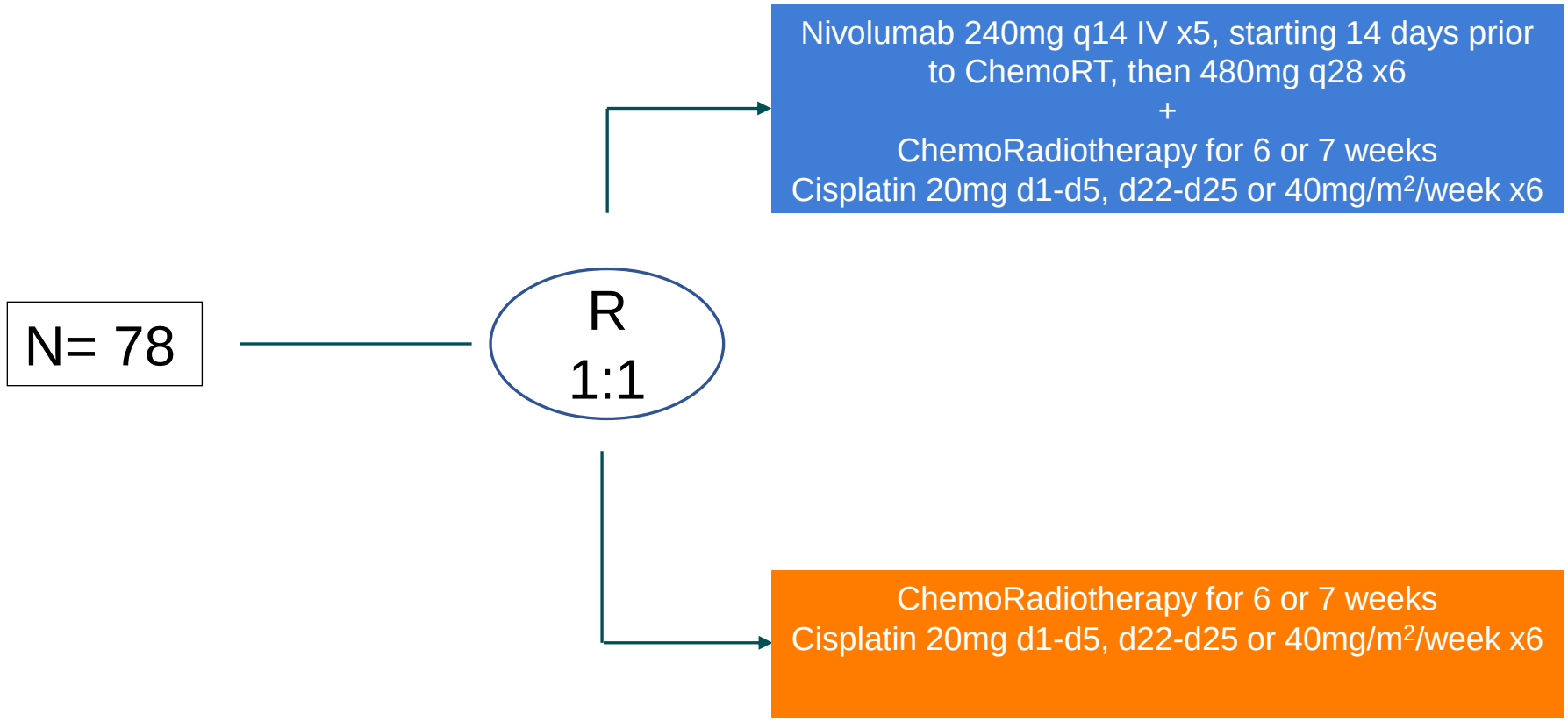

T-Cell
Anti-PD-L1
Tumor Cell
Anti-CTLA4
Radiation Therapy
cGAS STING
Immunotherapy
antigen release
Antigen-Presenting Cell

IO-CRT studies in bladder cancer

NCT02662062	MIBC	Phase II	RT + cisplatin + Pembrolizumab
NCT03171025	Localized MIBC	Phase II	Chemoradiation with Adjuvant Nivolumab
NCT02621151	MIBC	Phase II	RT + Gemcitabine + Pembrolizumab
NCT03421652	Locally Advanced UC Ineligible for Chemotherapy	Phase II	RT + Nivolumab
NCT03775265	Localized MIBC	Phase III	Chemoradiation ± Atezolizumab
NCT03950362	BCG Unresponsive NMIBC	Phase II	RT + Avelumab
NCT04543110	MIBC	Phase II	RT + Durvalumab
NCT03747419	MIBC	Phase II	RT + Avelumab
NCT03702179	MIBC	Phase II	RT + Durvalumab + Tremelimumab
NCT04216290	Node-positive Bladder Cancer	Phase II	Chemotherapy + RT ± Durvalumab
NCT03915678	anti-PD-1/L1 refractory Bladder Cancer ‡	Phase II	RT + Atezolizumab + BDB001
NCT03529890	Locally Advanced UC	Phase II	Neoadjuvant RT + Nivolumab
NCT03115801	Metastatic UC	Phase II	Atezolizumab or Pembrolizumab ± RT
NCT03511391	UC ‡	Phase II	(Pembrolizumab or Nivolumab or Atezolizumab) ± SBRT

Study design

Key Eligibility:
- Treatment naïve MIBC
- cT2-T4aN0M0
- Urothelial, squamous, glandular histology
- GFR≥ 40ml/min
- treatment within 3-8 wks of the most recent TURB



End points

- Primary

Locoregional control rate(LCR) at 2 years

- Secondary

Safety

Bladder cancer failure-free rate (BCFFR) at 2 years

OS

QoL

CONCLUSIONS

- Concurrent chemotherapy should be given in conjuction with radical radiotherapy in patients with MIBC who will not undergo cystectomy.
- There is no proven benefit by the addition of neoadjuvant or adjuvant chemotherapy to concurrent chemotherapy.
- CDDP and 5-FU are the most studied agents
- The addition of IO to the trimodality approach seems promising and is the object of intense clinical research.